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The antisaccade task as an index of sustained goal activation in working memory: modulation by nicotine

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Abstract

The antisaccade task provides a laboratory analogue of situations in which execution of the correct behavioural response requires the suppression of a more prepotent or habitual response. Errors (failures to inhibit a reflexive prosaccade towards a sudden onset target) are significantly increased in patients with damage to the dorsolateral prefrontal cortex, and patients with schizophrenia. Recent models of antisaccade performance suggest that errors are more likely to occur when the intention to initiate an antisaccade is insufficiently activated within working memory. Nicotine has been shown to enhance specific working memory processes in healthy adults. We explored the effect of nicotine on antisaccade performance in a large sample (N=44) of young adult smokers. Minimally abstinent participants attended two test sessions and were asked to smoke one of their own cigarettes between baseline and retest during one session only. Nicotine reduced antisaccade errors and correct antisaccade latencies if delivered before optimum performance levels are achieved, suggesting that nicotine supports the activation of intentions in working memory during task performance. The implications of this research for current theoretical accounts of antisaccade performance, and for interpreting the increased rate of antisaccade errors found in some psychiatric patient groups are discussed.

Keywords

Nicotine, intention, antisaccade, working memory, inhibition

Introduction

It is well established that administration of the cholinergic agonist nicotine results in improvements in basic, or low-level psychomotor performance in humans. For example, nicotine has been shown to increase finger tapping rate (West and Jarvis 1986) and decrease reaction times (Bates et al 1994;Witte et al 1997, Greisar et al 2002). Nicotine also improves performance on tests involving sustained attention such as the Rapid Visual Information Processing task (e.g. Warburton and Arnall 1994, Foulds et al 1996) and Continuous Performance test (Levin et al 1998).

A number of studies have suggested that nicotine may additionally improve performance on tasks that require high level cognitive control processes such as error detection and correction, planning, updating working memory and active response inhibition. For example, administration of nicotine can lead to better performance on the n-back task (Ernst et al 2001, Kumari et al 2003) and random letter generation (Mancuso et al 2001), both of which require monitoring and updating information held in active or “working” memory.

The ability to inhibit the processing of irrelevant information and withhold prepotent or habitual responses to external stimuli is a key function of working memory (Roberts et al 1994). Nicotinic enhancement of inhibition of irrelevant or conflicting material has been demonstrated using the Stroop test (Della Casa et

al 1999) and the retrieval-induced forgetting paradigm (Edginton and Rusted 2003). The antisaccade task (Hallet 1978) also provides a laboratory measure of the ability to inhibit prepotent responses. The sudden appearance of an object in the visual periphery typically captures attention, and elicits a “reflexive” prosaccade in its direction (Findlay and Walker 1999). In the antisaccade task participants are required to inhibit the prosaccade towards the target and instead initiate a voluntary eye-movement (an antisaccade) to the opposite hemifield. As a tool with which to study the effects of nicotine on cognitive function, the antisaccade task has a number of advantages over neuropsychological measures of inhibition such as Stroop. The neural mechanisms underlying saccadic control are comparatively well charted (e.g. Leigh & Kennard, 2004), and the oculomotor system has a limited output, which can easily be measured with a high degree of precision using modern oculographic recording equipment. In addition, the prosaccade task (in which participants are asked to make a saccade towards a target) provides a useful control condition.

Antisaccade errors are significantly increased in patients with damage limited to the dorsolateral prefrontal cortex (DLPFC) but not frontal eye fields (FEF) (Pierrot-Deseilligny 2003). Accordingly, increased antisaccade errors have been taken as evidence of dysfunctional dorsolateral prefrontal cortex in a number of clinical populations (see Munoz & Everling, 2004) most notably schizophrenia. Importantly, antisaccade errors are also significantly increased in the first degree

relatives of patients with schizophrenia, and as such are considered a potentially important marker of genetic vulnerability to the disorder (Calkins et al 2004).

According to recent models of antisaccade performance (Massen, 2004; Munoz & Everling, 2004; Reuter & Kathmann, 2004), the sudden appearance of the peripheral target triggers a “race” between two separate saccade programs – a exogenously driven prosaccade towards the target, and an internally generated (endogenous) antisaccade to the opposite hemifield. If the antisaccade can be programmed fast enough, it “wins” the race, and the prosaccade is cancelled. Alternatively, if the prosaccade is programmed fast enough (or the computation for the antisaccade is too slow) an erroneous prosaccade is made first, and the correct antisaccade follows. Parallel programming of saccades has been demonstrated in several other tasks (e.g. Godijn and Theeuwes, 2002) but is worth noting that the extent to which correct and incorrect responses are always programmed in parallel is unclear – on some antisaccade trials errors may be compounded by one or more further saccades toward the target before being corrected.

Within the framework outlined above error rates can be considered to be a function of the levels of activity in the neural systems responsible for initiating the two competing saccades – the higher the baseline activity or the faster the rate of rise, the sooner the threshold required to trigger a saccade is reached. Thus, Massen (2004) argues that any experimental manipulation that non-selectively

influences activity in both systems (e.g. increases or decreases activity equally in both) will not result in a change in error rate. In contrast, a manipulation that either selectively increases activity in the neural systems responsible for the prosaccade, or decreases activity in the neural systems responsible for the antisaccade, should result in increased errors. Similarly an experimental manipulation that does the opposite (e.g. either decreases activity in the neural systems responsible for the prosaccade or increases activity in the neural systems responsible for the antisaccade) would be expected to result in a decrease in antisaccade errors.

According to this model, if nicotine is acting simply to increase general arousal, and this increase impacts equally on activity in the neural systems underlying both the endogenous and exogenously driven processes, then the likelihood of either reaching threshold before the other would be unchanged, and there would be no change in antisaccade error rate. However, if the effects of nicotine are greater on high level endogenous processes (such as the ability to adequately maintain the intention to initiate an antisaccade within working memory) than on lower level exogenously driven processes, then nicotine ought to result in a decrease in errors (as increased activity in the neural system underlying the endogenous antisaccade would increase the likelihood of it reaching threshold before the exogenous prosaccade).

Two studies have reported that nicotine decreases antisaccade errors in patients with schizophrenia (Larrison-Faucher et al 2004, Depatie et al 2002). However, schizophrenia is associated with increased rates of smoking and alpha 7 nicotinic receptor abnormalities (de Leon & Diaz, 2005; Martin-Ruis et al, 2003). Findings in healthy populations are less consistent (Larrison-Faucher et al 2004; Larrison et al, 2004; Roos et al, 1995; Powell et al 2002). Both Depatie et al (2002) and Powell et al (2002) used overnight abstinent smokers , so the reduction in antisaccade errors they report could be due to a reversal of a withdrawal-induced deficit in performance. The only study to use minimally abstinent smokers delivered 4mg nicotine gum (Larrison et al 2004) to task naïve subjects participating in two sessions. They reported a trend towards fewer errors but no effect on saccade latencies on single-task blocks of the antisaccade task. However, Larrison et al (2004) did not address the confounding of practice effects and novelty effects, and thus did not compare performance amongst those administered nicotine during their first experimental session to those receiving nicotine on the second session.

In this study we used a crossover design that allows an easy differentiation between improvements resulting from practice and those resulting from enhancement by nicotine. Nicotine was delivered through smoking, and the volunteers were moderate smokers (10-20 cigarettes per day) who were minimally (two hours) abstinent prior to testing. As a delivery system for nicotine in habitual users, smoking provides better opportunity for self-titrated ‘optimal’

delivery than recently available systems such as nasal spray (Myers et al, 2004) nicotine patch (Poltavski & Petros, 2005) and gum (Harris et al, 2004). This avoids negative side effects, such as nausea, and the experiential differences associated with unfamiliar delivery systems, which can significantly change the outcome (Dar & Frenk, 2004). The two hour deprivation procedure minimises the likelihood of subjective experience of 'withdrawal' or 'craving' in moderate smokers during the test session and thus militates against an interpretation of any cognitive effects in terms of deprivation reinstatement (see Heishman et al, 1994; Heishman, 1998 for reviews and discussion).

Methods

Participants

Participants were recruited for two separate studies with identical inclusion criteria. These were that participants should be aged between 18-35, smoke 10-20 cigarettes a day, habitually smoke before lunchtime and have normal or corrected to normal vision. Both studies were part of the first author's DPhil programme. The second study was identical to the first, but contained an additional third testing session and participants performed another variant of the AS task at baseline. We do not present this additional data here. Twenty volunteers (7 male) took part in study 1, mean (s.d.) age 22.3 (4.06) years. These participants scored 3.95 (1.61) on the Fagerström (1978) measure of nicotine

dependence, had been smoking on average for 6.13 (3.63) years and were 183 (88.1) minutes abstinent at the start of the experiment. Twenty four volunteers (4 male) took part in study 2. These participants were aged 20.6 (1.93), scored 4.46 (1.91) on the Fagerström (1978) questionnaire, had been smoking for 5.38 (2.18) years and were 149 (34.3) minutes abstinent at the start of the experiment. The larger mean and standard deviation in the time-to-last cigarette data from study 1 is due to one participant choosing not to smoke in the morning before her second session. Independent t-test showed no differences ($p>0.1$) between participants in the two studies on the above demographics and smoking characteristics. The fact that the majority of participants were female reflects the gender bias in the undergraduate psychology populations. Research has demonstrated that acute effects of nicotine are not significantly mediated by gender related issues (see Perkins et al, 1999 for a review). To increase experimental power data was collapsed across both studies and the combined data is reported here. All participants were volunteers from the existing pool of subjects at the University of Sussex, gave informed consent at the start of the first session and were paid £10 (study 1) or £15 (study 2) or received Psychology course credits for their participation. The University of Sussex School of Life Sciences Ethics Committee gave approval for this experiment.

Tests

Participants were seated approximately 70cm from a 21inch monitor and eye-movements were recorded with an Eyelink II eye tracker (SR-Research, Ontario, Canada). The antisaccade task required participants to fixate a small red circle (subtending approximately 0.5 degs) in the centre of the screen. In order to increase the potential for observing facilitatory effects of nicotine we manipulated the length of the gap between the offset of the fixation stimulus and the onset of the peripheral target. Previous research has demonstrated that antisaccade errors are significantly increased when a 200msec gap is introduced compared to the 0msec gap or "step" version of the antisaccade task that is traditionally used. We therefore used a 200msec gap condition and also a 500msec gap condition that results in similar error rates as the standard 0msec "step" version (Fischer and Weber 1997), but does not require attention to be disengaged from the fixation stimulus at the time of target onset. After a random interval between 1000 and 1500 msec the central fixation stimulus disappeared and, after a gap (200 or 500 msec), was replaced by a peripheral target (a red circle of the same diameter). The peripheral target appeared at one of four possible locations, +/- 4 and 8 degrees from fixation. Participants were instructed to look as quickly and as accurately as possible to the mirror image location of the target. Two blocks of 72 trials were performed at each baseline and retest. Within each block an equal number of trials had 200 and 500 msec gaps, and the target appeared at each location an equal number of times. Target location and gap length were varied pseudorandomly such that no gap length or target location was used more than

three times in a row. A 800Hz tone sounded for 50 msec at exactly the same time as the target appeared.

Procedure

All participants were tested on two separate sessions, separated by between 2 and 7 days. Participants were requested to abstain from smoking for at least two hours prior to arrival, and compliance with this request was monitored with end-tidal CO readings taken on arrival. Mean (s.d.) end-tidal CO measures of 10.1 (5.12) for session 1 and 8.09 (4.56) for session 2 were taken as compliance with this request. Both experimental sessions involved a baseline test of two 72-trial blocks , a short break and a retest of two further 72-trial blocks. In counter-balanced sessions participants were either asked to smoke one of their own, preferred brand of cigarettes during the break, or to abstain throughout. Thus, 22 of the participants smoked between baseline and retesting in their first session and abstained during the second. The remaining 22 participants abstained during the first session and smoked between baseline and retesting in the second session. During the first session an 8-trial practice block of the antisaccade task was performed to ensure that all participants had understood the task instructions.

Analysis

The performance measures were percentage errors, latency for correct antisaccades and correct antisaccade gain (the ratio of correct saccade

amplitude and target amplitude). At each baseline and retest in the two sessions mean scores were calculated from the two 72-trial blocks combined. In order to explore between session effects baseline data were entered into a mixed ANOVA with session (session 1 vs. session 2), gap length (200msec or 500msec gap), smoking order (smoked in session 1 vs. smoked in session 2) and study (participation in study 1 or 2) entered as factors. Less than 6% of the cells in the ANOVA on error data had 0% errors. In order to explore the effects of nicotine, we calculated difference scores (retest minus baseline) and entered these into a mixed ANOVA with nicotine (smoked vs. abstained), gap length, smoking order and study entered as factors. Less than 4% of the cells in the ANOVA on error data had 0% errors.

Results

There were no significant differences on any baseline measure between those who took part in study 1 or study 2 ($p>0.1$ for all main effects). There was a trend towards faster latencies for correct antisaccades ($F(1,40) = 3.23$, $p=0.08$) and fewer errors ($F(1,40) = 2.93$, $p=0.09$) at the 200msec gap length amongst those who took part in study 2. These reflect practice effects due to the additional block of antisaccade trials performed in experiment 2. There were no main effects of, or interactions with study ($p>0.1$) for the difference scores.

Baseline data:

Significant main effects of session revealed practice effects for percent errors and correct antisaccade latencies. Percentage errors : $F(1,40) = 22.4$, $p<0.001$ and latencies for correct antisaccades, $F(1,40) = 43.1$, $p<0.001$ were lower at the baseline test in the second session compared to the baseline test in the first session. Participants made more errors overall for the 200 msec gap trials compared to the 500 msec gap trials $F(1,40) = 9.76$, $p < 0.01$) and were also generally faster to initiate correct antisaccades for 500msec gap trials compared to 200 msec gap trails ($F(1,40) = 57.1$, $p < 0.01$). These main effects of session and gap length were qualified by significant interactions between session and gap length (see Figure 1). These revealed that the improvement in percentage errors occurred only for the 200msec gap length ($F(1,40) = 24.8$, $p=0.003$) and that the reduction in correct antisaccade latency between the sessions was greater for the 500msec gap compared to the 200msec gap trials $F(1,40) = 29.7$, $p<0.001$).

In the baseline data, prior to delivery of nicotine, a significant interaction between session and smoking order for antisaccade errors revealed a greater reduction in errors from the first to the second session amongst those who had smoked in session 1 ($F(1,40) = 5.94$, $p<0.02$), see table 1. Paired t-tests confirmed that the difference in error rates between session 1 and 2 is significant for those who smoked in session 1 ($t=4.56$, $df=21$, $p<0.001$) and significant at a trend level for those who smoked in session 2 ($t=1.87$, $df=21$, $p=0.077$). An independent t-test

revealed that the apparent difference in session 1 error rates between the two smoking order groups is not significant (p=0.36).

For correct antisaccade amplitude the main effect of session was not significant ($F(1,40) = 0.24$, $p = 0.63$). However, a significant session by gap interaction ($F(1,40) = 4.37$, $p < 0.05$) arose because correct antisaccade amplitudes are more hypometric at the baseline of the second session for 200 msec gap trials, but not 500 msec gap trials. This was further qualified by a significant 3-way interaction between session, gap and the between subjects factor smoking order ($F(1,40) = 14.6$, $p < 0.01$). This unexpected interaction reflects the fact that amplitudes were reduced for both gap lengths at the second session compared to the first for participants who smoked in session 2, whereas participants who smoked in session one showed a reduction in amplitude for 200 msec gap trials, but an increase in amplitude for 500 msec gap trials.

Insert Table 1. here

Nicotine effects

Smoking significantly reduced the number of antisaccade errors made ($F(1,40) = 11.2$, $p < 0.01$) and the latency with which correct antisaccades were initiated ($F(1,40) = 5.61$, $p < 0.05$) compared to abstaining. As is clear from figure 2, these main effects of nicotine were qualified by significant nicotine by

smoking order interactions (percent errors, $F(1,40) = 9.6$, $p < 0.01$; correct antisaccade latencies $F(1,40) = 5.78$, $=< 0.05$). The interaction for percent errors reflects the fact that errors were reduced after nicotine if the cigarette was smoked during the first session ($t = -4.31$, $df = 21$, $p < 0.01$) but not during the second session ($t = -0.31$, $df = 21$, $p = 0.76$). The interaction between nicotine and smoking order for correct antisaccade latencies occurred because for those participants who smoked in session 1 smoking resulted in significantly greater reduction in correct antisaccade latencies than abstaining ($t = -4.32$, $df = 21$, $p < 0.01$), whereas, for those participants who smoked in session 2, both smoking and abstaining resulted in small reductions that were equivalent ($t= -0.01$, $df = 21$, $p = 0.99$). A three way interaction between nicotine, gap length and smoking order for antisaccade errors ($F(1,40) = 5.2$, $p< 0.05$) occurred because nicotine, when smoked in session 1, reduced errors on trials with a 200 msec gap to a greater extent than errors on trials with a 500 msec gap. Paired t-tests performed on data from each smoking order group separately confirm that errors on 200msec ($t=-4.3$, $df=21$, $p<0.001$) and 500msec ($t=-2.58$, $df=21$, $p< 0.02$) gap trials are reduced after nicotine amongst those who smoked in session 1, while there is no reduction in errors after nicotine at either gap length for those who smoked in session 2 ($p's>0.1$).

There was very weak overall effect of nicotine on correct saccade amplitude ($F.(1,40) = 3.06$, $p = 0.09$) with nicotine generally resulting in a slight increase in amplitude whereas abstinence resulted in a slight decrease. As with error rate

and correct antisaccade latency, the nicotine by smoking order interaction was significant ($F(1,40) = 7.07$, $p < 0.01$). However, unlike the equivalent interactions for error rate and correct antisaccade latency, nicotine increased correct saccade amplitude only if smoked in session 2. This interaction is not readily interpretable and suggests that the trend for an overall effect of nicotine should be treated with caution. The nicotine by gap interaction was also significant ($F(1,40 = 11.7$, $p < 0.01$). The interaction occurs because correct antisaccade amplitude is not affected by nicotine or abstinence for 200 msec gap trials whereas nicotine increases amplitudes and abstinence decreases amplitudes for 500 msec gap trails. In general, the effects of nicotine on correct antisaccade amplitude are complex, and are difficult to interpret in the light of the baseline differences that were observed.

Discussion

We investigated the effect of nicotine (administered in the form of a single preferred brand cigarette) on antisaccade performance in a non-clinical population. We found that nicotine led to a significant reduction in antisaccade errors when it was received during the first experimental session. Nicotine also led to a reduction in the latencies of correct antisaccades, and again, the reduction was greater for participants who smoked in the first session. These findings support previous work showing a nicotine-induced reduction in antisaccade errors (Depatie et al 2002; Powell et al 2002; Larrison et al 2004) and latencies (Larrison et al 2004) in healthy young adults. Further evidence for

cholinergic modulation of antisaccade performance comes from reports of an increase in antisaccade errors amongst schizophrenic patients administered the cholinergic antagonist procyclidine (Ettinger et al 2003a).

A number of studies using similar designs have observed effects of nicotine only when administered in the first session. Powell et al (2002) reported fewer antisaccade errors after smoking in smokers permitted to smoke prior to the first testing session but not those who smoked in the second session. Also, using a complex visual search task, we found that nicotine reduced the number of fixations and refixations of stimuli made during the search only if the cigarette was smoked in the first session (Rycroft et al, 2005).

We found significant between sessions practice effects – average baseline error rates were 20.1% in the first session compared to 14.5% in the second session. Other researchers have also demonstrated significant between sessions practice effects for the antisaccade task (e.g. Ettinger et al, 2003b). One explanation of our findings, and those described above, is that any facilitatory effects of nicotine are more likely to be observed when performance is least optimal - as practice improves performance towards the higher end of the range of possible scores, ceiling effects reduce the potential for nicotine to induce any further improvements. Our finding that nicotine led to a greater reduction in errors for the 200msec gap compared to the 500msec gap trials supports this interpretation – baseline errors were higher for the 200msec compared to 500msec trials. This

interpretation also clarifies the failure to observe facilitatory effects of nicotine on antisaccade performance in a subgroup of schizophrenic patients who did not have abnormally increased antisaccade errors (Larrison-Faucher, 2004, and the fact that, in general, facilitatory effects of nicotine on antisaccade performance have been more consistently observed in patients with schizophrenia (who have high baseline levels of antisaccade errors) compared to healthy controls (Roos et al 1995; Depatie et al 2002). This interpretation is also consistent with the finding that participants with poor antisaccade performance benefit most from practice effects (Ettinger et al 2003b).

If nicotine were acting to increase levels of arousal, one potential consequence would be faster processing of the target – in which case (according to the model of antisaccade performance outlined in the introduction) an increase in error rates would be predicted. Alternatively, if a general increase in arousal led to faster processing of the visual stimulus and faster programming of the correct response, then no change in error rates would be expected. Our results support the suggestion that nicotine has a facilitatory effect on endogenous, but not exogenous, processes during antisaccade performance. In other words, nicotine may be increasing activity in the neural systems responsible for initiating the correct antisaccade response (Nieuwenhuis et al, 2004; Munoz & Everling, 2004) over and above any influence they have on activity in the neural systems responsible for target detection.

Several converging lines of evidence confirm that working memory processes are important moderators of antisaccade performance. Secondary tasks that place demands on working memory capacity increase antisaccade errors while tasks with the same motor or stimulus processing requirements (but no working memory requirements) do not (Stuyven et al, 2000; Mitchell et al, 2002; Roberts et al, 1994). Individuals with low working memory spans have slower latencies for correct antisaccades and more antisaccade errors than individuals with high working memory spans (Unsworth et al, 2004). Several studies have demonstrated increased antisaccade errors in populations with known working memory limitations. For example antisaccade errors and correct antisaccade latencies are increased in patients with schizophrenia (Hutton et al, 1998; 2002), and the degree of impairment correlates significantly with working memory dysfunction in these patients (Hutton et al, 2004). Similarly, increased antisaccade errors reported in healthy elderly participants (e.g. Eenshuistra et al, 2004, Nieuwenhuis et al, 2004) have been attributed to lower activation of task goals within working memory.

In the context of these findings, our results are consistent with current models of antisaccade performance, and suggest that nicotine increases the extent to which healthy participants are able to maintain the intention to initiate an antisaccade within working memory. This results in a reduction in the time taken to program a correct antisaccade, and consequently a reduction in the number of trials in which an erroneous prosaccade is programmed first. It is worth noting

that another study exploring pharmacological manipulation of antisaccade performance found results that are difficult to interpret within the general model of antisaccade performance outlined in the introduction. Khan et al (2003) administered ethanol to healthy participants and found that it increased correct antisaccade latency, but reduced the number of errors. Activation models would predict that if the correct response is slowed, the erroneous response has a greater likelihood of reaching threshold first, and therefore errors should increase. The authors argued that the reduction in errors occurred because ethanol slowed down the processing of the target. Activation models would still be able to account for this pattern of results if the effect of ethanol was to slow the processing of the peripheral stimuli to a greater extent that it slowed the generation of the correct response. Further research using variants of pro and antisaccade tasks and different pharmacological agents will provide important insights into the interactions between stimulus and goal based behaviour.

In addition to a reduction in antisaccade errors and correct antisaccade latencies we also found a novel “carryover” effect of nicotine on antisaccade error rate – the improvement in baseline performance the first to the second session was superior in those participants who had received nicotine in the first session compared to those who had abstained. In other words those participants who benefited maximally from nicotine by receiving it in the first session maintained the improvements gained in that session for a period of a week. A similar effect in monkeys was reported by Buccafusco et al (1995) following administration of

nicotine or ABT-418, a centrally acting nicotinic cholinergic agonist. Both compounds improved performance on the delayed-matching to sample task 10 minutes post-administration but only those given nicotine showed better performance 24 hours later as well. Indeed, it has recently been suggested that such long term effects of nicotine may reflect its action on cellular mechanisms underlying learning and memory such as LTP (Buccafusco et al, 2005). These findings suggest that acute effects of nicotine on cognitive function may have consequences that last significantly longer than the pharmacokinetic properties of the compound.

The pharmacological effects of nicotine are extremely complex. As well as modulating the release of as a variety of different neurotransmitters such as acetylcholine (Moore-Arnold et al 2003), glutamate (Vidal & Changeux, 1993), dopamine (Corrigall et al 1994), serotonin (Reuben & Clarke 2000) and noradrenalin (Clarke & Reuben 1996), there are a number of different receptor subtypes with different affinities for nicotine binding (Paterson and Nordberg 2000). Since these have different thresholds for nicotine effects, behavioural consequences of selective modulation of these subtypes are likely to be dose-dependent (Kumari & Postma, 2005). Both of the major subtypes of nicotinic receptors, alpha-4 and alpha-7, reliably influence memory and attention (Nordberg, 2001; Levin et el, 2006), but receptor subtype selectivity for specific cognitive processes has been difficult to establish. Both selective alpha-4 (Levin & Christopher, 2002) and selective alpha-7 (Bettany and Levin 2001) compounds

have been shown to modulate working memory performance in rat models, for example. Previously, alpha-7 receptors particularly have been linked to lower level processes - auditory gating, prepulse inhibition, priming (Freedman et al, 1994; Leonard et al, 1998)). Whether goal activation in working memory is mediated by effects on early perceptual processes or more direct prefrontal activation is a focus for further research.

In summary, this study found that nicotine reduces the number of antisaccade errors and increases the speed with which correct responses can be made. One interpretation of these findings is that nicotine increases the strength of activation in the memory representations supporting the goal to make antisaccades. As all participants were minimally abstinent and allowed to maintain a relatively naturalistic smoking pattern prior to the experiment the effects of nicotine are unlikely to be due to a reversal of a withdrawal-induced deficit in performance. In addition, we have shown that the performance benefits derived from a single acute dose of nicotine persist over a period of at least a week, possibly reflecting the potential for nicotine to influence long term learning processes.

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Tables

	Smoked in session 1		Smoked in session 2	
	Session 1	Session 2	Session 1	Session 2
% errors	22.00 (3.05)	13.46 (2.85)	18.23 (3.05)	15.49 (2.85)

Table 1. Mean (s.e.) percentage errors for both smoking order groups' baseline tests.

Figure Legends

Fig. 1. Percentage errors (1a) and latencies for correct antisaccades (1b) at the baseline tests for both gap lengths.

Fig 2. Change in percentage errors (a) and antisaccade latency (b) after smoking and abstinence for both smoking order groups.