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Research report

Nicotinic modulation of auditory attentional shift in the rat

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ABSTRACT

Numerous studies have demonstrated cognitive improvements resulting from the application of nicotine, especially in those tasks aimed at measuring attention. While the neuro-pharmacological relationship between nicotine and acetylcholine-driven attentional processes has been examined, studies tend to focus on the duration of time in which a subject can attend to a specific stimulus or series of stimuli rather than on the subjects' adaptive attentional capabilities. The present study addresses the possibility that the cholinergic agonist nicotine could improve performance on a task testing the ability to shift attention between sensory modalities under both normal and pharmacologically impaired conditions.

In a pilot set of experiments, we tested the effects of nicotine in a cross-modal experimental task designed to tax both the auditory and visual systems of male Sprague–Dawley rats. Nicotine (0.2 mg/kg) significantly improved performance on both auditory and visual trials, under repetitive trial conditions, and significantly decreased overall response latency. For the primary study, we tested the effects of decreasing cholinergic neurotransmission by systemic administration of the muscarinic antagonist atropine. Atropine (12.5 mg/kg) significantly impaired performance in auditory shift trials and perseverative trials, while significantly increasing the overall response latency. We then tested the effect of nicotine within the impaired model. Systemic administration of nicotine significantly improved performance in auditory and visual shift trials, while showing moderate improvements in response latency and perseverative trial conditions. These results indicate the potential therapeutic use of nicotine as a cognitive enhancer, as well as provide evidence for *cholinergic system compensations*.

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1. Introduction

Ample evidence regarding nicotine's overall effect as a cognitive enhancer is well documented [12,14,22,23]. Previous findings indicate that in the presence of nicotine, subjects consistently show improvement in tasks designed to test the sustainability of attention over time, through stimulus variation regarding localization, duration, or modulation. And, not surprisingly, nicotine's effect on various types of attentional performance has been shown in cases of chronic nicotine use in humans [2,3,7,10,28]. While all attentional paradigms involve some level of stimulus detection, the primary dimension of measure involves task vigilance, the assumption that nicotine's global effect on cognitive function can be relegated to an enhancement in alertness over a specified length of time that under normal conditions would tax the attentional exertion of a subject. This generalization, though somewhat limited within the broader scope of attention, does provide a foundation through which other paradigms may be developed to test multiple aspects of attention simultaneously. Beyond the notion of sustainability, there are studies which focus on nicotine's role in selective attention, often through utilization of a sustained attention task modified to include the occurrence of distracters during target stimulus presentation [4,11].

Expanding on single mode stimulus detection and recognition is the concept of divided attention. Sarter and colleagues have published numerous studies delineating the role of acetylcholine in divided attention, using a dual modal apparatus which randomly alternates the presentation and relevance between visual and auditory cues [27]. It is this particular aspect of attention which could prove most useful in our understanding of the neurological mechanisms underlying certain pathological conditions such as Alzheimer's disease, schizophrenia, and autism, whose symptoms are associated with lack of cognitive adaptability [15,31]. Despite the abundance of data supporting nicotine's effect on sustained attention, there is limited evidence concerning nicotine's effect on other cognitive features like attentional shift or adaptability. Thus we examined whether nicotine could improve performance on a task specifically designed to measure the rats' ability to shift attentional focus under both normal and pharmacologically impaired conditions. We further sought to identify any disruption or improvement in simple stimulus detection through the use of repetitive trial conditions aimed at measuring both accuracy and

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response latency, yet requiring little demand on the adaptive processes involved in attentional shifting.

Our preliminary data showed that the muscarinic antagonist atropine administered intraperitoneally could be used to impair cognitive performance without causing significant changes in motor function or coordination. Data from these experiments provided the basis for a timing and dosage protocol that effectively suited our needs for inducing an impairment referencing the cholinergic hypothesis [5,25]. These findings correspond directly with previous studies utilizing atropine and other anti-cholinergics in performance alteration studies in rats [32], while requiring dosage levels dramatically less than previous studies involving spatial navigation [6,8,16,29], which required as much as ten times the concentration of systemic atropine injection. The use of the muscarinic antagonist scopolamine was rejected as scout experiments in our laboratory as well as previous studies have shown that rats show an increase in aggressive behavior and are more difficult to handle following scopolamine injections [18,24].

The present study was designed to identify nicotine's performance effects in an experiment combining elements from previously established attentional paradigms: discrimination in the presence of distracters (selective attention), stimulus variations measured over time (sustained attention), and cross-modal relevance shifting (divided attention), while also providing intermediate conditions which allow the gauging of nicotine's effect on simple stimulus detection in both drug naïve rats and in those pharmacologically impaired with atropine (focused attention). Our hypothesis was that nicotine's effect on cognitive performance was not necessarily confined to a specific substrate of attention, and that the global effect of nicotine could counteract impairments in the muscarinic system when both systems are activated simultaneously.

2. Methods

2.1. Subjects

Male Sprague–Dawley rats ($n = 10$) weighing 300–350 g at the onset of experimental training were housed in groups of two in a temperature controlled animal facility on a 12-h reversed light/dark cycle. Throughout the training and testing periods, a strict feeding schedule of eighteen grams/rat per day was maintained to provide adequate nutrition while still maintaining a proper level of task motivation. Rats were given *ad libitum* access to water throughout the duration of the study. All experimental protocols and animal facilities were in accordance with the guidelines set forth by the Commission on Life Sciences, Institute for Laboratory Animal Research (ILAR) and by the Office of Laboratory Animal Welfare (OLAW). All efforts were made to reduce the number of animals used and to minimize animal suffering. Where applicable, target dosage information was obtained via Medline search.

2.2. Drugs

Atropine sulfate (Neogen, Lexington, KY, USA) and nicotine base (Acros Organics, Geel, Belgium) were dissolved in 0.9% saline and injected intraperitoneally using 1 ml 26G 3/8 syringe. The two drugs were administered twenty and ten minutes respectively prior to the start of each experimental session. Optimal dose and time course of action for atropine sulfate were determined in a preliminary series of experiments in order to minimize non-central effects, while nicotine optimal dosage/timing was based on previous findings [24], reflecting its effectiveness and time course on the performance of other attentional tasks. During the initial dosage testing for both atropine and nicotine, all sessions were recorded via webcam in both lighted and dark conditions and later reviewed to ensure no peripheral symptoms resulting from administration.

2.3. Data analysis

Accuracy was determined from the number of correct responses calculated as a percentage of the total number of responses registered. Anticipatory responses were not viable, as the apparatus's retractable levers insured that no response could occur during the inter-trial interval. Omission errors were registered if no response was made within the maximum allotted response time (MaxRT = 3 s). Correct response latency was defined as the interval between lever presentation and correct lever selection. Data were analyzed using two-group, paired *t*-testing, with a maximum value of $p = 0.05$ allowed for significant effects. Two-way ANOVA measures were precluded as potential carryover effects limit the sensitivity to mean changes in repeated measure sampling.

2.4. Apparatus

After initially learning the lever press on a set of conventional stationary levers, the subjects were moved to an advanced cage, equipped with retractable levers, multi-stimuli capability, and concealed in a sound attenuating chamber (ENV-022 V, 55.9 cm × 38.1 cm × 35.6 cm). Light emitting diodes (l.e.d.) located above the lever presentation slots provided the visual stimulus, while speakers inside the chamber provided auditory cues.

All the devices (levers, pellet dispenser, l.e.d.s and loudspeakers) were controlled by a PC connected via DAC/ADC converter (Measurement Computing, Norton, MA) through MatLab software which also randomly generated the target modality of the sequential presentations. The system also automatically recorded success probabilities, submission errors, omissions, and response latencies into a text file which was analyzed off-line after the experiment. Correct presentation of the left lever was cued with a 2 kHz tone, while the right lever was cued with a 10 kHz tone (Fig. 1).

2.5. Training

Properly gauging the subjects' ability to shift attention within the experimental setting required clear stimuli presentation coupled with the flexibility to adjust reward parameters over the course of each session. Animal behavioral shaping consisted of a three phase preparatory procedure. During the initial phase, in order to receive reward (a 45 mg food nutrient pellet), the subjects were required to respond only to the retractable lever designated with a lighted diode above the lever presentation slot. Once the subjects could discriminate the localized light source at an accuracy level greater than 80% over 100 trials, the subjects began the second experimental phase. During this phase, both lighted diodes were activated during each trial, with a pre-conditioned tonal stimulus unique to each lever now designating the correct lever press. Once the subjects could identify the correct lever press under this condition at an accuracy level greater than 80% over 100 trials, the two conditions were merged into the final testing protocol, with each condition alternating randomly throughout. In effect, the subjects were required to ignore previously established emphasis on either sensory modality (visual or auditory) now acting as a distracter for the other sensory modality (auditory or visual respectively), and instead *shift* their attention to the other sensory cue in order to receive reward (Fig. 1).

2.6. Parameters

We eliminated the need for a punishment schedule by instead manipulating the parameters associated with the reward response. By increasing the duration of time between lever presentations from 5 to 20 s, we essentially increased *trial significance*. Since a reward could only be achieved an average of three times per minute, each possibility of reward (lever presentation) became increasingly significant to the animal. This, in turn, caused an apparent decrease in the natural impulsivity of the rats, resulting in higher success rates and virtually eliminating all non-submission type errors. Moreover, this method allowed for a more consistent pattern for training across subjects (because of the individual differences among subjects, the amount of punishment and length of training sessions would otherwise vary). This extended duration between stimuli presentations allowed for *ad libitum* access to water throughout the experiment, as the subjects were able to effectively execute water consumptions and return to task posture within the allotted time. This feature removes potential confounds associated with dehydration, while demonstrating an additional attentional parameter (the ability to execute water consumptions without registering trial omissions).

2.7. Evaluation

While the apparatus itself offers two separate reward-seeking conditions alternating throughout (visual vs. auditory shift), we evaluated attentional performance by measuring: (i) probability of success on those trials which constitute a visual shift (only visual discrimination trials *directly* preceded by auditory cue trials); (ii) probability of success on trials constituting an auditory shift (only auditory cue trials *directly* preceded by visual discrimination trials); (iii) response latency measured in milliseconds; (iv) number of omission errors tallied during each session.

Although the primary aim of the study was to measure attentional processes, our experimental design offered additional information concerning stimulus detection. Perseverative conditions and repetitive trial blocks were analyzed for each pharmacological comparison in order to illustrate the role cholinergics play in inter-trial behavior. For this study, a repetitive trial block consisted of four or more consecutive trials utilizing the same criterion for reward. In contrast, a perseverative condition was defined as any trial which immediately followed a repetitive trial block, thus constituting a change in reward criterion. In order to eliminate any possible experimental bias, the success probabilities for each condition were extrapolated after the conclusion of each experimental session. In order to observe the effects of nicotine without any limitations involving multiple drug interactions, a pilot study was performed using nicotine alone. The primary study was performed using a sepa-

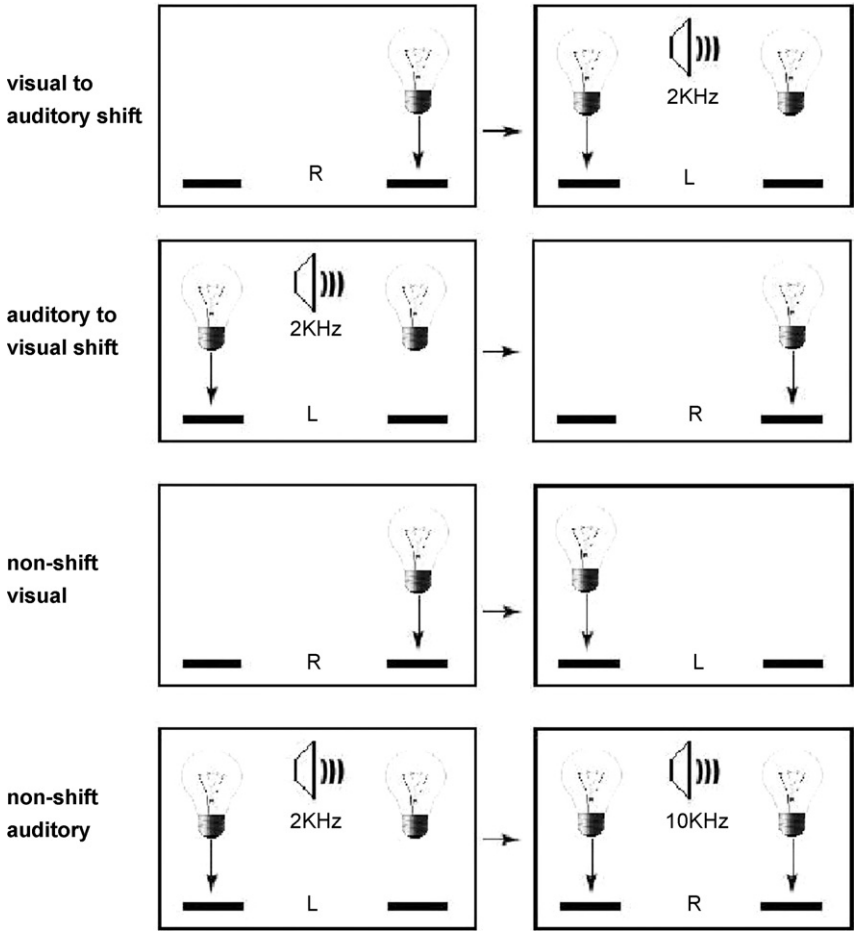

Fig. 1. Illustration of the response rules comprising the attentional shift task. All shift and non-shift-type events are presented in a randomized sequence such that each constitutes one-fourth (25) of the total number of trials (100) per experimental session. Vertical arrows designate the correct lever press necessary to gain reward for the specified condition. Horizontal arrows designate the proceeding event type which determines what type of shift is recorded for measure: auditory, visual, or non-shift.

rate group of animals to avoid complications arising from alterations in receptor expression.

3. Results

3.1. Pilot study

3.1.1. Enhancing effects of nicotine

Previous studies testing the effect of nicotine (0.0, 0.05, 0.015, 0.2, and 0.4 mg/kg) have shown dose-related improvement in response accuracy reaching a maximum at 0.2 mg/kg and a decline at 0.4 mg/kg [24]. Here, optimal administration of nicotine (0.2 mg/kg) increased the subjects' success probability on the auditory shift trials ($64.5 \pm 1.81\%$ vs. $70.3 \pm 2.01\%$; $p = 0.0012$, $n = 4$; Fig. 2). To ensure that increases in success probability during the drug trials were the result of nicotine administration and not attributed to the animals' natural learning curve, *t*-tests were performed on the arrays for each experimental condition separately. Comparisons between saline sessions revealed no significant differences ($p = 0.1184$). Further comparisons between nicotine sessions failed to reach significance as well ($p = 0.8013$). Nicotine also had a significant effect on visual shift trials ($79.3 \pm 3.4\%$ and $90.0 \pm 4.9\%$; $p = 0.016$; Fig. 2). Administration of nicotine decreased correct response latency on auditory shift trials by an average of 12.5% (494.6 ± 52.8 ms vs. 432.9 ± 57.8 ms; $p = 0.0129$; Fig. 2) and on visual shift trials by an average of 23% (510.5 ± 75.6 ms vs. 395 ± 35.1 ms; $p = 0.0448$; Fig. 2). There was, however, no significant effect on the average number of omissions between conditional arrays ($p = 0.1216$), a result consistent with previous studies on divided attention [1]. Nicotine also significantly decreased correct response latency during perseverative trial conditions (491.1 ± 34.4 ms vs. 400.4 ± 41.3 ms; $p = 0.0036$; Fig. 3) with a trend in improving performance ($71 \pm 11.12\%$, and $85.05 \pm 2.2\%$; $p = 0.16$, $n = 4$; Fig. 3). Within repetitive trial blocks the reverse occurred, as nicotine showed a trend in decreasing correct response latency (505.7 ± 94.7 ms vs. 408.9 ± 46.5 ms; $p = 0.0862$, $n = 4$; Fig. 3), while significantly improving performance ($64.5 \pm 4.2\%$ and $76.9 \pm 3.3\%$; $p = 0.0048$, $n = 4$; Fig. 3).

3.2. Primary study

3.2.1. Impairing effects of atropine sulfate

Previous studies testing the effect of atropine sulfate (doses ranging 5–50 mg/kg) on spatial navigation showed no significant impairment in motor activity [6,16]. And in studies involving anti-cholinergics in performance alteration studies, atropine sulfate proved most effective at approximately 12 mg/kg [32]. Here, administration of atropine sulfate (12.5 mg/kg) caused a significant decrease in performance on the auditory shift trials ($84 \pm 3\%$ in control vs. $64.4 \pm 1.6\%$; $p < 0.0001$, $n = 6$), as the subjects' success probability decreased by an average of 20% (Fig. 4). However, in both drug and control conditions, subjects were able to perform the auditory-to-visual shift portions of the task consistently *above 90%* (Fig. 4). Administration of atropine also produced a significant increase in correct response latency on auditory shift trials (519.1 ± 74.9 ms vs. 918.9 ± 224.3 ms; $p = 0.0253$, $n = 6$; Fig. 4)

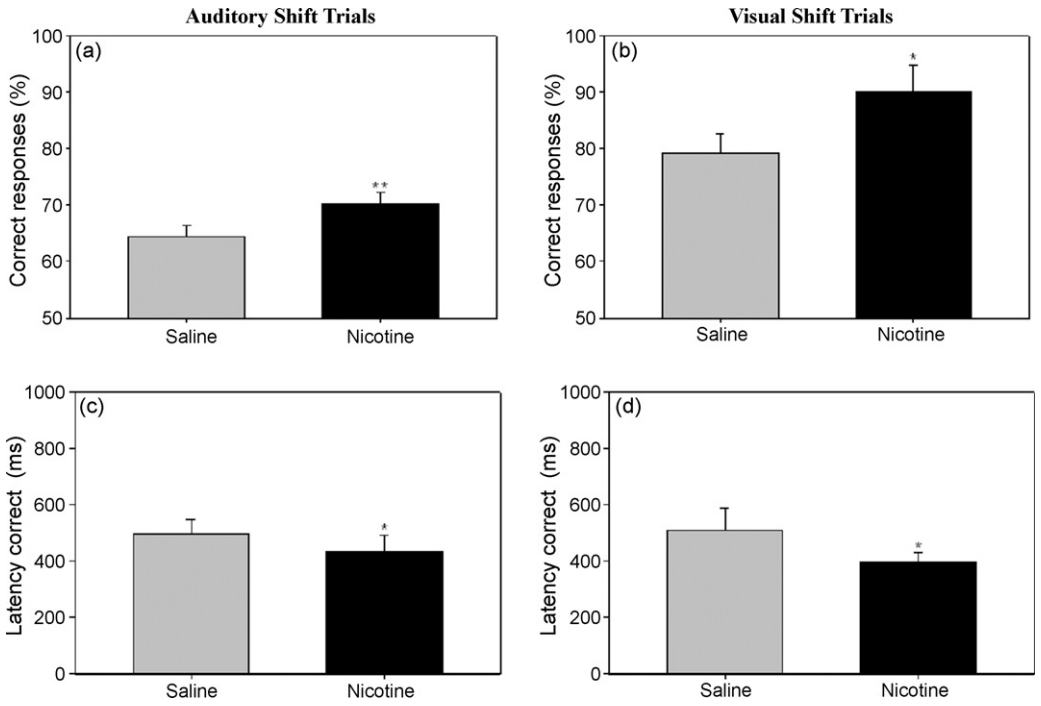

Fig. 2. Pilot. The effects of systemic injection of nicotine 0.2 mg/kg (black bars) compared to vehicle (gray bars) on accuracy (a and b) and correct response latency (c and d) in auditory and visual shift trials. Bars represent mean performance (SEM) of four rats in 30-min sessions with ITI 20 s. Please note axis breaks in (a and b). Conditions where nicotine produced a significant difference compared to vehicle are marked (*adjusted $p < 0.05$, **adjusted $p < 0.01$; paired *t*-tests).

and on visual shift trials (595.3 ± 134.1 ms vs. 982.9 ± 208.8 ms; $p = 0.0153$, $n = 6$; Fig. 4). There was, however, no effect on the average number of omissions between conditional arrays (8.34 ± 7.54 vs. 11.2 ± 5.7; $p = 0.2238$, $n = 6$), understandable given the amount of diligence required to perform the task. Accuracy measured during perseverative trial conditions was also significantly impaired in the presence of atropine ($86.2 \pm 3.3\%$ vs. $74.6 \pm 2.6\%$; $p = 0.004$, $n = 6$; Fig. 5). With respect to the simple stimulus detection portion of the task, there was no effect on accuracy (Fig. 5), though atropine did significantly increase correct response latency in repetitive trial blocks (587.2 ± 146.9 ms vs. 1129.7 ± 371.6 ms; $p = 0.0485$, $n = 6$; Fig. 5).

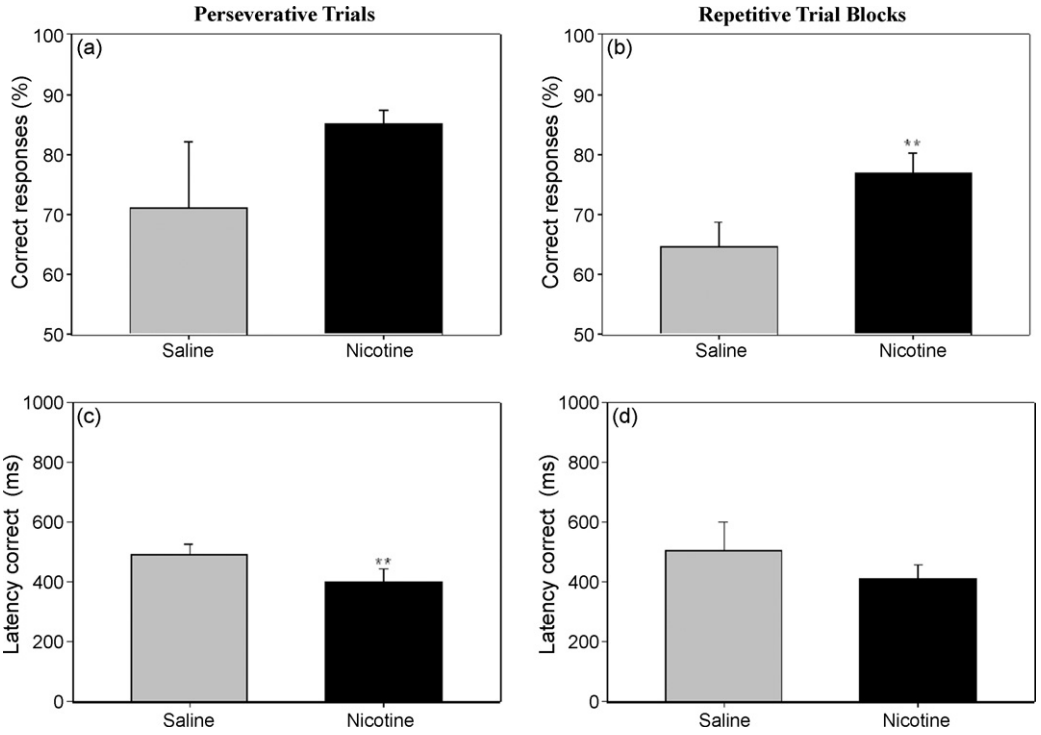

Fig. 3. Pilot. The effects of systemic injection of nicotine 0.2 mg/kg (black bars) compared to vehicle (gray bars) on accuracy (a and b) and correct response latency (c and d) in perseverative and repetitive trial conditions. Bars represent mean performance (SEM) of four rats in 30-min sessions with ITI 20 s. Please note axis breaks in (a and b). Conditions where nicotine produced a significant difference compared to vehicle are marked (*adjusted $p < 0.05$, **adjusted $p < 0.01$; paired *t*-tests).

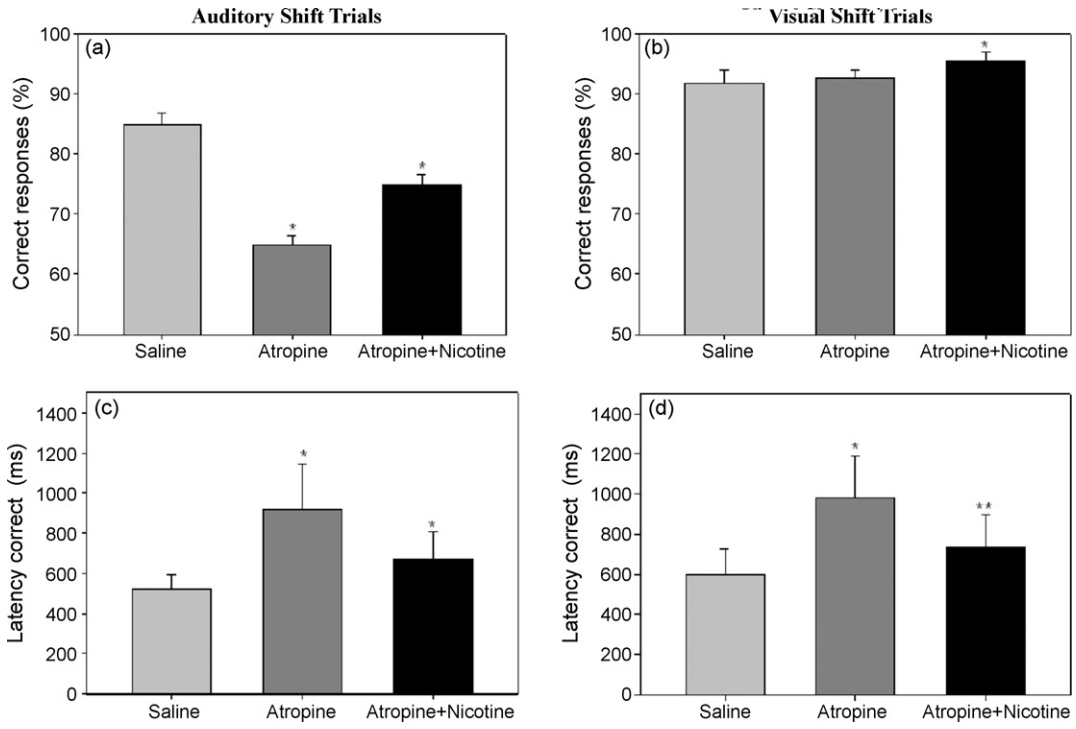

Fig. 4. The effects of systemic injection of atropine sulfate 12.5 mg/kg (dark gray), simultaneous injection of atropine sulfate and nicotine 0.2 mg/kg (black bars), and vehicle (light gray bars) on accuracy (a and b) and correct response latency (c and d) in auditory and visual shift trials. Bars represent mean performance (SEM) of six rats in 30-min sessions with ITI 20 s. Please note axis breaks in (a and b). Conditions where atropine produced a significant difference compared to vehicle or where atropine + nicotine produced a significant difference compared to atropine alone are marked (*adjusted $p < 0.05$, **adjusted $p < 0.01$; paired t-tests).

3.2.2. Compensating effects of nicotine in the presence of atropine sulfate

Administration of nicotine on atropine-impaired rats increased the success probability on auditory shift trials by an average of 10% ($64.8 \pm 1.6\%$ in control vs. $74.8 \pm 1.8\%$; $p < 0.0001$, $n = 6$; Fig. 4). Though not as prominent as the effect shown in the pilot experiment, nicotine did have a significant effect on visual shift performance accuracy ($91.8 \pm 2.2\%$ and $95.4 \pm 1.6\%$; $p = 0.042$, $n = 6$;

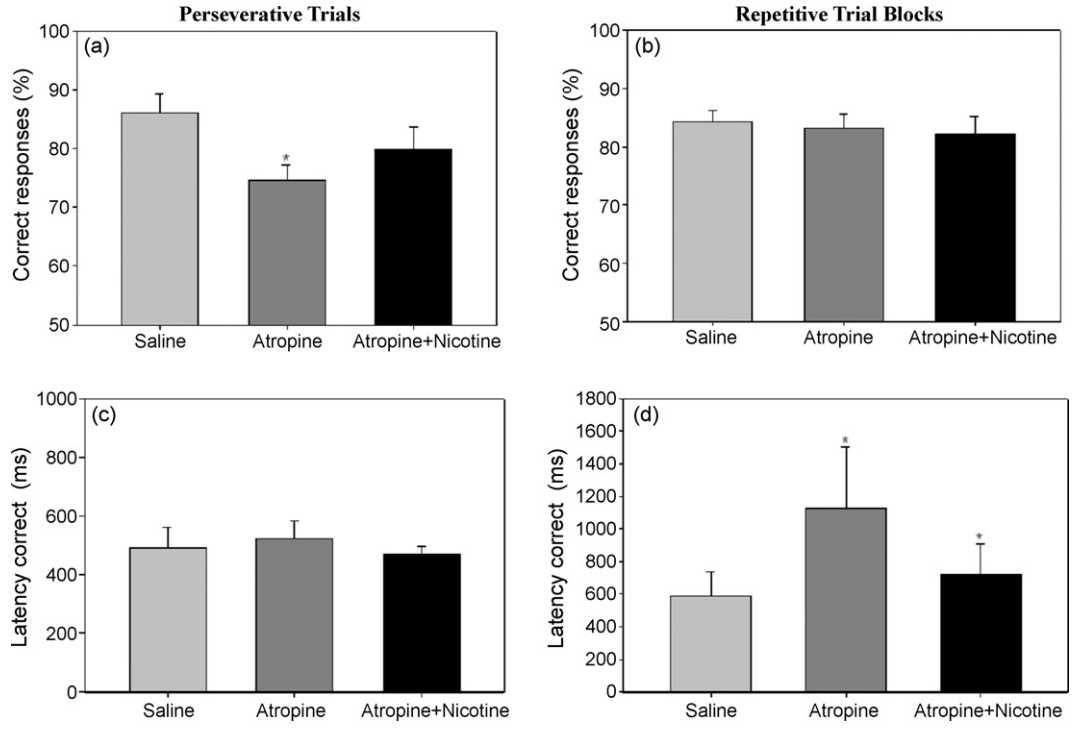

Fig. 5. The effects of systemic injection of atropine sulfate 12.5 mg/kg (dark gray), simultaneous injection of atropine sulfate and nicotine 0.2 mg/kg (black bars), and vehicle (light gray bars) on accuracy (a and b) and correct response latency (c and d) in perseverative and repetitive trial conditions. Bars represent mean performance (SEM) of six rats in 30-min sessions with ITI 20 s. Please note axis breaks in (a and b). Conditions where atropine produced a significant difference compared to vehicle or where atropine + nicotine produced a significant difference compared to atropine alone are marked (*adjusted $p < 0.05$, **adjusted $p < 0.01$; paired t-tests).

Fig. 4). Administration of nicotine also significantly decreased correct response latency on auditory shift trials (918.9 ± 224.3 ms vs. 668.3 ± 140.3 ms; $p = 0.0474$, $n = 6$; Fig. 4) and on visual shift trials (982.9 ± 208.8 ms vs. 733.2 ± 162.2 ms; $p = 0.0018$, $n = 6$; Fig. 4) on the atropine-impaired rats. Comparable to the results obtained with nicotine alone, there was no significant effect on the average number of omissions between conditional arrays ($p = 0.071$). And although nicotine did significantly decrease correct response latency in repetitive trial blocks (1129.7 ± 371.6 ms vs. 718.1 ± 186.7 ms; $p = 0.0424$, $n = 6$; Fig. 5), no significant differences in accuracy were found in either perseverative trial or repetitive trial block conditions (Fig. 5).

4. Discussion

Attentional shifting, by revealing a subject's ability to monitor and react to changes in the environment, represents a crucial criterion when evaluating cognitive impairments in both normal aging and pathological conditions [1,17,19]. The present investigation sought to test the hypothesis that nicotine's effect on cognitive performance was not necessarily confined to a specific substrate of attention, and to identify possible task-dependent cholinergic compensations via simultaneous manipulation of nicotinic and muscarinic systems.

Pilot results demonstrated nicotine's ability to improve attention in virtually all measurable facets. Auditory shift events, with inherent properties of both sustained and selective attention, were especially sensitive to the nicotine regimen both in terms of accuracy and latency of correct responses. Visual shift events, comprising similar attentive properties though lacking the presence of distracters, also proved amendable in the presence of nicotine, showing significant improvements in trial accuracy and decreases in correct response latency. During the primary study, our findings revealed that the muscarinic antagonist atropine uniformly increased correct response latencies irrespective of shift-type conditions, while impoverishing trial accuracy during auditory shift events. And while both systems were activated simultaneously, nicotine proved capable of compensating for the impairments caused by the muscarinic system, though not completely restoring baseline performance. Differences in the nicotine-induced improvements between auditory and visual conditions may be explained in part by previous studies suggesting that nicotine acts primarily to optimize rather than enhance cognitive performance [21]. Because the complexity of the behavioral task required vigorous training to ensure suitable compliance, and because the visual shift portion required less attentional effort, it is reasonable to consider a ceiling effect on visual shift performance both in the normal and atropine-impaired subjects. This helps explain the disparity in mode-specific improvements following nicotine application.

Curiously, the pilot study also revealed a converse relationship between nicotine's effect on the unique parameters governing simple stimulus detection. Accuracy during repetitive trial blocks was significantly enhanced, while no significant effect was found on latency of correct responses. The opposite was true for the perseverative trial conditions, as correct response latency was significantly enhanced, while no significant improvement was shown with respect to accuracy. It is important to note that all parameters did show at least a trend *toward* significance. A larger sampling taken during the primary study showed that atropine significantly impaired accuracy during perseverative trials, and significantly increased correct response latencies during repetitive trial conditions. In addition, nicotine (in the presence of atropine) was able to significantly decrease response latencies during repetitive trials verses atropine administered alone.

These findings would suggest that the nicotinic and muscarinic systems have a reciprocal relationship with reference to simple stimulus detection. During patterns of repetitive behavior, activation of nicotinic receptors improves the recognition of relevant stimuli, while muscarinic receptors affect the speed at which a subject is able to process the characteristics of the incoming stimuli. However, in cases of non-repetitive behavior, when a subject is forced to change focus onto a previously non-relevant stimulus (as is the case in perseverative trial conditions), the systems act conversely. Activation of nicotinic receptors improves processing speed, while muscarinic receptors enhance performance accuracy during these perseverative conditions.

At the physiological level, evidence that the auditory system is particularly sensitive to nicotine derives from in vivo experiments demonstrating that auditory event-related potentials and gamma-band oscillations are blocked by the nicotinic blocker mecamylamine [20], and by experiments on thalamo-cortical brain slices showing a specific increase in synchrony and probability of firing of auditory thalamo-cortical axons [13]. Our results complement the findings that nicotinic receptors are highly expressed along the sensory corticopetal pathway where they modulate cognitive and sensory processes [9], and confirm that activation of nicotinic receptors promotes alertness mechanisms in conditions where no prior inference is possible [26].

Our results suggest that application of nicotine is an effective means of improving attentional shift irrespective of modality change congruent with the findings by White and Levin [30], demonstrating that nicotine patches improve cognitive function in patients experiencing mild to moderate Alzheimer's symptoms when actively engaged in the Conner's continuous performance test. Furthermore, we suggest an *equal but opposite* relationship during stimulus processing between the nicotinic and muscarinic systems, especially prevalent in trial conditions not taxing of higher attentive functioning. By coupling an experimental model designed to tax various aspects of attention with a regimen of nicotine application that has proven effective in other cognitive tasks, our findings suggest that nicotine's role as a cognitive enhancer extends beyond a means for merely sustaining attention on a given task. The increase in success probability on both shift event types over impaired conditions combined with decreased response latency and continued task vigilance indicate that application of nicotine could prove beneficial not only to healthy individuals, but those suffering pathological symptoms stemming from a deficiency of the muscarinic system as well.

Acknowledgements

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