*RELATIONS AMONG ACUTE AND CHRONIC NICOTINE ADMINISTRATION,
SHORT-TERM MEMORY, AND TACTICS OF DATA ANALYSIS*

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Emerging evidence suggests that nicotine may enhance short-term memory. Some of this evidence comes from nonhuman primate research using a procedure called delayed matching-to-sample, wherein the monkey is trained to select a comparison stimulus that matches some physical property of a previously presented sample stimulus. Delays between sample stimulus offset and comparison stimuli onset are manipulated and accuracy is measured. The present research attempted to systematically replicate these enhancement effects with pigeons. In addition, the effects of nicotine were assessed under another, more dynamic, memory task called titrating-delay matching-to-sample. In this procedure, the delay between sample offset and comparison onset adjusts as a function of the subject's performance. Correct matches increase the delay, mismatches decrease the delay, and titrated delay values serve as the primary dependent measure. Both studies examined nicotine's effects under acute and chronic administration. Neither provided clear or compelling evidence of memory enhancement following nicotine administration despite reliable and systematic dose-related changes in response latency measures. A modest dose-related effect on accuracy was found, but the magnitude of the effect appears to be directly related to tactics of data analysis involving best-dose analyses of a very circumscribed subset of trial types.

Key words: nicotine, delayed matching-to-sample, titrating-delay matching-to-sample, memory, key peck, pigeons

Emerging evidence suggests that nicotine enhances short-term memory (reviewed in Levin, McClernon, & Rezvani, 2006; Rezvani & Levin, 2001) and, as a result, has been discussed as a pharmacological intervention for those suffering memory loss. Although the reliability and validity of enhancement remains unclear, experimental nicotinic therapies continue for those suffering from dementias, including Alzheimer's disease (e.g., Jones, Sahakian, Levy, & Warburton, 1992; Knott, Engeland, Mohr, Mahoney, & Ilivisky, 2000; Newhouse, 1986; Wallace & Porter, 2011; White & Levin, 1999). This approach appears to be sensible because a loss of cholinergic nicotinic receptor density is

observed in the postmortem brains of Alzheimer's patients (Coyle, Price, & DeLong, 1983).

Nicotine's effects on memory have been most extensively studied in the animal laboratory using the radial-arm maze with rats. Although some procedural details vary across experiments, the basic task involves baiting each of eight arms with food and placing the rat in the center of the maze. Because under this preparation the food is not replaced during a session, only the first entry in each arm is reinforced, and subsequent entries are scored as errors. Daily sessions continue until the rat enters all eight arms or 5 min has elapsed. The primary dependent variable is the number of entries until a repeat is made (Entries to Repeat [ETR]). Because optimal performance involves entering and obtaining each reinforcer without repeating, memory is thought to be central to optimal performance. And indeed, rats are able to engage in this task well with baseline ETR measures usually between 6.5–7.0 (8.0 indicating an errorless session). After a baseline is established, a range of nicotine doses is administered, typically via implanted osmotic minipumps, which provide a constant release over several days. Typical results indicate that moderate doses of nicotine (e.g., 5–10 mg/kg per day)

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are related to modest improvements in the memory task, that is, fewer session-wide repeats, usually approximating an ETR of 7.5 (e.g., Levin, Briggs, Christopher, & Rose, 1993; Levin, Christopher, Briggs, & Auman, 1996; Levin, Christopher, Briggs, & Rose, 1993; Levin, Lee, Rose, Reyes, Ellison, Jarvik, & Gritz, 1990; Levin & Rose, 1990; 1995; Levin & Torry, 1996; and see Levin, 2002 for a recent review).

Another often-cited empirical demonstration of nicotine's enhancement of memory is research examining performance under the delayed matching-to-sample task with nonhuman primates (e.g., Buccafusco & Jackson, 1991; Buccafusco, Jackson, Jonnala, & Terry, 1999; Elrod, Buccafusco, & Jackson, 1988; Katner, Davis, Kirsten, & Taffe, 2004). Delayed matching-to-sample (DMTS) is a commonly employed recognition task that is believed to test short-term memory (e.g., Berryman, Cumming, & Nevin, 1963; Blough, 1959; Kangas, Berry, & Branch, 2011; McCarthy & White, 1985). In a DMTS task, a subject is presented with a sample stimulus. Completion of an observing response to the sample stimulus terminates sample presentation and initiates a delay (retention interval) between sample offset and the onset of comparison stimuli. A response to the comparison stimulus that matches some physical property (e.g., hue) of the previously presented sample stimulus results in reinforcement whereas selecting the other comparison stimulus results in a timeout. Accuracy, typically percent correct, is plotted across different delay values to determine a forgetting function for a given subject under this procedure.

Elrod et al. (1988) trained 5 adult rhesus monkeys on a DMTS procedure using visual stimuli (i.e., illuminated colored keys). After establishing a stable baseline of accuracies under a range of delay values, several doses of nicotine were studied both with and without pretreatment by nicotine antagonists (e.g., mecamlamine, hexamethonium). Nicotine was shown to increase accuracy approximately 5-10% after longer delay values (e.g., 30 s and 60 s) using a *best-dose analysis* that assessed memory-enhancement following particular doses that varied among the 5 monkeys (0.625, 2.5, 5.0, or 7.5 $\mu\text{g}/\text{kg}$ i.m.). Mecamlamine pretreatment abolished the enhancing effects of nicotine, suggesting that central

nicotinic receptors are involved in short-term memory. Buccafusco and Jackson (1991) systematically replicated these memory enhancing effects of nicotine in 4 young (10 years old) and 2 aged (34 and 35 years old) rhesus monkeys. Despite poorer baseline memory performance in the older monkeys, a similar accuracy enhancement of 5-10% was observed during the longest retention intervals tested (60 sec for young, 10 sec for old monkeys) following administration of the best dose of nicotine tested that again varied among monkeys (1.25, 2.5, 5.0 or 10.0 $\mu\text{g}/\text{kg}$ i.m.). Buccafusco et al. (1999) reported memory enhancement in 6 male and 7 female rhesus monkeys that received a series of nicotine doses over 5 weeks. The males demonstrated a variable but on average 5% increase in accuracy following administration of a range of nicotine doses (5-20 $\mu\text{g}/\text{kg}$ i.m.) on the short and medium (but not long) retention intervals tested, but 5-10% improvements in female accuracy were only observed at the two highest doses (10 and 20 $\mu\text{g}/\text{kg}$ i.m.) following medium and long (but not short) delays. Importantly, this line of research is not confined to one laboratory. For example, Katner et al. (2004) assessed the effects of nicotine across a battery of three memory tasks including DMTS, the self-ordered spatial search (SOSS) task, and the visuo-spatial paired-associate learning (vsPAL) task. As reported, "In the overall dose-response analysis, there were no mean effects of drug treatment conditions on DMTS, SOSS, or vsPAL performance... The 'best dose' analyses, in contrast, demonstrated that nicotine administration significantly improved performance on all three memory procedures; this improvement was observed at different doses for individual animals." (p. 230). And indeed, enhancement of approximately 10% was observed when assessing DMTS accuracy under the two longest tested retention intervals (60 and 90 sec) following individually tailored best doses (3.2, 24.0, 32.0 or 56.0 $\mu\text{g}/\text{kg}$ i.m.) for each monkey. This sample of nonhuman primate research illustrates that improvements in accuracy relative to control are observed after particular doses of nicotine that vary across subjects (i.e., best-dose analyses) following certain retention intervals that also vary, either across experiments or sometimes across subjects within an experiment.

These memory-enhancing effects of nicotine appear reliable at the group-average level but the magnitude of this effect for individual subjects has yet to be determined. For example, in the studies described above, mean enhancement effects were usually between a 5 and 10% increase in accuracy, but both the retention intervals and drug doses included in the analyses varied, with no details of individual-subject outcomes provided. Instead, the accuracy increases were shown as group data, and individual data on which doses and which retention intervals comprised the analysis were not reported. This approach in data presentation leaves unanswered the question of enhancement magnitude at the individual-subject level and the replicability of the effect between subjects. Also unclear is the extent to which these memory enhancing effects of nicotine can be demonstrated in other species and under other memory tasks with a focus on the behavior of individual subjects.

Therefore, the first rationale for the present studies was to systematically replicate the memory-enhancing effects of nicotine in a different species (pigeons) using DMTS. Pigeons were selected as a logical species for comparison because pigeon and monkey forgetting functions under the DMTS procedure often overlap (see Etkin & D'Amato, 1969; Overman & Doty, 1980; Moise, 1976, for individual monkey studies, and Berryman, Cumming, & Nevin, 1963; Blough, 1959; Roberts & Grant, 1976, for individual pigeon studies; see review by Wright, 2007). Indeed the negative exponential function that best fits pigeon forgetting functions (e.g., McCarthy & White, 1985) also provides excellent fits of DMTS performance in nonhuman primates (e.g., White & Harper, 1996), rats (e.g., Harper, McLean, & Dalrymple-Alford, 1994), human children (e.g., MacDonald & Hayne, 1996; Pipe, Gee, Wilson, & Egerton, 1999), typically-developing adult humans (e.g., Rubin & Baddeley, 1989), and adults with mental retardation (e.g., Williams, Johnston, & Saunders, 2006). In addition, although operating primarily on different systems, cocaine's effects on DMTS forgetting functions in the pigeon (e.g., Branch & Dearing, 1982) and monkey (e.g., Baron & Wenger, 2001) as well as *d*-amphetamine's effects on DMTS forgetting functions in the pigeon (Spetch & Treit, 1984) and monkey (e.g., Baron & Wenger,

2001) are very similar in shape and dose-related effect. Indeed, there are no known qualitative differences in drug effects on DMTS performance, among pigeons, rats, or monkeys.

A second rationale for the present study was to investigate the effects of nicotine on memory enhancement under another DMTS procedure. This titrating-DMTS (TDMTS) procedure (Cumming & Berryman, 1965) appears to be less susceptible to ceiling effects than the DMTS procedure (see Kangas, Vaidya, & Branch, 2010). Ceiling effects are problematic when the goal is, as in the present investigation, to assess memory enhancement. In addition, the TDMTS procedure does not require that the experimenter select delay values, a process that is often arbitrary and can influence the shape of the forgetting function (see Sargisson & White, 2003). In the TDMTS procedure, the delay between sample offset and comparison onset adjusts within-session as a function of the subject's performance. Specifically, some number of consecutive correct matches increases the delay on the next trial, and mismatches decrease the delay. The primary dependent variable in the TDMTS procedure is titrated delay. The variant of the TDMTS task used in the present study detected systematic dose-related effects of acute and chronic cocaine administration on performance (Kangas & Branch, 2012), suggesting that behavior under this procedure is sensitive to pharmacological variables (see also, Wenger & Wright, 1990). Therefore, a second rationale for conducting the present studies was to evaluate the effects of nicotine in pigeons under the TDMTS procedure.

METHOD

Subjects

Eleven experimentally naive White Carneau pigeons (*Columba livia*), approximately 1 yr old, were obtained from Double-T Farms, Glenwood, Iowa, and were maintained at approximately 85% of their free-feeding weights by postsession feeding as needed. Subjects were housed in individual cages, in a temperature- and humidity-controlled colony room, with exposure to a 16:8-hr light/dark cycle. Water and grit were available continuously in the birds' home cages. Sessions were

conducted 7 days a week at approximately the same time each day.

Apparatus

Studies were conducted in sound- and light-attenuating BRS/LVE pigeon operant-conditioning chambers with inside dimensions measuring 35 cm high, 30 cm long, and 35 cm deep. One side wall (the intelligence panel) contained a houselight, three horizontally arrayed response keys (2.5 cm in diameter) and a 6-cm by 5-cm opening for access to a solenoid-operated hopper filled with mixed grain. The opening was located 10 cm above the floor directly below the center key. During each feeder operation, the aperture was illuminated, and all other lights in the chamber were extinguished. The center key was horizontally centered on the intelligence panel 25 cm above the floor. The houselight was centered 7 cm above the center key. The two side keys were located 8 cm to the left and right of the center key (middle of center key to middle of side key). Each key could be transilluminated red, green, or white, and a peck with a force of at least 0.15 N counted as a response and was accompanied by a 30-ms feedback tone (2900 Hz) via the operation of a Mallory Sonalert™. To mask extraneous sounds, white noise at approximately 95 dB was present in the room in which sessions were conducted. Scheduling of experimental events and data collection was controlled via a dedicated computer system (Palya & Walter, 1993) operating with a resolution of 1 ms.

Procedure

Each pigeon was first trained to eat food from the hopper and then trained by shaping (see Catania, 1998) to peck the center key (illuminated white). After the pigeon pecked the center key reliably when it was lit, shaping was employed to induce it to peck the right and left keys when individually illuminated with white light. After pecking occurred reliably on all three keys, the key color was changed to red or green and pecks to the illuminated key resulted in access to grain. Additional shaping was used if necessary to produce reliable responding.

Matching-to-sample. All pigeons were then trained using a simultaneous matching-to-sample (MTS) procedure (e.g., Carter & Eckerman, 1975; Cumming & Berryman,

1961). Specifically, discrete trials began with the illumination of the houselight and the center (sample) key with either a red or green hue. A single peck to the sample key illuminated the two side (comparison) keys with matching and nonmatching hues (i.e., sample and comparison keys were illuminated simultaneously). A single peck to the side key illuminated with the same color as the sample key (i.e., the correct match) turned off the houselight, the sample key, both comparison keys, and raised the food hopper for 3 s followed by a 10-s intertribal interval (ITI). An ITI was employed because it improves the accuracy of pigeon MTS performance (e.g., Thomas, 1979; White, 1985). A single peck to the nonmatching comparison key (i.e., the incorrect response) turned off all lights in the chamber and initiated a 13-s ITI.

A two-color (red [R] and green [G]), two-comparison MTS procedure yields four possible trial configurations (R–R–G, G–R–R, R–G–G, G–G–R [left–center–right key]). Trial configuration was randomly selected without replacement. When needed, a correction procedure (i.e., repeating a trial configuration if an error was made) was programmed to eliminate side or color biases (Kangas & Branch, 2008).

Delayed matching-to-sample. We trained 6 of 11 pigeons on the DMTS task. The general structure and consequences of the DMTS procedure were the same as that of the simultaneous MTS procedure with three exceptions. First, five responses to the sample stimulus were required; second, the sample stimulus was terminated after completion of the response requirement; and third, a variable delay was programmed between the offset of the sample stimulus and the onset of the comparison stimuli. The retention intervals programmed were 0, 2, 4, 8, and 16 s. Combinations of the four trial configurations and five retention intervals (20 trials) were randomly selected without replacement three times to produce a 60-trial session. A fixed time-interval stability criterion (Perone, 1991; Sidman, 1960) of 300 daily sessions of DMTS served as an extended baseline before determining the acute effects of nicotine on accuracy.

Titration-delay matching-to-sample. The remaining 5 pigeons were trained on the TDMTS task where the delay between sam-

ple-stimulus offset and comparison-stimuli onset was adjusted as a function of the pigeon's accuracy on immediately preceding trials. Specifically, every two consecutive correct matches increased the delay by 1 s, and every mismatch decreased the delay by 1 s (unless the delay was zero). The first trial of the first session in this condition began with a zero-delay; thereafter, each daily session began with the delay value from the last trial of the previous session. Sessions consisted of 48 trials. A single sample-observing response was required for the first 15 sessions and this response requirement was increased across conditions (2, 4, 8, and 16; 15 sessions per condition). Increasing the sample-observing response requirement was designed to increase titrated delay values to a duration sufficiently long to observe drug effects in either direction (see Kangas & Branch, 2012; Kangas et al., 2010). The sample-observing response requirement was held at 16 for a minimum of 100 sessions and until visually stable. After titrated delays stabilized, acute determinations began.

Drug procedure. Nicotine ([-]-Nicotine Hydrogen Tartrate Salt; Sigma, St. Louis, MO) was dissolved in a potassium phosphate (KPO_4) distilled water solution to buffer against nicotine's acidity and to obtain a pH of 7.4; the KPO_4 solution was used in vehicle-control sessions. Doses were selected based on previous nicotine research with pigeons (e.g., Chadman & Woods, 2004). Injection volume (1.0 ml/kg) was adjusted according to the subject's weight. Drugs or vehicle were administered by an intramuscular injection in the pigeon's breast. During chronic administration the site of successive injections was alternated between the two sides of the breast.

Acute administration. Following DMTS or TDMTS training, one of several doses of nicotine was administered 5 min prior to a session once every 4 days. The doses were the vehicle—(KPO_4 [0.0]), 1.0, 0.3, 0.1 mg/kg nicotine examined in that order. A dose of 1.3 mg/kg was also administered to the TDMTS subjects. Two dose-response functions were determined for each subject. A descending fixed order of doses was used to facilitate observation of any systematic changes (i.e., lessening or increasing) in effects as a result of previous drug exposure.

Chronic administration and re-determinations of acute functions. After the acute dose-response functions were derived, a dose for chronic administration was chosen for each subject. The dose that was administered chronically was that which had the greatest change (increase or decrease) on performance relative to control without eliminating responding. The chronic dose was then administered for 30 consecutive daily sessions.

Following the 30th session of chronic administration, every 4th session, one of the doses used in the acute-dosing phase was administered instead of the chronic dose so as to re-determine the dose-response function. After this *during-chronic* re-determination, chronic nicotine administration ceased and was replaced with daily injection of the vehicle (KPO_4) alone. Following 30 sessions of daily KPO_4 administration, a final *post-chronic* dose-response function was determined in the manner described above.

RESULTS

Delayed Matching-to-Sample

Acquisition. A detailed account of DMTS performance development across the 300 sessions prior to drug testing can be found in Kangas et al. (2011). Briefly, high levels of accuracy developed relatively quickly under the shorter retention intervals, but increases in accuracy under the longer retention intervals sometimes were not observed until 100–150 sessions had passed, with some still displaying minor increases at Session 300.

Acute administration. Figure 1 shows the effects of delay (retention interval) and nicotine dose on each pigeon's DMTS accuracy. The thickness of each line is related to dose, with thicker lines representing performance under larger doses. The shaded area of each panel indicates the range of accuracy observed during vehicle control sessions (i.e., sessions that intervened between acute determinations). A vast majority of observed accuracies across delays and subjects are inside the shaded area (i.e., control) suggesting that accuracy under all doses of nicotine was not affected in any systematic fashion at any delay. If acute nicotine administration improved memory the lines would appear above the shaded area. However, no significant or reliable departure from control in either direction was observed. That

Fig. 1. Forgetting functions (percent correct as a function of delay) under each dose of nicotine during the acute determination. The thickness of the line is related to the value of the dose of nicotine with the thinnest representing 0.1 mg/kg nicotine and the thickest 1.0 mg/kg nicotine. The dashed line represents vehicle (KPO_4). All lines represent an average of the two determinations of each dose, and the gray shaded area indicates range of accuracies during intervening control sessions.

the doses of nicotine were active is supported by a reliable dose-related increase in sample-response latency during the first trial of each acute-dosing session. The filled circles in Figure 2 show that this curvilinear dose-related increase was reliable across subjects (error bars represent the range across the two acute determinations). These latencies limited the testing of higher doses because longer latencies could have pushed the session length outside of the plasma half-life of nicotine, although we cannot be sure, as that information is unknown in pigeons (it is approximately 45 min for rats; Matta et al., 2007). In addition, although not yet investigated with pigeons, nicotine toxicology studies in rats have revealed steep lethal-dose functions (e.g., Aceto et al., 1979).

Chronic administration. Because there was no significant change in DMTS accuracy resulting from acute nicotine administration, the dose chosen for chronic administration was that which had the largest effect on latency to

complete the first trial: 1.0 mg/kg for all subjects. Just as accuracies were largely unchanged during acute administration, they were also unchanged after 30 days of chronic administration (data not shown).

During-chronic assessment. Despite unchanged accuracies during the chronic administration condition, the latency to complete the first trial decreased over the course of this condition (i.e., drug tolerance); with 4 of 6 subjects' latencies approaching control levels (data not shown). To capture more fully the extent of tolerance to the latency effects of nicotine, the open circles in Figure 2 show dose-response functions for latency to complete the first trial during chronic administration. The rightward shifts of the dose-response function indicate tolerance; indeed a dose larger than the highest given during the acute determination (1.3 mg/kg nicotine) was included in this condition to characterize more fully the rightward shift.

Post-chronic assessment. To determine the persistence of changes in latencies to complete the first trial observed during chronic administration, 30 consecutive sessions of vehicle administration were conducted, after which the dose-response function was reassessed. The open squares in Figure 2 show the dose-response functions. For most doses in all subjects, the post-chronic function is between those for the acute and during-chronic determinations, suggesting a partial loss of tolerance.

Titration-Delay Matching-to-Sample

Acquisition. For all 5 subjects, when the sample-observing response requirement was low (FR 1–4), the titrated delay values were low, reflective of poor memory performance. Increasing the sample-observing response requirement to FR 8 increased the titrated delay for 3 of 5 subjects. When this response requirement was increased to FR 16 the titrated delays increased to consistently above-zero levels in all 5 subjects (data not shown).

Acute administration. Figure 3 shows trial-by-trial changes in titrated delay during acute drug administration sessions; data are separated across acute determinations. Both at the whole-session and within-session levels, no consistent nicotine dose effects on titrated delay values were observed across subjects. As with the DMTS procedure, nicotine produced a reliable dose-related increase on the latency

Fig. 2. Relationships between dose of nicotine and latency to complete the first trial of the session during the acute (filled circles), chronic (open circles), and post-chronic (open squares) conditions. Error bars indicate range.

to peck the sample stimulus at the beginning of the session (see filled circles in Figure 4).

Chronic administration. Because there was no significant change in titrated delay values during the acute nicotine administration, 1.0 mg/kg was chosen for chronic administration in all subjects because it produced a large effect on latency to peck the sample stimulus in all subjects. As in the DMTS procedure, titrated delay values in the TDMTS procedure were unchanged during the first 30 days of chronic administration (data not shown).

During-chronic assessment. Latency to complete the first trial systematically decreased over

the course of the chronic administration condition. To capture more fully the extent of tolerance to the latency effects of nicotine, the open circles in Figure 4 show dose-response functions of latency to complete the first trial as a function of dose. The rightward shift of the dose-response function indicates tolerance.

Post-chronic assessment. To determine the persistence of the tolerance observed during chronic administration on the latencies to complete the first trial, 30 consecutive sessions of vehicle administration were conducted, after which dose effects were reexamined. The open squares in Figure 4 show that for

Fig. 3. Effects of two acute determinations of nicotine for each subject. Each data series represents titrated delay values of all 48 trials observed during each acute administration session.

most doses in all subjects, the effects of the range of nicotine doses on first-trial latencies is between those from the acute and during-chronic determinations. This suggests a partial loss of nicotine tolerance.

DISCUSSION

Despite systematic latency effects that indicate a full, behaviorally active range of doses was tested, both experiments failed to add

evidence to support the view that nicotine enhances short-term memory. That is, neither DMTS accuracy nor titrated delay values were increased in any systematic fashion. However, previous studies have demonstrated and replicated a modest enhancement of memory with nicotine in nonhuman primate experiments using the DMTS procedure (e.g., Buccafusco & Jackson, 1991; Buccafusco, et al., 1999; Elrod, et al., 1988; Katner et al., 2004). These studies, along with experiments on the effects

Fig. 4. Relationships between dose of nicotine and latency to complete the first trial of the session during the acute (filled circles), chronic (open circles), and post-chronic (open squares) conditions. Error bars indicate range.

of nicotine in rats performing in a radial arm maze (see Levin, 2002; Levin et al., 2006, for recent reviews), have provided an empirical foundation for the exploration of nicotinic treatments in hopes that they may have similar enhancing effects on memory in clinical populations, including those suspected to have Alzheimer's disease (e.g., Jones et al., 1992; Knott et al., 2000; Newhouse, 1986; Wallace & Porter, 2011; White & Levin, 1999).

As discussed above, the pigeon is a logical species to compare to monkeys, especially when assessing drug effects on DMTS performance, considering their overlapping negative

exponential forgetting functions and similar dose-related drug effects. Nevertheless, there remains a possibility that our choice of subject was inadequate to elucidate nicotine-related enhancement effects. That is, although the pigeon is a very common experimental subject in the DMTS preparation, as well as behavioral pharmacology more generally, positive findings using the DMTS procedure were all with nonhuman primates. This species difference may be tempered by the fact that there have been recent and significant changes in the way in which some view the homology between mammalian and avian brains. Specifically, the

Table 1

Percent correct of the 8-s and 16-s retention interval trial types during the two acute determinations of nicotine effects. *Italic values indicate instances in which the accuracy for that trial type was higher than that of control.*

268	mg/kg	8-s	16-s	800	mg/kg	8-s	16-s
Acute 1	Control	59	49	Acute 1	Control	54	50
	1	75	50		1	58	50
	0.3	58	42		0.3	83	42
	0.1	50	50		0.1	50	50
Acute 2	Control	59	49	Acute 2	Control	54	50
	1	42	42		1	50	42
	0.3	58	50		0.3	58	58
	0.1	50	50		0.1	42	50
808	mg/kg			876	mg/kg		
Acute 1	Control	70	57	Acute 1	Control	54	56
	1	67	58		1	75	75
	0.3	58	58		0.3	67	50
	0.1	67	58		0.1	58	58
Acute 2	Control	70	57	Acute 2	Control	54	56
	1	50	33		1	50	33
	0.3	75	42		0.3	67	58
	0.1	75	67		0.1	83	50
930	mg/kg			939	mg/kg		
Acute 1	Control	52	51	Acute 1	Control	52	51
	1	50	50		1	42	42
	0.3	50	42		0.3	58	25
	0.1	42	50		0.1	50	50
Acute 2	Control	52	51	Acute 2	Control	52	51
	1	58	50		1	58	58
	0.3	58	58		0.3	50	33
	0.1	50	50		0.1	58	50

avian cerebellum has a large pallium that appears to perform similar functions to that of the mammalian cortex, supporting similar advanced cognitive abilities that avian species have displayed including categorization, symbolic behavior, transitive logic, tool use, spatial, episodic, and other types of memory (see Jarvis et al., 2005; Reiner et al., 2004; for reviews and discussion).

Another possible variable responsible for the failure to replicate memory-enhancing effects with nicotine is the limited robustness of the effect. That is, although a 5-10% increase in accuracy following nicotine administration is almost certainly a very important effect, it has been derived after assessing specific accuracy changes in particular retention interval categories under particular doses. To illustrate this point, Table 1 shows the mean accuracy values of two determinations for each of the 6 DMTS subjects for the 8-s and 16-s retention intervals (long delays) under each of the doses of nicotine, as well as control (i.e., mean accuracies during sessions that intervened between acute determinations). The

italicized cells highlight instances in which accuracy after a long retention interval under a dose of nicotine is higher than that of control. As the table shows, all 6 subjects had numerous sessions in which nicotine administration was associated with higher accuracies after long retention intervals relative to control. This reflects variability in DMTS performance even after extended baseline exposure (see Kangas et al., 2011). Moreover, because in all multidelay DMTS experiments each session is limited in the number of trials in which a given retention interval is programmed, getting one additional trial correct or incorrect can have a relatively large impact on overall accuracy, especially percent-correct measures after a particular retention interval. For example, in the present study there were 60 DMTS trials of five retention intervals (0, 2, 4, 8, and 16 s) each presented 12 times. When examining accuracy under only one of the retention intervals, getting one more trial type correct or incorrect relative to control will increase or decrease accuracy by approximately 8%. The protocol employed in several of the

previous studies with nonhuman primates described above typically involved 108 trials per session and six delays per session (i.e., 18 occurrences of each retention interval). Therefore, an additional trial correct relative to control would increase accuracy by approximately 5%. If all measurements at all retention intervals were included, these deviations in percent changes would probably cancel each other out. However, selection of particular retention interval categories that vary across subjects following particular doses of nicotine that also vary across subjects increases the probability that such selection will result in an effect that is not reliable.

To demonstrate this we used the italicized values in Table 1 and presented them in the exact manner used by Elrod et al. (1988) which is also very similar to that reported in Buccafusco and Jackson (1991) and Buccafusco et al. (1999). Specifically, three retention interval categories were created using accuracy values—Retention Interval 1 included those that led to performances yielding 95–100% correct, Retention Interval 2 included delay intervals that yielded 80–85% correct, and Retention Interval 3 included those that resulted in 65–75% correct. Then a dose was chosen for each subject that produced the greatest increase in accuracy (i.e., best-dose analysis), relative to control, under Retention Interval 3. Figure 5 shows the average (over two administrations) percent change from control under each of the three retention-interval categories during the acute determinations of a single dose (the same dose within-subject but different between-subjects). As the figure indicates, a positive percent increase from control is found during the functionally defined Retention Interval 3, for 5 of 6 subjects. Despite the clearly null effect suggested in Figure 1, by functionally defining retention interval categories, and choosing a nicotine dose that had the largest effect on Retention Interval 3 (which is usually the longer delay value, but excludes those at which the subject is performing at chance) we can appear to show an enhancement of accuracy on Retention Interval 3 during moderate nicotine dose administration (i.e., 0.1 and 0.3 mg/kg nicotine). This enhancement demonstrated even at the level of the individual subject, touts a 9.2% increase in accuracy if presented as a group average. In fact, our

Fig. 5. Percent change from baseline control levels during each of three functionally defined retention intervals under a dose that was related to the highest percent increase during Retention Interval 3.

percent change from control data (i.e., Figure 5) looks very similar in magnitude to results presented in previous research (cf. Fig. 2 in Elrod et al., 1988).

One potential explanation of the accuracy increases observed in Retention Interval 3 may be related to a *floor effect*. That is, because Retention Interval 3 is operationally defined as poor accuracy (65–75% correct), it has more room to increase rather than decrease (given that chance under DMTS contingencies is 50% correct) than the other retention-interval categories. Evidence supporting this may be observed in Retention Interval 1, where 5 of 6 subjects demonstrated a memory decrement.

To conclude, memory deficits that develop in aging creatures are a very real and significant problem, and experimental research towards attenuating those dementias will remain a laudable activity. The present results provided very little evidence supporting the notion that nicotine enhances short-term memory but showed that best-dose analysis techniques can inflate effect size. To be clear, it is a pharmacological fact that individuals

differ in their sensitivity to a drug, and best-dose analyses are often a reasonable tactic of data analysis. However, the effects presented in Figure 5 are not simply a product of a best-dose analysis, but an interaction between best-dose analyses and a selective subset of retention interval trial types. This cautionary point may very well be limited to the DMTS task. For example, although the literature on nicotine-related memory enhancement of rat radial arm maze performance discussed above uses best-dose analysis techniques, there does not appear to be a second selective analysis dimension akin to the retention interval category in the present study, although ceiling effects seem probable given the high baseline control measures. In any case, the present results suggest prudence, particularly when two dimensions of data analysis are allowed to vary, for example dose and retention interval category, because these tactics of data analysis have the potential to inadvertently exaggerate purported enhancements.

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