Express Saccades and Smooth Pursuit Eye Movement Function in Schizophrenic, Affective Disorder, and Normal Subjects

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Abstract

■ Saccadic and smooth pursuit eye movements were recorded in three groups of subjects: a schizophrenic group, a non-schizophrenic psychotic patient comparison group, and a normal control group. Schizophrenic subjects demonstrated a greater decrease in saccadic response time than did normal controls in a gap task (when the fixation point was turned off 150 msec before the target appeared). The psychiatric comparison subjects did not differ from normal controls. Further, only schizophrenic subjects demonstrated a relation between smooth pursuit and saccadic eye movement performance, such that subjects with impaired smooth pursuit showed a larger decrease in saccadic response time in the gap task. The relation between performance on the gap task and quality of smooth pursuit and its relevance for a prefrontal deficit hypothesis of schizophrenia are discussed. ■

INTRODUCTION

Latency to initiate a saccade in response to a peripheral target ranges from about 180 to 250 msec (Becker, 1989). By introducing a temporal gap between the offset of a central fixation point and the onset of a peripheral target light, saccadic latencies can be reduced. Saslow (1967) and Ross and Ross (1980, 1981) demonstrated saccadic latency reductions with such a gap paradigm. Fischer and colleagues (Fischer & Boch, 1983; Fischer & Ramsperger, 1984, 1986; Fischer & Breitmeyer, 1987) introduced the term "express saccades" to describe these very short latency saccades. Whether or not there exists in humans a truly separate population of saccades that can be described as express saccades and the effects of practice on the generation of these saccades, however, remain unanswered questions (Wenban-Smith & Findlay, 1991).

Express Saccades and the Superior Colliculus

Although both the superior colliculus and frontal eye fields (FEFs) are clearly involved in saccade control, the ability to generate appropriate saccades remains basically intact after either a superior colliculus lesion or a lesion of the frontal eye fields. The superior colliculus, however, is essential for express saccades as a lesion of the superior colliculus eliminates express saccades contralateral to the lesion site (Schiller, Sandell, & Maunsell, 1987). It has been suggested that express saccades are reflex eye movements mediated by the superior colliculus (Fischer & Breitmeyer, 1987) and possibly striate cortex (Boch and Fischer, 1986) that can be inhibited by directed visual attention.

The Role of the Frontal Eye Fields in Saccades

The frontal eye fields project directly to the superior colliculus (Lynch & Graybiel, 1983) as well as to other tegmental eye movement related nuclei. Recent work has suggested that an indirect projection from the frontal eye fields via the substantia nigra may be responsible for tonic inhibition of the superior colliculus (Hikosaka & Wurtz, 1985a,b; Fischer, 1987). Much behavioral observations of frontal brain-damaged patients and lesion studies in monkeys also support the idea that the FEFs play a controlling and often inhibitory role with respect to the superior colliculus (see, e.g., Guitton, Buchtel, & Douglas, 1982, 1985; Schiller et al., 1987).

Smooth Pursuit Eye Movements

The main processing of moving visual stimuli in primates seems to occur in the extrastriate visual cortex. Among the multiple extrastriate visual areas, two have been identified as being largely devoted to visual motion processing: the middle temporal area (MT) and the medial superior temporal area (MST) (Maunsell & Newsome, 1987; Wurtz, Komatsu, Dürsteler, & Yamasaki, 1988). Cells in these two areas project directly to the dorsolateral pontine nuclear areas of the brainstem in the monkey

(Glickstein, Cohen, Dixon, Gibson, Hollins, Lebossiere, & Robinson, 1980) and then on to premotor centers (brainstem and cerebellum) responsible for generating smooth pursuit eye movements (SPEMs). Lesions in MT result in deficits in both initiation of SPEM and perception of motion (discrimination and detection of moving targets). Lesions in MST result in an inability to maintain normal gain of pursuit eye movements (pursuit eye speed is less than target speed). Parietal cortex lesions impair SPEMs mainly to the ipsilateral side (Baloh, Yee, & Honrubia, 1980; Lynch & McLaren, 1982). Thus, signals relevant for SPEMs are assumed to be derived mainly from the parietotemporal association cortex.

The Role of the Frontal Eye Fields in Smooth Pursuit

Recently, pursuit-related neurons have been found deep within the arcuate sulcus in the FEF of prefrontal cortex of monkeys (Bruce, Goldberg, Bushnell, & Stanton, 1985). In addition, persistent pursuit deficits have now been described following lesions of the fundus of the FEF in prefrontal cortex of monkeys (Lynch, 1987; MacAvoy, Gottlieb, & Bruce, 1991). As noted above, the FEFs play an important role in the control of saccadic eye movements. That is, they appear to be important in suppressing unwanted reflex-like saccades and in triggering appropriate volitional saccades. Thus, a lesion of the FEFs may disrupt smooth pursuit merely by allowing an increase in unwanted saccadic activity (e.g., saccadic intrusions). However, there is evidence that a lesion in the fundus of the FEFs also produces specific and persistent smooth pursuit-related deficits in the gain of pursuit velocity and pursuit acceleration (MacAvoy et al., 1991).

Smooth Pursuit Performance in Schizophrenic Subjects

Smooth pursuit eye movement dysfunction in psychotic patients has been one of the most consistent findings in psychophysiological research of the psychoses (Holzman, 1985). There are two possible causes of abnormal tracking in schizophrenic patients: impaired smooth pursuit tracking (associated with low gain and catch-up saccades) and saccadic disinhibition (associated with increased saccadic intrusions). It is unclear how independent these phenomena are within a given patient. However, based on recent studies of physiology, it is possible that both smooth pursuit and saccadic deficits may result from a prefrontal dysfunction.

Prefrontal Deficit Hypothesis of Schizophrenia

Evidence from several different disciplines suggests a possible relation between schizophrenia and prefrontal cortex dysfunction (see Levin, 1984a,b for a review). Specifically, blood-flow studies of brain activity (using positron emission tomography and xenon-133 techniques) have shown reduced activity in the prefrontal cortex of schizophrenic patients (Ingvar & Franzen, 1974a,b; Franzen & Ingvar, 1975a,b; Buchsbaum, DeLisi, Holcomb, Cappelletti, King, Johnson, Hazlett, Dowling-Zimmerman, Post, Morihisa, Carpenter, Cohen, Pickar, Weinberger, Margolin, & Kessler, 1984; Berman, Zec, & Weinberger, 1986; DeLisi, Buchsbaum, Holcomb, Dowling-Zimmerman, Pickar, Boronow, Morihisa, van Kamman, Carpenter, Kessler, & Cohen, 1985; Weinberger, Berman, & Zec, 1986; see Buchsbaum & Haier, 1987, for a review). Schizophrenic patients are impaired on both the spatial delayed response tasks (Malmo, 1974) and the Wisconsin Card Sort (Weinberger et al., 1986); these tests are diagnostic of prefrontal cortex injury (Stuss & Benson, 1984; Milner, 1963, 1964, 1982). In addition, neuroanatomical evidence has shown that schizophrenic patients have reduced numbers of neurons in certain layers of prefrontal cortex (layers II, III, VI) (Benes, Davidson, & Bird, 1986).

Saccadic Performance in Schizophrenic Subjects

Using an electrooculographic technique, Levin, Holzman, Rothenberg, and Lipton (1981) showed that saccadic eye movement latencies were normal in both schizophrenic and manic-depressive patients. They also reported that the dynamic characteristics of saccades, including the peak velocity-by-amplitude and duration-by-amplitude functions defined by Bahill, Clark, and Stark (1975) as the main sequence, were normal in these patients. Another study (Levin, Jones, Stark, Merrin, & Holzman, 1982) confirmed these findings using an infrared reflected light technique and indicated that saccadic trajectories of schizophrenic patients were also normal. It is noteworthy that even patients with impaired smooth pursuit eye movements did not differ from normal controls in saccadic latency. Iacono, Tuason, and Johnson (1981) examined latencies of saccades in a group of remitted schizophrenic patients and reported no significant differences in saccade latencies between patients and normal controls.

Proposed Hypothesis

This study tests whether schizophrenic patients with pursuit dysfunctions exhibit a greater benefit in latency in the gap-saccade paradigm compared with schizophrenic patients who show normal smooth pursuit. This prediction is based on the following rationale: The prefrontal cortex exerts a controlling, modulating, and often inhibiting function with respect to the saccadic system. Prefrontal cortex also plays a role in the generation and control of smooth pursuit eye movements. Consequently,

a prefrontal dysfunction will result in both reflexive saccadic disinhibition and in smooth pursuit abnormalities. Their co-occurrence is expected in a majority of schizophrenics, if, as has been asserted, there is a prefrontal abnormality in schizophrenia.

Mean latency values in a gap paradigm vary considerably across different studies and there is often large intersubject variability within a given study (e.g., Reulen, 1984; Wenban-Smith & Findlay, 1991). Nevertheless, the latency reduction in a gap condition (versus a simultaneous or overlap condition) in normal subjects has been consistently replicated, with maximal saccadic latency reduction occuring with temporal gaps of 200 to 300 msec (e.g., Saslow, 1967; Wenban-Smith & Findlay, 1991).

In the present study, each subject performed two saccadic eye movement tasks: (1) a regular or no-gap saccade task, and (2) a gap-saccade task. The purpose of the no-gap saccade task was to provide a baseline performance measure for each subject in order to compare performance changes that were expected in the gap-saccade task. Furthermore, although some studies have reported no differences in latency and accuracy in saccades between schizophrenic and normal controls (e.g., Levin et al., 1982), some studies have reported that schizophrenic patients show longer latencies than normal controls for amplitudes greater than 10° (e.g., Levin et al., 1981). A brief report of the present study has appeared previously (Sereno & Holzman, 1991).

RESULTS

Scoring

Saccade Tasks

The distributions of saccadic responses were skewed and a natural logarithm transformation normalized the distributions. The following RT data analyses were performed on the natural log transform of the saccadic response times. RTs less than 135 msec were eliminated prior to analysis. These responses were considered anticipatory. Given an approximate average duration of 55 msec for a saccade of 10°, this removed responses in which the eye began to move less than 80 msec after presentation of the target. In the no-gap task, 1.3, 0.6, and 1.3% of the saccades were considered anticipatory for the schizophrenic, affective disorder, and normal group, respectively. In the gap task, 2.2, 1.9, and 3.9% of the saccades were considered anticipatory (schizophrenic, affective disorder, and normal group, respectively).

In addition, Tukey's fence method was used to remove outliers after the natural log transformation of correct saccadic responses and before removal of anticipatory responses. The Tukey procedure was performed separately for each group and task combination and was used to trim outliers only at the top end of the distribution. In most trials the lower fence fell below the 4.905 (135 msec) anticipatory cut-off. In a very few trials, the lower fence did fall above this anticipatory cut-off, but was not used so as not to remove inadvertently possible express saccades. Together, these trimming procedures removed 6.36% of the data. RTs from incorrect responses were also eliminated prior to the RT data analysis. This procedure removed 3.39% of the data. All data, however, were included in the error analysis.

We separately analyzed RTs and error rates and examined both between-group and within-group differences (with respect to quality of SPEM). To compare the performance of subject groups on the gap-saccade task, a measure of performance was constructed to control for possible baseline differences on the no-gap saccade task. Mean log saccadic RT in the gap-saccade task was subtracted from the mean log saccadic RT in the no-gap saccade task for each subject. This difference score between the no-gap and gap tasks was used as a measure of performance benefit that a subject incurred in the gap task relative to baseline performance in the no-gap task. Larger difference scores indicated a greater reduction in RT on the gap task. Similar difference scores for each subject were constructed from mean error rates. Comparisons between groups were performed on these RT and error rate difference scores.

Qualitative Ratings for Smooth Pursuit Tasks

The integrity of the tracking record was independently rated by two experienced researchers who were blind to the subjects' identity and diagnosis. Ratings were dichotomous as impaired or normal smooth pursuit tracking. Interrater correlation in this laboratory averages more than $r = 0.95$. An eye-tracking record of a schizophrenic subject with impaired pursuit and a record of a schizophrenic subject with normal pursuit are shown in Figure 1. Smooth pursuit eye movement recordings could not be obtained on three subjects, and there were artifacts (noise) that prevented valid assessment of the records of four subjects.

Based on the SPEM classification, each subject group was subdivided into those with normal or impaired smooth pursuit. Of the 14 subjects in the normal control group, 12 subjects were tested and all demonstrated normal SPEMs. Of the 16 subjects in the schizophrenic group, 14 subjects had scorable pursuit records. They were divided into two groups: those with normal pursuit ($N = 5$) and those with impaired pursuit ($N = 9$). Nine of the 12 subjects in the affective disorder group had scorable records. They were divided into two groups: those with normal pursuit ($N = 3$) and those with impaired pursuit ($N = 6$).

Response Time

A series of planned, unpaired, one-tail t tests for the effect of diagnostic groups was performed on the mean (trans-

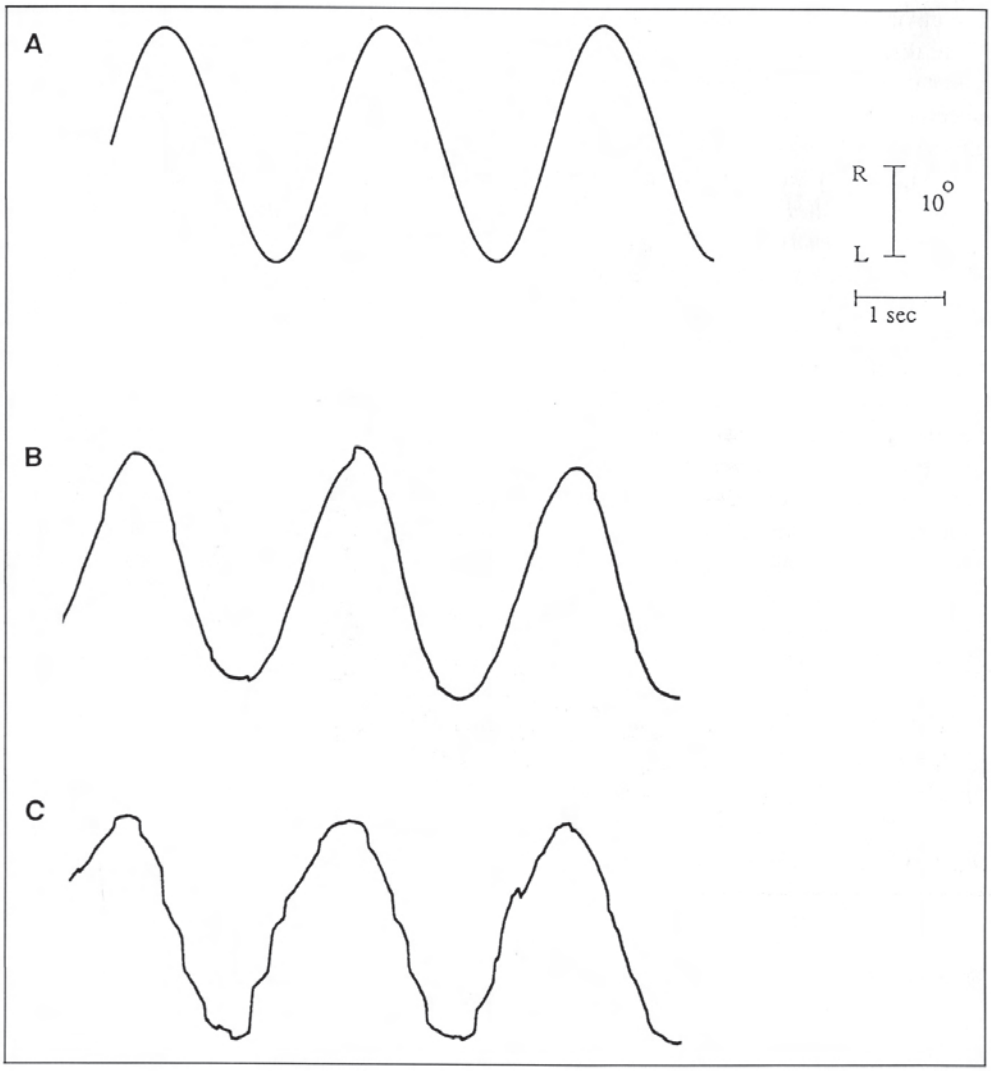

Figure 1. Examples of normal and abnormal eye tracking in two schizophrenic patients. (**A**) The sinusoidal target oscillating at 0.4 Hz. (**B**) Normal eye tracking. The pattern is relatively smooth, with only a very few small amplitude rapid eye movements. (**C**) Abnormal eye tracking. The pattern shows lowered gain with frequent catch-up saccades and an occasional back-up saccade. The time and amplitude scales are presented to the right of **A**.

formed) saccadic RT difference scores for all subjects. Table 1 presents group mean saccadic RT in both the no-gap and gap-saccade tasks, as well as the difference scores. Three two-group comparisons were performed. As expected, schizophrenic patients had a significantly larger mean gap difference score (25 msec, untrans-

Table 1. Group Mean Saccadic Response Time and Error Rate

	Schizophrenic			*Affective*			*Normal*		
Group tracking	All (N=16)	Normal (N=5)	Impaired (N=9)	All (N=12)	Normal (N=3)	Impaired (N=6)	All (N=14)	Normal (N=12)	Impaired (N=0)
No-Gap task									
RT (msec)	310	298	318	299	292	294	282	283	—
Errors (%)	3.59	2.50	4.72	3.13	5.00	2.50	2.50	2.71	—
Gap task									
RT (msec)	285	288	280	283	279	278	273	274	—
Errors (%)	3.13	3.00	3.89	4.38	3.33	4.58	3.75	3.96	—
Difference (no-gap − gap)									
RT (msec)	25	10	38	16	13	16	9	9	—
Errors (%)	0.46	−0.50	0.83	−1.25	1.67	−2.08	−1.25	−1.25	—

formed) than did normal subjects (9 msec, untransformed), suggesting that schizophrenic patients exhibit a greater RT advantage in the gap task than do normal subjects, $t(28) = 2.11, p < 0.023$. Although schizophrenic patients had a larger gap difference score (25 msec, untransformed) than affective disorder patients (16 msec, untransformed), this difference was not statistically significantly, $t(26) = 0.99, p > 0.16$. The RT benefit for affective disorder patients (16 msec, untransformed) did not differ from that of normal subjects (9 msec, untransformed), $t(24) = 0.95, p > 0.17$. Figure 2 depicts untransformed RT difference scores of the three groups.

A second series of planned, unpaired, one-tail t tests was performed within subject groups on the mean (transformed) saccadic RT difference scores to examine the relation between smooth pursuit quality and performance on the gap-saccade task. Since all normal subjects demonstrated normal pursuit, normal subjects were not included in this second series of comparisons.

As expected and illustrated in Figure 3, schizophrenic patients with impaired eye tracking showed a greater benefit in mean RT on the gap-saccade task (38 msec, untransformed) than did schizophrenic patients with normal eye tracking (10 msec, untransformed), $t(12) = 2.59, p < 0.012$. There was no such relation between impaired eye tracking and greater RT benefit on the gap-saccade task for affective disorder patients, $t(7) = 0.19, p > 0.42$. Furthermore, schizophrenic patients with impaired eye tracking showed a marginally significant greater benefit in mean RT on the gap-saccade task (38 msec, untransformed) than did affective disorder patients with impaired eye tracking (16 msec, untransformed), $t(13) = 1.69, p < 0.058$.

Error Rate

Error rates in these two tasks reflect anticipatory saccades (jumping the starting gun, as it were) with an incorrect assumption about where the target will appear. A positive difference score in error rate between the two tasks (i.e., no-gap minus gap error rate) reflects fewer errors and hence fewer anticipatory saccades on the gap task than on the no-gap task. Conversely, a negative difference score reflects more errors and a greater number of anticipatory saccades on the gap task. Thus, a negative difference score in error rate suggests that a lower mean saccade latency on the gap task may be due to an increase in the number of fast *correct guesses* rather than a faster *appropriate* response to the stimulus.

A series of planned, unpaired, two-tail t tests for the effect of groups was performed on the mean error rate difference scores of all subjects. Figure 4 and Table 1 present mean error rates in the no-gap and gap-saccade tasks. Schizophrenic patients show a positive mean error rate difference score (0.46%), whereas normal subjects and affective disorder patients show negative mean error

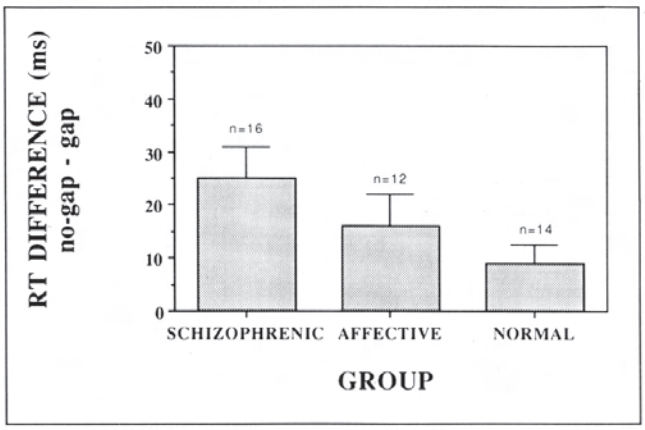

Figure 3. Mean saccadic RT difference scores with mean SE bars (untransformed, saccade minus gap) for schizophrenic and affective disorder subjects with normal and impaired tracking. All normal subjects with pursuit records demonstrated normal tracking.

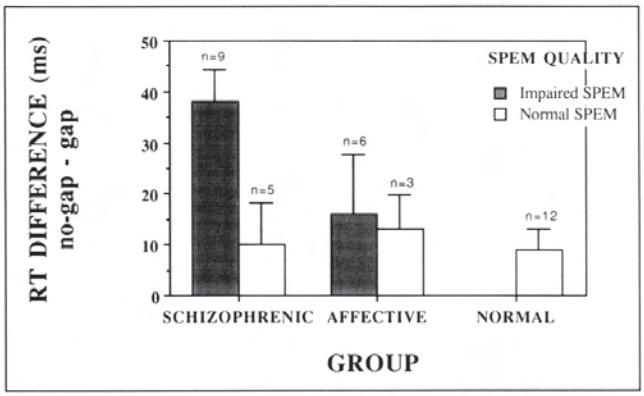

Figure 4. Mean percent error rate schizophrenic, affective disorder, and normal subjects on the no-gap and gap tasks. SEM values for the no-gap task: ±0.8, ±0.9, ±0.7, for schizophrenic, affective disorder, and normal subjects, respectively. SEM values for the gap task: ±0.7, ±1.2, ±0.6, for schizophrenic, affective disorder, and normal subjects, respectively.

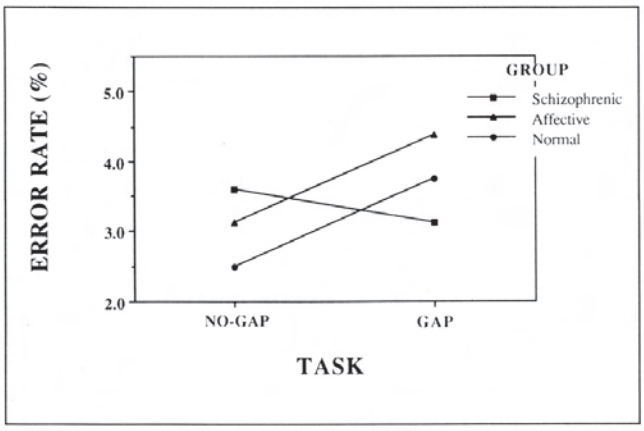

Figure 2. Mean saccadic RT difference scores with mean SE bars (untransformed, no-gap minus gap) for schizophrenic, affective disorder, and normal subjects.

rate difference scores (−1.25 and −1.25%, respectively). Since both normal subjects and affective disorder subjects have negative values on this difference score (i.e., more errors in the gap-saccade task), some of the RT benefit they show in the gap task may be due to more frequent anticipations and correct guesses rather than to faster latency to the target. Three two-group comparisons were performed to determine if any of the differences between groups were of significant magnitude. Schizophrenic patients, however, did not differ significantly from either normal subjects or affective disorder patients, $t(28) = 1.50$, $p > 0.15$ and $t(26) = 1.07$, $p > 0.29$, respectively. Affective disorder patients did not differ from normal subjects on mean error rate difference scores.

As with the RT analysis, another series of planned, unpaired, two-tail t tests was performed within subject groups on the mean error rate difference scores to examine the relation between smooth pursuit quality and error rate on the gap-saccade task. Since all normal subjects demonstrated good pursuit, normal subjects were not included in this second series of comparisons. Neither schizophrenic nor affective disorder patients demonstrated a relation between quality of eye tracking and changes in error rate in the gap-saccade task, $t(12) = 0.67, p > 0.51$ and $t(7) = 0.89, p > 0.40$, respectively. In addition, schizophrenic patients with impaired eye tracking did not differ in error rate from affective disorder patients with impaired eye tracking, $t(13) = 1.17, p > 0.26$. Thus, no speed-accuracy tradeoffs occurred in the analyses of errors such that impaired tracking was associated with an increase of errors in the gap task. Such a relation would have suggested that the RT benefit in the gap task may have in part been due to a greater number of short latency correct guesses.

DISCUSSION

General Findings

Schizophrenic subjects demonstrated a significantly greater decrease in saccadic RT than did normal controls in the gap-saccade task. Affective disorder subjects did not differ from normal controls. Furthermore, only schizophrenic subjects demonstrated a relation between quality of smooth pursuit and saccadic performance, such that schizophrenic subjects with impaired pursuit showed a larger decrease in saccadic RT in the gap-saccade task. These findings indicate a relation between performance advantage on the gap task and smooth pursuit abnormalities in schizophrenia. We are currently exploring whether the saccadic benefit in the gap task is related to specific quantitative measures of smooth pursuit such as the number of saccadic intrusions, the type of saccadic activity, or smooth pursuit velocity gain. Such findings will address whether the gap advantage is related to a disinhibitory process in the saccadic system, to a sluggish pursuit system, or to a combination of both processes, and thus point to more specific neuroanatomical loci of the deficits. The knowledge of deficits in particular pathways will provide further constraints for any proposed pathophysiological model of schizophrenia.

Previous studies have often demonstrated no differences in saccade latency for schizophrenic patients compared with normal subjects in a regular saccade paradigm (e.g., Levin et al., 1982 and Iacono et al., 1981). Levin and colleagues (1981), however, reported that saccade latencies of schizophrenic patients were slowed for displacements greater than 10°. In the present study, with target displacements of 11.9°, saccade latency for schizophrenic subjects was significantly longer than saccade latency for normal subjects on the regular saccade task; however, schizophrenic subjects did not differ from affective disorder subjects and affective disorder subjects did not differ from normal subjects in saccade latency on the no-gap saccade task.

One possible explanation of inconsistent findings in the literature is that the distribution of saccade latencies for schizophrenic subjects shows two effects in a no-gap saccade task that normals may not show: (1) given sufficient practice, schizophrenic patients produce more short latency ("express") saccades than do normal subjects, and (2) schizophrenic patients also produce a few longer latency saccades (see e.g., Levin et al., 1982). Hence, the trimming technique must be taken into account. With a less stringent outlier technique, both express and long latency saccades are included and their effects could average out so that schizophrenic saccade latency might approximate normal saccade latency. With a more stringent outlier technique (e.g., including latencies only between 150 and 350 msec, as did Levin et al., 1982), some of both express and long latency saccades are excluded and thus schizophrenic saccade latency might again approximate normal saccade latency.

In the present experiments, the differences observed between the two tasks cannot be attributed to different trimming techniques. A more stringent trimming technique, eliminating latencies greater than 2 standard deviations from the mean, did not alter baseline differences in the no-gap saccade task by eliminating more long latency saccades. In addition, it did not change the main finding: schizophrenic subjects demonstrate a greater benefit in the gap paradigm than do normal subjects. For humans, practice plays an important role in the ability to generate express saccades in a overlap saccade task (i.e., fixation point remains during target presentation; Fischer, 1987). In the present experiments, each subject was given very few practice trials and the resulting latency distributions show few latencies that may be considered express saccades, although there is a clear shift in the latency distribution toward faster responses. Differences in the amount of practice between studies may lead to differences in saccadic latency in a saccade para-

digm. Furthermore, the effects of practice may differ across subject groups. In the present study, each group received a short and equivalent amount of practice. It is probably the case that the latency of most saccades of schizophrenic patients is similar to that of normal subjects. A closer examination of differences in saccadic latency distribution, however, is needed to understand the processes generating these differences.

Magnitude of the Gap Effect

The reduction of saccadic latency that occurs in a gap paradigm (gap effect) is maximal if the fixation point is extinguished 200 to 300 msec before the target's appearance. In the present study, a gap duration of 150 msec was chosen so as to obtain a good size gap effect and yet avoid too many anticipations (Kalesnykas & Hallet, 1987). We saw very few anticipations and the rate of anticipations did not markedly increase in the gap task. Thus, it turned out that this consideration was not needed and the gap duration could have been longer in order to obtain a larger gap effect. The other main factor that reduced the size of the gap effect in the present experiments was the fact that we used a simultaneous condition for the no-gap condition (i.e., fixation offset coincided with target onset). The no-gap condition in many experiments is actually an overlap condition where the fixation remains present during the target presentation. Saccade latencies in the simultaneous condition are faster than those in the overlap condition and usually reduce the gap effect by nearly half (Saslow, 1967). Even when researchers use optimal conditions for a large gap effect (e.g., overlap condition vs. 200 msec gap condition), however, they often report small differences (e.g., less than 25 msec in Reuter-Lorenz, Hughes, & Fendrich, 1991 and about 40 msec in Wenban-Smith & Findlay, 1991). Hence, taking into account these factors, we believe that the gap effect obtained in the present study is commensurate with those obtained in previous studies.

Medication Effects

Typical neuroleptics do not seem to affect saccade latency (Crawford, Haeger, Henderson, Reveley, & Kennard, 1990) or pursuit integrity (Holzman, Levy, Uhlenhuth, Proctor, & Freedman, 1975; Levy, Lipton, Yasillo, Peterson, Pandey, & Davis, 1984). Lithium, however, has been shown to degrade SPEMs and has been associated with increased saccadic events during pursuit (Levy, Dorus, Shaughnessy, Yasillo, Pandey, Janicak, Gibbons, Gaviria, & Davies, 1985; Holzman, O'Brian, & Waternaux, 1991). In the present study, however, only 5 (3 schizophrenic, 2 affective) of the 14 patients on lithium showed impaired tracking, whereas 10 (6 schizophrenic, 4 affective) of the 14 patients not on lithium showed impaired tracking. Thus, lithium treatment in our sample did not seem to act as a contaminating variable affecting the integrity of SPEMs. One possible explanation is that many patients had relatively low blood concentration levels of lithium (abnormalities in tracking usually occur with higher concentrations).

The Gap Paradigm and Attention

The only difference between the gap and no-gap saccade tasks was a 150 msec gap (i.e., blank screen) between the fixation point screen and the target screen. The purpose of the gap was to induce express saccades (Fischer & Breitmeyer, 1987). Although previous work has consistently demonstrated that saccadic latency is reduced in a gap paradigm, whether or not a separate population of "express" saccades exists remains controversial (Wenban-Smith & Findlay, 1991; Fendrich, Hughes, & Reuter-Lorenz, 1991). Express saccades are reflex eye movements that require an intact superior colliculus. Recent studies of the neurophysiology of the superior colliculus shows that cells in the rostral pole of the superior colliculus are tonically active whenever a monkey fixates a target of interest, and the activity of these cells pauses immediately prior to the initiation of saccadic eye movements (Munoz, Waitzman, & Wurtz, 1990). In addition, induced deactivation of cells in the fixation zone of the rostral superior colliculus by muscimol, a GABA agonist, makes it difficult for the monkey to suppress saccades, whereas activation of this area with bicuculline, a GABA antagonist, makes it difficult to initiate saccades (Munoz & Wurtz, 1991). The occurrence of express saccades may depend critically on decreased activity of collicular fixation cells.

In humans, express saccades are normally inhibited; Fischer and Breitmeyer (1987) argue that directed visual attention largely reduces the occurrence of express saccades. Express saccades appear only under conditions that induce a disengaged attentional state, for example, when a fixation point is removed or when subjects are instructed to keep their gaze on a fixation point without paying attention to it (Fischer & Breitmeyer, 1987). They suggest that it is the disengagement of the attentional system that releases a reflex pathway from inhibition. The inhibition of express saccades by *engaged* fixation appears to involve prefrontal cortex, since frontal lobe lesioned patients have difficulties suppressing very short latency, visually triggered saccades (Guitton et al., 1985).

Although the superior colliculus plays an active role in the generation of express saccades, it is clear that other areas play a crucial role in the control of the colliculus and are, in some sense, "responsible" for the expression of express saccades. Thus, although express saccades may be the result of collicular mechanisms, they occur only with the permission, so to speak, of higher order centers. These other "higher order" influences on the colliculus can, perhaps, be most simply thought of as attentional or premotor processes.

Schizophrenia and Prefrontal Functions

Schizophrenia has often been related to prefrontal cortex dysfunction (e.g., Ingvar, 1980; Levin, 1984b; Luria, 1980/1966; Weinberger, Berman, & Zec, 1986). Holzman, Levy, and Proctor (1978) first suggested that smooth pursuit impairment may reflect a disinhibition of saccades during pursuit tracking. Levin (1984a) further elaborated this hypothesis in a detailed review of studies of schizophrenic eye movements and the neuroanatomy and neurophysiology of eye movement control, proposing a model of frontal lobe dysfunction for a subset of schizophrenics with smooth pursuit impairments. Levin asserted that the impairment was a functional, attention-related impairment of the mechanisms that regulate eye movements as opposed to specific lower-level oculomotor dysfunctions. It is difficult, however, to regard functional systems in the brain in isolation, particularly when a single cortical area, for example, the prefrontal cortex, may modulate several systems such as attention and the control of saccades and smooth pursuit. It is not surprising that eye movement impairments in schizophrenia are no longer regarded as limited to conditions of tracking a slowly moving or a stationary visual target (see, e.g., Fukushima, Morita, Fukushima, Chiba, Tanaka, & Yamashita, 1990; Sereno & Holzman, 1991). The present results further demonstrate that schizophrenics show an abnormal eye movement pattern in some *saccadic* eye movements.

Jacobsen's (1936) discovery that bilateral prefrontal resections produced a profound and selective deficit in spatial delayed-response (DR) tests provided an objective method to measure behavioral changes after prefrontal lesions. In addition to Jacobsen's initial explanation of the DR deficit as a loss of "immediate memory," several other explanations have been proposed over the years: (1) inadequate attention to cue properties (Nissen, Riesen, & Nowliss, 1938; Pribram, 1950), (2) susceptibility to interference effects during the delay period (Malmo, 1942), and (3) deficient regulation of motor processes (Konorski & Lawicka, 1964; Rosvold & Szwarcbart, 1964; Wegener & Stamm, 1966); for a review, see Stamm (1987).

Most investigators agree that the frontal lobes of the brain are involved at the highest level in goal-directed acts, including complex sequencing, the creation of long- and short-term plans, the internal manipulation of representational systems, and inhibition or control of interference (see, e.g., Fuster, 1987; Goldman-Rakic, 1987; Perecman, 1987). In particular, Goldman-Rakic suggests that the capacity to guide behavior by internalized representation ("working memory") accomplishes the *dual task* of commanding the correct response and disallowing or inhibiting incorrect ones (cf. Hughlings Jackson, in Taylor, 1958). Although one might try to map the neurophysiology of prefrontal cortex most closely to working memory, it is likely that this physiology is integral to many other higher order functions, including overt and covert orienting, that is, saccadic eye movements and attention (Sereno, 1992; Sereno, in press).

The present results provide support for the hypothesis that schizophrenic patients with smooth pursuit eye movement deficits show a disinhibition on a task of reflexive orienting (gap-saccade task). Both saccadic disinhibition and impaired eye tracking in schizophrenic patients are consistent with a prefrontal dysfunction hypothesis of schizophrenia.

These findings draw on, and, more importantly, draw together several areas of research: eye movement abnormalities of schizophrenic patients, the neurophysiology of prefrontal cortex, including its role in saccadic and smooth pursuit eye movements and its regulation of other brain areas (e.g., the superior colliculus) critical to the production of eye movements, and the prefrontal deficit hypothesis of schizophrenia.

METHODS

Subjects

Three subject populations were tested: (1) a schizophrenic group (N=16), (2) a psychiatric control group (predominantly patients with bipolar affective disorder) (N=12), and (3) a normal control group (N=14). Subjects were recruited for the study only if they met the following requirements: (1) less than 50 years of age, (2) no evidence of mental retardation, and (3) no evidence of organic brain pathology. Patients were recruited for the study if their condition was diagnosed as either schizophrenia or affective disorder by the hospital psychiatrist. The diagnosis was independently verified from information gathered from the Structured Clinical Interview for DSM-III-R (SCID), which was administered by an experienced interviewer. In addition, a comprehensive chart review and consultations with the patient's primary clinician provided information for the diagnostic decision. A summary of the diagnostic information on patient groups is presented in Appendix 1.

During independent diagnostic evaluation, four patients met diagnostic criteria for schizoaffective disorder, considered to be related to the schizophrenia spectrum of disorders (DSM-III-R). The 4 schizoaffective patients were indistinguishable from the 12 other schizophrenics on all measures. The affective disorder group consisted of 8 patients with bipolar disorder, three patients with major depression (one with an additional diagnosis of panic disorder, one with an additional diagnosis of general anxiety disorder, and one with an additional diagnosis of borderline personality disorder), and one patient whose admission diagnosis was bipolar affective disorder, but whose SCID diagnosis was borderline personality disorder. The predominant diagnosis for the psychiatric control group, nevertheless, was major affective disorder (11 of 12 subjects), and for convenience, this

group will be labeled the affective disorder group. Normal subjects were screened for the absence of serious mental or neurological disorders in themselves and in their first degree relatives.

Table 2 presents the demographic characteristics of the subjects. There were no significant differences between the groups in age, years of education, IQ, gender, or handedness. The patient groups did not differ with respect to age at onset of illness or for duration of illness.

All 16 schizophrenic and 11 affective disorder patients were taking medication. One affective disorder patient was medication free during the course of the testing. Table 3 summarizes the medication status of the patient groups.

Stimuli, Apparatus, and Procedure

Saccadic Tasks

The visual display for the saccadic tasks was generated on a Macintosh II screen. For both tasks (no-gap and gap-saccade), the target appeared 11.9° unpredictably to the left or right of a black fixation point (0.2° diameter). The target was a filled red circle 0.5° in diameter. In the no-gap saccade task, each trial consisted of several events (see Fig. 5): (1) a fixation point screen, which was experimenter-terminated by a click of the mouse, followed by a timed (800 msec) fixation point screen; (2) the target screen, which was terminated by (3) an eye movement to the target; and finally, a timed (500 msec) blank screen before the fixation point screen returned (not illustrated).

The gap task was identical to the no-gap saccade task except that a 150 msec blank screen was added after the timed fixation point screen (before the presentation of the target screen). Specifically, each trial consisted of the following events (see Fig. 6): (1) a fixation point screen, which was experimenter-terminated by a click of the mouse, followed by a timed (800 msec) fixation point screen, (2) a timed (150 msec) blank screen ("gap"), (3) the target screen, which was terminated by (4) an eye movement to the target, and finally, a timed (500 msec) blank screen before the fixation point screen returned (not illustrated).

Several features of the procedure were included in an effort to minimize anticipatory responses and equate response readiness in the gap and no-gap conditions. To minimize anticipatory responses, the positions of the target were unpredictable and the duration of the gap was relatively small (150 msec). The offset of the fixation point may alert the subject to the imminent occurrence of the target. The fixation offset precedes the target by 150 msec in the gap condition, perhaps resulting in a greater response readiness. In order to equate warning cues in the gap and no-gap conditions, there was a fixed interval between the clearly audible mouse click and the presentation of the target.

Subjects were seated 42 cm from a Macintosh II screen and rested their head on a chin support with their forehead against a restraint. An infrared light source was directed at the right eye. A video camera was also focused on the same eye. The output of the camera was sent to a Pupil/Corneal Reflection Tracking System (RTS), manufactured by ISCAN of Cambridge, Massachusetts. The RTS locates the pupil and the reflection of infrared rays from the subject's cornea. Using the difference in location of the pupil and cornea, the ISCAN equipment is able to calculate eye position independent of both head position and small head movements. Therefore it was not crucial that the subject's head be perfectly still.

At the beginning of each experiment, the subject was asked to look at five points on the screen–roughly the center point and the four corners. An Auto-Calibrator, also developed by ISCAN, read the eye position at those points. Using these five points as references it then calculated on-line the x- and y-axis screen coordinates corresponding to the current pupil position. These coordinates were updated 60 times per second.

The Macintosh II was connected to the RTS via a data acquisition board so that custom software on the computer located subject's point of regard. As the experiment

Table 2. Summary of Demographic Variables

	Subject Group		
Variable	*Schizophrenic* (N=16)	*Affective* (N=12)	*Normal* (N=14)
Age (in years)	32.6	29.9	32.3
Years of education	13.1	13.2	14.7
IQ	108	106	114
Gender (% female)	25	42	29
Handedness (% left-handers)	13	8	29
Onset of illness (in years)	21.9	20.8	
Duration of illness (in years)	10.0	9.3	

Table 3. Medication Status of Patients

Medication	*Schizophrenic* (*N*=16)	*Affective* (*N*=12)
Neuroleptic	16	10
Anti-Parkinson	14	7
Anxiolytic (antianxiety)	7	2
Antiseizure	7	5
Antidepressant	2	6
Lithium	6	8
No medication	0	1

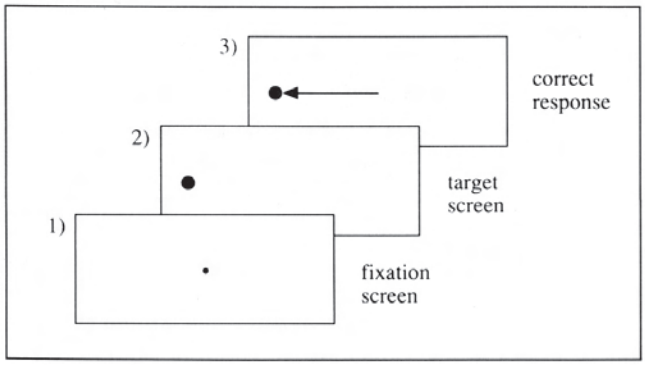

Figure 5. Schematic diagram of no-gap saccade task.

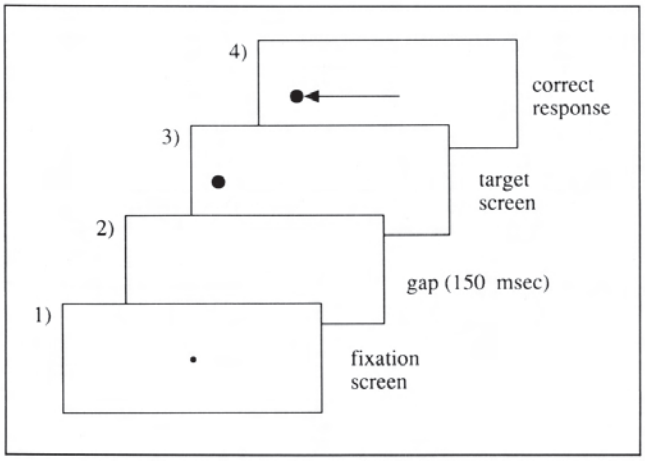

Figure 6. Schematic diagram of gap saccade task.

progressed, the computer presented stimuli on the screen, monitored eye movements, and recorded data on accuracy and timing of eye movements.

A small video monitor was also attached to the camera. It displayed the right eye of the subject. Thus, the experimenter could tell where the subject was looking in real time. The entire apparatus was located in an isolated room and the experiments were conducted under dim illumination.

After informed consent was obtained from the subjects or their guardians, a first testing session was arranged, in which subjects were given a brief introduction to the equipment. Subjects were then positioned on the chin rest. After successful calibration (error radius less than about 1.5° around the fixation point), subjects were shown sample trials depicting the different response conditions of the no-gap task. Brief instructions were presented reminding them to respond as fast as possible by moving their eyes to wherever the target appeared. They were also specifically warned to focus on the fixation point at the beginning of each trial and to keep fixating until the target appeared. They were told that if they moved their eyes from the fixation point before the target appeared, the computer would automatically cancel the trial and present it again later. There were 20 practice trials. The computer provided immediate feedback (a beep for an error). After the experimenter answered any questions about the procedure, each subject was allowed to complete the experiment. The experiment consisted of 40 trials. Subjects were instructed to pause during the fixation point screen, if they needed to, until they were ready for the next trial.

Eye movement deviations from the fixation point that exceeded 2.3° automatically cancelled a trial which was presented again later. There was a circular window of acceptability for a correct response: a radius of 4.8° centered about the target. If an eye movement landed within this window of acceptability during the presentation of the target the computer finished the trial by immediately presenting the blank intertrial interval (ITI) screen while it recorded a correct response and its latency. If there was not an eye movement to the acceptable window within 2500 msec after presentation of the target, the computer beeped and recorded an error.

In the saccadic eye movement experiments, saccadic latency was measured as the time from the onset of the target to the arrival of the eyes at the target well. Thus, saccadic latency as reported here actually measures the saccadic response time latency *plus* the duration of the saccade. The duration of saccades is quite stereotyped and for a 12° degree saccade is approximately 55 msec (see, e.g., Becker, 1989). Levin et al. (1982) demonstrated that the dynamic characteristics of saccadic eye movements, including their duration and velocity, are normal in schizophrenic patients.

The data obtained from the first day in both the practice and experimental sections were considered to be practice trials and were not used in the data analysis. Subjects were not aware, however, that the data obtained in this first session were actually practice. On the second day, subjects were tested on the gap-saccade task and retested on the no-gap saccade task. Subjects were counterbalanced across tasks, such that half of the subjects within each group received the no-gap task first and gap task second and vice versa for the other half of the subjects. After completing the saccade tasks, each subject

was briefly interviewed and then given the vocabulary subtest of the Wechsler Adult Intelligence Scale. A final session was scheduled during which smooth pursuit eye movements were recorded.

Smooth Pursuit Task

In this experiment, the subject's head was restrained by a chin and forehead brace. Eye position was measured by infrared light reflected from the iris and sclera of the eye to sensors attached to eyeglass frames worn by the subjects. The infrared signal was emitted from a diode that was centered between the two sensors. The amplified phototransistor signals, transformed by analog-to-digital conversion and controlled by a computer, were recorded on floppy disks for later scoring and evaluation. Each eye was recorded separately. The subjects were asked to follow a small X subtending 0.38° of visual arc that was displayed on a CRT monitor about 38 cm in front of them.

After subjects' eye position and gaze were calibrated, they were then asked to follow with their eyes a target that was displayed on the monitor in front of them. All subjects performed four trials in a fixed order. In trial 1, the target moved for 30 sec sinusoidally with a frequency of 0.4 Hz. In trial 2 (attention-enhancement trial), the target quasirandomly changed from an X to an O, and the subject was required to count silently the number of appearances of the O. In all other respects, this trial was similar to trial 1. Trial 3 repeated trial 1. In trial 4, the target moved at a constant velocity of 16.67° per second (triangular wave). All amplitudes were ± 10° from a central fixation point. For data reduction purposes, performance was evaluated from the eye that was better calibrated.

Appendix 1
Diagnostic Information on Patient Groups

Patient	*Diagnostic information*
	Schizophrenic patients
1	Schizophrenia, paranoid, chronic
2	Schizophrenia, paranoid, chronic
3	Schizophrenia, paranoid
4	Schizophrenia, paranoid
5	Schizophrenia, paranoid, in remission
6	Schizophrenia, undifferentiated, chronic
7	Schizophrenia, undifferentiated, chronic
8	Schizophrenia, undifferentiated, chronic
9	Schizophrenia, undifferentiated, chronic
10	Schizophrenia, undifferentiated, chronic with acute exacerbation
11	Schizophrenia, undifferentiated
12	Schizophrenia, undifferentiated
13	Schizoaffective disorder
14	Schizoaffective disorder
15	Schizoaffective disorder
16	Schizoaffective disorder
	Affective disorder patients
1	Bipolar disorder, mixed, unspecified
2	Bipolar disorder, depressed, with psychotic features
3	Bipolar disorder, depressed, with psychotic features
4	Bipolar disorder, manic, with psychotic features
5	Bipolar disorder, manic, with psychotic features
6	Bipolar disorder, manic, with psychotic features
7	Bipolar disorder, manic, with psychotic features
8	Bipolar disorder, manic, in partial remission
9	Major depression, recurrent, moderate, panic disorder, without agoraphobia
10	Major depressive disorder, borderline personality disorder
11	Major depression, with psychotic features, in full remission, generalized anxiety disorder
12	Borderline personality disorder

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