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<Study 1>
Impaired saccadic eye movements on stationary targets in patients with schizophrenia spectrum disorder.

<Study 2>
Saccadic eye movements and regional cerebral blood flow in schizophrenic patients.

Mié Matsui

<Study 1>

Impaired Saccadic Eye Movements on Stationary Targets in Patients with Schizophrenia Spectrum Disorder

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Summary

This study examined tracking eye movements on predetermined stationary targets in patients with schizophrenia spectrum disorder. The targets were 8 black points or 8 arabics' numbered points placed on the circumference of a circle. Self-paced eye movements during clockwise tracking of these points by 23 patients and 23 normal controls were recorded using an infrared eye-mark recorder. Eye movements were analyzed at two settings: first, when "fixation point" was defined as a point at which a gaze was held for at least 200 msec, and second, when held for at least 100 msec. The results indicated that at the 200-msec setting schizophrenic patients track with significantly fewer correct scores and more deviant scores than controls under black-point conditions. At the 100-msec setting, however, the correct scores of the patients were not significantly different from those of the controls, although the patients displayed more aberrant paths than the controls. The superfluous fixations in the patients improved significantly under numbered-point conditions, but patients still achieved lower correct scores than the controls. Four of the 23 patients exhibited centering (aberrant path directed toward the center point), suggesting immature control of eye movements under black-point conditions but not numbered-point conditions. These results suggest that some schizophrenic patients viewed the targets too quickly and that they have impaired directed attention, which can be improved by cues, and may have impaired preprogramming of eye movements, which is not improved by external cues.

Key words: Schizophrenia - Eye movements - Tracking test - Fixation time - Attention

Introduction

Eye movements consist mainly of two types of movements, smooth pursuit eye movements and saccadic eye movements. While smooth pursuit eye movements act to adjust eyeball velocity to target velocity, saccadic eye movements act to bring a visual target in the periphery of the visual field onto the fovea. Dysfunctions in smooth pursuit eye movements that track a moving object have been extensively studied in schizophrenic patients (Diefendorf and Dogde, 1908; Holzman, et al.1973), and more recently, impairment of saccadic movements in a step tracking task with a stationary target has also been reported (Schmid-Burgk et al. 1982,1983). In addition, several studies have examined exploratory eye movements in schizophrenic patients while they are viewing figures or pictures. When a static figure is being viewed, eye movements take the form of discrete periods of relative immobility (eye fixation) separated by quick jumps of the eye from place to place (saccades). Schizophrenic patients often exhibit fewer eye fixations, longer duration of eye fixation, shorter eye scanning length, or limited ranges of eye fixation on figures. In these studies various figures have been used such as a horizontal S-shaped figure (Moriya et al., 1972; Kojima et al., 1990), a Binet-Bobertag's picture (Gaebel et al., 1987), figures from the Benton Visual Retention Test (Tsunoda et al., 1992), and the WAIS Picture Completion Test (Matsui et al., 1993; Kurachi et al., 1994). Some of the characteristics seen in the patients seem to depend on the task used. For instance, basic eye movement parameters (e.g., number of fixations, mean duration of fixation) were not impaired, but the scanning styles of the patients were different from those of normal controls when situational pictures were used (Gaebel et al., 1987; Matsui et al., 1993). These tasks may involve many different factors, such as elementary afferent

information processing, perception of visuospatial relations, attention and cognitive strategy (top-down vs. bottom-up process), as well as the elementary motor aspects of saccades. Although these findings in exploratory eye movements seem to mainly represent the cognitive characteristics of the patients, elementary motor aspects should also be taken into account. In this respect, Reischies et al. (1988, 1989) reported disturbed eye movements guided by visuospatial cues in schizophrenic patients. In addition to direction perception, their task required other visuo-spatial elements, including peripheral target identification and distance determination.

The focus of the present study was to examine elementary motor aspects of eye movement in a simple saccadic tracking task using stationary targets. In most previous studies a fixation point has been defined as a point at which gaze is held for more than 200 msec (Gaebel et al., 1987; Reischies et al., 1988; Kojima et al., 1990; Matsui et al., 1993; Kurachi et al., 1994). In the present study, however, we have also included the results for 100 msec, because some subjects gazed at targets very quickly but correctly. The second aim of this study was to investigate the factor of attention in the saccadic tracking task. Shagass et al. (1976) provided evidence that defective eye tracking performance (smooth pursuit eye movements) can be improved by a simple procedure that requires the subject to read numbers on an oscillating pendulum. Therefore, we also used stationary targets on which numbers were placed.

Subjects and Methods

Subjects

Twenty-three patients with schizophrenia spectrum disorder recruited from the inpatient and outpatient clinics of Toyama Medical and Pharmaceutical University Hospital participated in

this study. Nineteen patients fulfilled DSM-III-R (American Psychiatric Association, 1987) criteria for schizophrenia, one for delusional disorder and three for schizotypal personality disorder (12 males and 11 females). Their mean age was 27.6± 9.2 (SD) years (range: 15-43 years), and their mean duration of illness was 6.4±7.0 years. The mean daily chlorpromazine-equivalent dosage was 503.1±805.0 mg. The control subjects consisted of 23 healthy volunteers (13 males and 10 females) and with a mean age of 26.7±5.6 years (range: 23-42 years). The purpose and procedures of the study were explained to the subjects, and their informed consent was obtained. Symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and selected items (delusion, conceptual disorganization, and hallucinatory behavior) from the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1986). Referring to Liddle's three syndrome hypothesis (1987), clinical symptoms were grouped under three subsyndromes: the total SANS score, the PANSS conceptual disorganization score, and the PANSS delusion plus hallucinatory behavior score.

Procedures

The subject sat on a chair equipped with a Nac V type eye-mark recorder, a device that detects corneal reflections of infrared light. The subject's head was held in place by a chin rest and lateral supports. As shown in Fig.1, two saccadic tracking figures were projected individually onto a translucent screen located 1.2 m directly in front of the subject's eyes. Eight points of 1 angular degree large were placed on the circumference of a circle having a diameter of 20 angular degrees (Fig.1). One figure contained 8 black points, while the other had 8 points with arabic numbers (1-8). The subject was first instructed to look at the center (+) of each figure. Then

he/she was asked to scan each of the 8 points once in clockwise order by moving the eyes. The order of the two figures was counterbalanced across subjects. Each task was self-paced. Eye movements during two tracking tasks were recorded on video tape using the eye-mark recorder, as described in the previous report (Kurachi et al., 1994). The eye-mark recorder consists of a helmet equipped with very small video cameras attached to the left and right sides and to the top of the helmet. The side cameras record the infrared lights reflected on the eyeballs. The camera on top of the helmet records figures on the screen. These recordings are stored in a video tape recording system. This technique enables us to see the eye-fixation points and eye movements on the figure simultaneously. Data for 2 figures recorded with the eye-mark recorder were analyzed by computer.

Measurement

The analysis of eye movement behavior was based on the following measures. We analyzed the data at two settings, first, when fixation point was defined as point at which a gaze held for at least 200 msec, and second, when held for at least 100 msec. Eye movements were assessed using the following parameters:

1. *Correct Score* composed of the number of target hits plus Normal Paths. The maximum possible score is 15 points.

1) *Target Hitting*: When a fixation hits a target, one point is scored. The maximum possible score is 8 points.

2) *Normal Path*: Normal saccade lines (straight lines from one point to the next point) are scored one point each. The maximum possible score is 7 points.

2. *Deviant Score* is composed of the number of superfluous fixations plus aberrant paths.

1) *Superfluous Fixation*: Some fixations occur elsewhere and do not hit a target. The total number of such events is the score.

2) *Aberrant Path*: A path deviating from the normal paths. The total number of such paths is the score. Paths directed toward the center point in aberrant paths are referred to as *Centering* and the number of centerings was included in the aberrant path score.

The cue effect was defined as attainment of a significantly higher correct score or lower deviant score under numbered-point conditions than black-point conditions.

Statistical analysis. Differences between eye movement parameters in controls and patients were examined using the Mann-Whitney U test. The Sign Test was performed for the effect of conditions within the same group of subjects. Fisher's exact test was performed for differences in frequency between groups on the correct score. Spearman's rank correlation test was used for correlations between eye movement parameters and clinical syndromes or drug dosage.

Results

Figure 2 shows the plots from three subjects which were selected as representative examples.

Analysis of Eye Movements at the 200-msec Setting

Table 1 shows the group means and standard deviations for eye movement parameters under both conditions (black points/numbered points) in the saccadic tracking task. At the 200-msec setting, the schizophrenic patients showed fewer correct scores ($P<0.05$), more deviant scores ($P<0.01$) and more superfluous fixations ($P<0.01$) than the normal controls under black-point conditions. The schizophrenic patients, but not the normal controls, exhibited a significant cue effect, that is, only the patients had fewer deviant scores ($P<0.05$) and fewer

superfluous fixations ($P<0.01$) under numbered-point conditions than under black-point conditions. The patients, however, still had fewer correct scores ($p<0.01$), fewer target hittings ($p<0.05$), fewer normal paths ($p<0.01$) and more aberrant paths ($p<0.05$) than the normal controls under numbered-point conditions.

Table 2 shows the number of subjects who achieved a perfect correct score (15 points) and who did not attain a perfect correct score. At the 200-msec setting, seventeen of the 23 normal controls attained a perfect correct score, while only 9 of the 23 patients attained a perfect correct score under black-point conditions ($p=0.0361$). Under numbered-point conditions, twenty of the 23 normals attained a perfect correct score, while only 10 of the 23 patients attained a perfect correct score ($p=0.0045$).

Four patients at the 200-msec setting exhibited centering under black-point conditions but not under numbered-point conditions. None of the normals showed centering under either conditions.

Analysis of Eye Movements at the 100-msec Setting

There were no significant differences between the correct scores, target hittings, or normal paths of the patients and the controls at the 100-msec setting, but the patients had more deviant scores ($p<0.05$) and superfluous fixations ($p<0.05$) than the controls under black-point conditions. A significant cue effect was seen in both the patients and normal controls, as they had more correct scores (patients, $p<0.05$; controls, $p<0.05$), more normal paths ($p<0.01$; $p<0.05$), and fewer deviant scores ($p<0.05$; $p<0.05$) under numbered-point conditions than under black-point conditions. The controls had also fewer aberrant paths ($p<0.05$) under numbered point conditions. The patients had more

aberrant paths ($p<0.05$) than the controls under numbered point conditions.

As shown in Table 2, at the 100-msec setting, twenty-one of the 23 normal controls and 16 of the 23 patients achieved a perfect score under numbered-point conditions, and there was no significant difference between the controls and the patients.

Five patients at the 100-msec setting exhibited centering under black-point conditions but not under numbered-point conditions. None of the normals showed centering under either conditions.

Comparison between eye movements at the 200-msec and 100-msec setting

Under black-point conditions, both the normal controls and the patients had more target hittings ($p<0.05$, $p<0.01$) at the 100-msec setting than at the 200-msec setting. However, both groups also had more deviant scores ($p<0.01$), more superfluous fixations ($p<0.01$) and more aberrant paths ($p<0.01$) at the 100-msec setting. Under numbered-point conditions, the patients had more correct scores ($p<0.01$), more target hittings ($p<0.01$), more normal paths ($p<0.01$), and more aberrant paths ($p<0.05$) at the 100-msec setting than at the 200-msec setting. Both the normal controls and the patients had more deviant scores ($p<0.01$ each) and more superfluous fixations ($p<0.01$ each) at the 100-msec setting than at the 200-msec setting.

Relationship of the eye movement parameters with clinical syndromes and neuroleptic dosage

There was no significant correlation between eye movement parameters and the three clinical syndromes scores.

Assessment of the effect of neuroleptics on eye movement parameters showed no significant correlation between eye movement parameters and chlorpromazine-equivalent dosage.

Discussion

In this study, eye fixation was analyzed at both 200-msec and 100-msec settings. It has been estimated that the duration of a complete eye movement cycle is approximately 230 msec, with 200 msec being the duration of fixation and 30 msec required for the movement itself (Russo, 1978). During eye fixation, information from the stimulus being fixated is presumably acquired for only the first 100 msec, while the rest of each fixation is probably spent computing where the next fixation will be made (Loftus, 1976). Consolidation of information may also take time (Inui and Miyamoto, 1981).

The results of this study revealed that patients with schizophrenia spectrum disorder track with slightly but significantly fewer correct scores than normal controls under black-point conditions at the 200-msec setting, and that perfect correct scores were obtained less frequently in patients (9 of 23) than in normal controls (17 of 23). The patients showed more superfluous fixations and deviant scores than normal controls under black-point conditions. Reischies et al. (1988) also demonstrated an increased number of fixations and multiple sequence repetitions at the 200-msec setting in schizophrenic patients in a saccadic tracking task on stationary targets. Thus, an increased number of fixations or superfluous fixations was observed in these stationary eye-tracking tasks in schizophrenic patients. In contrast, previous studies using situational pictures showed that schizophrenic patients had a normal number of fixations (Gaebel et al., 1987; Matsui et al., 1993). Furthermore, schizophrenic patients had been reported to exhibit fewer fixations in relatively simple figure tasks (Moriya et al., 1972; Kojima et al., 1990; Tsunoda et al., 1992). These differences among tasks should be assessed in the same subjects in the future.

At the 100-msec setting, the differences in correct scores between the controls and the patients were not statistically significant, and the number of the patients who achieved a perfect correct score was not significantly different from the number in the control group.

Differences between the patients and controls at the 100-msec setting were only seen in the deviant score item, however, these scores were higher at the 100-msec setting than at the 200-msec setting in both groups. These results indicate that some schizophrenic patients viewed the targets too quickly, i.e., their fixation time was more than 100 msec but less than 200 msec. Many normal controls, however, took more than 200 msec. If the latter part of the fixation time is spent computing the position of the next fixation, this may be one reason why some patients track with aberrant paths.

Several patients exhibited centering. Centering has been reported in normal children less than 7 years old, but it decreases as they grow up (Nomura and Noguchi,1973). Thus the centering in these patients may reflect immature control of their eye movements. Eye movements in schizophrenic patients may be easily triggered by peripheral events, most probably due to their poor ability to direct attention, as in children.

There was no evidence to suggest that medication was the cause of poor eye movements. Clinical syndromes were not significantly correlated with eye movements, but this study was performed in a relatively small sample and this should be reexamined with larger numbers of subjects, and comparisons should be made between the psychotic state and the remitted state.

As to the second aim of this study, the results provided evidence that defective saccadic eye-tracking performance, especially deviant scores, can be improved by using stationary targets on which numbers have been placed. Shagass et al.

(1976) reported that eye-tracking performance (smooth pursuit eye movement) is markedly improved in both patients and normals by replacing the fixation dot on the pendulum by numbers in order to maintain attention and aid focusing. Thus, additional stimuli, such as numbers, to direct attention had the same effect in smooth pursuit and saccadic eye tracking tasks. Shagass et al. (1976), however, showed that, although the eye tracking in schizophrenic patients improved to some degree, differences between schizophrenic patients and normals persisted under number-reading conditions. This residual impairment was called "involuntary inattention" by Shagass et al. (1976) (Holzman et al., 1976). In the present study, saccadic movements were also improved with a cue, but not completely. Under numbered-point conditions at the 200-msec setting, the number of patients who achieved a perfect correct score (10 of 23) was significantly less than in the controls (20 of 23), and the patients had lower correct scores and more aberrant paths than the controls. These results suggest that there are at least two components of impairment in the eye tracking task. The first component improved with cues to direct attention, but the second did not.

Schmid-Burgk et al. (1983) reported that schizophrenic patients exhibited more saccadic hypometria (undershooting of the target) than controls. Mather and Puchat (1983) also found that schizophrenic patients displayed an increased numbers of both hypometric and hypermetric (overshooting of the target) saccades than controls. Some of the impairments in the saccadic tracking task in the present study may be related to dysmetric saccades.

In saccadic tracking tasks, subjects should first identify target points. Their brains compute the distance to move the eyeball and then the signal to start movement is transmitted to the neurons. The programs for such eye movements are made before

movement starts, and since the movements are based on these programs, they are termed "preprogrammed movements". This operates on the basis of a feedforward regulatory mechanism. Once the movement starts, it cannot be voluntarily modified, so it is also called a ballistic movement (Russo, 1978; Komatsuzaki et al., 1985). In normals, there is little problem in identifying targets and making programs, leading to efficient performance. In patients, however, poor identification or maintenance of target points is likely to be the main cause of superfluous fixations and aberrant paths, because these features were improved by cues (numbers). The impairment that persists after the presentation of a cue may be accounted for by poor programming of eye movements. Further studies will be needed to clarify the neural mechanism of saccadic eye movements in schizophrenic patients.

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Table 1 Eye movements during a saccadic tracking task in controls and patients (mean ± SD)

Conditions	Eye movement parameters						
	Correct score	*Target hitting*	*Normal path*	Deviant score	*Superfluous fixation*	*Aberrant path*	*(Centering)*
200-ms setting							
Black point							
Normal controls	13.9±2.5	7.6±1.0	6.2±1.5	1.3±1.6	1.1±1.5	0.2±0.6	0
Schizophrenic patients	13.6±1.6*a	7.6±0.7	6.0±1.1	4.4±6.0**a	3.1±3.5**a	1.3±2.9	(0.1±0.5)
Numbered point							
Normal controls	14.7±0.9	7.9±0.3	6.8±0.6	0.7±1.1	0.7±1.1	0	0
Schizophrenic patients	13.4±2.3**a	7.3±1.0*a	6.0±1.4**a	2.1±3.3*b	1.5±2.5**b	0.6±1.1*a	0
100-ms setting							
Black point							
Normal controls	14.5±1.0	8.0±0*c	6.5±1.0	4.8±4.1**c	3.7±2.8**c	1.1±2.0**c	0
Schizophrenic patients	13.9±1.3	8.0±0**c	6.0±1.3	9.1±6.8*a;**c	6.7±4.0*a;**c	2.5±3.7**c	(0.2±0.5)
Numbered point							
Normal controls	14.8±0.6*b	8.0±0	6.8±0.6*b	3.3±2.7*b;**c	2.8±2.2**c	0.4±1.5*b	0
Schizophrenic patients	14.6±0.7*b;**c	7.9±0.3**c	6.7±0.6**b;**c	6.3±7.0*b;**c	5.1±5.1**c	1.2±2.1*a;*c	0

A perfect correct score is 15 points (number of target hits plus normal paths).

The deviant score equals the number of abberant paths plus superfluous fixations.

a Mann-Whitney U test, controls vs patients

b Sign Test, black-point conditions vs numbered-point conditions in the same group

c Sign Test, 200-ms setting vs 100-ms setting in the same group

** $P<0.01$, * $P<0.05$

Table 2 Numbers of subjects who attained a perfect correct score and less than a perfect correct score.

Condition	black points		numbered points	
Score	perfect(15 points)	less than perfect(<15)	perfect(15 points)	less than perfect(<15)
200-ms setting				
Controls	17	6	20	3
Patients	9*	14	10**	13
100-ms setting				
Controls	17	6	21	2
Patients	11	12	16	7

** P<0.01, * P<0.05 (Fisher's exact test on scores for controls and patients)

Legends

Fig. 1. A saccadic tracking task on 8 (A) black-point and (B) numbered-point target. The subject was instructed to look at the center (+) of the figure first. He/she was then asked to scan the 8 points clockwise, in order.

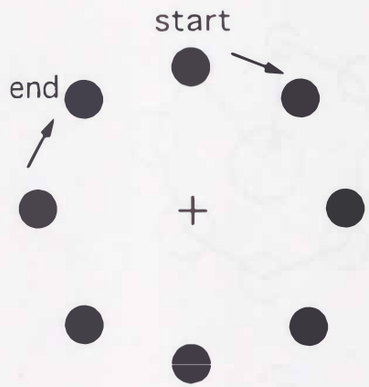
Fig. 2. Sequence of eye movements in a saccadic tracking task. A circle indicates a single fixation, and the size of the circle indicates the duration of fixation. The lines represent successive eye movements performed from the first to the last point of fixation. The upper figures are at the 200-msec setting and the lower figures are at the 100-msec setting.

(A) a normal control. This subject directed his gaze directly onto the targets, and the target hitting score was 8 points. His eye fixation also moved from one target to the next by normal saccade lines, and the normal path score was 7 points. Correct Score: 15 (Target Hitting: 8 plus Normal Path: 7) ; Deviant Score: 0 (Superfluous Fixation: 0 plus Aberrant Path: 0) in both settings.

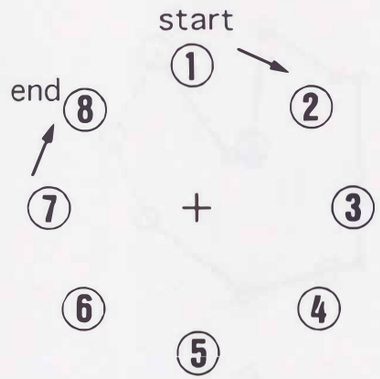
(B) a schizophrenic patient who omitted one target. Correct Score: 13 (Target Hitting: 7 plus Normal Path: 6) in the 200-msec setting and Correct Score: 15 (Target Hitting: 8 plus Normal Path: 7) in the 100-msec setting ; Deviant Score: 2 (Superfluous Fixation: 2 plus Aberrant Path: 0) in the 200-msec setting and Deviant Score: 3 (Superfluous Fixation: 3 plus Aberrant Path: 0) in the

100-msec setting.

(C) another schizophrenic patient who had a high deviant score. This patient's eye fixation moved toward the center twice. Correct Score: 12 (Target Hitting: 8 plus Normal Path: 4) ; Deviant Score: 18 (Superfluous Fixation: 8 plus Aberrant Path: 10, including Centering) in both settings.



A



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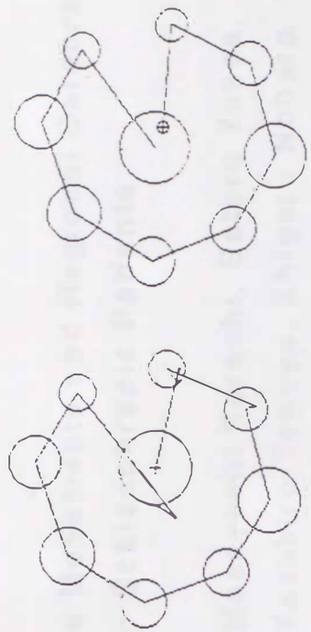
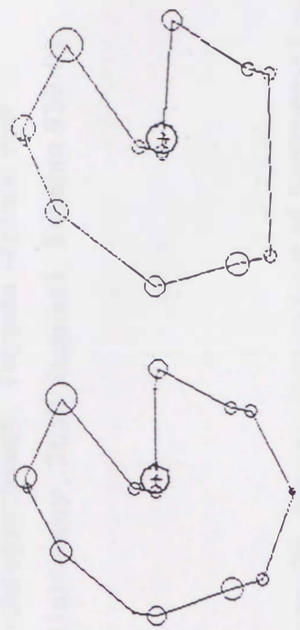
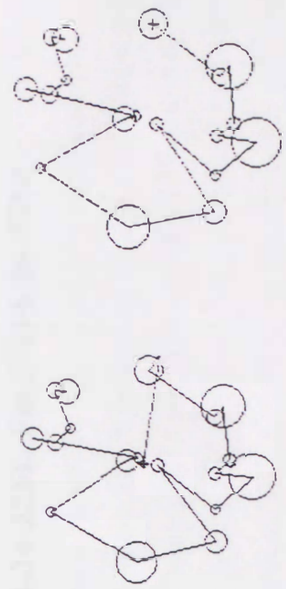


(A) a normal subject
(27-year-old man)



(B) a schizophrenic patient
(24-year-old woman)



(C) a schizophrenic patient
(18-year-old woman)

<Study 2>

Saccadic Eye Movements and Regional Cerebral Blood Flow in Schizophrenic Patients

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Summary

This study examined saccadic eye movements, using simple stationary targets, in schizophrenic patients. The targets were 8 black points or 8 arabic-numbered points placed in randomized order on the circumference of a circle. Self-paced eye movements during clockwise tracking of these points, by 23 patients and 23 controls, were recorded using an infrared eye-mark recorder. Then the relationship between the saccades and clinical syndromes was investigated. Finally, the relationship between the performance of the saccades and resting regional cerebral blood flow (rCBF) was examined using single photon emission computed tomography with 99mTc-hexamethyl propyleneamine oxime (HMPAO). The results indicate that patients track with significantly fewer correct scores and more deviant scores than controls, in agreement with our previous study. There were two groups of patients: an ordinary group who obtained a full target hitting score at a 200 ms setting and a fast group who obtained the full score at 100 ms but not at 200 ms. Some patients displayed significantly more hypermetria than controls. Significant correlations were found between alienation syndrome (auditory hallucination and disturbance of the self) and correct scores, or delusion syndrome and deviant score. With respect to relative rCBF, fast group patients showed significantly decreased rCBF in the left limbic and inferior parietal areas as compared with ordinary group patients. These findings suggest that some schizophrenic patients view the stationary targets too fast and this may be related to dysfunction in the limbic-parietal association area in the left hemisphere.

Key words: Schizophrenia - Eye movement - Regional cerebral blood flow -Clinical syndrome - Parietal lobe

Introduction

Several studies have indicated disturbance of saccadic eye movements in schizophrenic patients using a variety of tasks (Schmid-Burg et al 1982, 1983; Reichies et al.1988,1989; Fukushima et al.1990; Paus 1991; Park and Holzman 1992; Matsui and Kurachi 1995). Matsui and Kurachi (1995) examined elementary eye movements in a simple saccadic tracking task using stationary targets. It was found that schizophrenic patients track with significantly fewer correct scores and more deviant scores than controls, and that superfluous fixations in the patients improved significantly when numbered-points were placed on targets. In that study, under numbered point conditions, the patients showed fewer target hittings than controls when a fixation point had been defined as a point at which the gaze is held for more than 200-ms, but there was no significant difference between the patients and the controls at the 100-ms setting. That is, it was found that some patients viewed the targets too fast. This may possibly be due to the subjects being able to anticipate the next number because the arabic numbers were placed in order from 1 to 8. The first aim of the present study was to re-examine the experiment done by Matsui and Kurachi (1995), using numbered points placed in randomized order, in another cohort of patients. The second aim was to investigate the relationship between saccadic eye movements and clinical syndromes.

Saccades have been shown to be controlled by various cortical and subcortical regions. Some studies have reported changes in regional cerebral blood flow (rCBF) during various saccadic tasks in man (Melamed and Larsen 1979; Fox et al.1985; Frith et al.1992; Petit et al.1993; Paus et al.1993; Anderson et al.1994). Brain regions mentioned in these studies were the frontal lobes, frontal eye field, supplementary motor area, anterior cingulate,

parietal cortex, thalamus, basal ganglia, hippocampus, and cerebellum. In such studies on schizophrenic patients, Nakashima et al. (1994) reported that the left dorsolateral prefrontal cortex was not activated during volitional saccades in patients, but was activated in normal controls. The relationship between the eye movement parameters and resting rCBF in schizophrenic patients has also been reported. Tsunoda et al. (1992) showed that the mean duration of fixation on the Benton visual retention test was negatively correlated with rCBF in the left superior frontal area and left basal ganglia, and the mean scan path was positively correlated with the left superior frontal area. Matsui et al. (1993) reported that the number of "eye transfers" on eye movement from one element area of the figure to another in the WAIS picture completion test was positively correlated with rCBF in the left anterior cingulate and left thalamus. Thus, the third aim of this study was to examine the relationship between the performance of eye movements during a saccadic tracking task and resting rCBF in schizophrenic patients.

Subjects and Methods

Subjects

Twenty-three schizophrenic patients recruited from the inpatient and outpatient clinics of Toyama Medical and Pharmaceutical University Hospital participated in this study. All patients fulfilled DSM-III-R (American Psychiatric Association 1987) criteria for schizophrenia (10 males and 13 females) . Their mean age was 27.9±8.6 (SD) years (range: 15-43 years), and their mean duration of illness was 7.3±5.3 years. The mean daily chlorpromazine-equivalent dosage was 821.5±808.6 mg. The control subjects consisted of 23 healthy volunteers (14 males and 9 females) and with a mean age of 25.4

±3.9 years (range: 23-40 years). Neither age nor gender differed significantly between the patients and the controls. The purpose and procedures of the study were explained to the subjects, and their informed consent was obtained. Symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1984).

Assignment of syndrome scores

Syndrome scores were obtained by principal component analysis of symptom scores. Our previous study (Matsui et al. in preparation) found five principal components in 58 schizophrenics, including all patients participating in the present study: psychomotor poverty, alienation (auditory hallucination and disturbance of the self), delusion, disorganization, difficulty with behavior control. The principal component scores were employed as a measure of the severity of each syndrome.

Saccadic tracking procedure

The subject sat on a chair equipped with a Nac V type eye-mark recorder, a device that detects corneal reflections of infrared light. The subject's head was held in place by a chin rest and lateral supports. Two saccadic tracking figures were projected individually onto a translucent screen located 1.2 m directly in front of the subject's eyes. Eight points of 1 angular degree in size were placed on the circumference of a circle having a diameter of 20 angular degrees (Fig. 1). One figure contained 8 black points, while the other had 8 points with arabic numbers (1-8) in randomized order. The subject was first instructed to look at the center (+) of each figure. Then he/she was asked to scan each of the 8 points once in clockwise order by moving the eyes. The order of the two figures was counterbalanced across subjects. Each task was self-paced. Eye

movements during two tracking tasks were recorded on video tape using the eye-mark recorder. The recording system was as described in the previous report (Matsui and Kurachi 1995). This technique enables us to see the eye-fixation points and eye movements on the figure simultaneously. Data for two figures recorded with the eye-mark recorder were analyzed by computer.

Measurement of eye movement

The analysis of eye movement behavior was based on the following measures, as previously described by Matsui and Kurachi (1995). We analyzed the data at two settings; first, when the fixation point was defined as the point at which the gaze was held for at least 200 ms, and second, when the gaze was held for at least 100 ms. Eye movements were assessed using the following parameters:

1. *Correct Score* composed of the number of target hits plus Normal Paths. The maximum possible score is 15 points.

1) *Target Hitting*: When a fixation hits a target, a one point score is given. The maximum possible score is 8 points.

2) *Normal Path*: Normal saccade lines (straight lines from one point to the next point) are scored as one point each. The maximum possible score is 7 points.

2. *Deviant Score* is composed of the number of superfluous fixations plus aberrant paths.

1) *Superfluous Fixation*: Some fixations occur elsewhere and do not hit a target. The total number of such events is the score.

2) *Aberrant Path*: A path deviating from the normal paths. The total number of such paths is the score.

The cue effect was defined as attainment of a significantly higher correct score or lower deviant score under numbered-point conditions than black-point conditions.

In addition, eye movement errors were analyzed according to the following classification.

Omitting: Eye movements omitted a target.

Hypermetria: A fixation went at least 3 angular degrees beyond a target and then returned to the target.

Centering: Paths directed toward the center point.

Return: Paths returned to a point just anterior to the target.

Slipping: A fixation hit at least 3 angular degrees away from a target and thereafter went to the next target.

Superfluity: All superfluous fixations other than hypermetria, return, and centering.

Single photon emission computed tomography (SPECT)

Procedure

Measurements were taken in a dimly lit room with background noise from cooling fans. The subjects sat quietly with their eyes open for 10 min after the intravenous injection of 555 MBq (15 mCi) 99mTc-hexamethyl propyleneamine oxime (HMPAO). SPECT was performed with a three-head rotating gamma camera system (GCA9300A; Toshiba, Tokyo, Japan) by employing high resolution fan beam collimators combined with a minicomputer (GMS550U; Toshiba, Tokyo, Japan). The resolution is 7 mm full width at half maximum in the center of the reconstructed slice when the rotating radius is 13.2 cm. The computer slice width is 6.8 mm. The SPECT data were obtained in a 128×128 format for 30 angles in a 120° arc for each camera at 60 sec per angle. The total period of data acquisition was 30 min. The filtered-back projection method was used for SPECT image reconstruction after preprocessing projection data with a Butterworth filter. A series of 5.1mm thick coronal slices, approximately vertical to the orbitomeatal line (OM line), were obtained with each scan. Fourteen regions of interest (ROIs) were drawn in each hemisphere on 8 slices by referring to the individual magnetic resonance imaging scan with 5.1 mm

slices. Counts/voxel of each ROI were determined, and, to reduce artifacts, the values of ROI from two contiguous slices were averaged. Then, a regional index, that is, the percentile ratios between the value of the ROI and the mean value of all 14 regions, was calculated for each hemisphere. Thus, the regional indices of the 14 ROIs were obtained in each hemisphere: superior frontal area, middle frontal area, inferior frontal area, anterior cingulate area, supplementary motor area, orbital area, posterior cingulate area, superior temporal area, middle and inferior temporal area, limbic area (amygdala plus hippocampus), basal ganglia, thalamus, superior parietal lobule, inferior parietal lobule (Fig. 2).

Clinical symptoms and eye movements in patients were assessed within 2 weeks of the SPECT. Relationships between eye movement parameters and rCBF were analyzed for 21 patients, because two patients could not undergo SPECT within the 2 week period.

Statistical analysis

Differences between eye movement parameters in controls and patients were examined using the Mann-Whitney U test. The Sign Test was performed to determine the effects of conditions or settings within the same group of subjects. Fisher's exact test was performed for differences in frequency between groups on the error score. Spearman's rank correlation test was used for correlations between eye movement parameters and clinical syndromes or drug dosage. Differences in rCBF between the two groups of patients were examined using Student's t-test.

Results

Analysis of Eye Movements

Table 1 shows the group means and standard deviations for

eye movement parameters under both conditions (black points/randomized numbered points) in the saccadic tracking task. At the 200-ms setting, the schizophrenic patients showed significantly fewer correct scores ($P<0.01$), and more deviant scores ($P<0.01$) than the normal controls under both conditions. There were significant differences in all other subparameters (target hitting, normal path, superfluous fixation, aberrant path) between controls and patients. Under the black-point condition at the 100-ms setting, there was no significant difference between the patients and the controls in target hitting. Patients, however, still showed fewer correct scores ($P<0.01$: both conditions) and more deviant scores than controls ($P<0.01$ under the black-point condition; $P<0.05$ under the numbered-point condition). Neither the schizophrenic patients nor the normal controls exhibited a significant cue effect, that is, there was no significant difference in any of the parameters between numbered-point conditions and black-point conditions.

Comparison between eye movements at the 200-ms and 100-ms settings

Under the black-point condition, the patients had more correct scores ($P<0.05$), more target hittings ($P<0.01$) and more aberrant paths ($P<0.01$) at the 100-ms setting than at the 200-ms setting. Both the controls and the patients also had more deviant scores ($P<0.01$) and more superfluous fixations ($P<0.01$) at the 100-ms setting.

Under the numbered-point condition, the patients had more target hittings ($P<0.05$) at the 100-ms setting than at the 200-ms setting. Both the normal controls and the patients had more deviant scores ($P<0.01$ each), more superfluous fixations ($P<0.01$ each) and more aberrant paths($P<0.01$ each) at the 100-ms setting than at the 200-ms setting.

These results indicate that some patients viewed the targets

correctly at more than 100 ms but less than 200 ms, while almost all control subjects viewed the targets correctly at more than 200 ms.

Error analysis of eye movements

Table 2 shows the number of subjects who made each type of error in eye movements. Under the black-point condition at the 200-ms setting, ten of the 23 patients presented the omitting type error, while only two of the 23 normal controls manifested this error type ($P<0.05$). Thirteen patients and only three controls presented the superfluity type error ($P<0.01$). Under the numbered-point condition, nine patients but only one control presented the omitting type error ($P<0.01$).

Under the black-point condition at the 100-ms setting, hypermetria was evident in ten patients, while only 2 controls showed hypermetria. None of the normal controls showed hypermetria at the 200-ms setting. Two patients, but none of the controls, showed centering.

Relationship of the eye movement parameters with regional cerebral blood flow

The difference in rCBF between the two groups of patients was examined: the ordinary group (group O) who obtained full target hitting scores at the 200 ms setting under the black-point condition and the fast group (group F) who obtained full target hitting scores at the 100 ms setting, but not at 200 ms, under this condition (Table 3). The Group F patients showed significantly more deviant scores at the 100 ms setting as compared to the 200 ms setting. The group F patients showed decreased rCBF in the left limbic and inferior parietal areas as compared with the group O patients ($P<0.05$, each), (Fig.3). There were no significant differences between the two groups in rCBF in other brain regions.

Relationship of eye movement parameters with clinical syndromes and neuroleptic dosage

The alienation syndrome score correlated negatively with the correct score under the numbered-point condition at the 200-ms setting ($r=-0.54$, $P=0.0115$). The delusion syndrome score correlated positively with the deviant score under the numbered-point condition at the 200-ms setting ($r=0.43$, $P=0.0457$) and at the 100-ms setting ($r=0.43$, $P=0.0439$). There were no significant correlations between other syndrome scores and the correct score or the deviant score.

Assessment of the effect of neuroleptics on eye movement parameters showed no significant correlation between eye movement parameters and chlorpromazine-equivalent dosage.

Group F patients did not differ significantly from group O in the severity of any of the five clinical syndromes or in neuroleptic dosage.

Discussion

The results of this study confirm that schizophrenic patients show fewer correct scores and more deviant scores than normal controls in saccadic tracking of stationary targets, in agreement with the previous findings (Matsui and Kurachi 1995). Furthermore, Matsui and Kurachi (1995) showed that the deviant scores in patients improved significantly under numbered-point conditions in serial order. However, defective saccadic tracking in patients did not improve with the use of targets on which the numbers had been placed in randomized order. Shagass et al. (1976) reported that eye tracking performance (smooth pursuit eye movement) is markedly improved in both patients and normal subjects by replacing the fixation dot on the pendulum with pseudorandomly displayed numbers. The numbers on the

pendulum presumably enhanced the attentiveness of the patients by adding a simple perceptual-cognitive act, the recognition of digits. In contrast, randomized numbers on the stationary targets may have been burdensome for patients. Optimal conditions for patients, to enhance attentiveness in a saccadic tracking task may be arabic numbers placed in order from 1 to 8. Contrary to our prediction that the patients would view the target during the full time, in the situation in which the subjects were unable to anticipate the next number, patients showed significantly more target hitting at the 100 ms setting than at the 200 ms setting. This was true not only under the black point condition, but also under the randomized numbered condition, suggesting that some patients still view the target too fast. Consistent with this, at the 200 ms setting, the number of patients who made omitting type errors did not decrease under the randomized numbered condition as compared with the black-point condition.

Concerning the relationships between eye movements and rCBF, the group F patients, that is, the patients who viewed the target too fast showed decreased rCBF in the left inferior parietal and limbic area as compared with the group O patients who viewed the targets at a presumably normal duration (over 200 ms). The inferior parietal area in the present study overlaps the posterior parietal cortex. The posterior parietal cortex constitutes, along with the frontal eye field, the two main areas involved in triggering saccades and there are direct connections between the two areas (Kennard et al. 1994). Mountcastle et al. (1975) found neurons in the simian posterior parietal cortex that discharge before and in association with saccades. The posterior parietal cortex has the role of visuospatial integration and saccadic initiation, while the prefrontal cortex inhibits unwanted saccades and selects significant saccadic eye movements (Pierrot-Deseilligny et al. 1991a, 1991b). Nakashima et al. (1994) showed that left dorsolateral prefrontal cortex activation

and correlative left posterior parietal cortex activation were observed during volitional saccades in normal controls but not in schizophrenic patients. They suggested that the dorsolateral prefrontal cortex associates with the posterior parietal cortex during saccadic eye movements. In addition, the visual fixation neurons that accelerate discharge synchronously with fixation on a visual object have been recorded in the simian inferior parietal lobule (Lynch et al.1977). Clinically, square-wave jerks, that is, sporadic horizontal saccades followed after an interval by corrective saccades, during fixation have been reported to occur in subjects with presenile dementia (Feldon and Langston 1977) and in patients with parietal lesions (Sharpe et al.1982).

The parietal cortex also has direct connections with the limbic (parahippocampal) cortex (Pandya and Kuypers 1969; Van Hoesen 1982). There is growing evidence that schizophrenic patients have abnormalities in the medial temporal lobe (Roberts 1991). Decreased volumes of medial temporal lobe structures (amygdala, hippocampus, and parahippocampal gyrus) in schizophrenic patients have been reported by both postmortem histopathological evaluation and antemortem magnetic resonance imaging (MRI) (Bogerts et al.1985; Suddath et al.1989). Patients with schizophrenia showed a significantly lower regional cerebral glucose metabolic rate in the hippocampus and the anterior cingulate cortex than did normal controls (Tamminga et al. 1992). Frith et al. (1992) reported that the rCBF in the left hippocampus and parahippocampal gyrus increased during the internal monitoring of eye movements in normal subjects.

Thus, it seems possible that the overly fast fixation in the saccadic task in some schizophrenic patients is related, at least in part, to dysfunction in the inferior parietal and limbic areas. In one of the two patients who showed centering, atrophy of the right parietal lobe was observed on MRI. She also had several deviant scores and belonged to group O. The possibility that

impaired saccades may be related to morphological brain change should be studied in the future. The limitation of the present study is that rCBF was measured in the resting state rather than the activation state. However, as performance on the Wisconsin card sorting test in schizophrenic patients has been reported to correlate with prefrontal rCBF in the resting state (Sagawa et al. 1990) as well as the activated state (Weinberger et al.1986), studies on resting rCBF provide clues to the selection of adequate tasks for an activation study. Further research is needed to elucidate the differences in rCBF among normal controls, group O and group F.

The error analysis of eye movements revealed that some patients displayed hypermetria. Several other studies (Schmid-Burgk 1982,1983; Mather and Puchat 1983) have also reported hypermetria in schizophrenic patients. As to the neural mechanisms underlying the eye movements observed, it has been suggested that the cerebellum contributes to saccadic eye movements (Kase et al. 1980, Bruce and Goldberg 1985, Mano et al. 1991). Cerebeller atrophy in schizophrenic patients has been documented by computed tomography (CT), MRI (Weinberger et al.1982, DeLisi et al.1986, Rossi et al.1993) and postmortem studies (Weinberger et al.1980). Based on these findings, the hypermetria displayed in schizophrenic patients may be related to impairment of the neural network which involves the cerebellar hemisphere.

With regard to the relationship between clinical syndromes and eye movements, a significant negative correlation was found between alienation syndrome (auditory hallucination and disturbance of the self) and correct scores, as well as a positive correlation between delusion syndrome and deviant scores. Impairment of saccadic eye movements in the present task may be attributable to failure to monitor the intended eye movements, and this failure may be related to passivity experiences

(disturbance of the self) as proposed by Frith et al. (1992).

In conclusion, the present findings suggest that some schizophrenic patients view stationary targets too fast and this may be related to dysfunction in the limbic-parietal association area in the left hemisphere.

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Table 1. Eye movements during a saccadic tracking task in controls and schizophrenic patients (mean ± SD)

Conditions	Eye movement parameters					
	Correct score	*Target hitting*	*Normal path*	Deviant score	*Superfluous fixation*	*Aberrant path*
200-ms setting						
Black points						
Normal controls	14.8±0.6	7.9±0.3	6.9±0.3	0.2±0.5	0.2±0.5	0
Schizophrenic patients	12.8±2.3**a	7.1±1.1**a	5.7±1.3**a	3.3±5.8**a	1.9±3.0**a	1.5±2.9**a
Randomized numbered points						
Normal controls	14.9±0.5	8.0±0.2	7.0±0.3	0.3±0.8	0.1±0.5	0.1±0.3
Schizophrenic patients	12.7±2.5**a	7.0±1.2**a	5.7±1.3**a	2.6±4.6**a	1.3±2.7**a	1.3±2.0*a
100-ms setting						
Black points						
Normal controls	14.8±0.5	8.0±0	6.8±0.5	1.6±2.8**b	1.0±1.3**b	0.8±2.1
Schizophrenic patients	14.0±1.2**a;*b	7.9±0.3**b	6.1±1.0**a	6.8±6.9**a;**b	3.9±3.6**a;**b	2.9±3.6**a;**b
Randomized numbered points						
Normal controls	14.8±0.5	8.0±0	6.8±0.5	2.4±2.2**b	1.2±1.4**b	1.2±1.0**b
Schizophrenic patients	13.5±1.8**a	7.7±0.5*a;*b	5.8±1.4**a	7.0±9.0 *a;**b	3.6±4.9**b	3.5±4.3**b

A perfect correct score is 15 points (number of target hits plus normal paths).

The deviant score equals the number of abberant paths plus superfluous fixations.

a Mann-Whitney U test, controls vs patients

b Sign Test, 200-ms setting vs 100-ms setting in the same group

* $P<0.05$, ** $P<0.01$

Table 2. Numbers of subjects who made each type of eye movement error

Subject	schizophrenic patients				normal controls			
Condition	black		number		black		number	
Setting	200 ms	100 ms	200 ms	100 ms	200 ms	100 ms	200 ms	100 ms
error type								
omitting	10*	1	9**	3	2	1	1	0
hypermetria	4	10*	2	8	0	2	0	7
centering	1	1	2	2	0	0	0	0
return	1	1	2	3	0	0	0	1
slipping	4	1	2	2	0	0	0	1
superfluity	13**	18	10	17	3	12	4	10

* $P<0.05$, ** $P<0.01$ (Fisher's exact test was used to evaluate control and patient scores)

Table 3. Eye movements in two groups of schizophrenic patients under black-point conditions (mean ± SD)

	Eye movement parameters					
	Correct Score	*Target Hitting*	*Normal Path*	Deviant Score	*Superfluous Fixation*	*Aberrant Path*
group O (n=10)						
200-ms setting	14.5±0.7	8.0±0	6.5±0.7	5.0±8.4	2.8±4.3	2.2±4.1
100-ms setting	14.5±0.7	8.0±0	6.5±0.7	6.4±9.7	3.7±5.0	2.7±4.8
group F (n=9)						
200-ms setting	11.7±2.6**a	6.4±1.3**a	5.2±1.3**a	1.3±1.6	0.8±1.0	0.6±1.1
100-ms setting	14.1±0.9*b	8.0±0**b	6.1±0.9	5.6±3.1*b	3.4±2.0*b	2.1±2.1*b

group O; Patients who obtained the full Target Hitting score at the 200 ms setting.

group F; Patients who obtained the full Target Hitting score at the 100 ms setting, but not at the 200 ms setting.

A perfect correct score is 15 points (number of target hits plus normal paths).

The deviant score equals the number of abberant paths plus superfluous fixations.

a Mann-Whitney U test, group O vs group F

b Sign Test, 200-ms setting vs 100-ms setting in the same group

* $P<0.05$, ** $P<0.01$

Legends

Fig. 1. A saccadic tracking task on 8 (A) black-point and (B) randomized numbered-point targets. The subject was instructed to look at the center (+) of the figure first. He/she was then asked to scan the 8 points clockwise, in order.

Fig. 2. Location of regions of interest (ROIs). SPECT images from a representative patient. Abbreviation; 1, anterior cingulate; 2, superior frontal area; 3, middle frontal area; 4, inferior frontal area; 5, orbital area; 6, supplementary motor area; 7, basal ganglia; 8, thalamus; 9, limbic area; 10, superior temporal area; 11, middle and inferior temporal area; 12, posterior cingulate; 13, superior parietal lobule; 14, inferior parietal lobule.

Fig. 3. Relationship of the eye movement parameters with regional cerebral blood flow.
O; Patients who obtained the full Target Hitting score at the 200-ms setting (n=10).
F; Patients who obtained the full Target Hitting score at the 100-ms setting, but not at the 200-ms setting (n=9).
* $P<0.05$ (t-test; O vs F, in the same region of interest)

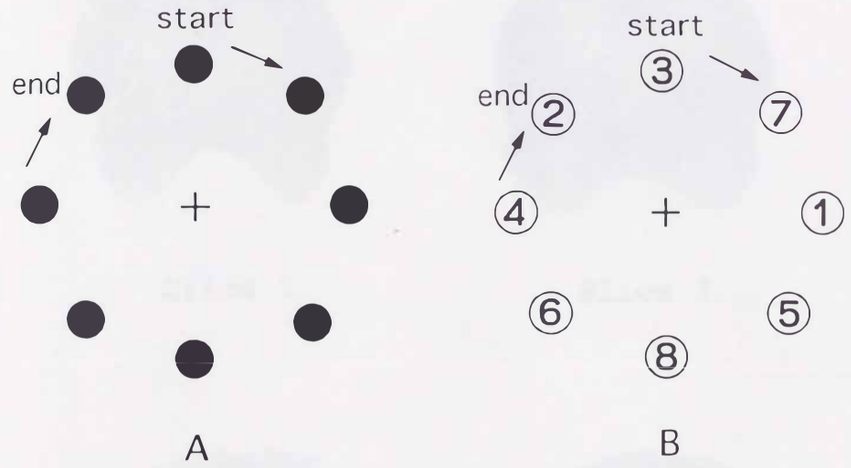
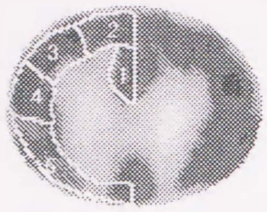
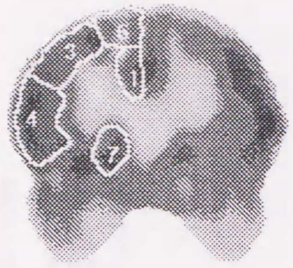


Fig. 1



Slice 1



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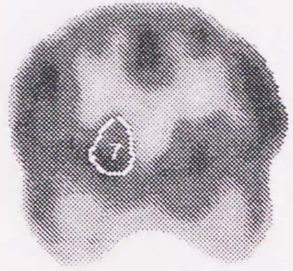

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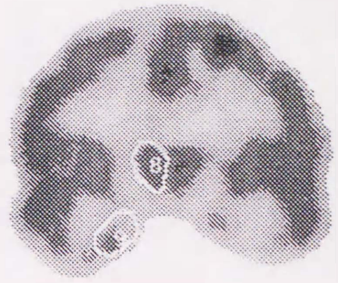

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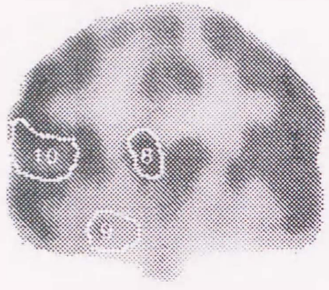

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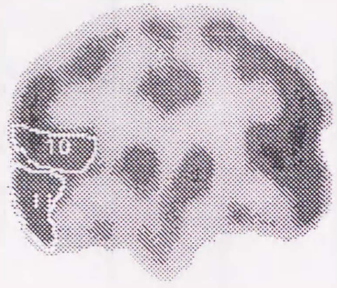

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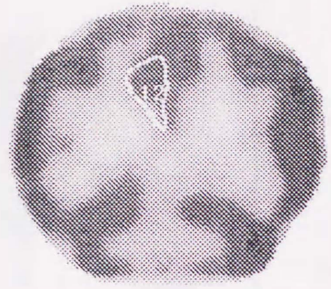
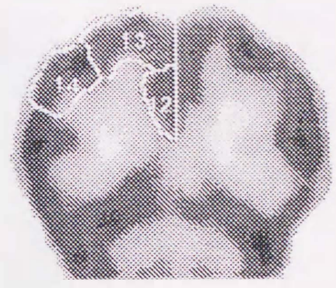


Slice 7



Slice 8

Fig. 2

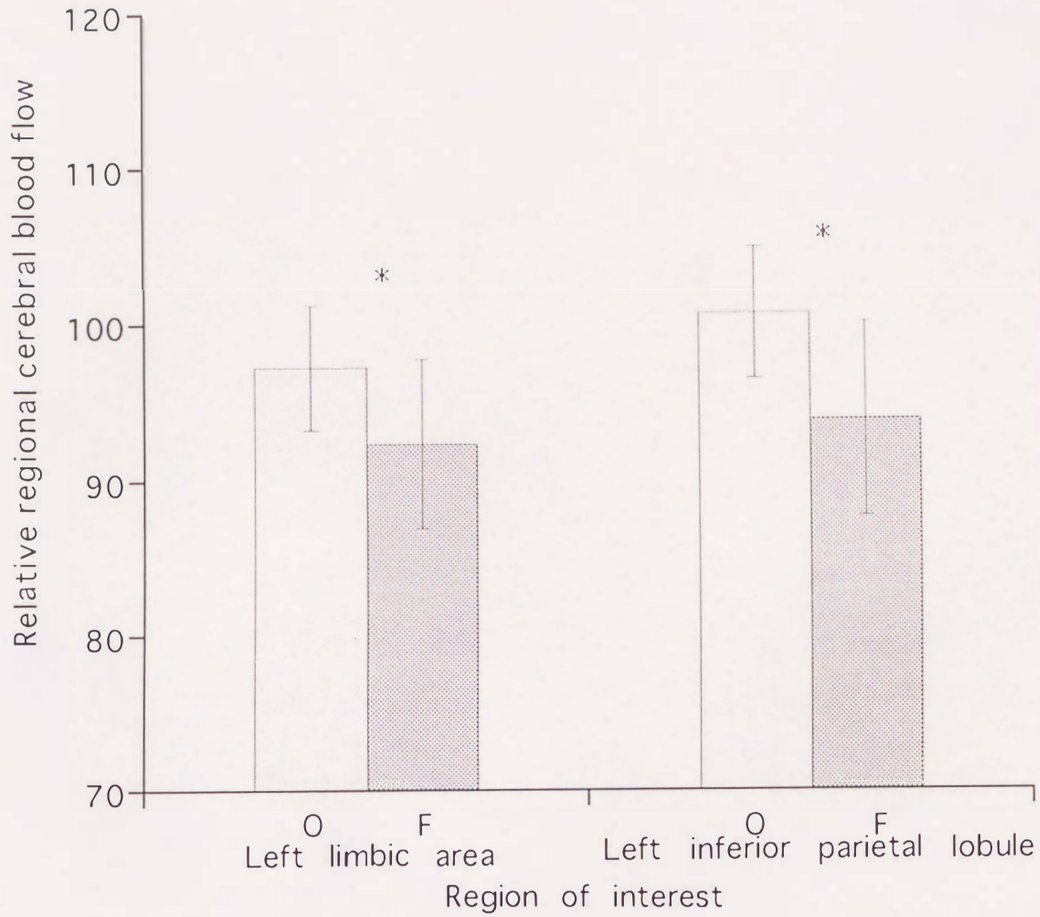
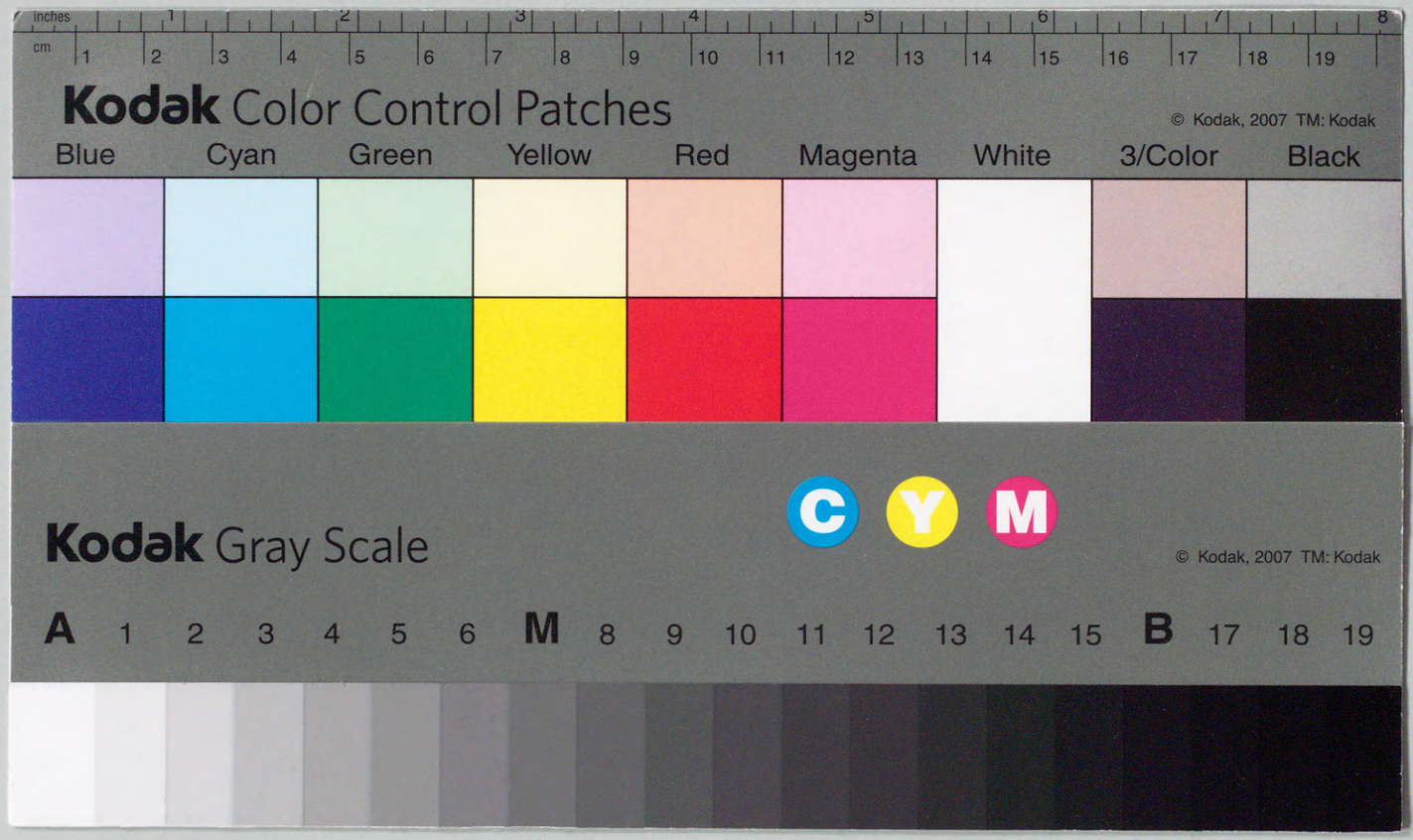

120
110
100
90
80
70
Relative regional cerebral blood flow
*
*
O
F
O
F
Left limbic area
Left inferior parietal lobule
Region of interest

Fig. 3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Yellow
Red
Magenta
White
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M
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A 1 2 3 4 5 6 M 8 9 10 11 12 13 14 15 B 17 18 19