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RESEARCH ARTICLE

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Saccadic disinhibition in schizophrenia patients and their first-degree biological relatives

A parametric study of the effects of increasing inhibitory load

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Abstract Several studies have reported that patients with schizophrenia and their relatives perform poorly on antisaccade tasks and have suggested that this deficit represents saccadic disinhibition. If this proposition is correct, then varying task parameters that specifically increase the difficulty with which unwanted saccades can be inhibited should exacerbate deficits. Forty-two schizophrenia patients, 42 of their first-degree biological relatives, 21 psychotic affective disorder patients, and 38 nonpsychiatric comparison subjects were given fixation and antisaccade tasks. The introduction of distracters and the presence of visible fixation stimuli were parameters used to vary the difficulty in suppressing unwanted saccades (inhibitory load). It is known that the presence of a fixation stimulus at the time when a saccade must be inhibited results in fewer reflexive errors on antisaccade tasks. Performance on fixation tasks without (low load) vs with distracters (high load) and antisaccade tasks that had fixation stimuli still visible (low load) vs already extinguished (high load) at the time when the reflexive saccade must be inhibited was compared. The schizophrenia patients and their first-degree biological relatives showed evidence of increased saccadic disinhibition that was most pronounced during high inhibitory load conditions. These data indicate that dysfunctional inhibitory processes, at least in the oculomotor domain, are associated with the liability to schizophrenia. Results also suggest that this genetic liability may be related to dysfunctional prefrontal cortical areas that provide top-down inhibitory control over reflexive saccade generation.

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Introduction

Antisaccade tasks (Hallett 1978; Hallett and Adams 1980) measure oculomotor response inhibition and require voluntary control over prepotent reflexive saccades. Reflexive errors made during antisaccade tasks occur when one has difficulty inhibiting saccades under conditions where they are context-inappropriate. It is now well established that schizophrenia patients perform poorly on antisaccade tasks (e.g., Clementz et al. 1994; Curtis et al. 2001; Fukushima et al. 1994; Katsanis et al. 1997; McDowell and Clementz 1997). Moreover, first-degree biological relatives of schizophrenia patients (Clementz et al. 1994; Curtis et al. 2001; Katsanis et al. 1997; McDowell et al. 1999), neuroleptic-free schizophrenia patients (Crawford et al. 1995), and even schizophrenia patients in full remission (Curtis et al. 2001) all show a marked increase in the number of reflexive errors on antisaccade tasks.

Poor antisaccade performance among schizophrenia patients has been interpreted to reflect dysfunctional inhibitory control over volitional oculomotion, because neurological studies of patients with prefrontal damage have demonstrated that these patients have difficulty inhibiting reflexive glances during antisaccade tasks (Gaymard et al. 1998a; Guitton et al. 1985; Pierrot-Deseilligny et al. 1995). However, before such brain-behavior inferences can be drawn, further research is needed into the nature and possible causes of poor antisaccade performance. Researchers have attempted to demonstrate that poor antisaccade performance is specifically tied to an increased number of reflexive errors and have provided evidence that other aspects of schizophrenia patients' saccade metrics on visually guided tasks are largely within the normal range (Clementz et al. 1994; Curtis et al. 2001; McDowell and Clementz 1997). This methodology is based on a subtractive procedure; the specific task demands that are implicated in poor antisaccade performance are inferred by discounting the task demands shared with another saccadic task on which patients perform within normal limits.

Another approach, used in this investigation, is based on parametric manipulation of task features that vary specific demands that are of interest. We focus here on the construct that antisaccade tasks putatively measure, namely reflexive saccadic suppression or inhibition. This study attempts to show that (a) the liability to schizophrenia is associated with evidence of saccadic disinhibition on different but similar measures of saccadic response inhibition, and (b) manipulating task parameters that increase the inhibitory demands placed upon the saccadic system results in a disproportionate worsening of performance among the schizophrenia patients and their relatives.

The research cited above implies that antisaccade task performance, as a measure of ability to inhibit undesired saccades, has great potential to be a marker of prefrontal dysfunction in those at risk for schizophrenia. But do schizophrenia patients have a generalized pattern of difficulty in suppressing unwanted saccades that is evident even during elementary fixation maintenance? Or does suppression failure become apparent only when inhibitory requirements are high as is the case when the patient is presented with a prepotent stimulus that competes for attention (e.g., a suddenly appearing distracting cue)?

This question of whether schizophrenia patients have difficulty in maintaining fixation during fixation tasks has been addressed by only a few studies. Typical fixation tasks simply require subjects to keep their eyes focused on a nonmoving target in the absence of other visual stimuli, and the number of saccades away from the target is determined. Some studies indicate that schizophrenia patients do not make more fixation-intrusive saccades than controls (Clementz et al. 1994; Kissler and Clementz 1998; Matsue et al. 1986; Radant et al. 1997; Ross et al. 1988; Schreiber et al. 1995) and others find that patients have difficulty in maintaining fixation (Amador et al. 1995; Ciuffreda et al. 1994). However, if to-be-ignored but distracting stimuli appear in the periphery, patients with schizophrenia generate more reflexive saccades to those distracters than control subjects (Fukushima et al. 1990; Paus et al. 1991).

Further evidence for saccadic disinhibition comes from studies of memory-guided saccade tasks as well. In this paradigm, subjects are asked to withhold making a saccade to a target that flashes briefly at the periphery for a given delay interval until the central fixation point disappears, at which point they move their eyes to the remembered target location. Schizophrenic patients have difficulty suppressing a reflexive saccade to the briefly flashed cue (Brenner et al. 1998; McDowell and Clementz 1996), further supporting the notion of a specific deficit involving saccadic inhibition.

Thus, past research suggests that if the task demands are low, in terms of ease with which unwanted saccades can be suppressed, as they are during fixation tasks, schizophrenia patients may perform no differently to nonpsychiatric controls. However, introducing distracters that are irrelevant to successful task performance is sufficient to elicit reliable deficits in their ability to inhibit unwanted saccades. It may be, therefore, that a certain threshold of inhibitory load must be surpassed before saccadic disinhibition becomes apparent. If deficits can be demonstrated on different saccadic measures and performance decline can be demonstrated to be a function of the amount of inhibitory load, this would implicate prefrontal substrates that provide top-down inhibitory control over saccadic generation and not other aspects of saccadic control. These hypotheses have not been tested before, and it is unknown how healthy relatives of patients with schizophrenia perform on tests of saccadic inhibition other than antisaccade tasks.

Table 1 Summary of the task parameters used to manipulate inhibitory load

Inhibitory load	Task type	
	Fixation	Antisaccade
High	With distraction	Step
Low	Without distraction	Overlap

The current study was designed to address several issues regarding the nature of saccadic disinhibition in schizophrenia. In a sample of schizophrenia patients, their nonpsychotic relatives, and psychiatric and nonpsychiatric comparison groups, we studied the influence of parametrically varying the inhibitory load on two tasks that assessed volitional saccadic control and the withholding of unwanted saccades (Table 1). “Inhibitory load” is a descriptive term referring to the relative ease with which unwanted saccades can be inhibited in the tasks we used.

First, we compared performance on two fixation tasks. The low inhibitory load condition was simply a fixation maintenance task. To increase inhibitory load, distracting stimuli were presented in the periphery while subjects attempted to maintain fixation. Second, we compared performance on two antisaccade tasks. During the low inhibitory load condition, the fixation stimulus remained visible for 200 ms after the peripheral cue was presented (overlap antisaccade). To increase inhibitory load, the offset of the fixation stimulus was simultaneous with the onset of the peripheral cue (step antisaccade). This condition has a higher inhibitory load because, at the time when a saccade must be withheld, there is no visible fixation stimulus. Presumably, in the absence of visible fixation, attentional resources are more prone to automatic orienting (i.e., in this case a reflexive saccade). Subjects commit significantly fewer reflexive errors during overlap versus step antisaccade tasks (Fischer and Weber 1992, 1997; McDowell and Clementz 1997). We hypothesized that increasing inhibitory load will result in disproportionate performance decrements in the schizophrenic and relative groups.

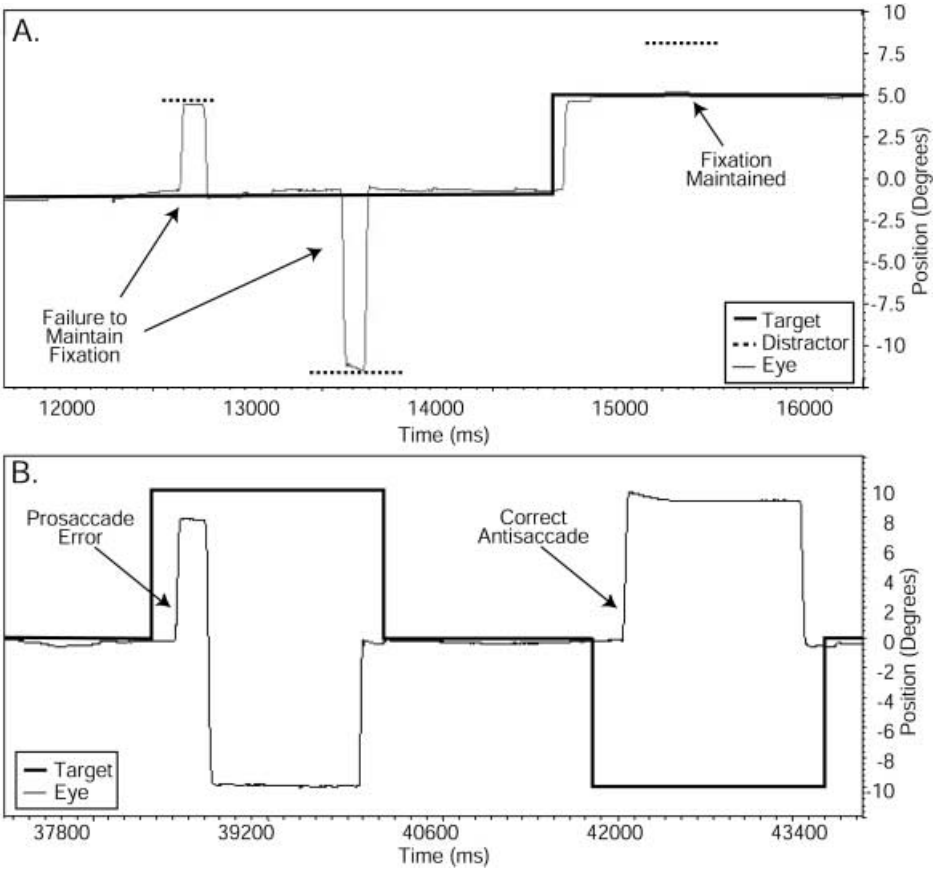

Fig. 1A, B Examples of fixation and antisaccade task performance. **A** Fixation with distraction task. The subject is instructed to maintain fixation and ignore stimuli that flash in the periphery (*dotted lines*). The subject fails to maintain fixation and makes a brief saccade to the distractor during trials 1 and 2. The subject correctly maintains fixation in trial 3. **B** Antisaccade step task. The subject is instructed to make a saccade to the side opposite the peripheral cue. On the 1st trial, the subject makes a reflexive prosaccade error in the direction of the cue followed by a corrective antisaccade. On the 2nd trial, the subject correctly inhibits making a reflexive saccade to the cue and generates a voluntary saccade to the correct imagined location in the opposite hemifield of the cue (antisaccade)

Materials and methods

Participants

A group of 42 schizophrenia patients (26 men, 16 women; mean age 36±09 years; mean Global Assessment of Functioning scale, GAF, 25.2±12.8) were recruited from the acute-care psychiatric units of a regional hospital that serves a large metropolitan area. In addition, 42 biological first-degree relatives (20 men, 22 women; mean age 42±10 years) of the probands were recruited. Two comparison groups, one composed of patients with an affective disorder with current psychotic features and another composed of community volunteers without a psychiatric disorder, were included. Twenty-three patients (10 men, 13 women; mean age 31±12 years; mean GAF 27.0±12) with a diagnosis of major depressive disorder with psychotic features (n=9) or bipolar disorder with psychotic features (n=14) participated. Thirty-eight nonpsychiatric participants (14 men, 24 women; mean age 34±12 years) were recruited from family practice and other medical clinics, trade schools, and churches. They were screened and included if they had never had a DSM-IV mood disorder, psychotic symptom, lifetime substance dependence, or current substance abuse. They were excluded if they reported that they or a first-degree biological relative had ever received treatment for any psychiatric disorder.

All participants were between the ages of 18 and 65 years, spoke English fluently, had not recently undergone electroconvulsive therapy (ECT), and had no history of neurological disease, systemic disease known to involve CNS functioning, clinically significant head injury, or mental retardation. All participants provided written informed consent prior to the experimental session. DSM-IV diagnostic information was obtained from interviews using the structured clinical interview for DSM-IV (SCID, modules A–E) and chart reviews. To confirm diagnostic assignments, a consensus diagnostic team reviewed the SCID and chart data.

All patients were currently taking psychiatric medications that fell into six classes: typical antipsychotics, atypical antipsychotics, mood stabilizers, antidepressants, anxiolytics, and anticholinergics. Trained technicians assessed medication side effects in each of the patients. Observations and examinations were made under standardized conditions that can provoke expression of neuroleptic-induced side effects if they exist. Widely used rating scales were used to measure the presence and extent of extrapyramidal side-effects (EPS), tardive dyskinesia (TD), and akathisia (Barnes 1989; Simpson and Angus 1970; Simpson et al. 1979).

Saccadic tasks

Oculomotor recordings were obtained in a quiet, darkened room, using both infrared (IR; Applied Science Laboratories, model 210) and electro-oculographic (EOG; Grass model 7 E polygraph) recording techniques. Head movement was minimized with the use of a bite-bar and dental impression. The eye tracking measures were derived from the IR recordings. Vertical EOG recordings were used to aid in the identification and removal of blinks from the IR record. All stimuli (yellow circles, 0.5° in diameter) were presented on a darkened computer monitor positioned 48 cm from the eyes of the participant.

Two fixation tasks were administered. During the simple fixation task (FIX), subjects were instructed to keep their eyes focused on a stationary, yellow-filled circular target. Infrared light can often irritate the eyes when fixating for an extended period without blinking or making eye movements. Thus, to minimize discomfort, the fixation stimulus was presented for only 5 s at a time at three locations (center, 5° left, center, and then 5° right). The total time was divided into 12 segments or trials, and if a saccade with amplitude greater than 0.5° off-target occurred within a trial it was considered an error. The proportion of trials in which an error was

made was computed. By using the proportion of errors as the dependent variables, the scoring of this task involved the same metric as the tasks described below.

In the fixation with distraction condition (FIX-D; Fig. 1A), the target was identical to that used in the FIX condition. But while fixating on the target, other yellow, hollow dots briefly (between 500 and 1,750 ms) flashed on the screen in the periphery between 2.5 and 17.5° left or right of the fixation stimulus and in the same horizontal plane. Twelve distracters were presented over the span of 30 s. Subjects were instructed not to look at the distracters, but instead to keep their eyes focused on the fixation target. The number of trials in which a reflexive saccade was made in the direction of a distractor was divided by the total number of valid trials.

Two antisaccade tasks were administered. In each, fixation was maintained centrally with a fixation point. Following a 2- to 3-s pseudorandom interval, a peripheral cue appeared at 10° either left or right in an unpredictable fashion. In the antisaccade overlap (AS-O) condition, the central fixation point remained visible for 200 ms following the onset of the peripheral cue, which lasted 2 s. In the antisaccade step (AS-S; Fig. 1B) condition, the central fixation point extinguished contemporaneously with the onset of the peripheral cue. Subjects were instructed not to look at the cue, but instead to direct their gaze to the side opposite the cue. The stimulus then returned to central fixation, signaling the beginning of a new trial. One block of 20 trials (10 leftward and 10 rightward) was presented. The proportion of incorrect reflexive saccades out of all valid trials was computed. Although rare, trials in which a reflexive error was made and a corrective antisaccade was not, were excluded from analyses. This helped assure that analyses were based upon trials in which subjects understood the instructions and were attentive. All subjects performed the tasks in the following order: FIX, FIX-D, AS-O, then AS-S. A portion of the AS-S data reported here are from a subset of subjects that come from a large family study of oculomotion, which has been presented elsewhere (Curtis et al. 2001). Subjects from the larger sample that are not included in this report did not have fixation or AS-O data, which were added to the battery later in the study. The results of analyses of saccade gain and saccade latencies are presented by Curtis et al. (2001) and show that patients with schizophrenia, but not their relatives, have increased saccadic reaction times only on trials in which a correct antisaccade is made.

Statistical analyses

To test the study hypotheses, several targeted statistical analyses were performed. Two omnibus repeated-measures MANOVAs were computed. One was used to test for the within-subjects effects of inhibitory load on performance of the two fixation tasks (FIX, FIX-D). Another was used to test the within-subjects effects of inhibitory load (task) on performance of the two antisaccade tasks (AS-O, AS-S). Group (schizophrenia, relative, affective, nonpsychiatric) was the between-subjects factor for both omnibus MANOVAs. If significant, the group effects were followed-up with Student-Newman-Keuls tests using an alpha of $P<0.05$. However, because the key predicted effect in this study involved a disproportionate decrement in performance among the patients with schizophrenia and their relatives when inhibitory load was increased, the analyses focused on the task-by-group interactions. Significant omnibus MANOVA interaction effects were followed-up with three simple repeated-measures MANOVAs to determine whether the specific group (schizophrenia, relative, or affective disorder vs nonpsychiatric comparison group) by task condition (low vs high load) interactions were significant. To confirm that the experimental manipulation of increasing inhibitory load was successful in causing more errors, paired *t*-tests, using an alpha of $P<0.05$, were computed within each group comparing performance on the low load vs high load conditions. In addition, since it is not necessarily the case that scores at different parts of the range of proportionally scored variables are equal in interval and the variance at the extremes of the distribution of proportions is compressed, an arcsine transformation (Neter et al. 1996) of all of the percentage error dependent variables was performed.

Results

Preliminary analyses

Analysis of variance indicated that the unipolar patients were not different from the bipolar patients in the number of inappropriate saccades made during FIX ($F_{1,22}$= 0.02, n.s.) FIX-D ($F_{1,22}$=0.37, n.s.), AS-O ($F_{1,22}$=0.29, n.s.), or AS-S ($F_{1,22}$=0.53, n.s.). Thus, these patients were collapsed into a single affective disorder group for the remaining analyses.

Gender [$\chi^2(3)=4.60$, $P>0.21$] but not age ($F_{3,132}$= 6.54, $P<0.002$) was balanced across the four groups. Gender was not related to the dependent variables and thus was ignored in the remaining analyses. The relatives were on average older than the other groups, which did not differ in age. Based on Pearson product-moment correlation coefficients, age was not significantly associated with any of the saccadic dependent variables (FIX, r=0.15; FIX-D, r=0.11; AS-O, r=0.04; AS-S, r=0.01). Additionally, age was not significantly associated with any of the dependent variables even when within-group correlations were computed (15 of the 16 *P*-values >0.25 and the remaining *P*-value=0.07). Thus, age was ignored in the remaining analyses.

Fixation tasks

The fixation task MANOVA revealed that the effects of task ($F_{1,135}$=15.88, $P<0.001$) group ($F_{3,135}$=17.24, $P<0.001$), and the interaction of task by group ($F_{3,135}$= 8.35, $P<0.001$) were all significant (Fig. 2A). Within-group paired *t*-tests indicated that more errors (i.e., saccades away from fixation) were made when distracters were presented (FIX-D>FIX) for all groups except the nonpsychiatric comparison subjects. The follow-up repeated-measures MANOVA revealed that the schizophrenia patients made more errors than the nonpsychiatric comparison participants on both the FIX and FIX-D, and the fixation task-by-group interaction was significant ($F_{1,78}$=19.81, $P<0.001$). The MANOVA for the relatives indicated that, compared with the nonpsychiatric comparison group, the relatives made more saccades that intruded on fixation, but only when distracters were present (FIX-D), and there was a significant group-by-task interaction ($F_{1,78}$=4.03, $P<0.05$). The final MANOVA revealed that although the affective disorder patients made more saccades than the nonpsychiatric comparison group during both fixation tasks, they did not show a significant group-by-task interaction ($F_{1,56}$= 1.96, n.s.). These various interaction effects indicate that the schizophrenia patients and their relatives, but not the psychotic affective disorder patients, showed a statistically significant, disproportionate worsening of saccadic control when the inhibitory load was increased by the introduction of distracters.

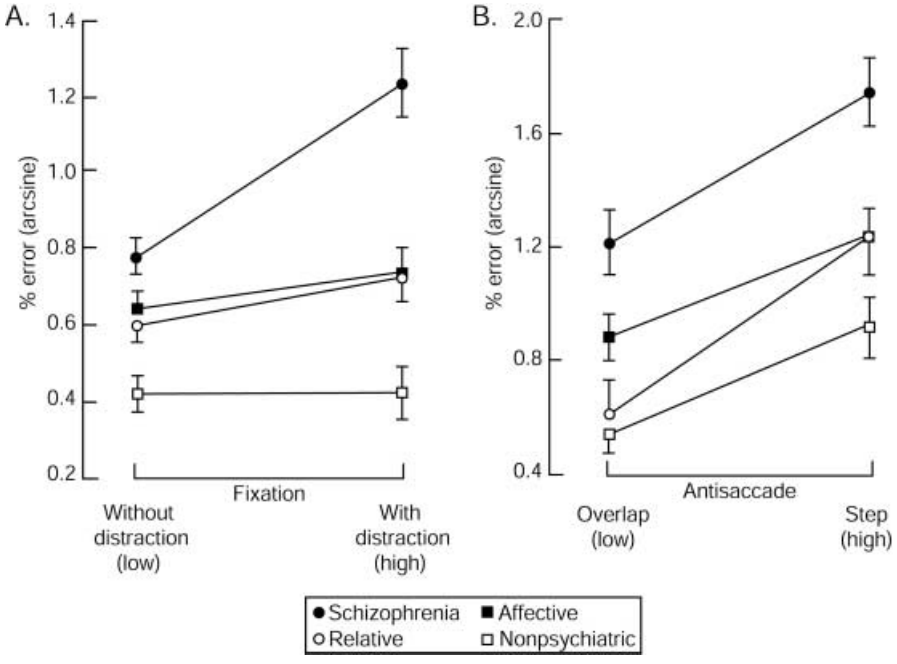

Fig. 2A, B The effects of increasing inhibitory load on the fixation and antisaccade tasks. **A** For each group, the mean percentage of trials (arcsine transformed) in which a saccadic error was made on the two fixation conditions is plotted. **B** For each group, the mean percentage of trials (arcsine transformed) in which a saccadic error was made on the two antisaccade conditions is plotted. Notice how the relatives' and the schizophrenia patients' performance deteriorates compared with the controls when inhibitory load is high

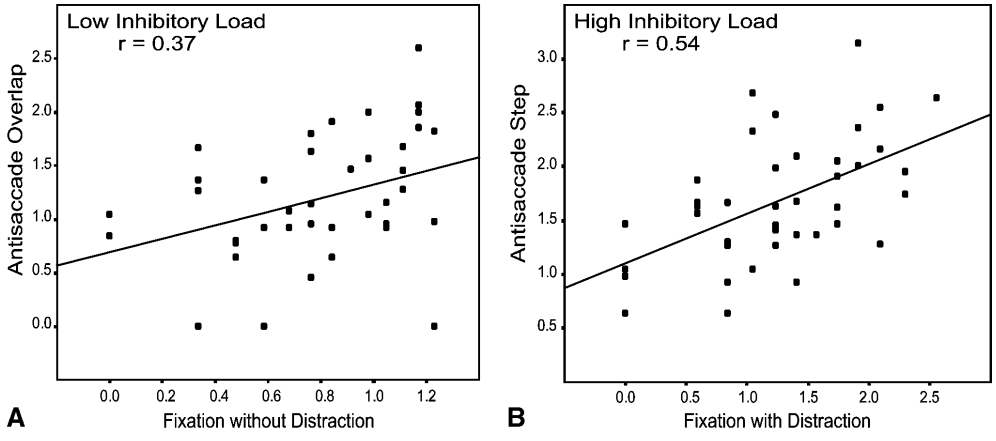

Fig. 3A, B Cross-task correlations between errors on the fixation and antisaccade tasks among the patients with schizophrenia (n=42). When the inhibitory load was low (**A**), errors on the fixation task and the overlap antisaccade task were moderately correlated. When the inhibitory load was increased (**B**), the correlation between errors on the fixation and antisaccade tasks was significantly stronger. Thus, as inhibitory load increased, the similarity in cross-task performance increased

Antisaccade tasks

The antisaccade MANOVA revealed that the effects of task ($F_{1,135}$=125.10, P<0.001), group ($F_{3,135}$=20.35, P<0.001), and the interaction of task by group ($F_{3,135}$= 2.85, P<0.04) were all significant (Fig. 2B). Within-group paired t-tests indicated that more errors (i.e., reflexive prosaccades) were made when fixation was absent (AS-S>AS-O) for all groups. The repeated-measures MANOVA for the schizophrenia patients revealed that they made more reflexive errors than the nonpsychiatric comparison participants on both AS-O (schizophrenia: mean 35.9, SD 24.6; nonpsychiatric: mean 9.9, SD 8.4) and AS-S (schizophrenia: mean 56.4, SD 25.7; nonpsychiatric: mean 24.4, SD 22.3), but the antisaccade task-by-group interaction failed to reach significance ($F_{1,78}$=2.33, P=0.15). The repeated-measures MANOVA for the relatives indicated that, compared with the nonpsychiatric comparison group, the relatives made more reflexive errors, but only when the fixation stimulus was absent at cue presentation (AS-O: mean 12.3, SD 11.6; AS-S: mean 35.48, SD 20.6), and there was a significant group-by-task interaction ($F_{1,78}$=6.21, P<0.02). The repeated-measures MANOVA for the affective patients revealed that, although they made more reflexive errors than the nonpsychiatric comparison group during both antisaccade tasks, they did not show a significant group-by-task interaction ($F_{1,56}$=0.29, n.s.). Based on these interaction effects, the relatives, but not the schizophrenic or affective disorder patients, showed a statistically significant, disproportionate worsening of antisaccade performance when the inhibitory load was increased. Although the interaction effect for the schizophrenia patients failed to attain the conventional level for statistical significance, as Fig. 2B shows, the performance pattern of these patients and their relatives was quite similar and obviously differs from that of the affective disorder patients.

To investigate whether it was the same patients who made more reflexive errors on the fixation tasks and the antisaccade tasks, Pearson correlations were computed across task conditions within the schizophrenia group. For the low-load tasks, the percentage of errors on the fixation and antisaccade tasks was significantly correlated (r=0.37, P<0.001). Similarly, on the high-load tasks, the percentage of reflexive errors on the fixation and antisaccade tasks was significantly correlated (r=0.54, P<0.001; Fig. 3). The cross-task correlation coefficient for the high-load condition was significantly greater than the correlation coefficient for the low-load condition (Z=1.35, P<0.05, one-tailed).

To examine whether fatigue or learning effects could possibly be responsible for the effects reported above, each task was rescored by halves. Within-group t-tests were used to test for performance differences between the first and second halves of each task. Of the sixteen t-tests conducted, none were significant.

Medication effects

To examine the possibility that medications may be affecting the ability of patients to inhibit unwanted saccades, separate ANOVAs for each of the six medication classes (see Materials and methods), with medication status (present/absent) as the independent variable and each of the four oculomotor measures as dependent variables, were conducted. None of the medication classes was significantly associated with any of the dependent measures (all P'>0.22). In addition, among the patients with schizophrenia, chlorpromazine equivalent dosage was not significantly correlated with any of the four variables (all P'>0.25).

To investigate the possibility that medication side effects may be causing increases in the frequency of inappropriate saccades noted above, all patients who had ratings of EPS, TD, or akathisia of "mild" or greater were excluded (six schizophrenic and two affective patients). Too few patients with medication side effects prevented analyses of the relationship between side effects and the saccadic measures. The statistical significance of results using only patients who were free of significant side effects was the same as reported above without exception.

Discussion

The current study demonstrated that patients with schizophrenia and their first-degree biological relatives made more reflexive errors during a fixation with distraction task as well as during antisaccade tasks. As predicted, when inhibitory load was increased on the fixation and antisaccade tasks, the patients and their relatives showed a disproportionate increase in reflexive saccade errors. Indeed, both of the omnibus MANOVAs and three of the four follow-up MANOVAs revealed significant group-by-task interactions. The predicted worsening in performance when inhibitory load was increased was found for both the fixation and antisaccade tasks for the relatives and for the fixation tasks for the schizophrenia patients. On the antisaccade tasks, the interaction just fell short of conventional statistical significance for the schizophrenia patients. However, after inspection of Fig. 2B, it is clear that the schizophrenia patients' performance worsened on the antisaccade step compared with the antisaccade overlap task.

The same patients with schizophrenia who had difficulties inhibiting saccades during the fixation tasks had difficulties suppressing reflexive saccades on the antisaccade tasks. Thus, a common mechanism of inhibitory control may underlie performance deficits among patients with schizophrenia on both fixation and antisaccade tasks. Two observations support this conclusion. First, significant correlations were found between reflexive errors during fixation and antisaccade tasks, regardless of inhibitory load (Fig. 3). Second, when the inhibitory load was increased, the correlation between errors on the fixation and antisaccade tasks was significantly stronger; as inhibitory load increased, the similarity in cross-task performance increased. In the high-load condition, compared with the low-load condition, inhibitory control processes that are implicated in the pathophysiology of schizophrenia were more emphasized. Greater taxation of these processes that are presumably impaired would then lead to variability in performance that is more constrained and to stronger correlations across tasks. Together, the pattern of performance deficits among the patients with schizophrenia implicates dysfunctional mechanisms of inhibitory control over the reflexive generation of saccades.

The experimental manipulation of inhibitory load was successful for both the fixation and antisaccade tasks as revealed by the significant worsening of performance for all groups when inhibitory load was increased. The one exception to this was that the performance of the nonpsychiatric comparison group did not worsen during fixation when distracters were added.

The schizophrenia patients made an increased number of errors on antisaccade and fixation tasks. However, the effect was especially evident under high inhibitory load task conditions. For instance, the schizophrenia patients made more intrusive saccades during the fixation task when distracting stimuli competed for their visual attention. The relatives did not differ significantly from the nonpsychiatric comparison subjects in their ability to maintain fixation in the absence of distraction. However, when distracters were presented they made more intrusive saccades toward the distracters than did the controls. The relatives showed performance deficits on the step but not the overlap antisaccade task. Thus, on both of the low-load conditions, the relatives performed within normal limits, while their performance was markedly affected when the inhibitory demands were increased. These data are consistent with the idea that performance deficits on fixation and antisaccade tasks that have been associated with schizophrenia are the result of saccadic

disinhibition. Additionally, these data indicate that saccadic disinhibition is associated with the liability to schizophrenia in the absence of illness expression and without the potential confounds of psychotic symptomatology.

The findings in the patients also seem unlikely to be the result of interfering psychotic symptomatology or medication effects. The affective disorder patients, despite being psychotic at the time of testing, performed better than the schizophrenia patients on all measures. For example, the affective disorder patients made more errors on the antisaccade tasks than the nonpsychiatric controls, but the performance of the schizophrenia patients was significantly worse than that of the affective patients. Performance on the fixation and antisaccade tasks was neither related to the medication status nor medication side effect ratings. Moreover, the deficits in suppressing unwanted saccades noted in the relatives obviously cannot be attributed to medications or psychotic symptoms.

In light of other basic and clinical science research on antisaccade tasks (for a review, see Everling and Fischer 1998), these findings also suggest that prefrontal dysfunction may underlie the saccadic disinhibition seen in the patients and their healthy relatives. The antisaccade task is now commonly thought of as an index of prefrontal function. We do not know which part of the prefrontal cortex is specifically involved in reflexive saccade suppression versus other aspects of saccadic behavior, but the dorsomedial and dorsolateral areas are likely candidates. Neurological patient studies have consistently implicated the dorsolateral (Fukushima et al. 1994; Guitton et al. 1985; Pierrot-Deseilligny et al. 1991) and medial (Gaymard et al. 1998b; Guitton et al. 1985; Paus et al. 1991; Pierrot-Deseilligny et al. 1991) prefrontal cortex in the inhibition of reflexive saccade generation. Patients with frontal eye field (FEF) lesions, on the other hand, do not typically produce a significantly greater proportion of reflexive errors on the antisaccade task (Gaymard et al. 1999; Pierrot-Deseilligny et al. 1991; Rivaud et al. 1994). The consistent finding of greater activity of the FEF during neuroimaging studies of nonpsychiatric humans performing antisaccade tasks compared with prosaccade tasks (Doricchi et al. 1997; O'Driscoll et al. 1995; Sweeney et al. 1996) is difficult to interpret for several reasons. First, single-cell recordings in the FEF have found lower saccade-related activity on antisaccade compared with prosaccade trials (Everling and Munoz 2000). Second, the increased FEF activity detected with neuroimaging techniques may be primarily related to the generation of the volitional antisaccades (i.e., glances made to internally determined or imagined targets; Gaymard et al. 1998a) and not the brief act of inhibition. The time needed to initiate an antisaccade is consistently longer than the time needed to initiate a visually guided reflexive prosaccade. This difference, which represents not only the time needed to inhibit a reflexive saccade but also the time needed to initiate an antisaccade, is less than 100 ms in humans. Of yet, neuroimaging studies have not been able to image this brief process convincingly. However, a recent, event-related cortical potential study, which has the requisite temporal resolution to detect such a brief event, compared evoked responses just prior to directional cue onset for correct and incorrect antisaccade trials (Everling et al. 1998b). The authors found a decreased negative potential over the dorsomedial frontal cortex prior to incorrect responses that possibly arose from neural activity in the supplementary eye fields (SEF) and is responsible for the inhibition of the reflexive saccade.

During the antisaccade task when the directional cue to respond is presented, competition between gaze-holding (fixation) and gaze-shifting (saccade) mechanisms determines the initiation or withholding of an eye movement. The outcome of this competition may be resolved within the superior colliculus (SC), which receives visual inputs and projects directly to brainstem saccade generators (Wurtz and Goldberg 1989). Reflexive errors on the antisaccade task are preceded by decreased activity of fixation-related neurons and increased activity of movement-related neurons in the SC (Everling et al. 1998a, 1999). It is thought that correct performance on the antisaccade task requires top-down control of fixation- and movement-related neurons in the SC. Stimulation of fixation-related neurons in the SC locks gaze and prevents reflexive saccades (Munoz and Wurtz 1992, 1993a, 1993b). Additionally, reflexive errors on the antisaccade task are likely unless activity in collicular movement-related cells remain below a critical firing-rate just prior to the onset of the directional cue (Everling et al. 1998a). During this period, gaze must be actively maintained until the command for the correct antisaccade can be generated. In the absence of a visible fixation point, neuronal activity decreases for fixation-related cells and increases for movement-related cells in the SC (Everling et al. 1999). This pattern of observations may explain the decrease in reflexive errors on antisaccade tasks that have a fixation point that overlaps, in time, the directional cue. The visible fixation point may drive fixation-related cells in the SC, thus reducing the probability of generating a reflexive saccade.

Prefrontal cortical regions are thought to provide inhibition of the reflexive saccade and/or the maintenance of fixation while the antisaccade is generated. Recordings of neural activity just prior to the onset of the directional cue in awake behaving monkeys has shown that neurons in the SEF (Schlag-Rey et al. 1997) have greater response on antisaccade compared with prosaccade trials, while the opposite is true of neurons in the FEF (Everling and Munoz 2000). To correctly inhibit a reflexive saccade during an antisaccade task, SEF activity, which excites fixation-related collicular cells, must be increased, and FEF activity, which excites saccade-related collicular neurons, must be diminished relative to prosaccade trials. In the monkey, electrical stimulation of the SEF fixes eye movements even in the context of flashed stimuli (Tehovnik and Lee 1993). Nonetheless, these studies do not indicate whether the SEF and FEF

are both necessary to inhibit reflexive saccades and whether other candidate areas such as the dorsolateral prefrontal cortex may be involved.

The results of the current study suggest that saccadic disinhibition is readily apparent among schizophrenia patients even when inhibitory load is low. For the relatives, disinhibition only becomes apparent when inhibitory load is increased. Such evidence supports the notion that the liability to schizophrenia is associated with vulnerability to distraction and disinhibition, at least within the saccadic system. The pattern of performance deficits is consistent with dysfunction of prefrontal cortical areas that provide top-down inhibitory control of subcortical areas involved in reflexive saccade generation. Current studies are underway to investigate whether this disinhibitory process is limited specifically to oculomotion. It may very well be that saccadic disinhibition represents a more general form of behavioral disinhibition that is characteristic of schizophrenia (Clementz 1998). For example, saccadic disinhibition may be related to other expressions of disinhibition such as those measured by the Continuous Performance Test AX version (Cohen et al. 1999; Servan-Schreiber et al. 1996), covert orienting and shifting of attention tests (Maruff et al. 1996, 1998), and tests of competitive response selection and inhibition (e.g., the Stroop Test; Barch et al. 1999; Carter et al. 1997; Cohen et al. 1999), all of which have been reported to elicit abnormal performance among schizophrenia patients. All of these tasks have in common the need to suppress reflexive or habitual, sensory-driven responses, in favor of less potent, voluntary responses.

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