Nicotine Stimulates Dendritic Arborization in Motor Cortex and Improves Concurrent Motor Skill But Impairs Subsequent Motor Learning

CLAUDIA L.R. GONZALEZ, OMAR A. GHARBAWIE, IAN Q. WHISHAW, AND BRYAN KOLB
Department of Psychology and Neuroscience, Canadian Centre for Behavioral Neuroscience, University of Lethbridge, Lethbridge, Alberta, T1K 3M4, Canada

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ABSTRACT The effect of the premature commitment of neurons to exuberant growth by nicotine on concurrent and subsequent learning is unknown and was the focus of the present study. Animals were trained on a tray reaching for food task (where lots of pieces of chicken feed were available) for 3 weeks before they received two daily injections of nicotine (0.3 mg/kg) or 0.9% saline for 12 days. Measures of tray-reaching performance were obtained before the administration of nicotine and every other week for a total of 7 weeks. Starting on week 8, animals were given a novel motor skill problem that required them to learn to use a forepaw to reach through a slot in a cage for single food pellets located on an external shelf. Pyramidal cells in the forelimb area of both hemispheres were then examined for dendritic length and branching using a Golgi-Cox procedure. Animals treated with saline displayed excellent performance in both reaching tasks and an increase in neuronal branching in Layer V pyramidal cells in the motor cortex contralateral to the reaching paw. In contrast, animals treated with nicotine showed bilateral increases in neuronal branching. Behavioral results showed that nicotine improved forelimb use in the concurrently administered tray-reaching task, but severely degraded quantitative and qualitative scores of skilled forelimb use in the subsequently administered single-pellet reaching task. The results suggest that plasticity coincidence with skilled training is essential to skilled motor learning, but this expenditure can impair subsequent learning. Synapse 55:183–191, 2005.

INTRODUCTION Administration of the psychostimulant nicotine has wide-ranging effects on brain and behavior in humans and nonhuman animals alike. Acute administration of nicotine can enhance vigilance (Mancuso et al., 1999; Lee et al., 1997), attention (Young et al., 2004; Hahn et al., 2003; Lawrence et al., 2002), and motor performance on skilled tasks, e.g., hand writing (Tucha and Lange, 2003). The periodic administration of nicotine can result in addiction as well as increases in neuronal dendritic length and synapse number in several brain regions, including the nucleus accumbens, and prefrontal cortex (Brown and Kolb, 2001). This association between nicotine administration and neuropil changes may underlie addiction (for review, see Mathieu-Kia et al., 2002). The ability of nicotine to stimulate neuronal plasticity has suggested that nicotine may be a useful treatment for enhancing recovery from brain injury, especially if behavioral therapy and nicotine administration are coincident (Brown et al., 2000, 2001).

Whereas the close association between nicotine administration and exuberant neuronal change may enhance learning, little is known of the consequences of premature commitment of neurons to plastic changes prior to subsequent motor learning. One line of evidence shows that exposure to an enriched environment can positively alter behavior and the dendritic mor-
phology of cortical pyramidal neurons (Greenough and Chang, 1988). For example, housing animals in complex environments produces a global increase in dendritic length that is correlated with enhanced behavioral capacities on both motor and cognitive tasks. Environmental enrichment, however, can arm animals with a variety of sensory and motor skills that may in themselves enhance subsequent behavioral performance. Recent findings that psychostimulants can enhance dendritic length and synapse number in the absence of behavior experience (Robinson and Kolb, 1999) raises the question of what effect the prior commitment of neurons to plastic change has on the subsequent ability of an animal to learn. One possibility is that the availability of enhanced neuronal arbor could provide a substrate for enhanced behavioral modification. On the other hand, it is possible that the prior commitment of plastic capacity is disadvantageous. This second possibility is supported by evidence that prior exposure to amphetamine or cocaine blocks experience-dependent changes in dendritic arborization in animals placed in complex environments (Kolb et al., 2003). A more direct answer to the questions related to the effects of the prior commitment of neuronal plasticity requires an explicit examination of how prior drug-induced neuronal enhancement affects subsequent novel learning. This was the purpose of the present study.

Here we asked whether exposure to a psychomotor stimulant (nicotine) would alter the concurrent performance of a skilled motor task and affect the learning of a subsequently administered motor task. Furthermore, we asked if nicotine would change the pattern of dendritic changes normally associated with motor learning. Rats were trained for 3 weeks on a tray-reaching task where many little pieces of chicken feed were available before receiving a schedule of 12 days of saline or low-dose nicotine administration. Rats were tested once before the administration of nicotine and every other week after the first day of nicotine for a total of 7 weeks. At least 2 months following the completion of the drug administration schedule, the rats were given a novel motor task in which they were required to learn to use a forepaw to reach through a slot in a cage to retrieve a single food pellet located on an external shelf. At the completion of the behavioral tests, dendritic changes in both hemispheres were examined using Golgi-Cox analyses of the pyramidal cells of layer V of the forelimb area.

MATERIALS AND METHODS

Subjects

Subjects were 14 male Long-Evans hooded rats, 4 months old and weighing 300–400 g at the beginning of the experiment. Detailed kinematic analyses were performed on only 10 rats (5 per group) but the anatomical analyses were done on all rats. Animals were raised in the University of Lethbridge vivarium and were housed in groups of two individuals in clear Plexiglas cages. The colony room was maintained on a 12:12 h light/dark cycle (08:00–20:00 h) and the temperature regulated at 22°C. Experiments were conducted according to standards set by the Canadian Council on Animal Care and approved by the University of Lethbridge animal care committee.

Drug administration

All animals were taken away from the colony into a separate room for 20 min where they received one injection in the morning and one in the afternoon for a period of 12 days. Rats were injected subcutaneously with 0.9% saline (saline) or nicotine hydrogen tartrate salt (Sigma, St. Louis, MO) 0.3 mg/kg (nicotine).

Food restriction

One week before the behavioral testing began, the rats were changed to a restricted food intake: Each animal received 20 g of food per day (normal daily consumption ranges from 18–25 g) an hour after the testing session was completed. Their body weight was maintained at about 95–98% until the completion of the behavioral testing.

Tray reaching

Tray boxes were made of Plexiglas with dimensions 26 cm high, 28 cm deep, and 19 cm wide (Fig. 1). The front of the boxes was constructed of 2-mm bars separated from each other by a 9-mm gap. Clear Plexiglas tops allowed access to the inside of the box. A 4-cm-wide and 0.5-cm-deep tray was mounted in front of the bars. The tray contained fragments of chicken feed weighing approximately 30 mg each. Animals had to reach between the bars, grasp the food, and retract it where they were able to freely eat. If the rat made a reaching movement (forepaw inserted through the bars, but no food was grasped or the food was dropped), the movement was scored as a “reach,” whereas if the rat obtained the food and consumed it, the movement was scored as a “hit.” Success was calculated as follows:

\[ \text{Success percent} = \left( \frac{\text{hit} + \text{reach}}{\text{hit}} \right) \times 100 \]

Single pellet reaching

Reaching boxes were made of clear Plexiglas, with the dimensions 45 cm deep by 14 cm wide by 35 cm high (Fig. 2). In the center of each front wall was a 1-cm-wide slit which extended from 2 cm above the floor to a height of 15 cm. On the outside of the wall, in front of the slit, mounted 3 cm above the floor, was a 2-cm-wide shelf. Two indentations on the floor of the shelf were located 2 cm from the inside of the wall and were centered on the edges of the slit where rats could reach. Food pellets (45 mg dustless precision food pellets, Bioserve Inc.) were placed in the indentation contralateral to the limb with which...
the rat reached (Whishaw and Pellis, 1990). Following each reach, a short pause preceded the presentation of the next pellet. This encouraged animals to return to the back of the box after each reach, which forced them to reposition themselves and prepare for the next reach. Reaching performance was assessed on two measures: (1) Success on first reach: if a rat obtained the food pellet following the initial limb advance, this reach was scored as a hit. (2) Total success: if a rat obtained a piece of food either following the first limb advance or after a number of limb advances, the reach was counted as a hit. Success scores were computed as follows:

\[
\text{Success percent} = \left( \frac{\text{number of hits}}{\text{total given number of pellets}} \right) \times 100
\]

**Qualitative reaching analysis**

Reaching movements made during the single pellet task were analyzed using a rating scale derived from Eshkol-Wachmann Movement Notation (EWMN: Eshkol and Wachmann 1958; Whishaw et al., 1993) analysis of reaching. A reach was subdivided into ten components. (1) Limb lift: the limb is lifted from the floor with the upper arm and the digits adducted to the midline of the body. (2) Digits close: as the limb is lifted, the digits are semiflexed and the paw is supinated so that the palm faces the midline of the body. (3) Aim: using the upper arm, the elbow is adducted so that the forearm is aligned along the midline of the body, with the paw located just under the mouth. This movement involves fixation of the distal portion of the limb, so that digits remain aligned with the midline of
the body. This posture is likely produced by a movement around the elbow that reverses the direction of movement of the paw to compensate for the adduction of the elbow. (4) Advance: the head is lifted and the limb is advanced directly forward above and beyond the food pellet. (5) Digits open: as the limb is advanced, the digits are extended and opened. (6) Pronate: using a movement of the upper arm, the elbow is abducted, pronating the paw over the food. Full pronation of the paw onto the food is aided by a movement of the paw around the wrist. (7) Grasp: as the pads of the palm or the digits touch the food, the food is grasped by closure of the digits. This closure can occur as an independent movement, or the grasp can occur as the paw is withdrawn. (8) Supination I: as the limb is withdrawn, the paw is dorsiflexed and is supinated 90° by a movement around the wrist and by adduction of the elbow. These movements can occur as soon as the food is grasped or can occur as the limb is withdrawn. (9) Supination II: as the rat sits back with food held in the paw, the paw is further supinated by 90° and ventroflexed to present the food to the mouth. (10) Release: the digits are opened and the food transferred to the mouth.

Five successful reaches were analyzed frame by frame on the video tapes. Each movement was rated on a one-point scale. If the movement appeared normal, it was given a score of “1”; if it appeared slightly abnormal but recognizable, it was given a score of “0.5,” and a score of “1” was assigned if the movement was absent or completely unrecognizable.

**Video recording**

Video records were made using a Sony video 8 CCD-VII camcorder. Illumination for high-shutter speed filming was provided by a two-arm Nikon Inc. MII cold light source. Frame-by-frame analysis at 30 frames/s was produced by a Sony digital videocassette recorder DSR-11 or through a computer-based frame grabber.

**Golgi-Cox analysis**

Animals were given an overdose of sodium pentobarbital and intracardially perfused with 0.9% saline. The brains were removed and weighed before being immersed in a 20-ml Golgi-Cox solution where they remained for 14 days. The brains were then placed in a 30% sucrose solution for 2 days and cut on a vibratome at 200 μm and developed using a procedure described by Gibb and Kolb (1998). The basilar tree of layer V pyramidal cells within the forelimb motor cortex of both hemispheres were traced using a camera lucida at 200× magnification. Measures of dendritic length and dendritic branching were obtained from those drawings. To be included in the study, the dendritic trees had to be well impregnated and in full view, unblocked by blood vessels, astrocytes, or clustering of dendrites from other cells. They also had to appear intact and visible in the plane of section. Cell bodies of pyramidal neurons had to be located within the sensorimotor cortex (as defined by Zilles and Wree, 1995). For branch order analysis, each branch segment was counted and summarized according to the methods of Coleman and Riesen (1968): branches emerging from the cell body (basilar) were first order. After the first bifurcation, branches were considered second order, and so on. Quantification of each branch type using this method provides an indication of dendritic arbor complexity. To obtain an indirect measure of dendritic length, the Sholl analysis (Sholl, 1956) of ring intersections was used. The number of intersections of dendrites with a series of concentric circles at 20-μm intervals from the center of the cell body was counted for each cell. A reflection of total dendritic length (in μm) was determined by multiplying the number of intersections by 20. The mean of the measurements of five cells per hemisphere per rat was used for statistical analyses.

**Procedures and time-line**

The following training, treatment, and testing procedures were given to the animals:

1. Tray reaching: On day 0 and for the following 21 days, animals were placed in the tray reaching apparatus for one half an hour daily session. On the last day of training (day 21), their performance was video recorded for 5 min. Animals were then tested once a week for 7 weeks (day 70).
2. Nicotine or saline administration: On day 22 animals were divided into two groups; saline and nicotine. From that day and for a total of 12 days (day 34), animals received two daily subcutaneous injections of nicotine or saline as previously described.
3. Single pellet reaching: Starting on day 80, all rats were trained on the single pellet reaching task for a total of 7 days. On day 88 and for a total of 13 days, their performance on the task was recorded. On day 102, the performance of all animals was video recorded.
4. On day 110, all animals were perfused and the brains were collected and processed for Golgi-Cox staining.

**Statistical analysis**

Analyses of variance (ANOVA) were used for all measures and Fisher’s LSD (P < 0.05) was used for post hoc evaluations.

**RESULTS**

**Tray reaching**

All animals quickly learned to reach for food and asymptote at about 60% accuracy before starting the nicotine regimen. Nicotine-treated animals improved by 20% from the time measured before the drug admin-
istration to the last week of testing (Fig. 1). A repeated measures ANOVA showed no significant effect of group \((F(1,8) = 0.22, P = 0.64)\), a significant effect of testing by week as nicotine-treated animals steadily improved over the 7 weeks whereas the means of saline animals randomly fluctuated over this period \((F(4,8) = 6.22, P < 0.001)\) and a significant interaction of group by week \((F(4,8) = 9.16, P < 0.001)\).

**Single pellet reaching**

The animals learned to retrieve 20 pellets from the shelf within a few days and after a week their performance was recorded and analyzed for a total of 13 days. Two kinds of analyses were performed: (1) total success (sometimes animals have to perform more than one reaching movement before they retrieve the pellet successfully), and (2) success on first reach. Analyses showed marked impairments in animals that received nicotine and this impairment was greater when success on first reach was analyzed. A repeated measures ANOVA on the total success showed (Fig. 2) a significant effect of group \((F(1,8) = 8.45, P < 0.05)\), a significant effect of test day, \((F(12,8) = 2.28, P < 0.05)\), but no interaction \((F(12,8) = 0.84, P = 0.60)\). When success on first reach was analyzed, a repeated measures ANOVA showed (Fig. 2) a significant effect of group \((F(1,8) = 14.56, P < 0.01)\), a significant effect of test day, \((F(12,8) = 3.85, P < 0.001)\), but no significant interaction \((F(12,8) = 0.94, P = 0.50)\).

**Qualitative analysis of single pellet reaching**

The ten movement components of five successful reaches for the last day (day 13) were carefully examined frame by frame. The analysis showed that animals that received nicotine were severely impaired in most of the components of the reach. A repeated measures ANOVA showed a significant effect of group \((F(1,8) = 22.29, P < 0.01)\), element, \((F(9,8) = 11.6, P < 0.001)\), and a group by element interaction \((F(9,8) = 4.67, P < 0.001)\) (Fig. 3). Illustrations of the early and late components of the reach for both saline and nicotine groups are presented in Figures 4 and 5, respectively. Nicotine-treated animals were impaired in aiming, pronating, and supinating the paw and in releasing the pellet to the mouth. During the aiming, nicotine animals showed an exaggerated adduction of the elbow that did not align with the midline of the body (Fig. 4). The advance of the forelimb to the slot was usually short and thus the reach would be incomplete and unsuccessful in retrieving a pellet. When the nicotine rats successfully grasped the food, they displayed a partial supination I to withdraw the food through the slot, but then they did not completely supinate their forepaw (supination II) to present the food to the mouth (Fig. 5). Rather the paw dropped to the floor of the cage at which point the other paw and snout came in contact with the food pellet.

**Anatomical results**

**Gross anatomy**

**Brain weight.** When the brains were analyzed for weight with a simple ANOVA, a marginal increase was observed in the brains of animals that received nicotine although it did not reach significance: \((F(1,8) = 4.62, P = 0.063)\).

**Brain measurements.** Because of the strong trend in the nicotine group to have heavier brains, a closer examination was conducted by capturing digital images of mounted Golgi-Cox impregnated sections at standardized levels (6 different planes). The cross-sec-
tional area of the entire brain hemispheres was measured with the NIH IMAGE software, Ver.1.62. Animals that received nicotine had a 5% increase in hemispheric area. A repeated measures ANOVA showed a significant effect of group \((F(1,8) = 6.86, P < 0.05)\), a significant effect of plane \((F(5,8) = 458.1, P < 0.0001)\), but no significant interaction \((F(5,8) = 0.56, P = 0.72)\).

**Dendritic analyses**

The basilar tree of pyramidal cells of layer V in the forelimb area was analyzed for both hemispheres. Analyses of length and branching showed marked increases in the nicotine group (Fig. 6). In order to elucidate if training had an effect on the morphology of the cells contralateral to the preferred paw, independent analyses with the side of the hemisphere as a factor were included. Saline animals showed an effect of training as the length of the dendritic arbor of the cells contralateral to the preferred paw was enhanced relative to the ipsilateral arbors. Although there was a general increase in dendritic morphology in animals treated with nicotine, there was no differential effect of experience on the contralateral versus ipsilateral hemisphere in the nicotine-treated animals (Fig. 7).

A two-way ANOVA on dendritic length with drug treatment and hemisphere as factors showed a main effect of drug treatment \((F(1,24) = 19.41, P < 0.001)\), but not of training \((F(1,24) = 1.02, P = 0.32)\), nor the interaction \((F(1,24) = 3.29, P = 0.08)\). Similarly, a two-way ANOVA on dendritic branching showed a main effect of drug treatment \((F(1,24) = 4.80, P < 0.05)\), but not of training \((F(1,24) = 0.29, P = 0.59)\), nor the interaction \((F(1,24) = 1.45, P = 0.23)\). Although there was no main effect of training, inspection of Figure 7 suggests that training did have an effect. Thus, we elected to conduct further analysis on the trained and untrained hemispheres.

**Effects of training on dendritic morphology**

Figure 6 illustrates the effects of training on dendritic morphology and it shows that in saline animals, training enhanced dendritic length in the contralateral hemisphere.

**Saline animals**

The effects of training were studied in saline animals by comparing the contralateral versus the ipsilateral hemisphere.
hemisphere and a significant difference was found in dendritic length \((P < 0.05)\) by unpaired Student’s \(t\)-test) but not in dendritic branching \((P = 0.17)\). Dendritic arbors of the cells contralateral to the preferred paw for reaching were longer than the ones of the ipsilateral hemisphere.

**Nicotine-treated animals**

Training had no effect on dendritic length \((P = 0.68)\) by unpaired Student’s \(t\)-test) or branching \((P = 0.82)\). The size of the cells in the contralateral and ipsilateral hemisphere was therefore similar.

**Effects of nicotine are dependent on hemisphere**

Figure 7 illustrates the effects of nicotine on the hemispheres ipsilateral and contralateral to the preferred paw for reaching. Dendritic arborization was enhanced in both hemispheres. In saline animals, in contrast, dendritic arborization was only enhanced in the hemisphere contralateral to the reaching paw.

**Ipsilateral to the preferred paw**

The ipsilateral hemisphere was analyzed for effects of nicotine and a significant effect of group was found on dendritic length \((P < 0.001)\) by unpaired Student’s \(t\)-test) and branching \((P < 0.05)\).

**Contralateral to the preferred paw**

When the contralateral hemisphere was analyzed for effects of nicotine, no significant effect of group was found on dendritic length \((P = 0.10)\) by unpaired Student’s \(t\)-test) nor on dendritic branching \((P = 0.56)\).

**DISCUSSION**

Administration of nicotine can enhance performance on cognitive tasks (for a review see Rezvani and Levin, 2001) and motor tasks (for review see Heishman, 1999). The objective of the present study was to confirm that administration of nicotine can enhance motor skills in the rat and then to examine if prior exposure to nicotine also facilitates learning of new motor skills. Two skilled reaching tasks were used. Nicotine was administered after animals had acquired the first skilled reaching task, to examine its effects on asymptotic performance. Then, the animals were given the second skilled reaching task without further nicotine treatment, to assess the effects of pre-exposure on new motor learning. At the completion of behavioral testing, changes in dendritic morphology in motor cortex were assessed in Golgi-Cox stained tissue. Nicotine improved performance when given concurrently with training but impaired subsequent learning success and motor movements in the new motor task. The nicotine treatment enhanced dendritic branching and length of pyramidal cells in the motor cortex. It is proposed that premature commitment of plasticity induced by nicotine in the normal brain may interfere with subsequent acquisition of new motor learning.

The present experiment was designed to first confirm previous work demonstrating that nicotine can enhance motor performance and then to evaluate whether previous nicotine administration would affect novel motor learning. For the experiment, animals were pre-trained in a tray-reaching task and then were given low doses of nicotine and further reach training for two weeks. This aspect of the experiment evaluated the effects of nicotine on ongoing motor performance. Two months after the last injection of nicotine, animals were given a novel motor skill task in which they had to learn to reach for single food pellets. The second phase of the experiment evaluated the effect of prior exposure of nicotine on new motor skill learning. Thus, the experimental design assessed the potential effects of nicotine on motor performance as well as on new learning.

The two motor tasks, tray reaching task and the single pellet task, were chosen both because of their similarities and because they are widely used in the assessment of motor deficits on a variety of neurological disorders. In the tray-reaching task, a rat is trained to reach through bars to retrieve food from a tray at the front of the cage and performance is measured by the success of the animal to retrieve and, ultimately, consume food. The task is relatively simple because no special limb targeting is required. The single pellet-reaching requires a rat to make a targeted reach and is more difficult in that the rat must first locate the food pellet and then make an accurate reach in order to retrieve it. Both tasks provide an end-point measure of reaching success, but in addition they also allow examination of the movements used for reaching from frame-by-frame inspection of the video records. Because one of the goals of the present study was to examine the effects of prior exposure to nicotine on motor performance, the presentation of the tasks (e.g., tray reaching first and then single pellet) was thus chosen in order to assess the effects of nicotine on concurrent performance as well as subsequently administered new motor learning on a similar task. It was expected that any facilitation of performance in the tray-reaching task would generalize to the single pellet task (Vergara-Aragon et al., 2003).

The results obtained on the first phase of the experiments confirmed previous findings that nicotine can enhance motor performance if given concurrently with a motor task. Previous studies have shown that finger tapping rate and motor reaction time during tests of attention can be enhanced by nicotine (for review, see Heishman, 1999). A recent study investigating the effects of nicotine administration on a handwriting task has also shown that after chewing gum containing nicotine, subjects reduced movement times, increased velocities, and showed more fluent handwriting move-
ments (Tucha and Lange, 2004). In the present study, animals treated with nicotine improved in hit percent from asymptotic base line performance. Hit percent is a measure of success that is sensitive to many kinds of motor system injury (for a review, see Whishaw, 2000). Examination of the video records of reaching did not reveal any obvious differences in the way that the rats reached prior to and following nicotine administration. Thus, the first phase of the study confirmed that concurrent administration of nicotine can enhance motor success.

In contrast to the beneficial effect of concurrent administration of nicotine in facilitating tray reaching performance, the prior exposure to nicotine had a detrimental effect on the subsequent acquisition and performance of single pellet reaching. This finding is novel and was unexpected. What was especially surprising was that the animals displayed severe impairments not only in reaching success but also in the movements that they used. The movements that were most severely affected in the rats treated with nicotine were aiming, advancing, pronating, and supinating of the limb. Rather than aiming the limb, nicotine-treated rats advanced the limb diagonally through the slot making many short attempts; rather than fully pronating the paw they grasped the food with an incomplete rotation, and rather than supinating the paw to present the food to the mouth they dragged their limb through the slot and dropped the limb down to the floor of the cage. These impairments are reminiscent of those displayed by rats with motor cortex injury (Whishaw et al., 1986; Whishaw, 2000). Although the finding of impaired skilled movements induced by nicotine is novel, there is substantial evidence suggesting that extensive behavioral training can produce similar results. Extensive motor training in primates (Byl et al., 1996; Byl, 2004) or in humans (musicians, professional athletes, etc) can lead to dystonias, which are characterized by enlarged but unusual patterns of cortical organization (Elbert et al., 1998; Candia et al., 2003; for a review, see Nudo, 2003).

It is puzzling that nicotine would improve performance on a reaching task but disrupt the acquisition of a second one. It is unlikely that the order in which the tasks were given had anything to do with this result. It has been shown previously that previous training on the tray-reaching task enhances subsequent performance on the single-pellet reaching task (Vergara-Aragon et al., 2003). That was our expectation in the design of the experiment. Although both reaching tasks share similar components (e.g., reaching for food), they differ in some fundamental features (e.g., precision and finesse). Reaching in the single pellet task makes a greater demand upon rotatory movements of the limb than does tray reaching, and it appeared that it was upon these aspects of reaching that prior exposure to nicotine had the most detrimental effect. Unfortunately, the design of the experiment did not allow us to distinguish between prior training combined with nicotine versus nicotine alone, and this will be the subject of further studies.

One possible explanation for the detrimental effects of nicotine on the acquisition of a novel skilled motor task is that nicotine changed the dendritic structure of motor cortex neurons. The finding that nicotine produced changes in dendritic arbor confirms previous studies that show that chronic administration of nicotine leads to increases in dendritic arborization and spine density in the nucleus accumbens and prefrontal cortex (Brown and Kolb, 2001). Although neuronal plasticity is usually associated with enhanced functional outcome, some studies have shown that it could be associated with pathological changes (Fiala et al., 2002; Purpura, 1974). In the present study, animals treated with nicotine showed an overall increase in dendritic arborization in the motor cortex but did not show an increase in the hemisphere contralateral to the preferred paw for reaching relative to the ipsilateral hemisphere. It is thus possible to propose that enhancement in dendritic arborization by nicotine, or combined nicotine and skilled training, used up or blocked the experience-dependent plasticity required for new motor learning (Greenough et al., 1985; Withers and Greenough, 1989; Rioult-Pedotti et al., 1998; Kleim et al., 1998; Plautz et al., 2000).

One prediction derived from the finding that nicotine had no effect if given after the animals had learned a skilled motor task but impaired the acquisition of a new one would be that there is a limit to neuronal plasticity and once this limit is reached, further behavioral modifications become difficult. That is, because nicotine stimulated dendritic arborization, there was little room for further dendritic changes for acquiring a new task. The idea that saturation of plastic processes systems can follow behavioral training has been addressed by Rioult-Pedotti and colleagues (2000). They have shown that learning-induced enhancement can place limits on further synaptic potentiation. Training animals on a skilled reaching task markedly reduced long-term potentiation, which led authors to suggest that synapses in the motor cortex of a trained animal were near the ceiling of their modification range. These findings present an immediate puzzle as discussed by Martin and Morris (2001). If the learning of one skill uses up almost all of the available capacity for synaptic enhancement, how can additional skills ever be learned? It is possible that exposing subjects to nicotine expends plasticity without allowing for pruning that may be associated with new learning. In this respect, the loss of motor skill associated with aging, which is itself associated with enhanced dendritic growth, may be similar to the acute effects of nicotine.

In conclusion, it is surprising given the popular notion that nicotine has negative impacts on athletic abil-
ity that there have been no studies of the effects of nicotine on subsequently acquired motor ability. In the present study, it was found that nicotine treatment could improve performance when administered concurrently with training but nevertheless could impair subsequent skill acquisition. Because the animals displayed increased branching of motor cortex pyramidal cell dendrites, it is proposed that nicotine may saturate dendritic plasticity thus reducing motor cortex function. Future work will be required to determine the extent to which nicotine alone or nicotine in conjunction with motor performance is associated with reduced motor skill.

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