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Cholinergic blockade impairs performance in operant DNMTP in two inbred strains of mice

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Abstract

Cholinergic blockade has been shown to impair performance in delayed nonmatching to position (DNMTP) paradigms in rats. In this study, a murine operant DNMTP task was used to assess the effects of cholinergic antagonism in two strains of mice (DBA/2 and C57BL/6) differing in spatial learning abilities. DNMTP was scheduled in operant chambers with retractable levers, where mice were trained until high levels of accuracy. Subsequently, proactive interference effects were assessed by manipulation of the intertrial interval (ITI), and animals were tested in this task under scopolamine (0.1–1.0 mg/kg) and mecamylamine (0.5–2.0 mg/kg) treatment. Data were analyzed according to the methods of signal detection theory. ITI manipulation decreased accuracy when the time between trials was reduced to 5 s. Cholinergic blockade failed to induce a pure mnemonic impairment but distinguishable effects of both receptor antagonists could be detected: scopolamine disrupted accuracy in a dose-dependent but delay-independent manner, whereas mecamylamine failed to impair accuracy, but decreased responsivity delay- and dose-dependently. Strains mainly differed in responsivity, with DBA/2 showing higher latencies to respond to the levers. These results are comparable to those obtained in rats. Thus, operant DNMTP can be applied to assess working memory in mice.

Keywords: Acetylcholine; Scopolamine; Mecamylamine; Delayed nonmatching to position; Mouse; Signal detection; Strain comparison; Spatial memory; Working memory; Proactive interference

1. Introduction

Spatial recognition memory can be defined as awareness that a stimulus has been previously experienced. It can be assessed in discrete trial delayed response procedures, based on the comparison of spatial stimuli (Steckler et al., 1997). Performance on such tasks requires both long-term reference memory (remembering the general rule of how to respond) and short-term working memory (trial-specific information about where to respond).

The purpose of this study was to assess the effects of reference cholinergic drugs and intertrial interval (ITI) manipulation in an operant delayed nonmatching to position (DNMTP) task — one of the most frequently used operant paradigms to assess spatial recognition memory in rats. In general, a delay-dependent deficit in accurate responding has been interpreted as working memory impairment and has been, e.g., observed after lesions of the entorhinal–hippocampal system in rodents (Aggleton et al., 1991, 1992; Cho and Jaffard, 1994; Chudasama and Muir, 1997). DNMTP deficits have also been reported following lesions of the cholinergic basal forebrain nuclei or their projections (Dunnett, 1985; Steckler et al., 1995; Torres et al., 1994) and pharmacological manipulations of the cholinergic system (Andrews et al., 1994; Anisman, 1975; Ballard and McAllister, 1999; Chudasama and Muir, 1997; Dunnett, 1985; Godding et al., 1982; Moran, 1993; Murray et al., 1991; Stanhope et al., 1995; Steckler et al., 1995).

New molecular approaches in the manipulation of neurotransmitter systems, e.g., the recent development of mouse mutants, have generated a need to design and validate novel behavioural paradigms for mice. In particular, automated paradigms, which allow a dissociation between specific and unspecific effects and also comparison across species, would be advantageous (Pontecorvo et al., 1996; Steckler and Muir, 1996; Van Hest and Steckler, 1996).

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Spatial recognition memory in mice has been successfully scheduled in a variety of maze paradigms, such as in water maze spatial navigation tasks (Means and Fernandez, 1992; Bernasconi-Guastalla et al., 1994; Schöpke et al., 1991), in T-maze delayed nonmatching to place tasks (Beracochea and Jaffard, 1995; Cho and Jaffard, 1994; Ward et al., 2001), radial maze (Marighetto et al., 1993; Ammasari-Teule and Caprioli, 1985; Furusawa, 1991) and Y-maze spontaneous nonmatching tasks (Dellu et al., 2000), where animals are able to learn the nonmatching-to-position rule with high levels of accuracy.

More recently, an operant DNMTP task for mice has been developed (Estape and Steckler, 2001). In addition to being fully automated, such paradigm also allows data analysis according to the mathematical methods of signal detection theory (SDT). SDT provides two independent measures of performance, which reflect the ability to detect the stimulus (sensitivity or accuracy) and the decision to respond to that stimulus (motor or motivational bias) (Marston, 1996; Marston et al., 1993; Sahgal, 1987; Steckler, 2001).

In the present study, we have extended investigations of the effects of cholinergic manipulations in a murine operant DNMTP task (Estape and Steckler, 2001) in two inbred strains of mice differing in spatial performance in a range of learning and memory paradigms (Ammassari-Teule et al., 1993; Arns et al., 1999; Paylor et al., 1993; Upchurch and Wehner, 1989) and in response to cholinergic drug challenge (Ammassari-Teule and Caprioli, 1985). These differences in performance may be explained by different cholinergic activities (Schwegler et al., 1996) and/or variations in other hippocampal, neurochemical (Fordyce and Wehner, 1993; Paylor et al., 1993, 1996) and anatomical (Crusio et al., 1987; Schöpke et al., 1991; Thinus-Blanc et al., 1996) features.

In addition, we studied the effects of manipulation of the time interval between trials (ITI). This manipulation has been reported to affect performance in rat operant DNMTP, presumably by altering the level of proactive interference (Dunnet and Martel, 1990; Dunnett et al., 1990). It is argued that an increase in proactive interference should result in a decrease in accuracy, as the animal would show a higher likelihood to respond to the stimulus which had to be remembered during the preceding trial, rather than to the stimulus presented in the present trial, i.e., information remembered during the preceding trial would interfere with the performance in the ongoing trial. In general, reducing the length of the ITI impairs accuracy, while increasing the ITI duration increases it in rats.

2. Materials and methods

2.1. Subjects

Male C57BL/6N Crl BR (B6) ($n = 19$) and DBA/2N Crl BR (D2) ($n = 20$) mice, aged 3 months at the beginning of the experiment, were purchased from Charles River (Sulzfeld, Germany). Animals were housed individually in Type II plastic cages and maintained on a 12:12-h light/dark cycle (lights on 0600 h). Over a period of 1 week prior to the beginning of the experiment, animals were food-deprived to 85% of their free feeding weights (standard food: Altromin 1314, specially treated). Testing and treatment were conducted during the light phase of the cycle. The experimental protocol was approved by the Ethical Committee on Animal Care and Use of the Government of Bavaria, Germany.

2.2. Apparatus

The behavioural equipment consisted of four mouse operant chambers (Coulbourn Instruments, Allentown, PA, USA), each fitted with two retractable levers (placed 1.5 cm above the grid floor and spaced 9 cm apart), two stimulus lights (one 3 cm above each lever), an illuminated

Table 1
Acquisition of nonmatching-to-position rule: signal detection measures (mean ± S.E.M.)

Measure	Strain	Session 2	Session 4	Session 6	Session 8	Session 10
P(hit)	DBA/2	0.51 ± 0.05	0.58 ± 0.02	0.75 ± 0.03	0.77 ± 0.05	0.82 ± 0.03
	C57BL/6	0.56 ± 0.03	0.60 ± 0.04	0.79 ± 0.03	0.90 ± 0.03	0.93 ± 0.02*,†
P(false alarm)	DBA/2	0.82 ± 0.03	0.36 ± 0.03	0.29 ± 0.03	0.21 ± 0.03	0.16 ± 0.02
	C57BL/6	0.53 ± 0.02	0.30 ± 0.04	0.21 ± 0.04	0.11 ± 0.02	0.07 ± 0.02*,†
A'	DBA/2	0.59 ± 0.05	0.67 ± 0.03	0.81 ± 0.02	0.88 ± 0.02	0.89 ± 0.02
	C57BL/6	0.54 ± 0.05	0.70 ± 0.05	0.85 ± 0.03	0.93 ± 0.02	0.96 ± 0.01*,†
SI	DBA/2	0.07 ± 0.09	0.19 ± 0.07	0.48 ± 0.05	0.81 ± 0.04	0.85 ± 0.02
	C57BL/6	0.04 ± 0.08	0.32 ± 0.07	0.60 ± 0.06	0.92 ± 0.02	0.94 ± 0.01*,†
B''	DBA/2	0.34 ± 0.09	0.32 ± 0.07	0.46 ± 0.05	0.64 ± 0.04	0.68 ± 0.05
	C57BL/6	0.16 ± 0.03	0.42 ± 0.08	0.60 ± 0.07	0.78 ± 0.05	0.86 ± 0.03*
RI	DBA/2	0.25 ± 0.07	0.14 ± 0.05	0.17 ± 0.04	0.11 ± 0.03	0.08 ± 0.01
	C57BL/6	0.15 ± 0.06	0.21 ± 0.05	0.23 ± 0.05	0.07 ± 0.03	0.03 ± 0.01*,†
Index *Y*	DBA/2	0.58 ± 0.09	0.37 ± 0.06	0.17 ± 0.03	0.20 ± 0.05	0.18 ± 0.03
	C57BL/6	0.57 ± 0.08	0.46 ± 0.08	0.17 ± 0.04	0.15 ± 0.04	0.13 ± 0.06*,†

* $P < .05$; significant effect of session.
† $P < .05$; Strain × Session interaction effect.

Table 2
Acquisition of nonmatching-to-position rule: responsivity measures

	Sample latency	Choice correct latency	Choice incorrect latency	Magazine latency	Percentage errors omission	Latency to nose poke
Session	$F(10,310)=15.01$, $P<.001$	$F(10,310)=63.290$, $P<.001$	$F(10,250)=23.905$, $P<.001$	$F(10,310)=12.996$, $P<.001$	$F(4,124)=34.194$, $P<.001$	$F(10,310)=232.018$, $P<.001$
Strain	$F(1,31)=9.18$, $P<.001$	$F(1,31)=17.608$, $P<.001$	$F(1,25)=9.928$, $P<.001$	$F(1,25)=9.076$, $P<.05$	$F(1,25)=5.440$, $P<.05$	$F(1,31)=9.757$, $P<.001$
Session × Strain	$F(10,310)=3.24$, $P<.001$	n.s.	n.s.	$F(10,310)=3.670$, $P<.001$	n.s.	n.s.

n.s. = Nonsignificant.

food pellet dispenser (placed centrally at the wall opposite to the levers, 1.2 cm above the grid floor, equipped with infrared photocells to detect nose pokes), which allowed delivery of 20 mg dustless food pellets (Noyes, Lancaster, UK), and a houselight, connected to a computer equipped with the Winlink Version 3.001-00 (Coulbourn Instruments). Stimulus lights in the equipment had been replaced by light-emitting diodes (ultrabright, 10 mm LED, 12–24 V, green, 40,900 cd/m^2; RS Components, Mörfelden-Walldorf, Germany). The boxes were housed in dark, ventilated and sound-attenuating compartments.

2.3. Training procedure

Over five 15-min sessions (one session per day), animals were habituated to the chambers. Ten food pellets were placed in the food tray. Shaping proceeded when all animals reliably consumed all pellets, using a continuous reinforcement procedure (equivalent to fixed ratio 1; CRF or FR1). Once all the animals reached the criterion of 50% responses made (11 sessions), nonmatching-to-position training commenced. During this stage, each of the 60 trials per session consisted of the following sequence of events: after a 10-s ITI, one of the two levers and the respective stimulus light were presented, left or right, in pseudorandom order (sample phase). Once the animal pressed the lever, the lever was retracted, and the first nose poke into the food tray triggered the immediate presentation of both levers and their stimulus lights (choice phase). A correct response constituted of pressing the lever not presented in the sample phase and resulted in retraction of both levers, a short 1-s illumination of the tray light and delivery of a food pellet. A response at the lever already presented in the sample phase was considered incorrect and was followed by a 5-s time out (TO) during which all the stimulus lights were extinguished. During the first six sessions, no time limit was scheduled for the interpolated nose poke, while a limited hold (LH) of 5 s was introduced during the last five sessions. If an animal failed to respond within this LH, the next ITI commenced. Likewise, a LH was introduced in the choice phase, and failure to press a lever within a LH of 5 s resulted in retraction of both levers and TO. During the initial two sessions of this stage, a strong positional bias was detected in the choice phase for the majority of animals. Therefore, a series of correction trials was run for all animals (30 trials prior to beginning of the training session) from Sessions 2–6 of this stage. During correction, an incorrect response led to presentation of the same sample lever as during the previous trial. Only a correct choice led to pseudorandom sample lever presentation. In a previous study, an intermediate training stage between FR1 and acquisition of the nonmatching rule (discrete trial forced choice alternation training) had been included (Estape and Steckler, 2001). In the present study, this intermediate training stage was successfully omitted. Once animals made 80% or more correct responses on this schedule for more than three consecutive sessions, four delays of 2, 5, 10 and 20 s duration were introduced between sample and choice phase (16 trials per delay, 8 left, 8 right sample lever presentations, in pseudorandom order). At this stage (DNMTP procedure), the first nose poke after the end of the delay led to the presentation of the two choice levers. The LH in the sample phase was extended to 10 s. Animals were trained for another 14 sessions under this schedule in order to establish stable baseline performance.

2.4. ITI manipulation

Once stable performance was established, three sessions where scheduled during which the standard ITI duration

Table 3
Acquisition of nonmatching-to-position rule: strain differences in responsivity measures (seconds; means ± S.E.M.); DBA/2: $n=19$, C57BL/6: $n=14$ (see Table 2 for detailed statistical analysis)

	Sample latency	Choice correct	Choice incorrect	Magazine latency	Percentage errors omission	Latency to nose poke
DBA/2	8.15 ± 0.64*	3.75 ± 0.15*	4.00 ± 0.19*	1.99 ± 0.09*	0.23 ± 0.03*	5.72 ± 0.46*
C57BL/6	6.77 ± 0.87	3.03 ± 0.22	3.35 ± 0.27	1.68 ± 0.13	0.16 ± 0.03	4.56 ± 0.43

* $P<.05$: significant effect of strain.

was reduced from 10 to 5 s or increased to 15 s, respectively. All animals were tested over three sessions with these ITI modifications in a pseudorandom order.

Subsequently, mice received daily 0.9% saline injections (intraperitoneally, 30 min before testing) for an additional four training sessions, before any drug testing was performed.

2.5. Drug treatment

Mecamylamine hydrochloride (Sigma Chemicals, Deisenhofen, Germany) was dissolved in saline and administered intraperitoneally in doses of 0.5, 1.0 and 2.0 mg/kg, 30 min before testing. One day lapsed between injections to allow sufficient elimination of the drug (washout pe-

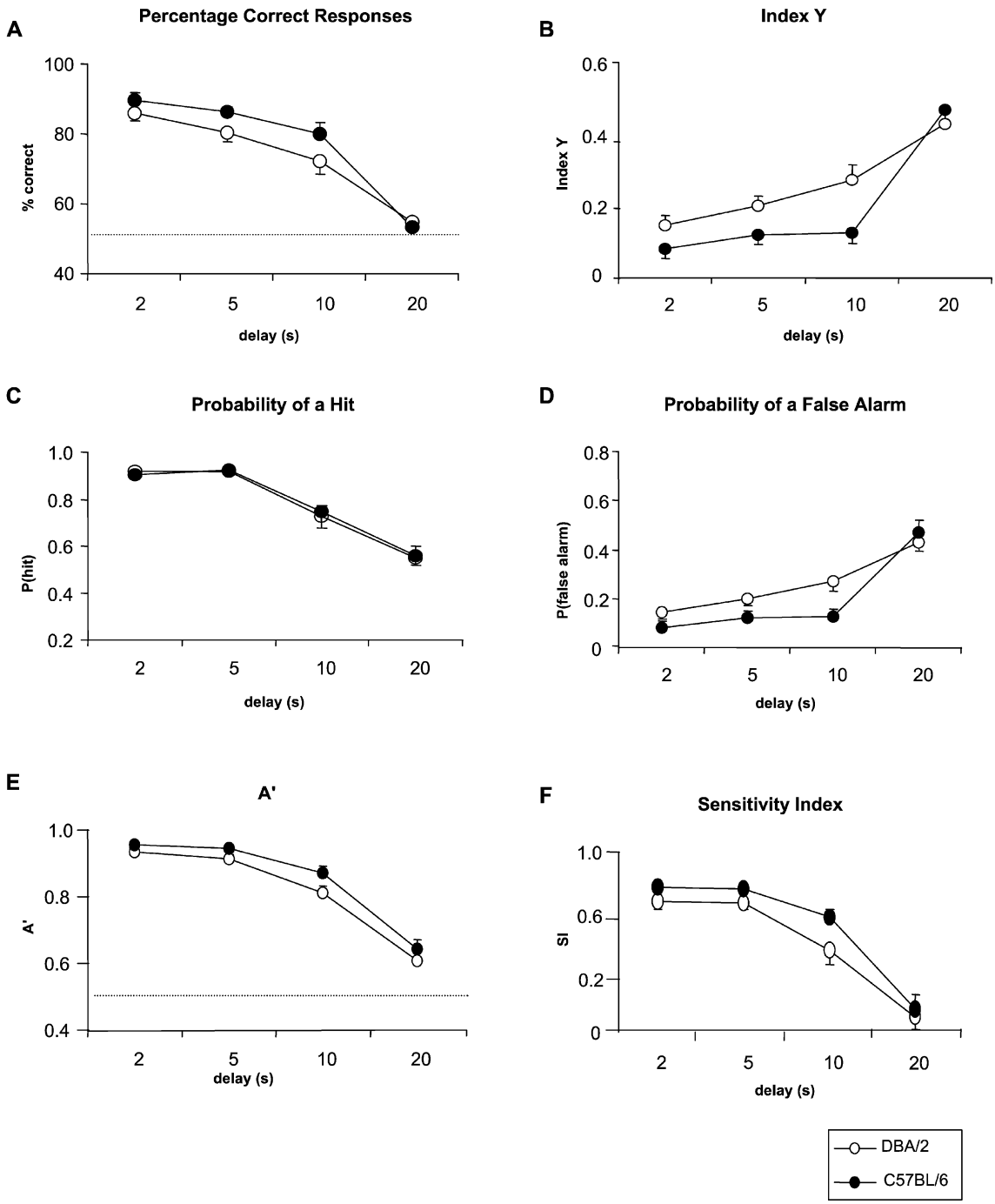

Fig. 1. DNMTP baseline responding (accuracy and bias measures): percentage correct responses (A), Index *Y* (B), *P*(hit) (C), *P*(false alarm) (D), *A′* (E) and SI (F). The dotted lines in (B) and (E), and the *x*-axis in (F) represent chance performance. Data represent average performance over the last four sessions and are presented as means, with error bars denoting S.E.M.

riod), during which mice were not tested, i.e., behavioural baseline was not assessed in-between drug testing. After an additional six training sessions, mice were treated with scopolamine hydrobromide (Sigma; dissolved in saline, intraperitoneally, 30 min before testing, 0.0, 0.1, 0.5 and 1.0 mg/kg) according to a Latin square design.

2.6. Behavioural measures

Percentage correct responding, calculated from the number of correct and incorrect responses, was considered as a measure of accuracy. Furthermore, the number of reinforcers earned was measured and the following responsivity indices were considered: (1) the relative number of errors of omission, i.e., the relative number of missed opportunities to respond at the sample stage (2) and choice stage; (3) the latency to respond to the sample lever, defined as the time from the beginning of the sample lever presentation until a response was made; (4) correct and (5) incorrect choice latencies, defined as the time from the beginning of choice lever presentation until a response was made; (6) the number of responses (nose pokes) into the food tray made during the delay period; and (7) the magazine latencies after a correct choice, defined as the time from the beginning of illumination of the tray light to nose poke. The numbers of reinforcers earned, percentage correct responding, percentage errors of omission at the choice stage, correct and incorrect choice latencies, magazine latencies and the number of responses made during the delay period were separately analysed for each delay, while sample latencies and relative number of errors of omission at the sample stage were analysed over all delays as it was assumed that the animal was unable to anticipate the duration of the delay.

In addition, data were analysed according to the methods of SDT. Correct responses to the left lever were designated a *hit*, incorrect responses to the left lever were defined as a *false alarm* (Sahgal, 1987). Indices of accuracy (A' and SI), of perceptual and response bias (B'' and RI), and the SDT-related 'cognitive' bias (Index Y) were calculated from the raw data by calculating the *hit* and *false alarm probabilities*. In this type of two-choice task, $P(\text{hit}) = h$ = number of correct left responses divided by the number of correct left responses plus the number of incorrect right responses, and $P(\text{false alarm}) = f$ = number of incorrect left responses divided by the number of incorrect left responses plus the number of correct right responses. Then, $A' = 0.5 + [(h-f)+(h-f)^2]/[4\times h\times(1-f)]$; $SI = [h-f]/[2\times(h+f)-(h+f)^2]$; $B'' = ABS[(h-h^2)-(f-f^2)]/[(h-h^2)+(f-f^2)]$; $RI = ABS[h+f-1]/[1-(f-h)^2]$; Index $Y = ABS[\text{left} - \text{right correct responses}]/[\text{total number of correct responses}]$. Only absolute values of B'', RI and Y were analysed, since only the magnitude of bias was of interest.

2.7. Statistical methods

Data were transformed as appropriate [arcsine after division by 100: percentage correct responses and relative number of errors of omission; arcsine after addition of one, followed by division by two: SI and A', arcsine: P(hit), P(false alarm), RI, B'' and Index Y; logarithmic: all latencies; square root after addition of 0.5: number of responses made during shaping, number of reinforcers earned and number of nose pokes made during the delay period] and analysed by parametric analysis of variance (repeated measures ANOVA; SPSS 10.0), including one-factor (Strain) independent measure, two-factor (Strain×Session, Strain×Delay, Strain×Dose, Dose×Delay, ITI×Delay) and three-factor (Strain×Dose×Delay, Strain×ITI×Delay) mixed measures analysis, with treatment, session, delay and ITI as the repeated measures. In case of a significant effect, data were subjected to further post-hoc analysis. Of note, the SDT measures were not included in the statistical analysis under both drug treatments as group sizes were too limited due to changes in responsivity. Instead, the number of animals from which not enough data points could be obtained to calculate the SDT measures was computed as 'drop outs' and was analysed using the nonparametric chi-square test (SPSS 10.0). However, these measures were fully analysed during the NMTP and DNMTP baseline training stages, and ITI manipulation. Only Index Y was analysed under drug treatment.

Table 4
DNMTP baseline: strain differences in reinforcers earned and responsivity measures (seconds; means ± S.E.M.); DBA/2: $n = 14$, C57BL/6: $n = 13$

		Number of reinforcers earned	Choice correct	Choice incorrect	Magazine latency	Percentage errors omission	Number nose poke responses
2-s delay	DBA/2	8.85 ± 0.45*	3.16 ± 0.093*	3.18 ± 0.121*	1.71 ± 0.07*	0.27 ± 0.028	0.80 ± 0.03
	C57BL/6	8.81 ± 0.44	2.28 ± 0.052*	2.52 ± 0.15	1.25 ± 0.03	0.25 ± 0.03	0.79 ± 0.03
5-s delay	DBA/2	8.56 ± 0.42*	2.93 ± 0.076*	3.05 ± 0.08*	0.73 ± 0.02*	0.23 ± 0.016	7.32 ± 0.82
	C57BL/6	9.62 ± 0.46	2.20 ± 0.037	2.25 ± 0.08	0.65 ± 0.03	0.15 ± 0.014	6.36 ± 0.48
10-s delay	DBA/2	6.11 ± 0.69*	2.88 ± 0.08*	2.86 ± 0.09*	1.80 ± 0.07*	0.35 ± 0.027*	13.07 ± 1.31
	C57BL/6	8.07 ± 0.55	2.13 ± 0.049	2.05 ± 0.06	1.18 ± 0.03	0.17 ± 0.02	15.21 ± 0.90
20-s delay	DBA/2	4.20 ± 0.41*	2.89 ± 0.08*	3.02 ± 0.08*	1.71 ± 0.06*	0.45 ± 0.03*	25.00 ± 2.13*
	C57BL/6	4.87 ± 0.37	2.10 ± 0.05	2.14 ± 0.08	1.13 ± 0.03	0.29 ± 0.04	31.60 ± 2.26

* $P < .05$: significant effect of strain.

3. Results

3.1. Shaping

All subjects increased the number of responses made over sessions [$F(1,33) = 74.053$, $P < .001$], but C57BL/6 mice learned faster as revealed by the significant Strain × Sessions interaction effect [$F(1,33) = 2.885$, $P < .05$; data not shown].

3.2. Acquisition of the nonmatching-to-position rule

Analysis of the accuracy measures revealed that subjects learned the general nonmatching-to-position rule with high levels of accuracy, as indicated by an increase in the number of reinforcers earned [$F(10,310) = 37.226$, $P < .001$], percentage correct responding [$F(10,310) = 84.831$, $P < .001$] and all the accuracy measures derived from SDT over sessions (Table 1). All responsivity measures significantly decreased as a function of experience (Table 2). Strains differed in all responsivity measures, and Strain × Session interaction effects were seen in sample latency and magazine latency. Further detailed inspection of the data revealed a constant pattern of performance across strains, in which C57BL/6 mice showed higher responsivity and lower latencies to respond to the levers compared to DBA/2 mice (Table 3).

3.3. DNMTP baseline

All measures of accuracy (Fig. 1A, E and F) and the number of reinforcers earned (Table 4) showed a delay-dependent decrease [number of reinforcers earned: $F(3,75) = 50.614$, $P < .001$; percentage correct responses: $F(3,75) = 71.992$, $P < .001$; A': $F(3,75) = 77.068$, $P < .001$; SI: $F(3,75) = 69.108$, $P < .001$]. An overall strain effect was observed in SI [$F(1,25) = 4.649$, $P = .05$; Fig. 1F] and in the number of reinforcers earned [$F(1,25) = 5.504$, $P = .05$; Table 4], where a Strain × Delay interaction effect was found [$F(3,75) = 3.101$, $P = .049$]. Delay-dependent changes were also seen in P(hit) [$F(3,75) = 80.268$, $P < .001$], which significantly decreased with longer delays (Fig. 1C), and P(false alarm) [$F(3,75) = 39.608$, $P < .001$] which increased over delays (Fig. 1D). ANOVA failed to reveal any further strain or Strain × Delay interaction effect (all P's $> .05$).

The cognitive bias measure, Index Y, increased [$F(3,75) = 25.910$, $P < .001$; Fig. 1B], while the responsivity bias measure B'' decreased with longer delays [$F(3,75) = 24.416$, $P < .001$]. The responsivity index, RI, failed to show any significant changes over delays [$F(3,75) = 2.159$, $P > .05$]. Strains did not differ in biased responding (all P's $> .05$), but a Delay × Strain interaction effect was seen in B'' [$F(3,75) = 3.271$, $P = .05$; data not shown].

Sample latency was significantly higher in DBA/2 mice than in C57BL/6 animals at this training stage [$F(1,25) = 40.145$, $P < .001$; DBA/2: mean 4.64 ± 0.086 and C57BL/6 mean: 3.70 ± 0.099; Table 4]. The same effect was seen in both correct [$F(1,25) = 95.159$, $P < .001$] and incorrect [$F(1,23) = 83.909$, $P < .001$] choice latencies (Table 4). Both latency types decreased over delays [correct latency: $F(3,75) = 13.359$, $P < .001$; incorrect latency: $F(3,69) = 6.627$, $P < .001$]. No Strain × Delay interaction effect was observed [correct latency: $F(3,75) = 0.546$, $P > .05$; incorrect latency: $F(3,69) = 0.987$, $P > .05$]. Likewise, food tray latencies appeared to decrease delay-dependently [$F(3,75) = 365.29$, $P < .001$] and an overall strain effect was seen [$F(1,25) = 54.977$, $P < .001$]. A Strain × Delay interaction effect revealed that DBA/2 mice showed significantly higher latencies to collect the pellet at shorter delays [$F(3,75) = 13.553$, $P < .001$].

Moreover, the relative number of errors of omission increased over delays [$F(3,75) = 18.483$, $P < .001$], and strains significantly differed in this measure [$F(1,25) = 15,035$, $P < .05$; Table 4]. A Strain × Delay interaction effect was observed in this measure [$F(3,75) = 4.761$, $P < .05$]. Further post-hoc analysis of the data revealed that C57BL/6 mice missed significantly less responses at 10- and 20-s delays than DBA/2 mice.

The number of nose poke responses made during the delay increased as a function of the length of the delay [$F(3,75) = 703.800$, $P < .001$] and again a Strain × Delay interaction effect was apparent [$F(3,75) = 6.694$, $P < .05$]. Strains differed only at 20-s delay, with C57BL/6 animals making significantly more nose pokes (Table 4).

3.4. Effects of ITI manipulation

Again, all accuracy measures were altered as a function of delay (all P's $< .001$). An effect of ITI manipulation was seen in the number of reinforcers earned [$F(2,34) = 6.366$, $P < .05$; Fig. 2B], P(hit) [$F(2,34) = 3.955$, $P = .05$; Fig. 2C] and SI [$F(2,34) = 3.904$, $P = .05$; Fig. 2F], but not P(false alarm) (Fig. 2D). However, a Delay × Strain [$F(3,51) = 6.151$, $P < .001$] and a ITI × Delay × Strain interaction effect [$F(6,102) = 3.412$, $P = .05$] was found for P(false alarm). Post-hoc analysis of the data revealed that the number of reinforcers earned, P(hit) and SI were significantly higher at 15 s than at 10 and 5 s ITI. P(false alarm) was significantly reduced at long ITI duration at the 20-s delay.

The bias measures B'' and Index Y were not altered as a function of ITI duration (all P's $> .05$), but increased delay-dependently [B'': $F(3,51) = 13.055$, $P < .001$; Fig. 3A; Index Y: $F(3,51) = 22.876$, $P < .001$; Fig. 3C]. However, RI was significantly increased at 5-s ITI duration [$F(2,34) = 6.649$, $P < .05$; Fig. 3B]. Moreover, errors of omissions were altered as a function of delay duration, but not affected by ITI manipulation ($P > .05$; Fig. 3D).

3.5. Effects of nicotinic blockade

Mecamylamine failed to impair the percentage of correct responses (all P's $> .05$; Fig. 4A). The number of reinforcers

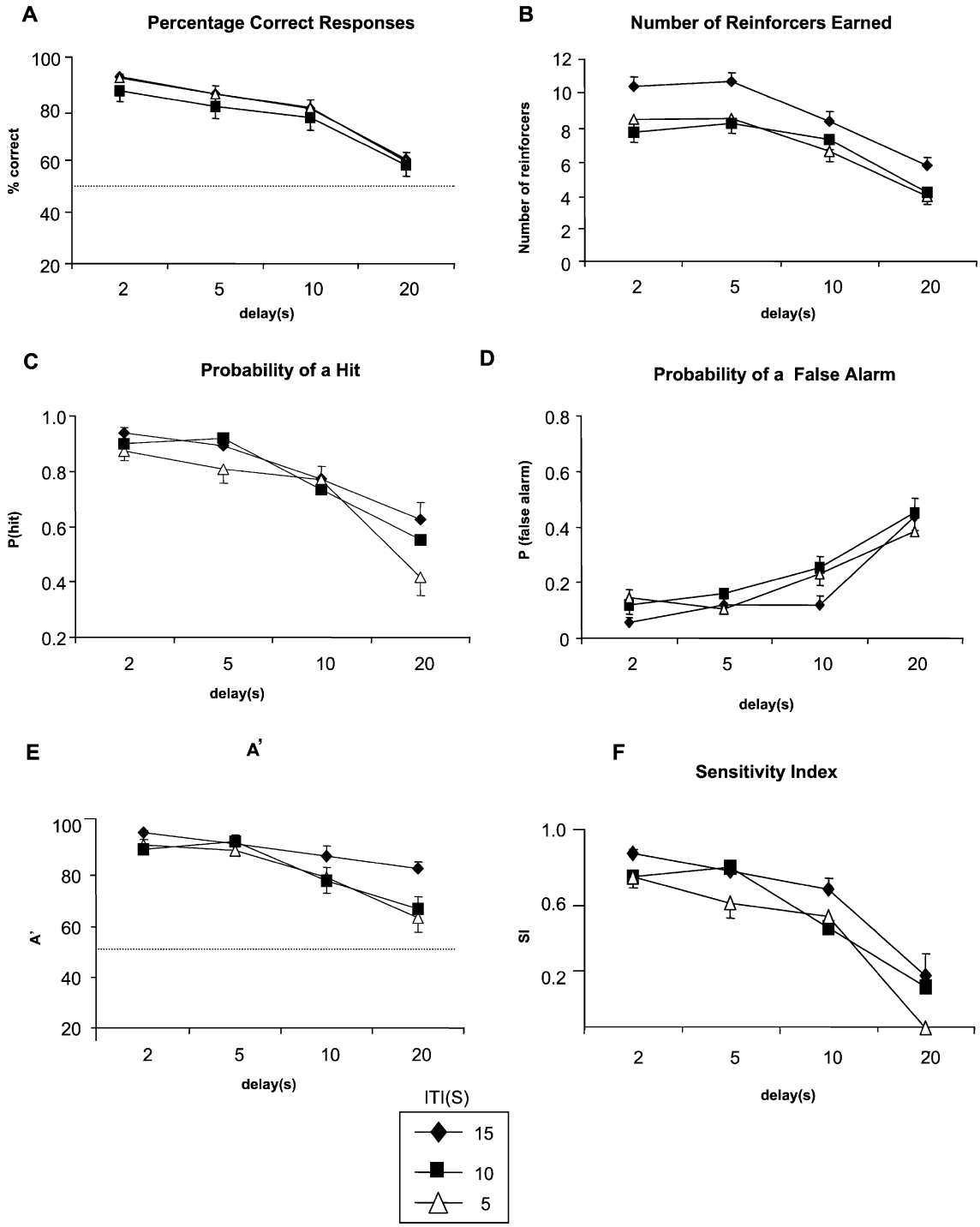

Fig. 2. Effects of ITI manipulation on accuracy measures: percentage correct responses (A), number of reinforcers earned (B), *P*(hit) (C), *P* (false alarm) (D), A' (E) and SI (F). The dotted lines in (A) and (E), and the *x*-axis in (F) represent chance performance. Data from the two strains were collapsed for clarity and are presented as means, with error bars denoting S.E.M.

earned decreased delay- [$F(3,69) = 38.679$, $P < .001$] and dose-dependently [$F(3,69) = 16.653$, $P < .001$]. Moreover, a Dose × Strain interaction effect was observed in this measure [$F(3,69) = 6.550$, $P < .001$]. Further inspection of the data revealed that DBA/2 mice earned significantly more reinforcers than C57BL/6 mice under a 0.5-mg/kg dose of mecamylamine, but strains did not differ at higher doses (data not shown). Due to low responsivity, SDT data were not subjected to statistical analysis, but the probabilities of a hit and of a false alarm are presented (Table 5). The drop out

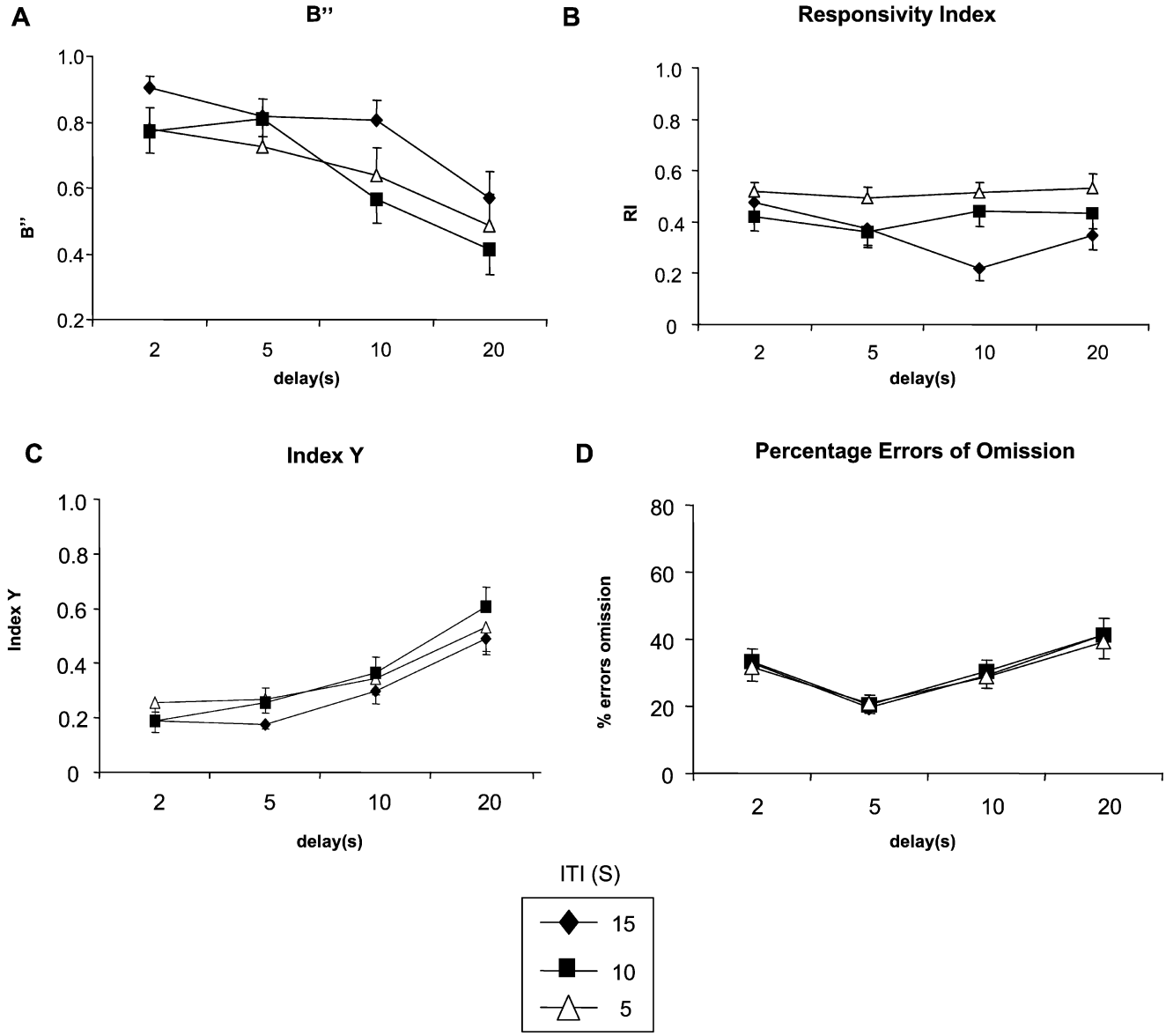

Fig. 3. Effects of ITI manipulation on bias and responsivity measures: B″ (A), RI (B), Index *Y* (C), percentage errors of omission (D). Data are presented as means, with error bars denoting S.E.M.

rate was not significantly altered under mecamylamine treatment ($\chi^2 = 0.779$, $P > .05$; Fig. 6A). No effect of mecamylamine was observed on biased responding (Index *Y*: $P > .05$; Fig. 4C).

Sample latencies depended on strain [$F(1,25) = 12.687$, $P < .05$], with DBA/2 mice having higher latencies. No effects of mecamylamine were observed on this measure (all *P*'s >.05; data not shown). Likewise, correct choice latencies revealed an effect of strain [$F(1,19) = 36.541$, $P < .001$], with C57BL/6 mice responding faster, but a dose effect was absent (all *P*'s >.05; data not shown). The relative number of errors of omission showed an overall dose- [$F(3,75) = 9.627$, $P < .001$] and delay-dependent [$F(3,75) = 8.903$, $P < .001$] effect (Fig. 4B). Moreover, a two-way interaction effect was seen for Dose × Strain [$F(3,75) = 3.133$, $P = .05$] and Delay × Strain interactions [$F(3,75) = 4.811$, $P = .05$]. Further post-hoc inspection of the data revealed an increase in errors of omission in C57BL/6 mice at all doses of mecamylamine compared to saline. Moreover, DBA/2 animals made more errors of omission at longest delays over all doses than C57BL/6 mice, which showed the opposite pattern. Mecamylamine increased the number of nose poke responses delay- [$F(3,75) = 7.928$, $P < .001$] and dose-dependently [$F(3,75) = 503.264$, $P < .001$; Fig. 4D]. Strains did not differ in this measure [$F(1,25) = 2.053$, $P > .05$], but a Strain × Delay interaction effect was bordering significance [$F(3,75) = 2.980$, $P = .054$]. Likewise a Delay × Dose interaction effect was detected [$F(9,225) = 4.759$,

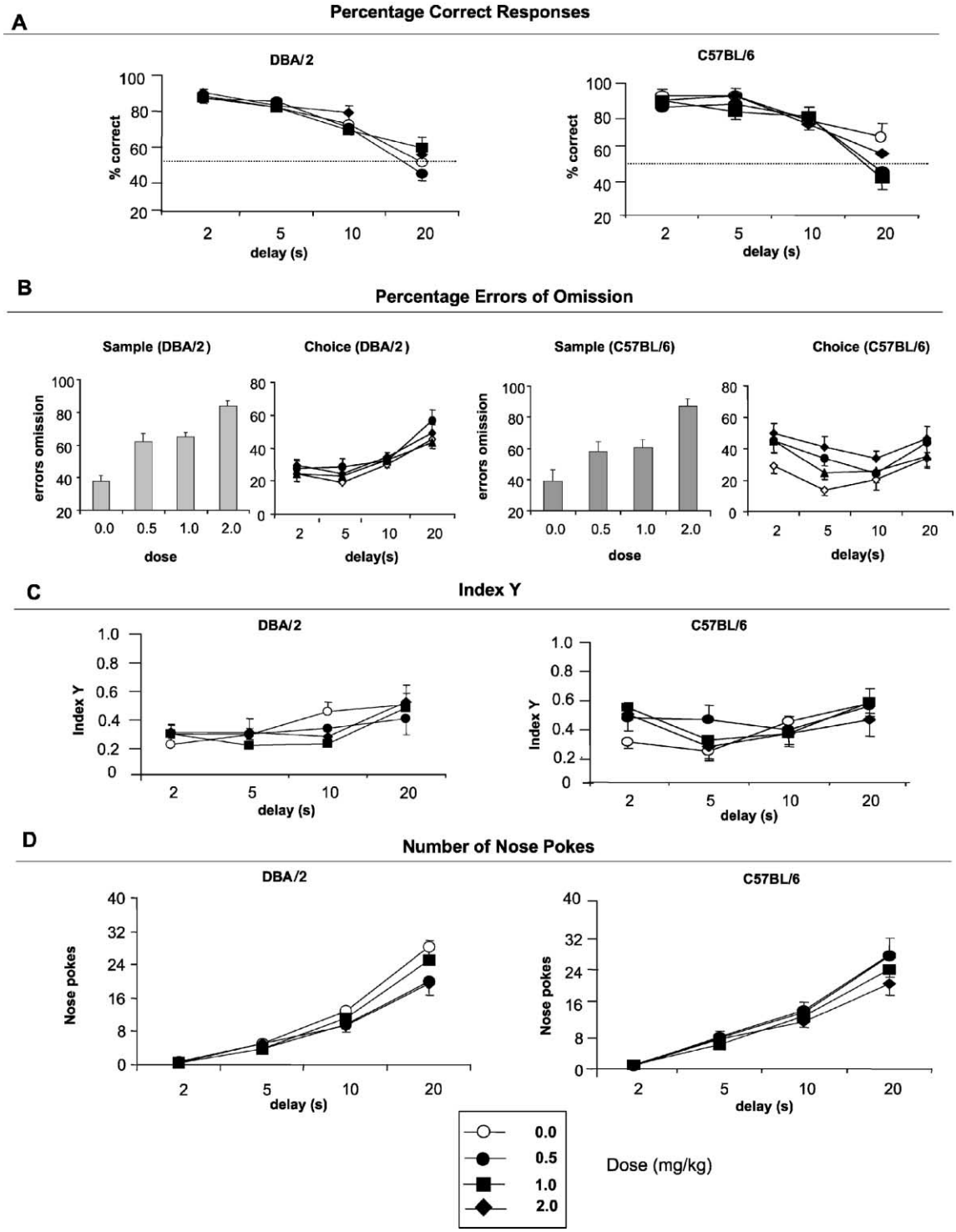

Fig. 4. Effects of nicotinic blockade on DNMTP accuracy and bias measures: percentage correct responses (A), percentage errors of omission at sample and choice stage (B), Index *Y* (C) and number of nose pokes (D). The dotted line in (A) and (C) represents chance performance. Figures from DBA/2 strain (column left). Figures from C57BL/6 strain (column right). Data are presented as means, with error bars denoting S.E.M.

$P=.001$]. Further detailed inspection of the data showed that DBA/2 mice made significantly more nose poke responses over all delays and that mecamylamine significantly decreased the number of nose pokes at a dose of 0.5 mg/kg when compared to saline at the 20-s delay.

3.6. Effects of muscarinic blockade

Scopolamine induced a dose-dependent decrease in percentage of correct responses [$F(2,44)=7.363$, $P=.05$; Fig. 5A]. Of note, animals who did not complete more than

Table 5
Effects of mecamylamine on *P*(hit) and *P*(false alarm) (mean ± S.E.M.); saline: 22 animals; 0.5 mg/kg: 17 animals; 1 mg/kg: 17 animals; 2 mg/kg: 13 animals

Mecamylamine	2-s delay				5-s delay				10-s delay				20-s delay			
Dose [mg/kg]	0.0	0.5	1.0	2.0	0.0	0.5	1.0	2.0	0.0	0.5	1.0	2.0	0.0	0.5	1.0	2.0
P(hit)	0.92 ± 0.03	0.91 ± 0.04	0.95 ± 0.03	0.92 ± 0.04	0.48 ± 0.07	0.91 ± 0.04	0.82 ± 0.05	0.88 ± 0.06	0.78 ± 0.04	0.77 ± 0.05	0.78 ± 0.05	0.80 ± 0.07	0.65 ± 0.06	0.48 ± 0.07	0.64 ± 0.06	0.68 ± 0.07
P(false alarm)	0.09 ± 0.03	0.17 ± 0.06	0.11 ± 0.03	0.11 ± 0.04	0.51 ± 0.08	0.17 ± 0.04	0.13 ± 0.04	0.16 ± 0.05	0.19 ± 0.04	0.25 ± 0.06	0.27 ± 0.06	0.26 ± 0.07	0.39 ± 0.07	0.51 ± 0.08	0.34 ± 0.07	0.41 ± 0.06

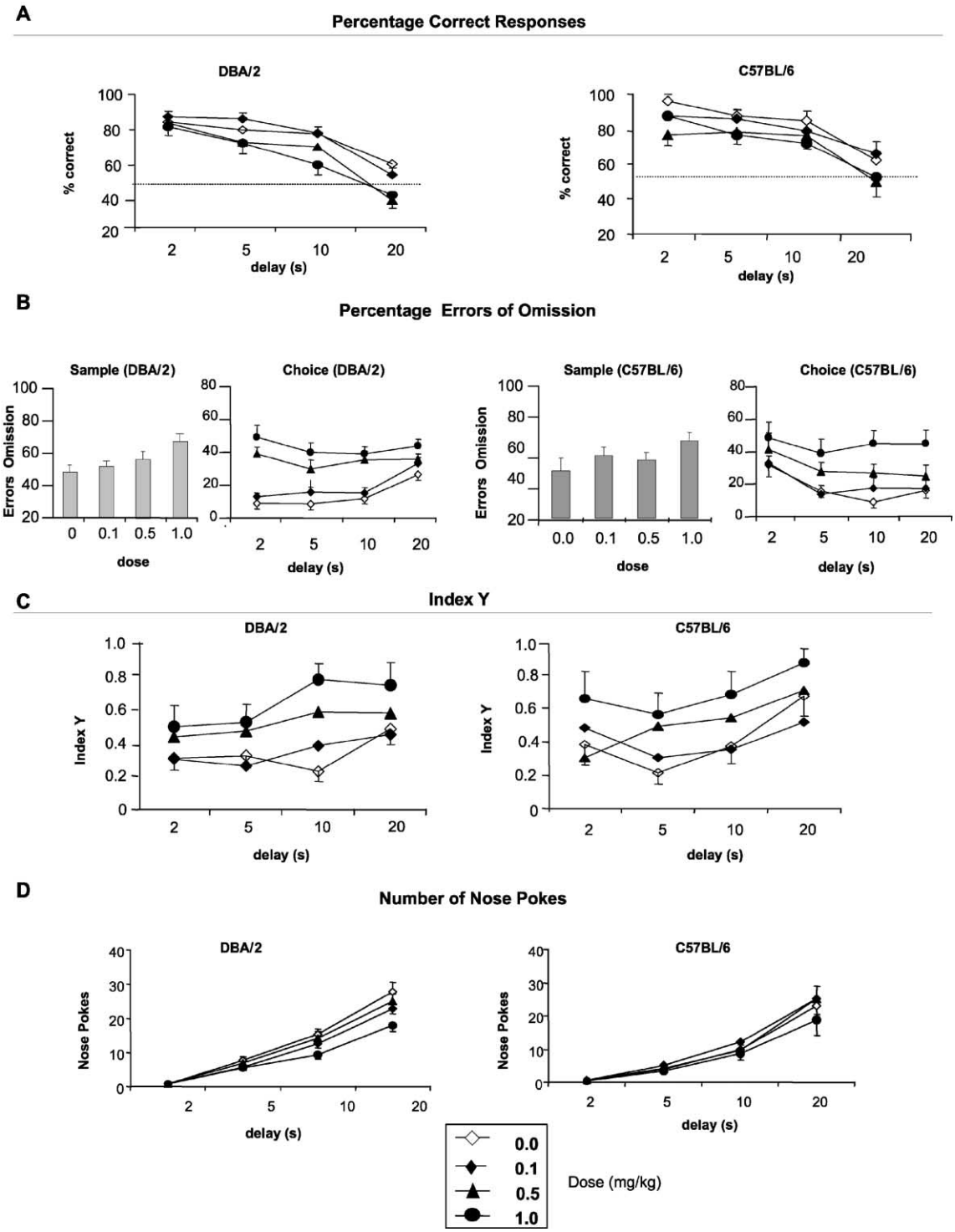

Fig. 5. Effects of muscarinic blockade on DNMTP accuracy and bias measures: percentage correct responses, (A) percentage errors of omission at sample and choice stage (B), Index *Y* (C). The dotted line in (A) and (C) represents chance performance. Figures from DBA/2 strain (column left). Figures from C57BL/6 strain (column right). Data are presented as means, with error bars denoting S.E.M.

50% of the total number of trials (30) were excluded from the data analysis for percentage correct responses. Therefore, only the first three doses of scopolamine (0.0, 0.1 and 0.5 mg/kg) were included as most of the animals failed to achieve this criteria under 1 mg/kg scopolamine.

An overall delay-dependent effect was observed in percentage correct responses [$F(3,66) = 29.065$, $P < .001$] but no two-way interaction effect was seen (all P's $>.05$). However, ANOVA revealed a Strain × Delay × Dose interMaction [$F(6,132) = 2.941$, $P = .05$]. Post-hoc inspection of

Table 6
Effects of scopolamine on *P*(hit) and *P*(false alarm) (mean ± S.E.M.); saline: 14 animals; 0.1 mg/kg: 12 animals; 0.5 mg/kg: 4 animals; 1 mg/kg: 3 animals

Scopolamine	2-s delay				5-s delay				10-s delay				20-s delay			
Dose [mg/kg]	0.0	0.1	0.5	1.0	0.0	0.1	0.5	1.0	0.0	0.1	0.5	1.0	0.0	0.1	0.5	1.0
P(hit)	0.94 ± 0.03	0.86 ± 0.05	0.81 ± 0.12	1.00 ± 0.00	0.82 ± 0.04	0.88 ± 0.05	0.88 ± 0.08	0.83 ± 0.17	0.81 ± 0.05	0.86 ± 0.05	0.56 ± 0.16	0.53 ± 0.03	0.67 ± 0.07	0.67 ± 0.07	0.50 ± 0.17	0.48 ± 0.08
P(false alarm)	0.12 ± 0.07	0.08 ± 0.04	0.06 ± 0.06	0.06 ± 0.06	0.11 ± 0.04	0.13 ± 0.05	0.10 ± 0.10	0.15 ± 0.08	0.15 ± 0.03	0.13 ± 0.04	0.38 ± 0.10	0.61 ± 0.20	0.28 ± 0.06	0.34 ± 0.07	0.41 ± 0.14	0.33 ± 0.17

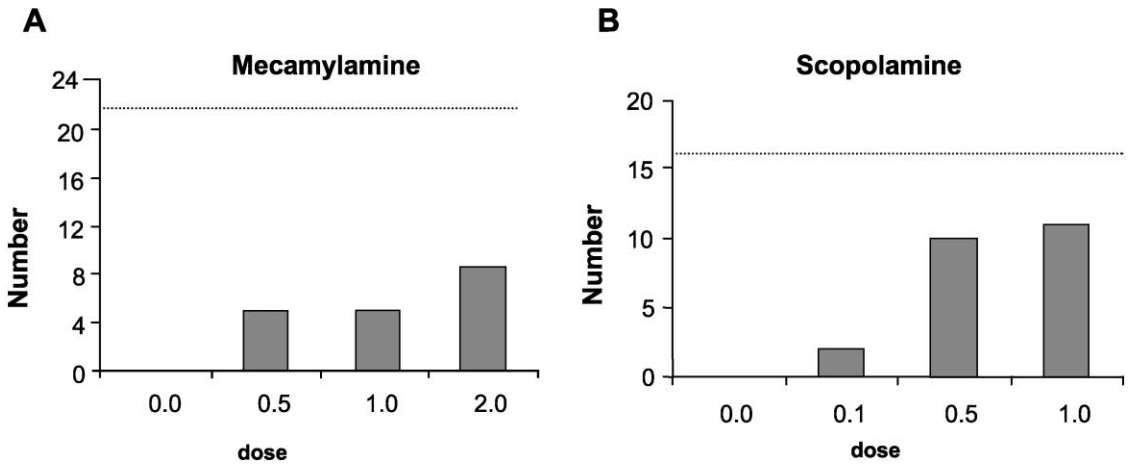

Fig. 6. Number of drop outs under drug treatment. Mecamylamine treatment (A). Scopolamine treatment (B). The dotted lines represent the total number of animals at the beginning of the drug treatment.

the data revealed that scopolamine decreased percentage correct responses dose-dependently at all delays, except for the 10-s delay, which did not reach significance, with the saline dose being different from the 0.5-mg/kg dose of scopolamine but not from the 0.1-mg/kg dose. Moreover, DBA/2 mice made significantly less percentage correct responses at the longest delay under the 0.5-mg\kg dose of the drug compared to C57BL/6 animals, but overall performance was comparable across shorter delay intervals. The number of reinforcers earned decreased delay-dependently [$F(3,18)=17.154$, $P<.001$], but no further effects were seen (all P's >.05).

The SDT measures derived from P(hit) and P(false alarm) were not analysed under the drug treatment due to the low levels of responsivity, but means are reported in Table 6. Analysis of the number of drop outs revealed a significant effect of scopolamine ($\chi^2=1.000$, $P<.001$; Fig. 6B). Index Y increased delay- [$F(3,69)=5.781$, $P=.05$] and dose-dependently [$F(3,69)=5.740$, $P<.05$; Fig. 5C], but no strain effect or further interactions were observed (all P's >.05).

Errors of omission showed an increase over delays [$F(3,66)=22.993$, $P<.001$] and doses [$F(3,66)=9.708$, $P<.001$; Fig. 5B], and a Strain × Dose interaction effect was observed [$F(3,66)=4.784$, $P=.05$]. Further post-hoc analysis of the data revealed that strains differed at longer delays only, with C57BL/6 mice responding more than DBA/2 mice at doses higher than 0.1 mg/kg. Sample latency also increased over doses [$F(3,66)=3.252$, $P=.05$] and strains differed in these measures [$F(1,22)=25.407$, $P<.001$], with DBA/2 mice showing higher latencies (Table 7). Moreover, effects of dose [$F(3,33)=14.211$, $P<.001$] and strain [$F(1,11)=5.848$, $P=.05$] were seen in choice latencies, but no delay-dependent variation was detected [$F(3,33)=0.925$, $P>.05$; Table 8]. ANOVA failed to reveal effects of delay or dose in latencies to collect the pellet (all P's >.05), but an overall strain effect was observed [$F(1,99)=13.270$, $P<.05$]. C57BL/6 mice had both shorter choice and pellet retrieval latencies (Table 8). Moreover, the number of nose pokes increased delay-dependently [$F(3,66)=775.011$, $P<.001$], and a strain effect was seen [$F(1,22)=9.801$, $P<.05$; Fig. 5D]. The Strain × Delay interaction effect just reached significance for this measure [$F(3,66)=3.476$, $P=.05$]. Post-hoc inspection of the data revealed that DBA/2 mice made significantly less nose pokes than C57BL/6 mice, and this effect was delay-dependent.

4. Discussion

A modified training procedure of the murine operant DNMTP task resulted in a reduction in the number of training sessions needed. Under the present schedule, animals could reach stable baseline performance within 32 sessions. This automated paradigm allows to run a large number of trials per session and several animals in parallel, and to accurately schedule time intervals and measure

Table 7
Scopolamine treatment: strain differences in sample latencies (seconds; means ± S.E.M.)

	Scopolamine dose [mg/kg]	0.0	0.1	0.5	1.0
Sample latency	DBA/2	4.797 ± 0.15 *	4.49 ± 0.204 *	5.201 ± 0.203 *	5.112 ± 0.173 *
	C57BL/6	4.017 ± 0.159	4.252 ± 0.154	4.295 ± 0.144	4.441 ± 0.174

* $P<.05$: significant effect of strain.

Table 8
Scopolamine treatment: strain differences in reinforcers earned and responsivity measures (means ± S.E.M.)

	Scopolamine	2-s delay				5-s delay			
	Dose [mg/kg]	0.0	0.1	0.5	1.0	0.0	0.1	0.5	1.0
Choice correct	DBA/2	2.97 ± 0.11	3.15 ± 0.13	3.46 ± 0.15	3.40 ± 0.20	2.86 ± 0.08	2.82 ± 0.13	3.30 ± 0.12	3.28 ± 0.20
latency (s)	C57BL/6	2.87 ± 0.27	3.17 ± 0.16	2.95 ± 0.22	2.92 ± 0.23	2.34 ± 0.11	2.93 ± 0.13	2.79 ± 0.19	2.94 ± 0.24
Choice incorrect	DBA/2	2.92 ± 0.25	3.34 ± 0.4	2.87 ± 0.27	3.69 ± 0.41	2.83 ± 0.19	3.45 ± 0.32	3.35 ± 0.21	3.27 ± 0.26
latency (s)	C57BL/6	3.13 ± 0.24	3.09 ± 0.29	3.18 ± 0.21	3.24 ± 0.019	2.65 ± 0.37	3.27 ± 0.46	2.78 ± 0.30	2.87 ± 0.24
Food tray	DBA/2	1.70 ± 0.075	1.619 ± 0.074	2.03 ± 0.11	2.56 ± 0.31	1.434 ± 0.138	1.46 ± 0.178	1.754 ± 0.20	1.851 ± 0.323
latency (s)	C57BL/6	1.19 ± 0.095	1.55 ± 1.114	1.373 ± 0.19	1.47 ± 0.178	1.287 ± 0.156	1.403 ± 0.198	1.727 ± 0.306	1.56 ± 0.396
Number of	DBA/2	0.867 ± 0.04	0.784 ± 0.048	0.778 ± 0.053	0.738 ± 0.082	7.898 ± 0.852	5.842 ± 0.79	7.05 ± 0.837	5.527 ± 0.8
nose pokes	C57BL/6	0.629 ± 0.085	0.671 ± 0.061	0.68 ± 0.072	0.529 ± 0.093	4.041 ± 0.692	5.20 ± 1.358	4.173 ± 0.873	3.624 ± 0.765

response latencies. Furthermore, the relatively high number of trials permits the use of signal detection analysis, which would be difficult to achieve in tasks with relatively low numbers of trials per session.

A potential drawback of the presently used paradigm could be the relatively short delay intervals possible (up to 20 s in the present study), which clearly differs from the longer delays which can be scheduled in, e.g., maze-based paradigms (Ammassari-Teule et al., 1993; Beracochea and Jaffard, 1995; Furusawa, 1991; Ward et al., 2001). Proactive interference could be one potential reason limiting the length of the retention interval in the operant task. In the present study, this was addressed by manipulating the ITI. Manipulation of the ITI induced changes in accuracy and bias measures, indicating a proactive interference effect. The reduction of the length of the ITI to 5 s impaired accuracy as revealed by changes in *P*(hit) and SI, but percentage correct responses were not affected by shortening the ITI duration. This suggests that SDT measures may be superior to conventional measures to detect a deficit, and that proactive interference effects may explain part of the limitations of this task in mice. The responsivity index, RI, increased with increasing ITI duration, while ITI manipulation had no effect on bias measures, B'' and Index *Y*, indicating that shortening the ITI had only relatively mild effects on biased responding. Responsivity measures remained unaltered by ITI manipulation, which supports the idea that proactive interference had no major effect on other motor or motivational factors. Thus, proactive interference interfered with accuracy in this task in both rats (Dunnet and Martel, 1990; Dunnett et al., 1990) and mice.

Scopolamine decreased accuracy in a dose-dependent but delay-independent manner and altered bias and responding at higher doses, suggesting a nonmnemonic effect on accuracy, e.g., an attentional impairment, in addition of changes in noncognitive measures. Along similar lines, the majority of studies assessing the effects of systemic injections of the muscarinic receptor antagonist scopolamine in rat operant DNMTP paradigms have shown delay-independent impairments in accuracy measures (Andrews et al., 1994; Chudasama and Muir, 1997; Godding et al., 1982; Granon et al., 1995; Moran, 1993; Steckler et al., 1995). Some studies reported that scopolamine decreased choice accuracy in a delay-dependent manner in rat operant delayed matching to position (DMTP) (Dunnett, 1985; Pache et al., 1999), but only few reports showed delay dependency in the equivalent operant DNMTP rat paradigm (Ballard and McAllister, 1999; Murray et al., 1991).

A previous study failed to find an DNMTP impairment in accuracy measures under scopolamine treatment in mice (Estape and Steckler, 2001). This discrepancy could be explained by the use of alternative response strategies or overtraining in the first study, which could have rendered mice resistant to the drug treatment. Supporting the first possibility, comparison of the evolution of Index *Y* over NMTP training showed a significant decrease over sessions only in the second, but not in the previous, study (Estape and Steckler, 2001). Index *Y* reflects the tendency to respond preferentially to one lever in a go/no-go-like manner, i.e., a tendency towards a simpler problem-solving strategy. If mice maintained this strategy over training sessions — as was the case in the first study — they may have been able to perform at high accuracy level and counteract the deleterious effects of scopolamine using this simplified response strategy.

Mecamylamine failed to alter accuracy and bias measures, but decreased some responsivity measures in a dose-dependent manner, consistent with findings in rats responding on this task under mecamylamine treatment (Decker and Majchrzak, 1992; Levin and Simon, 1998; Moran, 1993; Steckler et al., 1995; Stolerman et al., 2000; Widzowsky et al., 1994).

Strains acquired the task with comparable levels of accuracy. Strain differences were primarily seen in response to drug challenge. There was a different susceptibility to scopolamine treatment, with accuracy in DBA/2 mice being more impaired at longer delays than accuracy in C57BL/6 mice, which was comparable over delays. This finding is in agreement with a cholinergic septo-hippocampal hypofunction in DBA/2 mice (Paylor et al., 1993, 1996). However, we cannot exclude that pharmacokinetic differences between strains contributed to these results.

During the NMTP and DNMTP training procedures, the degree at which accuracy improved was comparable between strains. Strains differed only in responsivity meas-

10-s delay				20-s delay			
0.0	0.1	0.5	1.0	0.0	0.1	0.5	1.0
2.76 ± 0.12	2.85 ± 0.17	3.33 ± 0.15	3.18 ± 0.19	2.73 ± 0.15	2.82 ± 0.14	3.07 ± 0.22	3.04 ± 0.23
2.16 ± 0.14	2.78 ± 0.16	2.68 ± 0.20	2.62 ± 0.25	2.19 ± 0.21	3.01 ± 0.25	2.93 ± 0.24	2.60 ± 0.24
2.90 ± 0.28	2.81 ± 0.18	3.47 ± 0.31	3.27 ± 0.26	2.96 ± 0.16	2.78 ± 0.18	3.34 ± 0.227	3.12 ± 0.15
2.56 ± 0.37	2.38 ± 0.16	2.60 ± 0.18	2.79 ± 0.41	2.10 ± 0.24	2.81 ± 0.21	2.69 ± 0.17	2.78 ± 0.40
1.647 ± 0.07	1.781 ± 0.105	2.113 ± 0.20	2.265 ± 0.22	1.634 ± 0.114	1.781 ± 0.124	1.868 ± 0.203	2.267 ± 0.27
1.301 ± 0.168	1.652 ± 0.095	1.701 ± 0.157	1.67 ± 0.36	1.37 ± 0.164	1.498 ± 0.147	1.838 ± 0.236	1.725 ± 0.258
15.31 ± 1.683	12.67 ± 1.205	14.19 ± 1.959	9.435 ± 1.196	27.77 ± 2.871	22.76 ± 1.43	24.91 ± 2.264	18.09 ± 1.956
9.959 ± 1.016	12.24 ± 2.378	9.708 ± 1.51	8.807 ± 1.935	23.04 ± 2.532	25.26 ± 4.926	25.12 ± 3.914	18.72 ± 4.548

ures, with DBA/2 mice showing higher latencies to respond to the levers during both sample and choice phases.

In summary, the murine operant DNMTP paradigm is a valid model to study recognition memory and the results obtained are comparable to those reported from rat studies. Different effects were seen following muscarinic or nicotinic cholinergic receptor blockade, but both manipulations failed to induce a working memory impairment in this operant paradigm.

Acknowledgments

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