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Predictive eye and hand movements are differentially affected by schizophrenia

■ **Abstract** *Background* Schizophrenic patients are known to have problems suppressing reflexive eye movements. This is considered to indicate a dysfunction in prefrontal cortex. As the eye and hand motor systems are tightly coupled, we investigated whether predictive hand movements and eye-hand coordination are unimpaired in schizophrenic patients. *Methods* Saccades and hand movements of 19 patients during an acute schizophrenic episode and 19 controls were measured in a task in which the predictability of target timing was varied. *Results* Schizophrenic patients generated more anticipatory and less visually triggered saccades than controls with both non-predictable and predictable target timing. Anticipatory saccades in the wrong direction were clearly directed towards previous target positions, indicating that they are indicators of erroneous prediction rather than of fixation instability. In contrast to saccades, the number of anticipatory and visually triggered hand movements was the same in patients as in controls. As a consequence, patients took longer to initiate a hand movement after a saccade than controls. *Conclusions* Schizophrenic patients show increased predictive saccadic activity, but no qualitative changes in predictive saccades. Since prediction itself was not disturbed, the patients' deficit rather lies in the suppression or gating of anticipatory saccades than in their generation. This may be explained by a selective dysfunction of the basal ganglia oculomotor loop. As predictive hand movements were unimpaired, the problems in eye-hand coordination as expressed by a longer initiation time of hand movements relative to saccades are a direct consequence of impaired predictive saccadic behaviour.

■ **Key words** saccade · prediction · anticipation · eye-hand coordination

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Introduction

Impairments in certain types of eye movements such as smooth pursuit and antisaccades are regarded as a biological indicator for vulnerability to schizophrenia or dysfunctions in frontal cortical circuits. Besides antisaccades, schizophrenic patients also have deficits in the generation of other kinds of voluntary saccades, namely towards a remembered or imagined stimulus [19–21, 49]. Predictive saccades represent another type of voluntary movement. Nevertheless, studies on predictive saccades in schizophrenic patients are comparatively rare.

In general, prediction is seen as a function of the prefrontal cortex [17, 29, 67]. In healthy subjects, predictable target timing or direction typically leads to reduced latencies [9, 38]. In schizophrenic subjects, impaired [32, 39], unimpaired [10, 11] and enhanced [35] predictive saccades are reported. Impairments in anticiparory saccades were observed in the form of an

increased frequency [32], or reduced accuracy [11, 12, 32, 33, 39]. Enhanced predictive saccades were found in terms of shorter latencies of predictive saccades [35, 41] and a faster build-up of predictive behaviour [35] in schizophrenic patients than in controls. Such a faster build-up was, however, not corroborated in a similar paradigm applied by Clementz et al. [10].

Since eye and hand are closely coupled when it comes to intentional movements [58], one might expect that schizophrenic patients also show alterations in predictive hand movements. Whereas there is an evidence for impaired hand movements in button press tasks [for a review, see 51] and for delayed hand motor preparation [14], studies on coordinated eye and hand movements in schizophrenic patients are very rare. One exception is a study investigating eye movements during sequentially connecting digits and letters in alternative order on a video screen (the trail making test). Schizophrenic patients made more explorative fixations of the display (so-called "planning fixations") when the cursor stood still between two targets and less explorative fixations while the cursor was moving than controls did [70]. Thus, the patients' behaviour of eye and hand movements was sequential instead of parallel. This may be interpreted either as impaired eye-hand coordination or impaired dual-task performance when two or more tasks must be processed at the same time.

In our study we investigated predictive saccades as well as predictive hand pointing movements in order to evaluate if schizophrenic subjects exhibit predictive problems specific to eye movements or more general prediction impairments. Impairments in anticipatory eye movements would be in agreement with the idea of disturbed frontal circuits [17, 65], whereas impairments in both predictive eye and hand movements or in eye-hand coordination would rather point towards disturbed basal ganglia motor loops [2, 30].

Methods

■ Subjects

A total of 19 patients, 11 women and eight men, (mean age = 35.2 years, SD = 13.6) with an acute schizophrenic episode participated in the experiment. They were all inpatients at the Psychiatric Hospital of the Ludwig-Maximilians University Munich and gave their written informed consent prior to inclusion in the study. The study protocol was approved by the ethics committee of the medical faculty of the University of Munich. 17 patients had been diagnosed to suffer from paranoid schizophrenia, one from residual schizophrenia, and one from latent schizophrenia. Diagnosis was established by two independent psychiatrists on the basis of DSM IV criteria. All patients were administered the Positive and Negative Syndrome Scale (PANSS) [36] to assess the severity of their psychiatric symptoms. The mean total PANSS score for the group was 103.11 (SD = 15.38) with mean subscale scores of 24.74 (SD = 3.36) for the positive scale, 29.95 (SD = 6.60) for the negative scale, and 51.47 (SD = 8.96) for the general psychopathology scale. Patients were also administered the Global Assessment of Functioning (GAF) scale which is rated with respect to psychological and occupational functioning on a scale from 0 (bad) to 100 (good). The mean score of all patients was 41.63 (SD = 8.13), thus indicating serious symptoms. Moreover, the patients were assessed according to the Clinical Global Impression (CGI) scale [28] to assess their treatment response. The scale has a single item measured on a 7-point scale from 1 (not ill) to 7 (extremely ill). The mean CGI level was 5.95 (SD = 0.71).

Prior to testing, 11 of the 19 patients were completely medication free, i.e. they had not received any antipsychotic or antidepressant medication for a period of at least 3 months. The remaining eight patients had shown insufficient benefits from previous neuroleptic treatment. The duration of the washout phase for these patients before testing was at least 3 days, an interval which corresponds to the washout phase used in different studies dealing with motor control [66]. For all of the patients, benzodiazepines (lorazepam) and sleep medication (zopiclone) was the only medication allowed up to 24 h before the experimental session. Smoking or coffee consumption was not allowed in the 30–60 min before testing. Patients previously receiving depot neuroleptics were not included in the study.

Two patients were left-handed, one was ambidextrous, and 16 were right-handed [53].

A total of 19 age-matched control subjects, seven women and 12 men with a mean age of 34.2 years (SD = 12.0) were recruited from employees of the Ludwig-Maximilians University Munich. None had a previous history of neurological or psychiatric disorders and all were naïve with respect to the hypotheses tested in the experiment. Most had no or little experience with eye movement measurements. 18 control subjects were right-handed, one was ambidextrous [53]. There were no significant differences concerning gender distribution and handedness between patients and controls ($P = 0.15$ (Pearson chi-square test) and $P = 0.35$ (Fisher exact test)).

Apparatus

The subjects were seated in a dark room at a distance of approximately 35 cm from a 15-inch flat screen colour monitor (NEC MultiSync LCD 1525S) with a frame frequency of 72 Hz and a spatial resolution of $1,280 \times 1,024$ pixels. This screen was firmly screwed to a table at an angle of 50° and reinforced by an additional pane of plexiglass. The subjects' right elbow rested on a padded support and their head was stabilised by a chin rest. Horizontal eye movements were recorded using a Skalar IRIS infrared limbus reflection device and hand movements were recorded using a Zebris ultrasonic device. A detailed description of the apparatus and calibration procedures is provided in Sailer et al. [59, 61]. Eye and hand movements were detected if their peak velocity exceeded 70°/s, or 10°/s, respectively, and their amplitude 5°. The main interest of the study was large amplitude (>1–2°) saccades rather than microsaccades. The beginning or end of a hand or eye movement was defined as the moment at which velocity exceeded or fell below 10% of peak velocity. Outliers were defined separately for each subject and factor level as trials in which the position error (difference between target position and end position) of the eye or hand movement was outside the threefold inter-quartile range of all trials within this cell. Outliers were eliminated from the data set.

Procedure

The target always stepped from left to right, and then from right to left and back in steps of 10°. Thus, the direction and amplitude of target steps were always fully predictable. Target positions were −20, −10, 0, +10 and +20°. The first target appeared at +10°.

In the temporally predictable task, a white fixation spot was presented at the centre of the screen for 1,500 ms. In the temporally unpredictable task, the fixation spot was presented for a random interval ranging between 1,510 and 3,500 ms. In the moment the fixation spot disappeared, a white target spot appeared for 100 ms. When the target disappeared, the background illumination of the monitor was turned off, leaving the subject in complete darkness and obstructing the view of the moving hand. The fixation spot for
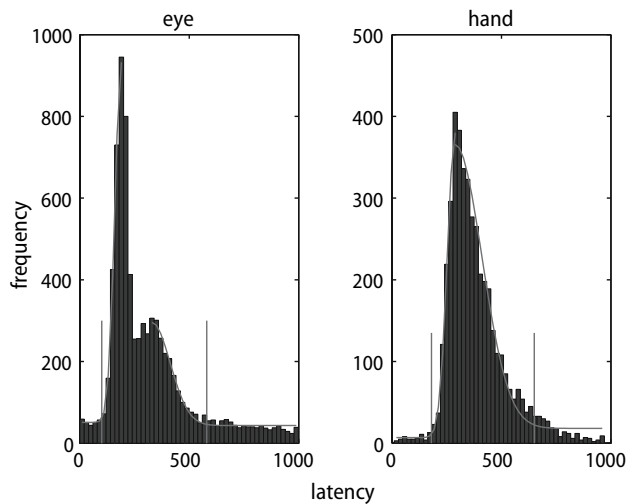
Fig. 1 Latency distributions for eye and hand movements of all subjects. Vertical lines denote the borders for the category of visually triggered movements

Fig. 2 Definition of different saccade and hand movement types

the next trial appeared at the previous target position 1,000 ms after a saccade was detected or 2,000 ms after target disappearance.

The subjects were instructed to look (eye-alone) or to look and point (eye-hand) at the target as soon as it jumped. They were told that the conditions differed with regard to the "temporal sequence of the target". They were not told, however, that the target always appeared within the same temporal interval after the fixation spot only in one condition, but not in the other.

Four conditions were administered within a single session: eye-alone predictable, eye-hand predictable, eye-alone non-predictable, eye-hand non-predictable. Each condition consisted of 50 trials. The eye-hand condition was preceded by a number of practice trials ending after the subjects reported they knew what to do and the experimenter had verified that they made at least six consecutive corrrect responses. The subjects either performed first the two predictable or the two non-predictable conditions. Within these two blocks, the order of eye-hand and eye-alone conditions was also varied across subjects.

■ Data analysis

Visually triggered movements were distinguished from other movements on the basis of eye and hand latency distributions, i.e. the time from target onset to movement initiation (see Fig. 1). One maximum for hand movements (288 ms) was observed. Saccade latencies were bimodally distributed with maxima at 190 ms and 330 ms marking the two groups of fast regular and slow regular saccades [15, 16], both of which are visually triggered. The rise of frequency to the lower maximum and the drop of the higher maximum were separately approximated by two gaussians. The limits for *visually triggered* saccades (100–580 ms) or hand movements (180–650 ms) were then defined by three standard deviations above the higher or below the lower maximum. Movements with a lower latency were termed *anticipatory*. For saccades, 100 ms is considered to be the minimal time for the integration of a visual stimulus [3, 13, 69] and is commonly used as latency border in studies on anticipatory or predictive saccades [32–35]. Saccades with a latency >580 ms and hand movements with a latency >650 composed the category of *tardy* [32] movements in order to get a clear-cut border around visually-triggered movements.

For each of these categories, it was then defined whether the saccade was in the direction of the target (a "correct" movement), or in the opposite direction (an "incorrect" movement). Thus, six categories of movements resulted (Fig. 2), of which the only rarely
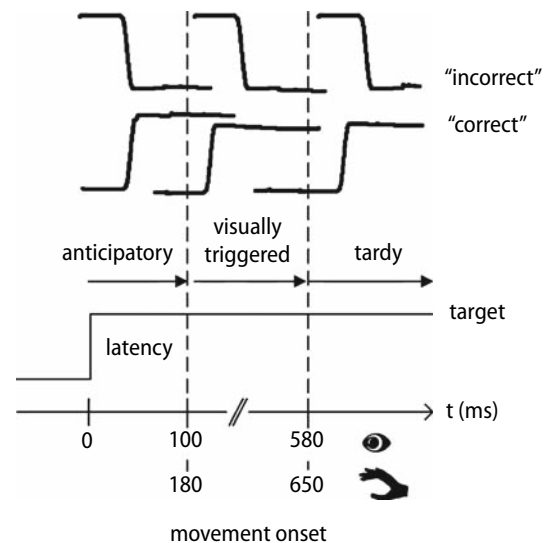
occurring incorrect visually triggered and incorrect tardy movements were not analysed any further. Thus, the term "visually triggered" or "tardy" as used in the following, refers only to correct movements.

Next, the primary movement in each trial was determined and assigned to these categories. It was defined as the first movement in a trial with a fixation duration of at least 150 ms before movement onset and at a maximal distance of 3° from the fixation point. All other movements were considered as secondary movements and not looked at further.

The frequencies of each movement type were counted and normalised to the total number of trials per subject and condition. The resulting "saccade/hand movement type frequency" can be interpreted as the probability of occurrence of a particular movement type. Since the number of observations was small for some movement types, e.g., incorrect anticipatory saccades in controls, standard ANOVA techniques could not be applied. Therefore, saccade and hand movement type frequency were analysed with a generalized linear model approach [50] based on logistic regression using the statistics package SAS/STAT 8 (Cary, North Carolina). The log-odds ratio of the observed saccade/hand movement type frequency was modelled as a linear function of the factors under consideration (see below). The interdependence of the frequencies of different movement types was accounted for by choosing an "exchangeable" covariance structure for the repeated-measures factors. The significance of the main effects and interactions of these factors were computed on the basis of TYPE3 contrasts using the Wald-Statistics (Chi-square test).

In a first step, the movement type frequencies were analysed separately for saccades and hand movements. In both of these two analyses one between-subject factor *group* (patients, controls) and the two within-subjects repeated-measures factors *movement type* (correct anticipatory, incorrect anticipatory, visually triggered and tardy) and *predictability* (predictable, non-predictable) were used. For saccades, the third repeated-measures factor *task condition* (eye-alone, eye-hand) was included. Post hoc comparisons between patients and controls as illustrated by the asterisks in Fig. 3 were performed by computing separate Mann-Whitney-*U* tests on the log-transformed frequencies for the four saccade conditions and the two hand movement conditions with subsequent Bonferroni-correction.

After analysing saccades and hand movements separately, comparisons of eye with hand movements were performed for the eye-hand condition only. For this analysis the between-subject factor group (patients, controls) and the three repeated-measures

Fig. 3 Mean frequency and standard deviation of different saccade (**A**) and hand movement (**B**) types (incorrect anticipatory, correct anticipatory, visually triggered, and tardy) for patients and controls in different conditions. Asterisks indicate significant differences for saccades at $P < 0.003$ and for hand movements at $P < 0.006$ (Bonferroni-corrected)
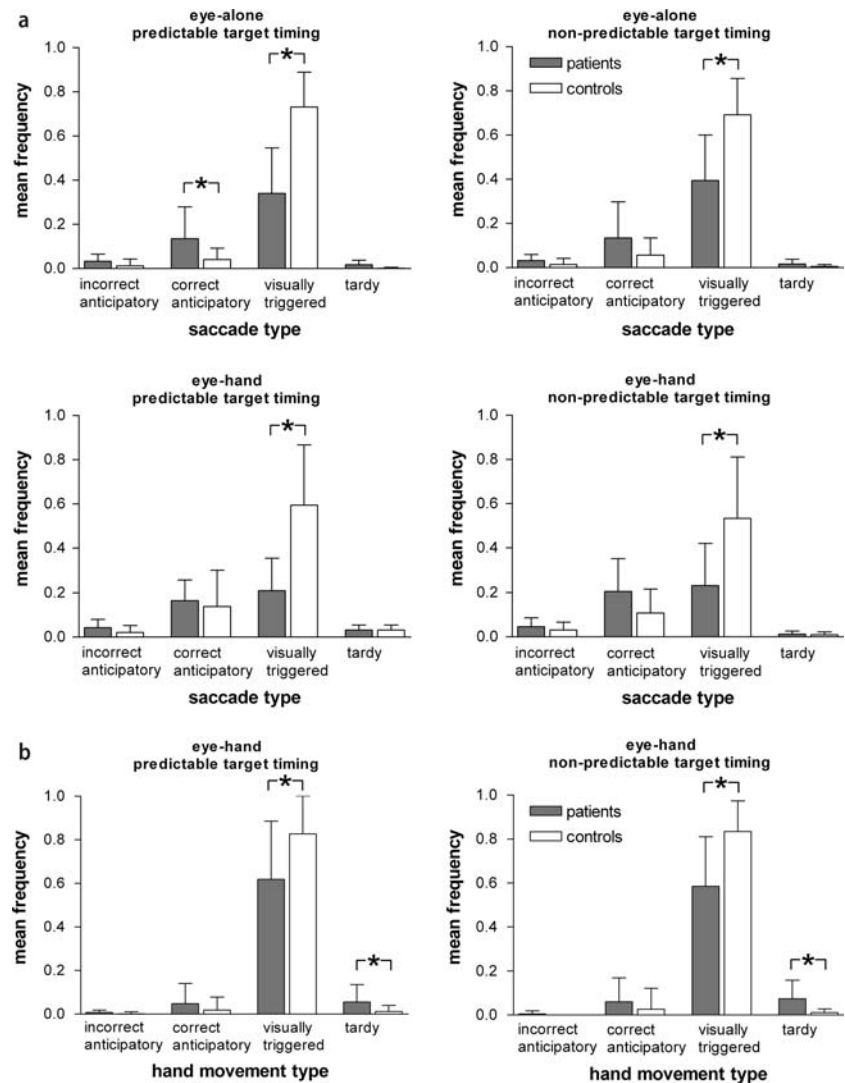
factors *effector* (eye, hand), *movement type* (correct anticipatory, incorrect anticipatory, visually triggered and tardy) and *predictability* (predictable, non-predictable) were used.

Results

■ Saccade and hand movement type frequency

Saccade type frequency

The fact that patients generated more correct anticipatory saccades and less visually triggered saccades than controls was reflected in a main effect of *group* (χ^2 (1) = 5.23, $P < 0.05$) that occurred in combination with an interaction of *group* and *saccade type*, χ^2 (3) = 51.11, $P < 0.0001$ (see Fig. 3A). There was also an interaction of *group* and *task condition*, χ^2 (1) = 9.91, $P < 0.01$. Patients and controls did not differ in the frequency of incorrect anticipatory saccades or with regard to *predictability*.

Further effects that were not related to differences between patients and controls were main effects for

movement type (χ^2 (3) = 456.79, $P < 0.0001$), indicating that the four saccade types occurred with different frequency within a trial, and *task condition* (χ^2 (1) = 11.48, $P < 0.001$). As further specified by an interaction between *task condition* and *saccade type*, χ^2 (1) = 38.62, $P < 0.0001$, there were less visually triggered saccades and more saccades of the other three types when the task was executed with eye and hand compared to the eyes alone. This effect was particularly pronounced when the target was non-predictable (interaction between *task condition* and *predictability*, χ^2 (1) = 4.48, $P < 0.05$). There was, however, no interaction between *group*, *task condition* and *saccade type*. This indicates that task condition, i.e. whether subjects followed the target with their eyes only or with both eye and hand, had the same effect on saccade type frequency in patients and controls.

Hand movement type frequency

A main effect for *group*, χ^2 (1) = 4.54, $P < 0.05$, together with an interaction of *group* and *movement*

type, χ^2 (3) = 41.72, $P < 0.0001$, showed that patients generated less visually triggered and more tardy hand movements than controls (see Fig. 3B). There was no difference in the frequency of anticipatory hand movements. In both patients and controls, different hand movement types occurred with different frequencies (main effect for *movement type*, χ^2 (3) = 373.08, $P < 0.0001$). There were no effects or interactions regarding the factor *predictability*.

Saccade versus hand movement type frequency

Again, a significant main effect for *group* occurred, χ^2 (1) = 5.23, $P < 0.05$. Patients generated more tardy and incorrect anticipatory movements and less visually triggered movements than controls (interaction of *group* and *movement type*, χ^2 (3) = 58.01, $P < 0.0001$; see Fig. 3B). Patients did not generate more correct anticipatory movements than controls, suggesting that this effect occurs in saccades only.

Both patients and controls groups generated more incorrect anticipatory saccades than hand movements (main effect for *effector*, χ^2 (1) = 4.82, $P < 0.05$, and interaction between *effector* and *movement type*, χ^2 (1) = 49.90, $P < 0.0001$), particularly when the target was non-predictable (interaction between *effector*, *predictability* and *movement type*, χ^2 (3) = 12.90, $P < 0.01$). Again, there was a main effect for *movement type* (χ^2 (3) = 607.52, $P < 0.0001$), indicating that the four movement types occurred with different frequency.

There was no general difference between patients and controls depending on whether they used their hand or eyes. The groups also did not differ with regard to *predictability*.
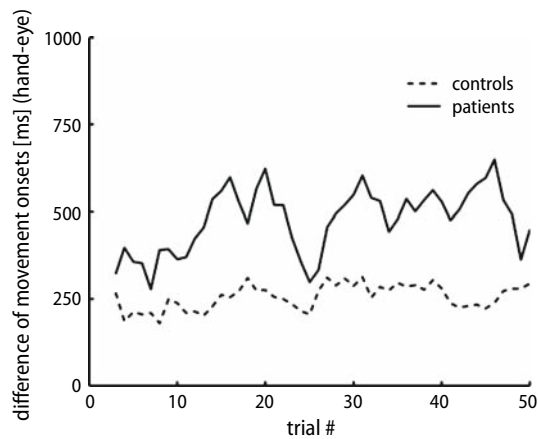
■ Movement latency

Because a categorisation into different movement categories neglects the latency variations within a category, we took a separate look at the mean latencies of the different saccade types (see Table 1). This procedure was performed without differentiating between predictability conditions, because no interaction between group and task predictability had been observed in the previous analyses of movement frequencies. Paired *t*-tests were computed separately for patients and controls. In these tests, the latencies of each saccade type in the single task were compared with the latencies of the same saccade type in the dual-task. After ensueing Bonferroni-correction of the comparisons, no effects were significant for any of the saccade types ($P < 0.006$). Thus, mean saccadic latencies were not different for any saccade type depending on whether the saccades were executed alone or together with a simultaneous hand movement. This was the case for both patients and controls. For hand movements, no such analysis was performed, since no hand-alone condition had been applied.

Since there were no effects for task condition, the saccade latency data were then collapsed across single- and dual-task conditions. Using these data, patients were compared to controls with regard to the saccade and hand movement latencies of each saccade and hand movement type by independent t-tests. A Bonferroni-correction was applied with respect to the number of different saccade types ($P < 0.013$) and hand movement types ($P < 0.013$). For none of the saccade or hand movement types, latencies in patients

Table 1 Mean latencies (ms) and standard deviation (SD) of different saccade and hand movement types in patients and controls ($N = 38$)

Effector	Task condition	Predictability	Saccade/hand movement type	Patients Mean	Patients SD	Controls Mean	Controls SD
Saccade latency	Eye-alone	Predictable	Incorrect anticipatory	−1,020	431	−1,304	92
			Correct anticipatory	−545	303	−439	436
			Visually triggered	273	72	236	51
			Tardy	769	141	991	–
		Non-predictable	Incorrect anticipatory	−1,612	722	−1,386	856
			Correct anticipatory	−1,144	563	−789	653
			Visually triggered	279	66	254	53
			Tardy	890	209	721	111
	Eye-hand	Predictable	Incorrect anticipatory	−969	366	−780	516
			Correct anticipatory	−631	251	−535	301
			Visually triggered	287	66	234	52
			Tardy	1,062	329	783	308
		Non-predictable	Incorrect anticipatory	−1,493	776	−1,461	708
			Correct anticipatory	−998	455	−1,049	438
			Visually triggered	324	88	250	43
			Tardy	898	199	1,071	442
Hand movement latency	Eye-hand	Predictable	Incorrect anticipatory	−830	438	−1,339	–
			Correct anticipatory	−290	242	−566	632
			Visually triggered	393	70	344	65
			Tardy	795	128	746	47
		Non-predictable	Incorrect anticipatory	−1,136	553	–	–
			Correct anticipatory	−771	489	−701	765
			Visually triggered	413	61	362	66
			Tardy	771	76	721	78

Fig. 4 Mean difference of onset times for saccades and hand movements in patients and controls across trials 1–50

were different to those in controls. There was only a tendency for increased latencies of visually guided saccades ($t = 2.19$, df $= 36$, $P = 0.035$) and hand movements ($t = 2.33$, df $= 36$, $P = 0.026$) in patients as compared to controls.

Difference between hand and eye movement onset

For each trial, we subtracted the onset times of primary saccades and hand movements in the condition eye-hand. A positive onset difference indicates that the hand started later than the eye. For this analysis, we did not differentiate between different movement types in order to increase the number of available values.

The difference values were averaged across the first 50 trials and subjected to repeated-measures ANOVA with the between-subject factor *group* and the within-subject factor *predictability*. Patients had a larger onset difference than controls (main effect for *group*, $F(1,35) = 6.35$, $P < 0.05$; see Fig. 4). After having generated a saccade, schizophrenic patients took on average 478 ms (SD = 289, $N = 19$) to initiate a subsequent hand movement, whereas controls took only 255 ms (SD = 197, $N = 19$). There were no effects or interactions regarding the factor predictability.

Movement amplitude

To further qualify the behaviour of eye and hand movements, the amplitude error was calculated as the difference of movement amplitude and target amplitude and recoded, so that positive values indicate an overshoot, and negative values an undershoot. The data were pooled over predictable and non-predictable conditions and over eye-alone and eye-hand conditions in order to increase the number of cases. The amplitude error of incorrect anticipatory saccades and hand movements was close to −20° (see Fig. 5). As the target amplitude was always 10°, incorrect anticipatory movements were clearly directed at previous target positions.

The amplitude errors of patients and controls were very similar (independent *t*-tests for each saccade and hand movement type with subsequent Bonferroni-correction). Thus, although the frequency of correct and incorrect anticipatory saccades was higher in patients than in controls, the accuracy was the same ($p > 0.05$). This was also true for visually triggered and tardy saccades and all the hand movements types, which were unimpaired in patients in terms of their accuracy ($P > 0.05$).

Discussion

Schizophrenic patients generated more correct anticipatory saccades than controls. This result corroborates the findings of Hommer and colleagues [32] who applied a similar frequency analysis. This behaviour resembles the enhancement of anticipatory activity described by McDowell et al. [41] and Karoumi et al. [35], indicating a lower threshold for executing a saccade. Its underlying reason may be that patients have problems in inhibiting inappropriate saccades which are triggered on the basis of an internal representation [35]. Such enhanced predictive activity in patients was, however, not reflected in the mean latencies of correct anticipatory saccades. This suggests that the smaller mean latencies reported in several studies indicate a gating problem rather than an altered prediction strategy.

Fig. 5 Mean amplitude error (deg) and standard deviation of saccades and hand movements, averaged across eye-hand and eye-alone conditions and across predictable and non-predictable targets. The numbers indicate the number of cases contained in each bar
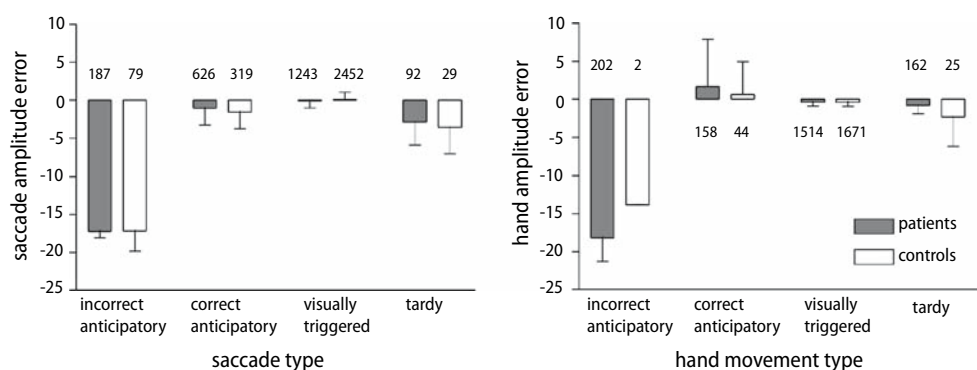
When looking at eye and hand together, patients generated more incorrect anticipatory movements than patients. However, this does not seem to be an effect of fixation instability. Both correct and incorrect anticipatory saccades were as accurate in patients as they were in controls, a finding also reported in other studies with spatially predictable targets [32, 34]. Moreover, incorrect anticipatory saccades were not distributed unsystematically across the layout of the scene, but were clearly directed at previous target positions. This indicates that the patients' spatial working memory, which is essential for generating predictive movements in periodic sequences, was intact. Previous target locations were correctly memorised.

In contrast to saccades, no enhanced anticipatory activity was manifest in hand movements. Although patients made less visually triggered hand movements than controls, there was only a non-significant tendency towards a larger number of correct anticipatory hand movements. Moreover, hand movements of all types were of similar accuracy and latency in patients and controls. This suggests that the failure of suppressing anticipatory movements was restricted to eye movements. This may be explained with reference to the brain structures responsible for the observed deficit. In the context of predictive tasks, the frontal eye fields (FEF) [27, 45, 64] and the basal ganglia [20, 31] have been discussed. The FEF is involved in the planning of internally generated saccades, whereas the basal ganglia are rather concerned with the gating and selection of saccades [7]. Since the schizophrenic patients in our study were not impaired in the generation of predictive saccades, a malfunction of gating and selection, a function attributed to the basal ganglia, seems more likely to be the case. Indeed, using fMRI it was shown that in healthy subjects FEF activity was modulated by advance knowledge of both target direction and target timing and was greatest with knowledge of both. However, only activity in the basal ganglia differentiated between an increase of predictive and express saccade or no such increase [23]. Similarly, increased errors of schizophrenic patients during inhibition tasks were found to be associated with a selective failure to activate the striatum [56]. Although the FEF was also active during inhibition, there was no difference in FEF activation between patients and controls [56]. Thus, the present data are more consistent with an impairment in basal ganglia [8, 24, 43] than FEF functioning.

The basal ganglia enable the target motor areas to predictively prepare for an action by suppressing unnecessary and inappropriate movements, and by triggering planned movements [31]. Given that the skeletomotor loop passes through the functionally corresponding portions of the basal ganglia independently of the oculomotor loop [2, 44], a differential impairment of eye and hand movements can be explained. Consistent with this interpretation, it has been suggested that the gating mechanism of the basal ganglia is working separately for different sensory modalities [7]. The present data may speak for the fact that the gating mechanism also works separately for different motor modalities. In schizophrenic patients, mainly the oculomotor loop may be affected.

As regards eye-hand coordination, patients took almost double the time than controls to initiate a hand movement after a saccade. This can, however, be explained by the increased number of anticipatory saccades in patients. Because anticipatory hand movements were not more frequent at the same time, the distance in temporal onsets between saccades and hand movements increased automatically. Thus, the deficit in eye-hand coordination is a consequence of enhanced predictive saccade activity. In the same vein, the sequencing tendency of eye fixations and hand movements observed by Wölwer et al. [70] may also be the result of an impaired gating mechanisms for eye movements.

Interestingly, patients did not behave differently than controls in the dual-task condition (eye and hand) as compared to the single-task condition (eye alone). This finding may appear somewhat surprising in view of the well-known processing capacity limitation in these patients. However, dual-tasks during which such processing capacity was reported typically used two tasks that were quite distinct from each other in terms of task requirements. For example, in one study a pegboard task was combined with repetitive tapping [22]. Whereas the pegboard task is highly dependent on manual skill, the tapping task demands producing a regular movement based on an internally generated rhythm Granholm et al. [26] combined a visual search task requiring a manual pointing response on the screen with a response time task that required pressing the space bar in reaction to a tone. In this case, only the response time task is a primarily motor task. A different study combined an auditory and visual continuous performance test [46]. Thus, tasks from two different modalities have to be combined. Each of these tasks can be considered to be more complicated than the predictive task employed in the present study. Moreover, in all these studies two tasks are combined that are quite different in nature.

In the present study, the dual-task condition consists of the execution of an eye movement together with a pointing movement. Since pointing movements are naturally accompanied by spontaneous eye movements [1, 6, 54, 55], the amount of extra processing capacity required for this dual-task condition is probably lower than in the tasks described above. This is even more the case as much research is pointing to the fact that although eye and hand movements are independent processes, they are interacting by exchanging information [18, 40, 59, 60, 62, 68]. Moreover, Bekkering and colleagues [4]

showed in a paradigm similar to ours that eye and hand movements did not interfere with each other when subjects knew in advance where the target would appear. With a spatially predictable, but temporally non-predictable target, the reaction time in the dual-task (eye and hand) was not different from the reaction time in the single tasks (eye alone, hand alone). In this case, advance selection of the required reponses is possible and this, in turn, frees processing capacity during the reaction time interval.

In the present experiment, interference between eye and hand was observed in terms of a higher number of anticipatory and tardy saccades and a smaller number of visually triggered saccades. However, this interference effect was the same for patients and controls. We believe that this was the case because processing load was not very high in the present experiment, firstly, because coordinated eye and hand movements share processing capacities, and secondly, because target predictability increased the availability of processing resources. Numerous studies have found that schizophrenic patiens reach the limits of their processing resources with higher, but not lower processing loads [25, 52]. Hence, potential limitations in schizophrenic patients did not become manifest. It would be interesting to investigate if an interference effect between eye and hand movements would become obvious in schizophrenic patients if the target were completely unpredictable.

The limitations of our study refer to the fact that eight of our patients received centrally active drugs until a few days before testing. However, a washout period of 3 days is common practice in other studies with schizophrenic patients, including studies on cognitive functions [5], SPECT investigations [42, 63], and medication effectiveness studies [37, 47, 48, 57] without evidence of interferences. Moreover, with regard to potential chronic medication effects on anticipatory saccades, neuroleptic and anticholinergic medication has been shown to leave the frequency of anticipatory saccades unaltered [32]. Only the amplitude of these types of saccades was found to be lower in treated compared to medication-free patients [12, 32]. In our study, saccade amplitude was not different in schizophrenic patients than in controls. It was only the frequency of anticipatory saccades that differed. Therefore, to our mind it seems unlikely that chronic medication effects skewed the results.

To sum up, schizophrenic patients in our study demonstrated enhanced predictive saccade activity but no differences regarding the predictive mechanism itself. The observed effects can be explained by an impaired gating mechanism for predictive saccades. This gating problem was specific for eye movements and did not concern hand movements, thus causing some related disturbances of eye-hand coordination. These results are in agreement with the idea of disturbed basal ganglia-cortex loops rather then a primary dysfunction of the prefrontal cortex.

References

1. Abrams RA, Meyer DE, Kornblum S (1990) Eye-hand coordination: oculomotor control in rapid aimed limb movements. J Exp Psychol: Hum Percept Perform 16:248–267
2. Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 9:357–381
3. Becker W (1989) Metrics. In: Wurtz RH, Goldberg ME (eds.) The Neurobiology of Saccadic Eye Movements, Elsevier, Amsterdam (Vol. 3), pp. 13–61
4. Bekkering H, Adam JJ, van den Aarssen A, Kingma H, Whiting HT (1995) Interference between saccadic eye and goal-directed hand movements. Exp Brain Res 106:475–484
5. Bender S, Dittmann-Balcar A, Schall U, Wolstein J, Klimke A, Riedel M, Vorbach EU, Kuhn KU, Lambert M, Dittmann RW, Naber D (2006) Influence of atypical neuroleptics on executive functioning in patients with schizophrenia: a randomized, double-blind comparison of olanzapine vs. clozapine. Int J Neuropsychopharmacol 9:135–145
6. Biguer B, Jeannerod M, Prablanc C (1982) The coordination of eye, head, and arm movements during reaching at a single visual target. Exp Brain Res 46:301–304
7. Brown JW, Bullock D, Grossberg S (2004) How laminar frontal cortex and basal ganglia circuits interact to control planned and reactive saccades. Neural Netw 17:471–510
8. Busatto GF, Kerwin RW (1997) Schizophrenia, psychosis, and the basal ganglia Psychiatric Clin N Am 20:897–910
9. Carpenter RHS, Williams MLL (1995) Neural computation of log likelihood in control of saccadic eye movements. Nature 377:59–62
10. Clementz BA, McDowell JE, Zisook S (1994) Saccadic system functioning among schizophrenia patients and their first-degree biological relatives. J Abnorm Psychol 103:277–287
11. Crawford TJ, Haeger B, Kennard C, Reveley MA, Henderson L (1995a) Saccadic abnormalities in psychotic patients. I. Neuroleptic-free psychotic patients. Psychol Med 25:461–471
12. Crawford TJ, Haeger B, Kennard C, Reveley MA, Henderson L (1995b) Saccadic abnormalities in psychotic patients. II. The role of neuroleptic treatment. Psychol Med 25:473–483
13. Di Lollo V (1980) Temporal integration in visual memory. Exp Psychol Gen 109:75–97
14. Dreher JC, Trapp W, Banquet JP, Keil M, Gunther W, Burnod Y (1999) Planning dysfunction in schizophrenia: impairment of potentials preceding fixed/free and single/sequence of self-initiated finger movements. Exp Brain Res 124:200–214
15. Fischer B, Weber H (1993) Modes of saccade generation and their attentional control. Behav Brain Sci 16:595–610
16. Fischer B, Weber H, Biscaldi M, Aiple F, Otto P, Stuhr V (1993) Separate populations of visually guided saccades in humans: reaction times and amplitudes. Exp Brain Res 92:528–541
17. Fox PT, Fox JM, Raichle ME, Burde RM (1985) The role of cerebral cortex in the generation of voluntary saccades: a positron emission tomography study. J Neurophysiol 54:348–369
18. Frens MA, Erkelens CJ (1991) Coordination of hand movements and saccades: evidence for a common and a separate pathway. Exp Brain Res 85:682–690
19. Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, Kato M (1988) Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. Biol Psychiat 23:670–677
20. Fukushima J, Fukushima M, Morita N, Yamashita I (1990a) Further analysis of the control of voluntary sacadic eye movements in schizophrenic patients. Biol Psychiat 28:943–958

21. Fukushima J, Morita N, Fukushima K, Chiba T, Tanaka S, Yamashita I (1990b) Voluntary control of saccadic eye movements in patients with schizophrenic and affective disorders. J Psychiat Res 24:9–24

22. Fuller R, Jahanshahi M (1999) Concurrent performance of motor tasks and processing capacity in patients with schizophrenia. J Neurol Neurosur Ps 66:668–671

23. Gagnon D, O'Driscoll GA, Petrides M, Pike GB (2000) The effect of spatial and temporal information on saccades and neural activity in oculomotor structures. Brain 125:123–139

24. Gangadhar BN, Jayakumar PN, Subbakrishna DK, Janakiramaiah N, Keshavan MS (2004) Basal ganglia high-energy phosphate metabolism in neuroleptic-naive patients with schizophrenia: a 31-phosphorus magnetic resonance spectroscopic study. Am J Psychiat 161:1304–1306

25. Granholm E (1992) Processing resource limitations in schizophrenia: implications for predicting medication response and planning attentional training. In: Margolin DI (ed) Cognitive neuropsychology in clinical practice. Oxford University Press, New York, pp 43–69

26. Granholm E, Asarnow RF, Marder SR (1996) Dual-task performance operating characteristics, resource limitations, and automatic processing in schizophrenia. Neuropsychology 10:11–21

27. Guitton D, Buchtel HA, Douglas RM (1985) Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. Exp Brain Res 58:455–472

28. Guy W, Bonato RR (1970) CGI: Clinical Global Impressions. In: Manual for the ECDEU Assessment Battery. National Institute of Mental Health 12-1–12-6

29. Hasegawa RP, Blitz AM, Geller NL, Goldberg ME (2000) Neurons in monkey prefrontal cortex that track past or predict future performance. Science 290(5497):1786–1789

30. Hikosaka O (1989) Role of basal ganglia in saccades. Rev Neurol (Paris) 145:580–586

31. Hikosaka O, Takikawa Y, Kawagoe R (2000) Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol Rev 80:953–978

32. Hommer DW, Clem T, Litman R, Pickar D (1991) Maladaptive anticipatory saccades in schizophrenia. Biol Psychiat 30:779–794

33. Hutton SB, Cuthbert I, Crawford TJ, Kennard C, Barnes TR, Joyce EM (2001) Saccadic hypometria in drug-naive and drug-treated schizophrenic patients: a working memory deficit? Psychophysiology 38:125–132

34. Iacono WG, Tuason VB, Johnson RA (1981) Dissociation of smooth-pursuit and saccadic eye tracking in remitted schizophrenics. An ocular reaction time task that schizophrenic perform well. Arch Gen Psychiat 35:991–996

35. Karoumi B, Ventre-Dominey J, Dalery J (1998) Predictive saccade behavior is enhanced in schizophrenia. Cognition 68:B81–B91

36. Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (panss) for schizophrenia. Schiz Bull 13:261–276

37. Keefe RS, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, Lewine RR, Yurgelun-Todd DA, Gur RC, Tohen M, Tollefson GD, Sanger TM, Lieberman JA (2004) Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry 161:985–995

38. Kingstone A, Klein RM (1993) Visual offsets facilitate saccadic latency: does predisengagement of visuospatial attention mediate this gap effect? J Exp Psychol: Hum Percept Perform 19:1251–1265

39. Krebs MO, Gut-Fayand A, Amado I, Daban C, Bourdel MC, Poirier MF, Berthoz A (2001) Impairment of predictive saccades in schizophrenia. Neuroreport 12:465–469

40. Lazzari S, Vercher JL, Buizza A (1987) Manuo-ocular coordination in target tracking. I. A model simulating human performance. Biol Cybern 77:257–266

41. McDowell JE, Clementz BA, Wixted JT (1996) Timing and amplitude of saccades during predictive saccadic tracking in schizophrenia. Psychophysiology 33:93–101

42. Meisenzahl EM, Dresel S, Frodl T, Schmitt GJ, Preuss UW, Rossmuller B, Tatsch K, Mager T, Hahn K, Möller HJ (2000) D2 receptor occupancy under recommended and high doses of olanzapine: an iodine-123-iodobenzamide SPECT study. J Psychopharmacol 14:364–370

43. Menon V, Anagnoson AB, Glover GH, Pfefferbaum A (2001) Functional magnetic resonance imaging evidence for disrupted basal ganglia function in schizophrenia. Am J Psychiat 158:646–649

44. Middleton FA, Strick PL (2001) Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res Rev 31:236–250

45. Milea D, Lobel E, Lehericy S, Duffau H, Rivaud-Pechoux S, Berthoz A, Pierrot-Deseilligny C (2002) Intraoperative frontal eye field stimulation elicits ocular deviation and saccade suppression. Neuroreport 13:1359–1364

46. Moriarty PJ, Harvey PD, Mitropoulou V, Granholm E, Silverman JM, Siever LJ (2003) Reduced processing resource availability in schizotypal personality disorder: evidence from a dual-task CPT study. J Clin Exp Neuropsych 25:335–347

47. Möller HJ, Boyer P, Fleurot O, Rein W, PROD-ASLP Study Group (1997) Improvement of acute exacerbations of schizophrenia with amisulpride: a comparison with haloperidol. Psychopharmacology (Berl) 132:396–401

48. Müller N, Riedel M, Scheppach C, Brandstatter B, Sokullu S, Krampe K, Ulmschneider M, Engel RR, Möller HJ, Schwarz MJ (2002) Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. Am J Psychiatry 159:1029–1034

49. Müller N, Riedel M, Eggert T, Straube A (1999) Internally and externally guided voluntary saccades in unmedicated and medicated schizophrenic patients. Part II. Saccadic latency, gain, and fixation suppression errors. Eur Arch Psy Clin N 249:7–14

50. Nelder JA, Wedderburn RWM (1972) Generalized linear models. J R Stat Soc A 135:370–384

51. Nuechterlein KH (1977) Reaction time and attention in schizophrenia: a critical evaluation of the data and theories. Schiz Bull 3:373–428

52. Nuechterlein KH, Dawson ME (1984) Information processing and attentional functioning in the course of schizophrenic disorder. Schiz Bull 10:160–203

53. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113

54. Paillard J (1982) The contribution of peripheral and central vision to visually guided reaching. In: Ingle DJ, Goodale MA, Mansfield RJ (eds) Analysis of visual behavior. MIT Press, Cambridge Mass, pp 367–385

55. Prablanc C, Echallier JF, Komilis E, Jeannerod M (1979) Optimal response of eye and hand motor systems in pointing at a visual target. I. Spatio–temporal characteristics of eye and hand movements and their relationships when varying the amount of visual information. Biol Cybern 35:113–124

56. Raemaekers M, Jansma JM, Cahn W, Van der Geest JN, van der Linden JA, Kahn RS, Ramsey NF (2002) Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. Arch Gen Psychiat 59:313–320

57. Riedel M, Müller N, Strassnig M, Spellmann I, Engel RR, Musil R, Dehning S, Douhet A, Schwarz MJ, Möller HJ (2005) Quetiapine has equivalent efficacy and superior tolerability to risperidone in the treatment of schizophrenia with predominantly negative symptoms. Eur Arch Psychiatry Clin Neurosci 255:432–437

58. Sailer U, Eggert T, Ditterich J, Straube A (2000) Spatial and temporal aspects of eye-hand coordination across different tasks. Exp Brain Res 134:163–173

59. Sailer U, Eggert T, Ditterich J, Straube A (2002a) Global effect of a nearby distractor on targeting eye and hand movements. J Exp Psychol: Hum Percept Perform 28:1432–1446

422

60. Sailer U, Eggert T, Straube A (2002b) Implications of distracter effects for the organization of eye movements, hand movements, and perception. Prog Brain Res 140:341–349

61. Sailer U, Eggert T, Straube A (2005) Impaired temporal prediction and eye-hand coordination in patients with cerebellar lesions. Behav Brain Res 160:72–87

62. Scarchilli K, Vercher JL (1999) The oculomanual coordination control center takes into account the mechanical properties of the arm. Exp Brain Res 124:42–52

63. Schmitt GJ, Meisenzahl EM, Dresel S, Tatsch K, Rossmuller B, Frodl T, Preuss UW, Hahn K, Möller HJ (2002) Striatal dopamine D2 receptor binding of risperidone in schizophrenic patients as assessed by 123I-iodobenzamide SPECT: a comparative study with olanzapine. J Psychopharmacol 16:200–206

64. Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, Carl JR (1996) Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. J Neurophysiol 75:454–468

65. Thaker GK, Nguyen JA, Tamminga CA (1989) Saccadic distractibility in schizophrenic patients with tardive dyskinesia. Arch Gen Psychiat 46(8):755–756

66. Tigges P, Mergl R, Frodl T, Meisenzahl EM, Gallinat J, Schröter A, Riedel M, Müller N, Möller HJ, Hegerl U (2000) Digitized analysis of abnormal hand-motor performance in schizophrenic patients. Schizophr Res 45:133–143

67. Tsujimoto S, Sawaguchi T (2005) Neuronal activity representing temporal prediction of reward in the primate prefrontal cortex. J Neurophysiol 93:3687–3692

68. Vercher JL, Lazzari S, Gauthier G (1997) Manuo-ocular coordination in target tracking. II. Comparing the model with human behavior. Biol Cybern 77:267–275

69. Wenban-Smith MG, Findlay JM (1991) Express saccades: is there a separate population in humans? Exp Brain Res 87:218–222

70. Wölwer W, Falkai P, Streit M, Gaebel W (2003) Trait characteristic of impaired visuomotor integration during trail-making test B performance in schizophrenia. Neuropsychobiology 48:59–67