Nicotine improves antisaccade task performance without affecting prosaccades

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Although there is ample evidence for a cognitive-attentional benefit of the stimulant nicotine, the source of this benefit is not as well understood. One approach is to address what aspects of performance nicotine affects at a functional systems level. It is currently debated whether the benefits produced by nicotine are the effect of enhanced higher cognitive function or reflect an overall increase in general arousal. In order to address this question, the effects of nicotine on two simple eye movement tasks were studied: the saccade (S) and antisaccade (AS) tasks. Because the S and AS tasks utilize identical sensory stimuli (peripheral targets) and require identical motor responses (eye movements) but differ significantly in their cognitive demands, the use of these two tasks should enable a parsing of nicotine effects on cognitive versus sensory-motor processes. In this study, the S and AS tasks were performed by two experimental groups, task naïve subjects and highly practised subjects. For the first group, that of the task naïve subjects, nicotine gum administration resulted in a decrease in AS errors. For the second group, that of two experienced subjects tested repeatedly over a 3 week period, nicotine also produced a significant decrease in AS task errors, as well as resulting in a significant decrease in AS response times. Neither task naïve nor experienced subjects showed any effects of nicotine on the S task. Examining the effects of nicotine on highly controlled and constrained tasks such as the S and AS task may provide another level of insight into the mechanisms underlying the beneficial cognitive effects of nicotine. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — antisaccade; attention; eye movement; frontal; nicotine; saccade

INTRODUCTION

The past decade has been marked by a dramatic increase in research dedicated to understanding the cognitive effects of nicotine. Part of what is driving this new initiative is the theory that smoking may reflect self-medication of certain cognitive deficits in groups with attentional impairments. Nicotine has been shown to improve cognitive impairments in a number of patient populations, including Alzheimer disease, schizophrenia and attention deficit disorder (for review see Newhouse *et al.*, 2004). If nicotine, an addictive compound, is to be considered for phar-

macological use in patient populations, it is of primary interest to determine the specificity of its effects on cognition such that it could be administered to an individual when appropriate and not in an overly casual fashion or when it might not necessarily be beneficial.

There is nearly a century of research on the beneficial effects of nicotine on human performance. Persistently, however, similar task paradigms have failed to demonstrate or replicate the reported benefits of nicotine (for reviews of negative and positive effects see Heishman *et al.*, 1994; Koelega, 1993; Levin, 1992; Levin and Simon, 1998; Pritchard and Robinson, 1998; Wesnes and Warburton, 1978; Warburton, 1998). Withdrawal, absorption, gender and individual differences, and other potentially limiting or confounding variables are only part of the problem in interpreting existing findings. In addition, the attempt to categorize nicotine effects on performance has been limited by the failure of the majority of studies to intentionally control for the complexity of their chosen task (see Heishman *et al.*, 1994 for a critical

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review). For example, any given cognitive task that requires the subject to make a response will necessarily involve a motor component, and any task that involves viewing or responding to a stimulus will involve a sensory component. If sense is to be made of the conflicting reports and to determine the level at which nicotine exerts its beneficial effects, task demands affected by nicotine must be carefully manipulated. Only then will it be possible to selectively determine the level of cognitive processing affected by nicotine.

Previous work examining the effects of nicotine can be divided into two basic categories. It can be supposed that nicotine has its effects on higher cognitive function and involves central mechanisms, especially later cortical regions (Rusted *et al.*, 1998), or that it acts on an earlier or more general lower level sensory or motor function including actions at the level of the peripheral nervous system (i.e. by affecting adrenaline or through increasing muscle efficiency), or by a combination of both. This study was designed to determine whether nicotine has an effect on higher cognitive centres separate from any effects it might have on lower sensory-motor functions.

In order to test whether nicotine affects higher cognitive centres independent of any sensory or motor effects, two simple eye-movement tasks were administered—a prosaccade task (S) and an antisaccade task (AS). The S and AS tasks are identical in their sensory stimuli and motor response elements but differ in the level of cognitive processing required (Leichnetz and Goldberg 1988; Everling and Fischer, 1998). Both tasks proceed identically: subjects are presented with a peripheral target to the left or right of a central fixation point and must respond to that target by making an eye movement. For the S task, subjects look to the target location. This is a stimulus driven eye movement, and is thought to be a natural, 'reflexive' response to a peripheral stimulus. For the AS task, subjects look to the location opposite the target stimulus. This requires suppression of the stimulus-driven response and activation of an intentional, 'voluntary' eye movement to a location where no sensory stimulus has appeared. The sensory-motor similarities and cognitive differences of the S and AS tasks enable us to determine whether nicotine is acting on higher cognitive centres by comparing performance across the two tasks. If nicotine acts to enhance higher cognitive function as has been suggested, comparing the effects of nicotine on S and AS performance should indicate benefits on the AS task only, whereas no higher cognitive benefits should be seen for the reflexive S task. However, if nicotine acts by enhancing sensory and/or motor processes, equivalent benefits of nicotine should be recorded for both the S and AS tasks.

Additionally, the effects of nicotine were examined on the gap effect for the S and AS tasks. The gap effect, previously described by Fischer and Ramsperger (1984), is produced during performance on the S and AS tasks by removing the central fixation point prior to the onset of the target thus producing a visuo-temporal 'gap' during which the subject sees a blank screen briefly before target presentation. The inclusion of a gap has been shown to decrease response times (RT) in the S task and to increase errors in the AS task (Reuter-Lorenz *et al.*, 1991). Given the normally low rate of errors in normal subjects on the AS task, using a gap paradigm may enhance our abilities to detect any effects of nicotine.

This study examined the effects of nicotine gum in two groups. First, performance was measured in naive subjects tested across two testing days and run through a single session each testing day. Second, the performance effects of nicotine were examined in two subjects tested repeatedly over 3 weeks on the S and AS tasks. It was hypothesized that nicotine would improve performance on the AS task more than the S task in both our testing populations as measured by decreased RTs and/or decreased errors.

MATERIALS AND METHODS

Subjects: task naive experiment

Sixteen task naive subjects were recruited from Rutgers University, Newark, and the University of Texas, Houston, and participated in two separate testing sessions on simple prosaccade (S) and antisaccade (AS) tasks. All subjects were self-reported smokers, and all subjects reported abstaining from smoking for at least 2 h prior to each testing session. Subjects taking any prescription or over the counter drugs with known central nervous system effects were excluded.

Subjects: psychophysics experiment

Two subjects, who were part of the laboratory staff and had previous practice on this and other psychophysical tasks, participated in 24 sessions of testing. One subject, female, was a light smoker (3–15 cigarettes/week) but abstained from smoking on the mornings of testing until all testing was completed. The second subject, male, was a non-smoker. A slightly modified version of the task was used in order to increase attentional demands and to reduce automaticity in these highly practised subjects (see below).

Informed consent was obtained from all subjects in each experiment before participating, and subjects were debriefed after completing the experiment.

Eye-tracking equipment and procedure

During testing, subjects were seated 72 cm from a computer screen and instructed to rest their head on a chin support. An infrared light source was directed at the left eye and a video camera was focused on the same eye. The output of the camera was sent to a pupil and corneal reflection tracking system (RTS), manufactured by ISCAN. The ISCAN equipment calculates eye position independent of both head position and small head movements and does not require the subject's head to be rigidly stabilized (e.g. by a bite bar).

At the beginning of each experiment, the subject was individually calibrated, using custom calibration software. For these experiments a spatial resolution of approximately 0.5° and a timing resolution of 6 ms were obtained. A small video monitor connected to the camera displayed the left eye of the subject and an experimenter continuously monitored the subject's performance throughout each testing session. All experiments took place in a quiet, darkened room.

Tasks

The saccade (S) and antisaccade (AS) tasks are identical in their sensory and motor requirements. The details of the S and AS tasks are shown in Figure 1. Subjects were required to fixate the central point for 800 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. A brief 13 ms tone sounded simultaneously with the onset of the target. Subjects were instructed to look towards the target for the S task or away from the target for the AS task and were told to respond as soon as they saw it appear. Subjects had 1000 ms to respond to the target before the trial was considered a time-out and rerun later in the session. Each testing session consisted of four blocks of 66 trials for each condition (S overlap = 66; S gap = 66; AS overlap = 66; AS gap = 66) for a total of 264 trials. The presentations of these four conditions were counterbalanced across subjects.

Task modifications

For the psychophysics experiment in task familiar subjects, the S and AS tasks were modified slightly. In the new version of the task, three factors were chan-
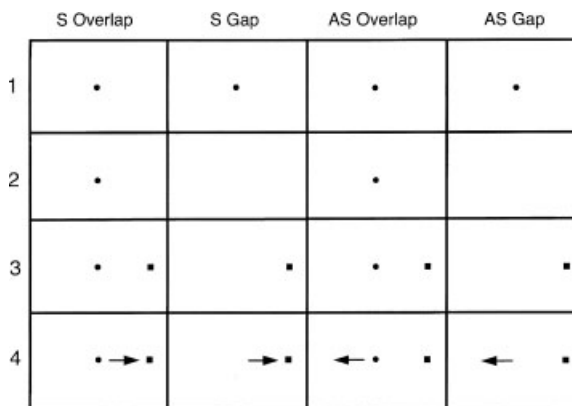

Figure 1. The saccade (overlap and gap) and antisaccade (overlap and gap) tasks. 1. Fixation: Subjects fixated the central point for 640 ms. 2. Overlap/Gap Conditions: Either the fixation point remained salient throughout this additional 160 ms period of the trial (overlap condition) or the central fixation point was extinguished for 160 ms prior to the onset of the target (gap condition). 3. Target Presentation: The target appeared with equal probability to the left or right of fixation (indicated as appearing to the right in these trials). 4. Eye Movement Response: Subjects responded by making an eye movement to the target location during the saccade task and to the location opposite the target during the antisaccade task

ged to increase task demands. Those were: (1) the inclusion of a variable target onset, (2) the elimination of the tone, and (3) the mixed presentation of gap and overlap trials. In order to decrease the predictability of target onset and thereby to reduce the extent to which the task would be automated, the fixation delay period was made variable. While previously the target always appeared after an 800 ms fixation period, it now appeared after a randomly presented variable interval of 800, 1000 or 1200 ms. Second, the previously presented 13 ms tone was eliminated since earlier studies demonstrated dramatic effects on RTs (Fischer, 1987). Third, the overlap and gap conditions were combined and randomly presented within the same testing block. Hence, instead of four blocks of 66 trials that were used with task naive subjects, for the psychophysics experiment, gap and overlap blocks were combined so that each block now contained 132 trials with gap and overlap conditions interleaved randomly (S overlap/gap = 132; AS overlap/gap = 132). The total number of trials per testing session remained the same (264 trials/session).

In a pilot study of two normal subjects who did not participate in any other part of this study, the effect of these design changes was compared on eye movement performance. It was verified that the revised version of
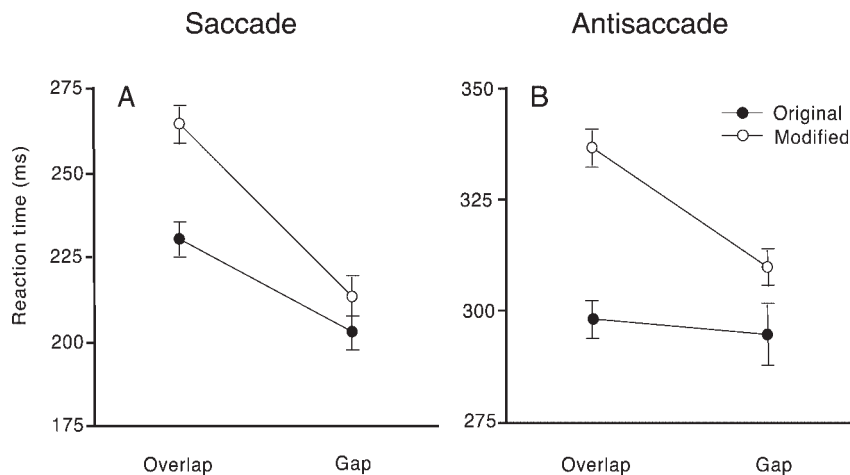
Figure 2.   Pilot study with original (task naive experiment) and modified (psychophysics experiment) tasks. The modified task produced slower RTs on both S and AS tasks and a greater gap effect. (Error bars = SEM)

the task produced slower RTs, and a larger gap effect, and was reported to be subjectively more tiring. These data are shown here for reference purposes only (see Figure 2).

The increase in RTs found using the modified version may be attributable to more than one of the task revisions. Previous studies demonstrate decreased RTs when auditory cues are presented at target onset (Fischer, 1987). In addition, the use of the variable fixation interval before target onset in the revised version could have reduced the subject's ability to prepare for the target onset and hence lengthen RTs (Weber *et al.*, 1995). Mixing gap and overlap trials would have had a similar effect. In sum, the revised version resulted in a more substantial gap effect, thus increasing the effectiveness of this manipulation.

Treatment and testing schedule

On each testing day, after calibrating the system, the subjects were brought into the darkened testing room and given a piece of gum containing 0 or 4 mg of nicotine. Subjects chewed the gum for 5 min at a rhythm of 60 beats per minute as determined by a metronome. For placebo sessions, only task naive subjects chewed a non-nicotine gum; practised subjects simply sat quietly in the darkened room with the metronome beating for 5 min. This time course was chosen based on initial studies performed in our laboratory (see Faucher, 2001). Naive subjects ran in two testing sessions. On each day of testing the subjects received either nicotine or placebo. The order was counterbalanced, so that each subject received both

treatments with half the subjects receiving placebo first and the other half receiving nicotine first. The second session was run no sooner than 24 h after the first. In contrast, testing sessions for the psychophysics were always paired so that practised subjects received both a nicotine and a no gum session on each testing day. These two sessions were separated by a 60 min break in which the subject participated in normal activity. In total, practised subjects participated in 24 testing sessions or 12 paired sessions. Treatment order was counterbalanced across testing days and between subjects.

Statistical analysis

Reported probabilities for all ANOVA analyses reflect the Greenhouse-Geisser adjustment. Data were analysed using two separate 3 within factor ANOVAs examining the effects of nicotine on (1) mean response times (RT) and (2) errors. For task naive subject data the within factors were: TASK (saccade, antisaccade), GAP (overlap, gap) and TREATMENT (nicotine, placebo). For the psychophysics subjects using the modified task, S and AS tasks were analysed separately to reduce the excessive number of within session variables. Thus, data were analysed using four separate 3 within factor ANOVAs with within factors of INTERVAL (800 ms, 1000 ms, 1200 ms), GAP (overlap, gap) and TREATMENT (P, N).

The majority of published studies that report significant effects of nicotine indicate that nicotine improves (as opposed to impairs) speed and accuracy. Based on this, we predicted that our treatment effects

would be unidirectional (i.e. a decrease in RTs and/or a decrease in errors), and therefore, treatment effects for naive subjects' data were examined using one-tailed t-tests. Four paired t-tests were run to assess effects of TREATMENT for S errors, S RTs, AS errors and AS RTs.

RESULTS

Results for task naive experiment

The RT data showed several significant effects for task naive subjects. There was a main effect of TASK, $F(1,15) = 157.8$, $p < 0.0001$, resulting from significantly faster RTs on the S compared with the AS task. There was also a main effect of GAP, $F(1,15) = 37.0$, $p < 0.0001$, due to significantly decreased RTs with the presence of the gap condition compared with the overlap condition. These factors did not interact. There were no significant effects of TREATMENT on S or AS RTs, nor were there any significant interactions with TREATMENT (Figure 3, panels A and B).

Error data also showed several significant effects for task naive subjects. There was a main effect of TASK that was due to greater errors on the AS compared with S task, $F(1,15) = 16.5$, $p < 0.0005$. This effect interacted significantly with the GAP condition, due to a greater increase in errors on the AS task with gap than overlap conditions compared with the S task, $F(1,15) = 12.3$, $p < 0.005$ (Figure 3, panels C and D). There was a trend toward a significant effect of TREATMENT that interacted with TASK, $p = 0.09$. Given that it was expected that nicotine might selectively affect the AS task and not the S task, separate ANOVAs were run for S and AS to determine which of these benefited from nicotine. These separate analyses indicated the trend was due to a trend toward decreasing errors in the AS task following nicotine, $p = 0.09$ (Figure 3, panel D), with an absence of treatment effects in the S tasks, $p = 0.99$ (Figure 3, panel C). These findings were in the direction of our predicted effects, and a planned one-tailed t-test confirmed significance of the increased accuracy on the AS task following nicotine treatment ($p < 0.05$).

Results for psychophysics experiment

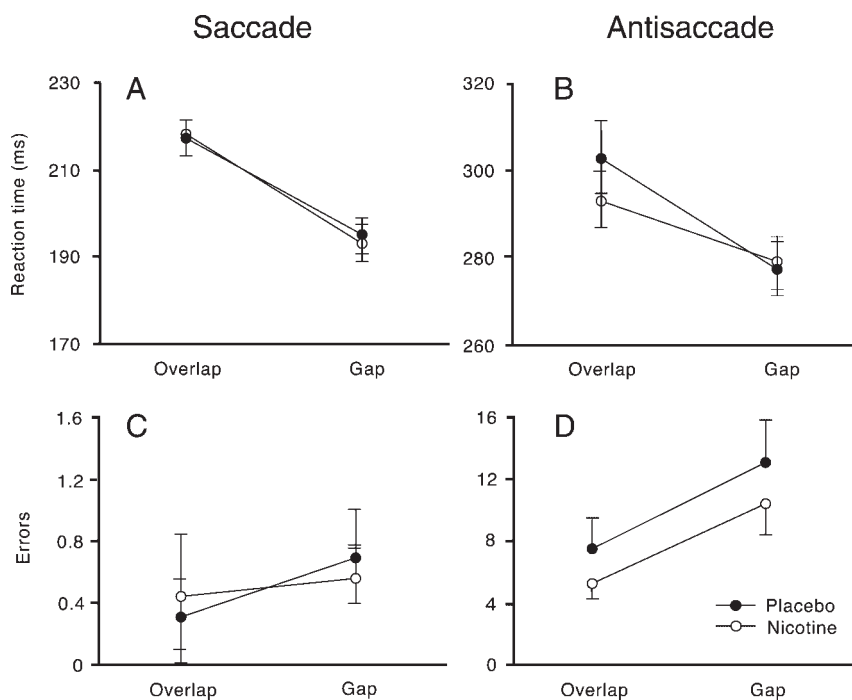The RT and error data were analysed using four separate ANOVAs presented here.

Figure 3. Nicotine effects on RTs and errors in the task naive experiment. Mean RTs and error rates for the S and AS tasks are presented for task naive subjects. Subjects were overall faster and made fewer errors on the saccade task compared with the AS task. There was a significant benefit of treatment on AS task accuracy ($p < 0.05$, panel D). (Error bars = SEM and are unidirectional in panel D for emphasis)
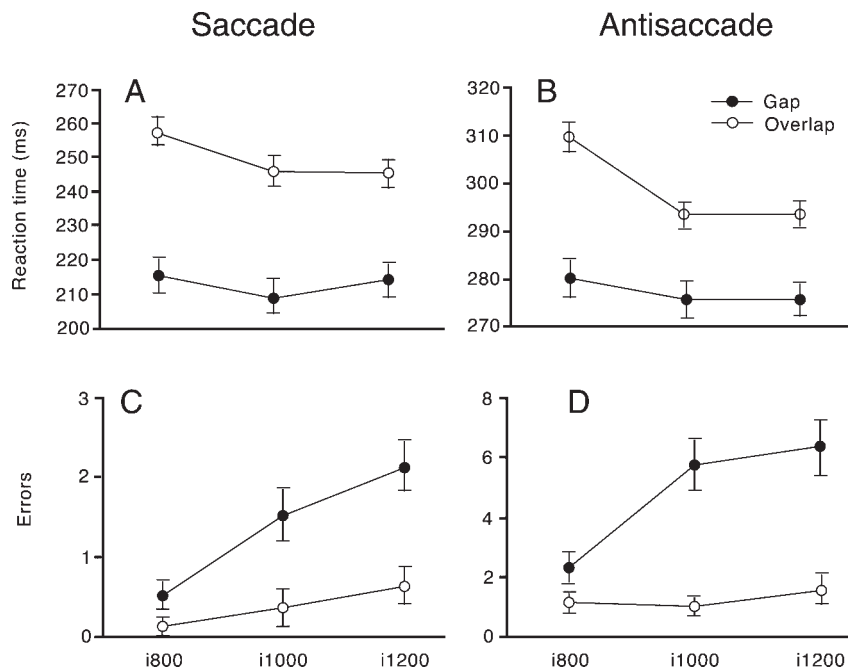
Saccade

Antisaccade

Figure 4.   Gap and fixation interval effects and interactions in the psychophysics experiment. Shorter fixation intervals were associated with longer RTs and fewer errors. The effect of interval on RTs (i.e. longer RTs at the shortest fixation intervals) varied depending on gap condition, occurring predominantly on trials in which the fixation point was not extinguished (overlap). Further, the effect of interval on errors (i.e. fewer errors at the shortest fixation intervals) also varied depending on gap condition; however, it occurred on trials in which the fixation point was extinguished (gap). (Fixation intervals: i800 = 800 ms, i1000 = 1000 ms, i1200 = 1200 ms; Error bars = SEM)

For saccadic RTs, there was a main effect of GAP, $F(1,23) = 303.9$, $p < 0.0001$, and fixation INTERVAL, $F(2,46) = 71.7$, $p < 0.0001$, on S RTs. Furthermore, these two task variables showed a significant interaction $F(2,46) = 11.2$, $p < 0.0001$, (Figure 4, panel A). There was no significant effect of TREATMENT on S RTs, $F(1,23) = 2.5, p > 0.12$. Treatment also showed no significant interactions with any measured variables (Figure 5, panels A and C, for GAP and INTERVAL, respectively).

For AS RTs, as in the S task, the subjects showed effects for both GAP, $F(1,23) = 130.5$, $p < 0.0001$, and INTERVAL, $F(2,46) = 30.7$, $p < 0.0001$. Also similar to the S task, these two task variables showed a significant interaction GAP × INTERVAL, $F(2,46) = 13.9$, $p < 0.0001$ (Figure 4, panel B). In contrast with the S task, however, there was a main effect of TREATMENT on AS RTs, $F(1,23) = 23.1$, $p < 0.0001$. This effect corresponded to decreased RTs in the nicotine treatment group compared with the placebo group. This effect further interacted with INTERVAL, $F(2,46) = 10.0$, $p < 0.001$ (Figure 5,

panel D), but did not significantly interact with GAP, $F(1,23) = 2.4$, $p > 0.13$ (Figure 5, panel B) or the 3-way interaction.

For S error rates, there were significant main effects for the within factors of GAP ($F(1,23) = 8.6$; $p < 0.01$) and INTERVAL ($F(2,46) = 9.2$, $p < 0.001$). These two variables did not show a significant interaction, $F(2,46) = 1.6$, $p > 0.21$ (Figure 4, panel C). There was no significant effect of TREATMENT on S errors ($F(1,23) < 1$), nor did TREATMENT show any significant interactions for S errors (Figure 6, panels A and C for GAP and INTERVAL, respectively).

Error rates on the AS task also resulted in several significant effects in our practised subjects. There were significant main effects on AS error rates for the within factors of GAP, $F(1,23) = 24.5$, $p < 0.0001$, and INTERVAL, $F(2,46) = 6.1$, $p < 0.01$, and these two variables showed a significant interaction, $F(2,46) = 5.5$, $p < 0.05$, (Figure 4, panel D). There was also a significant main effect of TREATMENT on AS errors, $F(1,23) = 6.4, p < 0.02$, for practised subjects. This effect did not significantly interact
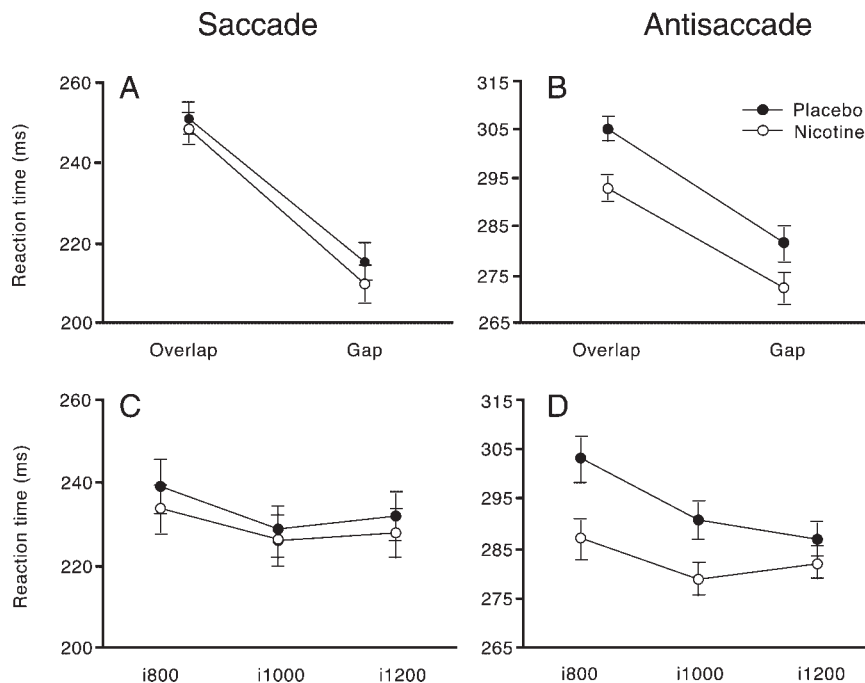
Saccade

Antisaccade

Figure 5. Nicotine effects on RT in the psychophysics experiment. The RT data are broken down by task (S and AS) and either gap (panels A and B) or fixation interval conditions (panels C and D). Nicotine significantly reduced RTs in the AS task, but had no effect on RTs in the S task. For the gap effect, there was no interaction between TREATMENT and GAP. The benefit of nicotine on the AS task was present equally in both gap and overlap conditions. However, there was a significant interaction between fixation INTERVAL and TREATMENT for the AS task. That is, the benefit of nicotine was present only at shorter fixation delays. With the longest fixation interval (1200 ms) there was no benefit of nicotine treatment. (Fixation intervals: i800 = 800 ms, i1000 = 1000 ms, i1200 = 1200 ms; Error bars = SEM)

with INTERVAL, $F(2,46) < 1$, (Figure 6, panel D), nor was there a significant TREATMENT by GAP interaction, $F(1,23) > 1$, (Figure 6, panel B).

DISCUSSION

This study examined the effects of low doses of nicotine on performance on simple eye movement tasks in order to determine the stage of information processing at which nicotine acts. Our finding that nicotine improves response speed and accuracy on the voluntary AS task only without affecting reflexive S task performance, suggests that nicotine may specifically enhance higher, more voluntary, cognitive processing rather than acting only to improve efficiency of simple sensory or motor function.

The reduction in errors by nicotine on the AS task alone, with no effect on the S task, is consistent with the prediction that nicotine plays a role in enhancing higher cognitive, or voluntary processes, and does not simply act to enhance simple sensory or motor performance. However, no effects of nicotine on RTs were found in the task naive subjects. One possibility for

the failure to find RT effects in that experiment was that the task design was too easy, resulting in maximal performance even in placebo conditions such that enhanced performance could not be detected, i.e. a statistical floor effect. Previous reports suggest the need for increased difficulty and effortful processing requirements of tasks in order to demonstrate significant effects of nicotine (Rusted *et al.*, 1998). Therefore, it is possible that our redesigned version (used in the psychophysics experiment) might be a more sensitive design for measuring the effects of nicotine.

Nicotine and disengaging attention

These studies examined nicotine effects across the overlap and gap conditions. This task manipulation, in which the fixation point remains visible throughout target presentation (overlap condition) or is extinguished prior to target presentation (gap condition), has been proposed as a measure of the disengagement of attention. Here we report no difference in nicotine effects across gap and overlap conditions. Nicotine improvements in AS accuracy in task naive subjects

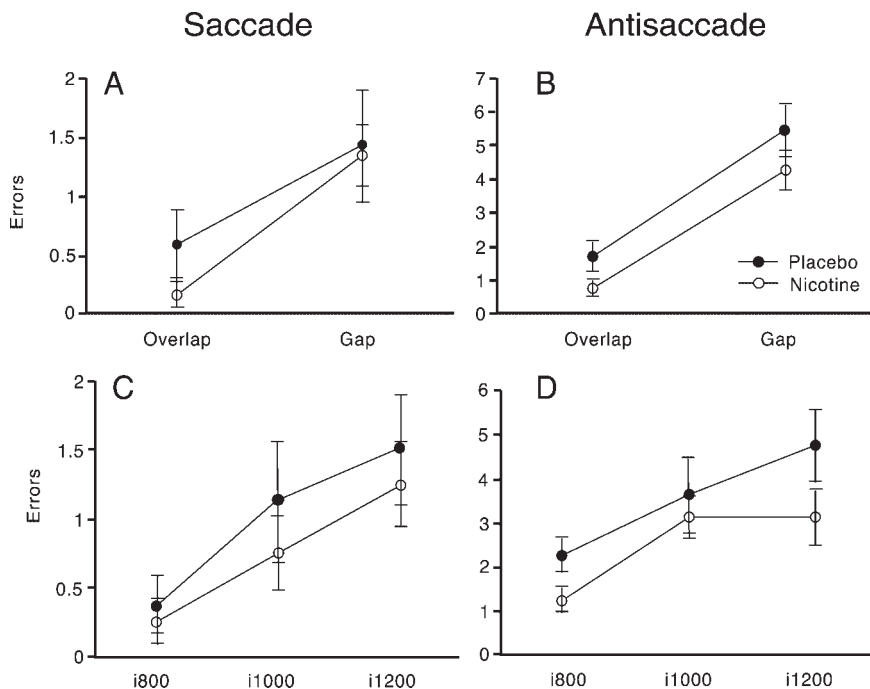## Saccade   Antisaccade

Figure 6.   Nicotine effects on errors in the psychophysics experiment. The error data are presented for gap effects (panels A and B) and for effects of fixation interval (panels C and D). Nicotine significantly decreased errors on the AS task, but had no effect on the S task. There were no significant interactions of TREATMENT with either GAP (panels A and B) or INTERVAL (panels C and D). (Fixation intervals: i800 = 800 ms, i1000 = 1000 ms, i1200 = 1200 ms; Error bars = SEM)

and AS speed and AS accuracy using psychophysical testing in highly practised subjects were equivalent for both gap and overlap conditions (Figure 3, panel D; Figure 5, panel B; and Figure 6, panel B). This suggests that nicotine did not affect attentional disengagement in this study.

Nicotine effects on eye movements

Mancuso *et al.* (2001) reported that nicotine improved performance only on tasks of non-elaborated information processing, and in direct contrast to our findings, reduced RTs for simple eye movements. However, their study did not directly measure eye movements but only inferred eye movement RTs based on manual response latencies, i.e. key press. Their subjects were required to discriminate the presence or absence of a notch in a box stimulus that was presented at the central fixation point or 15° to the left or right of the central fixation by making a key press. The authors recorded manual RTs and reported a decrease in manual RTs to discriminate peripherally presented boxes with no change in RT to discriminate centrally presented boxes following administration of nicotine. Thus, it was argued that the inferred but not measured

eye movement to the peripheral target was the factor that was speeded by nicotine. Although this is one possible explanation for the findings reported by Mancuso *et al.*, there are other potential explanations. One such explanation is that following nicotine administration, subjects were better able to shift their covert attention to the peripheral stimulus. Since the task required discrimination rather than merely detection, correct responses at peripheral locations also required attentional shifts. Consistent with their findings, a speeding of the shift of attention to the periphery would result in faster RTs for peripheral targets, whereas for central targets, where both eye position and attention are focused at the central location no attentional shift would be needed producing no change in RT. Consistent with this hypothesis, several studies have indicated a role of cholinergic function in visual attentional shifts (Voytko *et al.*, 1994; Witte *et al.*, 1997; Murphy and Klein, 1998).

Time course of nicotine effects

This study administered nicotine gum for a period of only 5 min before the start of eye movement testing. This brief time course was chosen in order to examine

performance during nicotine rise times, rather than at peak blood concentration levels. There are several advantages to using such a short time course. First, short exposure acts to minimize the problem of nicotinic receptor desensitization. Nicotinic receptors (in particular the alpha-7) are known to desensitize rapidly when activated by a ligand. Therefore, presumably, central activation of nicotinic receptors is best produced by fast rising nicotine levels that most mimic impulse like increases, rather than steady state, or slow increases. Second, short exposure reduces unwanted side effects and allows for a faster recovery. None of our subjects reported any negative side effects of gum exposure (e.g. sweating or nausea), with the exception of disliking the taste or experiencing a tickling in the throat. Side effects of nicotine are potential confounds to any experimental design and can potentially explain many of the reports that indicated impaired performance in non-smokers for whom the side effects are the most severe.

Our previous studies support the effectiveness of a short exposure time in the ability to produce measurable cognitive benefits (Larrison et al., 1998; Larrison-Faucher et al., 2004). Although 5 min exposures are particularly low, significant effects were shown. In the experienced subjects, mild but notable physical effects of the gum were reported as occurring as early as 3 min after the commencement of chewing. Future studies using nicotine gum might expand on this short exposure protocol by testing effects of higher doses of nicotine and including a range of short intervals.

Smoking withdrawal and nicotine effects

Nicotine withdrawal is associated with cognitive deficits that can be ameliorated given nicotine treatment or smoking (Warburton and Arnall, 1994). Thus, determining the effects of nicotine above and beyond the treatment of withdrawal symptoms is critical (c.f. Waters and Sutton, 2000). In our two studies all task naive subjects were smokers, however, in our psychophysics experiment, one subject was a non-smoker and the other was a light smoker, or 'chipper'. Benefits on AS performance were seen in the non-smoker as well as in the smoker.

One of the problems with interpreting the scores of smokers 'off' nicotine is that people who take up smoking might be more likely to have existing attentional deficits that are ameliorated by nicotine. It is often reported that populations with known attentional problems will self-medicate with stimulants such as nicotine or caffeine (Lerman et al., 2001; Batel,

2000; see also, Larrison et al., 1999). Therefore, studies reporting that abstaining smokers perform less well on tasks of attention and performance are difficult to interpret. It is just as possible that smokers as a group represent a separate population, and therefore comparing baseline differences in attention capacities between never smokers and abstaining smokers may not be appropriate. One way of addressing this issue might be to examine the performance of smokers, ex-smokers and never smokers on a wide range of tasks (Ernst et al., 2001). However, the question remains as to what extent the performance effects of nicotine reflect amelioration of withdrawal, absolute facilitation, or reduction of pre-existing attentional impairments.

Nicotine effect size, psychophysics, and eye movements

Robust effects of nicotine were demonstrated using a psychophysical design. The size of the RT effect of nicotine in this design was only 10 ms. When one considers that most experimental designs examining the effects of nicotine on attention have used single exposure and have examined complex tasks that involved multiple variables with intrasubject RTs that range far more than 10 ms, it is not surprising that one finds so many null effects. In contrast, studies employing simpler tasks, such as finger-tapping and critical flicker fusion, and those that have used repeated exposures to nicotine have been more successful in demonstrating significant effects (West and Jarvis, 1986; Sherwood et al., 1992). In particular, eye movements may hold additional merit in that they are arguably the fastest, most direct motor response that can be measured and hold special significance with tasks using visual stimuli. However, there may be some question as to whether effects seen when using eye movements as a motor response can be generalized to other motor response systems (see e.g. Briand et al., 2000; Khatoon et al., 2002) since there are differences with respect to the brain circuitry, load and complexity of the movements which may effect results. In either case, it will be useful to develop clear, effective measures of cognitive processing and to use repeated measures as a means of decreasing the within-subject variability and reducing the likelihood of type II errors.

Antisaccades, frontal lobe function and schizophrenia

Several studies indicate a role of the frontal lobe in normal AS task performance (Guitton et al., 1985; Gooding et al., 1997; Henik et al., 1994; see also

Sereno, 1992 and Everling and Fischer, 1998). This finding is potentially relevant to understanding smoking patterns in schizophrenia. In schizophrenia, hypofrontality is perhaps the most frequently reported electrophysiological symptom (see Buchsbaum, 1990 for review), and impaired AS performance has been clearly demonstrated (Arolt *et al.*, 1998; Crawford *et al.*, 1995; Fukushima *et al.*, 1988; Fukushima *et al.*, 1990a; Fukushima *et al.*, 1990b; Karoumi *et al.*, 1998; Sereno and Holzman, 1995; Thacker *et al.*, 1989). Furthermore, this population shows a much greater rate of cigarette smoking than the norm (deLeon, 1996; deLeon *et al.*, 1995; Hughes *et al.*, 1986; Lawrie *et al.*, 1995; Lohr and Flynn, 1992; O'Farrell *et al.*, 1983; Ziedonis *et al.*, 1994). It has been proposed that smoking by this population may be a means of self-medicating cognitive deficits such as the AS task deficit (Adler *et al.*, 1993; Levin *et al.*, 1996; Olincy *et al.*, 1998). To date, two studies have demonstrated a reduction in AS error rates in schizophrenic subjects following nicotine administration (Dépatie *et al.*, 2002; Larrison-Faucher *et al.*, 2004).

Conclusion

Examining the selectivity of cognitive effects of nicotine is an effective means of understanding where and how nicotine acts at a functional systems level to improve performance. The selective enhancement of performance on the AS task following nicotine treatment reported here suggests an effect of nicotine at higher cognitive processing levels, rather than predominantly at a motor or sensory level. A more complete picture of the systems level effects of nicotine can be achieved through parallel examination of studies using imaging, animal, physiological and psychophysical measures.

ACKNOWLEDGEMENTS

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