Original Article

Odor-Cued Taste Avoidance: A Simple and Robust Test of Mouse Olfaction

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Abstract

In odor-cued taste avoidance (OCTA), thirsty mice, offered either an odorized nonaversive fluid (S+) or an odorized aversive fluid (S−), quickly learn to use odor to avoid drinking the S−. Acquisition of both odor detection and odor discrimination tasks is very rapid with learning evidenced in most cases by either long response times or total avoidance on the second presentation of the S− stimulus. OCTA is perhaps one of the simplest conditioning procedures for assessing olfaction in mice; it requires only a test box, drinkometer circuit, and thirsty mice accustomed to drinking in the apparatus. Its advantages over the most commonly used alternatives, habituation–dishabituation, and the mouse dig test, are discussed.

Key words: mouse olfaction, olfactory test, odor detection

Despite burgeoning studies of mouse olfaction (Figure 1), no standard method to assess olfactory behavior in mice has been adopted by the chemosensory community and, in practice, a wide variety of measurement procedures have been and continue to be used. These range from tests in which an observer times by hand the visually judged investigation directed towards an odor source to precision olfactometry in which subjects are trained using operant conditioning to respond differentially to discrete presentations of well controlled odor streams (reviews by Slotnick and Schellinck 2002; Yang and Crawley 2009).

The test most often used with mice is some variant of odor habituation. Habituation, a decrease in response to a stimulus after repeated presentations, is a form of simple nonassociative learning (Thompson and Spencer 1966; Burrell and Sahley 2001). In practice, an odorized object (e.g., a cotton swab) is presented for a short period of time (generally 1–2 min) and the time the subject is judged sniffing the odor source is recorded. This procedure is then repeated several times. As attested to in numerous studies, the procedure results in a gradual decrease in attending to the repeated presentation of the same stimulus that, in turn, provides evidence for odor recognition. To assess odor discrimination, a novel odor can be presented in a final test. A significant increase in attending to the novel stimulus (dishabituation) provides evidence that the subject can discriminate between the 2 stimuli. The simplicity of the method contributes, in part, to its common use. However, as argued below, the habituation method has inherent limitations, often provides a relatively weak and somewhat subjective index of odor detection and discrimination, and has produced outcomes inconsistent with more exacting olfactory tests.

In contrast, associative conditioning methods, while generally more time consuming, have the advantage of yielding objective scores of performance accuracy and allow for multiple within-subject tests. Although a variety of idiosyncratic conditioning tests have been described including fear conditioning using a startle response (Jones et al. 2008), whole-body plethysmography (Youngentob 2005), T-maze, Y-maze, and multiple arm maze training (Yamazaki and Beauchamp 2005; Takiguchi et al. 2008; Blanco-Hernández et al. 2012; Kim et al. 2012) and find a buried cookie (Tucker et al. 2012; Kurtenbach et al. 2013), the most commonly used is the so-called dig test. This test provides a good example of a simple method that uses objectively defined accuracy measures of odor detection and discrimination in rats and mice. It involves training subjects to dig through a scented substrate to find a food reward. Animals so trained are tested by giving them a choice of digging in the original
scented or a different-scented container (Berger-Sweeney et al. 1998; Mihalick et al. 2000; Schellinck et al. 2001; Fadool et al. 2004; Kruzich and Grandy 2004; Breton-Provencher et al. 2009; Cleland et al. 2009; Akers et al. 2011). This report describes a different task, odor-cued taste avoidance (OCTA), one that retains all the advantages of the dig method but requires little or no training, is learned in just 1 or 2 trials and allows for arguably better control of odor stimuli. The method derives from Fombon and Polak (1987) who showed that rats will use the odor from the film of fluid at the tip of a standard drinking spout to avoid an electric shock to the tongue. The technique was successful in having rats make relatively fine odor discriminations but was inefficient, requiring several hundred trials over multiple days of training. A simple modification was that of Kimura et al. (1991) who showed that mice would quickly learn to use the odor of cycloheximide to avoid its bitter taste. That study appears to be the first demonstration of OCTA in mice. Darling and Slotnick (1994) assessed the reliability and validity of the OCTA method in rats. Each of 14 thirsty rats learned in 1–3 trials to avoid a solution of quinine and amyl acetate (S− stimulus) presented via a drink tube; those trained using massed trials in a single session had essentially perfect avoidance after only one contact with the adulterated fluid. Rats detected relatively low concentrations of the odor, easily discriminated between the odors of amyl acetate and ethyl acetate and most rats (5 of 7) demonstrated perfect memory for the odor detection task when tested after a 53-day rest period. Olfactory bulbectomized rats had no retention of the odor detection task and failed to relearn it. Except for a study of olfaction in feral kangaroos (Hunt et al. 1999) and to demonstrate an olfactory deficit in ApoE knock out mice (Nathan et al. 2004), the OCTA method appears not to have been further exploited. We have reexamined this method with mice, simplified and partly automated the test procedure and here provide results demonstrating its potential and its advantages over other simple behavior tests of olfaction in mice.

Methods

Subjects
Female mice from the CD-1 strain born in the Randolph Macon College Animal facility to timed pregnant dams obtained from Charles River Labs were used in these studies when 2–3 months old. Mice were housed in groups of 3–4 in 18×28×13 cm shoe box-type plastic cages in a temperature and humidity controlled vivarium maintained on a normal light–dark cycle. All experimental procedures were approved by the Randolph Macon College Institutional Animal Care and Use Committee.

Apparatus
An 18 cm long, 11 cm wide, and 20 cm high box constructed from 2-mm-thick black PVC board served as a test box (Figure 2). The floor of the chamber was fitted with two 8×5×0.3 mm thick stainless steel plates (Figure 2A and B) separated by a 0.5 cm gap. A 2.4-cm diameter hole drilled at one end of the box provided access to a 1-cm diameter, 0.2 cm deep plastic cup held on a removable stimulus tray. The top of the cup was located 1.2 cm below the floor and was fitted with a 1-mm diameter stainless steel wire which extended below the cup and contacted a stainless steel plate. A number of these cups were constructed so that different ones were used for different solutions.

Movements between the 2 floor plates and between the floor and the cup were monitored by lickometer (touch) circuits similar to that described by Slotnick (2009). The mouse completed a 12 vdc, 0.3 ua circuit when it crossed from Plates A to B and when it contacted fluid in the cup while standing on Plate B. An ACCES DIO digital interface connected the output of the touch circuits to a laptop computer that monitored inputs and recorded latencies.

Aversive stimuli
In preliminary studies on thirsty mice, we measured the time spent licking 5 and 1 mM aqueous solutions of quinine HCl and deneronium benzoate. Quinine proved to be somewhat more aversive
than denatonium benzoate at both concentrations and it was used in experiments described here.

Odorants

Aqueous dilutions of amyl acetate, ethyl acetate, ethyl butyrate, valeric acid, and a variety of food flavorings were used as odorants. Food flavorings were those made by McCormack and purchased from a local grocer; all other agents were purchased from Sigma–Aldrich. Positive (non aversive) stimuli were aqueous dilutions of the odorant. Negative (aversive) stimuli were diluted using a 5-mM aqueous solution of quinine HCl. Bottled spring water was used as the solvent for all dilutions and stimuli were stored in dedicated plastic bottles and kept refrigerated when not in use. The odorants and concentrations used in individual experiments are given below.

General training and test procedures

Mice were allowed 1 mL of water a day for at least 10 days prior to training. This resulted in a 13–15% loss before body weight stabilized.

Before training on an odor detection or discrimination task, mice were allowed to drink water in the test box using a discrete trials procedure: on each trial, the mouse was placed on Plate A of the box and removed 5 s after it made contact with the water cup. After 10–12 such trials, most mice reliably moved from Plate A to the water cup in 1–3 s. Those mice that did not readily drink on these trials were given a second such session on the next day. In the next session, mice were trained to detect an odor or discriminate between odors. For odor detection, water served as the positive stimulus (S+) and an odorant dissolved in 5 mM aqueous solution of quinine HCl (Q) served as the negative stimulus (Sx). The S+ stimulus was presented in the first 3–4 trials (S+ trials) of the session and, thereafter, several Sx trials were given although these were always separated by one or more S+ trials. In most cases, the unadulterated odor solution was used in the last S+ trial of the session. Generally, 10–13 trials were given in single daily sessions. Similar procedures were used to assess odor discrimination except that the S+ and S− stimuli were different odors.

Mice were trained in squads of 3–5. We used both massed and distributed trials in different tasks. For distributed trials, groups of mice were trained in a round robin fashion: on each trial the mouse was allowed unlimited time to cross from Plates A to B (Figure 2). The initial crossing between Plates A and B defined the beginning of the trial and the trial was terminated with removal of the mouse from the box 5 s after contact with the fluid in the cup or in 30 s if no contact occurred. Upon trial termination, the mouse was removed to a holding cage and the next mouse in the group was tested. The average inter-trial interval for each mouse was ~6–8 min. Similar procedures were used in massed training except that at trial termination a moveable barrier was used to gently restrict the mouse to the Plate A region of the box and, upon putting the next stimulus in place, the next trial was initiated by removing the barrier. The average inter-trial interval using this method was 30–45 s. The 2 methods produced essentially identical outcomes in odor detection and discrimination tasks but the massed trial procedure was more efficient as it eliminated handling mice between trials. For both methods, a computer program recorded response latency and the percent time spent drinking during the 5 s access to fluid on each trial. We also weighed cups before and after selected trials to measure the amount of fluid intake on S+ trials.

Olfactory bulbectomy

Five mice were olfactory bulbectomized after being trained on an odor discrimination task (described below). Deep surgical anesthesia was obtained using intraperitoneal Ketamine (90 mg/kg) and Xylazine (9 mg/kg) supplemented with a subcutaneous injection of buprenorphine (0.1 mg/kg). When the animal was unresponsive to toe pinch, the head was immobilize in a Kopf stereotaxic holder, the scalp was shaved, scrubbed with a germicidal solution, coated with iodine, and incised. The olfactory bulbs were exposed and removed by aspiration with the aid of a Leitz surgical microscope. The excavated cavity was packed with gelfoam, the scalp incision was closed using wound clips, and the scalp was covered with an antibiotic ointment. Mice were allowed to recover on a Deltaphase Isothermal Pad (BrainTree Scientific) which acts as a source of heat, but cannot overheat once it has reached its phase change. Animals were given acetaminophen adulterated water (3 mg/ml) for 72 h after surgery and wound clips were removed after 5 days under brief halothane anesthesia. The standard water deprivation schedule was instituted 7 days after surgery and, after 10 days, mice were retrained on the odor discrimination task.

Results

Odor detection

Separate groups of previously untrained mice were trained on one or more odor detection problems in which the S− stimulus was the odor...
of interest contained in a 5-mM aqueous solution of quinine and the S+ stimulus was water. Typically, on S+ trials and on the first S− trial, mice quickly approached the stimulus cup and made contact with the fluid within 1–2 s. On S+ trials, mice spent 60–90% of the 5 s access period in contact with the fluid and average intake was ~100 ul. On the first S− trial, the mice appeared to lick only once or twice at the fluid and then retreated from the cup. On the second S− trial, most mice sniffed at the fluid and either did not contact it or licked it after some hesitation. On the third S− trial, essentially all mice either avoided making contact or, in a few cases, did so after 10 or more seconds. In almost all cases, there was clear evidence of one-trial learning; latency scores on the second S− trial were greater than the latency on prior S+ trials.

Acquisition functions for a group of mice trained to detect isovaleric acid and another group trained to detect McCormack Pure Vanilla flavoring are shown in Figures 3 and 4, respectively. These mice had not previously been trained except, as described above, they had been given 10–12 water-only trials in the test box several days prior to the conditioning session. In each case, all mice acquired the task in one trial; that is, response latencies on the second presentation of the S− stimulus were elevated relative to latencies on prior S+ trials.

Figure 5 shows the performance of 5 mice first trained to detect isovaleric acid, then McCormack pure vanilla and, finally, McCormack peppermint flavoring. In the first detection task, each of the 5 mice briefly licked the S− stimulus on its first presentation. On the second task, 3 of the 5 mice sniffed at but did not sample the first presentation of the S− and, on the third task each of the mice sniffed at but did not lick the novel odorant. As naïve mice do not hesitate to drink these vanilla or peppermint-flavored stimuli these mice showed generalized inhibition to novel odors after being trained on a single odor detection task. Interestingly, this generalized inhibition did not occur when mice were trained on a series of odor discrimination tasks probably because in discrimination training some novel odors are S+ stimuli.

A separate group of 6 mice were used to examine task acquisition using sequentially lower concentrations of amyl acetate. In each task, the S+ stimulus was water and the S− stimulus was the designated concentration of isoamyl acetate contained in 2.5 mM quinine HCl. All mice quickly learned to avoid the 0.05% and 0.01% concentrations of amyl acetate on most S− trials (Figure 6). All 6 mice and 4 of the 6 mice had higher response latencies on S− trials than on S+ trials on the 0.001% and 0.0001% concentration tests, respectively. There was no evidence for odor detection on the last (0.00001%) test. Interestingly, although we have evidence that mice can be trained to detect the vapor from 2.5 mM quinine (not shown), that cue appears not to have been used in this study perhaps because mice were specifically trained to attend to the more salient amyl acetate vapor.

**Odor discrimination**

Mice performed almost as well on a variety of 2-odor discrimination tasks as they did on simple odor detection tasks. In these tests, the S+ stimulus is an aqueous solution of an odorant and the S− stimulus is a different odor contained in 5 mM quinine HCl.

Figures 7 and 8 shows the performance of 5 mice trained to discriminate between McCormick vanilla (S+) and almond (S−) food flavorings and for 4 mice trained to discriminate between McCormick anise (S+) and orange (S−) flavorings. A third group of 5 mice were trained to discriminate between an aqueous solution of 0.005% ethyl butyrate (S+) and 0.005% isovaleric acid (S−) (Figure 9).

For each of the 14 mice in these 2-odor discrimination tasks, response latency on the second S− trial exceeded those on all prior S+ trials. Note that most mice on the vanilla versus almond task hesitated before responding on the very first presentation of the S− stimulus (Figure 7) and all mice on the anise versus orange task had elevated latencies with their first encounter with both the S+ and S− stimuli. While it is unclear whether that hesitation is due to neophobia or to some vapor component of the McCormick almond flavoring, the slight but significant increase in latency is, by itself, evidence of discrimination.

Another group of 4 mice was used to assess memory for an odor discrimination task. These mice, initially trained to discriminate...
between ethyl butyrate (S+) and isoamyl acetate, were retested 3 days later. Quinine was omitted in the last S− trial in day 1 training and in all S− trials in the memory test. Figure 10 shows the median scores for acquisition of the task and the scores of individual mice on the retention test. On the retention test, each of the 4 mice had longer response latencies on the first S− trial than on the prior S+ trials, thus demonstrating memory for the odor discrimination task.

Olfactory bulbectomy
Five mice were trained to discriminate between ethyl butyrate (S+) and amyl acetate in a single 13-trial session. Each mouse was then olfactory bulbectomized and tested on this same task 14 days later.

As shown in Figure 11, the mice quickly acquired the discrimination task (Figure 11A) but, postoperatively, all mice responded with short latencies on each S− trial (Figure 11B). As shown by the percent time drinking on each trial (Figure 11C), these mice still found the quinine adulterated fluid aversive.

Discussion
These results demonstrate that the OCTA method yields reliable and objective measures across a variety of odor detection and discrimination tasks with mice. Acquisition functions across separate groups of mice were remarkably similar and essentially every mouse used in these studies acquired the odor detection or odor discrimination task after only 1 or 2 exposures to the bitter tasting odor solution. Control tests using odors without quinine demonstrated that discriminative performance did not depend on the presence of the aversive tastant. These results demonstrate that the OCTA method is at least as effective for mice as it is for rats (Darling and Slotnick 1994): for both species learning of either simple detection or discrimination tasks occurs quickly and is retained for at least some days. The present methods are much simpler than those used by Darling and Slotnick and extend the range of odor tasks that are acquired using OCTA.

The learning obtained in this study shares some of the characteristics of conditioned odor aversion learning in which animals made ill (the unconditioned stimulus) after exposure to a novel odor (the conditioning stimulus) avoid the CS in later tests (Tovar-Díaz et al. 2011). Odor aversion learning is considerably enhanced when odors are presented both ortho- and retronasally (Slotnick et al. 1997) and it is likely that this combined presentation of odors when mice sniff at and sample (lick) the S− stimulus enhances OCTA learning.

OCTA also shares several characteristics with mouse dig tests: both methods use motivated animals trained to detect a target odor, have well defined and objectively measured accuracy scores and require minimal equipment. OCTA has a number of practical advantages over dig type tests. The latter are clearly more time consuming: they require preliminary training in multiple sessions and additional training on the detection or discrimination task. Also, uncontaminated material, used to hide the target odor, needs to be prepared for each trial. Finally, the dig test is simply more troublesome to carry out than is the OCTA test: cups of material need to be prepared for each test and the test cage needs to be cleaned after each trial.

Relative to conditioning methods, habituation tests are easier to conduct and this undoubtedly contributes to their popularity. But despite this ease, there are serious disadvantages in using habituation. These are seldom addressed but need to be considered when deciding on a simple behavioral method for evaluating olfaction. As discussed below, these disadvantages include known constraints on habituation as a measure of sensory function, problems in measuring odor sampling behavior, validation of the method as a measure of odor detection, and the problem of interpreting null results (i.e., a failure to obtain habituation or dishabituation).
Constraints in using habituation to measure sensory function include that habituation recovers in time (spontaneous recovery) such that little or no habituation might occur with sufficiently long intervals between presentations and that the rate of habituation varies with stimulus strength; it occurs rapidly with weak stimuli and may not occur at all with sufficiently strong stimuli (Thompson and Spencer 1966; Rankin et al. 2009). The former characteristic limits its use as a measure of memory and the latter characteristic could prove a confound in certain outcomes. For example, an experimental manipulation that decreases odor sensitivity might result in an increased rate of habituation relative to controls while the use of weak habituating stimuli could result in slower habituation as, for example, in so-called super-smeller mice (Fadool et al. 2004). In addition, if similar odors are used as the habituating and dishabituating stimuli, a failure to show dishabituation may be due to stimulus generalization rather than inability to discriminate between the odors as, for example, in Linster et al. (2001). Finally, because there are strong carry over effects across a series of tests, the method does not lend itself to a within group study (“habituation of dishabituation”, Thompson and Spencer 1966; Thompson 2009). In any case, the need to control for order effects would sharply compromise one of the most attractive features of the method, its simplicity.

There are also potential problems measuring odor sampling in habituation studies: the time spent sampling is not measured directly but, instead, is defined generally by measuring the amount of time the subject's nose is in some close proximity to the stimulus source or when the subject appears to be sniffing at the source. Observer reliability is typically not reported and this type of measurement is particularly prone to unintended experimenter bias and interoperator variability. Measurement error due either to expectation of outcome or subtle changes in judging when the subject meets a positional criterion would probably not be an important consideration when effect size is large. But in a substantial number of reports the absolute decrease in odor sampling from the first to the last presentation of the same odor is often only 1–5 s (Penn and Potts 1998; Chaudhury et al. 2010; Wesson et al. 2011; Capilla-Gonzalez et al. 2012; Walton et al. 2012). Dishabituation (the increase in sampling a novel odor presented after habituation occurs) is generally observed but the magnitude of dishabituation for both within and between groups may, like habituation, be quite small (e.g., 1–4 s; Caroll et al. 2002; Capilla-Gonzalez et al. 2012; Walton et al. 2012). In a number of reports, significant treatment effects in habituation or dishabituation or both are based on differences in “odor sampling” in the order of 1 s or less (Caroll et al. 2002; Bath et al. 2008; Guérin et al. 2008; Moreno et al. 2009; Wilson et al. 2011). In other reports, only ratio or normalized scores are provided and the actual effect size is not

The validity of sniff time or orientation towards the odor object as a measure of olfaction is also problematic. As rats continue to engage in active sniffing behavior even after olfactory bulbectomy (Welker 1964), snout orientation towards a stimulus object or even sniffing of the object may occur even in mice with severe olfactory deficits. We have not found a report of odor habituation in olfactory bulbectomized mice but tests using control stimuli such as saline (Wilson et al. 2011), mineral oil solvent (Woodley et al. 2004; Pan et al. 2012; Zou et al. 2012), and water (Gheusi et al. 2000; Trinh and Storm 2003; Woodley et al. 2004; Farley et al. 2011; Walton et al. 2012) generated habituation scores similar in form to those obtained with commonly used odorants. It is unclear whether the habituation obtained in these cases was to the odor or other property of the control substance but this uncertainty underscores a shortcoming of the habituation method for evaluating olfaction.

A separate issue concerns the interpretation of null outcomes. In some studies, experimental subjects habituate more slowly or more rapidly than do controls or show normal habituation but fail or show far less dishabituation. Such changes are generally attributed to a deficit in odor detection (in the simple sniff or habituation test) or in discrimination (in the dishabituation test). However, in studies using more stringent methods quite different outcomes have been obtained: for example, studies on learning in neural cell adhesion molecules null mice (Gheusi et al. 2000; Schellinck et al. 2004); on the effects of intranasal zinc sulfate (Slotnick et al. 2007; Lim et al. 2009); on discrimination of enantiomers (Linsner et al. 2001; McBride and Slotnick 2006); olfaction in Tg2576 strain mice (Wesson et al. 2010; Xu et al. 2014); and in within study comparisons of conditioning.
versus habituation methods (Escanilla et al. 2012; Zou et al. 2012). In all of these cases, the habituation–dishabituation method failed to demonstrate olfactory abilities that were subsequently revealed using conditioning. Clearly, the failure to voluntarily sniff at an odor source or the absence of a dishabituation effect must be interpreted with caution.

OCTA, dig tests and related conditioning procedures are largely free of such problems but are not without their own disadvantages or constraints; subjects need to be motivated and this often involves maintaining them on a schedule of restricted food or water. Training requires at least some minimal apparatus, time to familiarize subjects with test procedures, and a number of trials to establish an association between rewards and the stimuli of interest. OCTA itself has several limitations. The most obvious is that an odor of the aversive taste is a potential confound and might limit using OCTA for determining odor thresholds; it certainly requires running at least one control trial without the aversive taste to insure that detection is based on the odor of interest. Another potential limitation is the need to use odorants that are soluble in water. While suspensions of nonwater soluble substances could be used it would be difficult to manipulate concentrations of such mixtures.

In developing this test for mice, we have encountered only 2 relatively minor problems: insuring adequate motivation and the occasional response inhibition in trials following the initial licking of high concentrations of quinine. Mice can be trained only when they are strongly motivated and respond readily (i.e., within 1–2 s) in initial S+ trials. In our experience, adequate motivation requires at least 8 days on the water restriction schedule and the loss of at least 10% of initial body weight. The second problem, generalized inhibition, occurs occasionally when a very high concentrations of quinine HCl is used (e.g. 10 mM or greater) or when S− trials are not separated by at least one S+ trial.

The inhibition in responding to novel odors which occurred when mice were tested on a series of quite different odor detection tasks (Figure 5) was somewhat surprising but it probably reflects, in part, the strong aversive properties of the bitter tastant and the fact

Figure 9. Median response latencies for 5 mice trained to discriminate an S− solution of 5 mM quinine and 0.01% isovaleric acid from an S+ solution of 0.01% ethyl butyrate. Inset graphs show the performance of individual mice. Quinine was not used in the last S− trial (shaded data point).

Figure 10. Left: median response latencies for 4 mice trained to discriminate an S− solution of 5 mM quinine and 0.01% isoamyl acetate from an S+ solution of 0.01% ethyl acetate. Right: retention scores of each mouse when tested 3 days later. Quinine was not used in the last S− trial in acquisition or for the S− trials on the retention test (shaded data points).
that the first novel odor the mouse encountered had a bitter taste. The strength of this generalization could be reduced by using lower concentrations of the bitterant. While this would result in slower acquisition, it might provide a more sensitive test for odor similarity.

Despite these potential constraints, OCTA is probably among the simplest associative conditioning procedure for demonstrating odor detection and discrimination in mice; it requires relatively few subjects, needs only the simplest apparatus, learning is exceptionally rapid, it allows for multiple tests of the same subjects, and the dependent measure, response latency, yields an objective, and easily made measure of learning.

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