PET activation study on saccade control in schizophrenia

精神分裂病のサッケード制御に関するＰＥＴによる賦活研究

中 鳴 護 文

論文題目

PET activation study on saccade control in schizophrenia

精神分裂病のサッケード制御に関するPETによる賦活研究

中 嶋 義 文

1. INTRODUCTION

1.1 Neural control of saccades

Among five different types of eye movements, neural control of saccade has been most extensively examined neurophysiologically. The five types of movements are saccade, the vestibulo-ocular reflex, smooth pursuit, optokinetic response, and convergence. Each is controlled relatively independently through separate neural pathways, which converge only at the level of the eye muscle motoneuron. Neural control of saccade is believed to occur via the lower saccade generating system (disinhibition of tonic inhibition of the oculomotor nuclei) by means of higher corticocortical associations, the center of which is the frontal eye field (Schiller et al., 1980).

The lower saccade generating system consists of the caudate nucleus to the substantia nigra (SNr) and the superior colliculus (SC) that project to the brain stem reticular formation which are then transmitted to the extraocular motoneurons. These brain stem structures are called the saccade generator (SG). Hikosaka (Hikosaka, 1989) showed that the basal ganglia, especially SNr contributed to the suppression and initiation of saccades by imposing a tonic inhibition on SC and by removing it.

The higher corticocortical associations are involved in control of saccades. The role of the frontal eye field (FEF has been well established in physiological studies. Neurons in the FEF have anticipatory, visual and movement discharge patterns in all *purposeful* saccades (Bruce and Goldberg, 1985).

The role of the prefrontal cortex (PFC) in saccadic control has been suggested by several studies (Guitton et al., 1985; Funahashi et al., 1989, 1991, 1993). On the antisaccade trials, patients with prefrontal lobe lesions showed errors of looking the lit target (Guitton et al., 1985). The monkeys showed the prefrontal neurons activities when saccades were made toward a remembered target, and also when this prepotent response was suppressed and a saccade in the opposite direction was required (Funahashi et al., 1989, 1991, 1993).

The supplementary motor area (SMA) is involved in saccade control. The SMA activation occurs prior to and during self-initiated saccades and visually-guided saccades (Schlag and Schlag-Rey, 1987). This portion of SMA was named as the supplementary eye field (SEF) by Schlag and Schlag-Rey (Schlag and Schlag-Rey, 1987). SEF role in saccade control is supposed to be a regulation of initiation of a saccade, especially in terms of the degree of willed effort or self-generation required in saccade production (Schlag and Schlag-Rey, 1987).

1.2 Saccade disturbance in schizophrenia

Intrusion of saccade during smooth pursuit eye movement in schizophrenic patients and their relatives is a well established phenomenon (Holzman et al., 1973). In addition, longer latencies and higher error rates in antisaccade task performance among schizophrenia has

been reported (**Fukushima et al., 1988, 1990; Thaker et al., 1989; Rosse et al., 1993; Sereno et al., 1995**). These findings suggest that the saccade control system is disturbed in schizophrenia. This saccade control dysfunction was not related to medication (**Holzman et al., 1987; Fukushima et al., 1990; Sereno et al., 1995**).

The reason of this disturbance has not been fully elucidated yet and it has been a matter of discussion. Dysfunction of 1) the basal ganglia (SNr and SC) (**Thaker et al., 1989**), or of 2) the frontal cortex (**Fukushima et al., 1994**) especially the FEF (**Levin, 1984**), or of 3) both structures was postulated.

1.3 Positron emission tomography

1.3.1 General concepts

Positron emission tomography (PET) is a technique for measuring the concentrations of positron-emitting radioisotopes within a three-dimensional object by the use of external measurements of the radiation from these isotopes. This technology enables to visualize and quantify the varieties of physiological parameters such as cerebral blood flow (CBF), cerebral metabolism rate for glucose (CMRglu), and neurotransmitter functions in the living human brain (**Hoffman and Phelps, 1986**).

1.3.2 Task-evoked rCBF paradigm (Activation studies) (**Figure 1**)

Neural activities always accompany regional energy metabolism. Under physiological conditions, regional blood flow and energy metabolism are closely correlated with one another (*coupling*) (**Sokoloff, 1978**). Thus, regional cerebral blood flow (rCBF) could represent regional neural activities.

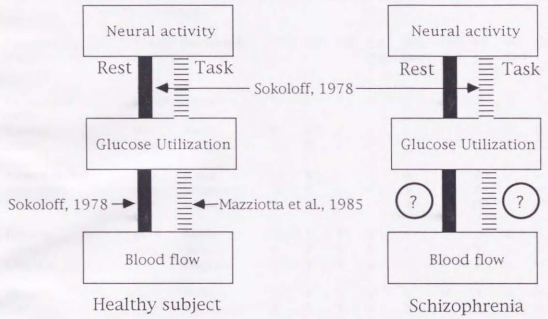
Task-evoked rCBF paradigm (or, more commonly, called as *activation studies*) refers to the paradigm where rCBF provides information about relative cerebral responses to different neurobehavioral tasks in subjects studied with PET and rCBF ligand such as oxygen-15 labeled (O-15) water. The validity of the paradigm has been tested in healthy volunteers. Visual stimulation studies in healthy volunteers demonstrated relative rCBF changes between control and stimulated states that are in good agreement with similar results obtained using the same stimulation paradigm with the use of fluorodeoxyglucose to determine cerebral glucose utilization (**Mazziotta et al., 1985**). Thus we could assume the paradigm should be applicable to examine cerebral activities in healthy volunteers.

In schizophrenic patients, the above coupling in either resting state or stimulated state has not been tested yet.

Since neural activity always accompany with energy metabolism, it is reasonable to assume a linear relationship between regional glucose utilization and neural activity in schizophrenia. If regional blood flow well represent glucose utilization under both resting

state and task condition, the paradigm would be also applicable to examine neural activities in schizophrenia as is in healthy controls. In study 1, the validity of the paradigm was tested in schizophrenia by comparing glucose utilization and blood flow under either resting or task condition.

Figure 1 Basis of task-evoked rCBF paradigm ("coupling")



Sokoloff (Sokoloff, 1978) validated coupling of neural activity and glucose utilization. In healthy subjects, coupling of glucose utilization and blood flow was validated at rest (Sokoloff, 1978) and during task (Mazziotta et al., 1985). In schizophrenia, coupling of glucose utilization and blood flow has not been examined either at rest or during task. Filled lines indicate "Resting state", barred lines indicate "during task".

1.3.3 Activation studies with neural control of saccades

Using the above paradigm, neural control of saccades has already been studied in healthy subjects **(Table 1)**. (*See* Next Page)

Table 1 Results of the neural control of saccade in healthy subjects examined by activation studies.

Y = activation observed, 0 = not observed, - = data not shown or reported. () = tendency. PVC = the primary visual cortex, FEF = the frontal eye field, SEF = the supplementary eye field, Ant. Cing = the anterior cingulate, PFC [sup/mid] = the prefrontal cortex [the superior frontal gyrus and the middle frontal gyrus], PFC [inf] = the prefrontal cortex [the inferior frontal gyrus], PC [sup/mid] = the parietal cortex [the superior parietal gyrus and the middle parietal gyrus], PC [inf] = the parietal cortex [the inferior parietal gyrus], Caud = the caudate, and Th = thalamus.

Researcher (Year)	Method	Saccade task	PVC	FEF	SEF	Ant Cing	PFC [sup /mid]	PFC [inf]	PC [sup /mid]	PC [inf]	Caud	Th
Melamed et al. (1979)	Xe-133	Simple	Y	Y	Y	-	-	-	-	-	-	-
Fox et al. (1985)	O-15 water	Simple	(Y)	Y	Y	-	-	-	-	0	0	0
		Reflexive	Y	Y	Y	-	-	-	-	0	0	0
Nakashima et al. (This study)	O-15 water	Simple	**Y**	**Y**	-	-	**0**	-	**0**	-	-	-
		Reflexive	**Y**	**Y**	-	-	**0**	-	**0**	-	-	-
		Volitional	**Y**	**Y**	-	-	**Y**	-	**(Y)**	-	-	-
Petit et al. (1993)	O-15 water	Simple	(Y)	Y	Y	Y	-	-	0	0	0	Y
		Memory	Y	Y	Y	0	-	-	Y	-	-	Y
Lang et al. (1994)		Imaginary	Y	Y	Y	0	-	-	0	-	-	0
Paus et al. (1993)	O-15 water	Reflexive	Y	Y	Y	Y	0	0	Y	0	(Y)	0
		Antistimulus	Y	Y	Y	Y	Y	0	Y	(Y)	0	0
Anderson et al. (1994)	O-15 CO_2gas	Reflexive	Y	Y	0	0	0	0	Y	0	0	0
		Remembered	Y	Y	Y	0	0	0	Y	0	0	(Y)
Law et al. (1995)	O-15 water	Reflexive	Y	Y	Y	Y	0	0	Y	0	0	0
		Selective	Y	Y	Y	Y	(Y)	Y	Y	0	0	0
O'Driscoll et al. (1995)	O-1 CO_2gas	Antisaccade (vs. Reflexive)	Y	Y	Y	0	0	0	Y	0	Y	Y

The results are not totally congruent. Melamed & Larsen showed rCBF increases in an area within the middle precentral and premotor regions which corresponds to human frontal eye field (FEF) using xenon 133 injection method and 254-channel dynamic gamma camera (**Melamed & Larsen, 1979**). Fox et al. applied O-15 water and PET to localize the activation foci in a stereotaxic space and to test the effects of the presence of targets, the modality of cues and the expectancy of targets appearance (**Fox et al., 1985**). They showed rCBF increases within the FEFs, the supplementary motor area (SMA), and the cerebellum. FEFs were consistently activated during the generation of voluntary saccades and uninfluenced by target presence, type of cue, or task complexity. The SMA was consistently active during all motor tasks and was uninfluenced by the degree of task complexity or stochasticity. Petit et al. also used O-15 water and PET to show rCBF activations during voluntary, memorized and imagined saccades (**Petit et al., 1993; Lang et al., 1994**). They showed the subcortical structures activation during the saccade execution. They also showed imagined saccade (without actual eye

movement) activated the FEF and the SMA. Paus et al. applied O-15 water and PET to show the anterior cingulate activation during saccade tasks (Paus et al., 1993). The role of the anterior cingulate in motor control was also examined. Anderson et al. used O-15 CO_2 inhalation method and PET to show the activation of striate and extrastriate cortex, PPC and the FEF during reflexive and remembered saccades (Anderson et al., 1994). During remembered saccades there was additional activation of SMA, insula, cingulate, thalamus, cerebellum and the right superior temporal cortex. O'Driscoll et al. performed O-15 carbon dioxide gas inhalation PET and compared antisaccade activation to saccade activation (O'Driscoll et al., 1995). She showed the FEFs involvement in antisaccade tasks. Cortical control of saccade in healthy subjects was examined in study 2.

1.3.4 PET studies with schizophrenia

Besides receptor studies, PET studies with schizophrenia have been done with rCBF and rCMRglu either under resting or baseline task condition (Bartlett et al., 1991a, 1991b; Brodie et al., 1984; Buchsbaum et al., 1982, 1984a, 1984b, 1987, 1990, 1992a, 1992b, 1992c; Cleghorn et al., 1989, 1990, 1992; Cohen et al., 1989; DeLisi et al., 1985a, 1985b; Dolan et al., 1993; Early et al., 1987; Farkas et al., 1984; Friston et al., 1992a, 1992b; Frith et al., 1992; Gordon et al., 1994; Guenther et al., 1989, 1994; Gur et al., 1987a, 1987b, 1989; Hazlett et al., 1993; Jernigan et al., 1985; Kaplan et al., 1993; Kishimoto et al., 1987; Kling et al., 1986; Levy et al., 1992; Liddle et al., 1992; Potkin et al., 1994; Resnick et al., 1988; Satoh et al., 1993; Schroeder et al., 1994, 1995; Sheppard et al., 1983; Siegel Jr., et al., 1993; Tamminga et al., 1992; Volkow et al., 1986a, 1986b, 1987, 1992; Weiler et al., 1991; Widen et al., 1983; Wiesel et al., 1987a, 1987b; Wik & Wiesel. 1991; Wolkin et al., 1985, 1988, 1992, 1994). Most repeatedly reproduced finding was an absolute or relative decrease in rCBF or rCMRglu of the frontal cortex. Another interest area was the limbic system and the temporal cortex.

Using SPECT (single photon emission CT) or xenon 133 inhalation method, task-evoked rCBF changes in schizophrenia were examined (Andreasen et al., 1992; Berman, 1987; Berman et al., 1986, 1988, 1990, 1992, 1993 ; Catafau et al., 1994; Daniel et al., 1991; Franzén & Ingvar, 1975; Guenther et al., 1986, 1991; Gur et al., 1994; Ingvar & Philipson, 1977; Kawasaki et al., 1993; Parellada et al., 1994; Rubin et al., 1994; Weinberger et al., 1986, 1992). They showed a lack of the prefrontal cortex activation (functional hypofrontality).

In PET activation studies, Volkow applied smooth pursuit eye tracking task and F-18 FDG PET, showing that relative hypofrontality of schizophrenia was more highlightened under task condition than under baseline condition (Volkow et al., 1987). Guenther applied simple and complex finger movement-sequence task. The normals showed significant activation in mesial frontal and contralateral sensorimotor and premotor areas during complex movement task. However, schizophrenia lacked this activation (Guenther et al., 1994). In study 2, activation patterns during saccadic tasks in schizophrenia were examined.

Some studies reported the relationship between clinical characteristics and rCBF or rCMRglu pattern (Cleghorn et al., 1990; DeLisi et al., 1985b; Dolan et al., 1993; Gordon et al., 1994; Gur et al.,

1989; Kaplan et al., 1993; Kishimoto et al., 1987; Liddle et al., 1992; Satoh et al., 1993; Schroeder et al., 1995; Siegel Jr., et al., 1993; Volkow et al., 1987; Wiesel et al., 1987a; Wik & Wiesel, 1991; Wolkin et al., 1992, 1994). Another pioneering study tried to relate physiological chatacteristics of the patients to their rCMRglu profile (Hazlett et al., 1993).

2. AIMS

ON THE METHOD (STUDY 1)

-To examine the validity of application of task-evoked rCBF paradigm (activation studies) by PET for schizophrenia

ON THE NEURAL CONTROL OF SACCADES IN SCHIZOPHRENIA (STUDY 2)

-To examine the neural control of saccades in normal living human brain

-To examine the disturbance of the neural control of saccades in schizophrenia

-To examine whether a regional activation could have significant partial correlations with several clinical dimensions of schizophrenia

3. GENERAL DESIGN

3.1 Procedure for participating in the studies

Overall, 13 healthy volunteers and 24 schizophrenic patients participated in this study after signing an informed consent according to the guidelines approved by the Committee on Medical Ethics, Faculty of Medicine, University of Tokyo. The informed consent form is attached as Appendix 1. As a general rule, each patient's will to participate in the study was assured twice, first a few weeks prior to the scan, and second on the scan day. Final consent and signing to the form were not taken by the attending psychiatrist who usually saw the patient but by another psychiatrist. It was to avoid subconscious pressure to participate in the study. One copy of the consent forms was kept by the volunteer.

Healthy volunteers were recruited from the community. They were university students, medical doctors, business people, and housewives. Each underwent a neuropsychiatric interview and examination, and none had any history of cerebral or psychiatric illness (including substance abuse). All denied use of psychotropic medications at any time, and none was taking medications at the time of the study.

All the schizophrenic patients were outpatients at Department of Neuropsychiatry, The University of Tokyo Hospital, Tokyo. They were diagnosed according to ICD-9 (The International Classification of Diseases: ninth revision) as schizophrenia by two psychiatrists independently. The diagnosis of schizophrenia was not told to the patient according to the general practice rule in Japan, but the result of PET experiments was explained by the patient's attending psychiatrist.

3.2 Clinical ratings

The patients were diagnosed according to ICD-9. The Brief Psychiatric Rating Scale (BPRS) **(Overall and Gorham, 1962)** and the Scale for the Assessment of Negative Symptoms (SANS) **(Andreasen, 1983)** were rated just before the scan by the psychiatrist. Each BPRS item score, BPRS positive score (=sum of the score on the items referring to positive symptoms), BPRS total score, each SANS item score, and SANS total score were used for the analysis.

3.3 Radiochemistry

O-15 and F-18 was produced by a cyclotron. Water labelled with O-15 was synthesized by an in-target direct method similar to a hot atom reaction. A target gas was trapped by bubbling into a saline-filled vial.

F-18 FDG was synthesized according to the standard method **(Hamacher et al., 1986)**.

3.4 Common method

Before PET-experiment, the subject underwent the psychiatric evaluation by a psychiatrist. BPRS (The Brief Psychiatric Rating Scale) and SANS (The Scale for Assessment for Negative Symptoms) were rated in the patient by the psychiatrist.

In each PET-experiment the subject was placed recumbent with his head in the PET-camera system. The head of the subject was fixed by a plastic head holder with the aid of laser alignment beams. The slices were parallel to the OM (orbitomeatal) line of the subject. Before PET, two cannula were inserted, one into the right antecubital vein and the other into the left radial artery.

$PaCO_2$ was measured before and after the data acquisition. To ensure that the subject was alert, electroencephalography (EEG) was recorded throughout the experiment. For analysis of task performance, horizontal and vertical electrooculograms (EOG) were obtained. For a detection of head movement errors, the subject's head was fixed in a plastic headholder and monitored.

3.5 PET camera system

The subjects were examined with the seven ring PET-camera system, the HEADTOME-IV **(Iida et al., 1989)**. This system produces 14 parallel slices of the brain with the in-plane resolution about 4.5 mm FWHM (Full Width of Half Maximum) for F-18 and 8 mm FWHM for O-15 and the slice thickness of 6.5 mm.

Water labelled with O-15 was administered as an intravenous bolus of 3 ml of saline containing 740-1480 MBq. A 90-second scan was initiated when the tracer bolus entered the brain (approximately 5 seconds after injection). Arterial blood samples were drawn to provide an arterial time-radioactivity curve **(Iida et al., 1986)**. Regional cerebral blood flow (rCBF) was measured using an adaptation of the Kety autoradiographic method **(Herscovitch et al., 1983)**.

Regional cerebral glucose utilization rate (rCMRglu) was measured by the FDG model **(Phelps et al., 1979)**. F-18 FDG (5 ml of saline containing 74-148 MBq) was administered intravenously for 2 minutes by a Harvard pump apparatus. After 58-minute dynamic scan, 10-minute static scan was performed. Intermittent arterial blood sampling during this scan period provided an arterial time-radioactivity curve, which produced rCMRglu.

3.6 PET determination of activation

Calculation of normalized rCBF and normalized rCMRglu

Absolute rCBF values are changing from time to time. This is a normal physiological fluctuation. Not only $paCO_2$ but also other physiological factors like arousal level can account for this flucutuation. For elimination of irrelevant fluctuation, the regional CBF values for

each scan were divided by the mean whole brain CBF, which was the average rCBF value for all ROIs in the same subject for each scan. This yielded a relative rCBF value, the whole brain CBF of each scan being 50 ml/min/100g. As was in blood flow, the rCMRglu values for each scan were divided by the mean whole brain CMRglu. This yielded a relative rCMRglu value, the whole brain CMRglu of each scan being 5 mg/min/100g.

Setting the regions of interest

To control the effect of the size of the ROIs, the circle ROIs, sixteen millimeter in diameter, were set closely according to the cortical rim line.

3.7 Analysis

All data analysis was conducted using the Statistical Analysis System Package 6.0.3 (**SAS Institute Inc, 1988**) and STATVIEW software.

4. STUDY 1

4.1 Objectives

Seven schizophrenic patients underwent both O-15 water PET-experiment (for blood flow) and F-18 FDG PET-experiment (for glucose utilization) on the same day under either resting state condition or saccade task condition. Regional correlation between blood flow and glucose utilization was calculated and compared in both conditions. This study was to test whether an coupling of blood flow and glucose utilization might be established even in the saccade task condition in schizophrenic patients. It was thus to examine the validity of application of task-evoked rCBF paradigm (so-called activation studies) by PET for schizophrenia.

4.2 Subjects & method

Seven schizophrenic patients (age 20-40; male : female = 5 : 2) participated. Three of them were never medicated and the other four were medicated. They were in their stable phase of illness. None showed worsening of the psychopathology of their illness after participating in the study.

The subjects underwent O-15 water PET scan followed by F-18 FDG PET scan. Three never-medicated patients were examined for rCBF and rCMRglu while they were at resting state. The other 4 medicated patients were examined while they were performing simple saccade task. Each subject received 3 successive O-15 water PET scans, one during saccade task and 2 during resting state, immediately followed by F-18 FDG PET scan during resting state or saccade task using the same transmission images. In the F-18 FDG PET scan during saccade task, the subject was required to continue saccades throughout the scanning period.

Sixteen millimeter in diameter circular ROIs were set on the same subject's blood flow images and glucose utilization images. Relative rCBF and relative rCMRglu of these ROIs which were located anatomically on the same position were compared.

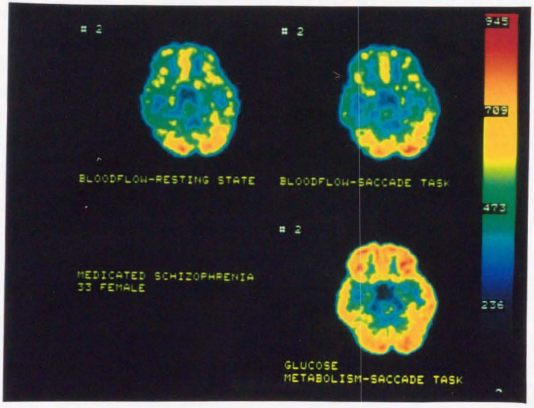
Regional relationships between the relative rCBF value and the relative rCMRglu value were calculated as a Pearson's correlation coefficient (r) after linear regression with least square method for all ROIs (n:number of ROIs) in each subject. r was transformed into $t = [(n-2)/(1-r^2)]^{1/2}$, where t showed t-distribution with a degree of freedom equal to n-2. Difference among subjects was tested after Z-transformation of r.

4.3 Result

Blood flow images during the resting state and the task condition, and glucose utilization image during the task condition were shown (**Figure 2**). The resolution of the images was

better in the glucose utilization image than in the flow images because of longer data acquisition time. Detailed structure was visible in the glucose utilization image.

Figure 2 O-15 water (blood flow) PET images during resting state (top left) and saccade task condition (top right) , and F-18 FDG (glucose utilization) PET image during saccade task condition (bottom right) in the same schizophrenic patient.



Pearson's correlation coefficients (r) between relative rCBF and relative rCMRglu for subjects during resting state were 0.65 (n=64, $p<0.01$), 0.42 (n=40, $p<0.01$), and 0.46 (n=54, $p<0.01$), respectively (n: numbers of ROI). That showed a linear and loose correlation between blood flow and glucose metabolism. During saccade task, correlation coefficients were 0.60 (n=50, $p<0.01$), 0.58 (n=104, $p<0.01$), 0.43 (n=88, $p<0.01$), and 0.35 (n=50, $p<0.01$), respectively. That indicated a linear and loose coupling was also established during saccade execution. There was no significant ($p<0.05$) difference among each subject's correlation coefficients. Coupling of blood flow and metabolism was established in the same way among these seven schizophrenic subjects against difference of physiological condition (rest, task).

4.4 Comment

This is the first study comparing rCBF and rCMRglu in one subject who performing motor task in schizophrenia. As shown, in this small number of subjects, no rCBF and rCMRglu discrepancy was observed notwithstanding difference of physiological condition (rest vs. task). Since a loose but significant linear glucose utilization-blood flow coupling either during resting state or during activated state was established, we suppose it appropriate to apply the task-evoked rCBF paradigm (activation study) for schizophrenia and to compare its results with those in healthy controls.

5. STUDY 2

5.1 Objectives

Thirteen healthy volunteers and twenty schizophrenic patients underwent O-15 water PET-experiments under the resting state condition and three different saccade task conditions on the same day. Regional activation under the task was determined and compared in both groups. Correlational regional coactivation was also analyzed. Clinical features of the twenty schizophrenic patients were analyzed in relation to the activation pattern. This study was to examine the neural control of saccade in normal living human brain and to examine its disturbance in schizophrenia.

5.2 Subjects & method

The subjects were 13 healthy volunteers (11 males and 2 females) with a mean age 28.8 years (SD, 8.2 years) and 20 ICD-9 schizophrenic patients **(Table 2)**.

Table 2 Demographic data of thirteen healthy subjects.

Subject	Sex	Age	Years of education
N1	M	23	16
N2	F	22	16
N3	M	21	15
N4	M	25	18
N5	M	36	22
N6	M	28	18
N7	M	25	18
N8	M	27	18
N9	M	28	18
N10	M	24	16
N11	M	26	16
N12	M	48	16
N13	F	42	14
Average	M:F	28.9	17
(SD)	11:2	(8.2)	(2)

The schizophrenic group **(Table 3)** comprised 10 unmedicated patients who were drug-free at least one month before scanning and 10 medicated patients. All schizophrenic patients were in a relatively stable phase of their illness. None showed worsening of their psychopathology after participating in the study. (*See* next page)

Table 3 Demographic data of schizophrenic subjects.

Subject	Sex	Age	Years of education	Duration of illness (yrs.)	ICD-9 subtype	BPRS Total	SANS Total
Unmedicated patients							
SN1	F	45	14	3	paranoid	39	83
SN2	M	25	14	3	unspecified	23	70
SN3	M	20	12	4	hebephrenic	44	113
SN4	F	25	14	8	hebephrenic	45	96
SN5	M	21	13	0.2	unspecifed	31	45
SN6	F	27	12	10	hebephrenic	28	71
SN7	F	34	12	16	hebephrenic	39	87
SN8	M	23	16	4	hebephrenic	17	78
SN9	M	20	13	1	hebephrenic	34	63
SN10	F	34	14	1	paranoid	16	28
Average	M:F	27.4	13.4	5.0		31.6	73.4
(SD)	5:5	(8.0)	(1.3)	(4.9)		(10.5)	(24.4)
Medicated patients							
SM1	M	38	12	15	hebephrenic	31	97
SM2	F	21	14	0.25	catatonic(in remission)	17	43
SM3	F	37	16	10	paranoid	14	38
SM4	F	39	16	8	paranoid	13	54
SM5	M	20	12	3	hebephrenic	38	67
SM6	M	22	12	5	hebephrenic	55	78
SM7	M	48	10	32	hebephrenic	29	107
SM8	F	42	16	4	catatonic(in remission)	14	59
SM9	F	36	12	19	hebephrenic	42	95
SM10	M	20	12	3	hebephrenic	25	67
Average	M:F	32.3	13.4	10.0		27.8	70.5
(SD)	5:5	(10.5)	(1.3)	(9.7)		(14.1)	(23.4)

The experiment consisted of five or six consecutive O-15 water PET scans. Each scan interval was 15-20 minutes. To reduce the effect of the subject's anxiety on rCBF, a 'sham' scan was obtained before the initial resting scan . For resting state scans, the subjects were required to remain immobile with their eyes closed and their ears covered. The resting state scan was followed by 2 or 3 task performance scans (task sessions). The last scan was either a resting scan or another task session not included in this saccade study **(Figure 3)**. The three tasks described in detail later were allocated to task performance scans in a pseudorandomized order for avoidance of an order effect **(Figure 4)**.

Figure 3 Experimental design of the study 2.

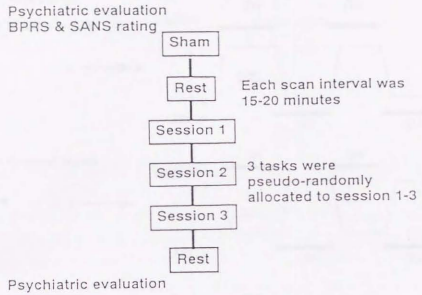
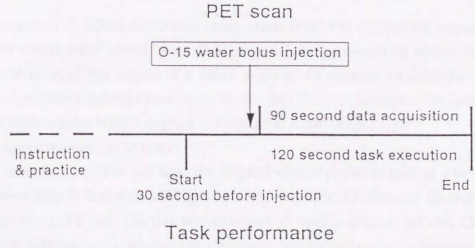


Figure 4 Task session scan.

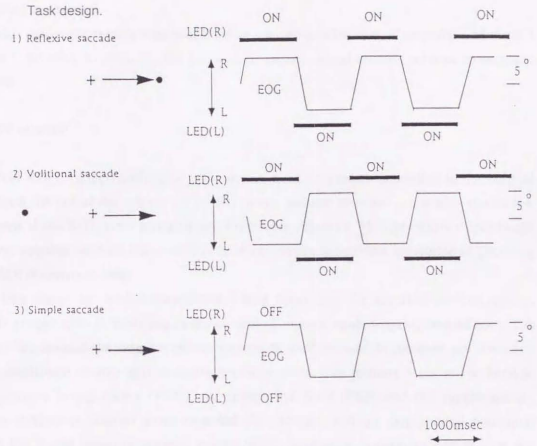


For each task session, the subjects were required to keep performing the task from 30 seconds before the injection of the tracer until the end of the scan. Prior to each scan, each task was instructed and practiced.

After the whole series of scans, the subject was evaluated by the psychiatrist's interview. The subject's self evaluation about his or her task performance and the strategy used were reported then and recorded.

Task Design **(Figure 5)**

Figure 5 Task design.



For delineation of differences among tasks, visual input and oculomotor output were controlled. The visual input stimuli were 2 (right and left) light-emitting diodes (LEDs) placed 40 cm in front of the subject at a visual angle of 10 degrees. Oculomotor output consisted of continuous saccadic eye movements toward the left and right targets. The amplitude and interval of each saccade were 5 degrees and 900-1100 msec., respectively.

We designed the tasks as follows ;

(1) Reflexive saccade task : For this task, the subjects were required to look at a lit target, which was alternatively lit (left-right-left-right-...) at intervals of 900-1100 msec. Each saccade had an initiation cue and a goal. The task thus consisted of visually-guided saccades. Cortical areas involved in both saccade execution and visual attention were expected to respond.

(2) Volitional saccade task : This task consisted of visually-guided saccades with distracting stimulus. The subjects were required to make a saccadic eye movement toward a target on one side while another target on the contralateral side was illuminated. The target illumination interval was the same as for the first task. Each saccade also had an initiation cue and a goal, but the lit target served as an distracting stimulus. Cortical areas involved not only in saccade execution and visual attention but also in inhibiting irrelevant responses and maintaining newly learned strategies were expected to respond.

(3) Simple saccade task : There was no lit target during this task. The subjects were required to saccade toward the left target and toward the right target alternatively (left-right-left-right-...)

at the same interval as in the above two tasks (approximately once per sec). This task can be regarded as a motor control task. Cortical areas involved in continuous saccade execution were expected to respond.

In this study, the resting state was used as a baseline condition. Comparison of these 3 tasks made it possible to examine the function of higher neural circuits relative to saccadic performance.

Regions of interest

Circle ROIs, sixteen millimeter in diameter, were set closely according to the cortical rim line. With the aid of the subject's CT/MRI image and the standard brain atlas (**Talairach & Tournoux, 1988**), these ROIs were grouped into functional subareas. Multiple ROIs were always used for any subarea because they could reduce variability which was inevitable in choosing only one ROI (**Kuwert et al., 1992**).

In this study, we took a hypothesis-testing approach. We selected cortical regions which were supposed to be involved in the control of saccade (**Anderson et al., 1994**) *ad hoc*. The reason why we limited the number of the regions to analyze was to increase the detection power for significant change against multiple comparisons. The primary 5 regions to analyze were the primary visual cortex (PVC), the frontal eye field (FEF) and the supplementary motor area (SMA) as cortical areas essential for saccade, and the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) as higher associative cortex over the FEF.

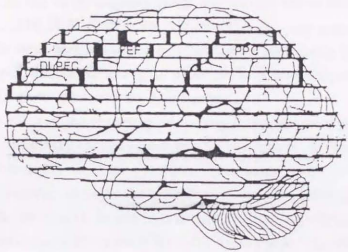
In a preliminary study comparing rCBF during fixation and at rest, we found a significant activation in PVCs (**Momose et al., 1991**). The PVCs were activated in presense of visual stimuli. We chose resting state as a control because of further analysis of resting state rCBF in comparison with previous publications. Considering the effect of the visual stimuli on the PVCs, we excluded the PVCs in this analysis.

The supplementary motor area (SMA) was apparently associated with the execution of saccades (**Schlag & Schlag-Rey, 1987**), however, in this analysis, this area was not included. The main reason was because it was difficult to decide the size of the SMA ROI. Though we observe the SMA activation during the saccade tasks, it was difficult to delineate the ROI in our ROI approach.

As a result, in this analysis, only three regions of FEF, DLPFC, and PPC were examined.

The ROIs for these regions were shown (**Figure 6**). Ambiguous regions at the border of the two adjacent cortices were omitted. Physiologically defined FEF set on 2 slices on precentral gyrus and the middle frontal gyrus; for DLPFC on 5 slices mainly on the superior frontal gyrus and the middle frontal gyrus; for PPC on 4 slices including superior lobule, supramarginal gyrus and angular gyrus. (*See* next page)

Figure 6 ROI scheme.



Analysis

Relative rCBF value changes were tested by a 4-way repeated-measure analysis of variance (ANOVA) with independent groups and repeated-measures for conditions (4), brain regions (FEF, DLPFC, PPC), and hemisphere (right and left); an interaction procedure was then applied to explain the source of the effects. For handling of the missing values, two types (Type II and Type III) of SS (Sum of Square) calculation were applied and compared (only Type II result was shown) (SAS Institute Inc, 1988). Only if both calculation showed significance, we took the result significant. For a*post hoc* analysis, a *paired-t* test was applied (after Bonferroni correction).

Correlational analysis among the regional activation under each condition was done. In order to avoid type I error, cut off level was set at $p = 0.01$, that might mean $r > 0.6$.

Relationship between the regional activation and the clinical features of schizophrenic patients was analyzed. The effect of medication, the difference between positive and negative schizophrenic patients, the effect of the chronicity and the severity of the illness, and the symptomatology were analyzed.

The effect medication was assessed by a group comparison between the medicated (n=10) and the unmedicated (n=10) patients. Under 4 conditions, the mean normalized rCBF in the ROIs of each group were compared.

The difference between positive and negative schizophrenic patients was assessed by a group comparison and a correlational analysis. In the group analysis, the patients in whom positive symptoms dominated (SN1, SN2, SN3, SN4, SN5, SN6, SN9, SN10, SM5) were included in the positive group (n=9). In the positive group, the patients whose BPRS positive

score > 10 and SANS total score < 70 (SN5, SN9, SN10, SM5) were especially categorized as the very positive group (n=4). On the other hand, the patients in whom negative symptoms dominated (SN7, SN8, SM1, SM2, SM3, SM4, SM6, SM7, SM8, SM9, SM10) were included in the negative group (n=11). In the negative group, the patients whose BPRS positive score < 5 (SN8, SM1, SM3, SM4, SM7, SM8) were categorized as the very negative group (n=6). Under 4 conditions, the mean normalized rCBF in the ROIs of each group were compared. In the correlational analysis, the normalized rCBF in the ROIs of each subject were compared with the subject's BPRS positive score or the SANS total score.

To analyze the effect of the chronicity, according to the length of the duration of the illness, a group comparison [very chronic (duration > 10 years; n=6) vs. subchronic (10 years > duration > 3 months; n=12) vs. acute (duration < 3 months; n=2)] and a correlational analysis with duration were performed on the normalized rCBF in the ROIs under 4 conditions.

The effect of the severity of the illness was analyzed by a correlation between BPRS total score and the normalized rCBF in the ROIs under 4 conditions. The symptomatology of the patient was analyzed by a correlation of each BPRS and SANS item score to the normalized rCBF in the ROIs under 4 conditions.

More sophisticated analysis like a factor analysis (Liddle et al., 1992) was not performed. It was because the observation number was not enough for those kinds of the analyses.

5.3 Result

Task Performance

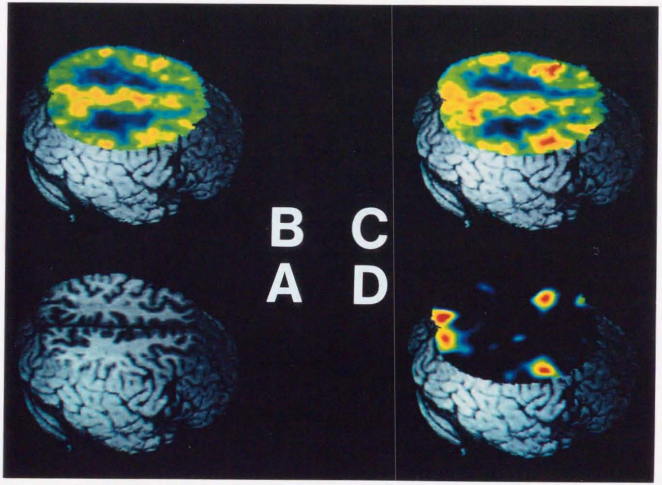
Analysis of EOG recordings showed that the accuracy of each saccade was almost 100%, which means that the task was complete throughout the scanning period. The highest error rate was 2 % in one patient during volitional saccade. Latencies of saccades could not be examine because the execution of saccades was done continuously, and thus the establishment of the fixation phase could not be assumed.

MRI-PET combination

Superimposing of the PET image onto the reconstructed MRI image by Watanabe's method (Watanabe et al., 1991) was shown **(Figure 7)**. The bottom left (A) is the reconstructed MRI image of one normal subject. The top left (B) and the top right (C) are the combining images of MRI and PET during resting state and during volitional saccade task performance, respectively. The bottom right (D) shows the subtraction image of the resting state image from the activated image. FEF and PVC are found to be activated. This physiologically defined FEF is located on Brodmann's area 8 (classical FEF). (*See* next page)

Figure 7 The superimposing of the PET image onto the reconstructed MRI image of one healthy subject.

The reconstructed MRI image [Bottom left (A)]. The combining images of MRI and PET during resting state [Top left (B)] and during volitional saccade task [Top right (C)] . The subtraction image of the resting state image from the activated image [Bottom right (D)]. FEF and PVC are activated.



RCBF Changes during Task Performance

Table 4 The rCBF changes in the FEF, DLPFC, and PPC during task performance. Mean normalized rCBF (ml/100g/min) (SD).

	Healthy		Schizophrenia	
	Left	Right	Left	Right
FEF				
Resting state	50.8	49.4	54.0	53.7
	(3.7)	(4.8)	(4.0)	(4.2)
Simple saccade	53.9*	53.3*	55.2	55.9
	(4.4)	(4.5)	(4.9)	(7.1)
Reflexive saccade	52.3*	52.7*	55.0	55.1
	(3.7)	(4.8)	(5.4)	(5.7)
Volitional saccade	53.7*	52.5*	53.6	54.9
	(4.2)	(4.9)	(5.0)	(5.7)
DLPFC				
Resting state	50.6	50.7	50.6	49.7
	(2.8)	(3.2)	(2.6)	(2.5)
Simple saccade	50.7	51.7	49.2	48.9
	(2.5)	(2.9)	(2.7)	(3.4)
Reflexive saccade	51.2	49.8	48.9	48.2
	(4.7)	(3.2)	(2.3)	(3.0)
Volitional saccade	53.5**	49.3	48.9	49.2
	(5.6)	(3.8)	(3.0)	(3.1)
PPC				
Resting state	50.5	49.1	52.8	51.9
	(5.5)	(4.5)	(5.4)	(5.8)
Simple saccade	50.3	49.5	51.7	51.6
	(4.2)	(3.6)	(6.4)	(4.0)
Reflexive saccade	50.8	48.9	52.1	51.2
	(7.6)	(5.4)	(4.8)	(5.0)
Volitional saccade	52.7	48.6	52.1	51.2
	(8.8)	(4.6)	(5.2)	(4.8)

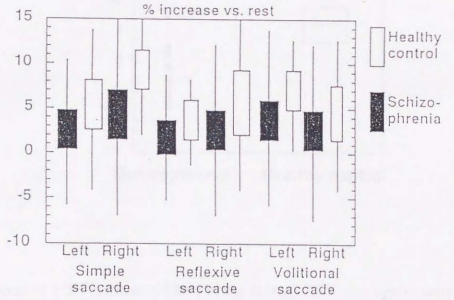
Repeated-measures ANOVA
Group effect: $F = 0.65$, $df = 1$, $p = .42$; structure: $F = 24.8$, $df = 2$, $p < .0001$; group by structure interaction: $F = 8.51$, $df = 2$, $p = .002$; hemisphere : $F = 11.8$, $df = 1$, $p = .0006$; group by hemisphere interaction: $F = 6.85$, $df = 2$, $p = .009$; group by structure by hemisphere by condition interaction: $F = 2.66$, $df = 6$, $p = .014$.
Simple interactions: FEF, group, $F = 4.56$, $df = 1$, $p = .03$, and condition, $F = 3.70$, $df = 3$, $p = .01$.: DLPFC, group, $F = 7.84$, $df = 1$, $p = .005$, hemisphere, $F = 15.3$, $df = 1$, $p = .0001$, and group by condition by hemisphere, $F = 6.83$, $df = 3$, $p = .0002$; PPC, group, $F = 5.02$, $df = 1$, $p = .02$.
Post-hoc analysis:
* Simple saccade vs. Rest: $t = -3.37$, $p = .01$; Reflexive saccade vs. Rest: $t = -4.33$, $p = .008$; Volitional saccade vs. Rest: $t = -4.38$, $p = .003$.
** Volitional saccade vs. Rest: $t = -3.49$, $p = .02$.

The FEF showed a significant increase in controls but no significant increase in the schizophrenic patient. The left DLPFC was activated during volitional saccade only in normal controls.

The rCBF changes in the FEF, DLPFC, PPC during task performance in the healthy and the schizophrenic groups are shown **(Table 4)**. The FEF showed a significant increase under all 3 task conditions in controls but no significant increase in the schizophrenic group **(Figure 8)**. Four-way ANOVA revealed a group by condition by hemisphere interaction, with

the relative rCBF during volitional saccade the highest under all conditions in the left DLPFC in the control group but no change in schizophrenic group.

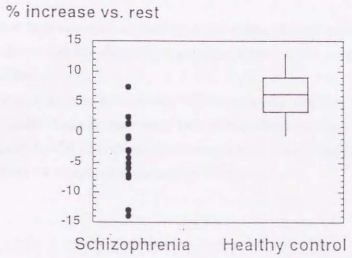
Figure 8 FEF activation in schizophrenia vs. healthy volunteers during 3 task conditions. Values are rCBF percent increase compared to the baseline condition. SD and SE are indicated. Schizophrenia showed lower activation during saccadic task.



Left DLPFC percent increase during volitional saccade in schizophrenics and in healthy volunteers (Figure 9). Schizophrenics clearly showed less activation.

Figure 9 The left DLPFC percent increase during volitional saccade in schizophrenics and in healthy volunteers

Healthy control's mean, SD, SE are shown. Values are rCBF percent increase compared to the baseline condition.



The percent of rCBF increase relative to the resting rCBF was significantly greater during volitional saccade (7.61%) than that under any other condition. Analysis of the percent increase in the bilateral DLPFC and PPC under saccade conditions revealed a significant correlation between the left DLPFC and the left PPC ($r = 0.97$; $p<0.001$), and the right DLPFC and the right PPC ($r = 0.97$; $p<0.001$) during volitional saccade. A similar correlation was not observed in the schizophrenic group (**Table 5**).

Table 5 The significant rCBF coactivation among bilateral FEF, DLPFC, and PPC during task performance.

Cut off level was $r>0.6$ and $p<0.01$.

condition	coactivation region	correlation coefficient
Healthy Volunteers		
Simple saccade	Lt-DLPFC vs. Rt-DLPFC	r=0.78*
Reflexive saccade	None	
Volitional saccade	Lt-DLPFC vs. Lt-PPC	r=0.97**
	Rt-DLPFC vs. Rt-PPC	r=0.97**
Schizophrenia		
Simple saccade	None	
Reflexive saccade	Lt-FEF vs. Rt-FEF	r=0.66*
Volitional saccade	None	

(* $p<0.01$; ** $p<0.001$)

Medication effect

No significant activation difference for each condition was indicated in comparison between unmedicated and medicated group (ANOVA, medication by region by hemisphere).

Regional activation and the clinical variables

The difference between positive and negative schizophrenic patients, the chronicity and severity of the illness did not show any significant effect on the normalized rCBF in the ROIs under 4 conditions.

In the correlational analysis between the BPRS and SANS item score and the normalized rCBF in the ROIs under 4 conditions, only two relationships reached a significant level. Those were, 1) alogia vs. left DLPFC during the resting state (r=-0.62) and 2) uncooperativeness vs. right DLPFC during the simple saccade task (r=0.61).

5.4 Comment

In schizophrenia who were reported to make more errors during antisaccade task (**Fukushima et al., 1988**), task performance was almost complete. This was primarily because in our task paradigm two laterally placed targets would have been spatially predictable or remembered. Since we did not find any significant error, the present activation findings could not be attributed to incomplete task execution.

In the analysis of the relationship between symptomatology and blood flow, we observed the negative correlation ($r = -0.62$, $p < .01$) between resting state left DLPFC rCBF and the severity of Alogia (Poverty of Speech and Thought) in a category of SANS. This was concordant with the findings of Dolan and Hammersmith group who stressed on the state dependency of the left DLPFC resting state rCBF related to psychomotor retardation or poverty of speech in schizophrenia and depression (**Bench et al., 1993**; **Dolan et al., 1993**).

6. GENERAL DISCUSSION

Coupling

In this study, we found a linear relationship between the relative rCBF by O-15 water PET and the relative rCMRglu by F-18 FDG PET during resting state in 3 unmedicated schizophrenic patients. During simple saccade a linear relationship between the relative rCBF and the relative rCMRglu was also established in medicated patients. There was no difference between those relationships among subjects.

Sokoloff and his colleagues showed a tight coupling between rCBF and rCMRglu in rats during resting state applying quantitative autoradiographic method using C-14-iodoantipyrine as a blood flow tracer and C-14-2-deoxyglucose as a probe to a glucose utilization (**Sokoloff et al., 1977; Sokoloff, 1978**). There were human coupling PET studies (**Baron et al., 1986; Hatazawa et al., 1988**), both of which showed a loose correlation.

In terms of coupling in an activated state, an double labelled autoradiographic method were applied in rats during tactile stimulation to show that the same column structure of 375-500 mm was found as a neuroanatomical topography both for CBF and CMRglu (**Greenberg et al., 1979**). In human with PET, continuous visual stimulation with illuminating checkerboard showed 50 % increase vs. resting state in rCBF and in rCMRglu, but only 5 % increase $rCMRO_2$ (**Fox et al., 1988**). This discrepancy between blood flow increase and oxygen utilization increase was also found in the same worker's tactile stimulation study (**Fox et al., 1986**). It is difficult to do a double labelled autoradiographic PET study in man. In these human studies including ours, rCBF and rCMRglu were determined at a different time point, which was a limitation of the methodology. In addittion, rCBF was determined by two minutes scan, besides rCMRglu was determined by 68 minutes scan. It was questioned whether we could compare two minutes and 68 minutes period at rest or when performing saccadic task in a strict sense. It was another limitation.

In this study we compared not absolute but relative values of rCBF and rCMRglu. Thus we could not tell whether an overall rCBF and rCMRglu coupling mechanism in schizophrenia is different from that in healthy subjects. However, at least in this small cohort, there was no absolute value difference in either rCBF or rCMRglu between schizophrenia and healthy subjects (data not shown).

Regions of interest

In order to quantify PET data in terms of anatomical regions, there are three strategies (**Bohm et al., 1992**). The first is to draw ROIs directly onto the PET images and calculate the average signal of each ROI (Drawing anatomic ROIs in the image under study). That approach is relatively simple to perform. However, to determine the region anatomically, the precise knowledge of the brain anatomy is required. Additionally, that approach is not free from the

problem of the effect caused by the size and the location of the ROIs (that is partial volume effect).

The second is to use the subject's CT/MRI template by transferring the ROIs drawn on CT/MRI images onto PET images (Combining several modalities). The average signal of each ROI is then calculated. That approach seems to be accurate. However, because of the thickness of each PET image (in this study, 6.5 mm thick), it is theoretically impossible to transfer the cortical ROIs which are drawn on the thinner (about 1 mm thick) MRI image since we cannot know how each gyrus runs within the PET image thickness. It is not free from the same problem of the size of the ROIs either.

The last is so-called stereotaxic method (Atlas based method). The stereotaxic method assumes interindividual variability of the human brain can be neglected in both an anatomical and a functional sense. Each individual brain can be either linearly or nonlinearly transformed into a standard brain (sometimes called as a brain atlas or a brain map), on which each subareas of the brain can be readily identified. Images of different individuals are transformed onto the brain atlas and then statistically processed as a group. Significant activation pinpoints are identified on the atlas with their magnitude usually shown as Z score or t-test value.

However the assumption has some weakness. Anatomical heterogeneity is one problem. As Steinmetz et al. **(Steinmetz et al., 1991; Rademacher et al., 1993)** wisely pointed out, even the primary sensory cortex could not be transferred onto the standard brain without any significant interindividual difference. To help desensitize the analys to variations in gyral anatomy and to improve the local signal-to-noise ratio, the original PET data were rescaled and smoothed with a two-dimentional filter with large (20mm) FWHM, which means their 'pinpoints' are always suffering large errors. Functional heterogeneity is another. If in different subjects some different points in a brain subarea serves the same function, the activation cannot be detected by this approach.

Considering these matters, in this study we chose the first approach with the aid of the second and the last. To control the effect of the size of the ROIs, the circle ROIs, sixteen millimeter in diameter, were set closely according to the cortical rim line. With the aid of the subject's CT/MRI image and the standard brain atlas **(Talairach & Tournoux, 1988)**, these ROIs were grouped into functional subareas. Multiple ROIs were always used for any subarea because they could reduce variability which was inevitable in choosing only one ROI **(Kuwert et al., 1992)**. Activation of a brain subarea was shown as an average rCBF value of the brain subarea, not as a maximal value within the subarea. We limited the number of the subareas in order to enhance the power of detection against multiple comparisons.

Location of FEF

The location of human FEF revealed by MRI-PET combination in this study was concordant with the previous results. Most studies except the first Xe-SPECT study by Melamed & Larsen applied the stereotaxic transformation method to show the location of

FEF (Melamed & Larsen, 1979). The stereotaxic method was advantageous in the sense of S/N, however, in the consequence of neglecting interindividual anatomical differences, might obscure the precise location of FEF. Actually the reported coordinate for FEF was so far apart from each other.

MRI-PET combination method like ours or Petit et al. (Petit et al., 1993; Lang et al., 1994) could overcome the mislocation problem, however, single study was not enough to show a significant increase against noise. The presented result was one representative case, and it was not clear whether this relatively large activation areas were all related to saccade execution, or including a spill-over from a narrower within this apparent activation.

Considering the results of Petit et al, which showed saccade-related activation in the precentral gyrus (Petit et al., 1993), the presented relatively large activation area designated as human physiologically-defined FEF might include two different components. One was so-called motor-related FEF located in area 6 on the precentral gyrus, and the other was more anterior part (area 8 and area 9), which could be involved in other functions such as attention. This anterior part that is on the middle frontal gyrus, was recently argued by Petrides et al. (Petrides et al., 1993) to be involved in monitoring external generated responses. In this study, we did not separate these supposed subareas. This could limit the interpretation of the following results.

To localize and clarify of these subareas in the human FEF, the use of functional MRI must be advantageous. It is because the method can relate the activation directly onto the subject's MRI slice and is free from a limitation of the number of the scans, while PET scans have the limit because of the radiation exposure limit.

Cortical control of saccades in healthy volunteers

In the previous studies (Melamed & Larsen, 1979; Fox et al., 1985; Petit et al., 1993; Paus et al., 1993; Lang et al., 1994; Anderson et al., 1994), neural control of saccades has already been studied in healthy subjects (Table 1). In this study, the frontal eye field (FEF) were activated during all the saccadic tasks. The result was in good agreement with the others. This was because FEF was engaged in saccade execution.

In our ROI analysis, left dorsolateral prefrontal cortex (DLPFC) activation was observed during volitional saccade task. However, other results from a stereotaxic analysis was not conclusive. Law et al. showed bilateral large DLPFC activations during antisaccade task (Law et al., 1995). Paus et al. showed a significant activation point during antistimulus saccade task in the right superior frontal sulcus (Paus et al., 1993). In the contrary, O'Driscoll et al. applied antisaccade task and reported no activation in DLPFC (O'Driscoll et al., 1995). As I pointed out in the method section, this in consistency might be explained by the fact that these stereotaxic method was not sensitive to a large and scatteringly distributed activation.

The DLPFC role in the saccade has been suggested as reflexive saccade suppression (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991) and as holding instructional information (Funahashi et al., 1993). Volitional saccade paradigm has both factors. In another view, the DLPFC activation

can be related to the subjects' intention (or sustained attention) to execute saccade tasks. Because even the volitional task was easy enough in a stochastic sense for the healthy subjects, it could have happened that they only kept performing the predetermined motor set (left...right...left...right). However, concerning the attentional aspect, in non-human primates DLPFC lesions generally improve performance on sensory discrimination tasks so that the DLPFC might not contribute to attention (Irle, 1990).

Laterality of the activation is a matter of a debate. There are lines of observation which showed the DLPFC activations during neuropsychological tasks in one hemisphere (Fletcher et al., 1995; Frith et al., 1991, 1992; Kapur et al., 1994; Pardo et al., 1991; Weinberger et al., 1986). Lack of DLPFC activation in one hemisphere did not always mean that the DLPFC in the hemisphere had nothing to do with the task performance. Possible activation in the hemisphere might have not reached a significant level in the study.

Recently the functional heterogeneity within the DLPFC has been drawing attention. Petrides et al. (Petrides et al., 1993) argued that mid-DLPFC was rather related to the monitoring of externally generated responses. Frith et al. (Frith et al., 1992) reported that the more lateral and inferior DLPFC related to the willed action. Kapur et al. (Kapur et al., 1994) argued that the left inferior DLPFC was involved in 'working with meaning', not in willed-action nor task-specific.

In this study, we did not analyze the lateral and inferior part of DLPFC, mainly consisted of the inferior frontal gyrus. That was because of the difficulties to identify the regions confidently in our method. However, this area might serve a different role from the DLPFC we analyzed.

Correlative alteration of the PPC during volitional saccade can be related to the role of this region as the center for spatial or motion vision (Mountcastle et al., 1975). Superior PPC activation was reported in memory or remembered saccade task (Petit et al., 1993b; Anderson et al., 1994) and in reflexive saccade task (Paus et al., 1993; Anderson et al., 1994). Our study did not show any PPC activation during the reflexive saccade task. It was mainly due to the difference of the task paradigm and the ROI strategy. Like our result, the PPC activation during antistimulus task was reported (Paus et al., 1993).

Subareas in the PPC are of interest as is in the DLPFC. Our ROI was located on the superior lobule, supramarginal gyrus and angular gyrus. This area included ROIs applied in other studies (Petit et al., 1993b; Paus et al., 1993), but was somewhat different from the activation location in the other study (Anderson et al., 1994). More detailed study should be conducted to clarify the functional heterogeneity within the PPC.

When focusing on the functional correlation patterns among regions, positive correlations between DLPFC and PPC in both hemispheres during volitional saccades were observed. There are reciprocal projection between DLPFC and PPC (Cavada and Goldman-Rakic, 1989) and in the rhesus monkey coactivation of PFC and inferior parietal cortex during working memory tasks (Friedman and Goldman-Rakic, 1994). This study's result is concordant with these results.

Some of the other important cortical regions in control of saccade such as the anterior

cingulate (Paus et al., 1993) and the supplementary motor area (SMA), some of which might overlap to the supplementary eye field (SEF) (Schlag and Schlag-Rey, 1987), were not analyzed in this study. It was also due to the difficulty to set a priori ROI reliably on those regions. Lack of these data limited the impact of the observation.

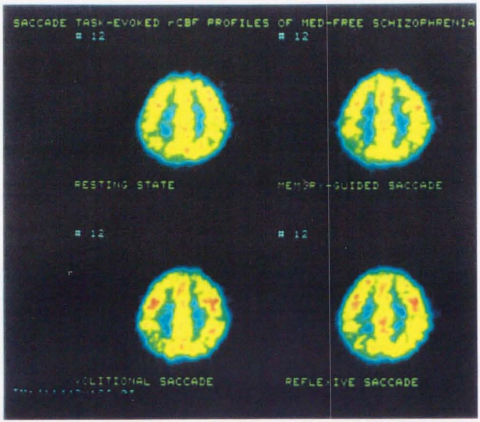
There was another limitation with these data. In saccade control, basal ganglia (Hikosaka, 1989), striatum and thalamus together with corticostriatal and corticothalamic pathways are important. However, current PET resolution and plane separation with O-15 water (8 mm in plane and 6.5 mm, respectively) is not sufficient for quantification of the basal ganglia, the striatum or thalamus. Thus this study could not afford the consideration on their role in control of saccades.

Cortical control of saccades in schizophrenia

Saccade control is critical in understanding the pathophysiology of schizophrenia. The smooth pursuit eye movement abnormalities and antisaccade distractions of schizophrenia can be related to the lack of normal inhibition of the saccadic system. Levin related this disinhibition to dysfunction of FEF mechanisms (Levin, 1984).

As was assumed by Levin, this study showed lack of FEF activation during saccadic tasks in schizophrenia as a group **(Figure 8)**, but not all the schizophrenic subject lacked the FEF activation. The following figure shows the one of the unmedicated schizophrenic subject, on whom the FEF activation during saccadic tasks could be seen **(Figure 10)**. No clinical characteristics could explain the individual activation difference. FEF of schizophrenia is thus dysfunctional, however, considering the individual difference, it may not be primarily impaired.

Figure 10 Unmedicated schizophrenic subject showed the FEF activation.



DLPFC of schizophrenia lacked activation during volitional saccade. This result was concordant with other rCBF studies involving prefrontal challenge tasks (**Andreasen et al., 1992; Berman, 1987; Berman et al., 1986, 1988, 1990, 1992, 1993 ; Catafau et al., 1994; Daniel et al., 1991; Franzén & Ingvar, 1975; Guenther et al., 1986, 1991; Gur et al., 1994; Ingvar & Philipson, 1977; Kawasaki et al., 1993; Parellada et al., 1994; Rubin et al., 1994; Weinberger et al., 1986, 1992**). A supposed prefrontal dysfunction of schizophrenia regarded as "*hypofrontality*" (**Ingvar & Franzén, 1974; Franzén & Ingvar, 1975**) might be highlightened when it was challenged (**Volkow et al., 1987**). The lack of DLPFC activation could be an expression of the dysfunction of the area.

The activation difference could not be explained by those patients' clinical features. It may be due to the number limitation of the observation. Neurochemical factors such as GABA or dopamine receptors activity in cortical areas rather than patients' clinical features may explain the activation pattern. In saccade control, D1-dopamine antagonist injection into DLPFC impaired delayed saccade task performance (**Sawaguchi et al., 1994**). Of interest, D1-dopamine receptor role in the pathophysiology of schizophrenia is now drawing an attention. There is a possibility that D1-dopamine receptor activity may explain the activation difference.

7. SUMMARY OF FINDINGS

ON THE METHOD

- Task-evoked rCBF paradigm (activation studies) by PET is applicable for schizophrenia with a reliability

ON THE NEURAL CONTROL OF SACCADES

- DLPFC, together with PPC is activated when saccade against a distractible stimuli is made.

- FEF and DLPFC in schizophrenia is not so activated when making saccades.

- No clinical variable can explain the cerebral activation difference in schizophrenia.

- Decrease of left DLPFC is related to the patient's severity of Alogia.

8. ACKNOWLEDGMENTS

I wish to express my profound gratitude to Professor Masaaki Matsushita, who is always cheerful and sound, encouraged me and gave me the oppotunity to work in this field home and abroad.

I'm sincerely grateful to Professor Shin-ichi Niwa for the kind interest and generosity which he has supported my work, whose scientific and human wisdom has encouraged me.

Multidisciplinary studies call for multiple tutors. I am particularly grateful that Professor Yasuhito Sasaki and Associate professor Jun-ichi Nishikawa were willing to support my work.

Dr. Toshimitsu Momose, a big brother, is the man who led and taught me in this field. I've had a lot of good time.

My co-workers and company, Dr. Iwao Sano, Dr. Shigemasa Katayama, Dr. Toru Nakajima, and Dr. Hidemasa Onai, who all started psychiatric residency and PET research at the same time, without whom, I couldn't have produced a bit of this work.

Dr. Toshiaki Watanabe for our memorable famous 3-D MRI-PET combination picture (though we two are often forgotten to be credited), and all the staff in the University of Tokyo PET center.

Dr. Junko Fukushima, for her scientific and intelligent comments.

My parents, brothers,

and last and forever, my wife Eri.

REFERENCES

Anderson TJ, Jenkins IH, Brooks DJ, Hawken MB, Frackowiak R SJ, & Kennard C (1994) Cortical control of saccades and fixation in man. a PET study. *Brain*, 117, 1073-1084.

Andreasen N (1983) *The scale for assessment of negative symptoms.* Iowa City: University of Iowa.

Andreasen N, Rezai K, Alligar R, Swayze I, Flaum M, Kirchner P, Cohen G, & O'Leary D (1992) Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the tower of London. *Arch Gen Psychiatry*, 49, 943-958.

Baron J, Rougemont D, Collard P, Bustany P, Bousser M, & Comar D (1986) Coupling between cerebral blood flow, oxygen consumption and glucose utilization: its study with positron emission tomography. *In Reivich M & Alavi A (Eds.), Positron Emission Tomography* (pp. 203-218). New York: Alan R Liss.

Bartlett, EJ, Barouche F, Brodie JD, Wolkin A, Angrist B, Rotrosen J, & Wolf AP (1991) Stability of resting deoxyglucose metabolic values in PET studies of schizophrenia. *Psychiatry Res*, 40(1), 11-20.

Bartlett EJ, Wolkin A, Brodie JD, Laska EM, Wolf AP, & Sanfilipo M (1991) Importance of pharmacologic control in PET studies: effects of thiothixene and haloperidol on cerebral glucose utilization in chronic schizophrenia. *Psychiatry Res*, 40(2), 115-24.

Bench C, Friston K, Brown R, Frackowiak R, & Dolan R (1993) Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. *Psychol Med*, 23, 579-590.

Berman K (1987) Cortical "stress tests" in schizophrenia: regional cerebral blood flow studies. *Biol Psychiatry*, 22, 1304-1326.

Berman K, Doran A, Pickar D, & Weinberger D (1993) Is the mechanism of prefrontal hypofunction in depression the same as in schizophrenia? Regional cerebral blood flow during cognitive activation. *Br J Psychiatry*, 162, 183-192.

Berman K, Illowsky B, & Weinberger D (1988) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. IV. Further evidence for regional and behavioral specificity. *Arch Gen Psychiatry*, 45, 616-622.

Berman K, Torrey E, Daniel D, & Weinberger D (1992) Regional cerebral blood flow in monozygotic twins discordant and concordant for schizophrenia. *Arch Gen Psychiatry*, 49, 927-934.

Berman K, & Weinberger D (1990) Lateralisation of cortical function during cognitive tasks: regional cerebral blood flow studies of normal individuals and patients with schizophrenia. *J Neurol Neurosurg Psychiatry*, 53, 150-160.

Berman K, Zec R, & Weinberger D (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. II. Role of neuroleptic treatment, attention, and mental effort. *Arch Gen Psychiatry*, 43, 126-135.

Bogerts B, Meertz R, & Schönfelt-Bausch R (1985) Basal ganglia and limbic system pathology in schizophrenia. *Arch Gen Psychiatry*, 42, 784-791.

Bohm C, Greitz T, & Thurfjell L (1992) The role of anatomic information in quantifying functional neuroimaging data. *J Neural Transm*, suppl 37, 67-78.

Brodie JD, Christman DR, Corona JF, Fowler JS, Gomez MF, Jaeger J, Micheels PA, Rotrosen J, Russell JA, Volkow ND, et al. (1984) Patterns of metabolic activity in the treatment of schizophrenia. *Ann Neurol*, S166-169.

Bruce CJ, & Goldberg ME (1985) Primate frontal eye fields. I.Single neurons discharging before saccades. *J Neurophysiol*, 53, 603-635.

Buchsbaum M, Haier R, Potkin S, Nuechterlein K, Bracha H, Katz M, Lohr J, Wu J, Lottenberg S, Jerabek P, et al. (1992) Frontostriatal disorder of cerebral metabolism in never-medicated scizophrenics. *Arch Gen Psychiatry*, 49, 935-942.

Buchsbaum M, Ingvar D, Kessler R, Waterz R, Cappelletti J, van-Kamen D, King A, Johnson J, Manning R, Flynn R, Mann L, Bunney Jr. W, & Sokoloff L (1982) Cerebral glucography with positron tomography. Use in normal subjects and in patients with schizophrenia. *Arch Gen Psychiatry*, 39, 251-259.

Buchsbaum M, Wu J, DeLisi L, Holcomb H, Hazlett E, Cooper-Langston K, & Kessler R (1987) Positron emission tomography studies of basal ganglia and somatosensory cortex neuroleptic drug effects: differences between normal controls and schizophrenic patients. *Biol Psychiatry*, 22, 479-494.

Buchsbaum MS (1990) The frontal lobes, basal ganglia, and temporal lobes as sites for schizophrenia. *Schizophr Bull*, 16(3), 379-389.

Buchsbaum MS, Cappelletti J, Ball R, Hazlett E, King AC, Johnson J, Wu J, & DeLisi LE (1984) Positron emission tomographic image measurement in schizophrenia and affective disorders. *Ann Neurol*, S157-165.

Buchsbaum MS, DeLisi LE, Holcomb HH, Cappelletti J, King AC, Johnson J, Hazlett E, Dowling ZS, Post RM, Morihisa J, et al. (1984) Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Arch Gen Psychiatry*, 41(12), 1159-1166.

Buchsbaum MS, Potkin SG, Marshall JF, Lottenberg S, Teng C, Heh CW, Tafalla R, Reynolds C, Abel L, Plon L, et al. (1992) Effects of clozapine and thiothixene on glucose metabolic rate in schizophrenia. *Neuropsychopharmacology*, 6(3), 155-163.

Buchsbaum MS, Potkin SG, Siegel BJ, Lohr J, Katz M, Gottschalk LA, Gulasekaram B, Marshall JF, Lottenberg S, Teng CY, et al. (1992) Striatal metabolic rate and clinical response to neuroleptics in schizophrenia. *Arch Gen Psychiatry*, 49(12), 966-974.

Burman D, & Segraves M (1994) Primate frontal eye field activity during natural scanning eye movements. *J Neurophysiol*, 71, 1266-1271.

Catafau A, Parellada E, Lomena F, Bernado M, Pavia J, Ros D, Setoain J, & Gonzalez-Monclus E (1994) Prefrontal and temporal blood flow in schizophrenia: resting and activation technetium ^{99m}-TcHMPAO SPECT patterns in young neuroleptic-naive patients with acute disease. *J Nucl Med*, 35, 935-941.

Cavada C, & Goldman-Rakic P (1989) Posterior parietal cortex in rhesus monkey. I. Parcellation of areas based on distinctive limbic and sensory corticocortical connections. *J Comp Neurol*, 287, 393-421.

Cleghorn J, Franco S, Szechtman B, Kaplan R, Szechtman H, Brown G, Nahmias C, & Garnett E (1992) Toward a brain map of auditory hallucinations. *Am J Psychiatry*, 149, 1062-1069.

Cleghorn JM, Garnett ES, Nahmias C, Brown GM, Kaplan RD, Szechtman H, Szechtman B, Franco S, Dermer SW, & Cook P (1990) Regional brain metabolism during auditory hallucinations in chronic schizophrenia. *Br J Psychiatry*, 562-570.

Cleghorn JM, Garnett ES, Nahmias C, Firnau G, Brown GM, Kaplan R, Szechtman H, & Szechtman B (1989) Increased frontal and reduced parietal glucose metabolism in acute untreated schizophrenia. *Psychiatry Res*, 28(2), 119-133.

Cohen RM, Semple WE, Gross M, Nordahl TE, King AC, Pickar D, & Post RM (1989) Evidence for common alterations in cerebral glucose metabolism in major affective disorders and schizophrenia. *Neuropsychopharmacology*, 2(4), 241-254.

Corbetta M, Miezin F, Shulman G, & Petersen S (1993) A PET study of visuospatial attention. *J Neurosci*, 13, 1202-1226.

Daniel D, Weinberger D, Jones D, Zigun J, Coppola R, Handel S, Bigelow L, Goldberg T, Berman K, & Kleinman J (1991) The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia. *J Neurosci*, 11, 1907-1917.

DeLisi L, Buchsbaum M, Holcomb H, Dowling-Zimmerman S, Pickar D, Boronow J, Morihisa J, van Kammen D, Carpenter Jr. W, Kessler R, et al. (1985) Clinical correlates of decreased anteroposterior metabolic gradients in positron emission tomography (PET) of schizophrenic patients. *Am J Psychiatry*, 142, 78-81.

DeLisi L, Buchsbaum M, Holcomb H, Langston K, King A, Kessler R, Pickar D, Carpenter Jr. W, Morihisa J, Margolin R, et al. (1989) Increased temporal lobe glucose use in chronic schizophrenic patients. *Biol Psychiatry*, 25, 835-851.

DeLisi L, Holcomb H, Cohen R, Pickar D, Carpenter W, Morihisa J, King A, Kessler R, & Buchsbaum M (1985) Positron emission tomography in schizophrenic patients with and without neuroleptic medication. *J Cereb Blood Flow Metab*, 5, 201-206.

Dolan R, Bench C, Liddle P, Friston K, Frith C, Grasby P, & Frackowiak R (1993) Dorsolateral prefrontal cortex dysfunction in the major psychoses; symptom or disease specificity? *J Neurol Neurosurg Psychiatry*, 56, 1290-1294.

Early T, Reiman E, Raichle M, & Spitznagel E (1987) Left globus pallidus abnormality in never-medicated patients with schizophrenia. *Proc Natl Acad Sci USA*, 84, 561-563.

Farkas T, Wolf AP, Jaeger J, Brodie JD, Christman DR, & Fowler JS (1984) Regional brain glucose metabolism in chronic schizophrenia. A positron emission transaxial tomographic study. *Arch Gen Psychiatry*, 41(3), 293-300.

Ferrier D (1875) Experiments on the brain of monkeys. *Philos Trans R Soc Lond B Biol Sci*, 165, 433-488.

Fletcher P, Frith C, Grasby P, Shallice T, Frackowiak R, & Dolan R (1995) Brain systems for encoding and retrieval of auditory-verbal memory. An in vivo study in humans. *Brain*, 118, 401-416.

Fox P, Fox J, Raichle M, & Burde R (1985) The role of cerebral cortex in the generation of voluntary saccades: a positron emission tomographic study. *J Neurophysiol*, 54, 348-369.

Fox P, & Raichle M (1986) Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci U.S.A.*, 83, 1140-1144.

Fox P, Raichle M, Mintun M, & Dence C (1988) Nonoxidative glucose consumption during focal physiologic neural activity. *Science*, 471, 462-464.

Franzén G, & Ingvar D (1975) Absence of activation in frontal structures during psychological testing of chronic schizophrenics. *J Neurol Neurosurg Psychiat*, 38, 1027-1032.

Friedman H, & Goldman-Rakic P (1994) Coactivation of prefrontal cortex and inferior parietal cortex in working memory tasks revealed by 2DG functional mapping in the rhesus monkey. *J Neurosci*, 14, 2775-2788.

Friston KJ (1992) The dorsolateral prefrontal cortex, schizophrenia and PET. *J Neural Transm Suppl*, 79-93.

Friston KJ, Liddle PF, Frith CD, Hirsch SR, & Frackowiak RS (1992) The left medial temporal region and schizophrenia. A PET study. *Brain*, 115 (Pt 2), 367-382.

Frith C, Friston K, Liddle P, & Frackowiak R (1991) A PET study of word finding. *Neuropsychologia*, 29, 1137-1148.

Frith CD, Friston KJ, Liddle PF, & Frackowiak RS (1992) PET imaging and cognition in schizophrenia. *J R Soc Med*, 85(4), 222-224.

Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, & Kato M (1988) Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. *Biol Psychiatry*, 23, 670-677.

Fukushima J, Fukushima K, Miyasaka K, & Yamashita I (1994) Voluntary control of saccadic eye movement in patients with frontal cortical lesions and parkinsonian patients in comparison with that in schizophrenics. *Biol Psychiatry*, 36, 21-30.

Fukushima J, Morita N, Fukushima K, Chiba T, Tanaka S, & Yamashita I (1990) Voluntary control of antisaccadic eye movements in schizophrenic and affective disorders. *J. Psychiatr Res*, 24, 9-24.

Funahashi S, Bruce C, & Goldman-Rakic P (1989) Mnemonic coding if visual space in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol*, 61, 331-349.

Funahashi S, Bruce C, & Goldman-Rakic P (1991) Neural activity related saccadic eye movements in the monkey's dorsolateral prefrontal cortex. *J Neurophysiol*, 65, 1464-1483.

Funahashi S, Chafee M, & Goldman-Rakic P (1993) Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature*, 365, 753-756.

Fuster J (1989) *The prefrontal cortex*. (2nd. ed.). NY: Raven press.

Gaymard B, Pierrot-Deseilligny C, & Rivaud S (1990) Impairment of sequences of memory-guided saccades after supplementary motor area lesions. *Ann Neurol*, 28, 622-626.

Goldman-Rakic P, & Friedman H (1991) The circuitry of working memory revealed by anatomy and metabolic imaging. *In Levin H, Eisenberg H, &Benton A (Eds.), Frontal lobe function and dysfunction.* (pp. 72-91). NY: Oxford UP.

Gordon C, Frazier J, McKenna K, Giedd J, Zametkin A, Zahn T, Hommer D, Hong W, Kaysen D, Albus K, et al. (1994) Childhood-onset schizophrenia: an NIMH study in progress. *Schizophr Bull*, 20, 697-712.

Greenberg J, Hand P, Sylvestro A, & Reivich M (1979) Localized metabolic-flow couple during functional activity. *Acta Neurol Scand*, 60(suppl2), 12-13.

Guenther W, Brodie J, Bartlett E, Dewey S, Henn F, Volkow N, Alper K, Wolkin A, Cancro R, & Wolf A (1994) Diminished cerebral metabolic response to motor stimulation in schizophrenics: a PET study. *Eur Arch Psychiatry Clin Neurosci*, 244, 115-125.

Guenther W, Moser E, Mueller-Spahn F, von Oefele K, Buell U, & Hippius H (1986) Pathological cerebral blood flow during motor function in schizophrenic and endogenous depressed patients. *Biol Psychiatry*, 21, 889-899.

Guenther W, Moser E, Petsch R, Brodie J, Steinberg R, & Streck P (1989) Pathological cerebral blood flow and corpus callosum abnormalities in schizophrenia: relations to EEG mapping and PET data. *Psychiatry Res*, 29, 453-455.

Guenther W, Petsch R, Steinberg R, Moser E, Streck P, Heller H, Kurtz G, & Hippius H (1991) Brain dysfunction during motor activation and corpus callosum alterations in schizophrenia measured by cerebral blood flow and magnetic resonance imaging. *Biol Psychiatry*, 29, 535-555.

Guitton D, Buchtel H, & Douglas R (1985) Frontal lobe lesion in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp Brain Res*, 58, 455-472.

Gur R, Jaggi J, Shtasel D, Ragland J, & Gur R (1994) Cerebral blood flow in schizophrenia: effects of memory processing on regional activation. *Biol Psychiatry*, 35, 3-15.

Gur R, Resnick S, Alavi A, Gur R, Caroff S, Dann R, Silver F, Saykin A, Chawluk J, Kushner M, et al. (1987) Regional brain function in schizophrenia. I. A positron emission tomogrphy study. *Arch Gen Psychiatry*, 44, 119-125.

Gur R, Resnick S, Gur R, Alavi A, Caroff S, Kushner M, & Reivich M (1987) Regional brain function in schizophrenia. II. Repeated evaluation with positron emission tomography. *Arch Gen Psychiatry*, 44, 126-129.

Gur RE, Resnick SM, & Gur RC (1989) Laterality and frontality of cerebral blood flow and metabolism in schizophrenia: relationship to symptom specificity. *Psychiatry Res*, 27(3), 325-334.

Hamacher K, Cohenen H, & Stocklin G (1986) Efficient stereospecific synthesis of no-carrier-added 2-[^{18}F]fluoro-2deoxy-D-glucose using aminopolyether supported nuleophilic substitution. *J Nucl Med*, 27, 235-238.

Hatazawa J, Ito M, Matsuzawa T, Ido T, & Watanuki S (1988) Measurement of the ratio fo cerebral oxygen consumption to glucose utilization by positron emission tomography : its consistency with the values determined by the Kety-Schmidt method in normal volunteers. *J. Cereb Blood Flow Metab*, 8, 426-432.

Hazlett E, Dawson M, Buchsbaum M, & Nuechterlein K (1993) Reduced regional brain glucose metabolism assessed by positron emission tomography in electrodermal nonresponder schizophrenics: a pilot study. *J Abnorm Psychol*, 102, 39-46.

Herscovitch P, Markham J, & Raichle M (1983) Brain blood flow measured with intravenous $H_2^{15}O$. Theory and error analysis. *J Nucl Med*, 24, 782-798.

Hikosaka O (1989) Role of basal ganglia in saccades. *Rev Neurol (Paris)*, 145, 580-586.

Holzman P (1987) Recent studies of psychophysiology in schizophrenia. *Schizophr Bull*, 13, 49-75.

Holzman P, Proctor L, & Hughes D (1973) Eye tracking pattern in schizophrenia. *Science*, 181, 179-181.

Iida H, Kanno I, Miura S, Murakami M, Takahashi K, & Uemura K (1986) Error analysis of a quantitative cerebral blood flow measurement using $H_2^{(15)}O$ autoradiography and positron emission tomography, with respect to the dispersion of the input function. *J Cereb Blood Flow Metab*, 6(5), 536-545.

Iida H, Miura S, Kanno I, Murakami M, Takahashi K, Uemura K, Hirose Y, Amano M, Yamamoto S, & Tanaka K (1989) Design and evaluation of HEADTOME-IV, a whole body positron emission tomograph. *IEEE Trans Nucl Sci*, NS-36, 1003-1010.

Ingvar D, & Franzén G (1974) Distribution of cerebral activity in chronic schizophrenia. *Lancet*, II, 1484-1486.

Ingvar D, & Philipson L (1977) Distribution of cerebral blood flow in the dominant hemispheric during motor ideation and motor performance. *Ann Neurol*, 2, 230-237.

Irle E (1990) An analysis of the correlation of lesion size, localization and behavioural effects in 283 lesion studies of cortical and subcortical lesions in old world monkeys. *Brain Res Rev*, 15, 181-213.

Jernigan TL, Sargent T, Pfefferbaum A, Kusubov N, & Stahl SM (1985) ^{18}Fluorodeoxyglucose PET in schizophrenia. *Psychiatry Res*, 16(4), 317-329.

Kaplan R, Szechtman H, Franco S, Szechtman B, Nahmias C, Garnett E, List S, & Cleghorn J (1993) Three clinical syndromes of schizophrenia in untreated subjects: relation to brain glucose activity measured by positron emission tomography (PET). *Schizophr Res*, 11, 47-54.

Kapur S, Rose R, Liddle P, Zipursky P, Brown G, Stuss D, Houle S, & Tulving E (1994) The role of the left prefrontal cortex in verbal processing: semantic processing or willed action. *Neuroreport*, 5, 2193-2196.

Kawasaki Y, Maeda Y, Suzuki M, Urata K, Higashima M, Kiba K, Yamaguchi N, Matsuda H, & Hisada K (1993) SPECT analysis of regional cerebral blood flow changes in patients with schizophrenia during the Wisconsin Card Sorting Test. *Schizophr Res*, 10, 109-116.

Kishimoto H, Kuwahara H, Ohno S, Takazu O, Hama Y, Sato C, Ishii T, Nomura Y, Fujita H, Miyauchi T, et al. (1987) Three subtypes of chronic schizophrenia identified using ^{11}C-glucose positron emission tomography. *Psychiatry Res*, 21(4), 285-92.

Kling A, Metter E, Riege W, & Kuhl D(1986) Comparison of PET measurement of local brain glucose metabolism and CAT measurement of brain atrophy in chronic schizophrenia and depression. *Am J Psychiatry*, 143, 175-180.

Kuwert T, Sures T, Herzog H, Loken M, Hennerici M, Langen K, & Feinendegen L (1992) On the influence of spatial resolution and the size and form of regions of interest on measurement of regional cerebral metabolism by positron emission tomography. *J Neural Transm*, suppl 37, 53-66.

Lang W, Petit L, Höllinger P, Pietrzyk U, Tzourio N, Mazoyer B, & Berthoz A (1994) A positron emission tomography study of oculomotor imagery. *Neuroreport*, 5, 921-924.

Law I, Svarer C, & Paulson O (1995) A characterization of cortical responses during the performance of reflexive and antisaccadic eye movements. *J Cereb Blood Flow Metab*, 15, s863.

Levin S (1984) Frontal lobe dysfunctions in schizophrenia-I. eye movement impairments. *J Psychiat Res*, 18, 27-55.

Levy A, Gomez-Mont F, Volkow N, Corona J, Brodie J, & Cancro R (1992) Spatial low frequency pattern analysis in positron emission tomography: a study between normals and schizophrenics. *J. Nucl Med*, 33, 287-295.

Liddle PF, Friston KJ, Frith CD, Hirsch, SR, Jones T, & Frackowiak RS (1992) Patterns of cerebral blood flow in schizophrenia. *Br J Psychiatry*, 179-186.

Mazziotta JC, Huang SC, Phelps, ME, Carson RE, MacDonald NS, & Mahoney K (1985) A noninvasive positron computed tomography technique using oxygen-15--labeled water for the evaluation of neurobehavioral task batteries. *J Cereb Blood Flow Metab*, 5(1), 70-78.

Melamed E, & Larsen B (1979) Cortical activation pattern during saccadic eye movements in humans: Localization by focal cerebral blood flow increases. *Ann Neurol*, 5, 79-88.

Mountcastle V, Lynch J, Georgopoulus A, Sakata H, & Acuna C (1975) Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *J Neurophysiol*, 38, 871-908.

Nakashima Y, Momose T, Sano I, Katayama S, Nakajima T, Niwa SI & Matsushita M (1994) Cortical control of saccade in normal and schizophrenic subjects: a PET study using a task-evoked rCBF paradigm. *Schizophr Res*, 12, 259-264.

O'Driscoll G, Alpert N, Matthysse S, Levy D, Rauch S, & Holzman P (1995) Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography. *Proc Natl Acad Sci USA*, 92, 925-929.

Pardo J, Fox P, & Raichle M (1991) Localization of a human system for sustained attention by positron emission tomography. *Nature*, 349, 61-64.

Parellanda E, Catafau A, Bernard M, Lomena F, Gonzalez-Monclus E, & Setoain J (1994) Prefrontal dysfunction in young acute neuroleptic-naive schizophrenic patients: a resting and activation SPECT study. *Psychiatry Res*, 55, 131-139.

Park S, & Holzman P (1993) Association of wrking memory deficit and eye tracking dysfunction in schizophrenia. *Schizophr Res*, 11, 55-61.

Paus T, Petrides M, Evans A, & Meyer E (1993) Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. *J Neurophysiol*, 70, 453-469.

Petit L, Orssaud C, Lang W, Pietrzyk U, Hollinger P, Tzourio N, Raynaud L, Mazoyer B, & Berthoz A (1993) PET activations of voluntary, memorized and imagined saccades. *J. Cereb Blood Flow Metab*, 13(Suppl 1), S535.

Petit L, Orssaud C, Tzourio N, Salamon G, Mazoyer B, & Berthoz A (1993) PET study of voluntary saccadic eye movements in humans: Basal ganglia-thalamocortical system and cingulate cortex involvement. *J Neurophysiol*, 69, 1009-1017.

Petrides M, Alivisatos B, Meyer E, & Evans,A (1993) Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proc Natl Acad Sci USA*, 90, 878-882.

Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, & Kuhl DE (1979) Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxyglucose : Validation of method. *Ann Neurol*, 6, 371-388.

Pierrot-Deseilligny C, Israël I, Berthoz A, Rivaud S, & Gaymard B (1993) Role of the different frontal lobe areas in the control of the horizontal component of memory-guided saccades in man. *Exp Brain Res*, 95, 166-171.

Potkin S, Buchsbaum M, Jin Y, Tang C, Telford J, Friedman G, Lottenberg S, Najafi A, Gulasekaram B, Costa J, et al., (1994) Clozapine effects on glucose metabolic rate in striatum and frontal cortex. *J Clin Psychiatry*, 55 Suppl B, 63-66.

Rademacher J, Caviness JVS, Steinmetz H, & Galaburda A (1993) Topographical variation of the human primary cortices: Implications for neuroimaging, brain mapping, and neurobiology. *Cereb Cortex*, 3, 313-329.

Resnick S, Gur R, Alavi A, Gur R, & Reivich M (1988) Positron emission tomography and subcortical glucose metabolism in schizophrenia. *Psychiatry Res*, 24, 1-11.

Rosse R, Schwartz B, Kim S, & Deutsch S (1993) Correlation between antisaccade and Wisconsin card sorting test performance in schizophrenia. *Am J Psychiatry*, 150, 333-335.

Rubin P, Hemmingsen R, Holm S, Moller-Madsen S, Hertel C, Povlsen U, & Karle A (1994) Relationship between brain structure and function in disorders of the schizophrenic spectrum: single photon emission computerized tomography, computerized tomography and psychopathology of first episodes. *Acta Psychiatr Scand*, 90, 281-289.

Russo G, & Bruce C (1994) Frontal eye field activity preceeding aurally guided saccades. *J Neurophysiol*, 71, 1250-1253.

SAS Institute Inc. (1987) *SAS 6.03*. In Cary, NC: SAS Institute Inc.

Satoh K, Narita M, Someya T, Fukuyama H, & Yonekura Y (1993) Functional brain imaging of a catatonic type of schizophrenia: PET and SPECT studies. *Jpn J Psychatry Neurol*, 47, 881-885.

Sawaguchi T, & Goldman-Rakic P (1994) The role of D1-dopamine receptor in working memory: Local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. *J Neurophysiol*, 71, 515-528.

Schiller P, True S, & Conway J (1980) Deficits in eye movements following frontal eye field and superior colliculus ablations. *J Neurophysiol*, 44, 1175-1189.

Schlag J, & Schlag-Rey M (1987) Evidence for a supplementary eye field. *J. Neurophysiol*, 57, 179-200.

Schroder J, Buchsbaum M, Siegel B, Geider F, Haier R, Lohr J, Wu J, & Potkin S (1994) Patterns of cortical activity in schizophrenia. *Psychol Med*, 24, 947-955.

Schroder J, Buchsbaum M, Siegel B, Geider F, & Niethammer R (1995) Structural and functional correlates of subsyndromes in chronic schizophrenia. *Psychopathology*, 28, 38-45.

Sereno A, & Holzman P (1995) Antisaccades and smooth pursuit eye movements in schizophrenia. *Biol Psychiatry*, 37, 394-401.

Sheppard G, Gruzelier J, Manchanda R, Hirsch S, Wise R, Frackowiak R, & Jones T (1983) ^{15}O positron emission tomographic scanning in predominantly never-treated acute schizophrenic patients. *Lancet*, 2, 1448-1452.

Siegel Jr. B, Buchsbaum M, Bunney Jr. W, Gottschalk L, Haier R, Lohr J, Lottenberg S, Najafi A, Nuechterlein K, Potkin S, et al. (1993) Cortical-striatal-thalamic circuits and brain glucose metabolic activity in 70 unmedicated male schizophrenic patients. *Am J Psychiatry*, 150, 1325-1336.

Sokoloff L (1978) Local cerebral energy metabolism: its relationships to local functional activity and blood flow. *In Purves M, & Elliott K (Eds.), Ciba Foundation Symposium 56: Cerebral Vascular Smooth Muscle and Its Control*, (pp. 171-197). Amsterdam: Elsevier/Excepta Medica/North-Holland.

Sokoloff L, Reivich M, Kennedy C, DesRosiers M, Patlak C, Pettigrew K, Sakurada O, & Shinohara M (1977) The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure and normal values in the conscious and anesthetized albino rat. *J. Neurochem.*, 28, 897-916.

Steinmetz H, & Seitz R (1991) Functional anatomy of language processing: neuroimaging and the problem of individual variability. *Neuropsychol*, 29, 1149-1161.

Szechtman H, Nahmias C, Garnett E, Firnau G, Brown G, Kaplan R, & Cleghorn J (1988) Effect of neuroleptics on altered cerebral glucose metabolism in schizophrenia. *Arch Gen Psychiatry*, 45, 523-532.

Tamminga CA, Thaker GK, Buchanan R, Kirkpatrick B, Alphs LD, Chase TN, & Carpenter WT (1992) Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. *Arch Gen Psychiatry*, 49(7), 522-530.

Tarairach J, & Tournoux P (1988) *A co-planar stereotaxic atlas of a human brain*. Stuttgart: Thieme.

Thaker G, Nguyen J, & Tamminga C (1989) Increased saccadic distractibility in tardive dyskinesia: functional evidence for subcortical GABA dysfunction. *Biol Psychiatry*, 25, 49-59.

Volkow ND, Brodie JD, Wolf AP, Angrist B, Russell J, & Cancro R (1986) Brain metabolism in patients with schizophrenia before and after acute neuroleptic administration. *J Neurol Neurosurg Psychiatry*, 49(10), 1199-1202.

Volkow ND, Brodie JD, Wolf AP, Gomez MF, Cancro R, Van GP, Russell JA, & Overall J (1986) Brain organization in schizophrenia. *J Cereb Blood Flow Metab*, 6(4), 441-446.

Volkow ND, Levy A, Brodie JD, Wolf AP, Cancro R, Van GP, & Henn F (1992) Low cerebellar metabolism in medicated patients with chronic schizophrenia. *Am J Psychiatry*, 149(5), 686-688.

Volkow ND, Wolf AP, Van GP, Brodie JD, Overall JE, Cancro R, & Gomez MF (1987) Phenomenological correlates of metabolic activity in 18 patients with chronic schizophrenia. *Am J Psychiatry*, 144(2), 151-158.

Watanabe T, Momose T, Ohtake T, Kosaka N, Nishikawa J, & Sasaki Y (1990) *J Nucl Med*, 31, 817.

Weiler M, Buchsbaum M, Gillin J, Tafalla R, & Bunney Jr. W (1990) Explorations in the relationship of dream sleep to schiophrenia using positron emission tomography. *Neuropsychobiology*, 23, 109-118.

Weinberger D, Berman K, & Illowsky B (1988) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism. *Arch Gen Psychiatry*, 45, 609-615.

Weinberger D, Berman K, Suddath R, & Torrey E (1992) Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. *Am J Psychiatry*, 149, 890-897.

Weinberger D, Berman K, & Zec R (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. *Arch Gen Psychiatry*, 43, 114-124.

Widen L, Blomqvist G, Greitz T, Litton JE, Bergstrom M, Ehrin E, Ericson K, Eriksson L, Ingvar, DH, Johansson L, Nilsson JL, Stone-Elander S, Sedvall G, Wiesel F, & Wik G (1983) PET studies of glucose metabolism in patients with schizophrenia. *AJNR Am J Neuroradiol*, 4(3), 550-552.

Wiesel F, Wik G, Sjogren I, Blomqvist G, & Greitz T (1987) Altered relationships between metabolic rates of glucose in brain regions of schizophrenic patients. *Acta Psychiatr Scand*, 76, 642-647.

Wiesel F, Wik G, Sjogren I, Blomqvist G, Greitz T, & Stone-Elander S (1987) Regional brain glucose metabolism in drug free schizophrenic patients and clinical correlates. *Acta Psychiatr Scand*, 76, 628-641.

Wik G, Wiesel F, Sjogren I, Blomqvist G, Greitz T, & Stone-Elander S (1989) Effects of sulpiride and chlorpromazine on regional cerebral glucose metabolism in schizophrenic patients as determined by positron emission tomography. *Psychopharmacol(Berl)*, 97, 309-318.

Wik G, & Wiesel FA (1991) Regional brain glucose metabolism: correlations to biochemical measures and anxiety in patients with schizophrenia. *Psychiatry Res*, 40(2), 101-114.

Wolkin A, Angrist B, Wolf A, Brodie JD, Wolkin B, Jaeger J, Cancro R, & Rotrosen J (1988) Low frontal glucose utilization in chronic schizophrenia: a replication study. *Am J Psychiatry*, 145(2), 251-253.

Wolkin A, Jaeger J, Brodie JD, Wolf AP, Fowler J, Rotrosen J, Gomez MF, & Cancro R (1985) Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. *Am J Psychiatry*, 142(5), 564-571.

Wolkin A, Sanfilipo M, Angrist B, Duncan E, Wieland S, Wolf A, Brodie J, Cooper T, Laska E, & Rotrosen J (1994) Acute d-amphetaminne challence in schizophrenia: effects on cerebral glucose utilization and clinical symptomatology. *Biol Psychiatry*, 36, 317-325.

Wolkin A, Sanfilipo M, Wolf A, Angrist B, Brodie J, & Rotrosen J (1992) Negative symptoms and hypofrontality in chronic schizophrenia. *Arch Gen Psychiatry*, 49, 959-965.

この検査の目的はPETスキャンと呼ばれる技術により、脳の局所の機能的活動を測定することにあります。この検査は、あなた御自身の治療にすぐ役立たない場合もありますが、神経の働き方の病気における脳の代謝機能の変化の特徴を測定し、将来的には治療効果の判定や新しい治療、よりよい診断を発展させる際に重要です。

検査は次の手順でおこなわれます。
まず精神神経科外来診察室で診察を受けていただきます。
そのあと、医師とともに中央放射線部核医学部門ポジトロンCT室へと移動します。
入室後、検査のための補助的装置（脳波計など）を装着します。
次に、検査のために微量の放射能を有する水（$H_2{}^{15}O$）の溶液を左右いずれかの前腕の静脈から注射します。注射する水の放射能は一回につき最大30mCi（ミリキューリー）で、注射四回分の被曝は胸部エックス線撮影一回分による被曝とほぼ同じ値です。この物質の安全性は臨床試験で確認されております。
検査の間、左前腕の動脈に刺入設置した採血管から規則的な間隔で採血がおこなわれます。採血量は1回につき約50mlで、採血四回で献血約一回分（約200ml）です。
注射後90秒の間にPETによる撮影が数回おこなわれます。
およそ15分間の休憩の後、今度は簡単な指示に従っていただきながら、前回と同様の手順で注射と採血と撮影がおこなわれます。指示は、その度毎に担当医から告げられます。
一連の注射・採血・撮影は六回以下です。
検査は、開始から終了まで3ないし5時間かかります。
この検査が終了した後再度診察を受けていただきます。

この検査に伴う危険や不快については、以下のものがあります。
(1) 採血の際の不快および局所出血：採血管の刺入設置の際には、局所麻酔がおこなわれます。このときに不快を感じるかもしれません。また、採血管の設置にともない少量の出血を見ることがあり青黒い内出血の跡が残る可能性があります。しかし、これらの操作は熟練した医師によっておこなわれますので、そのような事はほとんど起こりません。
(2) 胎児への危険：妊娠可能年齢の女性には、胎児への潜在的危険があります。妊娠の可能性がある場合検査はおこないません。
(3) 放射線による発癌危険率：この検査による発癌危険率は胸部X線撮影による発癌危険率とほぼ同等です。

検査の結果は医師から直接説明されます。
検査は求めればいつでも中止することができます。
この検査を受けることを拒否なさったとしても治療上不利益を被ることはありません。
この検査を受けて何らかの支障が生じた際は、下記の主治医または担当医連絡先に速やかに連絡してください。

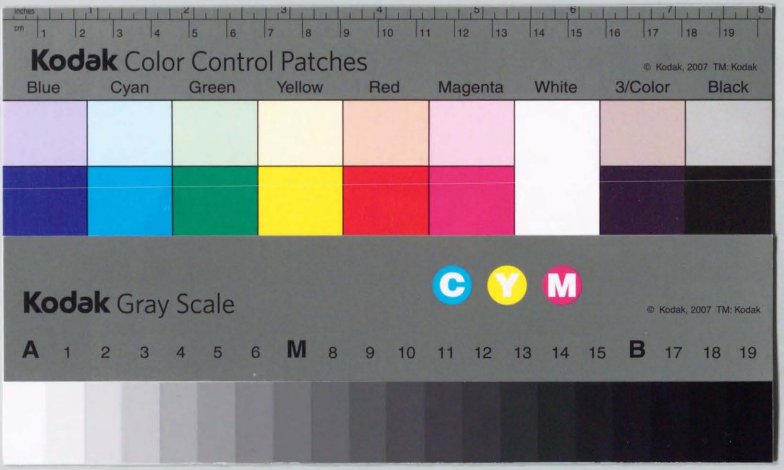
私は、以上の説明を平成　年　月　日　医師＿＿＿＿＿＿より受け、研究の主旨に賛同し検査の内容も十分理解したので、この検査を受けることに同意いたします。

平成　年　月　日
署名：＿＿＿＿＿＿＿＿＿＿印

以上の説明は　年　月　日　私が行ないました。

主治医：＿＿＿＿＿＿＿＿＿＿印
担当医：＿＿＿＿＿＿＿＿＿＿印

主治医、担当医連絡先：東京大学医学部付属病院精神神経科外来
電話：03-3815-5411
内線　3603、3604
住所：113　東京都文京区本郷7-3-1


inches
cm
Kodak Color Control Patches
© Kodak, 2007 TM: Kodak
Blue
Cyan
Green
Yellow
Red
Magenta
White
3/Color
Black
Kodak Gray Scale
C
Y
M
© Kodak, 2007 TM: Kodak
A 1 2 3 4 5 6 M 8 9 10 11 12 13 14 15 B 17 18 19