Table 2 (*continued*)

		Epileptic psychoses	Schizophrenia spectrum disorders
For schizophrenia subtyping	Farmer subtypes (1992)		
	paranoid-like type	64%	60%
	hebephrenic-like type	36	40

$^{**}p<0.01$ (chi-square test).

differences between the two groups in the percentages of patients diagnosed with schizophrenia (53% in the index group and 66% in the control group) (Table 2).

Five diagnostic criteria led to schizophrenia being the most common diagnosis in the index group. With the other operational criteria, the most common diagnosis in the index group was atypical psychosis by the

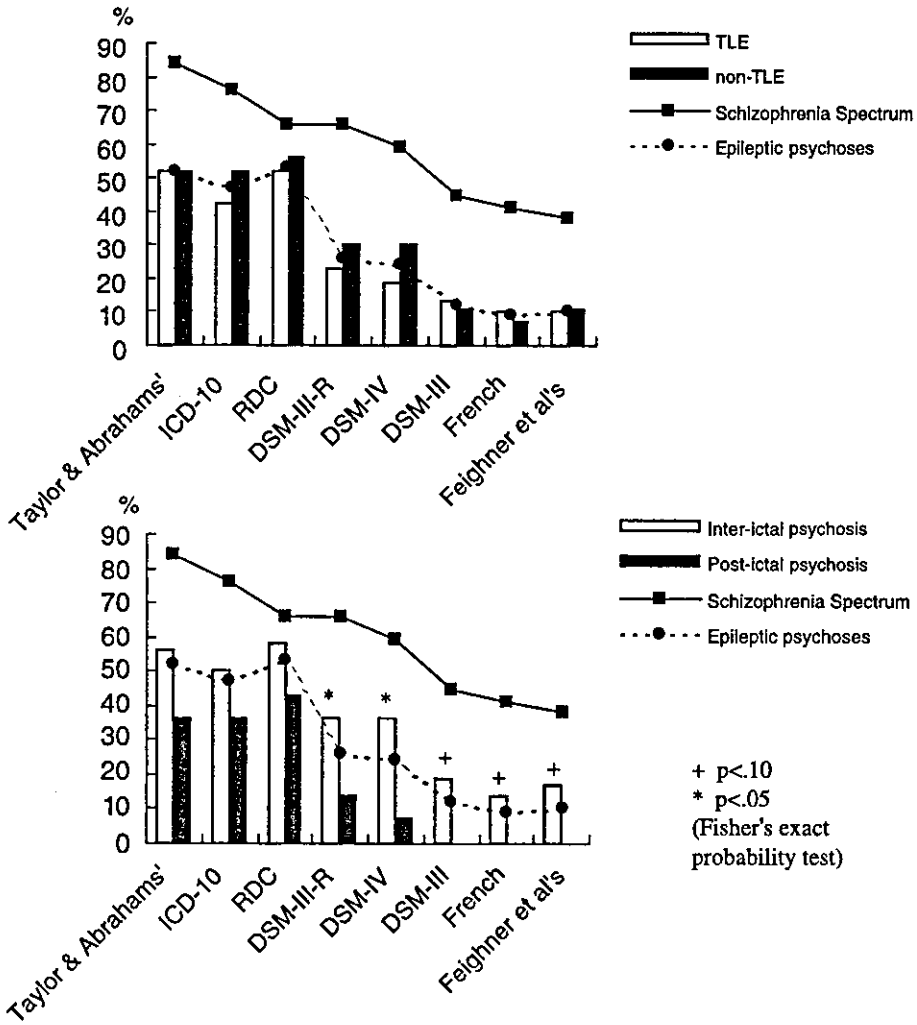

Fig. 1. Percentage of the distributions of operational diagnosis among subtypes of epileptic psychoses.

Table 3
Factor analysis

Factor (percent of variance) *Interpretation*	Epileptic psychoses	Schizophrenia spectrum disorders
Factor 1 (14.1%)	Factor score	
Manic symptoms	1.50 (2.16)	1.72 (2.61)
Factor structure (factor load)	Percentage of the presence	
Thoughts racing (0.82)	10%	24%*
Increased sociability (0.74)	31	24
Distractibility (0.72)	10	12
Pressured speech (0.71)	16	24
Elevated mood (0.71)	47	38
Excessive activity (0.69)	17	17
Reckless activity (0.66)	5	9
Increased self esteem (0.64)	7	10
Reduced need for sleep (0.55)	2	7
Factor 2 (10.4%)	Factor score	
Negative symptoms	0.67 (1.41)	2.79 (1.88)##
Factor structure (factor load)	Percentage of the presence	
Slowed activity (0.72)	16%	60%*
Negative formal thought disorder (0.69)	14	71*
Restricted affect (0.67)	12	36*
Blunted affect (0.64)	16	59*
Loss of energy/tiredness (0.57)	10	53*
Factor 3 (7.5%)	Factor score	
Depressive symptoms	1.02 (1.90)	1.31 (1.56)
Factor structure (factor load)	Percentage of the presence	
Dysphoria (0.73)	21%	16%
Loss of pleasure (0.68)	10	14
Initial insomnia (0.65)	14	22
Poor appetite (0.60)	14	33*
Irritable mood (0.54)	26	35
Poor concentration (0.53)	17	12
Factor 4 (5.5%)	Factor score	
Vegetative symptoms	0.05 (0.29)	0.10 (0.55)
Factor structure (factor load)	Percentage of the presence	
Weight gain (0.88)	2%	2
Excessive sleep (0.79)	2	5
Increased appetite (0.68)	2	2
Weight Loss (0.57)	0	2
Factor 5 (4.5%)	Factor score	
Positive symptoms	0.45 (0.82)	1.71 (1.84)##
Factor structure (factor load)	Percentage of the presence	
Third person auditory hallucinations (0.65)	10%	40%*
Thought withdrawal (0.64)	7	26*
Delusions of passivity (0.59)	0	9*
Thought broadcast (0.57)	2	7
Abusive/accusatory/persecutory voices (0.57)	12	16
Well organized delusions (0.55)	4	28*
Thought insertion (0.55)	10	47*

* $p<0.05$ (chi-square test).
\## $p<0.01$ (ANOVA).

DSM-III, delusional attack by the French system, atypical psychosis/schizophreniform disorder by the DSM-III-R, and psychotic disorder NOS by the ICD-10. While it was expected that the percentage of patients with a diagnosis of schizophrenia would be higher in the control group than in the index group, it was noteworthy that a substantial proportion of patients (9–53% depending on the different operational criteria) in the index group was diagnosed with schizophrenia.

As for the subcategories of schizophrenia diagnosis, while the diagnosis of Schneider's first-rank schizophrenia was higher in the control group (48%), it was diagnosed in 34% of the index group. Crow's mixed type schizophrenia with positive and negative symptoms was higher in the index group (78%) than in the control group (26%), but Crow's type II schizophrenia with pure negative symptoms was absent in both groups. The diagnosis of hebephrenic schizophrenia by Tsung and Winokur subtyping was lower in the index group (10%) than in the control group (38%), but the two groups had a similar rate (36–40%) of Farmer's hebephrenic-like subtype. The frequency of Carpenter's schizophrenia subtypes did not differ between the two groups. These results showed that while a subtype of schizophrenia with prominent positive and negative symptoms was more commonly found in the control group than in the index group, a considerable overlapping of schizophrenia subtypes exists between the two groups depending on the operational criteria used.

3.4. Distribution of operational diagnostic classification among subtypes of epileptic psychoses (Fig. 1)

The percentages of patients with a diagnosis of schizophrenia according to various diagnostic criteria paralleled those of the schizophrenia spectrum disorder group and those of the epileptic psychosis group, as shown in Fig. 1. For patients with epileptic psychoses, the proportion of patients with a diagnosis of schizophrenia among those with temporal lobe epilepsy with psychoses and among those with other types of epilepsy with psychoses did not differ, as shown in the upper part of Fig. 1. In contrast, the proportion of patients with a diagnosis of schizophrenia among those with inter-ictal psychosis was greater higher than among those with post-ictal psychoses, as shown in the lower part of Fig. 1. Schizophrenia was diagnosed only in the inter-ictal psychosis group and was not found in the post-ictal psychosis group using DSM-III, French, or St. Louis definitions for schizophrenia. Therefore, the overlap of schizophrenia diagnosis increases when epileptic psychoses were restricted to the inter-ictal psychosis.

3.5. Factor analysis (Table 3)

Exploratory factor analysis resulted in five factor solutions of manic, negative, depressive, vegetative, and positive symptoms, which explained 42% of the total variance of epileptic psychoses and schizophrenia spectrum disorders. The first factor identified was manic symptoms, which did not differ between the two groups. The second factor, characterized by negative symptoms, was significantly higher in the control group than in the index group. Although the incidence of individual symptoms was lower in the index group than in the control group, negative symptoms also were found in the index group. The third factor showing depressive symptoms and the fourth factor showing vegetative symptoms did not differ between the two groups. The fifth factor identified positive symptoms, which were significantly higher in the control group than in the index group. While the incidence of individual symptoms was lower in the index group than in the control group, positive symptoms except for delusions of passivity also were present in the index group. The incidence of some first-rank symptoms, such as thought broadcasting and abusive/accusatory/persecutory voices, did not differ between the two groups. These results showed that although the positive and negative symptoms were more severe among those with schizophrenia spectrum disorders than among those with epileptic psychoses, the two groups showed similar symptomatic profiles (Table 3).

4. Discussion

Historically, the association between epileptic psychoses and schizophrenia has been discussed from a descriptive phenomenological approach (Matsuura

and Trimble, 2000). As early as 1937, Akimoto (1937) reported three patients with epilepsy who developed psychosis, and stated that the psychopathology alone was insufficient to differentiate epileptic psychoses from true schizophrenia. Donigier (1959/1960) reported that psychotic episodes found in patients with epilepsy revealed all schizophrenic subtypes with paranoid episodes, hebephrenic episodes, and catatonic episodes, in a decreasing order of frequency. Hachiya (1960) reported 21 patients with epilepsy and schizophrenia-like symptoms, and stated that while paranoid–hallucinatory symptoms were, in themselves, difficult to distinguish from those in schizophrenia, they could be differentiated from schizophrenia by fewer disturbances in interpersonal attitudes and by the presence of so-called epileptic personality. Slater et al. (1963) published an influential paper postulating that the whole range of schizophrenic symptoms are exhibited at some stage of epileptic psychoses, and they could be regarded as a mock-up of true schizophrenia. They also argued that the majority of the patients with epileptic psychoses did not show the emotional withdrawal that is typical of schizophrenia.

However, many subsequent studies using a descriptive phenomenological approach have noted that epileptic psychoses are distinguishable by the retention of a normal affect response (Matsuura and Trimble, 2000; Sekine et al., 1980) or by the presence of a peculiar content of delusions, such as religious delusions (Inoue and Toichi, 1992). Based on a review of the literature, Parnas and Korsgaard (1982) concluded that psychotic profiles of epileptic psychoses seldom fulfill the Bleulerian concept of schizophrenia and that consequently the term "schizophrenia-like psychoses" should be avoided.

On the other hand, Davison and Bagley (1969) performed an extensive literature review for schizophrenia-like psychoses in cerebral diseases and stated that the clinical differences between symptomatic schizophrenic syndromes and true schizophrenia were largely illusory. Diehl (1989) examined symptoms among their own cases with epileptic psychoses and reviewed the relevant literature, and concluded that no distinction between epileptic psychoses and schizophrenia could be made. Conclusions of the studies using descriptive approaches are highly controversial. Indeed, the descriptive phenomenological approach is plagued by its inclusion of subjective judgement on the part of the diagnostician.

A categorical diagnostic approach has also been applied for comparing the symptomatology of epileptic psychoses and schizophrenia. As a primary example of the categorical diagnosis of schizophrenia, Schneider's first-rank symptoms have been considered as the model of the psychotic condition. The present study revealed that first-rank symptoms were more common among those with schizophrenia spectrum disorders, while they were found in 34% of patients with epileptic psychoses. Wing et al. (1974) postulated that first-rank symptoms are the primary features of nuclear schizophrenia and proposed the Present State Examination (PSE) and CATEGO program for operational schizophrenia diagnosis. Two studies comparing symptomatology of epileptic psychoses and schizophrenia using the PSE and CATEGO program have been reported. Perez and Trimble (1980) reported that the symptomatology of patients with epileptic psychoses, especially those with temporal lobe epilepsy, is similar to that of patients with nuclear schizophrenia. Toone et al. (1982) also reported that patients with epileptic psychoses could not be discriminated from those with functional psychoses. These data showed that a categorical diagnostic approach using the PSE and CATEGO criteria for schizophrenia could not reveal a distinction between epileptic psychoses and schizophrenia.

The significance of first-rank symptoms in a diagnosis of schizophrenia remains controversial. The St. Louis criteria (Feighner et al., 1972) and the French classification system (Pichot, 1984) do not emphasize first-rank symptoms, whereas Spitzer et al. (1975) advocated first-rank symptoms as a primary diagnostic element for schizophrenia and proposed the Research Diagnostic Criteria (RDC) for that purpose. In the present RDC results, more than half of the epileptic psychosis group was diagnosed with schizophrenia, and the proportion did not differ in the schizophrenia spectrum disorder group. This was in agreement with Oyebode and Davison's report (1989) that found no differences between epileptic psychoses and functional schizophrenia using RDC criteria. Although Cutting (1987) reported that first-rank symptoms were useful in differentiating acute schizophrenia from acute psychoses with various physical illnesses, several studies reported that first-rank symp-

toms could not discriminate epileptic psychoses from schizophrenia (Davison and Bagley, 1969; Sekine et al., 1980; Oyebode and Davison, 1989). The latter claim is reasonable because Schneider himself accepted by implication that first-rank symptoms can be generated by organic brain disease (Schneider, 1959). Therefore, categorical diagnostic approaches that heavily rely on Schneider's first-rank symptoms for a diagnosis of schizophrenia are limited in their ability to distinguish between epileptic psychoses and schizophrenia.

Nevertheless, the influence of RDC criteria has been enormous, and therefore first-rank symptoms have been included in the diagnostic criteria in most influential operational diagnostic systems including the DSM-III, DSM-III-R, DSM-IV and particularly in the ICD-10. Mendez et al. (1993) reported that no distinction was obtained between epileptic psychoses and schizophrenia using DSM-III-R criteria and concluded that most epileptic psychoses conform to the usual schizophrenia category. In the present polydiagnostic study, although the frequency of a schizophrenia diagnosis was lower in the epileptic psychosis group than in the schizophrenia spectrum disorder group, the percentage of patients diagnosed with schizophrenia among those with epileptic psychoses paralleled that of those with schizophrenia spectrum disorders depending on the operational criteria used. This means that the proportion of schizophrenia diagnosis in epileptic psychoses depends on the operational definition used for schizophrenia.

Although several reports have noted a similar symptomatology for schizophrenia and psychotic disorders of temporal lobe epilepsy (Slater et al., 1963; Perez and Trimble, 1980; Kanemoto et al., 2001), this was not confirmed by the present study. This result is compatible with that of Bruton et al. (1994), who denied that a particular association exists between temporal lobe pathology and schizophrenia-like symptoms in epilepsy based on a neuropathological study. Recently, Stevens (2002) postulated that excessive inhibition might occur at the anterior basal forebrain to preclude hyperexcitability and seizures prior to the onset of schizophrenia symptoms. Enhanced inhibition may be present in post-ictal psychosis as well as in alternative psychosis. However, the present results revealed a higher percentage of patients diagnosed with schizophrenia among those with inter-ictal psychosis than among those with post-ictal psychosis in the epileptic psychosis group. This is consistent with the findings of Kanemoto et al. (1996), who reported a higher proportion of schizophrenia-like symptomatology among individuals with inter-ictal psychosis than among those with post-ictal psychosis.

Using OPCRIT symptom items, several studies have explored the symptomatologic profiles that underlie the categorical diagnosis. Cardno et al. (1997) identified eight factors in RDC schizophrenia, which were in accordance with a conventional three-factor model of schizophrenia symptomatology, with six factors corresponding to positive symptoms, one to disorganized symptoms, and one to negative symptoms. When mood disorders were included, Serretti et al. (1996) identified four factors: excitement, depression, disorganization, and delusions. In chronic psychotic disorders, Van Os et al. (1999) found five factors: manic, depressive, negative, positive, and disorganization symptoms. The present study revealed a five-factor structure based on epileptic psychoses and schizophrenia spectrum disorders. Although the severity differed between the schizophrenia spectrum disorders and epileptic psychoses, the two groups shared similar symptom structures, indicating that the difference in symptom profile was quantitative rather than qualitative, and that a complete distinction between the symptomatology of epileptic psychoses and schizophrenia cannot be maintained even from the dimensional approach.

Although we matched the age and sex of the patients of the two groups at the study point, the average age at onset of psychoses was higher in the epileptic psychosis group than in the schizophrenia spectrum disorder group. This may relate to several demographic and clinical background differences, such as a higher frequency of an abrupt or acute onset of psychoses, a lower proportion of deterioration from a premorbid level of function, a lower rate of continuous chronic course in the epileptic psychosis group compared with the schizophrenia spectrum disorder group. However, these background differences, including a low family history of schizophrenia and a high frequency of premorbid personality disorder in the epileptic psychosis group, could be clinical features of epileptic psychoses. To clarify the demographic and clinical background differences between epileptic psychoses and schizophrenia spec-

trum disorders, a large-scale population-based comparative study may be needed.

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Functional MRI mapping of brain activation during visually guided saccades and antisaccades: cortical and subcortical networks

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Abstract

Antisaccade tasks require a subject to inhibit a saccade toward a briefly appearing peripheral target and instead to immediately generate a saccade to an equivalent point in the opposite hemifield. Using functional magnetic resonance imaging (fMRI), we investigated the neural networks required to inhibit reflexive saccades and to voluntarily generate saccades. The results demonstrated that saccade and antisaccade tasks often bilaterally activate frontal, parietal and supplementary eye fields, lenticular nuclei and occipital cortex. Additional activation of bilateral dorsolateral prefrontal cortices, supramarginal gyri, anterior cingulate cortices and thalamus was observed during antisaccade tasks. These results indicate that fronto-parietal and fronto-striato-thalamo-cortical circuits are involved in antisaccade tasks. The fronto-parietal circuit is thought to be related to the planning of saccadic eye movements that involve attentional control, while the fronto-striato-thalamo-cortical circuits connect to cortical region as a feedback network. We speculate that the abnormalities in spatial attention and eye movement control observed in schizophrenia stem from dysfunctions in the fronto-parietal and fronto-striato-thalamo-cortical circuits.

Keywords: Saccade; Antisaccade; Functional MRI; Eye movements; Fronto-parietal network; Fronto-striato-thalamo-cortical network

1. Introduction

Saccadic eye movements represent the primary mechanism used by primates to visually explore their environment. Saccades serve to focus points of visual interest on the fovea or parafoveal region of the retina. Several processing steps are usually performed before the neural command signals are sent to the oculomotor nuclei in the brainstem for saccade execution. These processes include disengagement of attention from a fixated target, saccade target selection, reallocation of spatial attention to the saccade target, calculation of spatial information for the saccade target, and the decision of when to give the signal to execute saccade.

Single unit recording studies in animals have revealed contributions from several cortical and subcortical regions to the generation of saccades. Knowledge of the human cortical control of saccades has been accumulated from observations of cerebral lesions (Guitton et al., 1985; Evdokimidis et al., 1996; Crevits

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et al., 2000), transcranial magnetic stimulation (TMS) (Kapoula et al., 2001; Leff et al., 2001), positron emission tomography (PET) (Anderson et al., 1994; O'Driscoll et al., 2000), and functional magnetic resonance imaging (fMRI) (Gaymard et al., 1999; Connolly et al., 2000; Nobre et al., 2000; Matsuo et al., 2003). These previous studies have indicated that saccadic eye movements are controlled by a cortical network that includes the parietal eye field (PEF) located in the intraparietal sulcus and superior parietal lobule (SPL), the frontal eye field (FEF) located in the precentral gyrus, and the supplementary eye field (SEF) located in the upper medial wall of the frontal lobe. The PEF is thought to be involved in visuospatial integration, the FEF may be involved in the preparation and triggering of intentional saccades, and the SEF is probably involved in the temporal control of sequences of visually guided saccades and eye-hand coordination (Gaymard et al., 1998; Heide and Kompf, 1998). Saccades and voluntary blinks are associated with similar loci of activation patterns (Bodis-Wollner et al., 1999).

Recent research has revealed an association between some psychiatric and neurological disorders and inability to inhibit unwanted reflexive saccades. One task used to investigate the inhibition of saccades is the antisaccade task (Everling and Fischer, 1998), which requires subjects to inhibit a saccade toward a briefly appearing peripheral target, and instead to generate a saccade to an equivalent point in the opposite hemifield. Inhibitory ability can be examined using the same oculomotor task with visually guided saccades by presenting a visual stimulus at one side and asking the subject to look at the opposite side.

In an experiment comparing reflexive saccade and antisaccade generation, a higher BOLD activation was found in the antisaccade than in the reflexive saccade task (Kimmig et al., 2001). The FEF and IPS were reported to be activated during voluntary eye movements, and FEF activity was related to the suppression of reflexive saccades (Mort et al., 2003). Within frontoparietal networks, the human FEF, but not the IPS, was reported to be critically involved in preparatory set, coding both the readiness and intention to perform a particular movement (Connolly et al., 2002; DeSouza et al., 2003). Curtis and D'Esposito (2003) investigated interactions between voluntary top-down and reflexive bottom-up processes using event-related fMRI, and reported that activity in the pre-SMA and SMA was higher than in the FEF and IPS during the preparatory period, and that FEF and IPS activity was higher than pre-SMA and SMA activity in the stimulus response period. The rostral portions of the SEF and FEF, as well as the rostral and lateral parts of the PEF, were reported to contribute to the suppression of prepotent responses (Merriam et al., 2001; Cornelissen et al., 2002).

In an animal study, saccade-related neurons in the FEF and superior colliculus (SC) were reported to decrease their rate of firing and those in the SEF were reported to increase their rate of firing before antisaccade (Schlag-Rey et al., 1997). Neural activity in the SC is known to be involved not only in the generation of fast saccades but also in antisaccade generation, and this neural activity is concerned with top-down signals from the frontal cortex (Everling et al., 1999).

A deficit in the inhibition of reflexive responses may result in a high number of saccades towards the visual stimulus. Previous studies have shown that patients with frontal brain lesions (Vilis and Hore, 1986), schizophrenia (Fukushima et al., 1988, 1990), and Alzheimer's disease (Currie et al., 1991) display difficulty generating antisaccades. Some authors have argued that the dorsolateral prefrontal cortex (DLPFC) is responsible for the correct performance of antisaccade tasks (Pierrot-Deseilligny et al., 1991).

McDowell et al. (1999) reported that poor antisaccade performance is related to genetic risk for schizophrenia. Furthermore prefrontal activity was not found during antisaccade tasks in schizophrenic patients (McDowell et al., 2002). However, Raemaekers et al. (2002) reported that schizophrenic patients did not show a selective dysfunction of the prefrontal region, but that they showed abnormalities of a frontostriatal network that is engaged in the suppression of automatic eye movements.

The aim of this study is to use fMRI to investigate the physiological neural bases of antisaccade performance, suppression of reflexive saccades, and generation of voluntary saccades.

2. Methods

2.1. Subjects

Twenty-one healthy volunteers (mean age 39.2 ± 10.2) participated in this study. All subjects were free

from neurological or psychiatric illness, and no abnormalities were observed on brain structural MRI. Written informed consent was obtained from all subjects. The project was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of Nihon University School of Medicine.

2.2. Magnetic resonance imaging

MRI data were acquired using a 1.5-T Siemens Symphony system (Siemens, Erlangen, Germany). Gradient-recalled echo planar imaging (EPI) was used for the fMRI sequence to obtain blood oxygen level-dependent (BOLD) 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°, field of view=192 mm, 64 × 64 matrix). Each subject performed five series contrasting saccade and control tasks and five series contrasting antisaccade and control tasks. For each series, subjects alternated between 40 s of control task and 40 s of oculomotor task. 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.

2.3. Task design

Subjects were instructed to fixate on a central fixation point. A visual stimulus was then presented in the visual periphery, at which point subjects were required to generate a saccade towards the stimulus (saccade task) or towards the horizontal mirror position (antisaccade task). Fixation point offset occurred after 500–1500 ms before a peripheral (randomized left or right on the horizontal axis) target appeared for a duration of 1000 ms. During the control task, subjects were in total darkness and were asked to maintain fixation and not blink. The target size was 1° of visual angle. The number of left and right saccadic eye movements was equated, with position of 10° in either direction. While subjects performed either the saccade or antisaccade task and baseline control tasks, fMRI scans were obtained. Visual targets were generated using a personal computer (OS: Windows 98) and customized 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). To measure performance during saccade and antisaccade tasks, electro-oculography (EOG) was undertaken outside the MRI scanner before functional imaging.

2.4. Data analysis for fMRI

Activity related to saccades and antisaccades relative to activity during the control task was analyzed independently. Image analysis was performed using an Ultra5 work-station (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.filion.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 transformed into the Montreal Neurological 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 × 8 × 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.

Data were analyzed using random-effect analysis. Statistical significance was set at the level of $P<0.001$, uncorrected for multiple comparisons; $T=3.35$. Intra-individual comparisons between saccades and antisaccades were analyzed using paired t-tests, and statistical significance was set at the level of $P<0.029$, uncorrected for multiple comparisons; $T=2.00$.

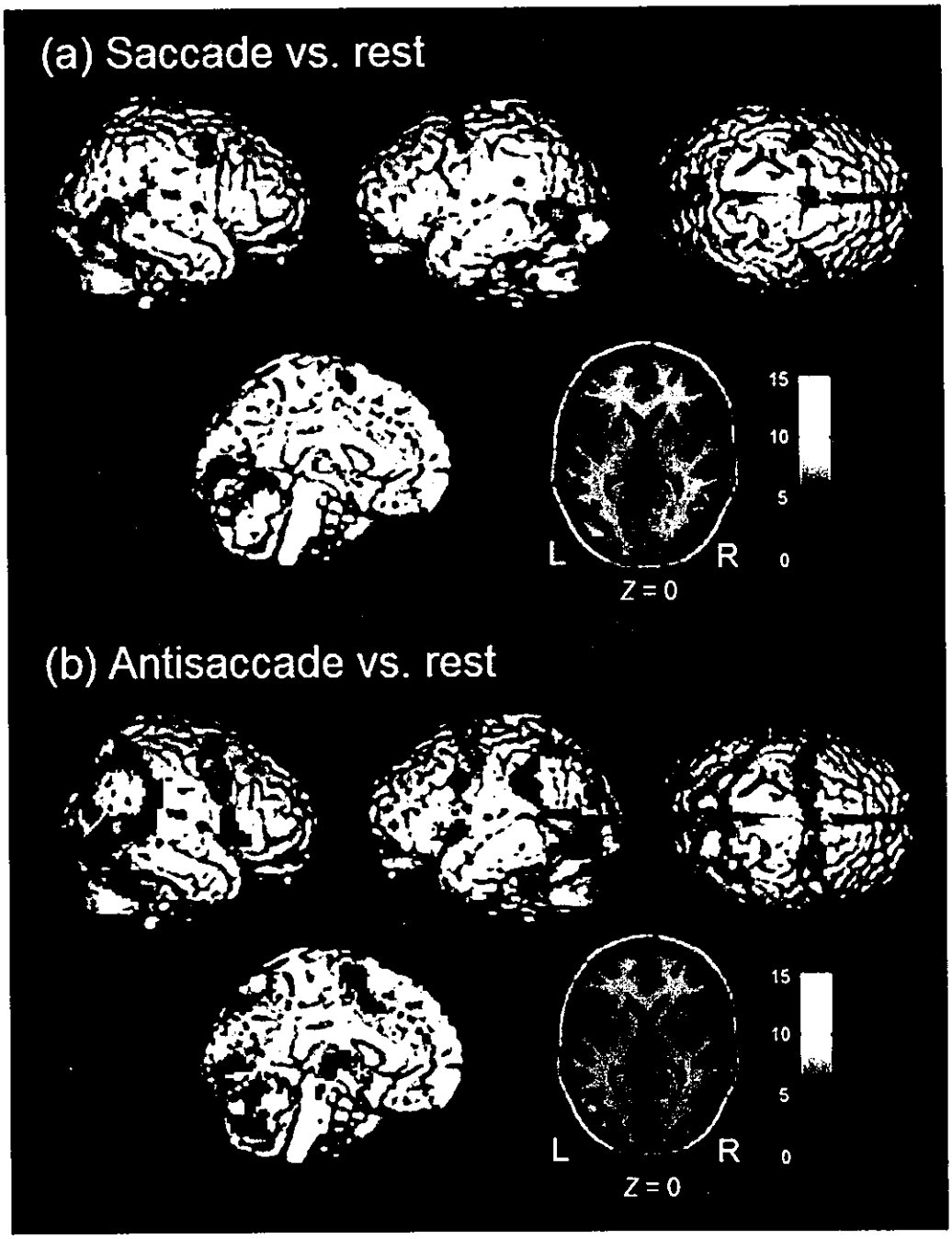

Fig. 1. Brain regions displaying greater activity during saccades (a) or antisaccades (b) than during control conditions. Statistical parametric maps, rendered onto standard brain close to MNI space. Height threshold at $P < 0.001$, uncorrected to demonstrate extent of each activated cluster; $T = 3.35$.

3. Results

Analysis of EOG revealed that no subjects exhibited directional errors during saccade tasks, and the mean percentage of errors during antisaccade tasks was $1.12 \pm 2.7\%$.

Activation areas are shown in Fig. 1a for saccade tasks, in Fig. 1b for antisaccade tasks and in Table 1 for both. Montreal Neurological Institute coordinates were determined based on averaged activation maps ($P<0.001$, uncorrected for multiple comparisons: $T=3.53$). During saccade tasks, regional activation was observed in bilateral FEF, SEF, and PEF, left lenticular nucleus and bilateral occipital cortices (V1). During antisaccade tasks, activation was observed in the same regional areas as in saccade tasks. Additional sites of activation were observed in bilateral inferior parietal lobules (IPL), ACC and thalamus, right lenticular nucleus and left DLPFC during antisaccade tasks.

Fig. 2 and Table 2 show the regions that were more active during antisaccade than during visually guided saccade tasks ($P<0.029$, uncorrected for multiple comparisons: $T=2.00$). Activation of bilateral FEF, PEF, IPL, ACC, thalami and DLPFC was observed.

4. Discussion

In this study, fMRI was used to reveal thalamic activation during antisaccade tasks, and lenticular nucleus activation during both saccade and antisaccade tasks. A previous PET study (Sweeney et al., 1996) reported task-related activation in the right

Table 1
Brain regions more active during visually guided saccade and antisaccade than during control tasks

Brain region		Saccade vs. rest coordinates			*T*-value	Antisaccade vs. rest coordinates			*T*-value
		X	*Y*	*Z*		*X*	*Y*	*Z*	
DLPFC	R				N.S				N.S
	L				N.S	−44	50	4	4.24
FEF	R	46	6	50	5.34	40	−2	50	8.87
	L	−42	−4	58	6.66	−22	−2	68	8.30
SEF	R	6	4	62	3.64	8	8	52	4.20
	L	−4	4	60	5.87	−2	10	46	5.56
PEF	R	22	−68	60	3.80	12	−64	64	12.36
	L	−30	−56	56	4.28	−10	−72	56	11.30
Lenticular nucleus	R				N.S	22	8	−2	6.93
	L	−20	8	2	4.45	−20	6	0	4.71
Visual cortex	R	38	−90	−8	9.81	26	−102	−6	8.12
	L	−22	−102	−8	10.75	−22	−102	−12	8.11
SMG	R				N.S	64	−36	28	6.14
	L				N.S	−64	−40	34	5.75
ACC	R				N.S	8	8	52	4.20
	L				N.S	−2	10	46	5.56
Thalamus	R				N.S	10	−14	8	8.30
	L				N.S	−12	−16	2	5.61

DLPFC: dorsolateral prefrontal cortex, FEF: frontal eye fields, SEF: supplementary eye fields, PEF: parietal eye fields, SMG: supramarginal gyrus, ACC: anterior cingulate cortex.

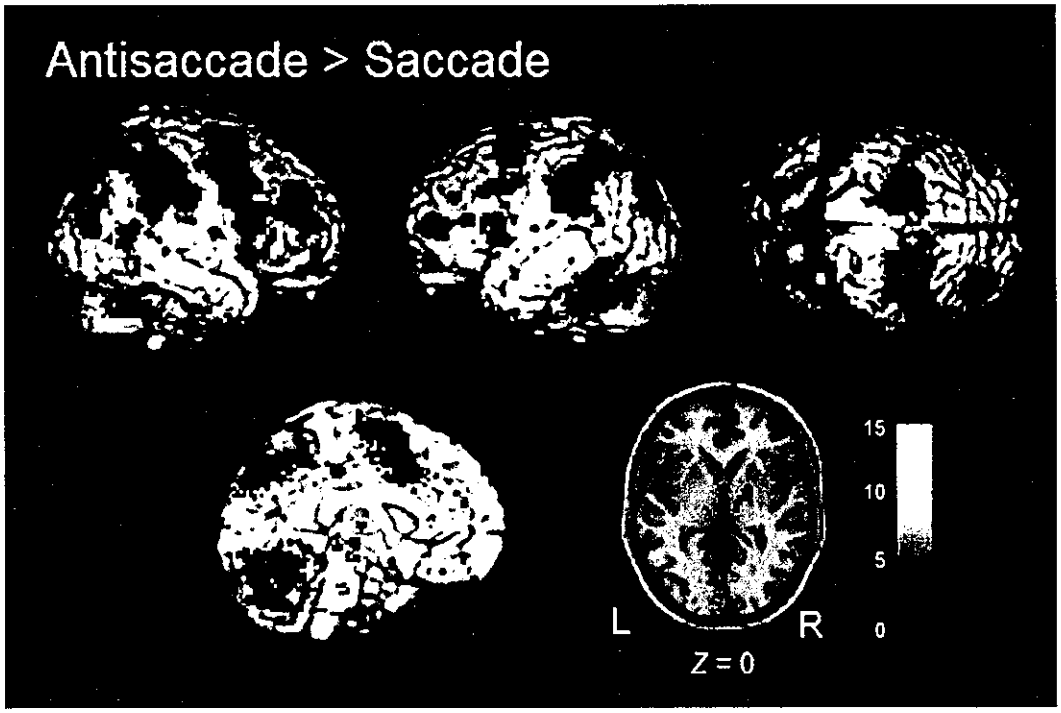

Fig. 2. Brain regions displaying greater activity during antisaccade than during saccade. Statistical parametric maps, rendered onto standard brain close to MNI space. Height threshold at $P < 0.029$, uncorrected to demonstrate extent of each activated cluster; $T = 2.00$.

posterior thalamus during visually guided saccades and in the left pulvinar during antisaccade tasks. The thalamus is known to subserve visual attention, and monkey studies have revealed thalamic activation during spatial working memory tasks (Petersen et al., 1985). Patients with thalamic infarcts display disrupted saccades (Brigell et al., 1984). The present result also indicated an important role for the thalamus in facilitating and inhibiting voluntary saccadic eye movements.

The basal ganglia tonically inhibit the thalamus through two parallel pathways (Alexander and Crutcher, 1990). A direct pathway runs from the striatum to the thalamus, and activation of the striatum disinhibits the thalamus, thus increasing thalamo-cortical activity. An indirect pathway passes from the lenticular nucleus to the subthalamic nucleus, and finally to the brainstem nuclei. Activation of the indirect pathway further inhibits thalamo-cortical neurons. As a result, activation of the direct pathway facilitates saccades, whereas activation of the indirect pathway inhibits saccades.

Schizophrenia patients display dysfunction of the dopaminergic neural networks (Gerfen et al., 1990) and demonstrate fronto-striato-thalamic circuit dysfunction (Buchsbaum et al., 1992). The direct and indirect pathways from the basal ganglia are affected differently by dopaminergic projections from the substantia nigra pars compacta to the striatum. Striatal neurons that project directly to the two output nuclei possess D1 dopamine receptors that facilitate transmission, while those projecting in the indirect pathway display D2 receptors that reduce transmission (Gerfen et al., 1990). Dysfunction of the striato-thalamo-cortical dopaminergic circuitry may reduce inhibition and thus facilitate saccades in schizophrenia. Our results indicate that this dysfunction has an important role on subtle motor control and therefore affects antisaccade production through both the direct and indirect pathways.

The activation of bilateral DLPFC was observed during antisaccade tasks, but not during visually guided saccade tasks, according to a previous fMRI study (Muri et al., 1998) and a PET study (O'Driscoll

Table 2
Brain regions more active during antisaccades than visually guided saccades

Brain regions		Coordinates			T-value
		X	Y	Z	
DLPFC	R	42	46	18	2.72
	L	−38	52	12	4.73
FEF	R	28	4	54	6.24
	L	−28	4	48	6.40
PEF	R	16	−66	52	8.74
	L	−26	−50	56	6.84
SMG	R	64	−20	24	4.26
	L	−66	−36	28	6.17
ACC	R	10	18	36	3.04
	L	−12	12	38	5.83
Thalamus	R	12	−14	−4	2.76
	L	−12	−18	−2	2.31

DLPFC: dorsolateral prefrontal cortex, FEF: frontal eye fields, SEF: supplementary eye fields, PEF: parietal eye fields, SMG: supramarginal gyrus, ACC: anterior cingulate cortex.

et al., 1995). DLPFC activation confirms the results of previous lesion studies, in that patients with DLPFC lesions demonstrate an increased percentage of antisaccade errors, reflecting difficulties suppressing unwanted reflexive saccades (Guitton et al., 1985; Evdokimidis et al., 1996; Crevits et al., 2000). The fronto-striato-thalamo-cortical network (Alexander et al., 1986; Petit et al., 1993; McFarland and Haber, 2002), including the prefrontal cortex and thalamus, is important in the control of antisaccades. These results suggest schizophrenia patients displaying inhibition errors during antisaccades may have a dysfunction of the fronto-striato-thalamo-cortical network.

Bilateral FEF were activated during both saccade and antisaccade tasks, as in several previous fMRI studies (Muri et al., 1998; Connolly et al., 2000). In a monkey study, the majority of FEF neurons displayed vigorous presaccadic activity (Hanes et al., 1995). Patients with lesions restricted to the FEF demonstrate a normal percentage of directional errors during an antisaccade task, but increased antisaccadic latencies (Rivaud et al., 1994). The FEF is considered responsible for triggering antisaccades and suppressing unwanted reflexive saccades (Merriam et al., 2001; Cornelissen et al., 2002). The FEF is also concerned with preparatory set, which is involved in readiness and intention to perform a saccade (Connolly et al., 2002; DeSouza et al., 2003).

Bilateral SPL were activated during both saccade and antisaccade tasks, while the IPL, including the SMG, was activated only during antisaccades, in accordance with a previous fMRI study (Connolly et al., 2000). The SPL is active during covert orienting tasks (Nobre et al., 2000), and activation in the SPL might be associated with overt eye movement responses in addition to spatial attention shifts. Saccade tasks require only local attention, while antisaccade tasks require an attentional shift from local to global. Patients with lesions restricted to the right SMG make few saccades to the left, and show abnormal performance on covert attentional shift to the left. The SMG may not carry a topographic representation of visual space, and may instead be involved in switching from local to global features of a stimulus (Perry and Zeki, 2000). Co-activation between SPL and IPL may be needed to perform antisaccade tasks that require attentional shifts from local to global.

The fronto-parietal network, including the FEF, the SPL and the IPL, is considered important for control of attention, and has been implicated in planning saccadic eye movements. These regions also project from the thalamus. These two networks, the fronto-striato-thalamo-cortical and front-parietal networks, are thus considered to be important for accurate control of antisaccades.

In conclusion, saccade and antisaccade tasks commonly activate bilateral FEF, SEF, PEF, lenticular nuclei and V1. Additional activation of bilateral DLPFC, IPL, ACC and thalami were observed during antisaccade tasks. These results indicate the involvement of two important neural networks of fronto-parietal and fronto-striato-thalamo-cortical circuits in the control of inhibition of reflexive saccades and voluntary saccades (Alexander et al., 1986; Petit et al., 1993; McFarland and Haber, 2002). Specific antisaccade errors have been reported in patients with schizophrenia, who are believed to possess abnormalities in the dopaminergic neural network. We speculate that abnormalities in spatial attention and processing of voluntary movement information in schizophrenia stem from dysfunctions in the fronto-

parietal and fronto-striato-thalamo-cortical circuits networks.

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Development of quantitative neuropsychological tests for diagnosis of subclinical hepatic encephalopathy in liver cirrhosis patients and establishment of diagnostic criteria—multicenter collaborative study in Japanese

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Abstract

At present, there are no generally accepted diagnostic criteria or methods for subclinical hepatic encephalopathy (SHE) associated with liver cirrhosis. We therefore developed an easily conducted computer-aided quantitative neuropsychiatric function test system for use in routine medical practice. We established normal values in healthy Japanese subjects and determined differences between healthy persons and liver cirrhosis patients without clinical encephalopathy in a multi-center clinical trial. The test system consists of eight tests: number connection tests A and B, a figure position test, a digit symbol test, a block design test, and reaction time tests A, B and C. The test results were affected by age, but not by gender or facility. No learning effect was noted. The results were therefore reported by 5-year quartile ranges and differences were evaluated between 542 healthy subjects and 292 cirrhotic patients. When the cut-off value was set at the 10th/90th percentile of the results in healthy subjects, the results of each of the 8 tests were abnormal in about 25% of cirrhotic patients, and at least 1 of the 8 tests gave values greater than the 10th/90th percentile cut-off value in 58.2% of the 292 liver cirrhosis patients. SHE patients were thought to be

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included in these 58.2% of patients. The developed test makes it possible to quantitatively assess neuropsychiatric function, and the results obtained can be used as a basis for the diagnosis of SHE.

Keywords: Liver cirrhosis; Subclinical encephalopathy; Neuropsychological tests; Computer-aided test system

1. Introduction

Subclinical hepatic encephalopathy (SHE), which gives abnormal results to sensitive quantitative neuropsychiatric function tests without showing any abnormal physical findings, is seen in 30–84% of liver cirrhosis patients. The importance of SHE is being increasingly recognized as it may interfere with the activities of daily living [1–14]. Recently, Ferenci et al. [15] presented new proposals regarding the definition and classification of hepatic encephalopathy and the degree of associated coma. They named SHE "minimal hepatic encephalopathy (mHE)" as low-grade hepatic encephalopathy and emphasized its importance.

SHE includes pre-clinical hepatic encephalopathy and is associated with no clinical symptoms or signs of the degree of coma being grade I or 0 according to the conventional grading system. There are no standard diagnostic criteria, and it is diagnosed at individual medical institutions by their own diagnostic methods based on the paper–pencil test and electrophysiological tests, including EEG [3]. However, none of these tests is satisfactory in terms of ease in operation or reproducibility, and the need for development of a simpler quantitative test has been pointed out.

Since SHE is associated with a reduction in performance cognition, a combination of multiple neuropsychiatric function tests designed to assess performance cognition is used for its diagnosis. Recently, Kircheis et al. reported that the critical flicker-frequency (CFF) test alone makes it possible to easily diagnose SHE in liver cirrhosis [16]. However, because results of the CFF are normal in about 40% of SHE patients diagnosed by conventional neuropsychiatric function tests, the CFF has limitations as a diagnostic method although it is a simple, easy-to-use method [17].

We developed a computer-aided simple neuropsychiatric test system consisting of eight tests that can be easily conducted on outpatients using a touch panel. In order to evaluate the utility of this test system, we first conducted a pilot study in healthy subjects and identified factors that influence the results of the test. This was followed by a multiple cooperative study designed to establish standards for neuropsychiatric functions in healthy subjects and liver cirrhosis patients. The criteria for the SHE diagnosis were established based on the findings obtained.

2. Materials and methods

The test system consisted of the following eight tests and was designed to assess psychomotor, attention, memory and special functions: number connection tests A and B (NCT-A and B), figure position test (FPT), digit symbol test (DST), block design test (BDT), and reaction time tests A, B and C (RTT-A, B and C) [10–13,18,19]. The system was simplified so that two-dimensional operations using a computer were possible. All tests can be completed in about 20 min, including the time needed for practice and operation guide.

2.1. Neuropsychological (NP) test system

Software was developed by Otsuka Pharmaceutical Co., Ltd., Kokuyo Co., Ltd., and ISB Co., Ltd. Hardware consisted of a personal computer (OS: window3.1, ThinkPad 365X, IBM) and a 33 cm size touch panel connected to the PC (GUNZE Access Vision AV4833FT, Gunze Ltd., Tokyo, Japan).

2.2. Number connection tests (NCTs)

Two tests were conducted, NCT-A, in which the time needed to serially connect figures from 1 to 20 on the touch panel was determined (time limit: 60 s), and NCT-B, in which the time needed to connect figures from 1 to 10 and 10 Japanese characters was determined (time limit: 180 s).

2.3. Figure position test (FPT)

Subjects were asked to remember the shape and position of 2–4 figures displayed on the panel for 15 s. They were asked to return each figure to its original position after randomly moving them on the panel, and the time needed to complete this task was determined (time limit: 90 s). This test was developed after the tactual performance test.

2.4. Digit symbol test (DST)

Nine different symbols were displayed on the panel in 60 s, and subjects were asked to select a digit corresponding to each symbol on the panel. The number of correct answers was determined (maximum number of questions: 40).

2.5. Block design test (BDT)

Six different cards were displayed on the panel, and the time needed to complete the same design as that displayed on the panel was determined (time limit: 60 s).

2.6. Reaction time tests (RTTs)

Three types of RTT were conducted: RTT-A, in which the reaction time needed by subjects to press an enter key after the color of a circle on the panel changed from white to red; RTT-B, in which subjects were asked to press the enter key when the color changed from white, blue or yellow to red; and RTT-C, in which subjects were asked to press the enter key when a combination of white, blue and yellow changed to that of yellow and red.

2.7. Construction of the NP test system (pilot study)

A pilot study was conducted at three university hospitals in Japan between June 1996 and March 1997. One hundred and twelve healthy subjects under no medical treatment, who were almost evenly divided into 3 age brackets (40–49, 50–59, and 60–69), were enrolled. Informed consent was obtained from all volunteers after providing thorough information on the objectives and method of the study. One of the objectives of this pilot study was to determine if the test system could be operated without any problem. In addition, the correlation between the test results and factors that were thought to influence them (age, gender and facility) was evaluated. The tests were conducted three times by repeating the tests 1 and 7 days after the first tests in order to determine the presence or absence of learning effects (effects of familiarization with the tests). The tests were always conducted in an independent test room between 10 a.m. and 4 p.m. in order to minimize the environmental effects.

2.8. Establishment of normal ranges and estimation of cut-off values

Cut-off values were estimated in order to establish the normal ranges and extract a population showing abnormal neuropsychological function test results. The following number of subjects, aged between 40 and 69, were enrolled at 14 university hospitals between June 1996 and March 1997: 328 patients with hepatic cirrhosis and 550 healthy subjects (not included in the 112 enrolled in the pilot study). Healthy subjects under no medical treatment and without hepatic disease were enrolled. Hepatic cirrhosis was diagnosed based on liver biopsy, imaging diagnosis, or clinical diagnosis combining objective findings and hematological tests. Those with any of the following were excluded: previous neurological focal episode or other neurologic illness, history of psychiatric illness, history of consumption of psychotropic drugs, and clinical hepatic encephalopathy (≤grade II). Those under treatment with lactulose, poorly absorbed antibiotics or branched-chain amino acid to deal with hyperammonemia were enrolled if they could tolerate the tests.

Informed consent was obtained from all subjects after thoroughly explaining the objectives, methods and other relevant details of the study.

3. Statistical analysis

In data analyses, subjects were grouped by age at 5-year intervals since findings obtained in the pilot study showed that age affects analytical results when they are grouped at 10-year intervals. Subjects in each age bracket were classified into the healthy subject group and the cirrhotic patient group. Differences between the two groups were shown by the quartile range. The upper and lower 10, 20 and 30 percentiles were estimated for each test item in healthy subjects in order to evaluate cut-off values as percentages of upper and lower test values obtained in cirrhotic patients.

Test values were handled as mentioned below. Namely, the actual time needed to complete the task was reported in NCT-A and NCT-B. The number of correct answers were reported in the DST. The mean effective test time, i.e. the test time spent for correct operations divided by the number of correct operations, was reported for the FPT, BDT, RTT-A, -B and -C.

A subcommittee was created to establish a data handling policy. It excluded all "outliers due to apparent errors in operation" (data from subjects who did not completely understand the operation procedures and those who undertook the tests under apparently abnormal physical conditions due to night duties or a lack of sleep) from analysis. All data from subjects younger than 40 and those aged 70 or older were excluded from analysis as a deviation from the protocol.

4. Results

4.1. Construction of the NP test system

Results obtained from the 112 healthy subjects showed no significant differences in the test results by gender or facility or any significant learning effects on the test results due to repetition of the tests by each subject. However, the test results were found to be affected by age as is typically shown by the results of NCT-B shown in Fig. 1. As is evident from this figure, the test time clearly increased with age in healthy subjects when they were divided into groups at 10-year intervals.

4.2. Establishment of normal ranges and estimation of cut-off values

The NP test system was conducted in a total of 834 subjects, including 542 healthy subjects and 292 liver cirrhosis patients. However, 8 healthy subjects and 37 liver cirrhosis patients were excluded due to violations of the protocol in terms of the age. The backgrounds of healthy subjects and cirrhotic patients are shown in Table 1. Relatively old males were predominant among cirrhotic patients ($P < 0.0001$). The severity of liver cirrhosis was mild in most patients according to the child classification system, and the cause was viral in

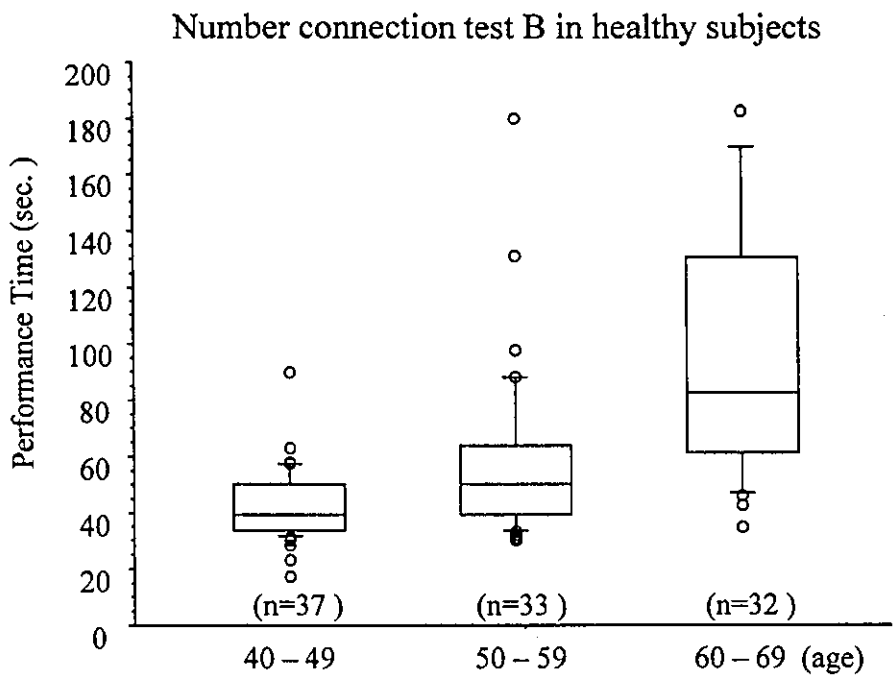

Fig. 1. Results of number connection test B in healthy subjects are indicated with horizontal bars. The vertical bars indicate the range and the horizontal boundaries of boxes represent the first and third quartiles.

the great majority of patients (81%). Overall, 131 cirrhotic patients (45.0%) were receiving at least 1 drug for hyperammonemia: 74 (25.3%) lactulose, 107 (36.6%) BCAA, and 9 (3.1%) poorly absorbed antibiotics.

The number of subjects analyzed with respect to each test item ranged between 517 and 542 healthy subjects (95.4–100%) and between 273 and 290 cirrhotic patients (93.5–99.3%). Because the pilot study showed that the test re-

Table 1
Clinical and laboratory characteristics of cirrhotic patients and healthy subjects

Items	Cirrhotic patients, *n* (%)	Healthy subjects, *n* (%)	*P*-value
Total	292	542	
Sex			
Male	191 (65.4)	275 (50.7)	
Female	101 (34.6)	267 (49.3)	<0.0001[a]
Age (years)			
40–44	14 (4.8)	98 (18.1)	
45–49	27 (9.2)	112 (20.7)	
50–54	33 (11.3)	109 (20.1)	
55–59	54 (18.5)	99 (18.3)	
60–64	82 (28.1)	79 (14.6)	
65–69	82 (28.1)	45 (8.3)	
Mean ± S.D.	59.0 ± 7.3	52.6 ± 7.9	<0.0001[b]
T-bilirubin (mg/dL) (mean ± S.D.)	1.6 ± 1.9		
ALT (IU/L) (mean ± S.D.)	70.1 ± 50.0		
Child classification			
A	130 (44.5)		
B	134 (45.9)		
C	28 (9.6)		
Etiology			
Virus	237 (82.2)		
Alcohol	39 (13.4)		
Others	16 (5.5)		

[a] Chi-square test.
[b] Student's *t*-test.