Psychopharmacology (1997) 132:324–334

ORIGINAL INVESTIGATION

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Effects of altering brain cholinergic activity on covert orienting of attention: comparison of monkey and human performance

Received: 8 July 1996 / Final version: 24 February 1997

Abstract Experiments were conducted to elucidate the role of the cholinergic neurotransmitter system in arousal and the orienting of attention to peripheral targets. Rhesus monkeys and humans fixated a visual stimulus and responded to the onset of visual targets presented randomly in two visual field locations. The target was preceded by a valid cue (cue and target at the same location), an invalid cue (cue and target to opposite locations), a double cue (cues to both spatial locations, target to one), or, the cue was omitted (no-cue, target to either location). Reaction times (RTs) to the onset of the target were recorded. For monkeys, systemic injections of nicotine (0.003–0.012 mg/kg) or atropine (0.001–0.01 mg/kg), but not saline control injections, reduced mean RTs for all trials, indicating general behavioral stimulation. In addition, nicotine significantly reduced RTs for invalid trials but had little additional effect on those for valid, double, or no-cue trials. Virtually identical effects were observed for human chronic tobacco smokers in performing the same task following cigarette smoking. Injections of atropine in monkeys had no effect on RTs for valid or invalid trials but significantly slowed RTs in double-cue trials that did not require the orienting of attention. These results suggest that in both species, the nicotinic cholinergic system may play a role in automatic sensory orienting. In addition, the muscarinic system may play a role in alerting to visual stimuli in monkeys.

Key words Attention · Covert orienting · Alerting · Nicotine · Atropine · Reaction times · Monkey

Introduction

The neurochemical mechanisms underlying attention and arousal in animals have been investigated in numerous recent studies. There is now strong evidence for the involvement of the noradrenergic, dopaminergic, and cholinergic neurotransmitter systems in the attentional systems of rats, monkeys, and humans (Aston-Jones and Bloom 1981; Clark et al. 1989; Robbins et al. 1989; Aston-Jones et al. 1991; Witte et al. 1992; Marrocco and Witte 1993; Witte and Marrocco 1993, 1997; Ward and Brown 1996). Several integrative summaries of these findings have suggested that the fundamental components of attention and attention-guided action may be controlled by distinct neurotransmitter systems (Posner and Petersen 1990; Colby 1991; Marrocco et al. 1994; Robbins and Everitt 1995; Marrocco and Davidson 1997). In the previous paper, the involvement of norepinephrine in non-spatial aspects of attention was demonstrated (Witte and Marrocco 1997). The current work focuses on the role of acetylcholine on the spatial component of covert orienting.

In primates, damage to the brainstem cholinergic projections impairs attentional orienting to visual targets. Voytko et al. (1994) made bilateral lesions of the basal forebrain nuclei in rhesus monkeys trained to perform tests of short-term memory (e.g., delayed match to sample) and covert orienting to cued targets. Compared to controls, lesioned animals showed no deficits in mnemonic tasks but had generally slower manual reaction times (RTs) to all stimuli and substantially slower RTs to invalidly cued targets, in which the cue and target appeared in different visual hemifields (see below). A similar deficit has been observed in tests of covert orienting in patients with dementia of the Alzheimer's type (Parasuraman et al. 1992). These data strongly suggest that normal cholinergic activity is necessary for visuospatial orienting.

In rats and humans with intact cholinergic systems, cholinergic drugs are known to affect attentional functions, including serial reaction time task, vigilance, and divided attention (Jones et al. 1992; Parrott and Craig 1992; Muir et al. 1994; see Levin 1992 for a review). Little is known, however, regarding the effects of cholinergic drugs on spatial attention in Old-World monkeys,

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whose attentional capacities are thought to be quite similar to those of humans (Bowman et al. 1993; Witte et al. 1996). In the present experiments, the effects of systemic cholinergic agents on the covert orienting of attention was studied in monkeys and humans. In monkeys, the levels of actylcholine were either increased with systemic injections of nicotine or reduced through administration of atropine; in humans, the cholinergic system was activated through the inhalation of tobacco smoke. Since impaired cholinergic function decreases the speed of covert orienting (Voytko et al. 1994), we postulated that increased levels of brain cholinergic activity ought to have the reverse effect on orienting. Preliminary accounts of these results have been published previously (Marrocco and Witte 1993; Witte and Marrocco 1993).

Materials and methods

Monkeys

The subjects were the same two female rhesus macaques (*Macaca mulatta*) used in the previous paper (Witte and Marrocco 1997). They were between 12 and 14 years of age and weighed between 12 and 15 lb during the study. All procedures used with these animals were done in accordance with the Guide for the Use and Care of Laboratory Animals (National Academy of Sciences 1996) and were supervised by the university veterinarian. These animals were trained using a water control reinforcement schedule. During a 2-week period prior to data collection, ad libitum water consumption was measured to determine the animals' daily baseline consumption. During data collection, water was removed from the animals' cage the evening before the experiment and the fluid intake was recorded following the next day's experiment. If the animals failed to drink their baseline amount, the difference between intake and baseline was given in the home exercise cage about 2 h after the session. Thus, in any 24-h period, the animals consumed their normal amount of fluid. Body weight, skin turgor, activity levels, and food consumption were also checked on a daily basis during the studies to be sure that weight loss or symptoms or other illnesses did not occur. As we frequently supplemented lab chow with peanuts, raisins, and fresh fruit, weight gains were most frequently observed.

Drug administration

Nicotine, a nicotinic cholinergic agonist, and atropine, a muscarinic antagonist, were the principal agents used in this study. Preliminary data using mecamylamine, a nicotinic antagonist, either by itself or co-administered with nicotine, have also been collected and will be reported separately. Muscarinic antagonists were not used because of their potentially disruptive side-effects, that include tremor, ataxia, and spasticity.

Monkey A received (−)-nicotine ditartrate (0.003 or 0.006 mg/kg), atropine sulfate (0.001 or 0.01 mg/kg), or saline in different sessions. Monkey B received nicotine (0.005–0.012 mg/kg), atropine sulfate (0.001 mg/kg) or saline. The range of nicotine doses was slightly different from the two animals because we attempted to bracket the effective doses for each animal through pretesting. In these tests, monkey A but not monkey B showed an increasing behavioral arousal that reduced performance with doses above 0.006 mg/kg dose, and the lowest dose for monkey A was completely without effect for monkey B. All drugs were obtained from Sigma Chemicals (St. Louis, Mo., USA), dissolved in sterile saline and injected IM 15 min prior to testing. Injections of sterile saline alone served as a vehicle control and the data obtained served as reference points against which drug data were compared. The order of drugs across sessions was randomized.

Atropine was given before six data collection sessions with monkey A, with three sessions for the high dose and three for the low dose. Monkey B received atropine before three sessions. Each dose of nicotine was given before three sessions in both monkeys. Atropine and clonidine were given to monkey A in two sessions. At least 2 days elapsed between injections of atropine and atropine+clonidine. Seven days intervened between nicotine injections, as preliminary testing suggested that tachyphylaxis to nicotine occurred at 2-day intervals. Saline was injected before seven data collection sessions for each monkey. A total of 19 data collection sessions were run with monkey A (11560 trials) and with monkey B (11825 trials).

Surgery

Using pentobarbitone anesthesia and sterile procedures, a head fixation socket was attached surgically to each animal several weeks before the start of training. Stainless steel screws coated with dihydroxylapatite were used to anchor the socket to the skull and dental acrylic was applied to cover the screws and exposed skull. In addition, a scleral eye coil (Judge et al. 1980) was placed in one eye. Post-operative care consisted of prophylactic administration of systemic antibiotics, ophthalmic antibiotic ointment, and pain relieving medication (buprenorphin).

Apparatus

The monkey was placed into a primate chair (Crist Instruments, Damascus, Md., USA) at the start of each session. Its head was immobilized by attaching it to the chair, using a bolt designed to fit into the head socket. Two vertical and two horizontal magnetic field coils were placed around the animal's head and the upper portion of the primate chair. The monkey was then placed into a large Formica chamber with a glass front window. The animal viewed stimuli on a computer monitor placed one meter from its eyes. A Sony video camera allowed the experimenters to monitor the animal's behavior continuously.

A Northgate 386 computer was used to run CORTEX, a program for conducting neurophysiological and behavioral experiments that was provided to us by Robert Desimone on the National Institutes of Health. Graphics were produced with a Pepper SGT-plus graphics card (Number Nine Computer Corp, Lexington, Mass., USA), and a D/A board (Computer Boards, Cambridge, Mass., USA) was used for measuring eye position, registering bar contact closures and controlling reward solenoids.

Behavioral training

The details of the training protocol are presented elsewhere (Witte et al. 1996). Briefly, after the animal was accustomed to the primate chair, fixation training was begun. The animal learned to maintain fixation within an area of 0.1 deg around a small spot on the monitor for about 1–2 s. Successful fixation was rewarded with water or juice. The animal next learned to press a bar that triggered a microswitch and produced the fixation spot. Successful fixations of criterion duration was rewarded, but failure to make or maintain fixation, or temporally inappropriate presses or releases caused the trial to be aborted. Once this training was complete, the animal began training on a modified version of the CTD developed by Posner (1980).

Cued target detection training

Each animal was trained on the peripheral version of the cued covert target detection task. In this task, two rectangular outlines and the central fixation spot appeared at the start of the trial (see Fig. 1A, B). The luminance of each stimulus was 50 cd/m^2 and the background luminance was 0.1 cd/m^2. After 500–1500 ms (deter-

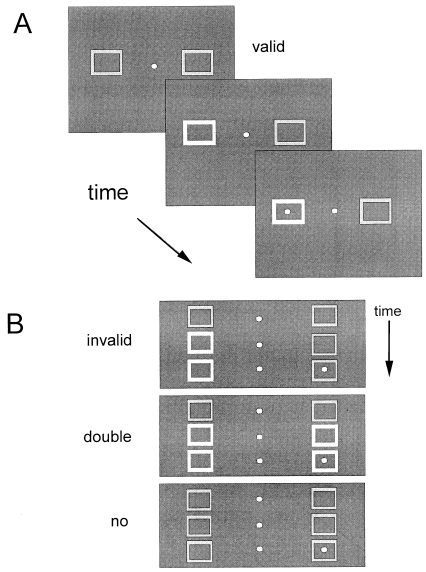

Fig. 1 **A** And **B** Illustrate stimuli used in peripheral CTD task. **A** Schematic of stimulus sequence for valid cue trials. See text for details. **B** Sequence of stimuli used for invalid, double, and no-cue trials

mined randomly), one of the outlined rectangles brightened to 75 cd/m^{2}, which served as a cue to attract attention. The fixation spot was 0.2 arc-deg in diameter, the rectangles subtended 1.0×1.5 arc-deg. At 100, 400, or 700 ms after the cue's onset, a target (0.5 arc-deg diameter, 5.71 arc-deg visual angle from fixation) was presented inside one of the rectangles (see Fig. 1B). The interval between cue and target was the cue-target intervals (CTI). The cue and target remained on until the bar was released. The animal was rewarded for responding to the target within 850 ms of target appearance. RTs under 100 ms were considered anticipatory and the trial was aborted. Loss of fixation, defined as an eye movement greater than 0.1 deg, or incorrect bar performance also caused the computer to abort the trial.

There were four cue conditions in this task. In the *valid* cue condition, the target appeared in the same hemifield as the cue (57% of trials). In the *invalid* cue condition, the target appeared in the opposite hemifield as the cue (14.3% of trials). The difference in RTs between the validly cued and invalidly cued trials (validity effect) was used as a measure of the effects of directed attention on target detection. The ratio of valid to invalid trials was 4:1.

The cues in both the valid and invalid trials were spatially informative and provided a general warning that the target would appear within 700 ms. In order to assess the individual contributions of each type of information, two additional kinds of trials were presented. In the *double* cue condition (14.3% of trials), cues were presented simultaneously on both sides of the fixation point. No spatial information was provided by this cue, but the abrupt onset of the cues provided the subject with the same warning that occurred in valid and invalid trials. In the *no-cue* condition (14.3% of trials), the cue was omitted altogether so that explicit spatial or general warning information about the target's subsequent appearance was absent. It should be noted that some implicit temporal information may have been present in the no-cue trials, as the certainty of target appearance increased with time (aging foreperiod). The difference in RTs between double and no-cue trials (alerting effect) indexed the effects of the warning cue on target detection.

Data analysis

RTs for correct trials were separated from early release, loss of fixation, and incorrect trials. A repeated-measures ANOVA was used to examine the data using trial RT as the dependent variable and drug, cue, cue-target interval, and visual field as independent variables. Post hoc comparisons were done with the Tukey HSD test. In addition, the error rates for each drug were examined. Finally, the overt sedation or stimulation caused by the drug was subjectively rated by an experimenter, who was uninformed as to the drug status of the animal, but familiar with the animal's usual behavior.

Humans

Subjects were nine tobacco smokers and eight non-smokers recruited by advertisements and paid for their participation in the study. The protocols used in this study were approved by the University Institutional Review Board and informed consent was obtained for all subjects. Participation in the study could be terminated at any time. The mean age of the non-smokers was 28.4 years (range 21–46). The mean age of the smokers was 31.1 years (range 18–45). To be considered a smoker, the subject had to smoke a minimum of two cigarettes per day, and have been smoking for at least 3 months. These subjects smoked a mean of 15.4 cigarettes per day (range of 2–23), with only three smokers smoking fewer than 15 cigarettes per day. The nicotine content of each subject's cigarettes was not tested. To be considered a non-smoker, a subject must not have smoked tobacco for at least 3 months prior to the experiment. The history of tobacco use varied between subjects, with the lighest users having smoked for the shortest time, and the heaviest users having smoked for the longest time. None of the subjects was taking medications that might have affected performance in the task. Caffeine consumption was not controlled.

Drug administration

The smokers increased brain micotine levels by smoking one cigarette of their usual brand immediately prior to testing. All subjects were tested between 9 a.m. and 4 p.m. During the period required for completion of the task, nicotine levels from smoking are relatively stable at about 11–16 ng/ml in chronic smokers (Henningfield and Keenan 1993).

Apparatus

The apparatus used was identical to that described for the monkey experiments, with the exception that the human subjects sat in a comfortable, padded chair within the Formica chamber, and head restraint was not used. Subjects were viewed with a video camera to insure that neither eye nor head movements were made on data collection trials. If movements were observed, the experimenter instructed the subject to refrain from moving his/her eyes or head, and restarted the session.

Cued target detection task

Each subject completed 20–30 practice trials and 250 data collection trials on the peripheral-cue task described for the monkeys in a session that lasted 20–25 min. The total number of trials (excluding pratice trials) for 17 subjects was 4250. The human subjects also completed a centrally cued version of the self-paced CTD task, in which symbolic (arrow) cues were presented at the fixation point. However, to make the comparison of the human results with the monkey results as parallel as possible, the data from the central task will not be reported here.

Data analysis

An examination of the homogeneity of variances of RTs between the smoker and nonsmoker groups showed non-significant differences. Therefore, the data were analyzed with a fully factorial AN-

OVA. The performance of chronic smokers was compared to the performance of non-smoker controls.

Results

Nicotine in monkeys

Accuracy

The proportion of trials completed correctly was examined for each drug and dose combination. The percentage of correct trials remained stable for each monkey over the course of data collection (monkey A, 75–80%, monkey B, 70–80%). Comparable proportions of completed trials were found for all drug trials. Thus, no major changes in accuracy were produced by nicotine or atropine.

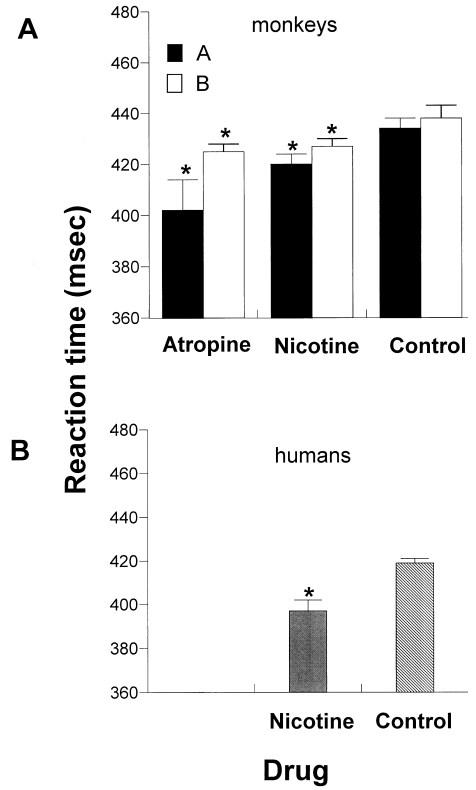

Fig. 2A, **B** Overall main effect of drug on reaction time, averaged across all trials. **A** Monkey A (*black bars*); monkey B (*unfilled bar*). *Asterisks* indicate significance level: * 0.0001). **B** Human smokers (*nic*, *grey bar*), non-smokers (*Con*, *hatched bar*); * 0.001

Main effects: drug, cue, cue-target interval, and visual field

Nicotine significantly decreased overall RTs [monkey A, $F(2, 11560)=24.11$, $P<0.0001$; monkey B, $F(2, 11825)=30.99$, $P<0.0001$] producing the largest reductions in monkey A (30 ms) and a smaller decrease (11 ms) in monkey B (see Fig. 2). RTs for different cue types were significantly different from each other [monkey A, $F(11560)=12.27$, $P<0.0001$; monkey B, $F(2, 11825)=56.44$, $P<0.0001$]. Consistent with previous work (Witte et al. 1996), valid cue RTs were faster than invalid cue RTs, and double cue RTs were faster than no-cue RTs (see Table 1).

As the cue-target interval increased, RTs for both monkeys decreased significantly over a range of 60–80 ms [monkey A, $F(2, 11560)=46.67$, $P<0.001$; monkey B, $F(2, 11825)=23.36$, $P<0.0005$)]. This indicates that the monkey benefited from the reduction of temporal uncertainty provided by the longer intervals. In contrast, the main effect for visual field was not significant [monkey A, $F(11560)=1.01$, $P=0.13$; monkey B, $F(2, 11825)=0.67$, $P=0.45$]; RTs for targets in the left and right visual fields were statistically indistinguishable.

Drug by cue interaction

In order to assess whether nicotine had specific effects on the alerting or the orienting component of attention, we computed the means for each cue, derived the validity and alerting effects from the differences between session means for valid and invalid trials, and for double and no-cue trials, respectively, and compared the results for each dose against the saline trials. The RTs for each dose are shown in Fig. 3A and B. For both monkeys, low doses of nicotine did not alter either the validity effect or the alerting effect (monkey A, Tukey HSD, $P=0.25$;

Table 1 Mean (SEM) RTs for cue type following nicotine or saline

	Monkeys							Humans	
	A			B					
	Saline	0.003	0.006	Saline	0.005	0.010	0.012	NS	S
Valid	433 (2.7)	419 (3.4)	415 (5.1)	393 (3.0)	420 (3.6)	415 (3.9)	410 (3.7)	408 (3.4)	386 (2.8)
Invalid	456 (3.8)	439 (5.7)	418 (6.3)	463 (6.7)	500 (7.5)	450 (8.2)	427 (6.4)	436 (6.2)	398 (5.7)
Double	439 (4.4)	418 (7.6)	408 (7.1)	438 (6.5)	440 (7.0)	424 (7.5)	415 (6.9)	412 (6.2)	396 (5.6)
No	449 (4.7)	425 (7.8)	413 (8.1)	471 (6.0)	493 (7.1)	460 (8.4)	483 (7.7)	434 (6.8)	409 (5.1)

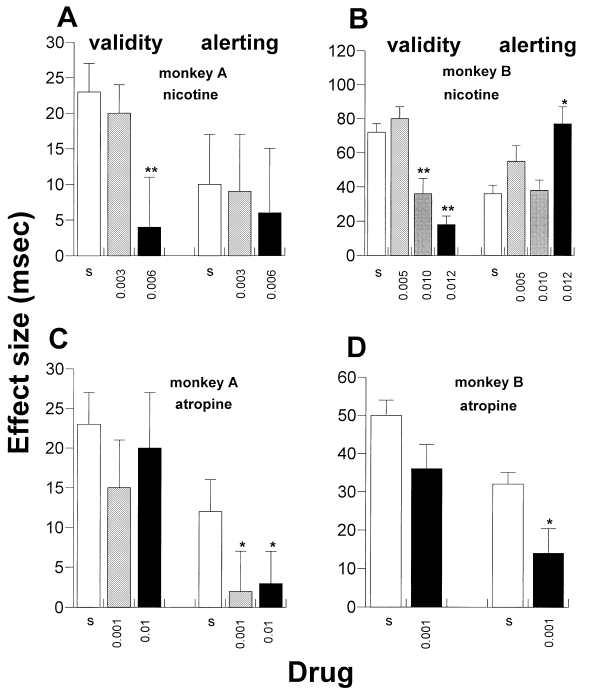

Fig. 3 **A** And **B** Effects of nicotine on RTs for different cue types for monkeys A and B. *s* Saline trials; drug doses (in mg/kg) appear on x-axis. * P<0.04; ** P<0.004. **C** And **D** Effects of atropine on validity and alerting scores for monkeys A and B; * P<0.035

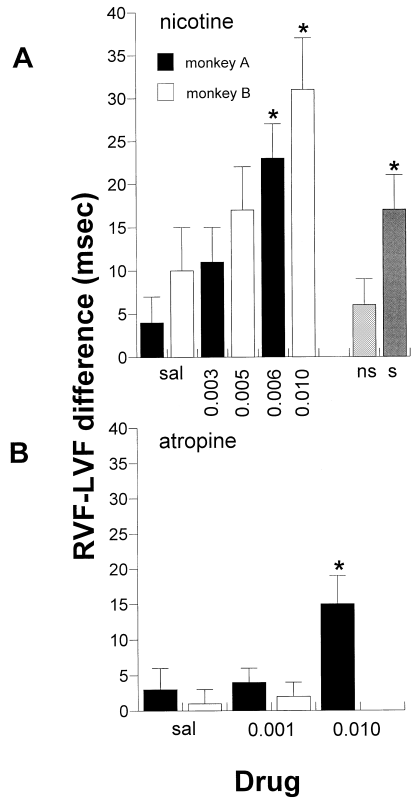

Fig. 4A, **B** Effects of cholinergic drugs on the difference between RTs to stimuli in right (*RVF*) and left (*LVF*) visual fields for each monkey. **A** *Sal* saline, * P<0.001. *s* Smokers, *ns* non-smokers, * P<0.0001. **B** Effects of atropine on visual field differences; *s* saline, low=0.001 mg/kg, high=0.01 mg/kg; * P<0.02

monkey B, P_s=0.33) and little overt behavioral stimulation was evident. However, intermediate and high doses produced a dose-dependent reduction in the validity effect in both animals (A, P=0.002; B, P=0.004), due to significantly faster RTs for invalid trials (see Table 1). No significant change was seen in valid trial RTs. These doses had no effect on the alerting effect for monkey A (P=0.15). However, in monkey B, the highest dose produced a significant increase in alerting (P=0.05), accompanied by overt behavioral stimulation. Thus, the main effect on manual RT for doses between 0.003 and 0.010 mg/kg was an increase in the speed of attentional orienting and the absence of effects on alerting.

Drug by cue-targed interval interaction

As stated previously, the decrease in RT with increasing cue-target interval (CTI) is usually interpreted as due to a reduction in the temporal uncertainty about target appearance. To examine whether the cholinergic drugs altered temporal uncertainty, we computed the change in RT whith increasing CTI across cue type and visual field. Nicotine did not alter the relationship between CTI and RT in either monkey (Tukey, P=0.40), suggesting that the drug did not change the animal's temporal expectancies of target presentation.

We also examined the interaction between drug and cue type at different CTIs to see whether or not the validity or alerting effects changed with time. Neither interaction was significant [monkey A, F(2, 11560)=1.15, NS; monkey B, F(2, 11825)=1.2, NS]. Therefore, the changes in validity were similar at each CTI tested.

Drug by visual field interaction

While hemispheric asymmetry of neural systems is not a feature usually associated with nonhuman primates, recent evidence suggests that the anatomical organization underlying some visuomotor tasks may be lateralized (Nudo et al. 1992). To determine whether nicotine preferentially altered activity in the right or left hemisphere for a cognitive task, we compared RTs for stimuli presented to the left and right visual fields (LVF, RVF: see Fig. 4A). Although the main effect of visual field was not significant [monkey A, F(2, 11560)=1.15, NS; monkey B, F(2, 11825)=1.2, NS], the interaction of drug with visual field was significant [monkey A, F(3, 11560)=2.12, P<0.015; monkey B, F(2, 11825)=3.2, P=0.01]. One average, there was a right-left visual field difference of 4.1 ms for monkey A and 10.0 ms of monkey B in saline trials. For nicotine trials, the right-left difference increased in a monotonic manner with dose. The mean differences for the low and high doses for monkey A were 11.1 and 23.0 ms (Tukey, P=0.09), and for monkey B were 17.3 and 31.2 ms, respectively, with the high dose for both monkeys significantly greater than saline (Tukey, P<0.001). Taken with the results for cue

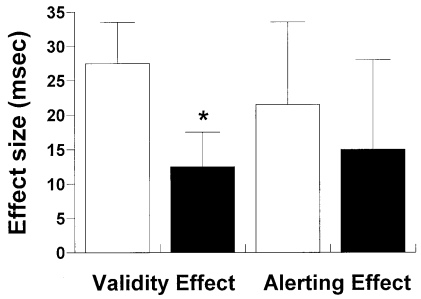

Fig. 5 Validity and alerting effects for smokers (*filled bars*) and non-smokers (*unfilled bars*). * $P<0.05$

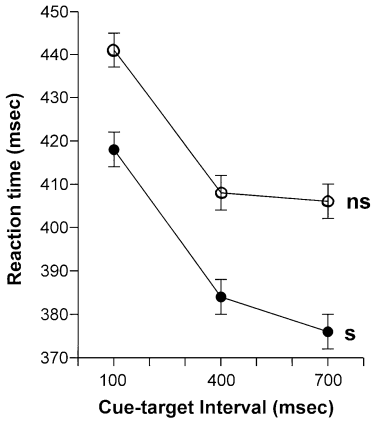

Fig. 6 Effects of increasing CTI on RTs for human subjects. *ns* non-smokers; *s* smokers. The group by CTI interaction was not significant

type, the data suggest that nicotine mainly affects invalid trials by reducing RTs to targets processed in the right hemisphere.

Nicotine in humans

The accuracy of non-smokers was 92%, not significantly different from that for smokers (94%).

Main effects: drug, cue, cue-target interval, and visual field

Tobacco smoking produced a significant overall reduction in RTs (Fig. 2B), comparable in magnitude to that produced by nicotine in monkeys. Subjects that smoked the fewest cigarettes tended to have less RT reduction than that found in heavy smokers. Significant differences were seen for visual field [$F(1, 4250)=30.55$, $P<0.001$]. However, subject age was not correlated (Pearson $r=0.06$, $P=0.43$) with the magnitude of the main effects or interactions.

Drug by due interaction

To examine the effects of tobacco smoking on validity and alerting, we compared the performances of smokers and nonsmokers. Smokers had a significantly smaller validity effect than did non-smokers (12.5 versus 28.1 ms, Tukey, $P=0.01$, see Fig. 5A). This difference was due to significantly smaller invalid cue RTs among smokers than in non-smokers (Tukey, $P=0.003$). No difference was seen between subject groups in the size of the alerting effect, however (Tukey, $P=0.7$).

Drug by cue-target interval interaction

To discover whether inhalation of tobacco smoke affected the reduction in temporal uncertainty with increasing CTI, we averaged across visual field and cue type. Both smokers and non-smokers show a significant decline in RT with increasing CTI [$F(2, 4250)=46.66$, $P<0.0001$]; see Fig. 6. Comparable to the effects seen for cue, the RTs reached a lower value in smokers than in non-smokers. However, the interaction between CTI and smoking was not significant [$F(2, 4250)=0.15$, $P=0.86$], suggesting that nicotine did not alter the temporal expectation of target appearance.

Drug by visual field interaction

To determine whether nicotine had differential effects on the cerebral hemispheres, we compared RTs for stimuli presented to the left and right visual fields (LVF, RVF: see Fig. 4A). On average, the non-smokers showed a non-significant right-left RT difference of 6.2 ms (Tukey=0.95). In contrast, smokers showed a significant right-left asymmetry of 16 ms (Tukey=0.039). The RT differences between visual fields of smokers and non-smokers was significant [$F(1, 4250)=60.425$, $P<0.0001$].

The mean visual field difference for non-smokers is comparable in magnitude to those for the monkey saline trials (6.2 versus 4.1 ms), and the mean difference for smokers is similar to that for nicotine trials in monkeys (16.0 versus 23.0 ms). In both species the differences were produced by a decrease in LVF RTs. As the invalid trial RTs are affected most, nicotine appears to speed processing of targets in the right hemisphere.

Effects of abstinence on covert orienting

Since members of the smokers group were not tested prior to cigarette use, there might have been a factor unrelated to the immediate effects of tobacco consumption, e.g., chronic hypoperfusion of cerebral tissue, or personality variables that caused the subjects to be more susceptible to nicotine use and/or dependence, that caused the observed results. To explore this, we have collected data from two of the chronic smokers who voluntarily abstained from cigarettes for 4 days. These subjects were students or postdoctoral fellows at the university and were well known to the experimenters. Therefore, we relied on verbal reports as an index of compliance with ab-

stention. Mild withdrawal symptoms, including tobacco craving and mild anxiety, were present, but according to subject self reports, these did not disrupt performance of the task. This was consistent with subject accuracy, which declined (non-significantly, $P>0.10$) from 94% after smoking to 92% during abstinence. Performance on the peripheral task was assessed immediately after smoking a cigarette, and at 45 and 92 h after cessation of smoking. The data are shown in Fig. 7. Overall RTs immediately after tobacco intake were substantially lower than RTs for non-smokers and the difference appeared to diminish with time. More importantly, the validity effect increased over time, from –3.4±0.8 ms immediately after smoking to +30.1±3.5 ms after 92 h, a change significant at the 0.005 level. These effects are not seen over time in non-smoking subjects. The alerting effect did not change during the abstinence period tested.

We also asked whether abstinence reversed the visual field differences observed in Fig. 4A. Our analysis showed that differences between fields were significant immediately following smoking and at 45 h after abstinence ($P<0.04$), but not significant after 92 h ($P>0.10$). Thus, it appears that the changes in invalid cue RTs follow the same time course as the visual field effects, and both are at least partly linked to a factor related to nicotine use.

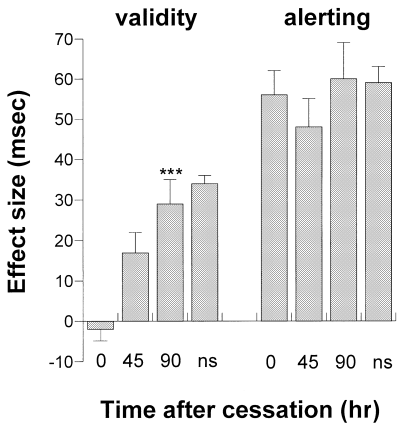

Fig. 7 The effects of tobacco abstinence on the validity and alerting effects for two chronic smokers performing the peripheral CTD task. Subjects were tested immediately before cessation (0), 45 h after cessation (45), and 92 h (92) after cessation. *ns* effect size for non-smokers. Size of validity effect at 90 h is significantly larger than that after smoking (*** $P=0.005$) and the same size as that for non-smokers

Atropine in monkeys

Main effects

Atropine produced a significant overall reduction in RTs in both monkeys [monkey A, $F(1, 4213)=20.4$, $P<0.0001$; monkey B, $F(1, 3827)=27.05$, $P<0.0001$] (Fig. 2A), but no other significant main effects. The overall reduction was about twice as large, on average, as that produced by nicotine.

Drug by cue interaction

Both doses of atropine in monkey A and the low dose in monkey B significantly decreased the alerting effect (monkey A: low, Tukey HSD, $P=0.01$; high, $P=0.04$; monkey B: $P<0.003$), see Fig. 3C. Taking the overall speeding of RTs into account, the decrease in alerting was produced by a relative slowing of double cue RTs. The validity effects were not affected significantly in either animal (monkey A, low, Tukey, $P=0.35$; high, $P=0.44$; monkey B, $P=0.57$).

Drug by cue-target interval interaction

Both the low dose [$F(2, 2446)=7.48$, $P<0.001$] and high dose of atropine [$F(2, 2446)=3.67$, $P=0.035$] in monkey A produced significantly faster overall RTs than that for saline controls, especially for the 100 ms CTI (Table 2). The same pattern was observed for monkey B's results [$F(2, 3827=4.14$, $P<0.02)$]. This suggests that atropine may affect temporal expectancies of target appearance.

Drug by visual field interaction

We asked whether there was any evidence that atropine's effects were hemispherically asymmetric. No difference between visual fields was found for saline or atropine at the low dose tested (Fig. 4B) in either monkey ($P<0.5$). In monkey A, however, RTs for left visual field stimuli were decreased ($P=0.02$) for the high dose. These results, combined with those for cue effects, suggest that low doses of atropine affects RT equally for targets in either hemisphere.

Table 2 Mean (SEM) RTs for each cue-target interval for saline and atropine

	Monkeys				
	A				B
	Saline	Atropine-low	Atropine-high	Saline	Atropine-low
100 ms	467 (3.1)	402 (5.2)	424 (10.4)	431 (1.9)	426 (4.2)
400 ms	429 (3.0)	395 (5.6)	418 (9.6)	429 (1.9)	400 (4.6)
700 ms	409 (3.2)	385 (5.0)	393 (8.9)	414 (1.9)	388 (4.7)

Discussion

The main hypothesis of this study was that increases in cholinergic activity ought to increase the speed of covert orienting. The hypothesis was confirmed for nicotine but not for atropine. In monkeys, nicotine generally reduced overall RTs, specifically reduced the validity effect and decreased RTs for stimuli in the left visual field, but did not alter the relationship between CTI and RT. In humans, tobacco smoke also generally lowered overall RTs, specifically reduced the validity effect for peripheral cue tasks, but had no significant effect on the CTI versus RT curve. For both monkeys and humans, nicotine appeared to affect primarily the invalid cue RTs, suggesting that it is the disengagement of attention that is speeded. In addition, nicotine had little effect on accuracy for either species. Atropine generally reduced overall RTs and specifically reduced the alerting effect by slowing reactions to double cues. We will discuss each of these findings, compare them to the extant literature, and point out the limitations of the study.

Nicotinic cholinergic role

Parenterally administered nicotine in both monkeys and inhalation of tobacco smoke in human chronic smokers decreased RTs for invalid cues in the peripheral CTD task. Similarly, nicotine failed to alter the alerting effect in humans, for either dose in monkey A, and for for low and intermediate doses in monkey B. However, the highest dose showed an increased alerting effect in monkey B. We think the most likely reason for this is that the dissociation between drug and task is dose-dependent. At the lowest levels of nicotine, no effects are seen on either validity or alerting. At intermediate doses, nicotine affects the orienting system, which might be true if the nicotinic cholinergic system acted directly on orienting centers. At the highest dose tested, the cholinergic system may stimulate noradrenergic neurons, which have cholinergic receptors (Adams and Foote 1978) and are known to regulate the alerting effect (Witte and Marrocco 1997). Some support for this hypothesis would be obtained if the co-administration of high doses of nicotine with an α_2 agonist blocked increases in alerting and perhaps general arousal as well.

A recent theoretical framework (Posner and Petersen 1990) suggests that covert shifts of attention are affected in three steps, the *disengagement* of attention from its current focus, the *movement* of attention to a new location, and the *engagement* of attention on the new location. According to this hypothesis, attention disengaged from the fixation point, moved in the direction of the cue, and engaged at the cued location during valid trials. In invalid trials, attention also disenaged from the fixation point, moved toward the cued location, and engaged at the cued location. This account also assumes that the appearance of the target in the contralateral location caused attention to shift through the same steps to engage the target. Note that the first shift of attention is likely to be identical for invalid and invalid trials. If the hypothesis is correct, the most likely interpretation of our data is that increased cholinergic activity facilitated disengagement of attention from the invalidly cued location, since RTs for valid cues in most subjects were not increased. This interpretation is consistent with the results of monkey basal forebrain lesion studies (Voytko et al. 1994) and studies of patients with Alzheimer's dementia (Parasuraman et al. 1992), in which cholinergic dysfunction led to an impairment of attentional disengagement. Because the target in the left visual field during invalid cue trials benefitted most from cholinergic facilitation, we further postulate that it is the disengage operation in the right visual field that is primarily facilitated. A similar conclusion has been reached by Murphy and Klein (in preparation), who noted a reduction in invalid cue RTs and an increase in accuracy in the CTD task following tobacco smoking. Comparable to the present work, these investigators failed to note any effect of nicotine on non-spatial target expectancies, a task designed to assess alerting-like effects.

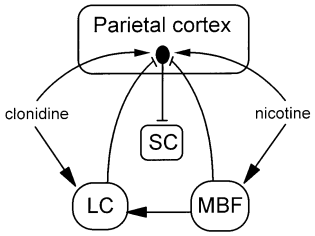

Fig. 8 Postulated interactions between locus coeruleus (*LC*), magnocellular basal forebrain (*MBF*), and parietal cortex. Nicotine may act postsynaptically on MBF dendrites or presynaptically on parietal cortex neurons to facilitate attentional disengagement. Clonidine may act postsynaptically on LC dendrites or presynaptically on LC terminals in parietal cortex to suppress alerting effect. The output of parietal cortex signals superior colliculus to move attention. Excessive nicotinic stimulation may alter alerting indirectly through cholinergic projections to LC or directly on nicotinic receptors on LC dendrites

The mechanism underlying the facilitaion is a matter of speculation. Attentional disengagement may occur through activity in the posterior attentional system, which includes the parietal cortex (Posner et al. 1984, 1987; Corbetta et al. 1993). Since the improved RT occurs only when the cue and target are in opposite visual fields, the facilitation must be spatially specific. One possibility is that stimulation of a subset of basal forebrain cholinergic neurons enhances glutamatergic neurotransmission in left parietal cortex. Whether these influences are sufficiently spatially selective to exclude facilitation in valid trials is not known. Another possibility is that basal forebrain projections to the parietal cortex act presynaptically on glutamate terminals of the left hemisphere to facilitate attentional disengagement. Figure 8 illustrates this model graphically, and incorporates the results of the previous paper (Witte and Marrocco 1997) as well. Projections from the magnocellular basal forebrain nuclei (MBF) and LC to parietal cortex are postu-

lated to mediate the orienting effect and the alerting effect, respectively. Nicotine may act to facilitate the MBF directly and/or presynaptically in the parietal cortex to facilitate the disengagement of attention. Clonidine and other noradrenergic drugs act in a suppressive fashion on the LC and/or parietal cortex to reduce the utilization of non-spatial information.

Some evidence for presynaptic effects has been reported in rat cerebral cortex (Wonnacott et al. 1990; Vidal and Changeux 1993; Wonnacott 1995). The model is also consistent with single cell work (Steinmetz et al. 1994; Robinson et al. 1995) which demonstrates that cells in the parietal cortex of monkeys signal attentional error, which in our hypothesis would mean that the invalid cue drew the animal's attention away from the stimulus in the contralateral hemisphere. Of course, the action of nicotine may not be restricted to cholinergic modulation of glutamatergic neurotransmission alone. Nicotine may also act as an agonist at heteroceptors on catecholaminergic neurons, as suggested by the increased behavioral stimulation at the highest nicotine doses.

Our results with nicotine are consistent with the broad range of reports indicating that nicotine facilitates cognitive function (Jarvik 1991; Levin 1992; Levin et al. 1992; Warburton 1992; Le Houezec et al. 1994). Indeed, one appealing interpretation of the present findings is that facilitated disengagement of attention may be beneficial to performance by reducing the cost of attentional reorienting. However, an equally plausible, but unappealing, interpretation of the data is that nicotine allows attention to be more easily drawn away from objects that need scrutiny, for example, in the presence of competing stimuli. It may be useful to modify the CTD task to include distractors in future experiments with nicotine.

Muscarinic cholinergic role

While atropine did not change the validity effect, it did decrease RTs overall (Fig. 2), particularly at the early cue target latencies, and reduced the alerting effect. At low doses, the drug produced the same facilitatory action for double cue targets presented to either visual field (see Fig. 4). These results suggest that the muscarinic receptor may be involved directly in general increases in arousal and specific reduction in alerting, but not the orienting component of visuospatial attention.

The specific muscarinic effects reported here are similar to those obtained from the administration of clonidine, an α_2 adrenergic agonist (Witte et al. 1992; Witte and Marrocco 1997). Both atropine and clinidine produce a slowing of double cue RTs and a selective slowing of RTs to stimuli presented in the left visual field. It is possible that these similarities occur because both muscarinic cholinergic and noradrenergic neurons synapse on a common site involved in cue-induced alerting (e.g., Adams and Foote 1988). However, the drugs have opposite effects on overal RTs. Further work using local injections of muscarinic drugs into cortical tissue may clarify this issue.

Our failure to disclose a role for muscarinic receptors in attention shifting is consistent with previous work in spatial attention in humans. Cockle and Smith (1996) and Smith (personal communication) reported that scopolamine failed to alter the validity effect in a cued threshold target detection task in human observers. Since no double or no-cue conditions were used in that study, however, it is impossible to say whether the drug affected alerting per se. In addition, our demonstration that RTs to double cues are slowed is consistent with reports of slowed processing of attended visual targets and impairments in sustained attention (Brandeis et al. 1992; Callahan et al. 1993; Jones and Higgins 1995). In this regard, however, the reduced overall RT found in the present work is opposite to the increased RTs reported for a sustained attention task following intraventricular injections of scopolamine (Callahan et al. 1993).

Lateralization of pharmacological effects

That nicotinic cholinergic drugs facilitated processing in the left hemisphere more than the right was evident in both humans and monkeys, and is compatible with the hemispheric asymmetries of the cholinergic pathway found in humans. For example, postmortem analysis of choline acetyltransferase activity in humans suggests that ACh activity is higher in the left hemisphere than in the right (Amaducci et al. 1981). No such evidence for a hemispheric asymmetry of the cholinergic system has been reported for monkeys. However, there is not necessarily a causal relationship between levels of ChAT and neuronal activity, since it is generally the number of functional receptor sites that determines the impact of neurotransmitter release. In chonic smokers, upregulation of nicotinic receptors (nAChRs) is likely and arguments for greater stimulation could be made for either hemisphere. It should be borne in mind, however, that the extent to which the same effects are seen in the anatomically asymmetric human and the anatomically symmetric monkey brain argues that the basis of the effect may depend on additional factors beyond synthetic enzymes and functional receptors. Perhaps the behavioral strategies used by the subjects caused use-dependent differences in hemispheric activity that were differentially affected by drugs.

The dynamics of attentional orienting

Of the two main classes of receptors for the cholinergic system, nicotinic and muscarinic, the nicotinic system appears well suited to fulfill several criteria required of an attention shifting system: 1) the anatomical distribution of nAChRs is appropriate for those areas known to be involved in attention, i.e., frontal and parietal cortices (Clarke et al. 1985; Wagster et al. 1990), which have

been shown also to be active during attention shifting (Corbetta et al. 1993); 2) ACh binding at nAChRs is ionotropic, thereby producing a physiological response whose time course is appropriate for the very rapid nature of covert attentional shifts (Saarinen and Julesz 1991); 3) the site of action of the cholinergic system may be spatially restricted, both by the relatively narrow target fields of individual cells (Baskerville et al. 1993; Losier and Semba 1993) and by the local effects of presynaptic and preterminal nicotinic action (Wonnacott et al. 1990; Wonnacott 1995), consistent with the spatial selectivity of attentional facilitation. In contrast, our results suggest that the muscarinic system is confined to a role in alerting, perhaps through interactions with noradrenergic neurons (Berridge et al. 1993). The time course of alerting is slower, involving changes that increase over 400 ms (Witte et al. 1996) which appears to be consistent with the slower postsynaptic response mediated by muscarinic second messenger systems.

Limitations of the study

We have shown that the effects of nicotine injections and chronic tobacco smoking are similar. Indeed, the comparability of the overall decline in RTs, the similarity of the visual field changes, and the lack of an effect on alerting scores argues that nicotine plays a major role in our results. These findings are consistent with previous work that suggests that nicotine is the major psychoactive substance in tobacco smoke (e.g., Surgeon General's Report 1988) and a large body of evidence establishing nicotine's effects on cognitive tasks (Wesnes and Warburton 1983; Wesnes et al. 1983; Snyder et al. 1989). However, the argument that the human results are due solely to levels of brain nicotine must be accepted with caution until it can be shown that substances like cotinine, acetaldehyde and carbon monoxide do not produce similar effects. Unlike nicotine, however, these components are present in tobacco in much smaller quantities than nicotine, and neither acetaldehyde or carbon monoxide act on specific transmitter systems. Their influence, if present, is likely to be more global than specific and might affect overall RTs rather than validity or alerting scores. Finally, our data on the growth of the validity effect following smoking abstinence argue that brain nicotine is not the sole factor that determines attentional dynamics. Behavioral recovery of the validity effect occurred in about 92 h, while the half-life of plasma nicotine is about 12 h (Surgeon General's Report 1988). This suggests that an additional factor contributing to the behavioral recovery is the down-regulation of nicotinic receptors.

If we accept the argument that nicotine is the main contributor to the observed effects, it is very difficult to say how much nicotine was needed to produce the observed result. The main drawback of our human study is that brain nicotine levels are unknown, although current estimates of plasma levels for chronic smokers range from 10 to 50 ng/ml (Benowitz et al. 1991). One of us has recently shown, however, that salivary nicotine level, which covaries with plasma and brain nicotine (Witte et al. 1995) is a good predictor of the magnitude of the behavioral validity effect and its change during abstinence.

Acknowledgements This work was supported by a grant from the James S. McDonnell Foundation and Pew Charitable Trusts, NIH grant NS 32973 (R.T.M.), and NICHD training grant 5T32 H07032 to the UCLA Mental Retardation Research Institute (E.A.W.). We thank Drs. Ray Klein, Barry Okken, and Thomas Marrocco for helpful comments and Mike Villareal for technical assistance.

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