Eur Arch Psychiatry Clin Neurosci (2001) 251 : 205 – 210

ORIGINAL PAPER

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Basic parameters of saccadic eye movements – differences between unmedicated schizophrenia and affective disorder patients

Received: 30 November 2000 / Accepted: 28 June 2001

Abstract *Background* Smooth pursuit eye movement (SPEM) dysfunctions are considered a biological marker for schizophrenia and have been studied widely. In contrast, saccadic eye movements have received less attention, although disturbances have been described previously. Basic neurophysiologic parameters of saccades in schizophrenics, especially in unmedicated patients, have not been studied extensively. *Methods* Saccadic eye movements of 38 unmedicated schizophrenic patients, 32 patients with major depression and 42 nonpsychiatric controls were examined using high-resolution infrared oculography. Two large-amplitude saccadic tasks were presented. The groups were compared on peak velocity, reaction time and accuracy. *Results* Peak velocity was significantly increased in schizophrenic patients. Depressive patients had a significantly longer reaction time. Both patient groups needed more corrective saccades to reach the target than controls. *Conclusions* Peak velocity distinguishes unmedicated schizophrenic patients from depressive patients and normal controls. This could be explained by deficits of the prefrontal cortex in the inhibitory control of saccades. Our findings suggest that schizophrenia affects not only SPEM but also saccadic eye movements.

Key words Eye movements · Saccades · Schizophrenia · Peak velocity · Biological marker

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Introduction

Diefendorf and Dodge first described abnormalities of eye movements in schizophrenic patients (Diefendorf and Dodge 1908). They observed disturbances of smooth pursuit eye movements (SPEM) and an increased saccadic reaction time. Saccadic eye movements and SPEM are functionally the most important of several possible eye movements and each is generated and controlled by a different neuronal system. In later studies, disturbances of SPEM were often described as an increased number of saccades (Holzman et al. 1974). Almost all subsequent studies replicated the original findings of disturbed smooth pursuit eye movements in schizophrenia (Grove et al. 1992; Clementz et al. 1992; Flechtner et al. 1997; Levy et al. 1993, 2000). The focus of interest in these studies was SPEM and only a few studies addressed saccadic functions. Most studies of saccadic eye movements in schizophrenics did not examine basic parameters, but complex saccadic functions like ANTI-saccades or remembered saccades (Hutton and Kennard, 1998; Hutton et al. 1998; Karoumi et al. 1998/2001; Straube et al. 1999; Nieman et al. 2000; Thaker et al. 2000; Nkam et al. 2001).

The initiation of saccadic eye movements involves several cortical and subcortical regions: the posterior parietal cortex (PPC), the frontal eye field (FEF), the prefrontal cortex, the basal ganglia and the superior colliculus (Pierrot-Deseilligny et al. 1995). For all saccades the burst generator located in the brainsteam is the final pathway (Wurtz 1996). Saccades in response to visual stimuli (reflexive saccades) are mainly controlled by the PPC and the FEF (Pierrot-Deseilligny et al. 1995).

Becker described three kinds of "basic parameters of saccadic trajectory": reaction time, dynamic characteristics (velocity, duration, acceleration), and static characteristics (accuracy, corrective moments) (Becker, 1989). Studies of these saccadic variables in psychiatric patients produced conflicting results showing an increase, no change, or a decrease. Using electrooculo-

graphic recordings, Levin et al. found a slight increase of the reaction time in schizophrenics compared to manic-depressive patients but only in saccades above 10°amplitude (Levin et al. 1981). A subsequent investigation with only 6 schizophrenic patients, using infrared oculometry, could not replicate this finding (Levin et al. 1982 b). Schmid-Burgk et al. and Mackert et al. described longer reaction times in schizophrenics than in depressive patients (Schmid-Burgk et al. 1983; Mackert and Flechtner 1989; Mackert et al. 1989).

Cegalis et al. (1982), using the electrooculography, found decreased peak velocities in medicated schizophrenic patients. In a later study, using an infrared technique, peak velocity was increased (Cegalis et al. 1983). Decreased peak velocity was found in medicated schizophrenics (Fukushima et al. 1990) and in schizophrenics with a positive family history (Schwartz et al. 1995). The only study investigating peak velocity in unmedicated schizophrenics found an increase of peak velocity for large saccades above 20°amplitude (Straube et al. 1999). After starting neuroleptic treatment, peak velocity decreased in the same patients.

Mather and Putchat (1982) did not find differences of peak velocity or reaction time between schizophrenics and controls, but described an increase of dysmetric saccades in schizophrenics. Clementz (1994) found an increase of hypometric saccades in schizophrenics compared to nonpsychiatric controls. Other studies (Iacono et al. 1981; Fukushima et al. 1988) did not find significant differences between schizophrenic patients and controls at all (overview in Hutton and Kennard 1998; Karoumi et al. 1998).

Purpose of this research

Basic parameters of saccadic eye movements, like peak velocity, reaction time and accuracy, which can be studied very accurately with infrared oculography, have not been studied extensively in larger groups of unmedicated schizophrenics. The purpose of this research was to investigate possible differences in these basic parameters between schizophrenics, depressive patients and normal controls. We wanted to gain insight whether the saccadic eye movement system in schizophrenics is intact or whether it is also affected in addition to the smooth pursuit system.

Methods

Subjects

We included 42 non-psychiatric controls (22 females, 20 males), 38 schizophrenic patients (16 females, 22 males) and 32 patients with major depression (25 females, 7 males). General exclusion criteria were age under 18 or above 65, history of substance abuse, and signs of neurological or ophthalmologic illnesses. All subjects had to be drug-free for at least 7 days. Participants provided informed consent prior to testing. The patients were evaluated by a clinical examination and met DSM III-R (American Psychiatric Association, 1987) criteria for schizophrenia or major depression. The normal controls were excluded if they or their relatives had a history of psychiatric diseases.

The following scales were used to describe the psychopathological status: the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Global Assessment Scale (GAS) (Endicott et al., 1976), the Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), the Schedule for the Assessment of Positive Symptoms (SAPS) (Andreasen and Olsen, 1982), the Hamilton Depression Rating Scale (Hamilton, 1967), the Bech-Rafaelsen Melancholia Scale (BRMS) (Bech and Rafaelsen, 1980), the Strauss-Carpenter Prognostic Scale (Strauss and Carpenter, 1974), and the Rating Scale for Extrapyramidal Side-Effects (EPS) (Simpson and Angus, 1970). Information was obtained about the history of medication (lifetime and 3 months prior to hospital admission) and smoking habits. Neuroleptic medication was converted into chlorpromazine equivalents (CPZ) (Davis, 1976).

Procedures

Recordings were obtained in a quiet, darkened room. Subjects were seated comfortably and had their head fixed to a headrest in order to minimize head movements. A red laser light spot, projected onto a white screen, served as the target that each subject was asked to watch closely at all times. Eye movements were measured with high-resolution infrared oculography (AMTech, Eye tracker 3). Calibration was done directly before and after testing. The course of the experiment and the recordings of eye movements were continuously monitored and supervised by the experimenter. Data were digitized on-line at 200 Hz and stored on a permanent computer hard disk.

The following two tasks were presented:

- *Prosaccade task* (Clementz et al., 1994). Beginning in the central position, the target jumped to positions of 5°, 10° or 15° to the left or right in a random manner and after each move returned to the middle. The target remained in each position for 500 ms. Each eccentric target position was presented 30 times.
- *Predictive task* (Bronstein and Kennard, 1987). The target regularly jumped back and forth between the positions 7.5° to the right and left of center, remaining 500 ms in each position. Ninety target jumps were presented.

Analyses

Digitized data were processed using the software EYEMAP written by AMTech for displaying and analyzing saccades semiautomatically.

The recordings were visually inspected on the computer monitor. Saccades were detected by EYEMAP using the following criteria: the starting point of a saccade was defined as eye velocity exceeding 30°/s, the end point as a velocity below 10°/s, amplitude between 0.2° and 20° to avoid artifacts. The experimenter had to verify and accept the proposed saccades. Blinks and artifacts were cut out. EYEMAP calculated the values for stimulus and eye position, latency (milliseconds between stimulus movement and start of saccade) and peak velocity for each single accepted saccade and stored these data as text files. For each recording mean averages were calculated for saccadic reaction time, peak velocity, accuracy and number of saccadic corrections. Since saccadic peak velocity is closely associated with the size of the amplitude, only saccades of amplitude 15°±1.25° were selected. Accuracy was calculated as ratio of saccadic amplitude to stimulus amplitude. Corrections were defined as the number of saccades necessary to match the size of the target movement. Saccadic reaction time or latency was measured as the time between the beginning of the target movement and the beginning of the subsequent saccade.

For the predictive task only peak velocity and corrections were calculated.

In all three groups age correlated significantly with reaction time. Therefore, we used reaction time data age-corrected by a simple linear regression model with age as an independent and reaction time as a dependent variable. Requirements for parametric test were not met so non-parametric tests (Kruskal-Wallis, Mann-Whitney U) were performed.

Results

Differences in demographic and clinical data

For all mean values see Table 1. The mean age in the group of depressive subjects was higher than in both other groups ($F = 28.1$, $p > 0.0001$; normals v. depressed: $Z = -4.49$, $P < 0.0001$; schizophrenics v. depressed: $Z = -5.87$, $P < 0.0001$). The group of depressed subjects contained more females (Pearson $\chi^2 = 9.51$, $P = 0.009$). Depressed subjects had a longer washout period ($Z = -2.01$, $P = 0.044$), less CPZ in the last 3 months before the examination ($Z = -2.34$, $P = 0.019$) and a tendency for a lower lifetime CPZ dose ($Z = -1.84$, $P = 0.065$). They also had a higher score in the Strauss-Carpenter Prognostic scale ($Z = -2.71$, $P = 0.007$). Schizophrenic subjects had a higher score in the BPRS ($Z = -5.15$, $P < 0.0001$) and GAS ($Z = -3.23$, $P = 0.0012$). There was no difference in number of cigarettes smoked daily between the patient groups.

Differences in basic parameters of saccadic eye movements

Oculomotor parameters for the three diagnostic groups are shown in Table 2.

Peak velocity

In both stimulus tasks, the schizophrenic subjects had the highest peak velocity. The difference to depressed subjects was significant in both tasks, to normal controls only in the prosaccade task. Between normal and depressed subjects, there was no significant difference. In the prosaccade task (Kruskal-Wallis: $\chi^2 = 11.57$, $P = 0.003$; Mann-Whitney-U: schizophrenic v. normal $Z = -2.39$, $P = 0.017$; schizophrenic v. depressed $Z = -3.14$, $P = 0.002$; normal v. depressed $Z = -1.41$, $P = 0.157$ n. s.), the differences were more pronounced than in the predictive task where there was a significant difference only between depressed and schizophrenic subjects (schizophrenic v. depressed $Z = -2.14$, $P = 0.03$).

Table 1 Demographic and clinical data

	Schizophrenia (N = 38)	Major depression (N = 32)	Normal controls (N = 42)
Age	30.3 ± 6.8	46.6 ± 11.1	34.4 ± 11.0
Female n	16 (38.1 %)	25 (73.5 %)	22 (52.4 %)
Cigarettes	13.8 ± 12.6	11.1 ± 10.8	
Lifetime CPZ	99982 ± 168157	13182 ± 36080	
Previous 3 months CPZ	6347 ± 12979	1113 ± 4185	
Washout period	54.9 ± 40.5	72.9 ± 34.0	
EPS	0.44 ± 1.21	0.03 ± 0.18	
Prognostic scale	47.0 ± 12.0	54.5 ± 6.2	
BPRS	42.6 ± 8.9	30.6 ± 6.7	
GAS	38.5 ± 8.9	46.3 ± 9.8	
SANS	14.0 ± 4.2		
SAPS	8.5 ± 3.1		
HAMD		18.9 ± 5.9	
BRMS		19.0 ± 6.0	

Table 2 Means and standard deviations for the saccadic peak velocity, accuracy, reaction time and number of corrections

Oculomotor parameter	Schizophrenia (N = 38) Mean S. D.	Major depression (N = 32) Mean S. D.	Normal control (N = 42) Mean S. D.
Prosaccades			
Peak velocity (°/s)	481.8 ± 62.9$^{**,+}$	430.0 ± 58.9	451.1 ± 46.1
Reaction time (ms)	181.3 ± 39.8	192.6 ± 32.0$^{\#\#}$	168.7 ± 27.0
Accuracy (%)	89.6 ± 11.1	93.3 ± 6.5	95.0 ± 6.0
Corrections	1.47 ± 0.23	1.43 ± 0.17	1.40 ± 0.15
Predictive saccades			
Peak velocity (°/s)	418.9 ± 62.1*	381.6 ± 71.3	397.2 ± 46.7
Corrections	2.11 ± 0.37^{++}	2.12 ± 0.30$^{\#\#}$	1.91 ± 0.27

Mann-Whitney U Test:
$^{*}/^{**}$ significant difference schizophrenic to depressive patients $p < 0.05$ /0.01
$^{+}/^{++}$ significant difference schizophrenic patient to normal controls $p < 0.05/0.01$
$^{\#\#}$ significant difference depressive patients to normal controls $p < 0.01$

Reaction time

Depressed subjects had longer mean reaction times than other groups. Between all groups, the Kruskal-Wallis test was significant ($\chi^2 = 9.53$, $P = 0.009$), the Mann-Whitney-U test indicated a difference between depressed and normals ($Z = -3.13$, $P = 0.002$), and all other tests were non-significant.

Accuracy

Schizophrenics had a tendency to be less accurate than the other groups, but the Kruskal-Wallis test for accuracy was not significant ($\chi^2 = 5.35$, $P = 0.069$).

Correction

In the prosaccade task, there were no significant differences in the number of corrections of saccadic eye movements between the three diagnostic groups. In the predictive task, there was no difference between the patient groups, but both patient groups made significantly more corrections than the normal controls ($\chi^2 = 12.94$, $P = 0.0015$; schizophrenic v. normal $Z = -2.73$, $P = 0.0063$; depressed v. normal $Z = -3.32$, $P = 0.0009$; schizophrenic v. depressed $Z = -0.55$, $P = 0.58$ n. s.).

Intraindividual correlations

Peak velocity and corrections were measured twice in two different tasks during the same session. In these parameters, there was a strong correlation between the two tasks in the same person (Spearman correlation coefficient $r = 0.784$, $P < 0.001$). In all diagnostic groups the mean of peak velocity was about 50°/s less in the predictive task than in the prosaccade task.

A higher number of corrections occurred in the pre-

dictive than in the prosaccade task. There was a significant correlation between the numbers of corrections in each task (Spearman correlation coefficient r = 0.557, P < 0.001).

Oculomotor parameters and demographic or clinical factors

Correlations between saccadic parameters and variables such as CPZ dosage, severity of EPS symptoms and number of cigarettes smoked daily were non-significant. The scores of the psychopathological rating scales did not correlate significantly with any of the oculomotor parameters.

Discussion

Peak velocity is a basic parameter of saccadic eye movements, which differentiated our schizophrenic patient group from depressive patients and normal controls. In the prosaccade task, schizophrenic patients had a higher peak velocity than normal controls and depressive patients. Although other studies have also reported increased peak velocities in schizophrenics (Cegalis et al., 1983; Straube et al., 1999), this is an unexpected finding. Straube et al. (1999) found a decrease of initially increased peak velocity after starting neuroleptic treatment. The Robinson model (Robinson, 1975) postulates the saccade dynamics, especially the saccadic velocity to be determined solely by the brainsteam burst generator. In contrast, Straube et al. (1999) conclude from their results that there exists a dopaminergic controlled cortical influence on saccade dynamics. Our finding of increased peak velocity, therefore, could be explained by the prefrontal cortex dysfunctions often described in schizophrenics (e. g., Weinberger et al., 1986). The main reason for the decreased peak velocity most other studies found could be that neuroleptic treated patients were examined.

In almost any test, it is rather rare that schizophrenics are reported to perform faster or better than control groups. Performance deficits of schizophrenics in psychophysiological tests are usually and most readily explained by general attentional deficits, which are considered to be at the core of the schizophrenic disorder (Nuechterlein and Dawson, 1984). Our results indicate that schizophrenic attentional dysfunctions do not affect peak velocity of saccades. Impairment of attentional functions induced by severe sleep deprivation has been shown to leave saccadic accuracy unaffected but to cause an increase of saccadic latency and a decrease of saccadic peak velocity in normals (De Gennaro et al., 2000). Attentional deficits in schizophrenics therefore appear to be different from general attentional impairments caused by sleepiness or similar factors. If this holds true, testing of oculomotor functions could be used to assess the specificity of schizophrenic attentional dysfunctions.

In various tests of manual reaction times, schizophrenics showed consistently prolonged reaction times, which was attributed to attentional deficits (Rodnick & Shakow, 1940; Zahn et al., 1963; Nuechterlein, 1977). In our test of saccadic reaction time, schizophrenics did not differ significantly from depressive patients or controls. Instead, the depressive patients had significantly longer reaction times than normals. Both patient groups displayed an unspecific prolongation of saccadic reaction times. This is most likely due to general attentional deficits that are unspecifically associated with psychiatric disorders and that can be seen in various mental states, such as sleepiness, distraction, neurocognitive impairment, lack of motivation, concentration or cooperation etc. The literature regarding saccadic reaction time in schizophrenics has produced conflicting results, with some finding no difference between schizophrenics, normals and depressed patients (Levin et al., 1982 a; Fukushima et al., 1988; Mather and Putchat, 1982) and others reporting increased saccadic reaction times (Schmid-Burgk et al., 1982, 1983), especially in schizophrenics with predominantly negative symptoms (Mackert and Flechtner, 1989; Mackert et al., 1989).

Schizophrenic s deviate from controls in accuracy of saccades. All groups of subjects made hypometric saccades in the prosaccade task. Schizophrenics, however, reached only 89.6 % of the originally targeted saccade, while depressive (93.3 %) and normal controls (95 %) made (not significantly) more accurate saccades. The number of corrections was increased in both patient groups but did not differ among one another. This finding is in accordance with two studies reporting an increase of hypometric saccades in schizophrenics and in their biological relatives (Mather and Putchat, 1982; Clementz et al., 1994).

Age had a significant effect on saccadic reaction time. Older patients had an increased reaction time. On all other saccadic parameters, there was no influence of age. Abel et al. (1983) reported that there were no effects of age on saccadic velocity or duration, but on the reaction time. Hutton et al. (1983) found no clear effects of age on eye movement parameters. Gender had no measurable effect on the studied variables.

Psychopathology, premedication, nicotine and EPS side effects of neuroleptic medication did not correlate significantly with the saccadic parameters studied by us. The influence of medication on eye movements has long been debated, but no conclusive evidence has been found to attribute SPEM dysfunctions to neuroleptic medication. Investigating saccadic eye movements, Crawford et al. (1995) described less accuracy under neuroleptic treatment.

Intraindividual correlations for peak velocity (r = 0.784) and number of corrections (r = 0.557) across the two different tasks suggested a moderate to good reliability of these parameters. There are only a few studies that examined the time course of saccadic parameters and they have found similar correlations (Iacono et al., 1981; Schmid-Burgk et al., 1983; Mackert and Flechtner, 1989; Schlenker and Cohen, 1995).

In conclusion, we found that saccadic eye movements of schizophrenics are characterized by an increased saccadic peak velocity and a higher number of hypometric saccades. Increased saccadic peak velocity appears to be specific to schizophrenia. This result is in accord with findings of other studies (Cegalis et al., 1983; Straube et al., 1999). Our data suggest that besides SPEM dysfunctions, deviations of basic saccadic functions are also associated with schizophrenia. Further studies are needed to gain insight into the nature of saccadic eye movement dysfunctions and to further delineate the specificity of attentional deficits in schizophrenia.

Acknowledgment This study was supported by the Deutsche Forschungsgemeinschaft (DFG), MA 1211/2–1,2. The authors are very grateful to Mrs. Traversi for the recording and processing of eye movement data.

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