automatic saccades is impaired in schizophrenic patients.[4] One task used to investigate saccade inhibition is the antisaccade task, which requires subjects to inhibit a saccade toward a briefly appearing peripheral target, and to instead immediately generate a saccade to a point in the opposite direction.[5] Antisaccade deficits have high sensitivity and high specificity for the diagnosis of schizophrenia and are thought to be a genetic marker for the illness. Reported rates of antisaccade deficits range from 24% to 71% in patients with schizophrenia and from 2% to 27% in normal controls.[6–9]

Several comparison studies to date have examined the brain regions associated with antisaccade tasks in schizophrenic patients and normal control subjects.[10–12] Most of these have reported reduced activity in the basal ganglia and the cortex, including the prefrontal area, in the schizophrenic group. As we will discuss further below, we question whether the activities of these brain regions were in fact reduced or not. Functional magnetic resonance imaging (fMRI) is a specialized MRI scan that measures hemodynamic responses related to neural activity in the brain. When two actions that generate neural activity are compared in fMRI, an analysis is based on the difference between a baseline signal and a signal measured at the time of task execution. Therefore, when comparing two groups, it is important to be able to assume that the baseline levels in the two groups are equivalent. Most previous fMRI research on antisaccade and saccade tasks used a target that required subjects to focus on a central fixation point during baseline imaging. One possibility is that patients with schizophrenia may exhibit greater cerebral activities during the fixation condition than healthy subjects. In order to examine this baseline effect, here we compared schizophrenic patients and normal subjects using a blank screen on which subjects were not required to focus at baseline.

MATERIALS AND METHODS

Subjects

Eighteen patients with schizophrenia (11 men and 7 women; mean age 34.8 ± 7.9) and 18 healthy subjects (9 men and 9 women; mean age 37.6 ± 4.8) participated in this study. All patients met the criteria for schizophrenia according to the DSM-IV. The mean duration of education was significantly longer ($P < 0.05$) in the healthy subject group than in the schizophrenia group. In the latter group, the mean age at onset of psychosis was 25.8 years old, the mean Brief Psychiatric Rating Scale total score was 41.9, and the mean total dose of antipsychotic medication per patients converted to haloperidol equivalency was 16.0 mg. All healthy subjects were free from neurological or psychiatric illness, and no abnormalities were observed on brain structural MRI. Written informed consent was obtained from all participants. All participants were right-handed according to the Edinburgh Handedness Inventory.[13] This project was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of Nihon University School of Medicine.

MRI acquisition

MRI data were acquired using a 1.5T Siemens Symphony system (Siemens, Erlangen, Germany). Gradient-recalled echo planar imaging (EPI) was used for the fMRI sequence to obtain blood oxygen level-dependent contrast. Interleaved multi-slice gradient EPI was used to produce 40 continuous, 3-mm thick axial slices encompassing the entire brain (echo time = 62 ms, repetition time = 4000 ms, flip angle = 90 degrees, field of view = 192 mm, 64*64 matrix). Each series comprised 104 scans with a complete duration of 416 s. The run began with four dummy volumes to allow for T1 equilibration effects. The head of the subject was fixed using cushions to minimize motion artifacts.

Behavioral methods

Saccade and antisaccade performance was recorded outside of the magnet. Horizontal and vertical eye movements and target position were measured using electro-oculography (EOG) (NEC) and a goggles-type display (SONY).

Stimulus projection

The stimulus was generated using a personal computer (OS: Windows 98) and made to order software. The stimulus was projected on a small screen attached to a head coil, using a liquid crystal display projector system customized to our MRI machine (Kiyohara Optics, Tokyo).

Prosaccade task

Each trial began with the target in central fixation (0 degrees) for a random duration of 500–1500 ms.

The target then shifted randomly to left or right horizontal peripheral locations (10 degrees from the center position), where it remained for 1000 ms. The target size was 1 degree of the visual angle. The number of left and right saccadic eye movements was the same. Participants were instructed to follow the target as quickly and accurately as possible, alternating between 40 s of control condition task and 40 s of prosaccade condition, completing 10 sets of trials in all. During the baseline condition, subjects were in total darkness and were asked to maintain fixation and not blink.

Antisaccade task

The parameters for the antisaccade task were identical to those for the prosaccade task. The antisaccade task required participants to fixate the target in the central position and to redirect their gaze in the opposite direction of the target as soon as it shifted to the periphery. Participants performed 10 sets of trials in total, alternating antisaccade and control conditions.

fMRI data analysis

Image analysis was performed using an Ultra5 workstation (Sun Microsystems, Palo Alto, CA, USA) using MATLAB (Mathworks Inc., Natick, MA, USA) and statistical mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Before statistical parametric maps were calculated, EPI images for each time series were realigned to the first functional image to remove residual head movement. Images were then coregistered and normalized to the Montreal National Institute template. Confounding effects of global volume activity and magnetic noise were removed using linear regression and cosine functions (up to a maximum of 1 cycle per 40 scans). Removing the latter confounds corresponds to high-pass filtering of the time series to remove low-frequency artifacts that can arise due to aliased cardiac and other cyclical components. After normalization, three-dimensional spatial smoothing was applied to each volume using a Gaussian kernel of $8 \times 8 \times 8$ mm. Alternating periods of baseline and activation were modeled using a simple delayed box-car reference vector to account for delayed cerebral blood flow after stimulus presentation. Significantly activated pixels were searched for using the General Linear Model approach for time-series data.

To create the subtraction activation image between saccade and antisaccade, data was analyzed using random-effect analysis. Statistical significance was set at the level of $P < 0.001$, uncorrected for multiple comparisons.

Intra-individual comparisons between saccade and antisaccade were analyzed using paired *t*-tests, and statistical significance was set at the level of $P < 0.005$, uncorrected for multiple comparisons.

RESULTS

Behavioral data

Demographic and performance data are summarized in Table 1. The analysis of EOG revealed no differences in prosaccades between the patients and normal controls. In contrast, error rates in antisaccades were higher and latencies of prosaccades and antisaccades were longer in the patient group than in the control group.

fMRI data

Activated areas in the normal control group are shown in Fig. 1a for the saccade tasks and in Fig. 1b for the antisaccade tasks ($P < 0.001$, uncorrected for multiple comparisons). During the saccade tasks, regional activations were observed bilaterally in the frontal eye fields (FEF), supplementary eye fields (SEF), and parietal eye fields (PEF), left lenticular

Table 1. Subjects and eye movement performance

	Patients with Schizophrenia	Control
Number of cases (male/female)	18 (12/6)	18 (9/9)
Age (year)	34.8 ± 7.9	37.6 ± 4.8
Education (year)*	11.2 ± 2.9	15.3 ± 2.2
Age at the onset (year)	25.8 ± 6.4	–
HPD equivalence (mg)	16.0 ± 16.1	–
BPRS total score	41.9 ± 7.9	–
Saccade error (%)*	0.5 ± 0.67	0.00 ± 0.00
Saccade latency (ms)*	212.2 ± 30.1	174.2 ± 11.8
Anti-saccade error (%)*	1.1 ± 1.6	0.14 ± 0.35
Anti-saccade latency (ms)*	244.9 ± 48.4	205.6 ± 18.5

Statistical analysis (T-test) *$P < 0.05$.
BPRS, Brief Psychiatric Rating Scale; HPD, haloperidol.

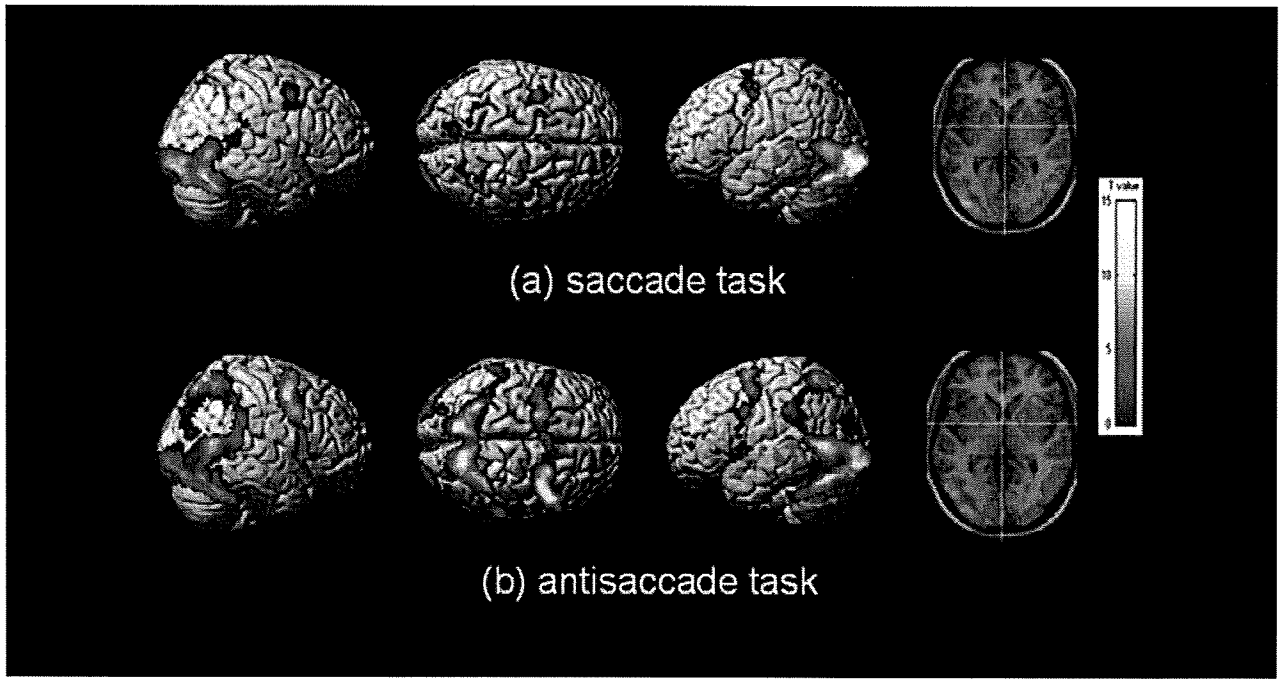

Figure 1. Brain regions displaying greater activities during (a) saccade and (b) antisaccade conditions than during control condition in healthy subjects. In the rightmost image, the activation map is overlaid onto a T1 SPM normalized brain image. The height threshold is set at $P < 0.001$, uncorrected.

nucleus, and bilateral occipital cortices (V1). During the antisaccade tasks, activations were observed in the same regions as during saccade tasks, as well as bilaterally in the inferior parietal lobules (IPL), thalami, right lenticular nucleus, inferior frontal gyrus (IFG), and left dorsolateral prefrontal cortex (DLPFC) (Table 2).

Activation areas in the patient group are shown in Fig. 2a for the saccade tasks and in Fig. 2b for the antisaccade tasks ($P < 0.001$, uncorrected for multiple comparisons). During the saccade task, regional activation was observed bilaterally in the FEF, SEF, and PEF, left lenticular nucleus, and V1. These regions are the same as those seen in the normal subject group. However, the patient group also showed activations in the IFG, DLPFC, IPL, lenticular nucleus and thalamus during saccade tasks. During the antisaccade tasks, activation was observed in the same regions as in the saccade tasks (Table 3).

Furthermore, in the normal control group, comparing brain activity during the antisaccade task with that during the saccade task revealed that antisaccade eye movements induced elevated activities in the bilateral FEF, PEF, IPL, ACC, IFG, and DLPFC ($P < 0.005$, uncorrected for multiple comparisons). In the patient group, however, only bilateral activation in the PEF was observed.

Correlation between fMRI activation and eye movement performance

In order to assess the effect of performance on brain activity, we analyzed the correlation between error rate and brain activity. Figure 3 shows the correlation between fMRI activation and eye movement performance in patients with schizophrenia. fMRI activation is calculated from each peak voxel. No significant correlation was observed between two parameters.

DISCUSSION

Our understanding of human cortical control of saccades is derived from observations of cerebral lesions[14–16] and from transcranial magnetic stimulation,[17,18] positron emission tomography,[19,20] and fMRI.[21–24] Previous studies in these areas have indicated that saccadic eye movements are controlled by

Table 2. Brain regions more active during visually guided saccades and antisaccades than during control tasks in healthy subject

Brain region		Saccade vs rest Coordinate				Antisaccade vs rest Coordinate			
		X	*Y*	*Z*	*t*-value	*X*	*Y*	*Z*	*t*-value
DLPFC	R	–	–	–	NS	*50*	*40*	*–8*	4.01
	L	–	–	–	NS	*–44*	*50*	*4*	4.24
FEF	R	*46*	*6*	*50*	5.34	*40*	*–2*	*50*	5.87
	L	*–40*	*–6*	*50*	6.08	*–38*	*–4*	*52*	6.52
SEF	R	*6*	*6*	*62*	4.20	*8*	*8*	*52*	4.20
	L	*–4*	*4*	*60*	5.87	*–2*	*10*	*46*	5.56
PEF	R	*32*	*–54*	*48*	3.80	*26*	*–58*	*54*	6.70
	L	*–30*	*–56*	*56*	4.28	*–26*	*–60*	*52*	7.91
IPL	R	–	–	–	NS	*64*	*–36*	*28*	6.14
	L	–	–	–	NS	*–64*	*–40*	*34*	5.75
Thalamus	R	–12	–18	10	3.96	*10*	*–14*	*8*	8.30
	L	–10	–18	–2	6.53	*–10*	*–16*	*8*	6.29

DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; IPL, inferior parietal lobule; L, left; NS, not significant; PEF, parietal eye fields; R, right; SEF, supplementary eye fields.

a cortical network that includes the PEF, located in the intraparietal sulcus and superior parietal lobule, the FEF, located in the precentral gyrus, and the SEF, located in the upper medial wall of the frontal lobe. Activation has also been observed in the bilateral dorsolateral prefrontal cortices, supramarginal gyri, anterior cingulate cortices, and thalami during antisaccade tasks.[25] In short, in normal subjects no

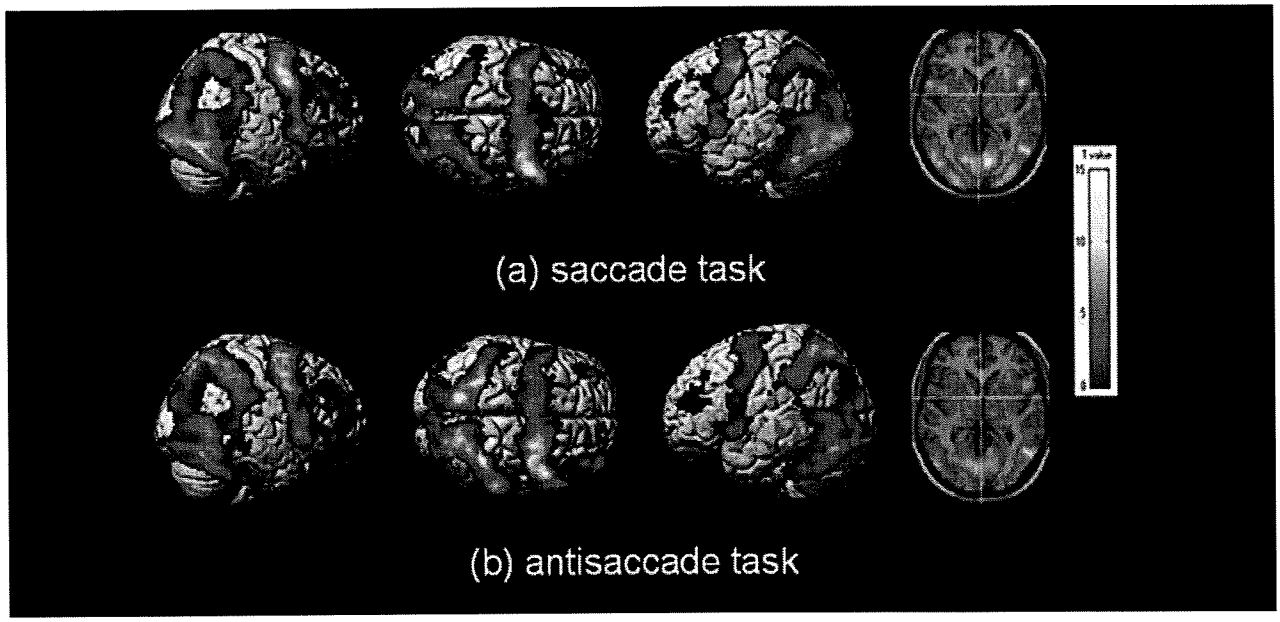

Figure 2. Brain regions displaying greater activities during (a) saccade and (b) antisaccade conditions than during control conditions in patients with schizophrenia. In the rightmost image, the activation map is overlaid onto a T1 SPM normalized brain image. The height threshold is set at $P < 0.001$, uncorrected.

Table 3. Brain regions more active during visually guided saccades and antisaccades than during control tasks in patients with schizophrenia

		Saccade vs rest Coordinate				Antisaccade vs rest Coordinate			
Brain region		*X*	*Y*	*Z*	*t*-value	*X*	*Y*	*Z*	*t*-value
DLPFC	R	*36*	*56*	*26*	8.80	*42*	*56*	*8*	6.05
	L	−38	54	14	4.26	*−36*	*44*	*12*	5.00
FEF	R	*34*	*2*	*64*	8.52	*26*	*0*	*48*	12.06
	L	*−44*	*−4*	*58*	9.91	*−36*	*−6*	*46*	8.99
SEF	R	*12*	*16*	*38*	5.38	*10*	*4*	*48*	5.30
	L	*−8*	*22*	*38*	5.23	*−12*	*0*	*46*	5.53
PEF	R	*30*	*−54*	*48*	7.25	*22*	*−60*	*54*	12.32
	L	*−28*	*−52*	*50*	10.71	*−28*	*−52*	*56*	12.89
IPL	R	56	−32	22	8.63	*62*	*−38*	*18*	5.09
	L	−58	−40	22	3.77	*−62*	*−38*	*18*	4.27
Thalamus	R	12	−14	2	6.70	*10*	*−18*	*−4*	7.09
	L	−12	−14	−2	6.92	*−12*	*−16*	*2*	6.23

DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields; IPL, inferior parietal lobule; L, left; PEF, parietal eye fields; R, right; SEF, supplementary eye fields.

activation of DLPFC, IFG, striatum, and thalamus were observed during the saccade tasks.

Contrary to previous reports, the present study showed the activations in the DLPFC, IFG, striatum, and thalamus during both the saccade and antisaccade tasks in patients with schizophrenia. In addition, differential activation maps between the antissacade and saccade tasks exhibited the bilateral activation of the FEF, PEF, IPL, ACC, IFG, and DLPFC in normal subjects, whereas only the PEF were activated bilaterally in the patient group. These results show that normal subjects process the saccade and antisaccade tasks in different brain regions, whereas patients with schizophrenia likely use virtually the same regions when processing both tasks. In the patient group, therefore, when brain activations during eye movement tasks were compared directly, the elevated activations of the DLPFC and thalamus normally seen in antisaccade tasks relative to saccade tasks were no longer observed. In comparing the patients to the normal controls, the present study demonstrated higher activity of the thalamus and broad cortical regions (including the prefrontal area), especially during saccade tasks. This suggests hyperactivation, not reduced activation, in the prefrontal cortex and thalamus in patients with schizophrenia. Taken together, though the antisaccade task is cognitively more demanding than the saccade task, these regions in the patients with schizophrenia did not seem to be activated at a level that corresponded to the degree of difficulty of the tasks presented.

The tasks used in most of the previous studies required subjects to focus on a gazing point, and the reduced activities of the DLPFC and thalamus were observed during the antisaccade tasks in patients with schizophrenia. Three recent studies using fMRI revealed reduced activation in the right DLPFC and reduced activation in the striatum in schizophrenia.[10–12]

In contrast, our results showed higher activities in broad cortical and subcortical regions during the saccade and antisaccade tasks in the patient group as compared with the normal control group. This suggests that these regions could already be activated by the time the schizophrenic patient focuses on the gazing point; therefore, the difference in activation levels between baseline and eye movements becomes smaller in the patient group.

In the present study, we demonstrated the activations in the DLPFC and thalamus during the saccade task in the patient group. The fronto-striato-thalamocortical network,[26–28] including the prefrontal cortex and thalamus, is important for control of antisaccades. Schizophrenia presents with dysfunction in dopaminergic neural networks[29] and the fronto-striato-thalamic circuit.[30,31] Dysfunction in the

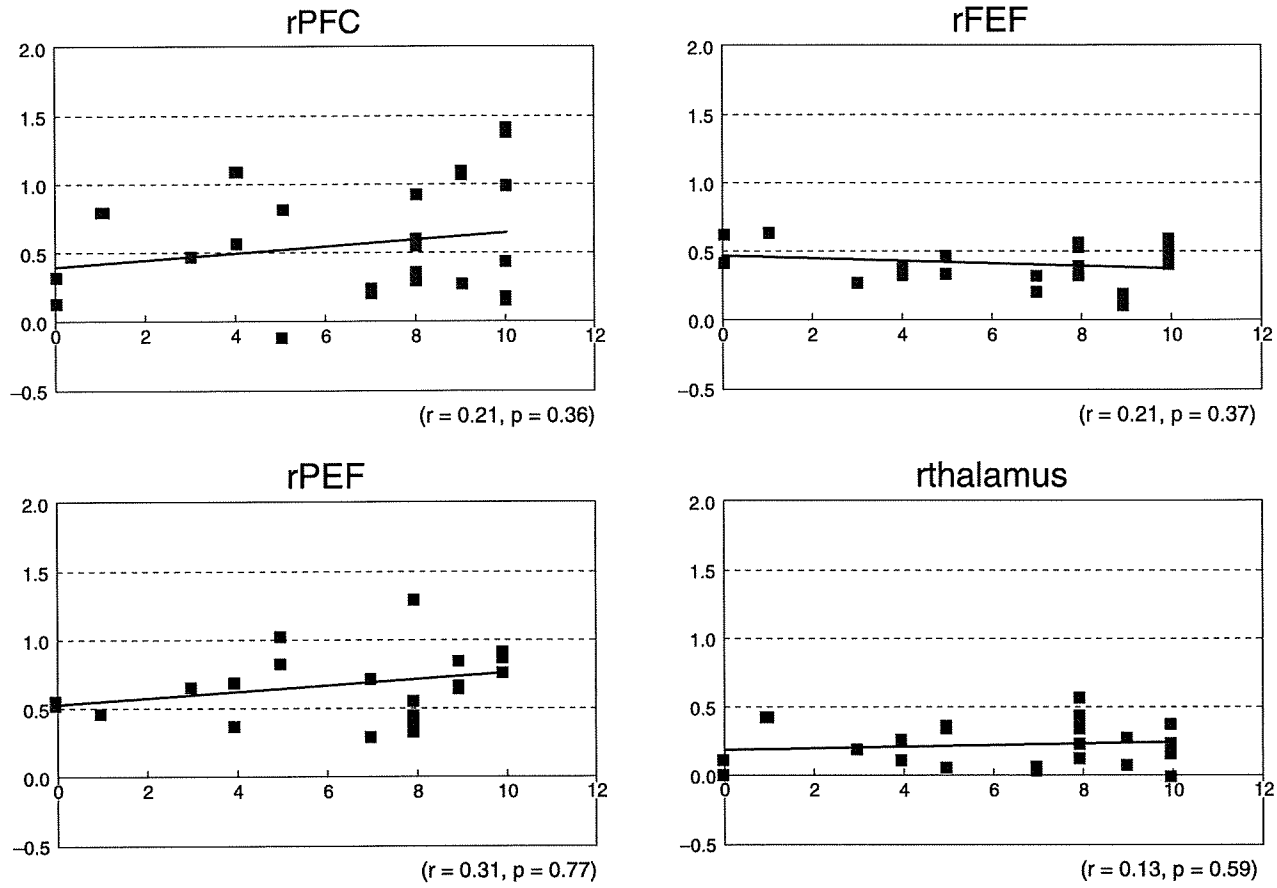

Figure 3. The correlation between brain activation and the number of antisaccade errors. The horizontal axis represents the number of antisaccade errors, and the vertical axis represents the estimated magnetic resonance imaging signal. rFEF, right frontal eye fields; rPEF, right parietal eye fields; rPFC, right prefrontal cortex; rthalamus, right thalamus.

striato-thalamo-cortical dopaminergic circuitry may reduce inhibition of reflexive saccade and thus facilitate saccades for the target direction during the antisaccade task in schizophrenics. Our results indicate that this dysfunction has an important influence on subtle motor control and therefore affects antisaccade generation through both the direct and indirect basal ganglia pathways. These findings suggest that patients with schizophrenia who display antisaccade inhibition errors may present with dysfunction in the fronto-striato-thalamo-cortical network.

Given that previous studies have targeted patients with schizophrenia with poor performance in cognitive tasks, a bias toward reduced brain activations may have been present.[32–36] In order to assess the effect of performance on brain activity, we analyzed the correlation between error rate and brain activity. No significant correlation was observed between the two variables. Therefore, we conclude that the performance did not directly affect the results.

CONCLUSION

In order to examine baseline effect, we employed an eye movement task that did not require subjects to focus on a fixation point during the baseline condition, and compared brain activity between patients with schizophrenia and normal control subjects. In normal subjects, activities in the DLPFC and thalamus were greater during antisaccade tasks than during saccade tasks, whereas no significant difference was observed in patients with schizophrenia. These results suggest that the brains of patients with schizophrenia did not seem to be activated at a level that corresponded to the degree of difficulty of the tasks presented. Previous studies that used target fixa-

tion at baseline assessment showed reduced activities of the DLPFC and thalamus in patients. In contrast, our study demonstrated hyperactivation of the DLPFC and thalamus in patients, suggesting that in patients with schizophrenia these brain regions were already activated by the time patients viewed a fixed target at baseline. We think that these results reflect the symptom that patients of schizophrenia can not adapt to the environment. Finally, we suspect that patients with schizophrenia may be affected by a defect in the fronto-striato-thalamo-cortical network associated with motor function control.

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Epileptic, organic and genetic vulnerabilities for timing of the development of interictal psychosis

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Background
Age at the first psychotic episode and an interval between the onset of epilepsy and that of psychosis reflect developmental processes of interictal psychosis. However, factors relating to these indices remain unknown.

Aims
To identify clinical variables that are associated with the timing of the development of interictal psychosis.

Method
In 285 adults with epilepsy with interictal psychosis, effects of epileptic (epilepsy type), organic (intellectual functioning) and genetic (family history of psychosis) variables on timing of the development of psychosis were examined.

Results
The mean interval between the onset of epilepsy and that of psychosis was 14.4 years. Some psychosis occurred within a few years of the first seizure. Generalised epilepsy, normal intellectual function and a positive family history of psychosis were associated with early onset of psychosis.

Conclusions
Early development of interictal psychosis in people with epilepsy may reflect other individual vulnerabilities to psychosis rather than epilepsy-related damage.

Declaration of interest
None.

Interictal psychosis in epilepsy was first studied systematically by Slater and his colleagues.[1] They reported three main pieces of evidence to delineate interictal psychosis (called schizophrenia-like psychosis in the paper) as a distinct entity from schizophrenia: psychopathological characteristics, psychosis occurring after the development of epilepsy and no genetic loading for schizophrenia. Subsequent studies have formed a general consensus that interictal psychosis is mainly related to various epilepsy-related factors such as type of epilepsy, seizure types and laterality and locality of electroencephalogram (EEG) abnormalities, rather than non-specific demographic factors.[2] However, studies on interictal psychosis have shown contradictive findings that some of the demographic characteristics such as intellectual function[3,4] and family history of psychosis[5] were associated with occurrence of interictal psychosis. This is similar to the positive associations between these demographic factors and a high risk of functional psychoses such as schizophrenia. Using a comprehensive, multicentre database of patients suffering from epilepsy with and without psychosis, our group has found that interictal psychosis occurred more frequently in individuals with certain risk factors, including partial epilepsies, complex partial seizures, generalised tonic–clonic seizures, earlier onset of epilepsy and borderline intellectual function.[6] Most of these risk factors were also common in different types of epilepsy psychoses (e.g. interictal, postictal and bimodal psychoses),[7] but some factors historically known as risk factors for interictal psychosis were not extracted with multivariate analyses because they overlapped or interacted with others.[6–8]

Age at the time of the first psychotic episode and the time interval between the onset of epilepsy and that of psychosis are key elements of studies in interictal psychosis, as these age-related variables likely reflect neurodevelopmental and/or neurodegenerative processes in the brain.[9] Indeed, Slater *et al*[1] showed that patients with interictal psychosis tend to suffer their first seizure in early adolescence, with psychosis developing in their late twenties or thirties (approximately 15 years after the onset of epilepsy). They interpret the long interval, during which epilepsy and its consequences could cause further damage to the brain, as a preparatory period for generation of psychosis. Whereas many studies have reported similar age-related variables,[2] some have suggested the interval is an artefact as a result of the wide range of distribution of time intervals and to the tendency of a shorter interval in individuals with late-onset epilepsy.[10,11] In our previous study,[12] age at onset of psychosis in a subgroup of patients with chronic interictal psychosis was comparable with that in those with schizophrenia, whereas the age at onset was more advanced in the whole group of patients with interictal psychosis (both episodic and chronic). We also showed no difference between various types of partial epilepsies in age at onset of psychosis and in time intervals.[8] However, few studies have examined the contributions of the other clinical factors to age-related variables; thus, it remains unknown whether particular clinical factors are related to the timing of development of interictal psychosis. In the current study, we investigated the timing of development of interictal psychosis in association with epilepsy-related and demographic characteristics in a large cohort of patients with interictal psychosis.

Method

Definition of interictal psychosis

In our study, psychosis was defined as the presence of hallucinations, delusions or a limited number of severe abnormalities of behaviour in accordance with the ICD–10.[13] The operational criteria for interictal psychosis were as follows: the psychosis developed after the onset of epilepsy;[1,14,15] the psychotic episodes occurred with no distinct antecedent seizures when the patient was seizure-free or between habitual seizures;[6,7] psychotic episodes lasted 24 h or more in a state of full consciousness. Interictal

psychosis included chronic schizophrenia-like psychosis (at least one episode lasting 1 month or more) and brief (acute, episodic) interictal psychosis (all episodes resolved within 1 month).[1,16–18] Postictal psychosis, which occurred within 7 days after a decisive seizure or cluster of seizures,[7,17,19] and ictal psychotic phenomenon[17] were excluded.

Participants

All participants met the criteria for epilepsy as set forth in the 1989 International Classification of Epilepsies and Epileptic Syndromes.[20] The participants all attended one of five institutions with adult epilepsy clinics: National Centre Hospital for Mental, Nervous, and Muscular Disorders; Nihon University Hospital; Tokyo Medical University Hospital; Tokyo Medical and Dental University Hospital; or Komagino Hospital. The five epilepsy clinics cover the greater Tokyo area of a population of approximately 35 million as the main neuropsychiatric institutions for adults with epilepsy. In addition, the National Centre Hospital is the only institution in the country that has a neuropsychiatric in-patient unit dedicated to patients with epilepsy, accepting tertiary referrals from outside the catchment area. Since August 1996, these epilepsy clinics have maintained a collaborative database designed specifically for epilepsy psychosis.[6–8,12] Our previous studies[6–8,12] were based on the database with patients who had been registered until the end of 1996. The current study was conducted with a data-set entered until December 2000, with a total of 313 patients with epilepsy and interictal psychotic episodes being identified. To focus on interictal psychosis, 19 patients with bimodal psychosis, who exhibited both interictal and postictal psychoses in distinct periods,[7] were excluded from the study. Five patients with epilepsy resulting from a neurodegenerative disorder and four without sufficient clinical information regarding the epilepsy were also excluded. Consequently, 285 patients with interictal psychosis were enrolled in the study. No participants showed evidence of substance misuse, dementing process or a recent progressive space-occupying lesion.

Variables studied

We investigated the following variables:

(a) age at the time of investigation;

(b) gender;

(c) family history of psychosis, i.e. any psychotic disorder (schizophrenia, other paranoid disorder, acute transient psychosis, etc.) in a first-degree relative, according to the Japanese version of the Family History Research Diagnostic Criteria;[21]

(d) age at the onset of epilepsy, i.e. age at the time of the first afebrile seizure;

(e) type of epilepsy based on ictal symptoms, EEG findings and neuroimaging in accordance with the International Classification of Epilepsies and Epileptic Syndromes[20] (i.e. localisation-related epilepsies and generalised epilepsies, including idiopathic and symptomatic);

(f) intellectual functioning: impaired (full-scale IQ on the Wechsler Adult Intelligence Scale–Revised[22] of 70 or below), borderline (of 71–84), or normal (of 85 or above) in accordance with the DSM–IV;[23]

(g) age at onset of psychosis (i.e. age at the time of the first psychotic episode);

(h) time interval between the onset of epilepsy and that of psychosis, calculated as age at onset of psychosis minus age at onset of epilepsy.

As different neuroimaging techniques were used during different time periods and by each institution, neuroimages were used only for diagnostic information. Diagnoses and evaluations were made by consultant neuropsychiatrists qualified in both psychiatry and epileptology. The study was approved by the ethics committees of the institutions.

Data analysis

Differences in linear variables (ages) for the categorical variables (gender, epilepsy type and family history) were subjected to analysis of variance (ANOVA). Correlation between categorical variables was examined by means of the chi-squared test or Fisher's exact test. Correlations between linear or rank-order variables (intellectual functioning) were examined by means of simple regression analysis or Spearman's rank-order correlation coefficient. Because age at the time of examination was correlated significantly with the other age-related variables (age at the onset of epilepsy ($r=0.39$, $P<0.0005$), time interval ($r=0.31$, $P<0.0005$), and age at the onset of psychosis ($r=0.62$, $P<0.0005$)), the weighted least squares procedure (weighted by age at the time of examination) was applied.[12] A P-value of <0.05 was considered significant. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 14.0 for Windows.

Results

Clinical characteristics of the 285 patients with interictal psychosis were as follows: mean age at the time of examination was 40.7 years (s.d. = 12.8, range 19–76, median 39). There were 146 men and 139 women. A total of 236 patients had localisation-related epilepsies and 49 generalised epilepsies (34 with idiopathic and 15 with symptomatic generalised epilepsies). With respect to estimated aetiologies of epilepsy, there were 22 patients with central nervous system infections, 26 with birth complications (including cerebral palsy), 15 with head trauma, 7 with brain tumours, 16 with migration disorders or other malformation, 5 with vascular disorders, and pathogenesis was unknown for the remaining 194 patients. Intellectual function was normal in 140 patients, borderline in 55, and impaired in 90. There were 244 patients with chronic schizophrenia-like psychosis, 27 with brief interictal psychosis and 14 with interictal psychosis of unknown duration. Twenty-one patients had a family history of psychosis.

Distributional relations between the patients' characteristics studied were as follows: gender and intellectual functioning ($\chi^2=2.6$, $P=0.280$), gender and epilepsy type (129 men and 107 women with localisation-related epilepsies, 17 men and 32 women with generalised epilepsies; $\chi^2=5.7$, $P=0.017$), gender and family history of psychosis ($\chi^2=0.11$, $P=0.736$), intellectual functioning and epilepsy type ($\chi^2=4.1$, $P=0.126$), intellectual functioning and family history of psychosis ($\chi^2=0.44$, $P=0.802$), and epilepsy type and family history of psychosis ($\chi^2=0.06$, $P=0.767$).

Age-related factors observed were as follows: mean age at onset of epilepsy was 11.7 years (s.d = 8.0, range 0–51, median 11), mean age at onset of psychosis was 26.1 years (s.d. = 9.6, range 12–65, median 24) and the mean time interval between the onset of epilepsy and that of psychosis was 14.4 years (s.d. = 9.3, range 0–51, median 13). Distribution of the time intervals for the entire patient group are shown in Fig. 1. Age at onset of psychosis correlated significantly with that of epilepsy ($r=0.47$, $P<0.0005$) and with the time interval ($r=0.64$, $P<0.0005$).

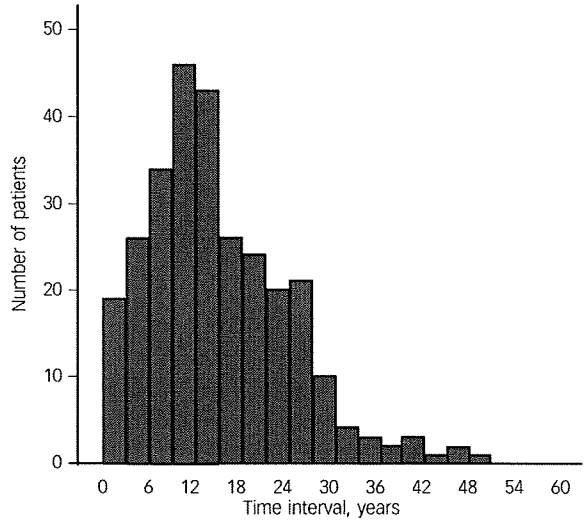

Fig. 1 Distribution of the time intervals (years) between the onset of epilepsy and that of interictal psychosis (mean 14.4 years, s.d. = 9.2, range 0–51, median 13).

The time interval was 3 years or less in 31 patients (10.9%), 5 years or less in 45 (15.8%), 10 years or less in 101 (38.6%).

The time interval also correlated significantly with age at onset of epilepsy ($r = -0.38$, $P < 0.0005$).

The estimated marginal means of age at onset of epilepsy, age at onset of psychosis and the time interval for each variable are shown in Table 1. The time interval and age at onset of psychosis differed significantly between epilepsy types: interictal psychosis developed at an earlier age and with a shorter interval in patients with generalised epilepsies, in particular with idiopathic generalised epilepsies, than those in patients with localisation-related epilepsies. Intellectual functioning correlated significantly with age at onset of epilepsy and the time interval: the onset of epilepsy was earlier and the interval was longer in those patients with intellectual disturbances than in those without. The onset of psychosis was significantly earlier in patients with a family history of psychosis than in those without.

We carried out further analyses on the participants with localisation-related epilepsies ($n = 236$) and obtained similar tendencies: intellectual functioning correlated significantly with age at onset of epilepsy ($r = 0.293$, $P < 0.0005$; impaired, estimated marginal mean 9.3 (s.e. = 1.1), borderline 11.3 (s.e. = 1.2), normal 15.3 (s.e. = 0.8)), with age at onset of psychosis ($r = 0.128$, $P = 0.049$; impaired 26.3 (s.e. = 1.4), borderline 29.8 (s.e. = 1.6), normal 30.0 (s.e. = 1.0)) or with time interval ($r = -0.157$, $P = 0.016$; impaired 17.0 (s.e. = 1.2), borderline 18.5 (s.e. = 1.4), normal 14.6 (s.e. = 0.9)). Likewise, in the family history of psychosis of the participants with localisation-related epilepsies, the estimated marginal mean age at onset of psychosis also differed significantly ($F = 5.45$, $P = 0.020$; positive 22.7 (s.e. = 2.8), negative 29.4 (s.e. = 0.8)). However, there was no significant difference in age at onset of epilepsy ($F = 1.33$, $P = 0.250$; positive 10.3 (s.e. = 2.3), negative 13.0 (s.e. = 0.6)) or in time interval ($F = 2.33$, $P = 0.129$; positive 12.4 (s.e. = 2.5), negative 16.4 (s.e. = 0.7)).

Discussion

In the current study, age at onset of interictal psychosis and time interval between onset of epilepsy and that of psychosis varied

Table 1 Estimated marginal mean (standard error, 95% CI) years for age-related variables per clinical variables (total $n = 285$)

		Age at onset of epilepsy				Age at onset of psychosis				Time interval			
	n	Mean (s.e.)	95% CI	Test statistic	*P*	Mean (s.e.)	95% CI	Test statistic	*P*	Mean (s.e.)	95% CI	Test statistic	*P*
Gender[a]				$F = 0.15$	0.696			$F = 0.00$	0.984			$F = 0.09$	0.765
Men	146	12.5 (0.7)	11.1–13.9			27.9 (0.9)	26.2–29.7			15.4 (0.8)	13.8–17.1		
Women	139	12.9 (0.7)	11.4–14.3			28.0 (0.9)	26.2–29.8			15.1 (0.8)	13.4–16.7		
Intellectual functioning[b]				$r = 0.305$	<0.0005			$r = 0.106$	0.074			$r = -0.167$	0.005
Impaired	90	9.6 (0.9)	7.8–11.4			25.6 (1.2)	23.3–27.9			16.1 (1.1)	14.0–18.3		
Borderline	55	11.4 (1.1)	9.2–13.6			29.1 (1.4)	26.3–32.0			17.8 (1.3)	15.2–20.4		
Normal	140	15.0 (0.7)	13.6–16.4			28.8 (0.9)	27.1–30.6			13.8 (0.8)	12.2–15.4		
Epilepsy type[a]				$F = 0.25$	0.615			$F = 13.2$	<0.0005			$F = 12.0$	0.001
Localisation-related epilepsies	236	12.8 (0.6)	11.7–13.9			29.1 (0.7)	27.8–30.5			16.2 (0.6)	15.0–17.5		
Generalised epilepsies	49	12.1 (1.3)	9.5–14.7			22.8 (1.6)	19.6–26.0			10.6 (1.5)	7.7–13.6		
Idiopathic	34	12.7 (1.0)	10.6–14.8			22.5 (1.0)	20.5–24.6			9.8 (1.3)	7.1–12.5		
Symptomatic	15	10.7 (1.5)	7.6–13.8			23.0 (1.5)	20.0–26.0			12.3 (1.9)	8.4–16.2		
Family history of psychosis[a]				$F = 1.23$	0.268			$F = 5.33$	0.022			$F = 2.28$	0.132
Positive	21	10.6 (1.9)	6.8–14.4			22.6 (2.4)	17.9–27.3			12.0 (2.2)	7.6–16.4		
Negative	264	12.8 (0.5)	11.8–13.9			28.4 (0.7)	27.1–29.7			15.5 (0.6)	14.3–16.7		

a. By analysis of variance with weighted least squares procedure (weighted for age at the examination).
b. By Spearman rank-order correlation coefficient.

considerably. Participants with generalised epilepsy, normal intellectual function or a positive family history of psychosis tended to show an early onset of interictal psychosis.

Distribution of the time interval

The mean interval between the onset of epilepsy and that of psychosis was 14.4 years, consistent with previously reported data.[1,2] This interval varied widely among patients, not showing a simple bell-curve distribution. The wide variation may be in part accounted for by the cumulative effects of various epilepsy-related factors on the development of interictal psychosis, i.e. repeated seizures, frequent epileptic discharges in the brain, adverse effects of anti-epileptic drugs and psychosocial stress.[2,18] However, it is important to note that interictal psychosis developed in a considerable number of patients shortly after their first epileptic event (within a few years). Indeed, this fact has been described in previous studies.[1,11] It is not likely that such quick development of interictal psychosis is as a result of the epilepsy-related process alone. There is little evidence that occurrence of interictal psychotic symptoms is precipitated by a higher impact of particular epilepsy processes (e.g. excessive seizures and extensive epileptogenesis),[17] although severe epilepsy can be a risk factor for the development of psychosis. Thus, in addition to the epilepsy-related process, the presence of certain preparatory conditions, such as individual vulnerabilities to psychosis[24] that may be common to organic psychoses or even functional psychoses, may play a role in generating psychotic symptoms in individuals with epilepsy.

Epilepsy type

The interval between onset of epilepsy and that of psychosis was significantly shorter in patients with generalised epilepsies than in those with localisation-related epilepsies, with the onset of epilepsy being comparable among these two groups. Patients with generalised epilepsies, unlike those with localisation-related epilepsies, tend to have fewer epilepsy (organic)-related risk factors for psychosis, i.e. no distinct brain insult, low seizure frequency, simple medications and normal cognitive functioning, which may be associated with a reduced frequency of development of interictal psychosis.[2,6] It is possible that patients with generalised epilepsies in whom interictal psychosis develops might be affected by non-epileptic precipitators of psychosis. This may be similar to the difference between patients with schizophrenia and those with epilepsy; psychosis is observed at a more advanced age in patients with epilepsy than in patients with schizophrenia that does not involve distinct brain damage.[12] Among patients with generalised epilepsies, only those with a strong vulnerability may suffer interictal psychosis at an early age regardless of acquired brain insults because of epilepsy.

Intellectual functioning

Our patients with normal intellectual functioning exhibited interictal psychosis sooner after the onset of epilepsy. This finding was also seen in the subgroup of participants with localisation-related epilepsies only. Impaired intellectual function is often associated with severe epilepsy and brain damage,[25] although it is also observed in people without such conditions.[26] Functional psychosis develops two to three times more frequently in people with impaired intellectual functioning than is reported in the general population.[26,27] Moreover, psychosis develops 1.3–4.7 times more frequently in patients with epilepsy with impaired intellectual functioning than in those without.[7] In contrast, normal intellectual functioning usually suggests having less brain damage and is not related to increased risks for the development of psychosis. Why do patients with a lower risk suffer psychosis earlier than those at a higher risk? Again, psychosis may develop more quickly in patients with normal intellectual functioning who have strong congenital vulnerabilities to psychosis than in those with acquired organic precipitators, i.e. intellectual dysfunction and epilepsy, but without such vulnerabilities.

Family history of psychosis

We have shown that interictal psychosis develops at an earlier age in patients with a family history of psychosis than in those without. A genetic tendency towards psychosis in patients with epilepsy has long been underestimated[2] since Slater's initial study.[1] However, large studies have shown that genetic factors play a significant role in the development of psychosis in patients with epilepsy.[5,6] These findings appear to be similar to those found in functional psychosis (i.e. schizophrenia); people with a positive family history tend to have a higher risk of psychosis and to exhibit their first psychotic symptoms earlier than those without.[28,29] A positive family history of psychosis may be a universal risk factor for developing psychosis, and it appears to reflect, at least in part, a congenital vulnerability to psychosis.[23] Even in patients with epilepsy and a positive family history of psychosis, psychotic symptoms are likely generated sooner regardless of acquired risk factors related to either epilepsy or brain damage.

Study limitations

Some limitations should be considered in relation to the current study. Analysis of age at onset of psychosis in patients with epilepsy is subject to some methodological issues.[10] Because epilepsy psychosis was defined operationally as psychosis developing after the onset of epilepsy in accordance with Slater & Roth's definition,[14] two patient groups were excluded: patients in whom psychosis developed before epilepsy[17] and patients in whom novel psychoses will develop after the time of the investigation or who died before the possible development of psychosis. However, neither group would have been large enough to markedly influence mean age at onset of psychosis or the mean time interval between onsets of the two disorders. Neither of these omissions explains the significant differences in age at onset of psychosis or in the onset interval between patients with particular clinical characteristics. In addition, despite the large cohort of participants with interictal psychosis, the number of patients in whom particular factors were analysed, such as a positive family history of psychosis and generalised epilepsies, was insufficient to produce strong statistical power. Factors that we did not consider may be associated with age-related factors, but would not have affected the result of our study. Although our findings point to the effects of certain vulnerabilities to psychosis (reflected by a positive family history), it is still unclear what these vulnerabilities are. Evidence supporting such vulnerability concepts is scarce, even for patients with functional psychosis.[24]

Results of the current study show some relationship between age at onset of interictal psychosis and several clinical variables that may reflect individual vulnerabilities. These vulnerabilities, in addition to epilepsy-related deficits, can affect the generation of interictal psychosis independently or interactively. Further comprehensive studies to confirm such vulnerabilities are required.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Relationships between Quantitative Electroencephalographic Alterations and the Severity of Hepatitis C Based on Liver Biopsy in Interferon-α Treated Patients

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Abstract

Objective We have observed alterations of quantitative (q)-EEG findings occurring in interferon (IFN)-α treated chronic hepatitis C (CH-C) patients, and found patient's age to be one factor influencing such EEG alterations. In the present study we evaluated the correlation between q-EEG alterations during IFN-α treatment and the severity of hepatitis based on liver biopsies.

Methods A total of 102 CH-C patients underwent blind, prospective and serial q-EEG examinations. The IFN-α was administered under the same therapeutic regimen to all patients. Serial EEGs were obtained before, at 2 and 4 weeks, and at 2-3 days after the conclusion of treatment. The absolute powers of each frequency band in different periods were determined by q-EEG. Staging (of fibrosis) and grading (of inflammatory cell infiltration) were scaled according to Desmet's classification. We evaluated the relationship between q-EEG and scales of staging or grading.

Results Age distributions did not differ significantly among stages or grades. As the stage or grade increased, the alterations of EEG during IFN-α treatment became more pronounced, and significant (repeated-measures analysis of variances; both, $p<0.0001$).

Conclusion Alterations of the EEG occurring during IFN-α treatment became pronounced with more severe pathological findings for CH-C. Alterations in the EEGs during IFN-α treatment should be carefully monitored in CH-C patients with severe pathological findings.

Key words: interferon-α, quantitative-EEG, chronic hepatitis C, staging, grading

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Introduction

Alterations of brain waves on electroencephalograms (EEGs) during treatment with interferon (IFN)-α have been described previously in several case reports (1-3). We have confirmed a diffuse slowing based on an analysis of blind, prospective and serial quantitative-EEG (q-EEG) examina-

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Table 1. Mean Values and Standard Deviations of Age for Each Stage and Grade Based on Liver Biopsies in 102 Subjects

Findings of liver biopsy	Number of patients	Mean ± standard deviation of patients' age (years old)	Difference in mean values between different stages or grades (Mann-Whitney U test)
Stage (intrahepatic fibrosis)			
Mild	49	48.4 ± 6.1	
Moderate	38	51.9 ± 7.4	NS
Severe	15	46.9 ± 8.9	
Grade (inflammatory cell infiltration)			
Minimal	43	48.2 ± 6.0	
Mild	30	50.6 ± 7.1	NS
Moderate	14	51.3 ± 6.8	
Severe	15	47.3 ± 8.8	

NS = not significant.

tions undertaken in many patients with IFN-α treated chronic hepatitis C (4). We speculated that such diffuse slowing on the EEGs could reflect a mild encephalopathy due to the IFN-α. We recently reported that the alteration of the q-EEG could be estimated clinically by the change in score on Mini-Mental State Examinations (5). We have also reported that the age of the patients was one of the factors affecting such alterations on the q-EEG (6). However, no other such factors have been reported. The present study was the first to evaluate the relationship between the alterations in q-EEG findings that occur during IFN-α treatment and the severity of hepatitis as estimated according to scales of staging and grading based on liver biopsies.

Methods

Patients

A total of 168 serial patients with chronic hepatitis C patients underwent our blind, prospective and serial q-EEG examinations, during the period from August 1997 to May 2007. These patients were independently registered at three different hospitals, viz. Nihon University Itabashi Hospital, Nihon University Surugadai Hospital, and Itabashi Medical Association Hospital, during the above period. All patients were investigated and treated under the same clinical regimen and conditions, including diagnostic criteria, q-EEG examinations, and IFN-α treatment, as reported previously (4). The clinical diagnosis of chronic hepatitis C was confirmed by serological findings of serum antibody for hepatitis C virus, histopathological findings obtained by liver biopsy, detection of the viral genome sequence for hepatitis C virus by the reverse transcriptase-polymerase chain reaction (RT-PCR), serum liver function tests, and the clinical course of the patients. Staging (of intrahepatic fibrosis) and grading (of inflammatory cell infiltration) of the chronic hepatitis based on liver biopsies was scored according to Desmet's classification (7). Based on grading of histopathological findings according to the Desmet's classification (7), the patients with liver cirrhosis (LC) were excluded from the present study. A total of 102 patients ranging in age from 40 to 59 years were included in this study. All patients were alert during IFN-α treatment as graded according to the Glasgow Coma Scale. The mean values and standard deviations of patient age at each stage and grade of chronic hepatitis are listed in Table 1. There were no significant differences in mean age among stages or grades (Mann-Whitney U test). IFN-α was administered intramuscularly at a dose of 9×10^6 IU daily for the first 4 weeks and then administered 3 times/week for the following 20 weeks, according to the same regimen of IFN-α treatment. Informed consent to perform the present study was obtained from all patients. The serological hepatic function parameters of the 102 patients improved during the IFN-α treatment. The means and standard deviations for the values of AST (GOT) (normal: 8-38 IU/L) were 126.2±75.1 before the treatment, 50.7±23.6 at 2 weeks of treatment, 43.2±24.1 at 4 weeks of treatment, and 40.4±23.1 IU/L after the treatment. The values for ALT (GPT) (normal: 4-44 IU/L) were 164.1±93.2 before the treatment, 60.4±33.2 at 2 weeks of treatment, 55.0±29.1 at 4 weeks of treatment, and 52.4±27.1 IU/L after the treatment. No patients exhibited elevation of serological hepatic function parameters during IFN-α treatment. There were also no patients with significant elevation of serum ammonia concentration during this treatment. All of the patients gave informed consent to participate in the present study according to a protocol approved by the Ethics Committee for Human Studies at Nihon University.

Q-EEG analysis

The EEG recordings and q-EEG analysis employed in the present study were as described previously (4). Briefly, serial EEGs were obtained before the IFN treatment, at 2 and 4 weeks of treatment and at 2-3 days after the conclusion of treatment. The serial EEGs at 2 and 4 weeks of treatment were obtained during the period from 1 to 6 hours after the injection of IFN-α. The EEGs in each subject were recorded on a magnetic optical disk from 16 electrode locations according to the 10-20 international system using a digital EEG instrument (Neurofax EEG-4518, Nihon Kohden, To-

kyo, Japan). The EEGs were referenced to the ipsilateral earlobes. Sixty seconds of q-EEG data were selected visually from each subject and digitized at 128 Hz with a time constant of 0.3, employing a high frequency filter of 60 Hz. Thirty epochs with a duration of 2 seconds each were collected from the subsequent resting period with eyes closed for analysis of the q-EEGs. The procedure used for analysis involved the application of fast Fourier transformation of the collected EEG signals by Rhythm, version 10.0 (Stellate Systems Inc, Montreal, Quebec, Canada). The frequency ranges were divided into 6 bands, as follows: delta (1.17-3.91 Hz), theta 1 (4.30-5.86 Hz), theta 2 (6.25-7.81 Hz), alpha 1 (8.20-10.16 Hz), alpha 2 (10.55-12.89 Hz), and beta (13.28-30.86 Hz). The absolute powers of each frequency band were calculated at each electrode location in all of the subjects. Each power value was obtained by integrating the appropriate part of the spectrum. The present quantitative analysis was carried out blindly during routine EEG work involving many other disease states, including epilepsy, cerebrovascular disease, encephalitis, meningitis, metabolic encephalopathy, and brain tumor, as well as in normal controls. The only knowledge that the EEG analyst (S. Kamei) possessed regarding each patient was the latter's identification number, and he had no other information regarding any other information concerning any of the studied subjects such as their clinical diagnosis, date of treatment, or type of treatment.

Statistical analysis

In September 2007, a statistical analyst (K. Hirayanagi) at another independent institute collected the analyzed q-EEG data, the data on patient ages, and that on histopathological findings on liver biopsy based on the Desmet's classification (7) for the 102 patients. Using Desmet's classification (7), the stage of intrahepatic fibrosis in each sample was classified as mild, moderate, or severe. The grade of inflammatory cell infiltration in each sample was classified as follows: minimal, mild, moderate, or severe. The distributions of the power values at each frequency band for each electrode location were evaluated in terms of their skewness and kurtosis. Based on findings regarding skewness and kurtosis, repeated measure analysis of variances (rANOVAs) was applied to the alterations in power values as the main factor among 4 different periods: before the IFN-α treatment, at 2 and 4 weeks of treatment, and after the treatment, with the frequency bands, electrode locations, and staging and grading on the hepatitis classifications as co-factors. SPSS statistical software Version 12.0 (SPSS Inc., Chicago, IL) was employed for statistical analysis. Relationships between q-EEG variables and stages or grades were evaluated by post hoc ANOVAs (Scheffe's test). The level of significance for this study was 0.05.

Results

There were no patients with IFN-α induced irreversible encephalopathy in the present study. Stages of the chronic hepatitis based on liver biopsies in the 102 subjects were distributed over the range from mild to severe fibrosis. Similarly, grades were also distributed from minimal to severe inflammatory cell infiltration. The results of serial q-EEG studies at each selected frequency of EEG during the IFN-α treatment for each staging and grading scale (Figs. 1, 2) revealed that increased slow waves (delta, theta 1 and 2) and decreased alpha 2 and beta waves were evident during the IFN-α treatment at all stages and grades. These EEG alterations during IFN-α treatment in the present study confirmed our previously reported observations (4). Moreover, the alterations in power values during the IFN-α treatment became more pronounced as the stage or grade of hepatitis increased. Statistical results obtained by rANOVAs (Table 2) for the interactions between the q-EEG alterations during the IFN-α treatment and differences of staging scale or grading scale were significant (both, $p<0.0001$). Results of post hoc ANOVAs results (Table 3) also indicated significant differences in the alterations of absolute power values during the IFN-α treatment for all comparisons with increasing staging or grading scale in the case of the delta, theta 1, and beta waves with the exception of several comparisons involving differences of only one grade or stage. There were no significant differences in the alterations of power values during the IFN-α treatment in the case of the alpha 1 and total power values. We also examined the correlations at each electrode location between severity based on liver biopsy findings and alteration of qEEG during the administration of IFN-α. These correlations were significant for all electrode locations (frontal pole location $p=0.03$ and $p=0.004$ for stage and grade, respectively; frontal location $p<0.0001$ for both stage and grade; temporal location $p<0.0001$ for both; central location $p=0.005$ and $p=0.002$; parietal location $p=0.002$ and $p=0.01$; occipital location $p=0.005$ and $p=0.01$).

There were only two patients with mild pyrexia (37.3 and 37.4℃) at the time of q-EEG examination after 2 weeks of IFN-α administration, and no patient with pyrexia at the time of examination at 4 weeks. The two patients with mild pyrexia had findings of mild severity on liver biopsy. No significant effects of pyrexia on q-EEG were found.

Discussion

Although numerous patients have undergone IFN-α treatment, detailed assessments of the adverse effects of IFN-α on central nervous system function have not yet been presented. Evaluations of alterations in brain function have been presented in only three previous reports based on data from small numbers of patients who underwent EEG examinations (1-3). We recently confirmed a significant, diffuse slowing on q-EEGs that occurred in chronic hepatitis C patients during IFN-α treatment at a relatively low dosage (4). With such a low dosage of IFN-α administration to chronic hepatitis C patients, the diffuse slowing of the EEG is re-

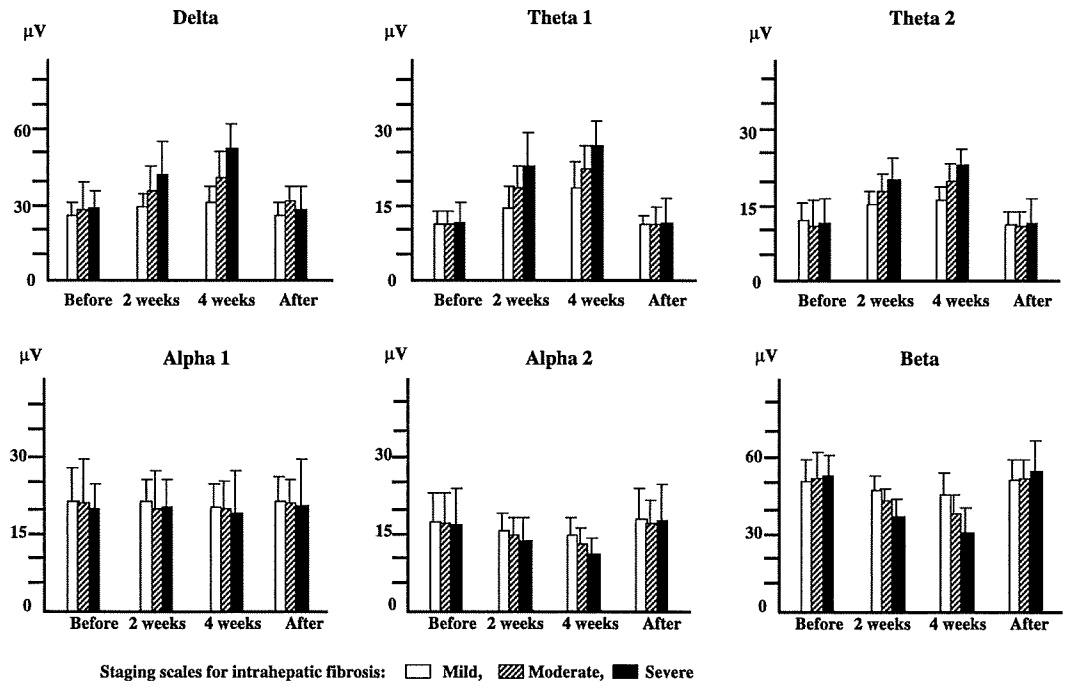

Figure 1. Alterations in absolute power values (means±standard deviations) by stage (of intrahepatic fibrosis) for each frequency band at the following 4 time points: before IFN-α treatment, at 2 and 4 weeks of treatment, and at 2-3 days after conclusion of treatment. Increasing power values for slow waves (delta, theta 1 and 2) and decreasing power values for alpha 2 and beta waves during IFN-α treatment, in comparison with those before and after IFN-α treatment, were evident for all stages. Moreover, alterations in power values became more pronounced as stage increased in all frequency bands except for alpha 1 and total power values.

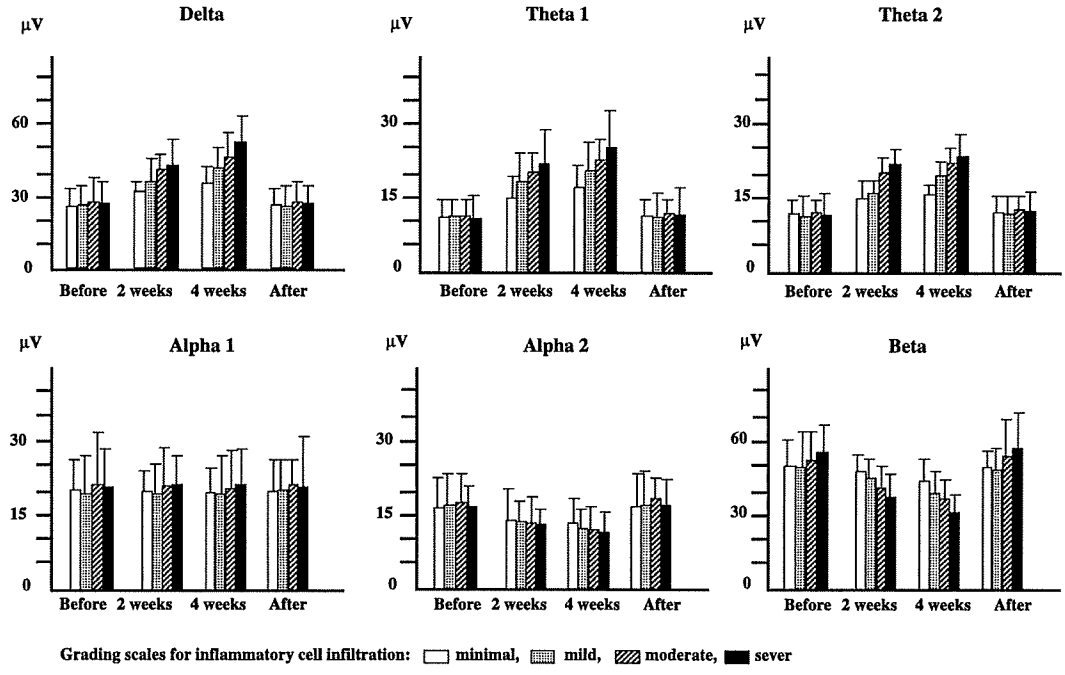

Figure 2. Alterations in absolute power values (means±standard deviations) by grade (of inflammatory cell infiltration) for each frequency band at the following 4 time points: before IFN-α treatment, at 2 and 4 weeks of treatment, and at 2-3 days after conclusion of treatment. Increasing power values for slow waves (delta, theta 1 and 2) and decreasing power values for alpha 2 and beta waves during IFN-α treatment, in comparison with those before and after IFN-α treatment, were evident for all grades. Moreover, the alterations in power values became more pronounced with increase in grade in all frequency bands except for alpha 1 and total power values.

Table 2. **Repeated Measures Analysis of Variances between Alterations in Power Values during IFN-α Treatment and Stage (Intrahepatic Fibrosis) or Grade (Inflammatory Cell Infitraion)**

Factors	
Alteration of power values during IFN-α treatment (Alteration of power values)	$p< 0.0001$ (F=30.338)
Alteration of power values × Difference of staging scale (Difference in stage)	$p< 0.0001$ (F=14.531)
Alteration of power values × Difference of grading scale (Difference in grade)	$p< 0.0001$ (F=12.071)
Alteration of power values × Frequency bands	$p< 0.0001$ (F=48.781)
Alteration of power values × Electrode location	NS
Alteration of power values × Difference in stage × Frequency bands × Electrode location	NS
Alteration of power values × Difference in grade × Frequency bands × Electrode location	NS

NS = not significant; × = interaction.

Table 3. **Statistical Comparisons by Post-hoc ANOVA of Alterations in Power Values during IFN-α Treatment for Each Frequency Band between Stages and Grades**

Comparison of stages and grades based on biopsies		Power values (μV)						
		delta	theta 1	theta 2	alpha 1	alpha 2	beta	total
Stage (intrahepatic fibrosis)	mild vs. moderate	**	**	*	NS	NS	**	NS
	moderate vs. severe	**	**	**	NS	*	**	NS
	mild vs. severe	**	**	**	NS	*	**	NS
Grade (inflammatory cell infiltration)	minimal vs. mild	**	**	**	NS	NS	*	NS
	minimal vs. moderate	**	**	**	NS	*	**	NS
	minimal vs. severe	**	**	**	NS	*	**	NS
	mild vs. moderate	**	**	**	NS	NS	*	NS
	mild vs. severe	**	**	**	NS	*	**	NS
	moderate vs. severe	**	**	**	NS	*	**	NS

NS = not significant; *= $0.01 \leq p < 0.05$; ** = $p < 0.01$.

versible after completion of the treatment (4). Moreover, neuropsychiatric complications have been described as difficult to evaluate following IFN-α treatment in patients with chronic viral hepatitis (8). In view of the considerable numbers of patients undergoing IFN-α treatment, detailed information on the factors affecting EEG alterations due to IFN-α treatment seems vital for prediction of the appearance of such adverse effects on brain function following IFN-α treatment. Patient age was recently identified as one of the factors involved in such alterations of EEGs during IFN-α treatment (6). However, no other factors affecting alterations of the EEG during IFN-α treatment have been reported. The findings of the present study indicated that severity of hepatitis based on liver biopsies is one such factor. However, there are some statistical limitations to the present study. Since we evaluated alterations of q-EEG during four different periods (pre-treatment, at 2 and 4 weeks of treatment, and post-treatment), the scales of severity based on liver biopsy findings were handled as continuous variables in rANOVA of present study.

The etiology of this type of encephalopathy remains unclear regarding whether it involves direct or indirect toxic effects on the central nervous system. Several possible indirect mechanisms can be considered. IFN plays a role in the production of secondary cytokines such as interleukin-1 and tumor necrosis factor (9). Neuroendocrine hormone alterations may also be induced by IFN. IFN displays structural and functional similarities to neuroendocrine hormones such as ACTH (10, 11), and increased cortisol levels have been observed during IFN treatment. Such metabolic vulnerability might result in the diffuse slowing of brain waves observed on the EEG. LC is the most severe stage in Desmet's classification. Some degree of asymptomatic hypofunction of the brain might thus be evident even in patients with CH, as in patients with LC. Our finding of a significant correlation between alteration of qEEG during IFN administration and the severity of liver biopsy findings suggests that the EEG alterations observed in the present study might be detected the brain hypofunction of mild encephalopathy due to IFN in addition to the some degree of brain hypofunction in the patients with severe CH.

The diffuse slowing of EEG observed in the present study was reversible after the completion of treatment (Figs. 1, 2). This alteration of EEG was thus considered to be an asymptomatic and mild type of encephalopathy. However, the alterations of the EEG occurring during IFN-α treatment were marked in older aged patients and also in those with a high stage and grade based on liver biopsy findings. These findings suggest that the administration of IFN-α should be discontinued in patients with neuropsychiatric complications such as depression in the presence of EEG slowing. Serial EEG monitoring thus appears to be of value in detecting alterations of brain function during IFN-α treatment in chronic viral hepatitis patients, and alterations on serial EEGs should be carefully monitored in older patients and in those with severe stage and grade on liver biopsies.

Acknowledgement

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