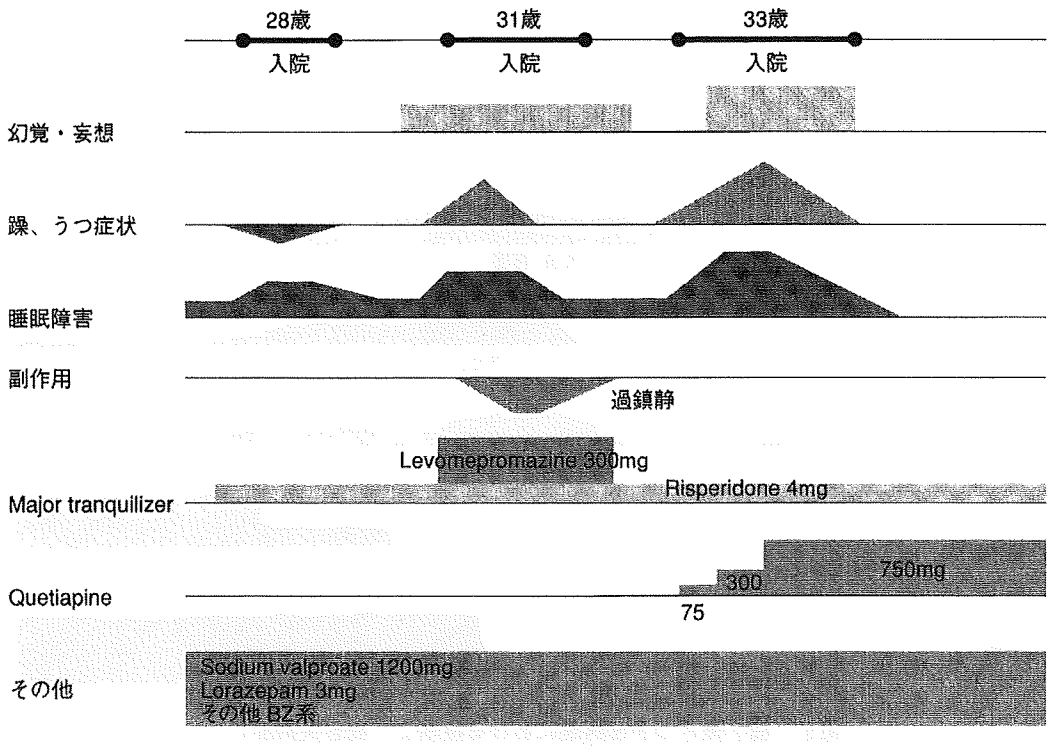

図4　袖ヶ浦さつき台病院における症例1（統合失調感情障害）

3例ほどご報告させていただきます。

まず，1例目は，統合失調感情障害（男性）の症例です（図4）。28歳時，幻覚妄想状態かつ抑うつ状態で発症しました。統合失調症の症状が基盤にあり，さらに病相ごとに抑うつ状態と躁状態を繰り返しています。重度の睡眠障害が目立ち，ベンゾジアゼピン系薬剤を7～8種類併用しても改善はみられません。感情調整薬としてsodium valproate，抗精神病薬としてrisperidoneを投与しましたが，睡眠障害は持続していました。

幻覚妄想状態と躁状態が重なった際に，levomepromazine 300mgを上乗せしましたが，過鎮静および脱抑制が出現しました。そのため，quetiapineに変更したところ，幻覚妄想状態や躁状態は消失し，さらに重度の睡眠障害も大幅に改善し，その結果ベンゾジアゼピン系薬剤を大幅に減らすことができました。

2例目は，18歳で発症した統合失調症（女性）の症例です（図5）。急性期治療の補助薬剤としてquetiapineを使用しました。注察妄想等で発症し，risperidone 2 mgで治療を開始しています。その後，幻聴が出現し，risperidoneを8 mgに増量した結果，幻覚妄想は消失しましたが，ささいな刺激で容易に興奮し，そのたびに入院を繰り返していました。そこでquetiapineを追加投与したところ，衝動性が非常に安定しました。Quetiapineが急性期の補助薬として奏効したといえるケースです。

3例目は，急性期後の使用例です（図6）。27歳発症の統合失調症（男性）の症例です。「他人の声が自分の口から出てくる」などの症状や興奮がみられ，入院しました。保護室で隔離および拘束せざるを得ない重症例でした。急性期はrisperidone 8 mgを使用し，錐体外路症状，特に流涎や前傾姿勢が目立ち，biperidenを追加して急性期を乗り越えてきたケースです。

急性期症状は大きく改善し，寛解で外来治療を続けていました。しかし，まもなく口周囲ジスキネジアが出現し，さらにはアカシジアも加わり，診察室では立ったまま足踏みしつつ口を動かしているといった状態でした。Biperiden，risperidoneともに減量し，最終的にはbiperidenを中止，risperidoneは1 mgとしましたが，それでもなお，ジスキネジアおよびアカシジアがともに存在

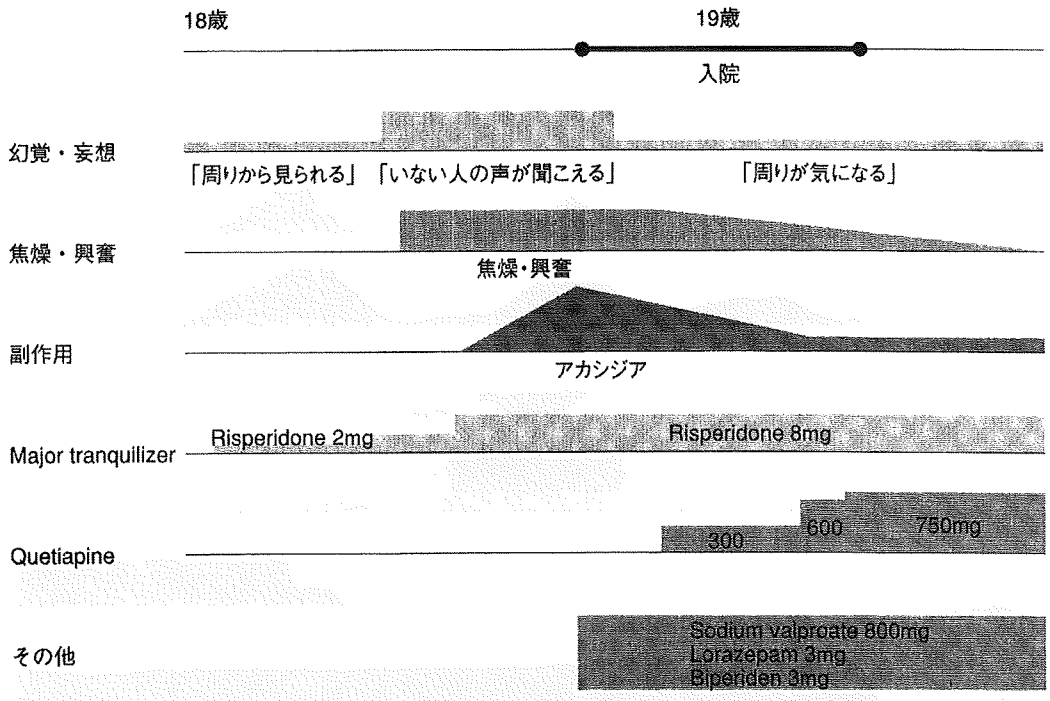

図5　袖ヶ浦さつき台病院における症例2（統合失調症）

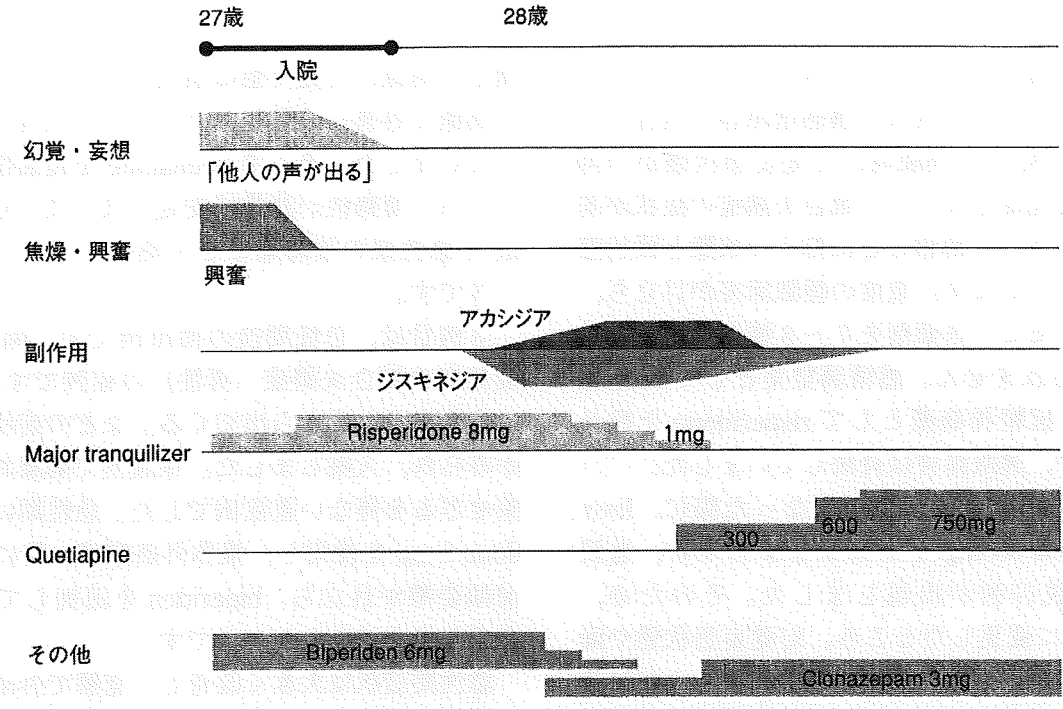

図6　袖ヶ浦さつき台病院における症例3（統合失調症）

していました。

そこで，risperidoneをquetiapine 750mgに置換しました。すると，ジスキネジア，アカシジアともに完全に消失しました。現在では，会社で発病前と同じように仕事ができ，再燃はみられていません。症例報告は以上です。

伊豫　石毛先生の症例では，1例目が急性増悪期の方ですね。この症例は，levomepromazineで

は過鎮静で退行してしまうところをquetiapineでは補助的に鎮静が可能で，良好なコントロールを得ることができたということですね。また，2例目は興奮や焦燥に関する有効例，3例目は急性期というよりは寛解維持期における有害作用発現時の切り替え症例といったところですね。

先ほど，浅野先生からお話があったように，quetiapineは気分障害や自殺企図を有する患者さんに対しても有効性が高いということですね。非常に興味深いのは，補助的に使う場合も最初から2剤を組み合わせていない点と，場合によっては3例目のように単剤でコントロールできる点です。実際の治療の場合には多くても2剤までです。単剤が推奨されていますが，なかには単剤のみでは効果を得られない患者さんもいらっしゃいます。また，副作用で「退行」がみられたケースがありましたが，他にも抗コリン作用による認知機能の低下や，いわゆる巨大結腸にも注意が必要になります。その意味からも，組み合わせる場合には2剤までで治療することもひとつの方法なのかもしれません。

石毛　Quetiapineは，半減期が短く，立ち上がりがはやいため，救急の場面において良好な効果が期待できると私は考えていますが，先生方は，どのようにお考えでしょうか。

早川　最近は，非定型抗精神病薬を救急外来で投与するケースが増えていると思いますが，quetiapineの救急場面での使用については，まだあまり経験がありません。

伊豫　「鎮静作用」について薬理作用から考えると，risperidoneやolanzapineはドパミンD_2受容体を比較的スムーズに遮断することで鎮静作用を示すのに対して，quetiapineを一度に大量投与してもドパミンD_2受容体の強い遮断作用があらわれない可能性があります。一方，2～3割の統合失調症の患者さんは，ドパミンD_2受容体を遮断するだけでは治療できないことが考えられます。

したがって，必ずしもドパミンD_2受容体遮断作用だけを目的とするのではなくて，ヒスタミン系やそれ以外の受容体に対する効果が期待できるquetiapineを急性期に単剤で使用することで，有効な症例が認められることが考えられます。あるいは，浅野先生からお話があったような自殺企図のあるような切迫している患者さんに投与することで，有効性が得られることも考えられます。

浅野　救急で切迫した患者さんでも，家族の方がしっかりしている場合などでは帰宅してもらっています。抗精神病薬を確実に服用できるのであればそれで落ち着くというケースもあります。

個人的な見解ですが，精神科救急に運ばれてくる患者さんのなかで興奮状態になっている人は，二次的な反応だと考えています。閉じ込められたり周りから押さえ込まれたりすると，一気にドパミンが放出され興奮状態に陥るため，周辺が保護的な環境であれば，病気がかなり悪い場合でも興奮は抑えられることもあります。病理的な機序も考える必要はありますが，反応によって出現する症状を防げるような環境や対応への配慮があれば，非定型抗精神病薬は有用だと思います。

伊豫　救急場面では，その後の治療に対する意欲も持っていただくことが必要であると考えると，救急というのはその救急場面だけではなく，その後も1～2日間くらいは続いているという捉え方が重要になると思います。そうすると，救急場面では，その後の情動面や自殺企図から，quetiapineの使用は十分に考慮すべきだと思います。

本日は精神科救急とその場面における治療ということで，臨床現場で精神科救急医療に従事されている3人の先生方にご討議いただきました。臨床現場でないとわからないようなお話なども聞くことができ，大変興味深かったと思います。本日はどうもありがとうございました。

文　献

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Does hypofrontality expand to global brain area in progression of schizophrenia?: A cross-sectional study between first-episode and chronic schizophrenia

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ABSTRACT

Although to date there have been no conclusive pathophysiological findings in support of the degenerative theory of the etiology of schizophrenia, the results of neuroimaging studies have suggested that progressive changes in the brain do occur during the clinical course of schizophrenia. However, there has been no report on alterations in regional cerebral blood flow (rCBF) under resting condition, which was compared between the first-episode and the chronic patients of schizophrenia and healthy controls. Therefore, in this study, we applied three-dimensional stereotactic surface projection analysis of resting SPECT (3D-SSP SPECT) in patients with first-episode ($n=18$) and chronic schizophrenia ($n=23$) and age-/sex-matched healthy controls ($n=40$). The rCBFs in the middle/inferior/medial frontal gyrus and the anterior cingulate gyrus were significantly decreased in both patient groups, relative to the respective controls ($Z>3.0$, $P<0.001$, uncorrected). The chronic group showed significant hypoperfused region in the left inferior parietal lobule and middle/inferior temporal gyrus. Furthermore, within-cases comparison between the first-episode and chronic schizophrenia, revealed that the significant hypoperfused regions in the chronic group, compared to the first-episode group, were not only the lateral and medial prefrontal cortex, but also the inferior parietal cortex, posterior part of the temporal lobe, and the cuneus. The present study suggested that the reduction in rCBF occurs in the posterior brain area in addition to the frontal lobe across all clinical stages of schizophrenia.

1. Introduction

Schizophrenia has been considered a progressive disorder in view of clinical symptoms and functional disability ever since the report of Kraepelin (1919/1971). The progressive disability has been considered to be associated with progressive biological changes in the brain; hence, it is important to clarify these changes in brain morphology and function for our understanding of the disease pathophysiology and the development of therapeutic strategies. Following the reports on hypofrontality in schizophrenia under the resting state by Ingvar and Franzen (1974), various neuroimaging studies using SPECT or PET have documented hypofrontality in patients with schizophrenia (Ashton et al., 2000; Gonus et al., 2003; Malaspina et al., 2004; Molina et al., 2005; Sachdev et al., 1997; Siegel et al., 1993). However, recent functional imaging studies under resting state (Andreasen et al., 1997; Kim et al., 2000), as well as studies conducted while subjects performed some cognitive tasks (Fletcher et al., 1999; Meyer-Lindenberg et al., 2005), have suggested that multiple regions including the lateral prefrontal cortex (LPFC), the medial prefrontal cortex (MPFC), and the temporal lobe cortices, rather than simple hypofrontality, are involved in the pathophysiology of schizophrenia.

On the other hand, recent MRI studies also indicate morphological changes with progression of the disease. The changes following the disease onset have been demonstrated as ventricular enlargement (Cahn et al., 2002; DeLisi et al., 1995, 1997) and degeneration in several

Abbreviations: ACG, anterior cingulate gyrus; BPRS, Brief Psychiatric Rating Scale; DSM-IV, Diagnosis and Statistical Manual of Mental Disorders-4th edition; LPFC, lateral prefrontal cortex; MPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; PET, positron emission tomography; rCBF, regional cerebral blood flow; SCID, Structured Clinical Interview for DSM- IV; SPECT, single photon emission computed tomography; 3D-SSP, three-dimensional stereotactic surface projection; WAIS-R, Wechsler Adult Intelligence Scale-Revised

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regions such as the prefrontal cortex (Gur et al., 1998; Ho et al., 2003; Mathalon et al., 2001) and temporal lobe cortices (Mathalon et al., 2001; Kasai et al., 2003a,b), although several studies have denied progressive volume reductions (Degreef et al., 1991; DeLisi et al., 2004; Gur et al., 1998; Whitworth et al., 2005). In addition, there is some evidence of these morphological changes at the initiation of disease, i.e., already before disease onset (Borgwardt et al., 2007; Job et al., 2005; Pantelis et al., 2003; Sun et al., in press). Progressive volume reduction in structural neuroimaging suggests that hypoperfusion in the brain, not only in functional neuroimaging but also under a resting state, becomes exacerbated over the clinical stages in schizophrenia. However, surprisingly, there have been few studies on this topic (Desco et al., 2003; Gur et al., 1995).

The three-dimensional stereotactic surface projection (3D-SSP) method used in this study has been known to minimize the effects of brain atrophy more than statistic parametric mapping (SPM), and thus is a method suitable for investigating regional cerebral blood flow (rCBF) and regional glucose metabolism ratio (rGMR) in diseases with brain degeneration, such as Alzheimer's disease and Parkinson's disease (Ishii et al., 2001; Matsui et al., 2005; Minoshima et al., 1995, 1997). The 3D-SSP method is considered a suitable tool for assessment of rCBF in schizophrenia as well, since volume reductions in the brain have been indicated. In this study, therefore, we used 3D-SSP SPECT to observe rCBF in patients with first-episode and chronic schizophrenia, in order to clarify whether or not brain hypoperfusion progresses with clinical stage in schizophrenia. In this study, each patient group had age-matched control groups, since several studies on normal subjects have suggested age-related alterations in rCBF, even if in relatively younger adults (Inoue et al., 2003; Kuji et al., 1999; Pagini et al., 2002; Van Laere and Dierckx, 2001).

2. Methods

2.1. Subjects and study design

We distinguished between the first-episode and the chronic patients, based on the duration of illness following the onset of positive symptoms. The first-episode group included those who had a continuous episode that lasted for up to 2 years, whereas the chronic group included those who had a duration of illness of more than 10 years prior to SPECT scanning. Both groups also met the DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994). From July 2005 to October 2008, we recruited inpatients and outpatients at Chiba University Hospital or Chiba Psychiatry Medical Center (CPMC), who met the above criteria in serial order. We then divided the patients who agreed to participate in the study into first-episode ($n=18$) and chronic ($n=23$) groups. All patients were also evaluated using the Structured Clinical Interview for DSM-IV (SCID; American Psychiatric Association, 1994). Furthermore, reevaluation of the diagnosis of schizophrenia at 6 months after SPECT scanning, based on a semi-structured clinical interview and medical records, was performed for each subject by two experienced psychiatrists (N.K. and E.S.). As regards pharmacotherapy, the first-episode group had either no history of taking antipsychotic medication (neuroleptic-naive; $n=7$) or had been treated with atypical antipsychotics such as risperidone (RIS), olanzapine (OLZ), quetiapine (QTP), or perospirone (PER) prior to enrollment in the study (mean duration of treatment: 3.0 months; $n=11$; RIS: $n=8$, OLZ: $n=1$, QTP: $n=1$, PER: $n=1$), whereas patients in the chronic group were drug-free ($n=6$) due to discontinuation of therapy, or they had been treated with atypical antipsychotics ($n=17$; RIS: $n=9$, OLZ: $n=8$) for at least one year. Patients' clinical symptoms were assessed with the 18-item Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1964) and concurrently, the shortened version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler 1981), consisting of knowledge, picture completion and digit span forward/backward to evaluate the estimated IQ. On the other hand, the control group consisted of 40 healthy volunteers, who are free from any Axis I or II psychiatric disorder, based on the Structured Clinical Interview for DSM-IV Non-patient Edition (SCID-NP), and was divided into two age- and sex-matched groups (control-1 corresponds to the first-episode patient group and control-2 corresponds to the chronic patient group) (Table 1). Exclusion criteria for the both patients and healthy groups were a history of loss of consciousness, organic brain disorder, alcohol/drug abuse for previous life time, pregnancy or any physical disease on the basis of medical interview, physical examination, brain MRI, and laboratory data. The study protocol was approved by the ethics committee of both Chiba University and CPMC. The patients gave their written informed consent.

2.2. SPECT scanning procedure

The SPECT images were obtained using ^{123}I-IMP and acquired on a PRISM3000XP (Picker International, Cleveland, OH), 3-headed SPECT camera with ultrahigh-resolution fan-beam collimators. All subjects were examined in the supine resting position with closed eyes in a silent room. They were injected with 111 MBq of ^{123}I-IMP in the antecubital vein, and scanning was begun after 30 min. The data acquisition parameters were 128 × 128 matrices, 3 per step, 120 views,

Table 1
Demographic characteristics of the groups.

Clinical variables	First-episode schizophrenia	Normal control-1	Chronic schizophrenia	Normal control-2	Statistical values ($df=39$) first-episode vs chronic
Male/female	M10/F8[a]	M10/F8	M19/F4[b]	M18/F4	N.S. (Fisher's exact)
Age	27.0 ± 4.5[c]	26.4 ± 4.7	38.0 ± 7.0[d]	36.1 ± 7.8	$P<0.001$
(Range)	19–36	19–35	27–53	22–51	
Duration of illness (years)	1.3 ± 0.3		15.5 ± 6.2		$P<0.001$
Age at onset	25.5 ± 4.7		22.0 ± 5.2		$P<0.05$
Years of education	14.7 ± 2.5[c]	15.0 ± 1.9	14.0 ± 2.3[d]	14.6 ± 3.1	N.S.
Dose of antipsychotics[e]	284.9 ± 319.5		447.8 ± 405.6		N.S.
Duration of treatment (years)	0.25 ± 0.34		6.57 ± 6.79		$P<0.001$
BPRS (total)	34.6 ± 11.7		36.8 ± 10.5		N.S.
Positive symptoms[f]	11.8 ± 5.6		10.4 ± 4.1		N.S.
Negative symptoms[g]	5.8 ± 4.3		7.7 ± 3.5		N.S.
Estimated IQ	86.4 ± 20.0		89.9 ± 23.6		N.S.

[a] n.s. in comparisons between the first-episode and normal control-1 (Fisher's exact test).
[b] n.s. in comparisons between the chronic patient and normal control-2 (Fisher's exact test).
[c] n.s. in comparisons between the first-episode and normal control-1 (t-test).
[d] n.s. in comparisons between the chronic patient and normal control-2 (t-test).
[e] Corresponding to daily chlorpromazine dose (mg).
[f] BPRS positive scores consist of those of conceptual disorganization, suspiciousness, hallucinations and unusual thought content.
[g] BPRS negative scores consist of those of emotional withdrawal, motor retardation and blunted affect.

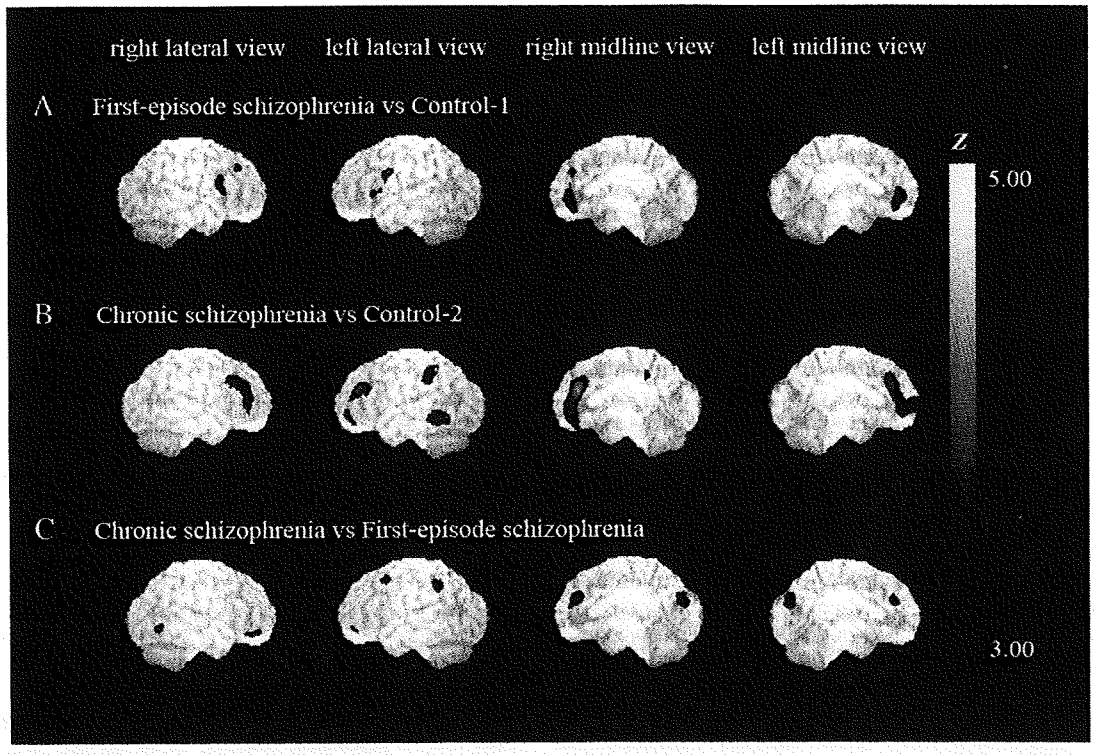

Fig. 1. 3D-SSP maps of the rCBF of patients with schizophrenia derived using ^{123}I-IMP, and compared with those of normal controls. (a) Significantly decreased regions in the first-episode patients compared with the controls; (b) Significantly decreased regions in the chronic patients compared with the controls; (c) Significantly decreased regions in the chronic patients compared with the first-episode patients ($Z>3.00$, corresponding to $P<0.001$, uncorrected).

7.5 s per view, and a 159-keV (±10%) energy window. Reconstruction was performed by filtered back projection using a Butterworth filter (cut-off frequency 2.5/order 4), and attenuation correction of ramp filters was performed using the Chang 8-order method. To confirm that there was no head movement or opening of the eyes, each subject was monitored by video camera.

2.3. Statistical analysis

Analysis with the interface software iSSP (version 3.5; Nihon Medi-Physics Corporation, Nishinomiya, Japan) followed the 3D-SSP method established by Minoshima (Bartenstein et al., 1997; Minoshima et al., 1994). We used the cerebellum as the reference region for normalization, as this was the approach taken in a number of similar studies (Sabri et al., 1997; Sachdev et al., 1997; Vita et al., 1995).

To demonstrate differences in the rCBF distributions, 2-sample *t*-test values were calculated on a pixel-by-pixel basis and then transformed to *Z* values by a probability integral transformation (Worsley et al., 1996). And we set the level of significant thresholds of $Z>3.00$ (corresponding to uncorrected $P<0.001$) revised on the basis of random Gaussian field theory (Hanyu et al., 2001). Regarding cluster size, we defined a region having more than 50 contiguous

Table 2
Regional cerebral blood flow assesses in first-episode and chronic schizophrenia groups, compared to normal healthy subjects ($Z>3.00$, $P<0.001$, uncorrected).

Region with decreased rCBF	First-episode schizophrenia				Chronic schizophrenia			
	Brodmann's area	Cluster size (ml)	Highest *Z* value	Coordinates (*x*, *y*, *z*)	Brodmann's area	Cluster size (ml)	Highest *Z* value	Coordinates (*x*, *y*, *z*)
Frontal lobe								
Middle frontal gyrus/ inferior frontal gyrus	L6/9	1.50	3.90	−55, 5, 32	L9/10/46	6.15	3.86	−44, 44, 25
	L44/45	0.82	3.35	−53, 23, 5	L10/47	3.96	3.41	−30, 32, −13
	R8/9	1.09	3.25	39, 39, 38	R9/45/46/47	8.95	3.47	46, 41, 27
	R44/45/46	2.87	3.20	57, 17, 16				
Medial frontal gyrus/ anterior cingulate gyrus	L10/11/32	4.03	3.40	−1, 44, −2	L9/10/32	12.02	3.73	−1, 39, 27
	R10/11/32	4.72	3.58	1, 46, −2	R6/9/10/11/32	12.51	4.21	1, 39, 23
	R6/9	1.30	3.24	1, 44, 34				
Parietal lobe								
Inferior parietal lobule					L40	4.17	3.48	−60, −40, 43
Temporal lobe								
Middle temporal gyrus/ inferior temporal gyrus/ fusiform gyrus					L19/21/37	5.26	3.71	−60, −49, −9
Limbic regions								
Cingulate gyrus					L31	0.22	3.40	1, −37, 38

significant pixels as a hypoperfused region and converted them to volume. These procedures were performed with stereotactic extraction estimation (SEE ver. 2; Nihon Medi-Physics Corporation).

3. Results

Table 1 shows the characteristics of the participants. Age and sex were matched between the two patient groups and the corresponding normal healthy subjects, respectively. Furthermore, BPRS positive and negative symptoms were not significantly different between the first-episode and chronic schizophrenia groups.

3.1. Comparisons of rCBF ratios between the first-episode schizophrenia and control-1, and between the chronic schizophrenia and control-2

The pixel-by-pixel based comparison with the significant threshold of $Z>3.00$ (uncorrected $P<0.001$) revealed that the LPFC (middle/inferior frontal gyrus) and MPFC (medial frontal gyrus and ACG [anterior cingulate gyrus]) were the significant hypoperfused regions common to both schizophrenia groups (Fig. 1a,b, Table 2). On the other hand, the regions that were significantly hypoperfused only in chronic schizophrenia, and not in the first-episode group, were the left inferior parietal lobule, the left middle/inferior temporal/fusiform gyrus, and cigulate gyrus (Fig. 1b, Table 2). The stricter significance threshold ($Z>4.53$, corrected $P<0.05$) revealed that neither the first-episode group, nor the chronic group have the significantly hypoperfused region.

3.2. Comparison of rCBF ratios between first-episode and chronic schizophrenia

In order to explore rCBF alteration depending on progressive clinical change of the disease, we performed a within-cases comparison (i.e., first-episode schizophrenia vs chronic schizophrenia). The analysis showed that rCBF ratios in the bilateral LPFC (middle frontal gyrus) and the MPFC (medial frontal gyrus and ACG) in the chronic group revealed the significant hypoperfused regions, compared to the ratios in the first-episode group ($Z>3.0$, uncorrected $P<0.001$; Fig. 1c and Table 3). Furthermore, rCBF ratios in the left parietal lobe (inferior parietal lobule and the supramarginal gyrus), the right posterior part of the temporal lobe (middle/inferior temporal gyrus), and the bilateral medial phase of the occipital gyrus (cuneus) in the chronic group were significantly lower than those in the first-episode group (Fig. 1c and Table 3). In the analysis with a stricter significance threshold ($Z>4.53$, corrected $P<0.05$), we did not find any significant region that indicated a greater decrease of rCBF ratios in the chronic group than in the first-episode group. On the other hand, the analysis indicated that there is no region, where is the significantly decreased in the first-episode group compared to the chronic group. In addition, the within-controls comparison (control-1 vs control-2) revealed no significant difference in rCBF ratios between the two groups.

Table 3
Significant hypoperfused regions in chronic schizophrenia compared to first-episode schizophrenia ($Z>3.00$, $P<0.001$, uncorrected).

Region with decreased rCBF	Brodmann's area	Cluster size (ml)	Highest Z value	Coordinates (x, y, z)
Frontal lobe				
Middle frontal gyrus	L6/8	1.23	3.38	−46, 17, 47
	L10/11	0.75	3.17	−39, 53, −7
	R11/47	2.94	3.70	39, 39, −11
Medial frontal gyrus/ anterior cingulate gyrus	L9/32	1.64	3.42	−1, 39, 27
	R6/9/32	3.35	3.60	1, 41, 27
Parietal lobe				
Inferior parietal lobule/ supramarginal gyrus	L40	2.12	3.48	−60, −46, 41
Temporal lobe				
Middle temporal gyrus/ inferior temporal gyrus	R19/37	1.37	3.16	53, −62, −7
Occipital lobe				
Cuneus	L18/19/31	3.55	3.57	−1, −78, 27
	R18/19/31	3.52	3.52	1, −78, 23

4. Discussion

In this study we found, first, that there was hypoperfusion in the LPFC and MPFC in both the first-episode and chronic schizophrenia groups compared with the respective control groups, which suggest the hypoperfusion in these regions is consistent throughout the course of the disease. Second, hypoperfusion in the frontal lobe tended to be more severe in chronic than in first-episode schizophrenia (Fig. 1a,b). Third, the results of this study were suggestive of a greater reduction in rCBF in the posterior brain regions (the parietal cortex, the posterior part in temporal lobe and the cuneus) in the chronic schizophrenia than in the first-episode schizophrenia. Taken together, these results suggest that hypoperfusion in the brain of the chronic schizophrenia may progress from the frontal regions to other regions, especially the posterior regions, over the course of the disease.

As far as we know, there has been no cross-sectional study or longitudinal study on rCBF distribution at different stages of schizophrenia. Our study employed strict age/sex-matched control groups (control-1 and control-2) for the corresponding patient groups, first-episode and chronic schizophrenia, respectively. Therefore, the significantly decreased regions in rCBF ratios in both first-episode and chronic schizophrenia, compared to their respective controls, indicate disease-related alterations at each clinical stage of schizophrenia (Fig. 1a, b, Table 2). Importantly, we found that the rCBFs in the posterior brain regions, in addition to the prefrontal cortex in the chronic group, were significantly lower than those in the first-episode group. This finding cannot be explained only by aging (first-episode group, 27.0 years: chronic group, 38.0 years), since the rCBF distributions in control-1 and control-2 were very similar. Moreover, the regions with different rCBF ratios between the two clinical stages (Fig. 1c), can be predicted from the two results showing the disease-related changes at each clinical stage (Fig. 1a, b).

Hypoperfusion in the frontal lobe, particularly the MPFC, showed the greatest reduction from healthy levels among all regions in the brain in both the first-episode and chronic stage patients. This result suggests that rCBF in the frontal lobe already begin to fall within 2 years of disease onset. Several recent MRI studies on the early stage in schizophrenia have shown that morphological alterations occur dynamically over the first 2–3 years following onset, which could be differentiated from subsequent phases of the disease (Ho et al., 2003; Whitford et al., 2006); they also support our results for the first-episode group.

The current finding of hypofrontality in subjects in a resting state starting at the early stage appears to be inconsistent with previous fMRI studies in which increased activity was observed in the frontal regions (Manoach et al., 1999, 2000). However, Manoach (2003) suggested that the level of activity may be influenced by the kind of cognitive tasks loaded, and that observations of increased activity may be reflective of hypofrontality in patients with schizophrenia. Therefore, results of fMRI studies showing increased activity (Manoach et al., 1999, 2000) may indeed be consistent with our results.

Contrary to our hypothesis, hypofrontality in the LPFC in the chronic group failed to show obvious exacerbation relative to the first-episode group (Fig. 1c, Table 3). Desco et al. (2003) conducted a comparative study on FDG-PET between recent-onset schizophrenia, with illness duration up to 3 years, and chronic schizophrenia, and found that the LPFC in the chronic group showed significantly lower rGMR than the recent-onset group. In addition to differences in rGMR

by PET and rCBF by SPECT, one of the possible explanations for the lack of significant progressive frontal rCBF reduction in our study may be the patients' profiles. Particularly in the chronic group, as shown in Table 1, negative symptoms and estimated IQ in this group were similar to those of first-episode, and there were no long-term institutionalized patients in the present study, suggesting that the chronic patients who participated in this study had better prognoses than more general chronic patients in clinical practice. Nevertheless, severe rCBF reduction in the ACG throughout clinical stages may be associated with abnormalities directly demonstrated by MRI studies showing volume reduction (Hanznedar et al., 2004; Mitelman et al., 2005; Wang et al., 2007) or postmortem studies showing histopathological changes in this region (Benes et al., 1991; Broadbelt et al., 2006; Jone et al., 2002).

On the other hand, results for the parietal, temporal, and occipital lobes, which indicated significant decreases in rCBF in the chronic group relative to the normal comparison, also showed a significant difference by within-cases comparison. These results suggest a greater alteration of rCBF in the posterior region than in the frontal region during a timeframe ranging from the early to the chronic phase of illness. Although little attention has been paid to the parietal lobe, the posterior temporal lobe, and the cuneus in schizophrenia, rCBF/rGMR in chronic schizophrenia was found to be significantly reduced in these lobes (Kim et al., 2000; Potkin et al., 2002; Wolkin et al., 1985). However, these studies did not show relationships between these abnormalities and illness duration. In recent fMRI researches on chronic schizophrenia, function in the inferior parietal lobule has been suggested to differ from that in healthy subjects in concept of self (Spence et al., 1997) and decision-making (Collete et al., 2005; Paulus et al., 2002); furthermore, the posterior part of the middle temporal gyrus involving semantic priming has been reported to be functionally disturbed in schizophrenia (Han et al., 2007; Kuperberg et al., 2007). Although there are far fewer reports on the medial phase of the occipital lobe than on the parietal/temporal lobe in schizophrenia, several studies found dysfunction of visual processing (Butler and Javitt, 2005; O'Donnell et al., 1996; Tek et al., 2002). In addition, structural MRI studies suggested that reduced brain volume in widespread regions including the posterior brain area are related with the duration of illness (Meisenzahl et al., 2008) or poorer outcomes of the disease (Mitelman et al., 2003). These cortices have strong connectivity with the prefrontal cortex, and disconnectivities among the prefrontal and other cortices are presumed to contribute to the core pathophysiology of schizophrenia (Fletcher et al., 1999; Frith et al., 1995; Quintana et al., 2003). These regions in the posterior brain area showing hypoperfusion in chronic schizophrenia in the current study may be responsible for the pathophysiology underlying the disease, but in combination with other regions, including the prefrontal cortex, rather than alone.

The results of the present study are preliminary, and it would therefore be inappropriate to conclude that they are reflective of a general pattern of progression of hypoperfusion across clinical stages of this disease, since this study has following some limitations related to study design. First, the present study was not conceived as a longitudinal study, i.e., there were no rigorous comparisons of changes in rCBF ratio at different stages of illness within the same patient group. Therefore, although the use of two age-matched control groups did enable us to observe a clear difference in rCBF ratio in some posterior brain regions between our two patient groups (Fig. 1c, Table 3), these results will require further examination in future studies. Second, antipsychotics administered to both patient groups may have had some effect on rCBF distribution. Different patterns of effects on perfusion have been reported for haloperidol and risperidone (Miller et al., 2001). Metabolic and perfusion changes have also been reported for clozapine and risperidone (Molina et al., 2003, 2005). However, our samples consisted of patients who had taken neither haloperidol nor clozapine. Furthermore, the chlorpromazine-equivalent dosages of antipsychotic drugs did not statistically differ between groups (Table 1). Thus, the effects caused by medication differences may have been low in this study. Finally, our sample size was relatively small. Despite these limitations, this study suggests that SPECT is a useful means to explore the alterations of rCBF over the stages of schizophrenia, beyond its relatively poor spatial resolution. In order to compare two patient groups with different clinical stages more strictly and reach conclusive evidence on this issue, a further longitudinal study with both larger and homogeneous samples should be conducted.

5. Conclusions

In conclusion, the present study demonstrated that hypofrontality in the LPFC and MPFC was unchanged between first-episode and chronic schizophrenia. In the chronic stage, however, the rCBF reductions in the frontal lobe tended to extend to posterior brain regions such as the parietal lobe, the posterior temporal lobe and the occipital lobe.

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