Published in final edited form as:

Behav Brain Res. 2019 July 23; 367: 176–180. doi:10.1016/j.bbr.2019.04.007.

Perinatal nicotine exposure impairs learning of a skilled forelimb reaching task in male but not female adult mice

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Abstract

Developmental tobacco or nicotine exposure is associated with various adverse outcomes in human and preclinical studies, respectively. For example, perinatal nicotine exposure in mice causes morphologic changes in neurons across sensory and motor cortices and results in impairments in sensory learning. However, the effects of developmental nicotine exposure on motor learning have not been reported. To determine whether nicotine-induced changes in behavior extend to motor tasks, we provided female C57Bl/6 dams with nicotine drinking water (200 µg/ml in 2% saccharin), or vehicle (2% saccharin), a standard paradigm to expose pups to nicotine *in utero* and postnatally through lactation. Male and female pups were subsequently tested in adulthood in a single-pellet reaching task with millet seeds, and also tested for gross motor function and feeding behavior. We found that male, but not female, mice exposed to nicotine throughout early development demonstrated impaired learning of single-seed reaching. Nicotine-treated animals did not differ from control animals in gross motor performance or millet seed intake, although female mice consumed more millet seeds than male mice when reaching was not required. These studies show that nicotine exposure during development can impair behavior in a skilled motor task that depends on cortical synaptic plasticity, and that this effect is sex-dependent.

Keywords

Nicotine; prenatal; perinatal; motor learning; sex differences

Maternal smoking during pregnancy is associated with premature birth, attention-deficit hyperactivity disorder and other adverse outcomes [1,2]. Despite this, 7.2% of US women overall report smoking tobacco during pregnancy, with rates as high as 16-25% in West Virginia, Kentucky, and Montana [3]. Further, the recent rise of nicotine exposure through vaping is likely to increase developmental nicotine exposure.

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DECLARATION OF INTERESTS

None.

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Nicotine is the major psychoactive component in tobacco and likely contributes to adverse outcomes of maternal smoking. In rodents, developmental nicotine exposure produces many of the same consequences observed in humans, including abnormal sensory processing [4–8]. Developmental nicotine exposure also increases spine density and dendritic complexity in neurons throughout the cortex [5].

While developmental nicotine affects both aversive [4–6,8] and appetitive [7] sensory learning, the accompanying neuronal changes are observed in both sensory and motor regions [5]. Therefore, nicotine-induced changes in morphology could alter motor cortex-dependent behaviors as well. We thus tested adult mice perinatally exposed to nicotine or vehicle with a single-pellet (millet seed) reaching task [9,10], which depends on motor cortex synaptic plasticity [11].

Nicotine was delivered to pregnant dams in drinking water to minimize the stress of repeated handling and provide diurnal variation in intake, as occurs in human smokers. Pregnant C57BL/6 mice (Charles River Laboratories) were obtained at E12–E15, and provided with either 0.2% tartaric acid (Sigma-Aldrich, St. Louis, MO) in 2% saccharin (Sacc) or nicotine bitartrate (200 µg/mL nicotine free base; NIDA) in 2% saccharin (Nic) from E12–E15 until pups were weaned at P21 (3–5 litters/experimental group). This method of nicotine delivery significantly increases plasma cotinine levels in dams and pups, and causes persistent neurodevelopmental and behavioral alterations in offspring without affecting maternal body weight, maternal care, or postnatal mortality [12–14]. Nicotine exposure in the postnatal period alone induces sensory learning [4], morphological and molecular changes [5]. Importantly, the effects of postnatal nicotine (E14–P21) on aversive sensory learning and cortical neuron dendritic morphology were attenuated by blocking a nicotine-dependent epigenetic pathway in sensory cortex at E14 [5]. After P21, pups were given normal chow and drinking water *ad libitum* until behavioral testing (males: 13–18 weeks old, females: 15–23 weeks). All procedures were approved by the Yale University Institutional Animal Care and Use Committee and conformed to the NIH Guide for Care and Use of Laboratory Animals.

Mice were handled for 3 days and food restriction to 85% baseline weight started on day 2. Mice were weighed and fed daily ~3 hours after shaping or training. Shaping (7 days) and training (8 days) [9] were performed in a Plexiglas chamber 38.5×18.5×21.5 cm with a 0.5 cm- wide vertical slit for reaching. During shaping, mice reached for a tray of millet seeds, and progressed after demonstrating 20 reaches, 70% with the same paw; mice failing to reach criteria by day 7 were excluded (4/12 male Sacc, 4/9 male Nic, 2/15 female Sacc, and 5/15 female Nic mice). There were no significant differences by sex, treatment group, or an interaction effect (F 's < 0.7, p 's > 0.4) in shaping days to reach criteria. Next (8 days), mice reached to grasp a single millet seed. Mice were allowed 20 minutes or 50 reaching attempts with the dominant forepaw. If within the first two training days a mouse demonstrated preference for the opposite forepaw, scoring was adjusted to accommodate the new preference (1 animal per group). Successful (reached, grabbed seed with forepaw, delivered seed to mouth), failed (reached, did not touch seed), dropped (reached, grabbed seed, failed to deliver to mouth), and in-vain (reached when no seed) reaches were recorded.

A subset of mice was subsequently tested for millet seed consumption without reaching (unskilled), and gross motor coordination and strength. Each animal was placed in the chamber with 20 dispersed millet seeds for 20 minutes (seeds consumed and seeds consumed/minute recorded). The next day, a seed was placed through the slit every 20 seconds (30 seeds over 10.5 minutes). The following two days, mice were tested using the horizontal bar test [15] and the weights test [16].

For single-seed reaching, performance was quantified for the preferred forepaw as (1) success rate = successful/(successful + failed + dropped) reaches, (2) success speed = successful reaches/total time, and (3) in-vain rate = in-vain/(successful + failed + dropped) reaches [9]. Each measure was analyzed with a 3-way mixed ANOVA using sex (male, female) and developmental exposure (Sacc, Nic) as between-subjects factors and training day (days 1-8) as a within-subjects factor. Significant 3-way interactions were followed by 2-way mixed ANOVAs within sex using developmental exposure and training day as factors. Sphericity was not assumed and the Geisser-Greenhouse correction was applied. Significant 2-way interactions within sex were followed by Sidak's multiple comparisons tests of nicotine vs. saccharin groups on each training day. Significant main effects of developmental exposure and training day were followed by unpaired two-tailed t-tests, and Tukey's multiple comparison tests, respectively. Data for gross motor and food intake tests were analyzed by 2-way ANOVA, with sex and developmental treatment as between-subjects factors. Analyses were conducted with GraphPad Prism version 8.0 (GraphPad Software, Inc., La Jolla, CA). Significance was assumed at $p < 0.05$.

Results showed that perinatal nicotine exposure impaired learning of a single-seed reaching task in male but not female mice. For success rate, there were significant training day x sex ($F_{(7, 224)} = 2.30, p = 0.028$) and 3-way sex x developmental exposure x training day ($F_{(7, 224)} = 3.84, p = 0.0006$) interactions. Subsequent 2-way ANOVAs within sex showed a significant effect of developmental exposure ($F_{(1, 11)} = 5.56, p = 0.038$) in males, where nicotine-treated mice had lower success rates ($t_{(14)} = 6.78, p < 0.0001$; Fig. 1A). In females, there was a significant interaction ($F_{(7, 147)} = 3.94, p = 0.0006$), and a significant effect of day ($F_{(3.68, 77.18)} = 3.62, p = 0.011$; Fig. 1B). However, Sidak's multiple comparisons test showed no significant differences between developmental treatment groups on any training day (p 's > 0.40). For success speed, there was also a significant 3-way interaction ($F_{(7, 224)} = 3.26, p = 0.0026$). Subsequently, a 2-way ANOVA in males showed a significant effect of developmental treatment ($F_{(1, 11)} = 7.88, p = 0.017$), where nicotine-treated male mice had lower success speeds ($t_{(14)} = 4.42, p = 0.0006$; Fig. 1C). A 2-way ANOVA in females showed only a significant main effect of training day ($F_{(3.28, 67.55)} = 11.23, p < 0.0001$; Fig. 1D). Tukey's multiple comparisons tests on data collapsed across developmental exposures in females showed significant differences between training day 1 and days 5 ($p = 0.048$), 6 ($p = 0.022$), 7 ($p = 0.0071$) and 8 ($p = 0.0015$), day 2 and days 4 ($p = 0.029$), 5 ($p = 0.012$), 6 ($p = 0.020$), 7 ($p = 0.0041$), and 8 ($p = 0.0011$) and day 3 and 8 ($p = 0.028$), indicating increased success speeds in the second half of the training period.

In-vain responding decreased over training days ($F_{(4.04, 129.1)} = 7.94, p < 0.0001$), but did not differ by developmental treatment or sex (Fig. 1E,F). Tukey's multiple comparisons tests on data collapsed across sex and developmental exposure indicated significant differences

between day 1 and days 4 ($p = 0.0059$), 5 ($p = 0.011$), 6 ($p = 0.0006$), 7 ($p = 0.0039$), and 8 ($p = 0.0006$), and day 2 and 4 ($p = 0.018$).

Developmental treatment did not affect unskilled millet seed consumption or gross motor function. There were no significant differences by treatment, sex, or an interaction effect in a 2-way ANOVA on number of seeds consumed out of 20 distributed around the chamber (Fig. 2A). In the speed of consuming these seeds, there was a significant sex difference ($F_{(1,20)} = 38.1$, $p < 0.0001$; Fig. 2B), such that females were faster. There was also a strong trend for a sex difference in the number of seeds consumed when they were presented through the slit at a fixed interval rate ($F_{(1,20)} = 4.32$, $p = 0.051$; Fig. 2C). Importantly, there were no effects of developmental treatment or interaction effects in any measure (F 's < 0.9 , p 's > 0.3). There were no significant differences by treatment, sex, or an interaction effect on the weights test (F 's $p < 1.5$, p 's > 0.2 ; Fig. 2D). In the horizontal bars test, all mice achieved maximum scores on all bars (2mm, 4mm, and 6mm; data not shown).

Our results demonstrate that male mice with perinatal nicotine exposure achieve less successful and slower reward retrieval in a skilled motor learning task than control, saccharin-treated mice (Fig. 1 A,C). Female mice were able to learn the task, as demonstrated by increases in success rate and speed over training days, but developmental exposure had no significant effects (Fig. 1B,D).

Nicotine and saccharin-exposed males start the training period with similar success rates and speeds, but diverge as training progresses. Saccharin-exposed mice learn the proper sequence of gestures necessary to execute a successful reach [10] maintaining a high success rate and increasing in speed as this learned strategy becomes more efficient. In comparison, the decreasing success rate in nicotine-exposed mice may reflect "learned bad-use", where mice use an inefficient reaching strategy but achieve the occasional success, which forms a variable ratio reinforcement schedule that perpetuates this "bad-use" [17]. In saccharin-treated males, the increased speed but not success rate may reflect "over-shaping" such that mice begin training with high success rates that do not significantly improve [9]. However, the increases in speed demonstrate motor learning. Interestingly, female mice do not start training with a high success rate, and both success rate and speed increase for both developmental treatment groups. Female mice also seem not to reach as high a success rate or speed as saccharin-exposed male mice, although this difference is not statistically significant. Additional experiments could test whether more training would allow female mice to reach similar success rates and speeds as saccharin-exposed male mice.

A greater proportion of nicotine- vs. saccharin-exposed mice (44% vs. 33% in male, 33% vs. 13% in female) failed to progress to training by making fewer than 20 reaches or less than 70% of reaches with a preferred forepaw during shaping. Developmental nicotine can increase latency to feed in a novelty-suppressed feeding test, although only in male mice [12]. This may suggest that nicotine exposure increased anxiety in the novel testing environment, reducing reaching and causing failure to make 20 reaches. Unskilled millet seed consumption was likely unaffected because it was measured after prolonged exposure to the testing chamber (Figure 2). It is unclear how nicotine exposure might cause failure to demonstrate paw preference during shaping, although reaches made with the non-dominant

paw could be considered aberrant gestures interfering with the successful sequence of gestures, similar to “learned bad-use” [17].

Several other factors may have contributed to the impaired performance of nicotine-exposed male mice. For example, developmental nicotine exposure may have affected consummatory behavior rather than motor learning. However, unskilled millet seed consumption was unaffected in either sex, suggesting that nicotine-induced reaching impairments could not be explained by deficits in motivation to consume seeds (Fig. 2A-C). Female mice did consume more seeds more quickly in these tests (Fig. 2B), consistent with studies showing higher food consumption in female C57Bl/6 mice, despite lower body weight [18]. Importantly, there was no effect of developmental treatment. Additionally, developmental treatment did not affect performance in the weights test (Fig. 2D) and horizontal bar test, suggesting that nonspecific motor deficits in strength or coordination did not contribute. Rats and mice use olfaction to locate food [10], and although we did not test olfaction, developmental nicotine exposure did not impair mice in locating and consuming millet seeds distributed throughout the chamber (Fig. 2A,B). Together, these data suggest that perinatal nicotine exposure impaired learning of single-pellet reaching due to features specific to this task.

The single-pellet reaching task depends on plasticity in the primary motor cortex of rodents [11,19]. Developmental nicotine exposure increases synaptic density and dendritic complexity across cortical regions [5], so we hypothesized that dendritic rearrangement might alter learning in this motor task. Increased synaptogenesis or dendritic branching does not necessarily mean better motor learning [17]. Further, developmental nicotine exposure can alter nicotinic signaling in corticothalamic circuits, with significant behavioral consequences in adulthood [4]. In adult rats, lesioning cholinergic projections to sensorimotor cortex impaired not only learning of single-pellet reaching, but also the cortical plasticity on which this behavior depends, without affecting overall sensorimotor function [19]. In contrast, nicotine in adult rats improved single-pellet reaching and increased dendritic complexity when administered chronically after a stroke [20]. These studies suggest that developmental nicotine alters signaling and synaptic plasticity in motor cortex such that learning a skilled reaching task, which depends on proper cholinergic signaling, is impaired in adulthood.

The observed sex difference in single-seed reaching is consistent with previous studies showing more pronounced effects of prenatal nicotine exposure in male offspring on hyperactivity [14], emotional and social behaviors [12], and cortical cholinergic and serotonergic function [21] in rodents, and audiovisual attention and visuospatial learning in human adolescents [22], although others have found no sex differences [5,23], or stronger effects in female offspring [24]. Our results extend existing literature by demonstrating sex-dependent effects on a learning task dependent on plasticity in a primary somatosensory cortex, rather than emotional or locomotor behaviors.

A limitation to the current study is that although single-pellet reaching depends on cortical plasticity, this was not measured directly. The observed sex differences in behavior may be reflected in the functional reorganization of the motor cortex [11]. Alternatively, developmental nicotine may differentially alter compensatory systems to produce divergent

behaviors [17]. Furthermore, we did not test whether additional training or manipulations would enhance motor learning in saccharin- and/or nicotine-exposed mice. For example, chronic nicotine injections in adulthood may enhance motor learning [20], but disruptions to the cholinergic system caused by developmental nicotine exposure may preclude such enhancements [6]. Finally, our study only tested adult mice, whereas developmental nicotine induced hypersensitive passive avoidance learning in adulthood [4] and at P22-P24 [5]. We may similarly see skilled motor learning impairments after weaning. Interestingly, aged mice (18-20 months old) learned a skilled reaching task as well as young mice (3-5 months old), but lacked the typical motor cortex functional reorganization [25]. Thus it would be interesting to investigate how developmental nicotine exposure interacts with age and sex in the single-pellet reaching task.

In conclusion, our study demonstrates that developmental nicotine exposure impairs skilled motor learning in male but not female mice, without affecting general consummatory behavior or gross motor function. These results add to the body of literature demonstrating persistent and sex-specific effects of developmental nicotine exposure on learning in adulthood, and provides novel evidence for a nicotine-induced deficit in a motor task that depends on cortical plasticity.

ACKNOWLEDGEMENTS

This work was supported by the National Institute on Drug Abuse at the National Institutes of Health (F30 DA043943 to A.M.L and DA14241 to M.R.P.) and the National Institutes of Health Medical Scientist Training Program Training Grant (T32 GM007205 to A.M.L.).

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Highlights

- Perinatal nicotine exposure impairs single-pellet reaching in male but not female mice
- Overall consummatory behavior and gross motor function are not affected
- Results link known cortical morphology changes to altered cortex-dependent behavior

Fig. 1.

Perinatal nicotine exposure impairs learning in the single-pellet reaching task in male but not female mice. In male mice, (A) success rate and (C) success speed are significantly decreased in Nic ($n = 5$) vs Sacc ($n = 8$) groups. In female mice, Nic ($n = 10$) vs Sacc ($n = 13$) did not affect (B) success rate or (D) success speed. (E,F) In-vain rates significantly decreased over training days across treatment groups and sex. Graphs show mean $\pm$ SEM. * $p < 0.05$.

Fig. 2.

Unskilled millet seed intake and gross motor function were not affected by perinatal nicotine exposure. When 20 millet seeds were distributed around the chamber, perinatal exposure did not affect (A) total seeds consumed or (B) seeds consumed per minute, but there was a significant effect of sex on seeds consumed per minute. Similarly, perinatal treatment did not affect (C) number of millet seeds consumed when delivered through the slit at fixed intervals, but there was a near-significant effect of sex ($p = 0.051$). (D) Neither sex nor developmental treatment affected performance on the weights test. Graphs show mean $\pm$ SEM and individual data points (Male Sacc $n = 7$, Male Nic $n = 3$, Female Sacc $n = 8$, Female Nic $n = 6$). * $p < 0.05$.