Original Investigation

Nicotine Self-administration Is Not Increased in the Methylazoxymethanol Acetate Rodent Model of Schizophrenia

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Abstract

Introduction: Patients with schizophrenia (SCZ) smoke at a rate of 4–5 times higher than the general population, contributing to negative health consequences in this group. One possible explanation for this increased smoking is that individuals with SCZ find nicotine (NIC) more reinforcing. However, data supporting this possibility are limited.

Methods: The present experiments examined self-administration of NIC, alone or in combination with other reinforcers, across a range of doses in the methylazoxymethanol acetate (MAM) rodent model of SCZ.

Results: MAM and control animals did not differ in NIC self-administration across a range of doses and schedules of reinforcement, in both standard 1-hour self-administration sessions and 23-hour extended access sessions. However, MAM animals responded less for sucrose or reinforcing visual stimuli alone or when paired with NIC.

Conclusions: To the extent that MAM-treated rats are a valid model of SCZ, these results suggest that increased NIC reinforcement does not account for increased smoking in SCZ patients.

Implications: This study is the first to utilize nicotine self-administration, the gold standard for studying nicotine reinforcement, in the methylazoxymethanol acetate model of schizophrenia, which is arguably the most comprehensive animal model of the disease currently available. Our assessment found no evidence of increased nicotine reinforcement in methylazoxymethanol acetate animals, suggesting that increased reinforcement may not perpetuate increased smoking in schizophrenia patients.

Introduction

Despite success in reducing tobacco use in the general population over the last several decades, rates of smoking remain highly elevated among those with schizophrenia (SCZ). An estimated 60%–80% of SCZ patients are smokers, as compared with 15%–20% of the general US population.^{1,2} Smokers with SCZ smoke more heavily and more intensely, which contributes to negative health consequences in this population. Though this pattern of heavy smoking in smokers with

SCZ is well-documented, no mechanistic explanation has yet been established. Two potential, but not mutually exclusive, hypotheses are that (1) nicotine (NIC), the primary reinforcing component of tobacco, mitigates some negative cognitive and/or sensory symptoms of SCZ, with smoking serving as a form of “self-medication”, or (2) SCZ confers an increased magnitude of reinforcement derived from NIC.

Numerous clinical studies indicate that NIC administration to SCZ patients fails to impact positive psychotic symptoms but may

be associated with improvements in cognitive deficits and negative symptom severity, contributing to the “self-medication” hypothesis.^{3,4} For example, one study found that both current and former smokers with SCZ showed higher performance in a neuropsychological assessment than SCZ “never-smokers,” while control subjects did not vary by smoking history.⁵ However, evidence of improvement in negative symptoms and cognitive deficits, as well as alleviation of side effects from antipsychotic drugs, remains mixed. Conclusive study on the effects of NIC in SCZ patients is complicated by several factors including differences in the withdrawal status and antipsychotic drug history of patients at the time of study. Many, but not all, studies require short-term or overnight abstinence before participation, which may contribute to variability in findings on the effect of NIC on cognitive function. For example, smoking after acute abstinence has been demonstrated to improve visuospatial working memory performance among SCZ patients.^{6,7} However, other research suggests that the cognitive “costs” of NIC withdrawal and the relative benefits of NIC consumption are not specific to a psychiatric population. A study by AhnAllen et al.⁸ found that in both control and SCZ smokers, switching to very low NIC content cigarettes reduced performance on measures of smokers’ attention and visual processing, an effect mitigated by coadministration of NIC patch. Other studies report no effects of early (1 day) or extended (3 weeks) NIC abstinence on attention or cognitive and behavioral tests in SCZ patients,^{9,10} suggesting NIC withdrawal may not have any effect on cognitive performance. Thus, while a “self-medication” hypothesis of smoking in SCZ is quite pervasive, experimental findings supporting this idea are limited.

Several lines of biological and behavioral evidence lend support to the hypothesis that NIC reinforcement is increased in SCZ individuals. The current dopamine hypothesis of SCZ posits that alterations in dopamine function lead to impairments in appropriately ascribing salience to relevant stimuli, which in turn contributes to dysfunction in motivated behavior and value learning.^{11–13} NIC-stimulated dopamine responses are thought to be increased in the mesolimbic dopamine system in SCZ, resulting in increased NIC reinforcement.^{14,15} Additionally, smokers with SCZ place higher incentive valuation on cigarettes than controls and are twice as likely to select smoking over alternative reinforcers, such as money or candy, suggesting a particular sensitivity to smoking reinforcement.^{16,17} Limited impulse control may also drive persistent smoking among SCZ patients by undermining attempts to abstain from reinforced smoking behavior.¹⁸

In addition to the broad range of clinical studies on smoking in SCZ subjects, preclinical work provides a valuable source of highly controlled research on the effects of NIC in SCZ and can address questions that cannot be approached in human subjects. Though evidence suggests some effect of acute NIC on cognitive performance in control animals,^{19,20} studies using animal models of SCZ have demonstrated limited support for increased cognitive or reinforcing effects of NIC in SCZ. For example, a study using the maternal immune activation model of SCZ found that maternal immune activation animals showed modest improvements in a working memory task after extended NIC self-administration. However, maternal immune activation animals did not differ in self-administration from controls, except at a single dose with a high response requirement.²¹ A study by Berg et al.²² using the neonatal ventral hippocampal lesion (NVHL) model of SCZ found that lesioned animals self-administer more NIC than controls only at a moderate dose of NIC. These limited positive results are complicated by the inclusion of

daily subcutaneous injections of saline or NIC during the adolescent period. NVHL rats are particularly vulnerable to stress²³ and stress associated with these injections might have differentially impacted NVHL and control rats.²²

Thus, the data on whether NIC reinforcement is increased in animal models of SCZ are limited and unclear. The present studies examined NIC self-administration, the gold standard in studies of NIC reinforcement,²⁴ in the model of SCZ produced by prenatal administration of methylazoxymethanol acetate (MAM), which is arguably the most comprehensive available rodent model of SCZ.²⁵ The MAM model recapitulates many core features observed in SCZ and, compared to other rodent models of SCZ, consistently shows a high degree of both construct and predictive validity.^{25,26} Importantly, MAM treatment on gestational day 17 (GD17) has been consistently validated in numerous carefully controlled experiments both within and between labs.^{25–29} Adult MAM animals demonstrate physiological, pharmacological, behavioral, and anatomical perturbations consistent with observed SCZ phenotypes including amphetamine and phencyclidine hyper-responsivity, disrupted prepulse inhibition of startle and latent inhibition, thinning of cortical limbic structures, selective loss of parvalbumin-labeled GABAergic interneurons of the hippocampus, and hippocampal hyperactivity, as well as resulting increased dopamine population activity.^{25,29} Because of the critical role of dopamine neurophysiology in reward and reinforcement, as well as the high construct and predictive validity of this model, the MAM model is a strong yet previously unexplored paradigm to study questions of NIC reinforcement.

The following experiments thus sought to characterize NIC reinforcement in the MAM model of SCZ. Importantly, we aimed to study the primary reinforcing effects of NIC alone and in combination with its reinforcement-enhancing effects on other rewards. Although we hypothesized that MAM-treated rats would self-administer more NIC than control rats, the results show that in this model of SCZ there is no difference in NIC self-administration across a variety of doses and schedules of reinforcement, suggesting that SCZ pathophysiology modeled by MAM does not produce increased NIC reinforcement.

Methods

Subjects

All experiments utilized Sprague-Dawley rats aged postnatal day (P)65–P75 at the start of experimental sessions. Rats were born in-house to timed pregnant dams (Envigo) injected intraperitoneally with saline (CTL; 1.0 mL/kg) or MAM (25.0 mg/kg, 1.0 mL/kg) on GD17.^{25,28} After weaning on P22, litters were mixed, and pups were separated by treatment group and sex. Initial studies were performed in female animals as males were used for separate sex-dependent experiments, but subsequent experiments used both males and females to examine potential sex differences (experiment 3). Animals were housed in groups of 2–3 in tub cages with woodchip bedding in a ventilated rack until the time of surgery (P60–P70), after which they were housed individually. Each experiment utilized pups from at least two MAM-treated (MAM) and two saline-treated (CTL) litters and common features of the MAM phenotype (cortical thinning, reduced hippocampal volume²⁵) were confirmed in adult littermates through postmortem histological assessment. Additionally, some adult littermates were used in electrophysiological experiments and displayed characteristic increases in dopamine neuron population activity.²⁹ Animals had ad libitum access to water in the home cage throughout the duration of

the experiment and began food restriction at least 48 hours before the first experimental session unless otherwise noted. Rats were allotted 20 g (males) or 15 g (females) of chow (LabDiet Rodent 5001; LabDiet, St. Louis, MO) daily to maintain body weight at approximately 80% of free-feeding weight. Facilities were maintained on a reversed 12-hour light-dark cycle (lights-off 0700), and all experimental procedures were carried out during the dark phase. All experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the University of Pittsburgh Institutional Animal Care and Use Committee.

Apparatus

All experimental sessions were conducted in 38 operant chambers (30.5 cm × 24.1 cm × 21.0 cm; ENV-008CT; Med-Associates, Fairfax, VT) enclosed in sound-attenuating cubicles with a ventilation fan. Operant chambers were outfitted with two nose-poke holes (2.5 cm in diameter), spaced 14 cm apart. White cue lights (3.5 cm in diameter) were located 6.25 cm above the top of each nose-poke portal. A houselight located 1 cm below the ceiling of the chamber in the center of the wall containing the nose-poke portals was covered with a red filter sleeve except in experiments using a reinforcing visual stimulus (VS; see experiment 3). Intravenous (i.v.) infusions were delivered via an infusion pump through tubing connected to each animal's catheter. Tubing was protected by a flexible metal spring casing connected to a swivel system that allowed for largely unrestricted movement.

Nicotine

Nicotine hydrogen tartrate salt (MP Pharmaceuticals, Solon, OH) was dissolved in 0.9% sterile saline and passed through a 0.22 μ M filter to ensure sterility. NIC solutions were made every 2–4 weeks and stored at 4°C until experimental use. Syringes for self-administration sessions were freshly made each day. Doses are expressed as free base.

Surgery and Maintenance of Catheter Patency

Surgery was performed between P60 and P70. Rats were anesthetized using isoflurane (2%–3% in 100% O₂) and implanted with indwelling catheters into the right jugular vein.³⁰ Ports were capped with plastic tubing and flushed daily with 0.1 mL heparinized (30 U/mL) saline containing streptokinase (9.333 U/mL) and gentamicin (66.67 mg/mL) for 5–6 days of recovery before self-administration. During the experimental period, catheters were flushed with 0.1 mL heparinized saline before and 0.1 mL heparinized saline with gentamicin (66.67 mg/mL) after each self-administration session. Catheter patency was confirmed via rapid loss of muscle tone after infusion of methohexital (5 mg/kg) following the final self-administration session at each dose and the final self-administration session of each experiment. Rats that failed a patency test (1–4 rats per experiment) were excluded from data analysis.

Self-administration Sessions

Self-administration sessions took place for 1 hour daily within the first several hours of the dark cycle (except where otherwise noted). One nose-poke portal was assigned as active and resulted in the delivery of an i.v. infusion in approximately 1 second at a volume of 0.1 mL/kg after meeting the fixed ratio (FR) response requirement, followed by a 60 second timeout period during which responses were recorded but not reinforced.³¹ As noted in each experiment, infusions

were paired with either a neutral cue (10-second illumination of the cue light above the active nose-poke) or a reinforcing VS (1-second illumination of cue light, followed by 1-minute extinction of house light and cue light). Prior studies have consistently demonstrated that rats will respond for the VS when presented alone, and this responding is enhanced by NIC.³² Conversely, rats do not respond to the 10-second illumination of the cue light alone,³³ demonstrating that it is not inherently reinforcing. It can, however, become a conditioned reinforcer when associated consistently with an unconditioned reinforcer, including long-term pairing with high doses of NIC.³⁴ Infusion delivery was adjusted daily for body weight. Responses at the second, inactive nose-poke portal were recorded but had no consequence. Left and right nose-poke portals were randomly assigned as active and inactive. In applicable experiments, criteria for acquisition of NIC self-administration on an FR2 schedule were an average of five or more earned infusions over a 3-day period and twice as many active responses as inactive per session during that period.

Experiments

Experiment 1: Primary Reinforcing Effects of NIC in MAM and CTL Animals

To assess primary NIC reinforcement in MAM ($n = 22$; 4 litters) and CTL ($n = 17$; 4 litters) animals, female rats were allowed to respond for infusions of NIC paired with a neutral cue (10-second illumination of cue light above active nose-poke). Rats were allowed to respond for 60 μ g/kg/infusion on an FR2 schedule for 10 days. The schedule was then changed to FR5, and NIC dose was reduced every 5 days (60, 15, 7.5, 3.75 μ g/kg/infusion).³¹

Experiment 2: Responding for NIC in Extended Access Sessions

One-hour self-administration sessions may fail to capture differences in behavior that may emerge over an extended period of access to NIC, as well as potential changes in self-administration over the light-dark cycle as a result of MAM administration. To examine differences in NIC intake within extended access sessions and patterns of NIC-taking across the light-dark cycle, female MAM ($n = 8$; 2 litters) and CTL ($n = 6$; 2 litters) animals were allowed to self-administer NIC (30 μ g/kg/infusion) in 23-hr self-administration sessions (11 hour lights-off, 12-hour lights-on) through nose-poke responding on a FR2 schedule. Animals were not food restricted and had ad libitum access to water and to chow pellets on an FR1 schedule via responding at a single lever on the wall opposite the nose-pokes. Animals were returned to tub cages for one hour during the dark phase each day (1000–1100 hours) for cleaning of operant chambers.

Experiment 3: Dual-Reinforcing Effects of NIC in MAM and CTL Animals

NIC acts as a primary reinforcer on its own and potently enhances the reinforcing value of other rewards.³² Indeed, nonpharmacological stimuli accompanying NIC play a critical role in driving NIC self-administration³³ and little is known about the NIC enhancement of nondrug reinforcers in the SCZ population. To examine both primary reinforcing and reinforcement-enhancing effects of NIC in MAM and CTL animals, MAM ($n = 9$ males, 13 females, 7 litters) and CTL ($n = 10$ males, 11 females, 7 litters) rats were allowed to respond as described above for infusions paired with a VS. All sessions began with the white houselight illuminated. Completion of the response requirement

produced a 1-s illumination of the cue light above the active nose-poke portal followed by a complete lights-off lasting 60 seconds. During this time, responses at the active nose-poke were recorded but produced no consequence. Animals were allowed to acquire responding for VS paired with infusions of saline on an FR2 schedule. Dose of NIC was increased every 7 days from 0, 3, 10, 30, 100, and 150 $\mu\text{g/kg/infusion}$.

Experiment 4: Sucrose Reinforcement in MAM and CTL Animals

To compare responding for a natural reinforcer in MAM and CTL animals, female MAM ($n = 12$, 3 litters) and CTL rats ($n = 14$, 3 litters) were allowed to respond for 45 mg sucrose pellets (Bio-Serv, Flemington, NJ) in daily 1-hour sessions on FR1 (2 days), FR5 (2 days), and then FR10 (3 days) schedules, before completing 6 days on a progressive ratio schedule of responding in which the response requirement increased with each successive reinforcer delivered.³⁵

Statistical Analyses

Average responding over the final 3 days of each dose or response requirement was analyzed for each experiment; values are reported

as mean $\pm$ SEM. ANOVA tests with repeated measures (dose or day, where appropriate) were followed by post hoc tests ($\alpha = 0.05$; reported p values are adjusted for multiple comparisons using Bonferroni correction) comparing by group (MAM and CTL). Data analyses were conducted in IBM SPSS Statistics and GraphPad Prism.

Results

Experiment 1: MAM and CTL Animals Do Not Differ in NIC Primary Reinforcement Across Doses

MAM and CTL rats reliably self-administered NIC, responding more at the active portal than the inactive (Figure 1A). There was a significant effect of dose ($F_{3,35} = 8.47$, $p < .001$), but no effect of group ($p = .886$) and no interaction of dose $\times$ group ($p = .913$) in NIC self-administration. Both MAM and CTL animals demonstrated a characteristic inverted-U dose-response relationship, but did not differ significantly in infusions earned at any dose (Figure 1B). MAM animals required significantly longer to meet acquisition criteria for NIC self-administration (8.7 ± 1.5 days vs. 4.2 ± 0.6 among CTL animals, $p < .01$).

Figure 1. (A) Average responding for NIC at the active and inactive nose-poke portals. MAM and CTL animals reliably acquired NIC self-administration, responding more at the active than inactive nose-poke. (B) Average infusions earned by MAM and CTL rats at each NIC dose. Data points express the mean number of infusions earned over the last three sessions at each dose. MAM and CTL animals did not differ significantly at any dose tested. CTL, control; MAM, methylazoxymethanol acetate; NIC, nicotine.

Experiment 2: MAM and CTL Animals Do Not Differ in NIC Self-administration in an Extended Access Paradigm

Compared with CTL rats, there was no impact of MAM on NIC self-administration in 23-hour extended access sessions (Figure 2A and B). There was no significant effect of day ($F_{20,251} = 1.085$,

$p = .37$) or of Group ($F_{1,251} = 0.91$, $p = .34$) on mean infusions earned. Additionally, MAM and CTL rats did not differ in patterns of responding within each session (Figure 2C). Within the light-dark cycle of a single session, there was a significant effect of Light on responding ($F_{1,24} = 31.26$, $p < .001$), as both MAM and CTL animals responded markedly less during the light phase. MAM and

Figure 2. (A) Average responding for NIC at the active and inactive nose-poke portals over each 23-hour session. Both MAM and CTL animals reliably responded more at the active than inactive portal. (B) Average infusions earned across all 23-hour access sessions. MAM and CTL animals did not differ significantly in the number of infusions earned in each session across the 21 days of self-administration. (C) Representative infusion data for a single 23-hour access session (day 17). Each row of data points represents the infusions earned by one rat across the 23 hours of self-administration, wherein each point is a single infusion. Shaded boxes represent the dark phase of the session. MAM and CTL animals did not demonstrate any differences in patterns of responding across the 23-hour access period. CTL, control; MAM, methylazoxymethanol acetate; NIC, nicotine.

CTL animals did not differ in mean food pellets earned per session over the final three experimental sessions (MAM = 535.0 ± 15.0 , CTL = 548.6 ± 7.6 pellets; $p = .18$).

Experiment 3: MAM Animals of Both Sexes Respond Less for NIC Paired With a Reinforcing VS

Both male and female MAM rats responded less than controls for NIC paired with a mildly reinforcing light stimulus (Figure 3). There was a significant effect of group ($F_{1,242} = 40.74$, $p < .001$) and dose ($F_{4,242} = 47.11$, $p < .001$), as well as a group $\times$ dose interaction ($F_{4,242} = 4.88$, $p < .005$). There was no effect of sex ($p = .155$) or interaction of sex $\times$ group ($p = .88$), sex $\times$ dose ($p = .66$), or sex $\times$ group $\times$ dose ($p = .91$). MAM animals earned significantly fewer VS presentations than CTL animals when paired with saline or with 3, 10, 30, or 150 $\mu\text{g/kg}$ NIC infusions ($p < .05$). There was no effect of sex ($p = .25$), group ($p = .71$), or sex $\times$ group ($p = .40$) on days to meet acquisition criteria. Across doses, MAM and CTL animals made an average of five or fewer inactive nose-poke responses per session and at least twice as many active as inactive responses.

Experiment 4: Sucrose Reinforcement Is Reduced in MAM Animals

Average responses for sucrose pellets on a progressive ratio schedule of reinforcement over the final 3 days of the experiment were compared between MAM and CTL animals. MAM and CTL animals made comparably low (<15) inactive responses per session, but MAM animals responded significantly less than CTL animals at the active nose-poke ($t_{24} = 2.25$; $p < .05$, unpaired t -test; Figure 4) and reached lower breakpoints, suggesting that sucrose rewards are less reinforcing to MAM rats than CTL.

Discussion

The Primary Reinforcing Action of NIC Is Not Increased in the MAM Model of SCZ

The present study utilized the MAM model of SCZ, which is arguably the most comprehensive rodent model of SCZ currently

available,^{25,26} to study NIC reinforcement. The results of our experiments demonstrate that MAM-treated rats do not differ from controls in the primary reinforcing effects of NIC. Both groups responded comparably for NIC across a range of doses in 1-hour sessions. Moreover, when rats were allowed to self-administer NIC in 23-hour access sessions, MAM-treated and CTL animals did not differ in infusions earned across sessions or in their patterns of responding across the light-dark cycle within each session. These findings suggest that E17 MAM administration does not promote increased NIC intake in both short and long access periods.

Combined Primary Reinforcing and Reinforcement-Enhancing Effects of NIC Are Reduced in MAM-Treated Animals

In the presence of non-NIC reinforcers, NIC self-administration is driven by the combined actions of NIC as a primary reinforcer, as well as its enhancing effects on reinforcement from other rewards.³³ In our experiments, MAM rats responded significantly less for NIC paired with a reinforcing VS relative to controls across several NIC doses, a measure that reflects a reduction in the combined primary reinforcing and reinforcement-enhancing effects of NIC. However, comparing the reinforcement-enhancing action of NIC between MAM-treated and CTL rats is complicated by the observation that MAM-treated animals responded less than controls for VS reinforcers even in the absence of NIC. The reinforcement-enhancing effect of NIC is correlated with the reward strength of the reinforcer that is enhanced.³³ Thus, one potential interpretation of these results is that NIC reinforcement enhancement, like primary reinforcement, is similar between MAM-treated and CTL animals, as MAM-treated animals responded less for VS alone but showed a proportionally similar magnitude of enhanced responding when reinforcers were delivered with NIC. Additionally, while previous studies have reported small sex differences in self-administration at certain NIC doses,³³ key differences in design between those and the present study may account for the lack of sex differences observed here.

Figure 3. Average infusions + VS earned by MAM and CTL rats of each sex at each NIC dose. Data points express the mean number of reinforcers earned over the last three sessions at each dose. CTL animals earned significantly more reinforcers than MAM animals at 0 $\mu\text{g/kg/inf}$ ($*p < .05$), 3 $\mu\text{g/kg/inf}$ ($*p < .005$), 10 $\mu\text{g/kg/inf}$ ($*p < .001$), and 30 $\mu\text{g/kg/inf}$ ($*p < .001$), but did not differ significantly at 100 $\mu\text{g/kg/inf}$ ($p = .164$). There was no effect of sex at any dose ($p = .611$). CTL, control; MAM, methylazoxymethanol acetate; NIC, nicotine; VS, visual stimulus.

Figure 4. Average active and inactive responding for sucrose pellets on a progressive ratio schedule of reinforcement. Bars represent average responses made over the final 3 days of testing. CTL animals responded significantly more than MAM animals at the active nose-poke ($t_{30} = 2.19$; $p < .05$; significant difference indicated by *). CTL, control; MAM, methylazoxymethanol acetate.

Reinforcing Effects of NIC Relative to Other Rewards in MAM-Treated Animals

The reduced level of responding for VS or sucrose among MAM animals suggests features of anhedonia consistent with those observed in SCZ.¹³ In contrast, MAM and CTL animals responded comparably for NIC alone. This might suggest that NIC is more reinforcing than other rewards to MAM-treated animals, but is not more reinforcing in MAM-treated rats compared with CTL animals. Indeed, there is an observed relationship between severity of anhedonia and smoking status in SCZ, and many SCZ smokers cite positive affective effects of NIC particularly when they are feeling “low.”^{36,37} Interestingly, other studies employing the MAM model have found inconsistent results in reward-related behavior. One study found that MAM-treated rats consistently pursued the highest reinforced option in a behavioral flexibility task, and made fewer perseverative choices compared to CTL animals.³⁸ Though this reported reduction in perseverative behavior is counter to previous observations in MAM-treated animals,³⁹ the tendency to choose the more highly reinforced option may suggest an increased sensitivity to natural rewards.³⁹ While there are no previous reports of NIC self-administration in MAM-treated animals, a study by Ruda-Kucerova et al.⁴⁰ demonstrated that MAM-treated animals did not differ from controls in methamphetamine self-administration, despite a link between SCZ and methamphetamine use in clinical populations. It is important to note, however, that complex variables beyond reward, such as stress and environmental factors, likely interact with neurobiological factors to influence smoking in SCZ patients and should be considered when studying the issue as a whole.⁴¹

Studies of NIC in Other Animal Models of SCZ

Although this is the first study of NIC self-administration in the MAM rodent model of SCZ, published studies using other rodent models of SCZ report mixed results. The NVHL model, for example, was found in one study to produce a modest increase in rate of acquisition and rate of responding for a moderate dose of NIC + VS, but not higher or lower doses, after animals were administered chronic injections of NIC or saline throughout adolescence.²² NIC self-administration also did not improve performance in a spatial learning and working memory task in NVHL or sham animals, suggesting a lack of cognitive effect.²² Another study from this group observed an increase in responding during extinction and reinstatement of NIC + VS self-administration but no differences in acquisition,⁴² suggesting a possible role of stress from adolescent injections in the results observed in the prior study, as NVHL rats are particularly vulnerable to stress.²³ While the MAM and NVHL models are both neurodevelopmental disruption models of SCZ, it is important to note several key differences in these models that could ultimately influence differences in behavior. Administration of MAM on GD17 approximates a developmental disruption taking place in roughly the second trimester of human pregnancy and produces a subtle pattern of pathologies analogous to many observed clinically.²⁸ The NVHL is typically performed on P6–P8, considerably later in development, and is more invasive in nature due to the process of direct surgical lesioning.⁴³ Though these models share a number of features in common, key differences in the timing and method by which neurodevelopment is disrupted may result in different behavioral and neurophysiological profiles. For example, MAM animals exhibit consistent ventral tegmental area dopamine neuron spontaneous hyperactivity as well as enhanced nucleus accumbens dopamine release.²⁵ In contrast, NVHL does not alter basal dopamine release²³

but produces increased nucleus accumbens dopamine release in response to stress or amphetamine. Differences such as these could ultimately influence behaviors including NIC self-administration.

Observations in other types of animal models have been mixed as well. Pharmacological models of SCZ such as phencyclidine administration and amphetamine sensitization, which aim to capture elements of hyperglutamatergic and hyperdopaminergic states in SCZ, respectively,⁴⁴ consistently failed to increase NIC self-administration in rats,⁴⁵ and have even demonstrated a reduction in NIC + VS self-administration relative to controls.⁴⁶ Moreover, while the maternal immune activation model also did not alter NIC self-administration, NIC self-administration did mitigate cognitive deficits observed in maternal immune activation animals, lending further support for a self-medication hypothesis.²¹ Additionally, mice with a mutation commonly observed in human SCZ patients in *CHRNA5*, which codes for the $\alpha 5$ subunit of the nicotinic receptor, demonstrated cortical hypofunction that could be normalized with chronic NIC delivery.⁴⁷ This diversity of findings may reflect differences in the elements of SCZ pathophysiology captured by each particular model and their impact on the effects of NIC, as well as limitations in certain experimental designs. The MAM model is distinct from other animal models of SCZ in its encapsulation of behavioral, anatomical, pharmacological, and physiological perturbations observed in the disease, namely those of the midbrain dopamine system, achieved through neurodevelopmental disruption.^{25–29} The overall impression conferred by our findings in the MAM model as well as those in observed in several different models of SCZ^{21,45,46} is that NIC self-administration is not consistently or robustly exaggerated, in contrast to the increased smoking seen among SCZ patients. These findings are consistent with the hypothesis that the reinforcing effects of NIC are not altered in SCZ. Thus, this suggests that increased smoking is not driven by increased NIC reinforcement but rather by another motivating factor, such as improved cognitive or social functioning, that is not captured in animal self-administration studies.

Differences in Valuation of Cigarettes Versus Non-NIC Rewards Observed in SCZ Smokers

The findings of our experiments align with some aspects of NIC use and smoking in human SCZ patients. While we did not observe increased NIC intake among MAM-treated animals, which would parallel heavier smoking in SCZ patients, our results reflect a difference in the relative valuation of NIC versus non-NIC rewards that may also be observed clinically. Studies of human patients completing tasks to earn chocolate rewards have also suggested that observed deficits in goal-directed learning are not due to insensitivity to reward value or reward prediction error.⁴⁸ However, studies of SCZ smokers have suggested a specific overvaluation of cigarette reinforcement. SCZ smokers report greater hedonic response to NIC than control smokers, and SCZ smokers select cigarettes over alternative reinforcers twice as often as controls in a hypothetical choice task.^{17,49} Such findings provide an alternative hypothesis to the notion that smoking serves as a form of “self-medication” of aberrant sensory and cognitive symptoms and has more robust pro-cognitive effects in SCZ than in controls, which has also been challenged by direct studies.⁵⁰ Thus, our results in the MAM model may parallel differences in the valuation of cigarettes relative to other reinforcers observed in human subjects to some degree, though direct evaluation of reinforcing efficacy could be better studied through experiments assessing elasticity of demand or choice procedures between

NIC and other reinforcers. Regardless of experimental approach, however, concomitant use of antipsychotic drugs in patients within human studies is an additional difference between clinical and preclinical results, as varying side effects of these drugs could influence NIC effects, including reinforcement.⁵¹

Final Conclusions

Overall, these findings suggest that SCZ pathophysiology, as modeled by E17 MAM administration, does not produce an increase in NIC reinforcement. To the extent that MAM-treated rats are a valid model of SCZ, these results suggest that increased NIC reinforcement does not account for increased smoking in SCZ patients. Despite modeling many neurobiological aspects of SCZ, the MAM model fails to recapitulate SCZ entirely, and thus, alternatively, could fail to capture a specific biological or symptomatic feature that would increase NIC reinforcement. While our results do not directly follow the increased smoking observed in clinical SCZ populations, the differences observed in MAM-treated animals' responding for NIC relative to other rewards may have relevant implications. Smokers with SCZ are a vulnerable subpopulation that may be differentially affected by tobacco control policies, such as mandated reduction of NIC content in tobacco products, and a more thorough understanding of NIC behavioral pharmacology in this population would be helpful in informing proposed policies. Further clinical study is necessary to better understand motivators and outcomes of smoking in SCZ, which can be supplemented by preclinical exploration of mechanistic solutions.

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Declaration of Interests

None declared.

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