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Versatility of the mouse reversal/set-shifting test: effects of topiramate and sex

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Abstract

The ability to learn a rule to guide behavior is crucial for cognition and executive function. However, in a constantly changing environment, flexibility in terms of learning and changing rules is paramount. Research suggests there may be common underlying causes for the similar rule learning impairments observed in many psychiatric disorders. One of these common anatomical manifestations involves deficits to the GABAergic system, particularly in the frontal cerebral cortical regions. Many common anti-epileptic drugs and mood stabilizers activate the GABA system with the reported adverse side effects of cognitive dysfunction. The mouse reversal/set-shifting test was used to evaluate effects in mice given topiramate, which is reported to impair attention in humans. Here we report that in mice topiramate prevents formation of the attentional set, but does not alter reversal learning. Differences in the GABA system are also found in many neuropsychiatric disorders that are more common in males, including schizophrenia and autism. Initial findings with the reversal/set-shifting task excluded female subjects. In this study, female mice tested on the standard reversal/set-shifting task showed similar reversal learning, but were not able to form the attentional set. The behavioral paradigm was modified and when presented with sufficient discrimination tasks, female mice performed the same as male mice, requiring the same number of trials to reach criterion and form the attentional set. The notable difference was that female mice had an extended latency to complete the trials for all discriminations. In summary, the reversal/set-shifting test can be used to screen for cognitive effects of potential therapeutic compounds in both male and female mice.

Keywords

Reversal learning; Attentional set-shift; Topiramate; GABA; Female

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1. Introduction

Cognitive dysfunction is a common behavioral symptom of autism, Tourette syndrome, Rett syndrome and schizophrenia [1–3]. Patients that suffer frontal lobe deficiencies can easily learn and follow individual rules, but have great difficulty modifying their responses to new rules. Performance deficits are observed on the Wisconsin Card Sorting Test (WCST), in which the subject must sort a series of cards dependent upon changing rules, such as suit and color [4, 5]. Patients can learn simple rules for sorting the cards, but they are unable to change established behavior once the relevant category changes [6–8]. Damage to the prefrontal cortex, specifically the dorsal lateral prefrontal cortex in humans, leads to impaired formation of the attentional set and shifting between sets, which is measured in the WCST by the intradimensional to extradimensional (ID-ED) shift [9–11]. In addition, patients with damage to orbitofrontal cortical areas are impaired in learning simple reversal tasks, in which the cues signaling correct and incorrect responses are switched [12].

The components of the WCST and reversal learning employed in patient studies have been modified and adapted for research animal models [13–16]. In agreement with the patient data, lesion studies in the dorsal lateral prefrontal cortex in the primate, and in medial prefrontal cortex in the rat, and most recently mouse, demonstrated that disruption in medial prefrontal areas reduces the ability to shift between attentional sets [13, 14, 17–21]. Lesion damage to the orbital frontal cortical (OFC) region or improper neural development of the OFC GABAergic interneurons impairs reversal learning [15, 18, 22–24].

The current study investigated the consequences of the anti-epileptic drug topiramate, which has been shown to increase GABA signaling [25–27]. Reversal learning and set-shifting are dependent upon the number of GABAergic interneurons in frontal cortical areas [24], implying a role for GABA. While many anti-epileptic drugs act to increase GABA levels and suppress seizure activity, the drugs may also impair cognition [28]. The anticonvulsant topiramate has known side effects of difficulty with concentration and memory problems in >10% of the patients [29, 30]. In this study, the mouse reversal/set-shifting paradigm was applied to test if topiramate affects two types of flexible behavior, reversal learning and set-shifting, in mice, as it does in humans.

Many neuropsychiatric disorders present with select sex biases. For example, schizophrenia, autism and Tourette syndrome are more common in males than females [31–33]. The majority of rat and mouse studies using reversal and set-shifting tasks selectively used males [14, 19, 20, 34–42] or grouped both sexes together [21]. To our knowledge, the effect of sex has not been examined. We evaluated whether both sexes performed similarly by testing female mice using the previously published test parameters [18], and then an altered paradigm with additional discrimination tasks.

The current results extend the knowledge beyond our previous lesion data [18]. The first experiment tests whether the anti-epileptic drug topiramate affect reversal learning or ID-ED, as suggested by the human reports. In the second experiment, we evaluate the responses of female mice on the reversal/set-shifting test. Finally, we modify the procedure to achieve the ID-ED shift and then compare the behavior of male and female mice.

2. Materials and methods

2.1 Animals

Adult C57BL/6 mice (>12 weeks of age) were purchased from the Jackson Laboratory (Bar Harbor, ME) and housed for 1–2 weeks prior to behavioral testing. All research procedures using mice were approved by the Institutional Animal Care and Use Committee at

University of Maryland and conformed to NIH Guide for the Care and Use of Laboratory Animals. Mice were individually housed and food restricted to reach 85% baseline free-feeding weight with 12 h light cycle from 07:00 to 19:00 hours with a room temperature of 20–22°C and 40–50% relative humidity. To familiarize the mice with the testing materials, the materials were introduced into the home cage at least 1 day (d) prior. Food deprived mice were trained to perform compound discriminations by digging in bowls of scented media. Mice were tested in the late afternoon during the end of the light cycle.

2.2 Reversal/set-shift task

A set-shifting task was performed but modified from the task as described previously [18]. At the start of each trial, the mouse was placed in the testing arena to explore two bowls with combinations of odors and digging media until digging in one bowl to signify a choice. The bait was a piece of Honey Nut Cheerio cereal (~5 mg), and the cues, either olfactory (odor) or somatosensory and visual (texture of the digging medium which hides the bait) were altered and counterbalanced. All cues were presented in identical small animal food bowls (All Living Things Nibble Bowls, PetSmart) that were identical in color and size. Digging media was mixed with the odor (0.01% by volume) and Honey Nut Cheerio powder (0.1% by volume). All odors were ground dried spices (Penzeys, Milwaukee, WI; Hershey Chocolate Co, Hershey, PA; or McCormick Spice Co, Hunt Valley, MD) and unscented digging media was purchased from PetSmart (KayKob, bedding, wood chips, aquarium gravel, aquarium stone, kitty litter (2 types)) or local discount stores (cotton balls, feathers, moss, plastic pellets, shredded paper, perlite, bark, packing peanuts). The mice were housed in Softcard bedding. The digging media did not contain any components used in the animal bedding. On the first day of training, the mice were given 4 consecutive trials with the baited food bowl to ascertain they could reliably dig. All mice were able to dig for the reward. The testing was performed over a 4 d period.

Mice were tested through a series of discriminations where the exemplar pair was changed, but the dimension (odor or medium) of the correct choice remained the same. The dimension was relevant if its attributes predicted outcome. For example, if odor was the relevant dimension, then the mouse was required to choose the correct odor from each pair and ignore the attributes of the digging medium. In this example, the digging medium is considered the irrelevant dimension.

The discriminations (Tables 1 and 3) were as follows:

- A single series of simple discriminations (SD) in which the mouse was presented with two choices of the relevant dimension and one choice of the irrelevant dimension (i.e. two odors within the same medium);
- A single series of compound discrimination (CD) in which the mouse was presented with the same choices of relevant dimension as in the SD and two choices of irrelevant dimensions (the exemplar used in the SD and a new exemplar);
- A series of multiple intradimensional shifts (IDS1, IDS2, IDS3,...) in which the mouse was presented with compound discriminations using two novel exemplars from the relevant and irrelevant dimensions for each IDS. The relevant dimension of the correct choice (i.e. odor) was maintained throughout the discriminations.
- An extradimensional shift (EDS) in which the mouse was presented with a novel compound discrimination, except for the first time the correct choice was an exemplar that was previously from the irrelevant dimension. The previously relevant dimension has become irrelevant.

- Reversal discriminations (CDrev, IDSrev, or EDSrev) in which the mouse was presented with the same set of exemplars as in the previous discrimination, but the stimulus-reward pairing was reversed within the relevant dimension.

The baited bowl was randomly presented on either side of the testing cage, and the relevant exemplar was randomly presented with the irrelevant exemplars. The trial was stopped if the mouse did not dig within 3 min in the testing cage. Stopped trials were uncommon (< 3% of all trials), and they occurred most frequently during the SD. Aborted trials were not observed after completion of the CD and were not included in the latency calculations. The order of discriminations and exemplars was the same for all mice, but the direction of the extradimensional shift (EDS, odor to medium or medium to odor) was counterbalanced within each experimental group. A criterion of six consecutive correct trials was required to complete each task. Data are reported as the number of trials to criterion required for each discrimination and the number of errors that occurred..

2.3 Experiment 1 – Effect of topiramate

To test the effects of the anti-epileptic drug, male mice were food deprived and acclimated to the testing materials. Adult male mice were injected (subcutaneously) 30 min prior to testing with either vehicle (sterile phosphate buffered saline, $n = 5$) or topiramate (25 mg/kg in phosphate buffered saline, Sigma Chemical Co, St. Louis, MO, $n = 5$) at least 30 min prior. Power analysis predicted that a sample size of 5 was sufficient to obtain power = 0.900, $\alpha = 0.05$, based on the difference in means obtained previously with this task [18]. The mice were tested on the schedule of tasks in Table 1 with the exemplars given in Table 2.

2.4 Experiment 2 – Effect of sex

Initially female mice were tested on the same paradigm used for male mice, using 4 IDS trials as described in Table 1, with the exception that the reversal was moved to after IDS4 as published [18] and with the exemplars given in Table 2. However, this paradigm did not show the formation of the attentional set (Fig. 2). Therefore, a new paradigm was tested. A new cohort of male and female mice were tested in the order described in Table 3 with the exemplars given in Table 4. Female mice underwent vaginal lavage to stage for estrus cycle before, during and after behavioral testing [43]. Food deprivation stopped cycling and the mice appeared to be in anestrus. Groups of 5 mice of the same sex were tested each week with 2–3 days of no testing in the room to remove odors of the opposite sex. A total of $n = 10$ males and $n = 8$ females were tested.

2.5 Data analysis

Values are reported as the mean $\pm$ standard error of the mean (SEM). For trials to criteria and errors, a two-way ANOVA was used to determine statistical significance between treatment groups and discrimination tasks, followed by Student-Newman-Keuls (SNK) post hoc analysis. One-way ANOVA was used for the group with only female mice. Statistical significance was considered as $p < 0.05$, and denoted by asterisks.

3. Results

3.1 Evaluation of reversal/set-shifting performance in the presence of topiramate

We evaluated the effects of topiramate in the reversal/set-shifting test. The topiramate did not alter overall exploratory behavior or gross motor function. A two-way ANOVA demonstrated an overall effect of task ($F(8,89) = 2.677$, $p = 0.012$), and no overall effect of drug ($F(1,89) = 0.518$, $p = 0.474$), but a task $\times$ drug interaction $F(8,89) = 30.945$, $p < 0.001$, Fig. 1A). In the *post-hoc* analysis, the trials to criterion were similar in control and

topiramate groups for the initial discriminations (SD, CD, IDS1, IDS2, and IDS3, $p > 0.1$ for all). For IDS4, the topiramate group required significantly more trials (13.2 ± 2.5) to reach criterion than the control group (7.0 ± 0.5 , $p = 0.03$). Both groups performed the reversal tasks (CDrev and EDSrev) similarly ($p > 0.4$). For the EDS task, the number of trials in the topiramate group (7.2 ± 1.0) was significantly less than the control group (18.2 ± 0.4 , $p = 0.003$). The control group demonstrated the ID-ED shift, from 7.0 ± 0.5 trials for IDS4 to 18.2 ± 0.4 trials for EDS ($p < 0.05$), whereas the topiramate group did not show this shift, (13.2 ± 2.5 trials for IDS4 to 7.0 ± 0.5 trials for EDS, $p = 0.865$).

The number of errors corresponded with the trials to criterion data (Fig. 1B). There was an overall effect of task ($F(8,89) = 3.835$, $p < 0.001$), but no overall effect of drug ($F(1,89) = 0.588$, $p = 0.446$), or task $\times$ drug interaction ($F(1,89) = 1.108$, $p = 0.368$). Finally, the latency data was the same for both groups (Fig. 1C). An overall effect of task was observed ($F(8, 89) = 5.189$, $p < 0.001$), but not of drug ($F(1,89) = 0.001$, $p = 0.973$), or task $\times$ drug interaction ($F(8,89) = 1.027$, $p = 0.424$). For both groups, the latency diminished over the course of testing; for example control mice required 40.4 ± 5.8 s for SD and 17.4 ± 6.3 s for IDS4 ($p = 0.063$). The topiramate group had an similar decrease in latency, from 48.4 ± 11.7 s for SD to 21.6 ± 7.0 s for IDS4 ($p = 0.296$).

3.2 Effect of sex on performance on the reversal/set-shifting test

Initially female mice were tested in the published sequence [18], with four IDS tasks, followed by a reversal (IDS4rev), the ID-ED shift (EDS), and ID-ED reversal (EDSrev, Fig. 2A). One-way ANOVA demonstrated an effect of task ($F(8,62) = 3.766$, $p < 0.001$). Post hoc analysis reported a significant difference between CD and IDS1 ($p = 0.006$) and IDS4 and IDSrev ($p = 0.03$), but not for the ID-ED shift (IDS4 to EDS, $p = 0.256$). The pattern of errors followed the trials to criterion (Fig. 2B), with an effect of task ($F(8, 53) = 8.034$, $p < 0.001$). Post hoc analysis showed a significant difference between CD and IDS1 ($p = 0.014$) and IDS4 and IDSrev ($p < 0.001$). Finally, the latency data demonstrated that the female mice required much longer times to complete the tasks, but they did show a decrease in latency from CD to IDS4, implying learning (Fig. 2C). In summary, the female mice appeared to have similar reversal learning capacity as the male mice, but did not show the ID-ED shift, indicating an inability to form an attentional set.

In adapting the digging task for mice, we found that increased numbers of IDS tasks improved the ability to form the attentional set [18]. We used a similar strategy for the female mice, and increased the number of IDS from 4 to 5. Separate cohorts of male and female mice were tested on the reversal/set-shifting paradigm as described in Table 3. Two-way ANOVA showed an overall effect of task ($F(9,169) = 4.797$, $p < 0.001$), but no overall effect of sex ($F(1,169) = 0.199$, $p = 0.656$), or task $\times$ sex interaction ($F(9, 169) = 1.086$, $p = 0.377$). Both male and female mice required more trials to criterion for the IDSrev compared to IDS5 ($p < 0.001$). Males demonstrated the ID-ED shift, from 6.2 ± 0.1 trials for IDS5 to 9.2 ± 1.1 trials for the EDS ($p = 0.042$). Female mice showed a similar shift, from 7.4 ± 1.4 trials for IDS5 to 11.6 ± 2.5 for the EDS ($p = 0.018$).

The errors committed by the mice reflected the same pattern as the trials to criterion, with an overall effect of task ($F(8,158) = 5.148$, $p < 0.001$) and no overall effect of sex ($F(1,158) = 2.356$, $p = 0.126$) or task $\times$ sex interaction ($F(8, 158) = 1.180$, $p = 0.315$, Fig. 3B). The latency data showed overall effects of task ($F(1,158) = 11.937$, $p < 0.001$) and sex ($F(1,158) = 155.575$, $p < 0.001$, Fig. 3C). For both sexes, the latency decreased as the mice proceeded through the tasks. Male mice required 55.5 ± 9.5 s for the SD task and 8.3 ± 1.4 s for the IDS5 ($p < 0.001$), whereas female mice needed 101.0 ± 18.4 s for the SD and 51.2 ± 16.5 s for the IDS5 ($p = 0.008$). For all tasks, the female mice used more time (1.8 – 7.0 times greater time per trial) than the male mice ($p < 0.028$).

Discussion

These results demonstrate that the reversal/set-shifting test in mice can be used to evaluate the effects of drugs on cognition mediated by the orbitofrontal and medial prefrontal cortical areas. In addition we report that female mice perform reversal learning tasks similar to males, but that female mice appear to require additional discriminations in order to form the attentional set. These experiments broaden the applicability of this behavioral paradigm from wildtype and genetically altered mice to drug testing and evaluation of sex on cognition.

In the first experiment, the anti-epileptic and mood stabilizer drug, topiramate, impaired the formation of the attentional set, but not reversal learning, in agreement with human reports [44–46]. Topiramate did not alter the overall performance on the simple and compound discrimination tasks or change the latency, implying that topiramate did not affect learning of the task. In control mice, the number of trials to criterion decreased with more tasks, or practice. This trend was not apparent in the topiramate treated mice, supporting a deficit in formation of the attentional set. In fact, the topiramate treated mice required significantly more trials to reach criterion on the final IDS (IDS4) before performing the EDS.

The inability to form the attentional set observed after topiramate in the current study is consistent with human data, in which some cognitive tasks, including attention and language are impaired in up to 35% of adults [30] and 70% of children while treated with topiramate [47]. The actions of topiramate have been localized to the human prefrontal cortical areas [48]. The exact mechanism of action of topiramate is not known; it has been implicated in blocking sodium channels, enhancing GABA binding to GABA_A receptors, and antagonizing AMPA type glutamate receptors [25]. Therefore, topiramate may have multiple pharmacological sites for disrupting the formation of the attentional set.

Disorders in frontal cortical function often affect men and women differently, yet the sex disparities are not always observed in animal models. The lesion study of the reversal/set-shifting used IDS1-IDS4 tasks to achieve a significant ID-ED shift with male mice [18]. When the same paradigm was used for adult female mice, only a fraction of the female mice demonstrated the ID-ED shift, and thus the overall effect was no difference in trials to criterion between the IDS and the EDS (Fig 2). The paradigm was altered to include an additional discrimination (IDS5) and the female cohort performed similarly to the males on the ID-ED shift (Fig. 3A). While the data show that the female mice perform the reversal discrimination similarly to the male mice, the females required a greater number of trials to reach criterion, with a larger variability between subjects.

In a different reversal/set-shifting paradigm [21], groups of 3 females and 8 males or 2 females and 4 males were tested on a variable schedules over many months. The effect of sex was not reported. Our paradigm differed in task design and in housing conditions. However, the reported task did include overtraining in order to achieve formation of the attentional set, and the addition of the IDS5 task is a form of overtraining, supporting the literature. In a visual touchscreen operant format of discrimination learning, mice have been reported to successfully demonstrate reversal learning, but not set-shifting [19, 49].

The greatest difference between male and female mice while performing the reversal/set-shift test was the latency. Throughout the entire testing time, the female mice required dramatically more time to complete the task. Measurements of overall movement show no differences between groups (open field data not shown and [50]). The increased latency was not correlated to overall weight loss or other behavioral parameters. The female mice often sampled the odors and textures (by whisking) repeatedly from both bowls prior to making a final decision by digging into the medium. The female mice continued to investigate the

testing environment in the same manner for all the discriminations. By contrast, the male mice ran directly to their bowl of choice, without investigating the other bowl. This sex difference in latency may reflect the variation in neurotransmitters or circuitry in prefrontal areas [51].

The latency for the male mice to complete the task decreased such that the time to complete the EDS and EDSrev tasks was much less than for the SD and CD. The female mice displayed a strategy that was similar to (male) mice lacking the D3 dopamine receptor, which are described as ‘checking’ both bowls and correcting approaches to the incorrect bowl [38]. Perhaps the female mice had differential activation of dopamine receptors in the frontal cortex. The female mice may have been more anxious during the task or had altered motivation, compared to male mice. In the Barnes maze, some reports indicate sex differences in performance and that female mice appear to use an altered strategy [52], dependent upon maze design parameters. Yet, the increased latency did not alter the ability of the female mice to perform the tasks similarly to the male mice. These aspects of the female decision making can be addressed in future studies.

Conclusions

In the current study, a reversal/set-shifting test was used to show that mice given the drug topiramate display cognitive impairments, in agreement with the literature for human patients. The test has been modified to include male and female subjects, with similar performance outcomes. Thus, the mouse reversal/set-shifting paradigm may have a wide role in assessing the cognition effects of psychoactive drugs and in developing effective treatments for human neurological and psychiatric disorders.

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Highlights

Digging set-shift test is easily modified for pharmacological evaluation

Topiramate impairs formation of the attentional set in mice, but not reversal learning

Female mice can perform similarly to male mice on reversals and ID-ED shifts

Fig. 1.

Effect of topiramate on reversal learning and set-shifting. (A) Trials to criterion for each discrimination show that the topiramate treated mice needed more trials on the fourth discrimination (IDS4), and did not demonstrate an ID-ED shift (compare IDS4 to EDS). (B) The numbers of errors were similar between groups. (C) Topiramate did not affect the time to complete the tasks. Asterisks (*) denote a difference between groups for a specific discrimination ($p < 0.05$), whereas the ampersand (&) designates a significant ID-ED shift ($p < 0.05$).

Fig. 2.

Female mice had difficulty on the intradimensional shift and did not show formation of the attentional set. Adult female mice were tested on the reversal/set-shift task [18]. (A) Females showed a significant increase in trials between the IDS1 and the SD ($\# p < 0.05$) and between IDSrev and IDS4 ($*, p < 0.05$), but not between IDS4 and EDS. (B) Errors for each discrimination followed the same pattern as trials, with significant increase in errors between IDS1 and the SD ($\#, p = 0.004$), and between IDSrev and IDS4 ($*, p < 0.001$). (C) Latency to complete each trial was higher for the female cohort than previous male cohorts. Although latency decreased as the trials progressed, implying learning.

Fig. 3.

Effect of sex on reversal learning and set-shifting. (A) Trials to criterion for male and female groups show similar performance for each. (B) Errors for each discrimination were the same for each sex. (C) Latency per trial was dramatically more in the female group for all discriminations. Asterisks (*) denote a difference between groups for a specific discrimination ($p < 0.05$), whereas the ampersand (&) designates a significant ID-ED shift ($p < 0.05$).

Table 1

Order of tasks for Experiment 1- Effect of topiramate

Task	Dimension		Exemplar combinations	
	*Relevant	Irrelevant	Correct	Incorrect
SD	Odor (O)	Medium (M)	O1, M1	O2, M1
CD	Odor	Medium	O1, M1, M2	O2, M1, M2
CDrev	Odor	Medium	O2, M1, M2	O1, M1, M2
IDS1	Odor	Medium	O3, M3, M4	O4, M3, M4
IDS2	Odor	Medium	O5, M5, M6	O6, M5, M6
IDS3	Odor	Medium	O7, M7, M8	O8, M7, M8
IDS4	Odor	Medium	O9, M9, M10	O10, M9, M10
EDS	Medium	Odor	M11, O11, O12	M12, O11, O12
EDSrev	Medium	Odor	M12, O11, O12	M11, O11, O12

* The order of discriminations was the same for mice, but the relevant dimension, and thus the direction of the EDS (odor to medium or medium to odor) was counterbalanced within each experimental group. The number of trials required to reach criterion (6 correct consecutive trials) was independent of choice of relevant dimension.

Table 2

Exemplar combinations for Experiment 1 – Effect of topiramate

Pair	Exemplar	Dimension	
		Odor (O)	Medium (M)
1	1	Rosemary	Aspen bedding
	2	Cloves	Gravel
2	3	Cinnamon	Kaykob bedding
	4	Sage	Moss
3	5	Onion	Perlite
	6	Paprika	Bark
4	7	Garlic	Cat litter
	8	Coriander	Feathers
5	9	Thyme	Plastic pellets
	10	Black pepper	Cotton balls
6	11	Cumin	Shredded paper
	12	Cardamom	Packing peanut pieces

Table 3

Order of tasks for Experiment 2 – Effect of sex

Task	Dimension		Exemplar combinations	
	*Relevant	Irrelevant	Correct	Incorrect
SD	Odor (O)	Medium (M)	O1, M1	O2, M1
CD	Odor	Medium	O1, M1, M2	O2, M1, M2
IDS1	Odor	Medium	O3, M3, M4	O4, M3, M4
IDS2	Odor	Medium	O5, M5, M6	O6, M5, M6
IDS3	Odor	Medium	O7, M7, M8	O8, M7, M8
IDS4	Odor	Medium	O9, M9, M10	O10, M9, M10
IDS5	Odor	Medium	O11, M11, M12	O12, M11, M12
IDSrev	Odor	Medium	O12, M11, M12	O11, M11, M12
EDS	Medium	Odor	M13, O13, O14	M14, O13, O14
EDSrev	Medium	Odor	M14, O13, O14	M13, O13, O14

* The order of discriminations was the same for mice, but the relevant dimension, and thus the direction of the EDS (odor to medium or medium to odor) was counterbalanced within each experimental group. The number of trials required to reach criterion (6 correct consecutive trials) was independent of choice of relevant dimension.

Table 4

Exemplar combinations for Experiment 2 – Effect of sex

Pair	Exemplar	Dimension	
		Odor (O)	Medium (M)
1	1	Rosemary	Aspen bedding
	2	Cloves	Gravel
2	3	Cinnamon	Kaykob bedding
	4	Sage	Moss
3	5	Onion	Perlite
	6	Paprika	Bark
4	7	Garlic	Cat litter
	8	Coriander	Feathers
5	9	Thyme	Plastic pellets
	10	Black pepper	Cotton balls
6	11	Dill	Colored beads
	12	Caraway	Yarn pieces
7	13	Cumin	Shredded paper
	14	Cardamom	Packing peanut pieces