The Different Effects of Cholinergic Neuromodulation via Muscarinic and Nicotinic Receptors on Olfactory Discrimination Learning

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Abstract

Cholinergic neuromodulation has long been associated with various neural functions, such as learning and memory. In particular, cholinergic modulation in the olfactory bulb has been shown to affect olfactory discrimination learning, and there are two different types of cholinergic receptors, muscarinic and nicotinic. The effects of cholinergic input into the olfactory bulb via muscarinic receptors differ from those via nicotinic receptors. The present study tests to what extent behavioral conditioning and the activation of muscarinic and nicotinic receptors interact and compensate for each other in modulating the strength and specificity of an odor-reward association. In the study, the mice were infused with either a muscarinic antagonist, a nicotinic antagonist, or a saline vehicle control directly into the olfactory bulb, and then were trained over either 4, 8, or 12 trials to associate a given odor with a reward by digging for a reward in scented sand. Digging times measured in the test trials showed that blocking muscarinic receptors slowed down learning across all test odors while blocking nicotinic receptors impaired discrimination between perceptually similar odors by affecting their odor representations, independently of learning. Moreover, extended periods of learning allowed mice to compensate for lack of muscarinic, but not nicotinic, receptor activation.

Introduction

Differentiating sensory stimuli is very important for our survival, and some animals rely primarily on the olfactory system in order to survive. In vertebrates, the olfactory bulb (OB) integrates all the afferent information carried by the olfactory sensory neurons (OSNs) with ascending cortical and neuromodulatory inputs from structures such as piriform cortex, the basal

forebrain, and the brainstem (Cleland & Linster, 2003). The olfactory bulb consists of cell layers synapsing onto each other, in which the olfactory sensory neurons synapse to a glomerular layer of interneurons, which synapse to deeper processing layers of mitral and granule cells (Devore and Linster, 2012) (see Figure 1). One of the important modulatory pathways to the OB are the dense projections of cholinergic fibers from the nucleus of the horizontal limb of the diagonal band of Broca (HDB), a part of the basal forebrain (Zaborszky et al, 1986). The effects of these cholinergic inputs in the OB are mediated by both muscarinic and nicotinic receptors (Castillo et al., 1999; Pressler et al., 2007).

Cholinergic modulations of cortical networks have long been associated with attentional processing that is important for learning and memory (Yu and Dayan, 2005). In particular, cholinergic inputs within the olfactory bulb have been proposed to serve a critical role in olfactory learning and memory (Devore et al., 2014). In previous computational models of the olfactory bulb processing, it has been suggested that cholinergic modulations via nicotinic receptors sharpen the receptive fields of mitral cells for odor stimuli, which strengthens the perceptual discriminability of similar odorants (Linster & Hasselmo, 1997; Linster & Cleland, 2002). The effects of cholinergic input into the OB via muscarinic receptors differ from those via nicotinic receptors. It was found that blocking muscarinic receptors impairs discriminatory learning for nearly all odor sets, while blocking nicotinic receptors only deters discrimination between perceptually similar odors (Devore et al., 2014). The suggested underlying mechanism for this phenomenon is that muscarinic receptor blockade in the olfactory bulb reduces synchronization between output cells which in turn can lead to decreased activation of pyramidal cells. In contrast, nicotinic receptor blockade renders olfactory bulb output signals to similar odorants more overlapping, and therefore can hinder the cortical network from resolving highly

overlapping inputs (Devore et al., 2014). In other words, it is possible that blocking muscarinic receptors hinders odor discrimination learning while blocking nicotinic receptors affects odor representations, which makes it harder to discriminate between perceptually similar odors.

The present study further tests the different effects of muscarinic and nicotinic receptor-mediated cholinergic modulations in the OB on odor discrimination learning. More specifically, we tested to what extent training and functioning muscarinic and nicotinic receptors interact and compensate for each other in modulating the strength and specificity of an odor-reward association. Here, the strength of the odor- reward association was measured by how long the mice look for a reward in a previously reward-associated odor, and the specificity of the association was measured by how long the mice look for the presumed reward in the odor that was similar to the one they were trained on.

To test our hypothesis that extended learning could compensate for a lack of cholinergic receptor activation, mice were infused with either saline, the muscarinic antagonist scopolamine, or the nicotinic antagonist MLA in the olfactory bulb, and then were trained during either 4, 8, or 12 trials to associate a given odor with a reward. Then, we tested for the strength and specificity of the odor-reward associations by presenting them with either the learned or perceptually similar odors during non-rewarded test trials. Our results showed that infusion of scopolamine slowed down learning for nearly all odor sets while infusion of MLA impaired discrimination between perceptually similar odors by affecting their odor representations, independently of learning. Extended learning allowed mice to compensate for lack of muscarinic, but not nicotinic, receptor activation.

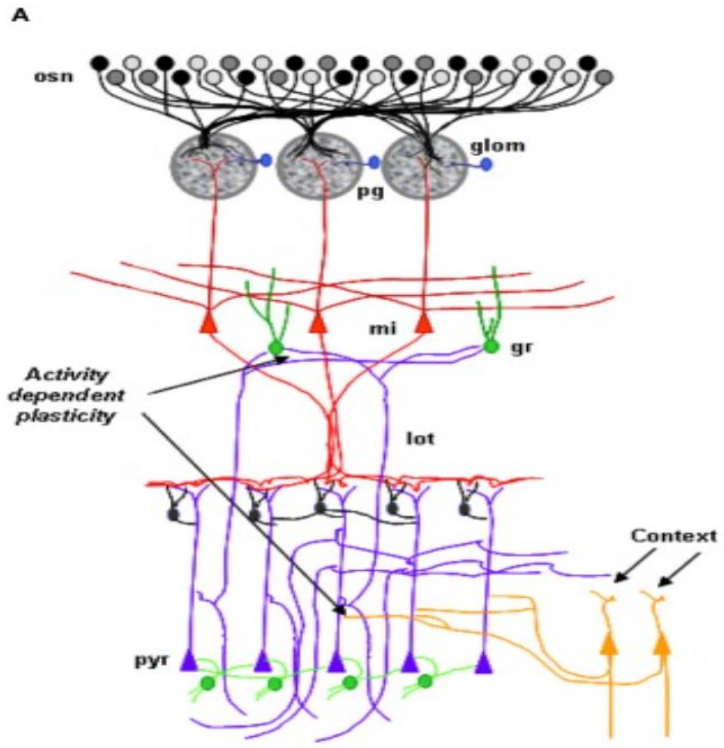

Figure 1. Olfactory bulb processing showing muscarinic ACh receptors (green) on granule cells and nicotinic ACh receptors (red) on mitral and periglomerular cells. The structures shown are olfactory sensory neurons (osn), glomerular (glom) and periglomerular cells (pg), mitral cells (mi), granule cells (gr), and pyramidal cells (pyr).

Methods

Subjects

The subjects of the experiment were eight male C57BL/6J mice. They were given unlimited access to water, but were food restricted and singly housed once behavioral training started. After their daily free food consumption was measured and averaged for four days, they were given 60% of the daily free food weight each day. From then on, their daily weight, behaviors, and amount of food consumed were monitored closely. If their weight fell to within 2g of 80% of their original weight, their food given was increased by 2g; if their weight fell within 1g of 80% of their original weight, the food ration was increased by 4g. Since mice are

nocturnal, their light-dark periods were reversed so that we could test them during afternoons. All experiments followed a protocol approved by the Cornell University Institutional Animal Care and Use Committee (IACUC) in accordance with NIH guidelines.

Behavioral Apparatus

A clear Plexiglas chamber was used that consisted of a resting side, a removable opaque black barrier in the middle, and a testing side. This testing side later contained two 35 mm petri dishes filled with white, dried play sand (YardRight). After each mouse completed testing, the chambers were cleaned by wiping with unscented baby wipes.

Behavioral Shaping

The conditioning procedure was done as the pre-training protocol outlined by Michelle Tong (Tong et al, 2018). The conditioning period was needed to get the mice to the point where they will dig in sand-filled petri dishes for rewards in response to scent cues. During phase 1, each mouse was allowed to wander around freely inside the chamber without the black barrier for 10 minutes. This helped them get used to the chamber. Then, a petri dish containing 20 sugar pellets was left inside their home cage for two days in order to familiarize them with the sugar pellets.

During phase 2, each mouse was exposed to two petri dishes, each containing 10mL of unscented sand, that were placed in the testing side of the chamber. The mice were given 10 minutes in the chamber without the black barrier. It was noted whether the mice explored the

petri dishes and dug in the sand. During this phase, food deprivation started in order to motivate the mice to search for the sugar pellets used in the reinforcement trials.

During phase 3, trials were conducted for each mouse. Per trial, the mouse was initially placed in the resting side while the black moveable barrier separated the resting side from the testing side. The testing side contained one petri dish containing scented sand with the sugar pellet placed on top of the sand and another petri dish containing unscented sand. Then, the black barrier was lifted up, and the mouse was able to explore in the testing side for one minute. After a minute since lifting up the black barrier, the moue was ushered back to the resting side regardless of whether it found and ate the sugar pellet at the scented sand. When lifting the barrier, usually the mouse went back to the resting side by itself, but if the mouse refused to go back to the resting side, it was gently ushered back without any physical contact. Between trials, both petri dishes were taken out and the sugar pellet was replaced. Petri dishes were replaced with new sand after the first 10 trials. Each trial was recorded as either X, 0, or 1. The X indicated that the mouse failed to find and eat the sugar pellet, 0 indicated that the mouse found the sugar pellet but dug in the unscented sand first instead of in the scented sand, and 1 indicated that the mouse dug in the scented sand first and also found and ate the sugar pellet. Each mouse was run on 15 trials per day.

After the mice went through cannulation surgery and had a resting period, the mice continued to be run on the same 15 trials. However, during this fourth phase of shaping, the sugar pellet was always hidden at the bottom of the scented sand instead of being placed at the top of the scented sand. This phase continued until all the mice succeeded with at least 93% accuracy, which was getting recorded as ‘1’ for at least 14 out of 15 trials per day.

Odorants

In order to have a different odor set for each combination of drugs and number of training trials, nine different odor sets were used in the experiment. In each odor set, three compounds were similar aliphatic compounds differing by one carbon length, and one compound was dissimilar. The conditioning odor was labeled as C2, the odor most similar to C2 was labeled as C3, the odor that was less similar to C2 was labeled as C4, and X was the dissimilar odor. Such compounds were used in each odor set because according to previous study, varying carbon length for aliphatic compounds can be used as a measure of similarity in odor (Linster and Hasselmo, 1999). All the 36 odorants were diluted in mineral oil (Table 1; total resulting volume 50 ml) so as to produce a vapor-phase partial pressure of 1.0 Pa (Cleland et al. 2002). Odors were prepared ahead of time (see Table 1), and a large amount of scented sand was made two weeks in advance for the training period; the ratio of sand to odorant was 15mL of sand to 100 microliters of 1.0 Pa carvone-(+), diluted in mineral oil (2358 microliters in 50mL). A large amount of scented sand was made prior to the testing trials as well; the ratio of sand to odorant was 17mL of sand to 60uL of each odorant.

Surgery

The surgical procedure for cannulation in the olfactory bulbs was done as the protocol used in Guerin et al. (2008). After being anesthetized with isoflurane, mice were injected intraperitoneally with 0.05mg/ kg atropine. Then, the brain region above the nasal area was sterilized with 32% Novalsan/2% chlorhexidine solution and xylocaine (4% lidocaine). Next, a cut was made at the skull, and two holes were drilled above the olfactory bulbs at AP +5.0mm from bregma. The needle went through the dura and a 22-gauge double-bore guide cannula was

inserted into the two holes. Then, stylets were used to plug the guide cannula. Two days after surgery, the mice were injected with ketoprofen (2 mg/kg intraperitoneally) and subcutaneous saline solution. The infusion of ketoprofen was for pain relief and infusion of saline solution was to prevent dehydration. Then, the mice rested for 7 days, during which period their weights were measured daily.

Table 1

List of Odorants used in Experiment.

	C2	*μL* in 50mL MO	C3	*μL* in 50mL MO	C4	*μL* in 50mL MO	X	*μL* in 50mL MO
A	Propanoic acid	20	Butanoic acid	65	Pentanoic acid	225	3-Heptanone	33
B	Hexyl acetate	114	Amyl acetate	36	Butyl acetate	11	Anisole	26
C	Pentanol	38	Hexanol	128	Heptanol	420	Benzaylamine	150
D	Hexanoic acid	745	Heptanoic acid	2300	Octanoic acid	6900	Neryl acetate	8200
E	Butyl hexanoate	815	Pentanoate	290	Butyrate	83	Cironellal	830
F	Octanal	74	Heptanal	36	Hexanal	12	Trans-2-hexenyl acetate	82
G	Ethyl butyrate	10	Propyl	26	Butyl	280	2-Hexanone	10
H	Butanal	4	Pentanal	4	Hexanal	12	Methyl butyrate	4
I	Heptyl butyrate	2300	Hexyl butyrate	815	Pentyl butyrate	290	Isovaleric acid	190

Vol/vol dilutions are calculated to evoke a theoretical odorant vapor-phase partial pressure of 1.0 Pa.

Drug Administration

Before drug infusion, mice were anesthetized in an infusion chamber connected to oxygen and an anesthetic vaporizer for about 2 minutes, using isoflurane at 4 vol % in oxygen.

After the mouse became anesthetized, it was taken out of the infusion chamber so that we could remove its stylets and connect tubes from a syringe pump to its double cannula. Then, the mouse was placed back in the infusion chamber and maintained under slight anesthesia while being infused bilaterally into the olfactory bulbs, at a rate of 0.02 microliters/minute, with either 2 uL of saline, 22mM scopolamine hydrobromide (Sigma-Aldrich) dissolved in saline (Baxter Healthcare Corporation), or MLA (Methyllycaconitine) dissolved in saline. These volumes of drug were determined from previous research that enabled the drugs to diffuse across the olfactory bulbs without to adjacent structures (Guérin et al., 2008), and the drugs were made about two weeks in advance before the start of the experiment, in which they were kept in a freezer at 21°C**.** After the infusion completed, the mouse was left in its home cage to rest for 10 minutes, and stylets were placed back into its double cannula. Such wait time helped the drugs diffuse more sufficiently.

Experimental Timeline

The experiment aimed to measure the effects of learning, and muscarinic and nicotinic receptor activation on the acuity of odor discrimination. Per day, each mouse was trained to associate a reward with odor C2 for either 4,8, or 12 trials before going through 4 unrewarded test trials with the four test odors, C2, C3, C4, X in randomized order. On a given day, each mouse was tested under either saline, scopolamine (muscarinic antagonist) or MLA (nicotinic antagonist). Each odor set was used only once, and the order of odor sets and drug treatments were randomized and counterbalanced among mice.

Per day, each mouse was first infused with either 2uL of saline, scopolamine, or MLA in each OB via a syringe pump, and then was given 10 minutes to rest before starting the training

trials. Each training trial consisted of the mouse being presented with a petri dish of scented sand and a sugar pellet (reward) inside and another petri dish of unscented sand with no reward, both petri dishes in the testing side of the chamber. Each mouse was given one minute in the testing side of the chamber, and the C2 odor of a specific odorset was used for the scented sand. It was recorded whether the mouse ate the sugar pellet without digging the unscented sand first. Both petri dishes were taken out between each training trial, and the sugar pellet was replaced.

After either 4, 8, or 12 of these training trials, the mouse underwent 4 testing trials, in which it was presented with a petri dish of scented sand and another petri dish of unscented sand, both petri dishes in the testing side of the chamber. This time, the scented petri dish either contained the same C2 odor, the similar C3 odor, the less-similar C4 odor, or the dissimilar odor X. The sequence of the presentation of these odors was random, and the mouse's digging times in the scented sand were recorded per testing trial. Each testing trial lasted for a minute. The order of drugs, order of odor presentation, and order of number of training trials was counterbalanced and pseudo-randomized. Each mouse was run once on each combination of number of trials and drug group, and each mouse was trained on a given odor set only once. As a consequence, 9 different odor sets were used (see Table 1).

Table 2

Table of training trials x drug x odorset combination schedule (Day/Mouse)

Day/Mouse	1	2	4	5	6	7	8	10
1	Sal A 4	Sal E 4	Sal I 4	Sal B 4	MLA F 8	MLA D 8	MLA H 8	MLA C 8
2	MLA C 12	MLA A 12	MLA H 12	MLA D 12	Sal B 8	Sal F 8	Sal G 8	Sal I 8
3	Scop B 8	Scop B 8	Scop B 8	Scop C 8	Scop D 4	Scop G 4	Scop E 4	Scop F 4

4	Sal D 12	Sal F 12	Sal A 12	Sal E 12	MLA G 12	MLA H 12	MLA D 12	MLA E 12
5	MLA E 4	MLA C 4	MLA G 4	MLA A 4	Scop I 8	Scop I 8	Scop B 8	Scop B 12
6	Scop F 4	Scop G 4	Scop C 4	Scop G 4	MLA A 4	MLA B 4	MLA C 4	MLA A 4
7	MLA G 8	MLA H 8	MLA E 8	MLA H 8	Sal C 12	Sal A 12	Sal F 12	Sal D 12
8	Scop H 12	Scop D 12	Scop F 12	Scop I 12	Sal E 4	Sal C 4	Sal A 4	Saline H 4
9	Sal I 8	Sal I 8	Sal D 8	Sal F 8	Scop H 12	Scop E 12	Scop I 12	Scop G 12

Each alphabet corresponds to an odor set (corresponding with table 1) and each number (4,8,12) corresponds to the number of training trials.

Results

The behavioral test allowed us to measure the effects of training and blockade of cholinergic receptors on the strength of the learned odor-reward association and on the specificity of this association.

1. Overall results.

Repeated measures ANOVA using digging time in seconds as the dependent variable with *drug* and *number of trials* as between-subjects factors and *test odor* as a within-subjects factor showed an overall significant effect of test odor ($F(3, 49) = 31.350$; $p < 0.001$), significant interactions between test odor and drug ($F(6, 98) = 2.852$; $p = 0.014$), test odor and number of trials ($F(6, 98) = 2.855$; $p = 0.009$), and test odor, number of trials, and drug ($F(12, 129.993) = 1.825$; $p = 0.042$). These results suggest that drug treatments and the numbers of training trials

both affected how much the mice dug in unrewarded test odors, and further that the drugs modulated the effects of training trials. Figure 2 shows the average digging times of each experimental group in response to the test odors (C2, C3, C4 and X) as a function of the number of training trials (4, 8 or 12).

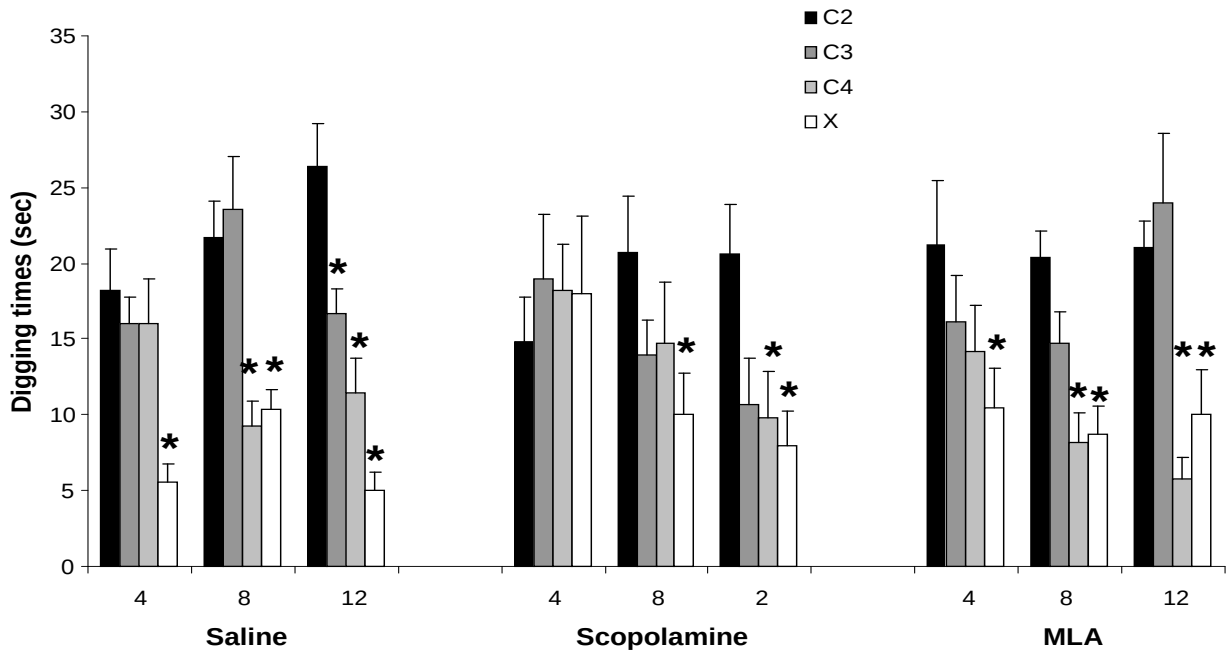

Figure 2. Digging times during unrewarded test trials with odors C2 (conditioned odor), C3 (highly similar odor), C4 (similar odor) and X (unrelated odor) as a function of conditioning trials (4, 8 or 12) and drug treatment (saline control, muscarinic antagonist scopolamine, and nicotinic antagonist MLA). Saline treated mice dug more in the conditioned odor as training progresses. * indicate a significant difference from conditioned odor ($p < 0.05$)

2. Activity and digging times

We found no effect of drug or number of trials on mice average digging times ($F(2, 63) = 0.058$; $p > 0.05$ and $F(2, 63) = 0.159$, $p > 0.05$), indicating that these did not affect animals' overall activity levels or interest in the odors.

3. Strength of association

In this paradigm, saline treated mice became more certain about the conditioned odor as they received more training, as evidenced by a significant correlation between the number of training trials and their digging times in the conditioned odor ($R= 0.597$; $p =0.002$). This correlation was weaker in scopolamine treated mice, though still significant ($R=0.425$; $p = 0.038$), and similar to saline treated mice in MLA treated mice ($R=0.611$; $p = 0.002$). These data indicate that learning was slowed down in scopolamine-treated mice as compared to saline treated mice (Figure 3A), but was still dependent on the degree of learning and that MLA does not impair learning per se.

4. Specificity of association or discrimination ability.

We then tested to what extent the degree of learning affects odor discrimination or the specificity of the odor reward association. Further pairwise testing analyzed to what degree mice in each drug group were able to discriminate between the conditioned odor and the test odors (Table 3 and Figure 2). Saline treated mice discriminated better as training increased (X after four trials, X and C4 after 8 trials and all three odors after 12 trials), as suggested previously for rats (Devore et al., 2014). Scopolamine treated mice learned more slowly: after 8 trials they discriminated only X, but after 12 trials they were able to discriminate all three odors; in other words, they proceeded with the same slope but delayed by 4 trials. Interestingly, MLA treated mice behaved similarly to saline treated mice with the exception of C3, which they did not learn to discriminate. This result is in agreement with our previous data in rats (Devore et al., 2014).

To further analyze to what degree the number of training trials affected odor discrimination, we defined a *discrimination index* (DI), which was calculated as the difference between two odor responses divided by their sum. The higher the discrimination, the index tends toward 1 and the lower the discrimination, the index tends toward zero and negative values. We found that for saline treated mice, discrimination between the conditioned odor (C2) and C3 ($R=0.451$, $p = 0.035$), and C2 and C4 ($R= 0.743$, $p = 0.001$) were highly correlated with the number of training trials (Figure 3Bi). On the other hand, there was no significant correlation between the amount of training and discrimination of X ($R=0.267$, $p = 0.284$) because this odor was always well discriminated. Scopolamine treated mice also showed strong correlations between the number of training trials and the discrimination of all three test odors against C2 ($R= 0.458$; $p = 0.028$, $R=0.525$; $p = 0.01$ and $R=0.445$; $p = 0.033$) , which shows that the mice had to learn to discriminate X as well and generally increased their discrimination ability (or the specificity of the association) as training increased (Figure 3Bii). This fact reveals that while scopolamine slows the learning process, learning does increase with more training trials. Interestingly, MLA treated mice showed significant correlation between number of training trials and discrimination of C4 ($R=0.498$; $p = 0.018$), but not of C3 or X ($R=-0.393$; $p = 0.094$ and $R=0.026$; $p = 0.914$) (Figure 3Biii). MLA treated mice could always discriminate X, but not C3 Thus, this suggests that MLA impairs discrimination of C3 independently of learning by affecting odor representations, as suggested by our previous experiments (Devore et al., 2014).

Table 3

Summary showing to what degree mice in each drug group discriminated between the conditioned odor (C2) and test odors (C3, C4, X). * indicates significant discrimination between the test odor and C2. ($p < 0.05$)

	4	8	12
Saline			
C3			*
C4		*	*
X	*	*	*
Scop			
C3			*
C4			*
X		*	*
MLA			
C3			
C4		*	*
X	*	*	*

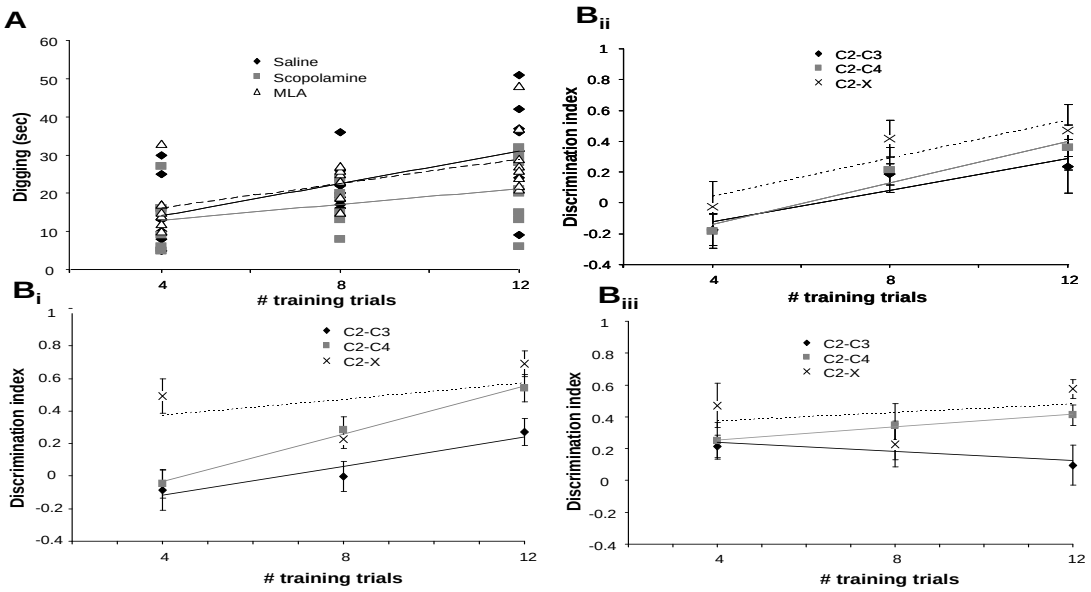

Figure 3. Correlations between odor- reward association strength (A) and specificity (B) as a function of learning trials. A. The graph shows individual digging times in the conditioned odor during unrewarded test trials as a function of number of training trials and experimental group. B. The graphs show the discrimination index as between the conditioned odor and similar odors (C2-C3, C2-C4) and a dissimilar odor (C2-X) for each treatment group (Bi: Saline, Bii: scopolamine, Biii: MLA).

Discussion

Cholinergic modulation in the olfactory bulb is thought to play a major role in olfactory learning and memory (Devore et al., 2014). We here investigated to what extent training and functioning cholinergic receptors modulate the strength and specificity of an odor-reward association and interact with each other. Our results show that saline-infused mice are better able to discriminate chemically similar odors as the number of conditioning trials increases, while scopolamine or MLA- infused mice showed impaired performance. More specifically, scopolamine-infused mice learned more slowly, but eventually were able to discriminate as well as saline-infused mice, whereas MLA-infused mice behaved similarly to saline-infused mice with the exception of never learning to discriminate the most similar odor even after a great number of training trials.

These results corroborated previous findings showing that muscarinic receptor blockade impairs learning of discrimination of nearly all odor sets while nicotinic receptor blockade hinders discrimination of only mostly perceptually similar odor sets. The results further showed that muscarinic receptor blockade slows down the learning, but does not completely eliminate the mice's ability to learn the discrimination whereas nicotinic receptor blockade hinders odor representations, independently of learning. This finding allows us to better understand the difference in the roles the muscarinic and nicotinic receptors play in cholinergic modulation of olfactory discrimination learning.

This phenomenon can be explained by the muscarinic receptor blockade in the olfactory bulb reducing synchronization between output cells, which in turn can lead to decreased activation of pyramidal cells. In contrast, nicotinic receptor blockade renders olfactory bulb output signals to similar odorants more overlapping, which can hinder the cortical network from

resolving highly overlapping inputs (Devore et al., 2014). Thus, muscarinic receptor blockade impairs learning whereas nicotinic receptor blockade hinders odor representations. However, there is still more to be found about the specifics of the underlying mechanisms that connect muscarinic and nicotinic receptor activation with these behaviors.

Cholinergic modulation does not only play an important role in olfactory learning, but it also does in other sensory systems as well, such as gustatory and auditory systems. A previous study has shown that inducing cholinergic inputs in the gustatory cortex genetically improves the learning of conditioned taste aversions (CTAs) and memory retention of the CTAs in the mutated mice (Neseliler et al., 2011). In addition to the gustatory system, previous work has shown that there is a greater concentration of acetylcholine present in the auditory cortex during auditory conditioned learning than during non-associative learning tasks (Butt et al., 2009).

As such, acetylcholine is closely implicated with associative learning in many sensory systems. Thus, it is very important to have a deeper understanding of the roles acetylcholine plays in these stimuli learning processes, and to find out more about how cholinergic modulation differs based on which receptor type (muscarinic or nicotinic) is activated. By further understanding the mechanisms of associative sensory learning, impaired learning processes can be cured and people can better process and integrate various sensory stimuli that will benefit their lives.

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