

Nicotine reduces antisaccade errors in task impaired schizophrenic subjects

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Abstract

Nicotine and/or smoking have been shown to reduce various cognitive deficits associated with schizophrenia. Here, we examine the effects of nicotine gum on repeated performance on a simple eye movement task. Eight schizophrenic subjects and eight controls participated in three days of testing on saccade (S) and antisaccade (AS) tasks. On each testing day, subjects participated in four testing sessions and received both of two nicotine gum treatments (4 and 6 mg) and both of two control conditions (placebo gum and no gum), each followed by a recovery period. Overall, schizophrenics showed significant impairments on the AS task. However, upon individual examination only four schizophrenics showed significant differences in AS errors or reaction times (RTs) when compared to controls. The other four schizophrenic subjects showed control level performance. All schizophrenic subjects showed normal and better than control level performance on the simple S task. Furthermore, no effects of nicotine were seen on the simple S task. There were significant treatment effects on the AS task. Nicotine treatment significantly decreased errors in the task impaired schizophrenic group and this effect was most pronounced at the 6 mg level. No nicotine effects were demonstrated for non-impaired schizophrenic subjects or controls. This study demonstrates a benefit of short exposure to nicotine in cognitively impaired schizophrenic subjects. These results support previous findings of cognitive benefits of nicotine in schizophrenics.

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1. Introduction

It is well documented that schizophrenia is associated with a high rate of smoking (Dalack and Meador-Woodruff, 1996; deLeon, 1996; deLeon et al., 1995; Hughes et al., 1986; Lawrie et al., 1995; Lohr and Flynn, 1992; O'Farrell et al., 1983; Poirier et al., 2002; Ziedonis et al., 1994). Several lines of investigations, including behavioral, physiological, and genetic studies, support a theory of self-medication to explain this increased rate of smoking.

Specifically, it has been proposed that nicotine use by this population is an implicit means of ameliorating existing behavioral, physiological and/or neurochemical deficits (Adler et al., 1993; Freedman et al., 1995, 1997; Leonard et al., 1996; Levin, 1992).

There is a considerable body of literature demonstrating attention and performance enhancing effects of nicotine in a normal population (Wesnes and Warburton, 1978, 1983; Warburton, 1998; Pritchard and Robinson, 1998). More recently, studies have directly examined nicotine's effects in schizophrenia. Nicotine and/or smoking by schizophrenics has been shown to improve performance on several cognitive tasks, including smooth pursuit eye movements (SPEM) (Klein and Andresen, 1991; Olincy et al., 1998; Dépatie et al., 2002; Sherr et al., 2002); a sensory gating deficit (Adler et al., 1993); continuous performance test (CPT) performance (Levin et al., 1996; Dépatie et al., 2002); the Automated Neuropsychological Assessment Metrics (ANAM) spatial organization and verbal memory

Abbreviations: AS, antisaccade; ANAM, Automated Neuropsychological Assessment Metrics; CO, carbon monoxide; CPT, continuous performance test; CONT, control group; EP, evoked potentials; IP, identical pairs; ISI, interstimulus interval; RT, reaction time; S, saccade; SPEM, smooth pursuit eye movements.

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subtests (Smith et al., 2002); and an antisaccade (AS) task (Dépatie et al., 2002). Here, we review these studies and present new data examining nicotine's effects on schizophrenics' performance on repeated testing on a simple saccade (S) and antisaccade task.

1.1. Smooth pursuit eye movements

Perhaps one of the most studied neurological findings in schizophrenia is the impairment in SPEM. For three decades, researchers have documented the presence of eye tracking dysfunction in schizophrenia (Holzman et al., 1973, 1976; Levy et al., 1993, 1994). To date, four studies have examined the effects of nicotine on SPEM in schizophrenics (Klein and Andresen, 1991; Olincy et al., 1998; Dépatie et al., 2002; Sherr et al., 2002).

The SPEM task was the first to be measured with regards to smoking effects in schizophrenia (Klein and Andresen, 1991). In an initial report presented in abstract form, Andresen et al. (1989) indicate a correlation between performance on a SPEM task and the number of cigarettes smoked per day in schizophrenic subjects. Following this line, Klein and Andresen (1991) examined the effects of smoking using a simple experimental design (Table 1). In this study, they report that the administration of a single cigarette resulted in a decrease in large amplitude saccades on the SPEM task. This effect was present in both schizophrenic and control subjects and was greater in control subjects.

Olincy et al. (1998) also examined the effects of smoking on SPEM (Table 1). Olincy et al. report that smoking resulted in a decrease in the percentage of catch-up and leading saccades and a trend towards increasing gain in schizophrenic subjects but not in controls.

Similarly, Dépatie et al. (2002) showed a significant decrease in catch-up saccades and a significant increase in pursuit gain when subjects were given 6-h exposure to a nicotine patch (Table 1). Unlike Olincy et al. (1998), Dépatie et al. report this effect for both schizophrenic and control subjects.

Sherr et al. (2002) report an effect of nicotine nasal spray in patients and controls (Table 1). They report that nicotine resulted in increased gain in patients and healthy subjects equally and that nicotine increased initiation acceleration in schizophrenic patients but not in control subjects.

In normal subjects, several studies have indicated a negative effect of nicotine on SPEM. Thaker et al. (1991), Long and Franklin (1989), and Sibony et al. (1987, 1988) have shown that cigarette smoking results in an increase in square-wave jerks. One study using schizophrenic patients (Dépatie et al., 2002) also reports an increase in square wave jerks under specific high attentional task conditions. The effects of nicotine on SPEM performance will need to be investigated using manipulations that aid in parsing the cognitive processes involved in order to better determine the mode of action on SPEMs in schizophrenic subjects and whether nicotine may have differential effects on SPEM of non-schizophrenic subjects.

Table 1
Nicotine studies in schizophrenic subjects

Study	Patient <i>n</i> 's	Diagnosis	Neuroleptic medications	Nicotine administration	Nicotine control
Klein and Andresen, 1991	<i>n</i> = 13	not specified	all medicated-NS	tested within 10 min of smoking one cigarette	abstain 2 h
Adler et al., 1993	<i>n</i> = 10	3 paranoid 7 undifferentiated	all medicated 50% anticholinergics	tested after two to four cigarettes over 30–45 min	abstain overnight
Levin et al., 1996	<i>n</i> = 15	not specified	haloperidol	4-day counterbalanced nicotine patches of 0, 7, 14, and 21 mg doses	abstain overnight
Olincy et al., 1998	<i>n</i> = 15	13 paranoid 2 disorganized	6 typical neuroleptics 6 clozapine 1 typical + clozapine 2 non-medicated	ad lib smoking one to four cigarettes for 10 min	abstain overnight
Dépatie et al., 2002	<i>n</i> = 15	not specified	9 typical, 6 atypical (8 anticholinergic)	14 mg nicotine patch after 5 h of exposure	abstain overnight
Sherr et al., 2002	<i>n</i> = 29	not specified	3 typical, 9 clozapine 1 resperidone 16 olanzapine (2 + haloperidol)	1 mg nicotine nasal spray 5 min before testing	abstain 2 h
Smith et al., 2002	<i>n</i> = 31	schizophrenia NOS schizoaffective	2 clozapine 14 olanzapine 5 resperidone 1 fluphenazine 1 haloperidol 1 combo atypicals 7 combo typical + atypical	one to two sprays each nostril nicotine nasal spray 10 mg/ml smoking 2 cigarettes	abstain overnight

1.2. P50 gating

Adler et al. (1993) have demonstrated a benefit of smoking in schizophrenia using the P50 gating paradigm. The P50 gating paradigm has repeatedly been shown to be disrupted in schizophrenia patients (Adler et al., 1982; Franks et al., 1983; Freedman et al., 1983; Braff and Geyer, 1990). Adler et al. (1993) measured the effects of ad lib smoking in this paradigm (Table 1). In the standard procedure, evoked potentials (EP) are recorded as subjects are presented with two auditory clicks paired in time with interstimulus intervals (ISI) of 500 ms. For normal subjects, the positive EP recorded 40–90 ms from stimulus onset, the P50, is reduced in amplitude for the second click compared to the first. This effect is reported as the gating ratio, expressed as a percentage (second stimulus/first stimulus \times 100) and is presumed to estimate a form of gating of redundant sensory stimuli. This value is reported to be around 18% for normal subjects, much smaller than the value of around 95% that is typically reported in medicated schizophrenic subjects (cf. Adler et al., 1993).

Examining the effects of nicotine on the P50 in schizophrenic subjects, Adler et al. (1993) report that smoking resulted in a rapid onset of gating (P50 ratio = 25%) that was not present at baseline (P50 ratio >75% during the initial baseline measure). This effect of smoking was short lived. The significant effect was seen during the first post-smoking session only (5 min or less after smoking). By the second post smoking session taken at 15 min, this effect was no longer significant (P50 ratio about 65%).

By contrast, the control group findings showed an opposite effect of nicotine. After smoking, the P50 ratio became abnormally high (ratio = 65%), much higher than the typical 18% ratio reported for normal subjects, and this gating deficit was present at both the 5- and 15-min post-smoking session. The investigators leave open the question as to whether smoking might have contributed to or caused this abnormal P50 response in the control subjects.

1.3. Continuous performance task (CPT)

The CPT was first used as a systematic measure of cognitive deficits in schizophrenic patients by Orzack and Kornetsky (1966). Since then, CPT performance has been one of the most standard measures of attentional vigilance in schizophrenic and other populations. The original task presented a series of letters and required the subject to respond only to a target letter (X) or to a specified sequence (AX) (Rosvold et al., 1956). Variations of this task have been designed to increase perceptual and/or working memory demands or response control and produce varying results on task performance by schizophrenic subjects (Nuechterlein, 1991; van den Bosch et al., 1996).

Levin et al. (1996) examined the effects of nicotine and haloperidol interactions on cognitive performance (Table 1). All subjects were taking one of three doses of haloperidol:

low, average, or high. Schizophrenic subjects were tested repeatedly on the Conners CPT task (Conners, 1995) over four days. Each testing session the subjects were given one of four patch treatments: placebo, low, medium, or high dose. For CPT performance, there was a significant effect of nicotine on hit reaction time (RT) for the lower nicotine patch doses. There were no significant effects of nicotine or haloperidol on errors of omission or errors of commission, the typical measures of performance deficits in schizophrenic patients.

Olincy et al. (2003) examined the effect of nicotine patch using the CPT-identical pairs version (CPT-IP, Cornblatt et al., 1988). These researchers report that nicotine produced an increase in correct hits in schizophrenic patients but did not affect control performance. There was also a trend for an increase in signal detection (d') in both groups. Unlike, Levin et al. (1996) they report no significant effect of nicotine on RT for the CPT-IP. In contrast, one study (Sherr et al., 2002) has shown no effect of nicotine nasal spray in schizophrenics or controls when using the same version of the CPT (identical pairs, CPT-IP).

1.4. ANAM neurocognitive battery

In addition to the Conners CPT task, Levin et al. (1996) also administered several tests from the ANAM battery (Reeves et al., 1993). Four tests from the ANAM were given: a simple reaction time task, the Sternberg verbal memory task, a complex RT task (spatial rotation), and the delayed matching to sample task. There were no effects for the simple reaction time task or the Sternberg verbal memory task. Levin et al. (1996) report a significant benefit of nicotine for both the complex RT task (spatial rotation) and the delayed matching to sample subtests of the ANAM in participants receiving high and medium haloperidol doses. However, they found no benefit for low dose haloperidol subjects, again emphasizing the neuroleptic/nicotine interaction.

More recently, Smith et al. (2002) report the effects of smoking and nicotine nasal spray on the ANAM battery of cognitive tasks (Table 1). There were significant effects noted for the nicotine nasal spray on verbal memory (Randt memory test), accuracy of spatial rotation, and two-choice reaction time in schizophrenic patients. None of the ANAM tasks showed significant improvement with nicotine cigarettes when compared to placebo, although there was a *trend* for high nicotine containing cigarettes to improve spatial rotation efficacy.

The benefits of nicotine on such general information processing are consistent with studies showing detrimental effects of smoking abstinence on visuospatial working memory in schizophrenic subjects (George et al., 2002). A general benefit of nicotine on information processing deficits may account for its high use in attentional disorders. It will require more exacting experimental designs to systematically determine the specificity of nicotine's effects across different cognitive tasks and the difference between

absolute nicotine effects versus amelioration of withdrawal symptoms.

1.5. Antisaccades

The antisaccade (AS) task (Hallett, 1978) has been used to demonstrate cognitive deficits in a number of neurological and psychiatric disorders. In the AS task, subjects must respond to a visual target by making a saccade to the location directly opposite a target location. There is considerable literature showing an increase in antisaccade error rates in schizophrenic patients (Crawford et al., 1995; Fukushima et al., 1988, 1990a,b; Karoumi et al., 1998; Levy et al., 1998; Sereno and Holzman, 1995).

Dépatie et al. (2002) examined performance on the AS task in schizophrenics before and after a nicotine or placebo patch (Table 1). The task measured eye movements using an infrared eye tracker and recorded RTs for saccades and antisaccades to peripheral targets. A short session of 105 trials of the S and AS tasks were given on the two separate testing days. There was a further task manipulation involving the early offset (gap), simultaneous offset (step), or permanent presentation (overlap) of the fixation point. The early offset of the fixation point during target or just prior to the target presentation has been shown to produce what is commonly referred to as the gap effect (Fischer and Ramsperger, 1984): a decrease in latency of saccade response times (RT). The gap is shown to facilitate saccades (reflexive responses) but to increase the difficulty of antisaccades (voluntary responses) (Reuter-Lorenz et al., 1991). In schizophrenic patients, the inclusion of a gap has been shown to differentially affect reaction times in patients as compared to normal controls (Sereno and Holzman, 1993).

Dépatie et al. (2002) report that nicotine produced a significant decrease in AS errors in both the patient and control groups but had no effect on the S task errors, S RTs, or AS RTs. Overall, schizophrenic subjects in this study showed higher error rates (32%, compared to 9.3% for controls) and slower response times (312 ms compared to 257 ms for controls). No effects were noted between schizophrenic and normal groups for the gap, step, and overlap conditions, nor did these task conditions show any effects or interactions with nicotine.

Two previous studies have examined nicotine effects in normal subjects. Thaker et al. (1991) report no effect on an AS task following 2 min of smoking a single cigarette. Our lab, however, has shown a selective benefit of nicotine on AS error rates and AS RTs with no effects on the S task in normal subjects (Larrison-Faucher et al., 2003). Using a brief 5-min exposure to 4 mg nicotine gum in task-naïve subjects, we showed significant decrease in AS error rates ($p < 0.05$) with no effect on S performance. The same treatment given repeatedly to highly practiced subjects, for whom RT variability is minimal, resulted in significant decreases in AS RTs ($p < 0.001$). Again, no effects of

nicotine were seen for the S task. This effect was equally significant for both gap and overlap task conditions.

Here, we extend these results by examining the effects of nicotine gum on S and AS task performance in schizophrenic subjects.

2. Method

2.1. Subject sample

Eight schizophrenic and eight control subjects completed 12 testing sessions in the S and AS tasks (Table 2). Subjects were recruited from outpatient facilities and were on medication at the time of testing. All subjects were smokers and were taking typical or atypical neuroleptics at the time of testing. Subjects were matched for age, gender and education. Two of the 16 subjects were female, one in each group. One subject from the control group was left handed. Informed consent was obtained from all subjects.

2.2. Testing schedule

Subjects were tested over 5 h on three separate occasions. Sessions started at 9 AM and ended at 2 PM (Table 2). After obtaining consent, at the start of each testing day, subjects were tested for breath carbon monoxide (CO) using a handheld breath CO analyzer. Subjects were then given a brief eye movement test related to ongoing studies on inhibitory attentional mechanisms in schizophrenia (Larrison-Faucher et al., 2002). This testing was followed by a break, so that testing in the S and AS tasks reported here did not begin before 10:40, or 1 h 40 min after the subjects' arrival. This was done to ensure that each subject was free from any immediate effects of nicotine, given that we had no means of guaranteeing a subject's abstinence. S and AS task sessions were therefore administered at 10:40, 11:40, 12:40, and 1:40. Each testing session took approximately 13 min. Eight minutes was required for gum administration, and 5 min was required for the eye movement tasks. An additional few minutes was required for set up, so that

Table 2
Daily testing schedule

09:00	Introduction, Inhibitory Attention Tasks
10:00	Break
10:40	S/AS Session I
11:00	Break
11:40	S/AS Session II
12:00	Lunch
12:40	S/AS Session III
13:00	Break
13:40	S/AS Session IV
14:00	Debriefing

Testing in the saccade and antisaccade task (S/AS) began after a 1 h 40 min introductory testing session and break.

approximately 20 min of time was devoted to testing for each hour of a subject's participation. Hence, between each session, subjects were given breaks of approximately 40 min. During those breaks, subjects were administered a battery of psychological tests and a small low sugar lunch. Subjects participated in four S and AS sessions per testing day and were administered one of each of the four treatments with treatment order counterbalanced across subject and testing days.

2.3. Eye movement tasks

We administered a standard S and AS task with trials including gap and overlap conditions.

Each testing session consisted of one block of 72 trials each for the S and AS tasks, with overlap and gap conditions interleaved within task blocks. The task presentation proceeded as follows (Fig. 1): Subjects were required to fixate the central point for a variable interval (800, 1000, or 1200 ms) before the onset of the target. The target consisted of a 4×4 pixel square presented in one of two locations, 300 pixels (7.2°) to the left or right of fixation. Subjects were instructed to look towards or away from the target as soon as it appeared. Subjects had 2000 ms to respond to the target by making an eye movement. If no response was made within this time, the trial was considered a time-out and rerun later in the session. The order of S and AS blocks was counterbalanced.

2.4. Group assignment

Not all schizophrenic subjects showed impairments on the AS task. Therefore, schizophrenic subjects were assigned to one of two subject groups based on AS error

rates. Mean AS error rates for each schizophrenic subject were compared to overall control errors using individual *t* tests. Schizophrenic subjects showing significantly increased error rates ($p < 0.05$) compared to controls were classified as Impaired. Schizophrenic subjects showing no significant increase in AS error rates were classified as Non-impaired.

2.5. Data analyses

Data was analyzed for group differences between the two schizophrenic groups (Impaired, $n = 4$; Non-impaired, $n = 4$) and the control (Cont $n = 8$) subjects.

2.5.1. Session

Errors and RTs were submitted to a two-factor ANOVA (Group and Session) to determine whether there were changes in performance over the 12 testing sessions.

2.5.2. Reaction time

Median RTs were examined using a three within, one between factor ANOVA. Within factors were Task (S, AS), Gap (overlap, gap), and Treatment (no gum, placebo, 4 mg, 6 mg). The between factor was Group (impaired, non-impaired, and control). Post hoc: Separate ANOVAs for the two tasks (S and AS) were performed appropriately to determine the cause of a significant interaction between Task and Group. ANOVAs for the S task consisted of a two within (Gap, Treatment), one between factor (Group) ANOVA, and the same analysis was performed for AS RT.

2.5.3. Errors

Errors were submitted to the same three within, one between factor ANOVA as for RT data, post hoc. Separate

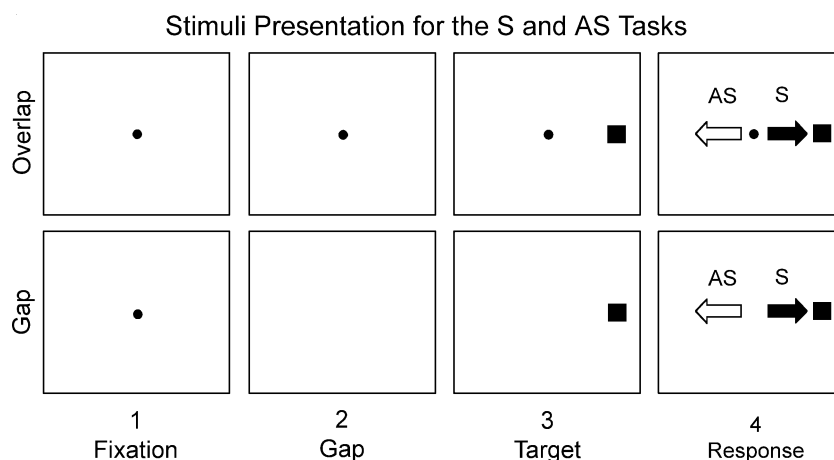


Fig. 1. The saccade and antisaccade stimulus presentation is shown here in four frames. S and AS tasks were blocked but are shown together for illustration purposes only. Frame 1: Subjects fixate the central point for a variable interval of 800, 1000, or 1200 ms. Frame 2: For half of the trials the fixation point remained salient throughout the trial (overlap condition) while for the other half the central fixation point was extinguished 160 ms prior to the onset of the target (gap condition). Overlap and gap conditions were randomly interleaved within each task block. Frame 3: The target appeared with equal probability to the left or right of fixation. Frame 4: Subjects responded by making an eye movement to the target location (S task, black arrow) or away from the target location (AS task, white arrow).

Table 3
Subject sample

	Age	Edu	BRTICO	Smoke	CAFF	ETOH	IQ
Cont	38.5 (7.8)	12.8 (2.1)	9.7 (7.7)	16.3 (10.6)	2.1 (2.1)	8.5 (14.1)	100.0 (11.5)
Scz-Imp	39.7 (6.4)	13.7 (0.9)	26.0 (12.1)*	30.0 (11.5)	4.2 (2.0)	0.7 (1.5)	93.0 (5.6)
Scz-Non	42.2 (7.1)	13.2 (1.1)	9.7 (5.3)	25.0 (5.7)	2.7 (2.2)	0.3 (0.5)	102.2 (12.3)

Schizophrenic and control subjects were matched for age, education, and gender. There was one significant difference between our groups; that was for breath carbon monoxide (BRTICO). Group means are presented with standard deviation in parentheses. BRTICO = first CO reading, Smoke = cigarettes/day, CAFF = number of caffeinated beverages/day, ETOH = number of alcoholic beverages/week.

* Significant at $p < 0.05$.

ANOVAs for the two tasks (S and AS) were applied appropriately as for RT data.

3. Results

3.1. Sample

Chronic smokers were selected, and patients and controls were matched for age and education (Table 3). Out of the originally recruited nine schizophrenic subjects, five showed the previously described AS deficit, with one patient's performance so impaired that she could not complete the study (100% errors on the AS task). Of the eight schizophrenic subjects who completed the study, four subjects did not show the reported increase in AS errors associated with schizophrenia (Table 4). This heterogeneity of cognitive performance in schizophrenic populations is not typically reported for the AS task (for one exception, see Sereno and Holzman, 1995). Several factors regarding our subject selection procedure may have contributed to this finding (see Discussion). Those subjects who showed the deficit (Table 5, shaded subjects) did not differ in diagnosis or any demographic measures. Overall, Impaired subjects tended to smoke more cigarettes and drink more caffeine, and they showed significantly higher breath CO at the beginning of testing than did controls or Non-impaired schizophrenic subjects, perhaps reflecting a greater level of stimulant dependence. All of the Non-impaired subjects were receiving risperidone, a drug associated with improved performance on the AS task (Reveley et al., 1996; Burke and Reveley, 2002). When examined statistically using a chi-square and looking at predicted contingency of task Impaired versus task Non-impaired and Risperidone versus Other neuroleptic, this effect was significant, chi-square = 4.8, $p < 0.05$.

Table 4
Antisaccade error rates and schizophrenia group assignment

Controls	PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8
7.4 (6.4)	28.9 (5.2)*	7.3 (4.8)	17.8 (3.8)*	2.0 (1.8)	38.1 (6.3)*	38.6 (7.1)*	6.2 (3.4)	11.0 (3.8)

Mean errors on the AS task, standard deviation presented in parenthesis. Schizophrenia patients were assigned to either task impaired and task non-impaired groups based AS error rate across the 12 testing sessions. Mean control performance was used as a comparison and individual t tests were used to evaluate patient performance. Only four of the eight subjects showed a significant increase in error rates compared to controls.

* Significant at $p < 0.05$.

3.2. Session

This design afforded us the opportunity to look at the effects of practice on the high rate of errors by schizophrenics in the AS task. In order to determine the effects of multiple sessions on RT and Errors, an ANOVA was run with testing session as a between factor. There was no effect of session number on S RTs, AS RTs, S Errors, or AS Errors (all F 's(11,180) < 1.0). There were also no significant interactions between session and any other factor. Fig. 2 shows Errors for both S and AS tasks across the 12 testing sessions for schizophrenics impaired on the AS task (Impaired, $n = 4$), schizophrenics showing normal AS task performance (Non-impaired, $n = 4$), and control subjects (Cont, $n = 8$). The persistence of AS task impairments demonstrated here shows that these deficits are not transient, nor are they related to an initial difficulty in learning the task. Few, although persistent, errors were seen on the S task across the twelve testing sessions. Although not statistically significant, this number was less for schizophrenic subjects not showing a deficit on the AS task than for schizophrenics impaired on the AS task and control subjects (Fig. 2a). For the AS task, there were consistent errors that did not diminish and that strongly distinguished the subgroup of impaired schizophrenic subjects from both the schizophrenic subjects with no task impairments and the control subjects (Fig. 2b).

3.3. Reaction time

There was a significant main effect for RT for each of the three within factors: Task, $F(1,45) = 199.9$, $p < 0.0001$, Gap, $F(1,45) = 134.9$, $p < 0.0001$, and Treatment, $F(3,135) = 5.12$, $p < 0.005$, and there was a trend for an effect of Group, $F(2,45) = 3.09$, $p < 0.10$. There was one significant interaction for RT, Group by Task, $F(2,45) = 13.6$, $p < 0.0001$ (Fig.

Table 5
Schizophrenic subject sample

SUBJECT	AGE	GEND	EDU	DIAGNOSIS	MEDICATION	ONSET
PT01	45	M	14	Paranoid	Risperidone 3mg	23
PT02	33	M	11	Paranoid	Risperidone 4mg	18
PT03	39	M	15	Paranoid	Haldol 5mg b,c	25
PT04	45	M	12	Paranoid	Risperidone 3mg a	21
PT05	31	M	13	Paranoid	Zyprexa 20mg b,h	23
PT06	44	M	13	Paranoid	Prolixin 5mg	20
PT07	41	F	14	Paranoid	Risperidone 3mg	35
PT08	50	M	16	Undifferentiated	Risperidone 2mg a,b,c	20

Subjects impaired on the AS task (>1.5 S.D. from control error rate) are highlighted. No notable differences were apparent between these impaired subjects and subjects showing control level performance. a = antidepressant, b = benzodiazepine, c = anticholinergic, h = antihistamine.

3). This was due to better performance on the S task and poorer performance on the AS task by the schizophrenic groups.

This interaction was further analyzed using separate ANOVAs for the S and AS tasks in order to determine the individual task contributions.

3.3.1. Saccade task

For the S task, there was a significant main effect of Gap, $F(1,45)=244.4$, $p<0.0001$. There was no main effect of Group, $F(2,45)=1.9$, $p=0.16$; nor of Treatment, $F(3,135)=1.2$, $p=0.30$ on S RTs (Table 6). There was a significant Group by Gap interaction, $F(2,45)=6.35$, $p<0.01$. Fig. 3a

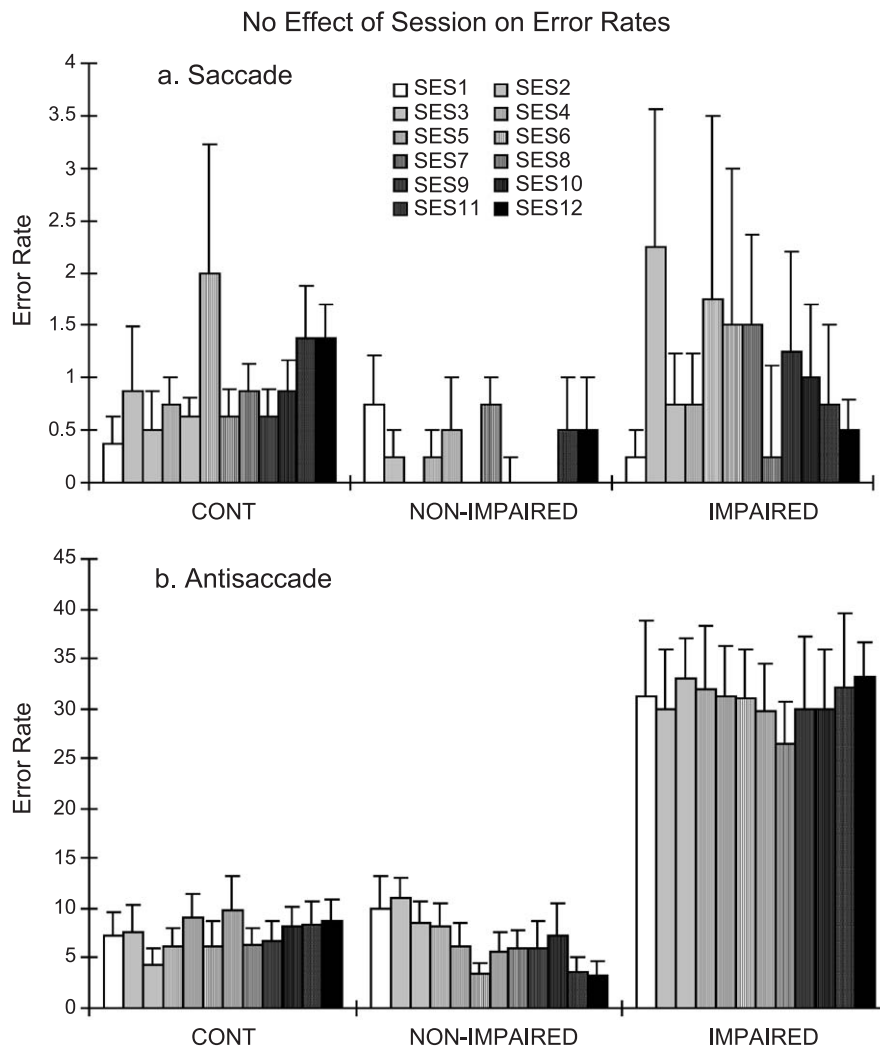


Fig. 2. The effect of session on error rates in controls and schizophrenic subjects. Only a subgroup of schizophrenic subjects showed an impairment on our antisaccade task (Impaired, $n=4$). For this group, the high error rate persisted and did not diminish even after considerable practice. Further, there were no significant effects of practice for controls (Cont, $n=8$) or schizophrenics not showing antisaccade deficits (Non-impaired, $n=4$). Error bars = S.E.M.

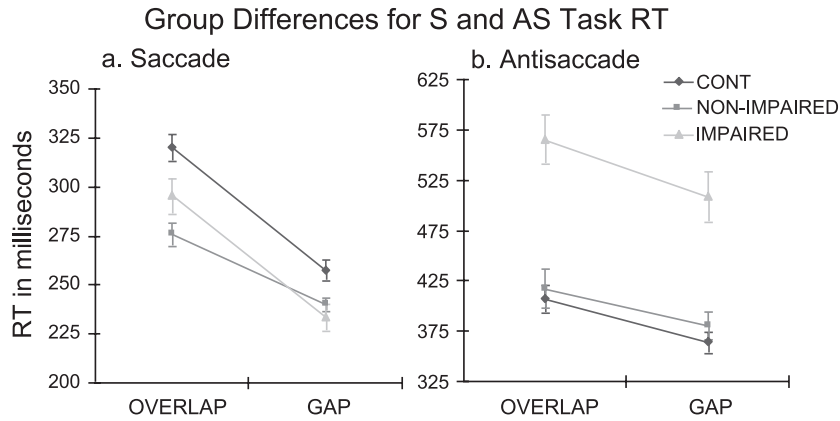


Fig. 3. There was a significant interaction between task and group. Schizophrenic patients were significantly faster than controls in the S task. This effect was reversed in the antisaccade task, but only significantly for a subpopulation of our schizophrenic group (Impaired). (Cont, $n=8$; Impaired, $n=4$; Non-impaired, $n=4$). Error bars = S.E.M.

shows this effect. Schizophrenic subjects, both impaired and non-impaired on the AS task, showed faster RTs on the S task, i.e., main effect Group, and non-impaired schizophrenic subjects showed particularly speeded responses on the overlap saccade condition, with no corresponding increase in the gap condition, i.e., interaction Group by Gap. There were no other significant effects for RT on the S task.

3.3.2. Antisaccade task

The separate ANOVA for AS task showed a significant main effect of Group, $F(2,45)=6.43, p<0.005$ and Gap, $F(1,45)=35.3, p<0.0001$, and a trend for a main effect of Treatment, $F(3,135)=2.52, p<0.10$. Fig. 3b shows the effect Group by Gap effects. From this figure, we can see that schizophrenic subjects showing increased errors on the AS task (Impaired) also showed poorer RT performance on the AS task, while schizophrenic subjects showing error rates on the AS task equivalent with controls (Non-impaired) showed RTs on the AS task that were also at control levels.

Table 6 shows RT means for S and AS tasks with each of the four treatments. Subjects had the fastest RT and smallest variance for both S and AS tasks after consuming 6 mg nicotine. However, none of the treatment conditions significantly differed for the S task. There was a significant difference between the placebo and 6 mg nicotine treatment conditions for the AS RT, $F(1,45)=6.71, p<0.05$. None of

Table 6
Nicotine effects on RT

	No gum	Placebo	4 mg Nicotine	6 mg Nicotine
Saccade	272.3 (6.8)	278.4 (6.4)	276.5 (6.1)	271.7 (6.0)
Antisaccade	425.9 (16.8)	438.5 (16.7)	430.2 (14.8)	411.1 (12.7)*

There was a main effect of nicotine on RT. Separate analysis of S and AS tasks revealed no significant differences for any of the S RT measures, but a significant effect of 6 mg nicotine compared to placebo for the AS task.

* Significant at $p<0.05$.

the treatment effects for S or AS RT measures interacted with Group.

3.4. Errors

For Errors, there was a significant main effect for the between factor: Group, $F(2,45)=57.9, p<0.0001$, as well as for each of the three within factors: Task, $F(1,45)=199.9, p<0.0001$, Gap, $F(1,45)=134.9, p<0.0001$, and Treatment, $F(3,135)=5.12, p<0.005$. Each of the within factors also showed significant interactions Group by Task, $F(2,45)=13.6, p<0.0001$, Group by Gap, $F(2,45)=41.4$, Gap by Task, $F(1,45)=165.8, p<0.0001$. Furthermore, there was a significant three-way interaction between Treatment, Task and Group, $F(6,135)=2.88, p<0.02$. To determine the cause

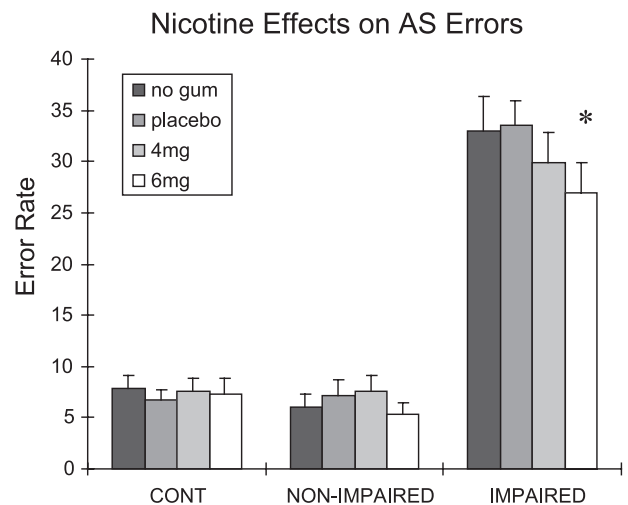


Fig. 4. A significant effect of treatment is seen in the schizophrenic subgroup that showed a baseline deficit in AS performance (Impaired, $n=4$). Control (Cont, $n=8$) and schizophrenic subjects not showing deficits (Non-impaired, $n=4$) on our AS task measure, showed no effects of nicotine treatment. Error bars = S.E.M. * Significant at $p<0.05$.

of this interaction, S and AS tasks were analyzed using separate ANOVAs.

3.4.1. Saccade task

For the S task alone, there were no significant main effects or interactions for any of the between or within factors. Treatment showed no main effect $F(3,135)=0.054$, $p=0.96$, and did not interact with Group, $F(6,135)=0.39$, $p=0.84$.

3.4.2. Antisaccade task

For the AS task alone, there was a main effect of Group, $F(2,45)=58.2$, $p<0.0001$, Gap, $F(1,45)=153.6$, $p<0.0001$, and as expected, for Treatment, $F(3,135)=4.91$, $p<0.005$. There was also a significant interaction between Gap and Group, $F(2,45)=51.5$, $p<0.0001$, and Treatment by Group, $F(6,135)=3.62$, $p<0.005$ (Fig. 4). Specifically, in Impaired schizophrenic subjects, increasing nicotine reduced errors on the AS task from 46.6% and 45.7%, for the placebo gum and non treatment session to 41.5% and 37.5% for the 4 and 6 mg nicotine gum treatment sessions, respectively. There were no other significant effects for AS Errors.

4. Discussion

This study examines the potential benefit of nicotine in ameliorating the AS task deficit in schizophrenia. Our data indicate a significant reduction in AS error rate in AS task impaired schizophrenic subjects following nicotine administration. No effects of nicotine were seen in the AS task in controls or non-impaired schizophrenic subjects. These findings are consistent with previous studies showing a benefit of nicotine on specific deficits in schizophrenia, i.e., CPT performance, sensory gating, and smooth pursuit eye movements.

4.1. Antisaccade performance in schizophrenic subjects

Here, we report a significant effect of nicotine on AS error rates in task impaired schizophrenic subjects and no effect in normal controls. Although we report no effects of nicotine in our normal group, this may reflect the smaller effect size due to good performance and the small sample. It is clear that nicotine can improve performance on various tasks in normal subjects (Wesnes and Warburton, 1978, 1983; Warburton, 1998; Pritchard and Robinson, 1998). Nicotine has also been shown to improve AS task performance in normals in some (Dépatie et al., 2002; Larrison-Faucher et al., 2003) but not all studies (Thaker et al., 1991). Here, we showed no significant effects of nicotine on AS task performance in normal subjects. However, using the similar task conditions and length of exposure to nicotine gum, we have shown a consistent benefit of nicotine on AS in normals (Larrison-Faucher et al.,

2003). In the previous study, we used highly practiced subjects and showed a reduction in RT of 10 ms. Due to the small effect size and the larger response variability, we may have been unable to record the effect of nicotine on our normal control subjects here. Secondly, the subjects in our patient and control groups were all heavy smokers. Based on calculations of buccal nicotine absorption, our highest dose of nicotine (6 mg, for 8 min) would only achieve approximately 1/2 to 2/3 the maximum blood nicotine levels obtained from a single cigarette (Benowitz et al., 1988). Some subjects in this study reported chain smoking five to seven cigarettes as a daily morning routine. Future studies might include a calibration of nicotine doses for these potentially less sensitive subjects.

4.2. Saccade performance in schizophrenic subjects

Although impaired performance on the AS task occurred in only a subpopulation of subjects, there were no impairments on saccade performance for any of our schizophrenic subjects. Both impaired and non-impaired schizophrenic subjects showed faster mean RTs and equal or even lesser errors for the S overlap and S gap tasks (Fig. 2). Although there were no significant differences in errors between the groups, there was an effect on RT for group and gap (Fig. 3). This could be due to a differential gap effect across our schizophrenic population. Non-impaired schizophrenic subjects showed a lesser gap effect than impaired or control subjects. The faster RT in the overlap condition by non-impaired subjects could also represent an ease of attentional disengagement or a lack of tonic inhibition on automatic responding. Further studies examining differences in the gap effect in schizophrenic populations might clarify the possible advantages these subjects show for reflexive attention tasks.

4.3. Heterogeneity of cognitive performance in schizophrenic subjects

Unexpectedly, only four out of eight of the schizophrenic subjects who completed the experiment showed any deficit on the antisaccade task. Several factors regarding our subject population may have contributed to this finding. First, all of the subjects participating were high functioning. All were living in the community, and some held full time employment. Second, we attempted to select subjects taking only neuroleptic treatments or as few adjunctive pharmacotherapies as possible (see Table 5). Half of our subjects were medicated solely with a single neuroleptic, reducing potentially confounding medication effects. However, this type of selection may have resulted in a population of subjects less impaired by their schizophrenia. Third, we chose only those subjects who were regular smokers. Recent epidemiological studies have reported that smoking does not occur in equal proportions across the different sub-syndromes of schizo-

phrenia. In particular, paranoid subtypes show the greatest level of smoking (Beratis et al., 2001; Combs and Advokat, 2000). This could explain the fact that our selected group consisted primarily of patients in the paranoid subtype. Furthermore, increased smoking has been associated with increased positive symptoms, whereas decreased smoking was associated with increased negative symptoms (Beratis et al., 2001). Thus, we may have inadvertently selected a group with fewer cognitive deficits. Finally, the effects of medication may have contributed to the exceptional performance in our patient group. Risperidone has been shown to be associated with better performance on the AS task both in cross-sectional studies (Reveley et al., 1996) and in a more controlled experimental design (Burke and Reveley, 2002). Five out of our eight schizophrenic subjects were taking risperidone, however only one of those subjects showed AS task deficits. Using a chi-squared contingency table, this distribution is significantly different than what would be expected, chi-squared 4.8, $p < 0.05$. Further, this chi-square value increases to 5.8, $p < 0.02$, if we include the subject who, due to the high level of AS task impairment (100% errors), was unable to complete the study (this patient's primary medication was Stelazine). However, because of our small sample size and cross sectional design, it is not possible to determine if/how these factors may have affected AS task performance in our patient group.

4.4. Nicotine–medication interactions

It has been recognized both in clinical and experimental settings that high doses of typical neuroleptics can impair cognitive performance (Cleghorn et al., 1990) and that some deficits are reduced in patients given atypical neuroleptic treatments (Light et al., 2000; Reveley et al., 1996; Burke and Reveley, 2002). In addition, neuroleptic treatments may interact with smoking and/or nicotine. For example, haloperidol has been shown to increase smoking (McEvoy et al., 1995a), and nicotine has been shown to increase neuroleptic drug metabolism and decrease extrapyramidal effects of the typical neuroleptic treatments (Miller, 1977). Unlike haloperidol, the atypical neuroleptic clozapine is associated with a decrease in smoking in schizophrenic patients (McEvoy et al., 1995b). These factors all emphasize the need to consider interactions between neuroleptic therapies, cognitive function, and nicotine when examining patient populations.

4.5. Practice effects

The repeated-measures design afforded us the opportunity to look at the effects of practice on eye movement task performance, particularly AS errors. It has been reported for normal subjects that 2 weeks of practice can significantly decrease AS error rates—from 13% to 11% (Fischer and Weber, 1992). No significant effects of practice were noted in our 3-day testing schedule. A stable response pattern

across the 12 testing sessions by our schizophrenic subjects indicates that the AS deficit is persistent and not the effect of an initial comprehension difficulty or novelty effect. Nevertheless, it is possible that these subjects could likely improve as well with increased practice and/or other forms of attentional training.

4.6. Nicotine self-medication

High rates of nicotine use are not unique to schizophrenia. Attention Deficit Disorder (ADD), depression, anxiety, alcoholism, drug addiction, and other personality and socioeconomic factors are all associated with increased smoking behavior (Schacter, 1978). Numerous questions remain regarding the complex issue of why the rate of nicotine use is greatly increased in schizophrenia. Two of the most pressing issues should be mentioned. (1) What is the specificity of nicotine's effects on cognitive function? Does nicotine improve global cognitive function, or are its effects specific, such as improving P50 gating or SPEN? (2) Is nicotine use directly related to its beneficial effects on cognition? Is nicotine really self-administered as a means of reducing cognitive deficits? In this study, only 50% of the schizophrenic subjects showed the AS deficit, whereas all of the subjects were heavy smokers. Although there was no correlation between smoking rate and AS task performance, as a group, the impaired subjects did have a higher daily consumption of cigarettes and caffeinated beverages. Cigarette smoke reduces Parkinsonian side-effects of neuroleptic treatments (Sandyk, 1993) and inhibits monoamine oxidase (Norman et al., 1982). Smoking also has significant mood altering effects (Pritchard, 1991; Waters and Sutton, 2000). Any number of these or other factors could contribute to the increased rate of smoking by the schizophrenic population.

5. Conclusion

Greater evidence must be obtained regarding the efficacy of nicotine and nicotine receptor targeted drugs. New treatments that reduce cognitive deficits in this patient population are greatly needed since these deficits are not treated by the typical neuroleptic therapies. Furthermore, such treatments may assist in reducing this population's high rate of smoking, a costly and physically harmful habit. Although there is great enthusiasm in these findings for the development of a novel treatment for the cognitive deficits in schizophrenia, great caution is also necessary. It is important to fully understand the costs and benefits of utilizing nicotine or a similar agent as a treatment before adding new drug therapies to an already heavily medicated population. An extensive understanding of nicotine's effects on specific cognitive deficits should be undertaken to better determine the pharmacological usefulness of nicotine and its analogs.

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