Department of Physics, Chemistry and Biology

Master Thesis

Olfactory and cognitive abilities in two strains of Alzheimer`s disease model mice

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Titel
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Sammanfattning
Abstract:

The present study assessed olfactory and cognitive abilities in two strains of Alzheimer's disease (AD) model mice and in healthy control mice over a four month time period. To this end an operant conditioning paradigm using an automated olfactometer and a spatial learning test with non-olfactory cues were employed and data on olfactory learning and memory, discrimination, and sensitivity as well as spatial learning and memory were collected. The mice were between 6 to 7 month old at the beginning of the study and 9 to 10 months old at the end of the data collection, that is, in the age range when the animals are supposed to display marked neuroanatomical changes typical of AD. The results demonstrate that there were no systematic differences in olfactory performance and spatial learning and memory abilities of AD model mice and the control mice up to the age they were tested. Further, there was no indication of an age-related decline in performance in any of the mouse strains across the testing period. Several reasons might account for the observed lack of difference in olfactory and cognitive performance between the mouse strains tested here: the AD model mice might not develop amyloid plaques and neurofibrillary tangles at all or they might develop them later than stated by the supplier. Alternatively, the AD model mice may have developed AD-typical neuroanatomical changes but these do not, or not yet, affect their olfactory performance and/or spatial learning and memory capabilities. Ongoing data collection will help to evaluate which of these explanations holds true.

Nyckelord
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AD model mice, tau, amyloid beta, Alzheimer`s disease, olfactory and cognitive abilities.

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1 Abstract

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Keywords: AD model mice, tau, amyloid beta, Alzheimer`s disease, olfactory and cognitive abilities.

2 Introduction

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder. It affects about 10% of people at the age of 65 and about 50% of people at the age of 85 (Evans et al. 1990, Brookmeyer et al. 1990). It is the most common form of dementia and causes abnormal changes in the brain which worsen over time and interfere with many aspects of the brain (Gong 2008). As the disease progresses persons affected with AD suffer from cognitive and sensory impairments, widespread loss of mental abilities and ultimately death (Welsh-Bohmer et al. 2009). It is not fully understood what the causes for the disease are but a number of neuroanatomical changes are characteristic for AD, among them are amyloid plaques and neurofibrillary tangles (Duyckaerts et al. 2008). Beta amyloid is a protein fragment that is formed after the sequential cleavage of a trans membrane glycoprotein named amyloid precursor protein (APP) (Hock et al. 1998). In a healthy brain beta amyloid is broken down and eliminated, in persons affected with AD these fragments accumulate and form extracellular plaques which are thought to be one of the main causes in the pathogenesis of AD (Yin et al. 2007). Tau proteins are microtubule associated proteins which are common in neurons and the central nervous system (Sergeant et al. 2008). Tau proteins belong to a family of factors that polymerize tubulin dimers and stabilize microtubules (Sergeant et al. 2008). Normal phosphorylation of tau protein causes disruption of the microtubule organization (Taniguchi et al. 2001), in humans with AD the tau protein is hyperphosphorylated and can lead to neurofibrillary tangles which are also thought to play an important role in the pathogenesis of the disease (Sorrentino et al. 2007). Currently there is no cure for AD and the mechanisms underlying the development of the disease are only poorly understood.

Recent progress in the development of transgenic mice now allow us to study animals that develop neuroanatomical changes such as amyloid plaques and neurofibrillary tangles that are characteristic of human AD. The study of such animal models of human AD shall contribute to our understanding of the disease and perhaps even to the development of a treatment. The diagnosis of human AD is difficult to this day and therefore includes a battery of cognitive and sensory tests. One of the earliest symptoms of AD in humans is an olfactory impairment (Doty et al. 1987, Serby et al. 2001) which is currently used, among other criteria, to diagnose human AD (McCaffery et al. 2000). Other typical clinical symptoms of human AD include cognitive impairment in learning and memory tasks. Therefore I decided to focus on olfactory performance and on learning and memory capabilities in the AD model mice. To this end I employed an operant conditioning paradigm using an automated olfactometer and a spatial learning test with non-olfactory cues. Both have been used in a variety of previous studies with different strains of mice (Rubin 2001, Vedin 2004, Kelliher 2003, Wessinger 2004, Laska 2005, McBride 2003)

It is not known whether AD model mice show an olfactory impairment as humans do. In this study I used two strains of AD model mice which overexpress proteins that are implicated in the neuroanatomical changes which characterize AD (the tau protein, and the beta amyloid protein). The AD mouse strain that overexpresses the Tau protein (Tau mice) has previously been used in one other study (Vloeberghs 2008) whereas the AD mouse strain that overexpresses the beta amyloid protein (Swede mice) has not previously been used in any study. These AD model mice provide a means to learn more about how the neuroanatomical changes in the brain caused by AD and the observed cognitive and olfactory impairments are linked. In the present study I therefore tested two strains of AD model mice for different aspects of their olfactory and cognitive performance over a four month period and compared these data to those of a group of control mice tested in parallel. More specifically, I tested the ability of both strains of AD mice as well as of control mice

1. to discriminate between odors, 2. to learn the reward value of new odors, 3. to remember the reward value of previously learned odors, and 4. to succeed in olfactory reversal tasks. Further, I determined olfactory detection thresholds and assessed the ability of the animals to succeed in a non-olfactory spatial learning and memory task.

3 Materials and methods

3.1 Animals

Testing was carried out using nine male adult mice of three different strains.

A) Tau mice:

Three mice of the strain B6SJL-Tg(APPSwFlLon, PSEN1*M146L*L286V) 6799Vas/J were used. This strain overexpresses both mutant human amyloid precursor protein APP(695) with the Swedish (K670N, M671L), Florida (I716V), and London (V717I) Familial Alzheimer's Disease (FAD) mutations and human presenilin 1 (PS1) harboring two FAD mutations, M146L and L286V. The following information is given by Jackson Laboratory on the development of the neuroanatomical changes in the Tau mice: $Abeta_{42}$ deposits (Amyloid fibrils in Alzheimer's disease mainly consist of 40- and 42-mer beta-amyloid peptides (Abeta40, Abeta42) that exhibit aggregative ability and neurotoxicity) (Morimoto2004), develop at 2 months of age; $Abeta_{40}$ levels are lower in amyloid deposits; mice show robust intraneuronal amyloid deposition, amyloid deposition increases rapidly with increasing age, plaques appear first in deep cortical layers and in subiculum, and spread with age to fill most

of cortex, subiculum and hippocampus; also, less numerous deposits are observed in thalamus, brainstem and olfactory bulb in older mice. Spatial learning deficits have been observed at 4-5 months of age.

B) Swede mice:

Three mice of the strain B6.Cg-Tg(APPswe,PSEN1dE9)85Dbo/J were used. This strain expresses a chimeric mouse/human amyloid precursor protein (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9). The following information is given by Jackson Laboratory on the development of the neuroanatomical changes in the Swede mice: plaques are abundant in hippocampus and cortex by 9 months of age, occasional deposits can be found in mice as young as 6 months of age, ratio of amyloid beta peptide 40:42 is 0.50:1. Spatial learning deficits develop by 6 to 7 months of age.

C) Control mice:

Three mice of the strain B6.Cg-*Mapttm1(EGFP)Klt* Tg(MAPT)8cPdav/J were used. This is an inbred strain with a genetic background similar to that of the Tau and Swede mice used as the control in this study.

The mice were between 6 and 7 months old at the beginning of the study. The animals were housed individually in standard plastic cages in a temperature- and humidity-controlled room and maintained under natural lighting conditions. During the experiments the animals were kept on a water deprivation schedule of 1ml of water per day. The experiments were performed at the Neurobiology Department of Yale University School of Medicine in New Haven, CT, USA. The experiments reported here comply with the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health Publication No. 86-23, revised 1985) and were performed according to a protocol approved by the Yale University Institutional Animal Care and Use Committee.

3.2 Stimuli

A set of 12 odorants was used (Table 1). With all discrimination tasks the odorants were presented at a gas phase concentration of 1 ppm (part per million) and with all threshold tasks testing started at a gas phase concentration of 1 ppm and then proceeded with lower concentrations. Gas phase concentrations for all odorants were calculated using the formulae provided by Weast (1987). All substances were obtained from Sigma–Aldrich (St. Louis, MO) and had a nominal purity of at least 99%. They were diluted using odorless diethyl phthalate as the solvent. The rationale for using this set of odor stimuli was that they have been successfully used in previous studies and are thus known to represent stimulus pairs differing in difficulty as well as stimuli for which olfactory detection thresholds have been established (Laska 2006, Laska 2007).

Table 1 Odorants used

Odorants	CAS#
anethole	104-46- 1
amyl acetate	628-63-7
eugenol	97-53-0
1,8-cineol	470-82-6
N-hexanal	66-25-1
1-octanol	111-87-5
(-)-carvone	2244-16-8
(+)-carvone	6485-40-1

(-)-limonene	7721-11-1
(+)-limonene	5989-27-5
(-)-2-butanol	14898-79-4
(+)-2-butanol	4221 -99-2

3.3 Behavioral test
3.3.1 General method
Olfactory performance of the mice was assessed using an automated liquid-dilution olfactometer (Knosys, Tampa, FL). Mice were trained using standard operant conditioning procedures (Bodyak and Slotnick, 1999) to insert their snout into the odor sampling port of a test chamber. This triggered the 2 s presentation of either an odorant used as the rewarded stimulus (S+) or an alternative odorant used as the unrewarded stimulus (S-). Licking at a steel tube providing 2.5 µl of water reinforcement in response to presentation of the S+ served as the operant response.

3.3.2 Assessment of olfactory discrimination performance
Olfactory discrimination performance was assessed by testing the animals' ability to distinguish between a given odorant used as the S+, and an alternative odorant used as the S-. Five blocks of 20 trials (totaling 50 S+ and 50 S- trials in pseudorandomized order) using a given stimulus pair were conducted per animal and task.

### 3.3.3 Determination of olfactory detection thresholds
Olfactory detection thresholds were determined by testing the animals` ability to discriminate between increasing dilutions of a given odorant used as S+ and a blank stimulus (headspace of the odorless solvent) used as the S-. Two blocks of 40 trials (20 S+ and 20 S- trials in pseudorandomized order) using the same concentration of the S+ were conducted per animal. Starting with a gas phase concentration of 1 ppm, an odor was successively presented in 10-fold dilution steps until the animal failed to significantly discriminate the odorant from the solvent. Subsequently, an intermediate concentration (0.5 log units between the lowest concentration that was detected above chance and the first concentration that was not) was tested in order to determine the threshold value more exactly.

3.3.4 Spatial learning test
The animals` ability for simple spatial learning was assessed using a unit consisting of a cardboard with a divider wall creating two equally sized compartments, one with a black wall and one with a white wall (fig 1). This was placed inside the animal`s home cage, making up one third of the total cage area. Another piece of cardboard, "the curtain", was placed in front of the two compartments separating them from the other two thirds of the cage, "the starting area". The mouse was placed into the starting area and the curtain was raised revealing the two compartments. When the mouse decided to enter the rewarded compartment after being put into the starting area it was rewarded with 0.1 ml of water presented from a syringe lowered into the compartment directly in front of the colored wall and the trial was recorded as correct. When the mouse decided to enter the unrewarded compartment after being put into the starting area no water reward was presented and the trial was recorded as wrong. After completion of a trial the animal was placed back into the starting area, the curtain was lowered concealing the two compartments and a new trial could begin. This process was repeated ten times per mouse and day for seven days. Half of the mice were always rewarded

when entering the black compartment, and the other half of the mice were always rewarded when entering the white compartment.

Fig 1. The spatial learning setup.
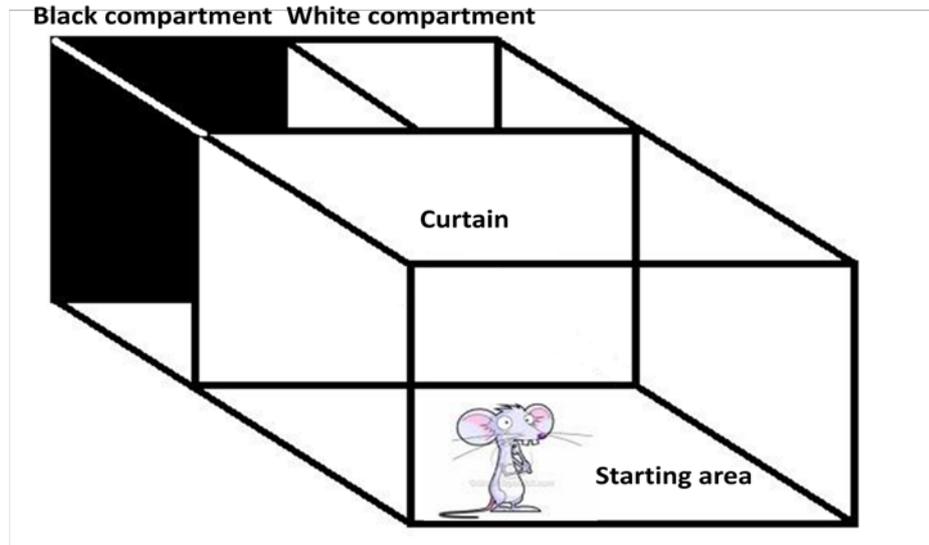
3.3.5 Initial task acquisition
The initial task acquisition included a series of steps allowing the animals to learn how to operate the olfactometer. After shaping, that is: a phase in which the animals were only presented with amyl acetate as rewarded stimulus (S+) and rewarded for each poking their head into the odor port, the mice were then trained to learn how to respond to different S+ and S- stimuli for two days each. Testing started with two sessions of 100 trials each, in which the mice learned to correctly respond to amyl acetate as S+ and eugenol as S-. For the following two days the S- was replaced with anethole, keeping amyl acetate as S+ (First negative transfer task). For the following two days the S+ was replaced with cineole, keeping anethole as the S- (first positive transfer task). And for the last two days of the initial task acquisition the S- was again replaced with eugenol, keeping cineole as the S+.

After completion of this series of initial tasks in which the animals acquired the basic discrimination paradigm, the mice were tested on a series of olfactory tasks in monthly intervals as described below. This was done in the hope to determine the onset and progression of possible olfactory impairment in the two strains of Alzheimer model mice.

3.3.6 Experimental series 1
Immediately after the completion of the initial task acquisition the mice were presented with a sequence of tasks summarized in table 2. After completion of these tasks one week of spatial learning was performed.

Table 2

Task	Odor pairs
1. Discrimination	(+)-2-butanol vs. (-)-2-butanol
2. Discrimination	hexanal vs. eugenol

3. Threshold	hexanal vs. blank

Task 1 allowed for testing differences between strains in the ability to acquire a double transfer (as the animals did not have a double transfer during the initial tasks). Task 2 allowed for testing differences between strains in the ability to master a new positive transfer. Additionally, the introduction of hexanal as a new S+ was the prerequisite for subsequent threshold testing. Task 3 allowed for determining a detection threshold value which builded a baseline for assessing possible changes in sensitivity as a function of age.

3.3.7 Experimental series 2

30 days after the start of the first experimental series, testing was resumed following the sequence of tasks summarized in table 3. After completion of these tasks one week of spatial learning was performed.

Table 3

Task	Odor pairs
1. Discrimination	amyl acetate vs. eugenol
2. Discrimination	(+)-carvone vs. (-)-carvone
3. Discrimination	(+)-2-butanol vs. (-)-2-butanol
4. Discrimination	(-)-2-butanol vs. (+)-2-butanol
5. Threshold	hexanal vs. blank
6. Threshold	octanol vs. blank

Task 1 allowed for testing long-term odor memory as the same stimulus pair had been presented to the animals during the initial task acquisition. Task 2 allowed for testing changes in the ability to acquire a new double transfer by comparing the animals' performance to that in the previous month's double transfer. Task 3 allowed for testing long-term odor memory with another stimulus pair as the same stimulus pair had been presented to the animals in experimental series 1. Task 4 allowed for testing the ability to learn a stimulus reversal. Task 5 allowed for testing changes in sensitivity as a function of age as the same task had been presented to the animals in experimental series 1. Task 6 allowed for testing the ability to acquire the reward value of a new S+ and for building a baseline for assessing possible changes in sensitivity as a function of age.

3.3.8 Experimental series 3

30 days after the start of the second experimental series, testing was resumed following the sequence of tasks summarized in table 4. After completion of these tasks one week of spatial learning was performed.

Table 4

Task	Odor pairs
1. Discrimination	amyl acetate vs. eugenol
2. Discrimination	(+)-limonene vs. (-)-limonene
3. Discrimination	(+)-carvone vs. (-)-carvone
4. Discrimination	(-)-carvone vs. (+)-carvone
5. Threshold	hexanal vs. blank

Task 1 allowed for testing the long-term odor memory as the same stimulus pair had been presented to the animals during experimental series 2. Task 2 allowed for testing changes in the ability to acquire a new double transfer by comparing the animals' performance to that in experimental series 1 and 2. Task 3 allowed for testing long-term odor memory as the same stimulus pair had been presented to the animals in experimental series 2. Task 4 allowed for testing changes in the ability to learn a stimulus reversal by comparing the animals' performance to that in the previous month's reversal task. Task 5 allowed for testing changes in sensitivity as a function of age.

3.3.9 Experimental series 4
30 days after the start of the third experimental series, testing was resumed following the sequence of tasks summarized in table 5.

Table 5

Task	Odor pairs
1. Discrimination	Amyl acetate vs. Eugenol
2. Discrimination	(+)-isopulegol vs. (-)-isopulegol
3. Discrimination	(+)-limonene vs. (-)-limonene
4. Discrimination	(-)-limonene vs. (+)-limonene

Task 1 allowed for testing the long-term odor memory as the same stimulus pair had been presented to the animals during experimental series 2 and 3. Task 2 allowed for testing changes in the ability to acquire a new double transfer by comparing the animals' performance to that in experimental series 1, 2 and 3. Task 3 allowed for testing long-term odor memory as the same stimulus pair had been presented to the animals in experimental series 2. Task 4 allowed for testing changes in the ability to learn a stimulus reversal by comparing the animals' performance to that in the previous month's reversal task.

3.4 Data analysis
With all olfactory discrimination tasks 100 trials (50 S+ and 50 S- trials in pseudorandomized order) were performed per stimulus pair and animal. The criterion for an animal to be regarded as capable of discriminating a given stimulus pair was set at two consecutive sessions of at least 85% correct (corresponding to $p < 0.01$, two-tailed binomial test). With all olfactory detection threshold tasks 40 trials (20 S+ and 20 S- trials in pseudorandomized order) were performed per concentration step and animal. Here too, two-tailed binomial tests were employed to assess performance ($p < 0.01$). With the spatial learning tasks 10 trials were performed per month and animal. Here too, two-tailed binomial tests were employed to assess performance ($p < 0.05$).

4 Results
4.1 Initial acquisition task
First two-odor discrimination task
Figure 1 shows the mean performance of the three mouse strains in discriminating between amyl acetate (S+) and eugenol (S-) across the 10 blocks of 20 trials. The control mice (squares) and the Tau mice (circles) reached the criterion of 85% correct decisions in the third block of trials while the Swede mice (triangles) reached criterion in the fourth block of trials.
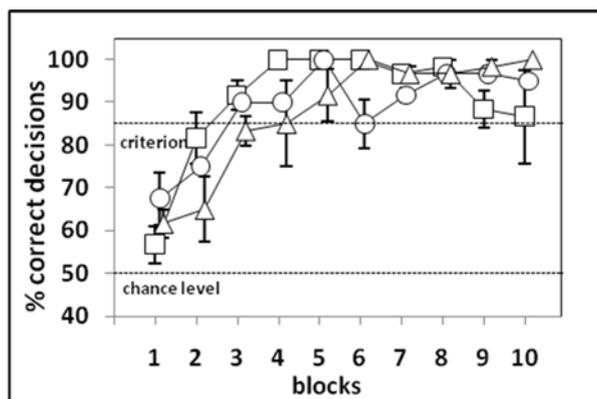
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Figure 1. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between amyl acetate (S+) and eugenol (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 2 summarizes the performance of the three mouse strains in discriminating between amyl acetate (S+) and eugenol (S-). When considering the mean percentage of correct decisions across all ten blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) performed above criterion and differed very little in their performance with the percentage of correct decisions ranging between 90% for control mice and 88% for the Swede mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed only slightly in their performance with the percentage of correct decisions ranging between 68% for the Tau mice and 57% for the control mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed markedly in their performance with the percentage of correct rejections of the unrewarded stimulus ranging between 40% for the Tau mice and 13% for the control mice.
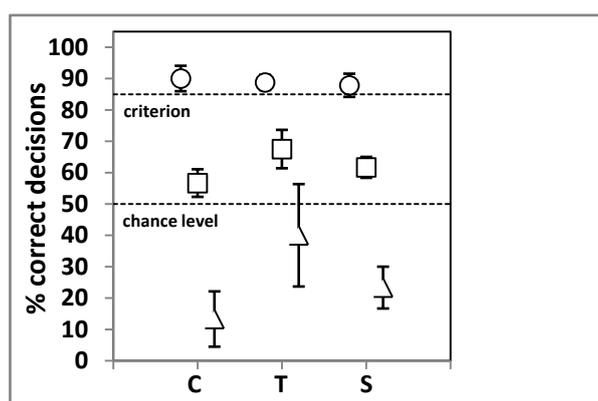

Figure 2. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between amyl acetate (S+) and eugenol (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the ten blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

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First negative transfer task

Figure 3 shows the mean performance of the three mouse strains in discriminating between amyl acetate (S+) and anethole (S-), that is: the first negative transfer task, across the 10 blocks of 20 trials. All three mouse strains, control mice (squares), Tau mice (circles) and Swede mice (triangles) reached the criterion of 85% correct decisions in the first block of trials and performed very similar across all blocks.
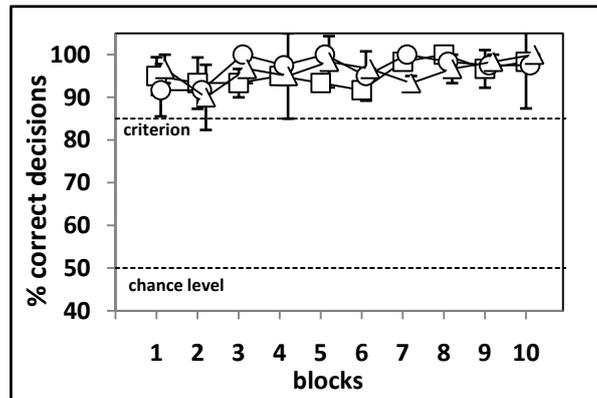

Figure 3. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between amyl acetate (S+) and anethole (S-). Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 4 summarizes the performance of the three mouse strains in discriminating between amyl acetate (S+) and anethole (S-). When considering the mean percentage of correct decisions across all ten blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) all performed above criterion and differed very little in their performance with the percentage of correct decisions ranging between 97% for the Tau mice and 96% for the control mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains, again, differed very little with the percentage of correct decisions ranging between 97% for the Swede mice and 92% for the Tau mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the mouse strains differed slightly with the percentage of correct rejections of the unrewarded stimulus ranging between 93% for the Swede mice and 83% for the Tau mice.
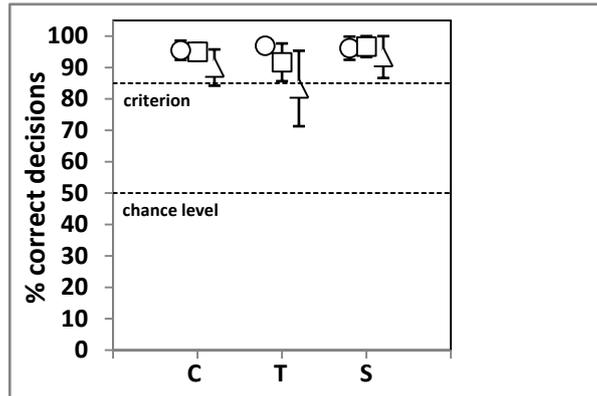
Figure 4. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between amyl acetate (S+) and anethole (S-), each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the ten blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

First positive transfer task

Figure 5 shows the mean performance of the three mouse strains in discriminating between cineole (S+) and anethole (S-), that is: the first positive transfer task, across the 10 blocks of 20 trials. The Tau mice (circles) reached the criterion of 85% correct decisions in the second block, while the control mice (squares) and the Swede mice (triangles) reached criterion in the fifth block. The mouse strains differed little in their performance after the fifth block of trials.
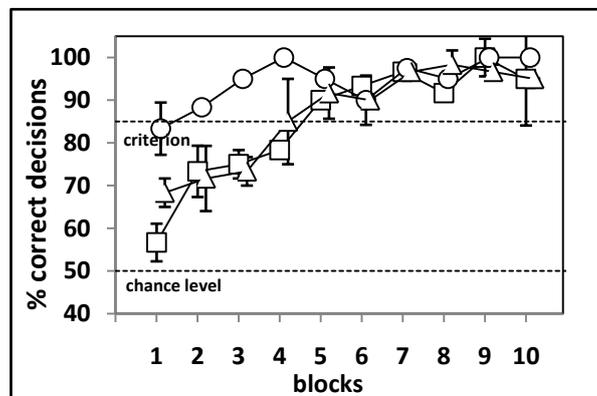

Figure 5. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between cineole (S+) and anethole (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 6 summarizes the performance of the three mouse strains in discriminating between cineole (S+) and anethole (S-). When considering the mean percentage of correct decisions across all ten blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) performed above criterion and differed only slightly in their performance with the percentage of correct decisions ranging between 94% for the Tau mice and 85% for the control mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed markedly in their performance with the percentage

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of correct decisions ranging between 83% for the Tau mice and 58% for the control mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the mouse strains differed markedly with the percentage of correct rejections of the unrewarded stimulus ranging between 97% for the control mice and 73% for the Tau mice.
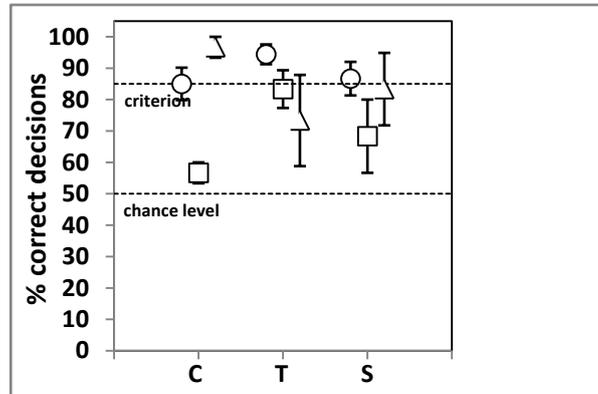

Figure 6. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between cineole (S+) and anethole (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the ten blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (square), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Second negative transfer task

Figure 7 shows the mean performance of the three mouse strains in discriminating between cineole (S+) and eugenol (S-), a second negative transfer task, across the 10 blocks of 20 trials. All three mouse strains, the control mice (squares), the Tau mice (circles) and the Swede mice (triangles) reached the criterion of 85% correct decisions in the first block of trials and performed similar across all blocks.
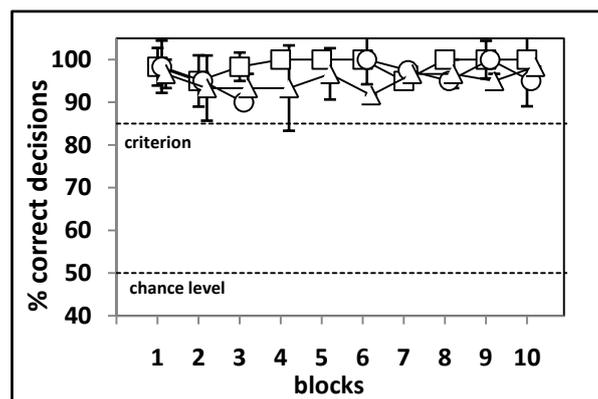

Figure 7. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between cineole (S+) and eugenol (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

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Figure 8 summarizes the performance of the three mouse strains in discriminating between cineole (S+) and eugenol (S-). When considering the mean percentage of correct decisions across all ten blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) performed above criterion and differed only slightly in their performance with the percentage of correct decisions ranging between 99% for the control mice and 95% for the Swede mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the mouse strains, again, differed very little with the percentage of correct decisions ranging between 98% for the control and Tau mice and 97% for the Swede mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the mouse strains differed not at all with the percentage of correct rejections of the unrewarded stimulus being 97% for all three mouse strains.
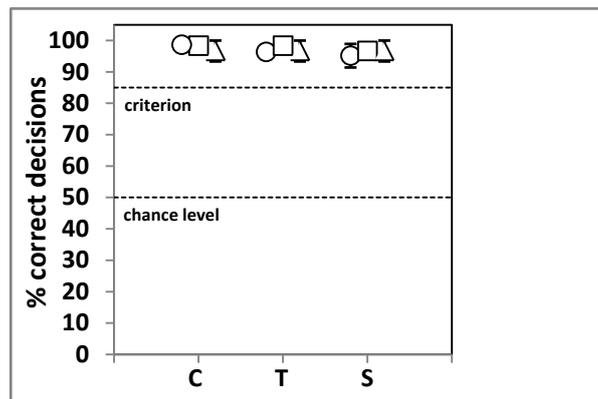

Figure 8. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between cineole (S+) and eugenol (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the ten blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

4.2 Experimental series 1
Double-transfer task
Figure 9 shows the mean performance of the three mouse strains in discriminating between (+)-2-butanol as rewarded stimulus and (-)-2-butanol as unrewarded stimulus, a double-transfer task, across the 10 blocks of 20 trials. The control mice (squares) reached the criterion of 85% correct decisions in the seventh block and the Swede mice (triangles) reached criterion in the eighth block while the Tau mice (circles) failed to reach criterion. On the first day with this task the Tau mice only performed three instead of the usual five blocks of trials. The control mice performed slightly better across most blocks of trials than the Swede mice and markedly better than the Tau mice.
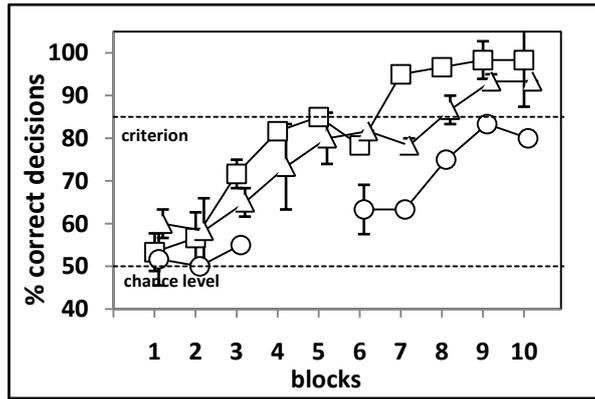
Figure 9. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between (+)-2-butanol as rewarded stimulus and (-)-2-butanol as unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 10 summarizes the performance of the three mouse strains in discriminating between (+)-2-butanol as rewarded stimulus and (-)-2-butanol as unrewarded stimulus. When considering the mean percentage of correct decisions across all ten blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) performed below criterion. The control and Swede mice performed markedly better than the Tau mice with the percentage of correct decisions ranging between 82% for control mice and 65% for the Tau mice. When considering the mean percentage of correct decisions in the first block of 20 trials (circles) the three mouse strains differed only slightly in their performance, with the percentage of correct decisions ranging between 60% for the Swede mice and 52% for the Tau mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed markedly with the percentage of correct rejections of the unrewarded stimulus ranging between 47% for the control mice and 20% for the Tau mice.
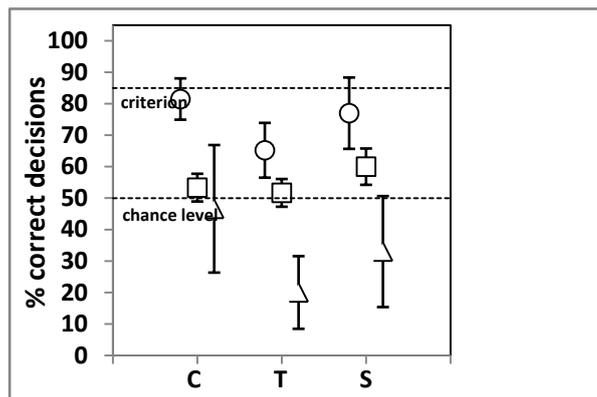

Figure 10. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between (+)-2-butanol as rewarded stimulus and (-)-2-butanol as unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the ten blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

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Positive transfer task

Figure 11 shows the mean performance of the three mouse strains in discriminating between hexanal (S+) and eugenol (S-), a positive transfer task, across the five blocks of 20 trials. The three mouse strains controls (squares), Tau mice (circles) and Swede mice (triangles) reached the criterion of 85% correct decisions in the first block of trials. Across all blocks the three mouse strains performed similarly.
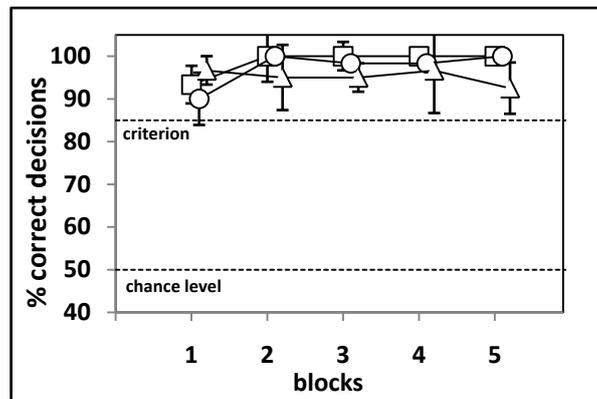

Figure 11. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between hexanal (S+) and eugenol (S-). Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 12 summarizes the performance of the three mouse strains in discriminating between hexanal (S+) and eugenol (S-). When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) performed above criterion with the percentage of correct decisions ranging between 99% for control mice and 95% for the Swede mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed only slightly in their performance with the percentage of correct decisions ranging between 97% for the Swede mice and 90% for the Tau mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the Swede mice performed slightly better than the control and Tau mice with the percentage of correct rejections of the unrewarded stimulus ranging between 100% for the Swede mice and 87 % for the control mice
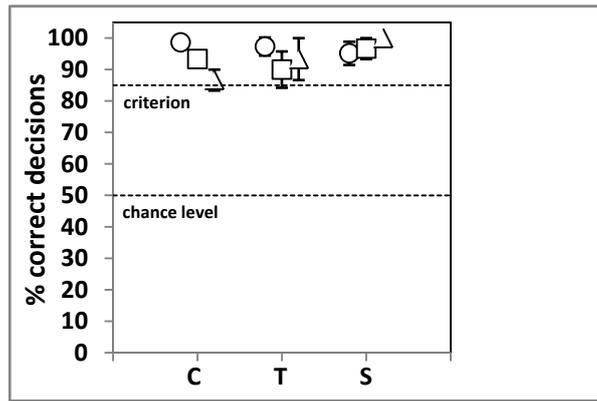
Figure 12. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between hexanal (S+) and eugenol (S-). Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions (a) across the five blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Detection threshold task

Figure 13 shows the performance of the control mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). The three mice reached the criterion of 75% corrects decisions when distinguishing between hexanal $3x10^{-6}$ ppm and the solvent but all failed with hexanal 10^{-6} ppm.
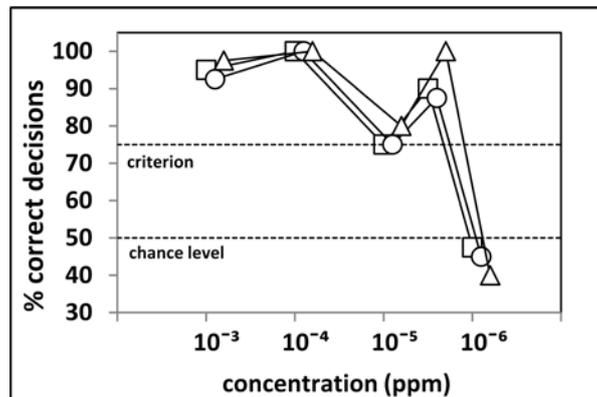

Figure 13. Performance of the three control mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal C1 (square), C2 (circle) and C3 (triangle).

Figure 14 shows the performance of the Tau mice discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). All three animals reached the criterion of 75% correct decisions when distinguishing between hexanal $3x10^{-6}$ ppm and the solvent . Mouse T2 (circle) failed with hexanal 10^{-6} ppm, mice T1 (square) and T3 (triangle) failed to complete their trials with the hexanal 10^{-6} ppm dilution and testing could not be completed.
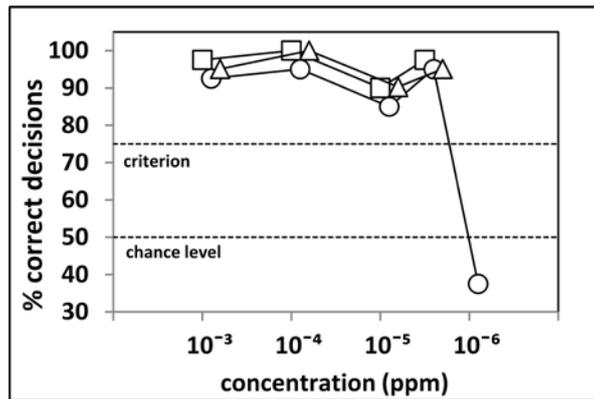
Figure 14. Performance of the three Tau mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal T1 (square), T2 (circle) and T3 (triangle).

Figure 15 shows the performance of the Swede mice discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). The three mice reached the criterion of 75% correct decisions when distinguishing between hexanal 10^{-5} ppm and the solvent but all three animals failed with hexanal 3×10^{-6} ppm.
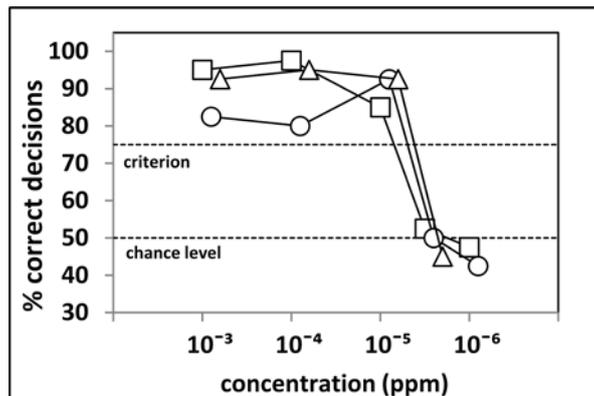

Figure 15. Performance of the three Swede mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal S1 (square), S2 (circle) and S3 (triangle).

Spatial learning test
Figure 16 shows the mean performance of the three mouse strains in the spatial learning task. The control mice (squares) reached the criterion of 90% correct decisions on the fifth day and a clear learning tendency could be seen across the seven days of testing with the percentage of correct decisions increasing from 63% on the first day to 93% on the seventh day of testing. The Tau mice (circles) failed to reach criterion but a clear learning tendency could be seen across the seven days of testing with the percentage of correct decisions increasing from 50% on the first day to 77% on the sixth day of testing. The Swede mice (triangles) reached

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criterion on the sixth day and a clear learning tendency could be seen with the percentage of correct decisions increasing from 50% on the second day to 90% the sixth day of testing.
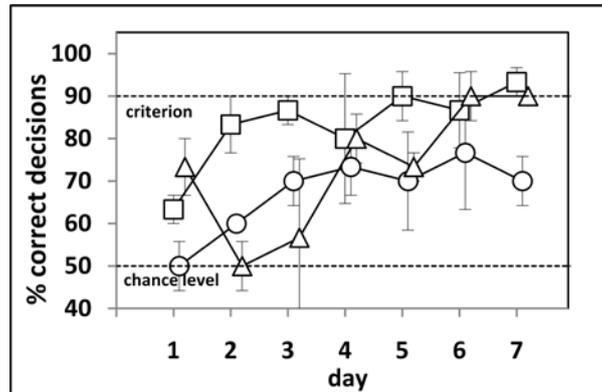

Figure 16. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in the spatial learning test. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions from 10 trials per day and animal. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 90%), respectively.

4.3 Experimental series 2

Long-term odor memory task

Figure 17 shows the mean performance of the three mouse strains in discriminating between amyl acetate (S+) and eugenol (S-), a long-term odor memory task, across the five blocks of 20 trials. The control mice (squares) and the Tau mice (circles) reached the criterion of 85% correct decisions in the first block of trials while the Swede mice (triangles) reached criterion in the second block of trials. The Swede mice performed slightly poorer than the control and Tau mice across all blocks.
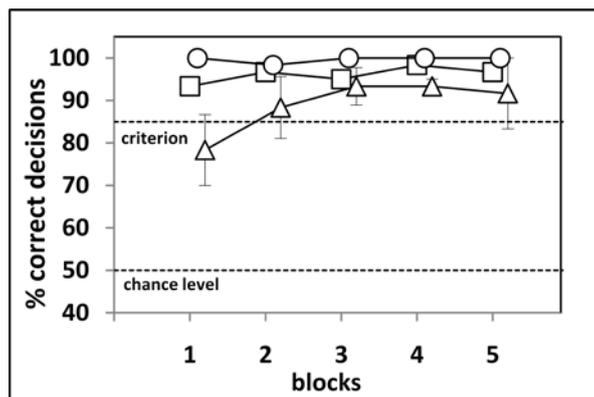

Figure 17. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between amyl acetate (S+) and eugenol (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

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Figure 18 summarizes the performance of the three mouse strains in discriminating between amyl acetate (S+) and eugenol (S-). When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) performed above criterion but differed to some degree in their performance, with the percentage of correct decisions ranging between 99% for the Tau mice and 89% for the Swede mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed markedly in their performance. The Swede mice performed poorer than the control and Tau mice with the percentage of correct decisions ranging between 100% for the Tau mice and 78% for the Swede mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed markedly in their performance. The Swede mice performed markedly poorer than the control and Tau mice with the percentage of correct rejections of the unrewarded stimulus ranging between 100% for the Tau mice and 63% for the Swede mice.
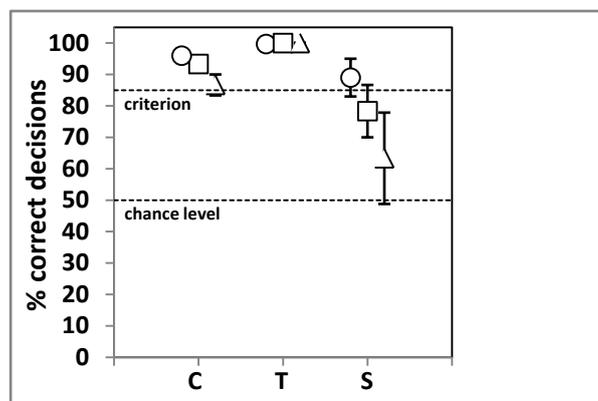

Figure 18. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between amyl acetate (S+) and eugenol (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct descisions (a) across the five blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Double-transfer task
Figure 19 shows the mean performance of the three mouse strains in discriminating between (+)-carvone as the rewarded stimulus and (-)-carvone as the unrewarded stimulus across the five blocks of 20 trials. The Swede mice (triangle) reached the criterion of 85% correct decisions in the fourth block of trials whilst the control (square) and Tau mice (circle) reached criterion in the fifth block of trials. The Swede mice performed better than the control and Tau mice across the first four blocks and performed similarly in the fifth block.
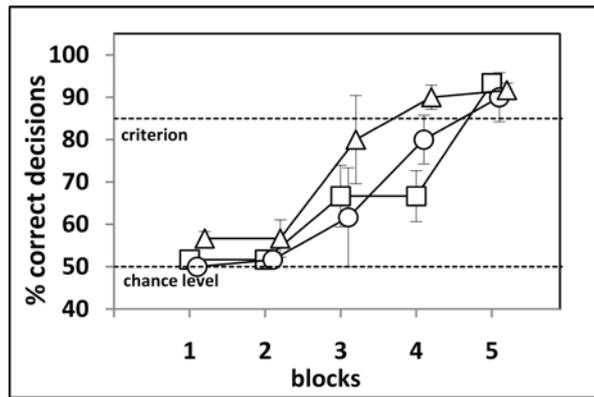
Figure 19. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between (+)-carvone as the rewarded stimulus and (-)-carvone as the unrewarded stimulus. Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 20 summarizes the performance of the three mouse strains in discriminating between (+)-carvone as the rewarded stimulus and (-)-carvone as the unrewarded stimulus. When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) performed below criterion and differed slightly with the percentage of correct decisions ranging between 75% for Swede mice and 66% for the control mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains performed similar with the percentage of correct decisions ranging between 57% for the Swede mice and 50% for the Tau mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed to some degree in their performance. The Swede mice performed, again, slightly better than the control and Tau mice with the percentage of correct rejections of the unrewarded stimulus ranging between 13% for the Swede mice and 0% for the Tau mice.
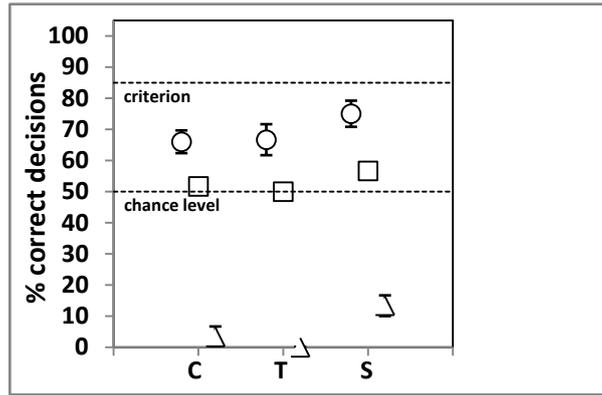
Figure 20. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between (+)-carvone as the rewarded stimulus and (-)-carvone as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the ten blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Long-term odor memory task

Figure 21 shows the mean performance of the three mouse strains in discriminating between (+)-2-butanol as the rewarded stimulus and (-)-2-butanol as the unrewarded stimulus across the five blocks of 20 trials. All three mouse strains controls (squares), Tau mice (circles) and Swede mice (triangles) reached the criterion of 85% correct decisions in the second block of trials. The three mouse strains performed similar across all five blocks.
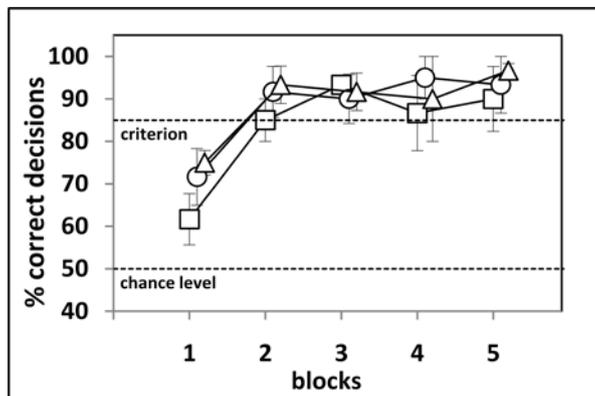

Figure 21. Performance of the control (squares) ,Tau (circles) and Swede (triangles) mice in discriminating between (+)-2-butanol as the rewarded stimulus and (-)-2-butanol as the unrewarded stimulus. Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 22 summarizes the performance of the three mouse strains in discriminating between (+)-2-butanol as the rewarded stimulus and (-)-2-butanol as the unrewarded stimulus. When considering the mean percentage of correct decisions across all five blocks of 20 trials the Tau mice (T) and Swede mice (S) performed above criterion while the control mice (C) barely failed to reach criterion with the percentage of correct decisions ranging between 89% for the

Swede mice and 83% for the control mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed to some degree in their performance, the Tau and the Swede mice performed slightly better than the control mice with the percentage of correct decisions ranging between 75% for the Swede mice and 62% for the control mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed markedly in their performance. The Swede mice performed to some degree better than the Tau mice and markedly better than the control mice with the percentage of correct rejections of the unrewarded stimulus ranging between 53% for the Swede mice and 33% for the control mice.
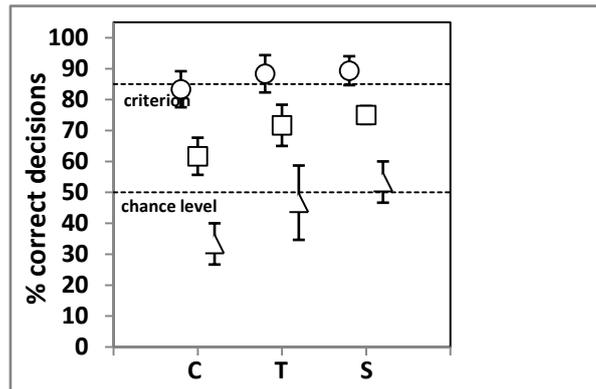

Figure 22. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between (+)-2-butanol as the rewarded stimulus and (-)-2-butanol as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the ten blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Stimulus reversal task

Figure 23 shows the mean performance of the three mouse strains in discriminating between (-)-2-butanol as the rewarded stimulus and (+)-2-butanol as the unrewarded stimulus, a stimulus-reversal task, across the five blocks of 20 trials. All three mouse strains controls (squares), Tau mice (circles) and Swede mice (triangles) failed to reach the criterion of 85% correct decisions across the five blocks.
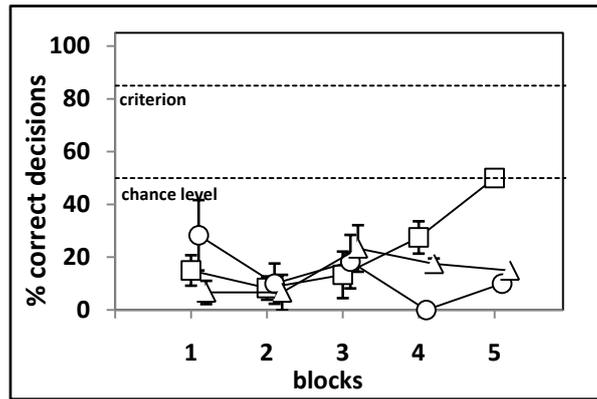
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Figure 23. Performance of the control (squares) ,Tau (circles) and Swede (triangles) mice in discriminating between (-)-2-butanol as the rewarded stimulus and (+)-2-butanol as the unrewarded stimulus. Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 24 summarizes the performance of the three mouse strains in discriminating between (-)-2-butanol as the rewarded stimulus and (+)-butanol as the unrewarded stimulus. When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) the three mouse strains performed below criterion and differed to some degree in their performance. The control mice (C) performed slightly better than the Tau mice (T) and the Swede mice (S) with the percentage of correct decisions ranging between 29% for the control mice and 13% for the Tau mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed markedly in their performance. The control mice performed better than the Tau and the Swede mice with the percentage of correct decisions ranging between 28% for the Tau mice and 7 % for the Swede mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed markedly in their performance. The Tau mice performed clearly better than the control and the Swede mice with the percentage of correct rejections of the unrewarded stimulus ranging between 43% for the Tau mice and 17% for the Swede mice.
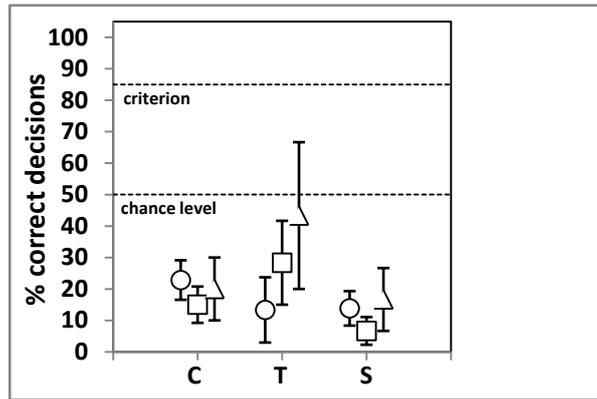
Figure 24. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between (-)-2-butanol as the rewarded stimulus and (+)-2-butanol as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the ten blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Detection threshold task

Figure 25 shows the performance of the control mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). Animals C1 (squares) and C3 (triangles) reached the criterion of 75% correct decisions when distinguishing between hexanal 3×10^{-4} ppm and the solvent but failed with hexanal 10^{-4} ppm. Animal C2 (circles) reached the criterion when distinguishing between hexanal 10^{-3} ppm and the solvent but failed with hexanal 3×10^{-4} ppm.
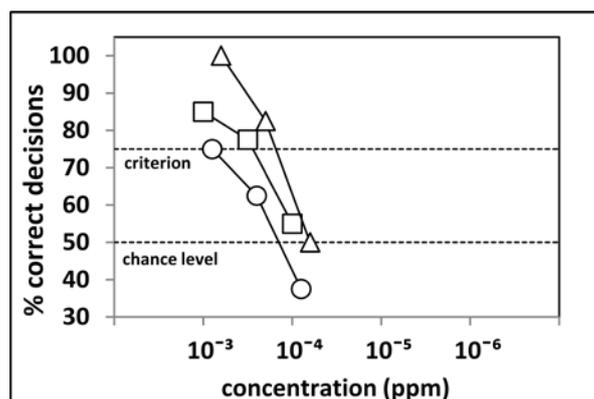

Figure 25. Performance of the three control mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal C1 (square), C2 (circle) and C3 (triangle).

Figure 26 shows the performance of the Tau mice discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). All three animals T1 (squares), T2 (circles) and T3 (triangles) reached the criterion of 75% correct decisions when distinguishing between hexanal 3×10^{-4} ppm and the solvent and all three animals failed with hexanal 10^{-4} ppm.
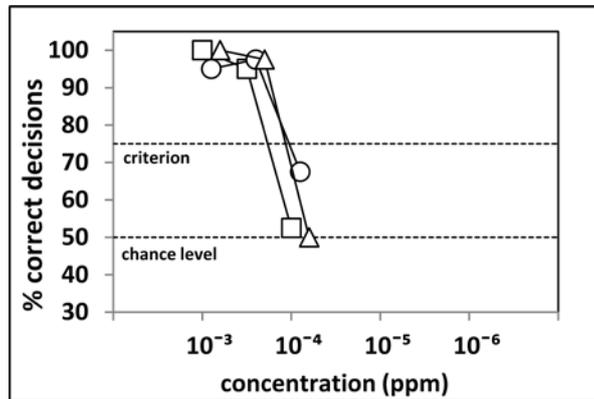

Figure 26. Performance of the three Tau mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal T1 (square), T2 (circle) and T3 (triangle).

Figure 27 shows the performance of the Swede mice discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). The three animals S1 (square), S2 (circle) and S3 (triangle) reached the criterion of 75% correct decisions when distinguishing between hexanal 3×10^{-4} ppm and the solvent and failed with hexanal 10^{-4} ppm.
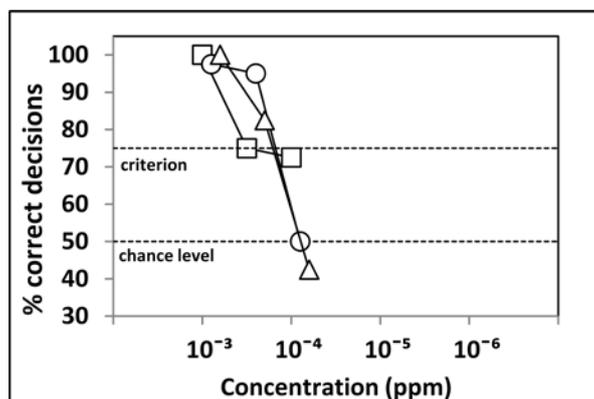

Figure 27. Performance of the three Swede mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal S1 (square), S2 (circle) and S3 (triangle).

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Detection threshold task

Figure 28 shows the performance of the control mice in discriminating between various dilutions of octanal (S+) and the odorless solvent (S-). Animals C1 (squares) and C2 (circles) reached the criterion of 75% correct decisions when distinguishing between octanal 3×10^{-7} ppm but failed with octanal 10^{-7} ppm. Animal C 3 (triangles) reached the criterion when distinguishing between octanal 10^{-6} ppm and the solvent but failed with octanal 3×10^{-7} ppm.
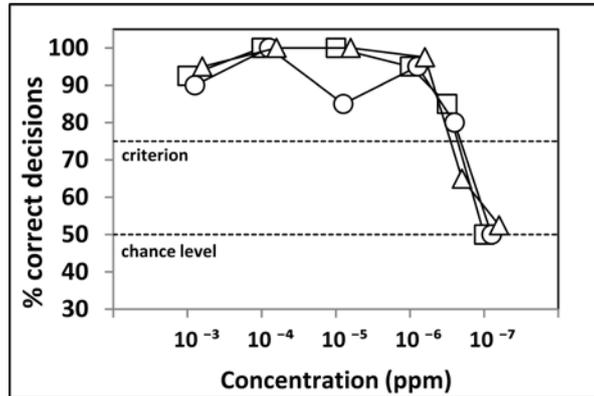

Figure 28. Performance of the three control mice in discriminating between various dilutions of octanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal C1 (square), C2 (circle) and C3 (triangle).

Figure 29 shows the performance of the Tau mice discriminating between various dilutions of octanal (S+) and the odorless solvent (S-). Animals T1 (squares) and T3 (triangles) reached the criterion of 75% correct decisions when distinguishing between octanal 3×10^{-7} ppm and the solvent but failed with octanal 10^{-7} ppm. Animal T2 (circles) reached criterion when distinguishing between octanal 10^{-6} ppm and the solvent but failed with octanal 3×10^{-7} ppm.
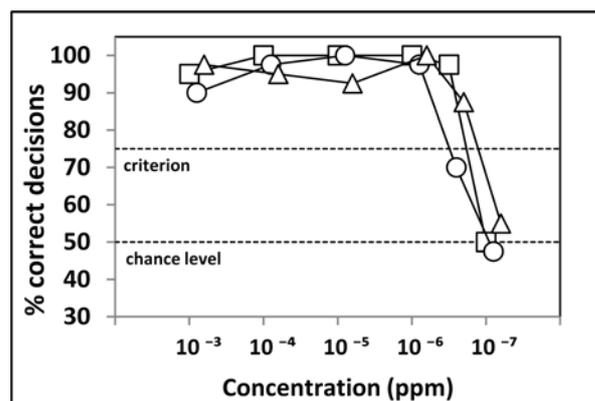

Figure 29. Performance of the three Tau mice in discriminating between various dilutions of octanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal T1 (square), T2 (circle) and T3 (triangle).

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Figure 30 shows the performance of the Swede mice discriminating between various dilutions of octanal (S+) and the odorless solvent (S-). The three animals S 1 (square), S2 (circle) and S3 (triangle) reached the criterion of 75% correct decisions when distinguishing between octanal 10^{-6} ppm and the solvent but failed with octanal $3x10^{-7}$ ppm.
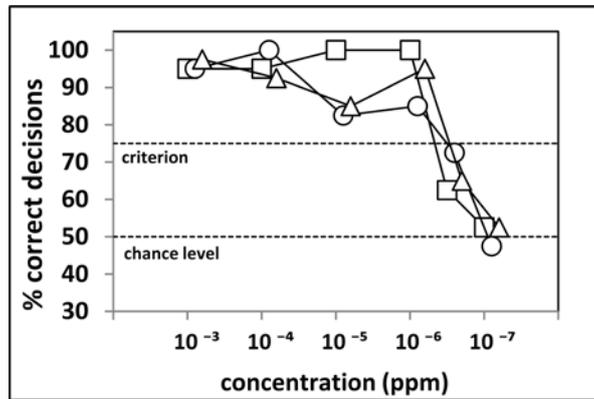

Figure 30. Performance of the three Swede mice in discriminating between various dilutions of octanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal S1 (square), S2 (circle) and S3 (triangle).

Spatial learning test
Figure 31 shows the mean performance of the three mouse strains in the spatial learning task. The control mice (squares) reached the criterion of 90% correct decisions on the first day with the percentage of correct decisions ranging between 93% on the sixth and 100% on the second day of testing. The Tau mice (circles) reached criterion on the first day with the percentage of correct decisions ranging between 80% on the third day and 93% on the second day of testing. The Swede mice (triangles) reached criterion on the second day with the percentage of correct decision ranging between 80% on the first day and 100% on the fifth day of testing.
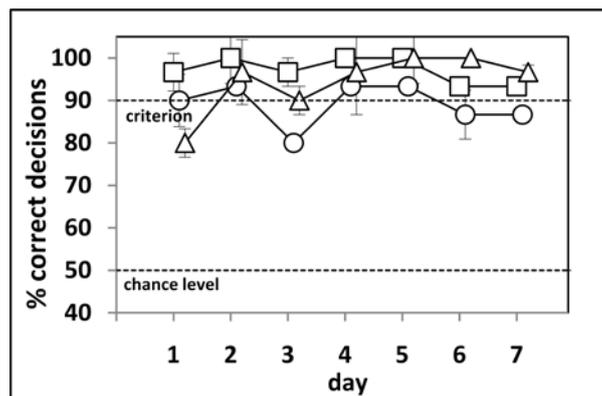

Figure 31. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in the spatial learning test. Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions from 10 trials per day and animal. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 90%), respectively.

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4.4 Experimental series 3

Long-term odor memory task

Figure 32 shows the mean performance of the three mouse strains in discriminating between amyl acetate (S+) and eugenol (S-) across the five blocks of 20 trials. All three mice strains, control mice (squares), Tau mice (circles) and Swede mice (triangles) reached the criterion of 85% correct decisions in the first block of trials and performed very similar across all blocks.
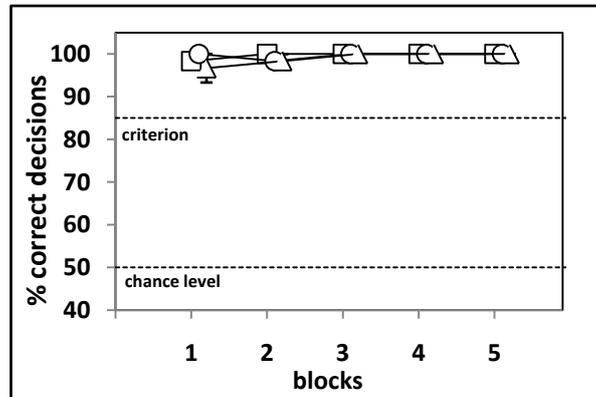

Figure 32. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between amyl acetate (S+) and eugenol (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 33 summarizes the performance of the three mouse strains in discriminating between amyl acetate (S+) and eugenol (S-). When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) performed above criterion and differed very little in their performance with the percentage of correct decisions ranging between 100% for the control and Tau mice and 99% for the Swede mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the mouse strains, again, differed very little with the percentage of correct decisions ranging between 100% for the Tau mice and 97% for the Swede mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the mouse strains differed, again, very little with the percentage of correct rejections of the unrewarded stimulus ranging between 100% for the Tau mice and 97% for the control and Swede mice.
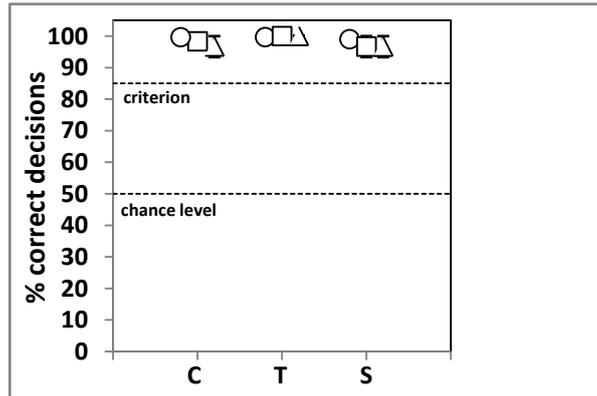
Figure 33. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between amyl acetate (S+) and eugenol (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the five blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Double-transfer task

Figure 34 shows the mean performance of the three mouse strains in discriminating between (+)-limonene as the rewarded stimulus and (-)-limonene as the unrewarded stimulus across the five blocks of 20 trials. The Tau mice (circles) reached the criterion of 85% correct decisions in the third block while the control (squares) and the Swede mice (triangles) reached the criterion in the fourth block of trials.
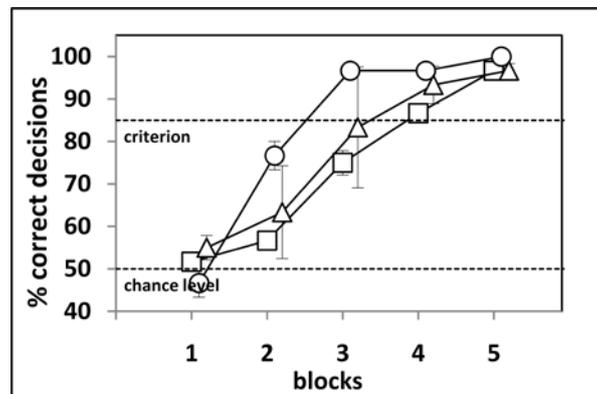

Figure 34. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between (+)-limonene as the rewarded stimulus and (-)-limonene as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 35 summarizes the performance of the three mouse strains in discriminating between (+)-limonene as the rewarded stimulus and (-)-limonene as the unrewarded stimulus. When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) performed below criterion and differed to some degree in their performance with the percentage of correct decisions ranging between 83% for the Tau mice and 73% for the control mice. When considering the mean

percentage of correct decisions in the first block of 20 trials (squares) the mouse strains performed similar with the percentage of correct decisions ranging between 55% for the Swede mice and 47% for the Tau mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the mouse strains differed to some degree with the percentage of correct rejections of the unrewarded stimulus ranging between 10% for the Tau and Swede mice and 3% for the control mice.
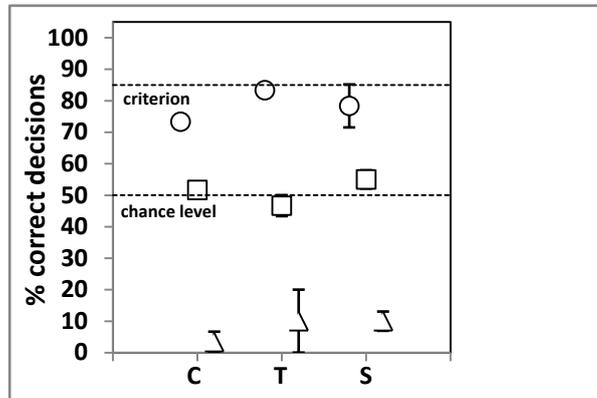

Figure 35. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between (+)-limonene as the rewarded stimulus and (-)-limonene as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the five blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (square), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Long-term odor memory task
Figure 36 shows the mean performance of the three mouse strains in discriminating between (+)-carvone as the rewarded stimulus and (-)-carvone as the unrewarded stimulus across the five blocks of 20 trials. The Tau mice (circles) and the Swede mice (triangles) reached the criterion of 85% correct decisions in the first block of trials while the control mice (squares) reached criterion in the second block.

Figure 36. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between (+)-carvone as the rewarded stimulus and (-)-carvone as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 37 summarizes the performance of the three mouse strains in discriminating between (+)-carvone as the rewarded stimulus and (-)-carvone as the unrewarded stimulus. When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) controls (C), Tau mice (T) and Swede mice (S) performed above criterion and they performed very similar with the percentage of correct decisions ranging between 98% for the Tau mice and 94% for the control mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the mouse strains differed to some degree with the percentage of correct decisions ranging between 81% for the control mice and 92% for the Swede mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the mouse strains differed markedly, the Tau and Swede mice performed better than the control mice with the percentage of correct rejections of the unrewarded stimulus ranging between 83% for the Swede mice and 67% for the control mice.

Figure 37. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between (+)-carvone as the rewarded stimulus and (-)-carvone as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the five blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (square), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Stimulus reversal task
Figure 38 shows the mean performance of the three mouse strains in discriminating between (-)-carvone as the rewarded stimulus and (+)-carvone as the unrewarded stimulus across the five blocks of 20 trials. All three mouse strains control (squares), Tau mice (circles) and Swede mice (triangles) failed to reach the criterion of 85% correct decisions across the five blocks.
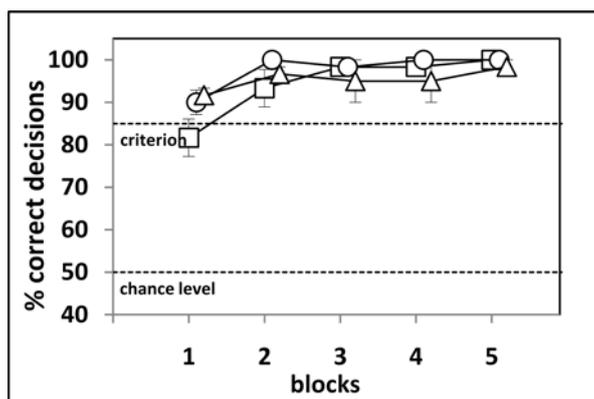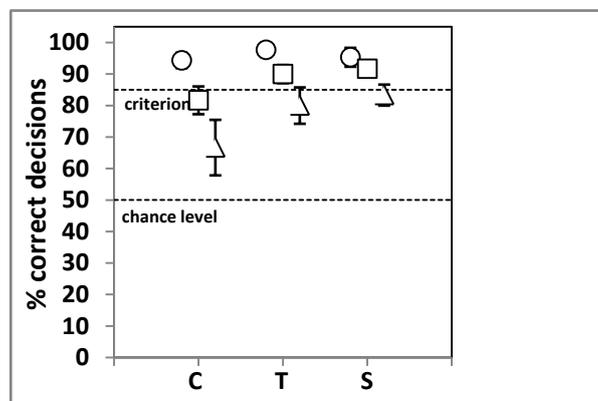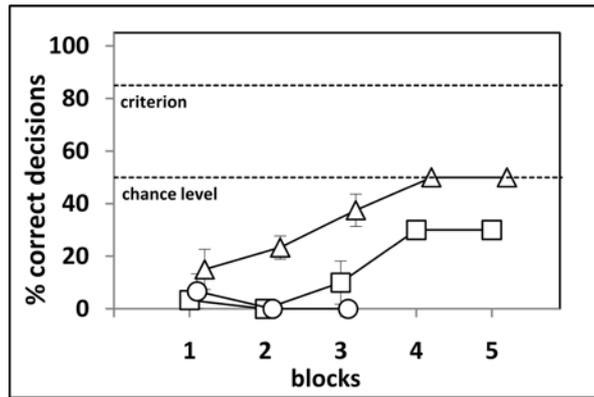
Figure 38. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between (-)-carvone as the rewarded stimulus and (+)-carvone as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 39 summarizes the performance of the three mouse strains in discriminating between (-)-carvone as the rewarded stimulus and (+)-carvone as the unrewarded stimulus. When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) the three mouse strains performed below criterion and differed markedly in their performance, the Swede mice (S) performed better than the Tau (T) and control mice (C) with the percentage of correct decisions ranging between 35% for Swede mice and 2% for the Tau mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed to some degree in their performance. The Swede mice performed better than the control and Tau mice with the percentage of correct decisions ranging between 15% for the Swede mice and 3% for the control mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed markedly in their performance. The Swede mice performed, again, better than the control and Tau mice with the percentage of correct rejections of the unrewarded stimulus ranging between 30% for the Swede mice and 3% for the control mice.
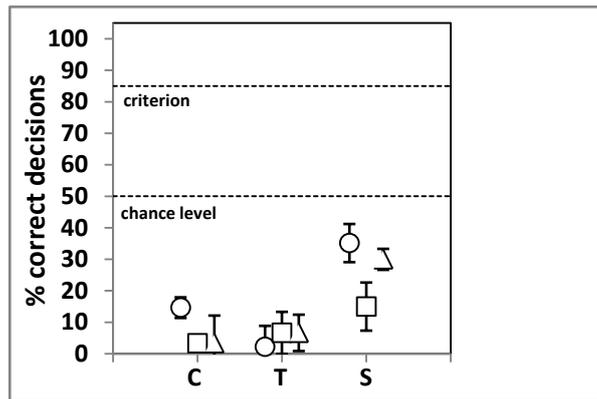
Figure 39. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between (-)-carvone as the rewarded stimulus and (+)-carvone as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the five blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (square), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Detection threshold task

Figure 40 shows the performance of the control mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). All three animals C1 (squares) C2 (circles) and C3 (triangles) reached the criterion of 75% correct decisions when distinguishing between hexanal 10^{-5} ppm and the solvent. Due to technical problems the mice were not able to complete the threshold test and thus a threshold value for the three mice could not be obtained.
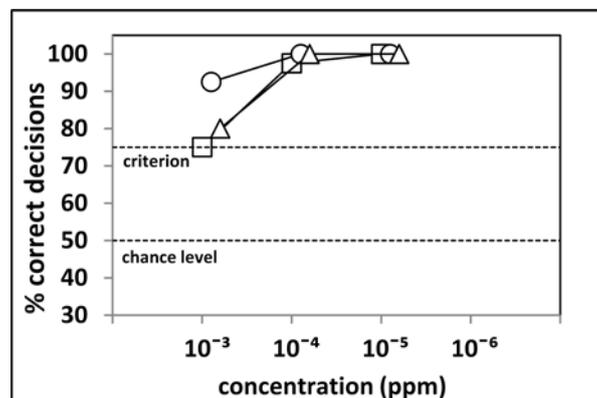

Figure 40. Performance of the three control mice in discriminating between various dilutions of hexanal and the solvent mineral oil. Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal C1 (square), C2 (circle) and C3 (triangle.

Figure 41 shows the performance of the control mice in discriminating between various dilutions of hexanal and the odorless solvent. All the animals T1 (squares) T2 (circles) and T3 (triangles) reached criterion of 75% correct decisions when distinguishing between hexanal 10^{-5} ppm and the solvent Due to technical problems the mice were not able to complete the threshold test and thus a threshold value for the three mice could not be obtained.

Figure 41. Performance of the three Tau mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal T1 (square), T2 (circle) and T3 (triangle).

Figure 42 shows the performance of the control mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). All three animals S1 (squares) S2 (circles) and S3 (triangles) reached the criterion of 75% correct decisions when distinguishing between hexanal 10^{-5} ppm and the solvent. Due to technical problems the mice were not able to complete the threshold test and thus a threshold value for the three mice could not be obtained.
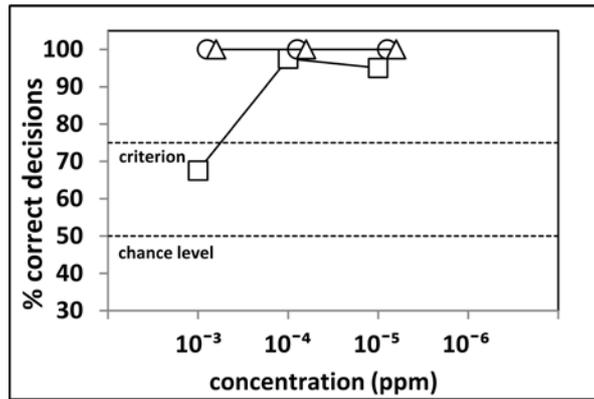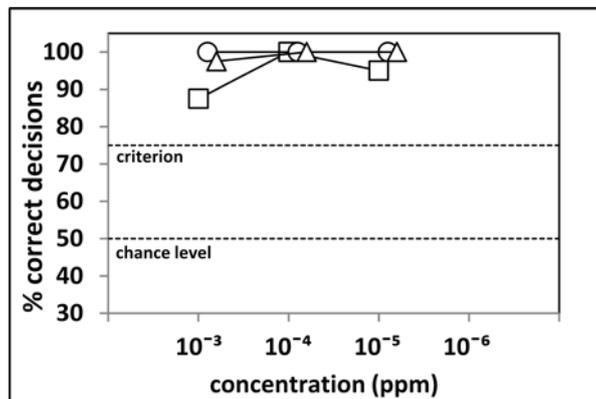

Figure 42. Performance of the three Tau mice in discriminating between various dilutions of hexanal (S+) and the odorless solvent (S-). Each data point represents the percentage of correct choices from a total of 40 decisions per individual animal. The three different symbols represent data from each individual animal S1 (square), S2 (circle) and S3 (triangle).

Spatial learning test
Figure 43 shows the mean performance of the three mouse strains in the spatial learning task. The control mice (squares) reached the criterion of 90% correct decisions on the first day with the percentage of correct decisions ranging between 97% on the first day and 100% the fourth day of testing . The Tau mice (circles) reached criterion on the first day with the percentage of

correct decisions ranging between 80% on the third day and 93% on the fourth day of testing. The Swede mice (triangles) reached criterion on the second day with the percentage of correct decision ranging between 87% on the first day and 100% on the fourth day of testing.
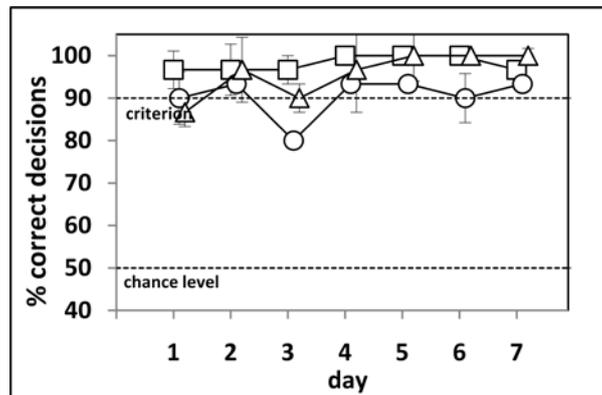

Figure 43. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in the spatial learning test. Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions from 10 trials per day and animal. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 90%), respectively.

4.5 Experimental series 4

Long-term odor memory task

Figure 44 shows the mean performance of the three mouse strains in discriminating between amyl acetate (S+) and eugenol (S-) across the five blocks of 20 trials. The control mice (squares) and Tau mice (circles) reached the criterion of 85% correct decisions in the second block of trials while the Swede mice (triangles) reached criterion in the fourth block. The control and Tau mice performed better than the Swede mice across all five blocks.

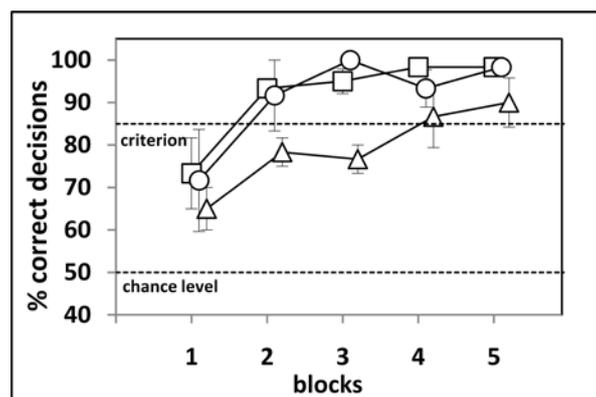*Figure 44. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between amyl acetate (S+) and eugenol (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.*

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Figure 45 summarizes the performance of the three mouse strains in discriminating between amyl acetate (S+) and eugenol (S-). When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) the control mice (C) and Tau mice (T) performed above criterion whereas the Swede mice barely failed to reach criterion with the percentage of correct decisions ranging between 92% for control mice and 79% for the Swede mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed to some degree in their performance. The Swede mice performed poorer than the control and Tau mice with the percentage of correct decisions ranging between 73% for the control mice and 65% for the Swede mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed markedly in their performance. The Tau mice performed markedly better than the control and Swede mice with the percentage of correct rejections of the unrewarded stimulus ranging between 87% for the Tau mice and 63% for the Swede mice.

Figure 45. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between amyl acetate (S+) and eugenol (S-). Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the five blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Double-transfer task

Figure 46 shows the mean performance of the three mouse strains in discriminating between (+)-isopulegol as the rewarded stimulus and (-)-isopulegol as the unrewarded stimulus across the five blocks of 20 trials. The control mice (square) reached the criterion of 85% correct decisions in the first block of trials whilst the Tau mice (circles) reached criterion in the second block of trials and the Swede mice (triangles) reached criterion in the third block.

Figure 46. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between (+)-isopulegol as the rewarded stimulus and (-)-isopulegol as the unrewarded stimulus. Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 47 summarizes the performance of the three mouse strains in discriminating between (+)-isopulegol as the rewarded stimulus and (-)-isopulegol as the unrewarded stimulus. When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) control mice (C), Tau mice (T) and Swede mice (S) performed above criterion and performed similarly with the percentage of correct decisions ranging between 95% for control mice and 90% for the Tau mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed to some degree in their performance. The control mice performed slightly better than the Tau and the Swede mice with the percentage of correct decisions ranging between 93% for the control mice and 80% for the Tau mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed markedly in their performance. The control mice performed markedly better than the Tau mice and the Swede mice with the percentage of correct rejections of the unrewarded stimulus ranging between 87% for the control mice and 50% for the Tau mice.
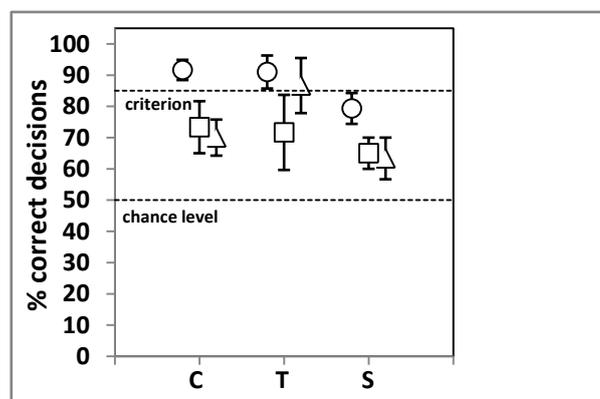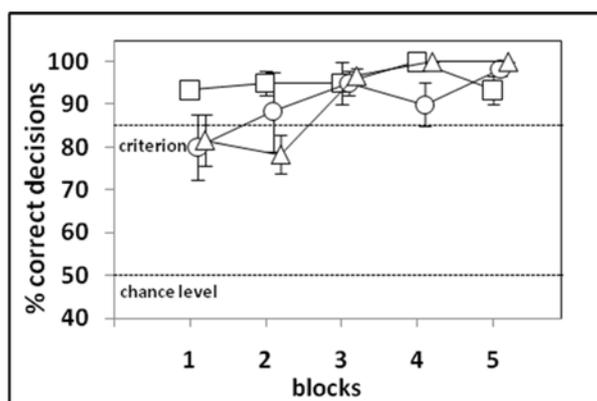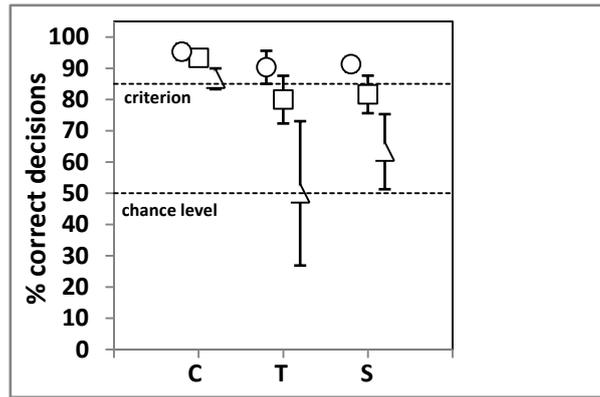
Figure 47. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between (+)-isopulegol as the rewarded stimulus and (-)-isopulegol as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the five blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Long-term odor memory task

Figure 48 shows the mean performance of the three mouse strains in discriminating between (+)-limonene as the rewarded stimulus and (-)-limonene as the unrewarded stimulus across the five blocks of 20 trials. The Tau mice (circles) reached the criterion of 85% correct decisions in the third block of trials whilst the control mice (squares) and the Swede mice (triangles) reached criterion in the fourth block of trials.

Figure 48. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between (+)-limonene as the rewarded stimulus and (-)-limonene as the unrewarded stimulus. Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 49 summarizes the performance of the three mouse strains in discriminating between (+)-limonene as the rewarded stimulus and (-)-limonene as the unrewarded stimulus. When considering the mean percentage of correct decisions across all five blocks of 20 trials

(circles) control mice (C), Tau mice (T) and Swede mice (S) performed above criterion and performed similarly with the percentage of correct decisions ranging between 78% for the Tau mice and 75% for the Swede mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed to some degree in their performance. The Swede mice performed better than the control mice and the Tau mice with the percentage of correct decisions ranging between 65% for the Swede mice and 50% for the control mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed markedly in their performance. The Swede mice performed markedly better than the control mice and the Tau mice with the percentage of correct rejections of the unrewarded stimulus ranging between 57% for the Swede mice and 0% for the control mice.

Figure 49. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between (+)-limonene as the rewarded stimulus and (-)-limonene as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the five blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

Stimulus reversal task
Figure 50 shows the mean performance of the three mouse strains in discriminating between (-)-limonene as the rewarded stimulus and (+)-limonene as the unrewarded stimulus, a stimulus-reversal task, across the five blocks of 20 trials. All three mouse strains controls (squares), Tau mice (circles) and Swede mice (triangles) failed to reach the criterion of 85% correct decisions across the five blocks.
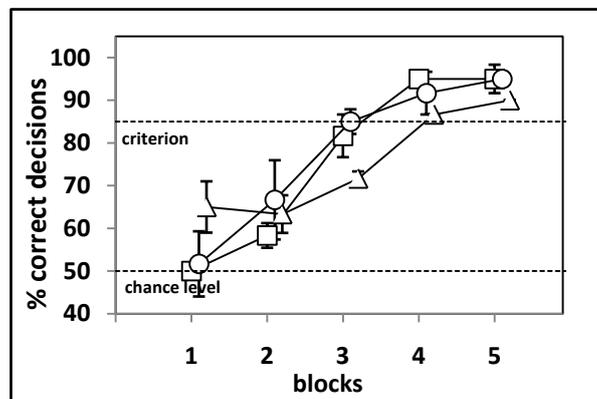
Figure 50. Performance of the control (squares), Tau (circles) and Swede (triangles) mice in discriminating between (-)-limonene as the rewarded stimulus and (+)-limonene as the unrewarded stimulus. Each data point represents the percentage (means ± se from n=3 animals per group) of correct decisions per block of 20 trials. The dotted lines indicate the chance level of performance (at 50%) and the criterion level (at 85%), respectively.

Figure 51 summarizes the performance of the three mouse strains in discriminating between (-)-limonene as the rewarded stimulus and (+)-limonene as the unrewarded stimulus. When considering the mean percentage of correct decisions across all five blocks of 20 trials (circles) control mice (C), Tau mice (T) and Swede mice (S) performed below criterion and differed to some degree in their performance with the percentage of correct decisions ranging between 33% for the Swede mice and 17% for the Tau mice. When considering the mean percentage of correct decisions in the first block of 20 trials (squares) the three mouse strains differed to some degree in their performance with the percentage of correct decisions ranging between 17% for the control mice and 3% for the Tau mice. When considering the performance of correct rejections of the unrewarded stimulus in the first block of 20 trials (triangles) the three mouse strains differed to some degree in their performance with the percentage of correct rejections of the unrewarded stimulus ranging between 17% for the control mice and 3% for the Tau mice.
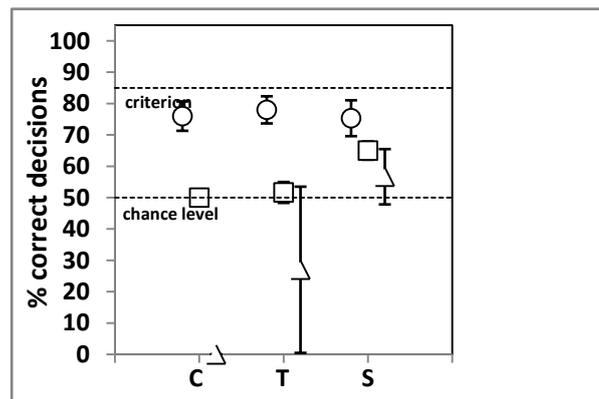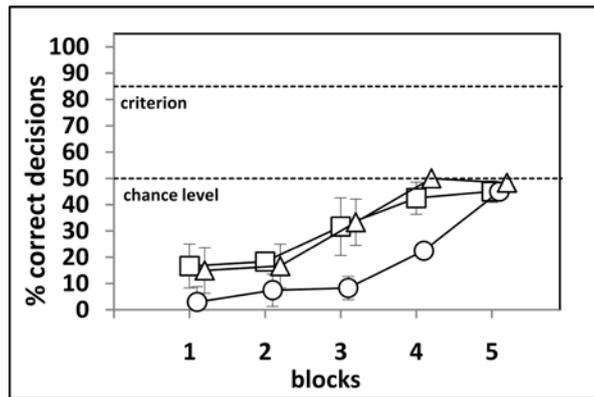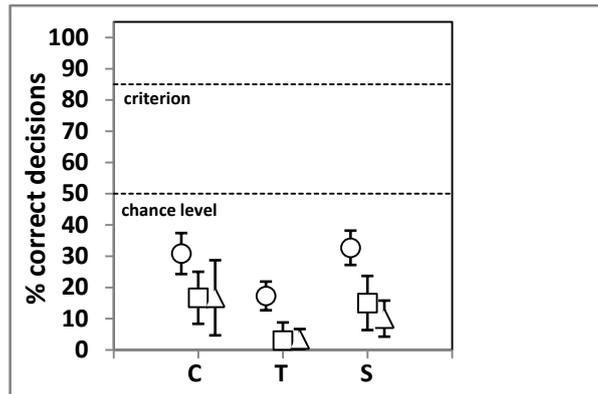
Figure 51. Performance of the control (C), Tau (T) and Swede (S) mice in discriminating between (-)-limonene as the rewarded stimulus and (+)-limonene as the unrewarded stimulus. Each data point represents the percentage (means ± SE from n=3 animals per group) of correct decisions (a) across the five blocks of 20 trials performed per animal (circles), (b) in the first block of 20 trials (squares), and (c) in corrects rejections of the S- in the first block of 20 trials (triangles).

5 Discussion

The results of this study demonstrate that there were no systematic differences in olfactory performance and spatial learning abilities of AD model mice (Tau mice and Swede mice) and the control mice up to the age they were tested. Further, there was no indication of an age-related decline in performance in any of the mouse strains across the testing period.

The finding that no difference in olfactory performance between the mouse strains used here could be seen is not trivial given that various other studies found such differences between strains when comparing mice with various genetic changes against control mice (Belluscio 1998, Dawson 2005, Tillerson 2006). Belluscio (1998), for example, demonstrated that mice homozygous for a null mutation of the G alpha subunit G(olf) showed an olfactory impairment relative to controls, Dawson (2005) found that NaSi-1 sulphate transporter knock-out (*Nas1−/−*) mice performed poorer compared to controls, and Tillerson (2006) reported that mice lacking the dopamine transporter or the D2 dopamine receptor showed an impaired sense of smell relative to controls. The lack of difference in performance between the mouse strains tested in the present study might be due to the mice not having been tested long enough as the AD-related impairments have to develop over time.

Age related changes in olfactory performance have been well documented in humans (Doty 1984) and should be expected to occur in other species as well. However, surprisingly few studies so far assessed age-related changes in olfactory performance in animals. Enwere (2004) reported that mice (C57BL/6) display an impairment in olfactory discrimination with age. When comparing 2 month old mice with 24 month old mice the latter showed an impairment in olfactory discrimination compared to the former (Enwere 2004). However, as no intermediate age classes were tested it is difficult to define the onset of the impairment. The mice used in the present study were 6 to 7 months old at the beginning of the study and 9 to 10 months old at the end of my data collection and thus considerably younger than the mice

in Enwere's study. Thus it is unlikely that age-related impairment in olfactory discrimination should have affected the mice used here and was indeed not seen.

It is commonly agreed that human smell impairment starts around 60 years of age (Doty 1984). Given an average life expectancy of 75 years this is well into the second half of the average life span. As mice have a life expectancy of approximately 2 years and the mice used in the present study barely approached half of their life span at the end of the data collection period, it should not be surprising that they failed to show any age-related smell impairment. At least in the case of the control mice this would plausibly explain why no changes in olfactory performance across the testing period was observed. However, it was surprising that the AD model mice did not show a smell impairment across the testing period.

According to Jackson Laboratory (Bar Harbor, Maine), the company that genetically engineered and bred the animals used here the Tau mice have been reported to develop intraneuronal amyloid beta-42 accumulation at 1.5 months of age, just prior to amyloid deposition and gliosis, which begins at two months of age and spatial learning deficits have been observed at 4-5 months of age. The Swede mice have been reported to develop beta-amyloid deposits in the brain and spatial learning deficits by 6 to 7 months of age. Thus, it should have been expected that both the Tau mice and the Swede mice display an impairment in olfactory performance and in spatial learning and memory at least during the last month that I tested them. Several hypothetical explanations may account for the finding that this did not occur:

Hypothetical explanation 1. The mice do not develop plaques and tangles at all. This possibility can only be verified histologically after their death. As the study is still ongoing it is at this moment not possible to verify whether or not the expected neuroanatomical changes have developed in the animals used in this study.

Hypothetical explanation 2. The mice will develop plaques and tangles later on. This possibility will be verified by continuing testing and by performing histology after the animals' death. If the expected neuroanatomical changes develop later on in the animals' life then the information given by Jackson Laboratory as to their onset is incorrect.

Hypothetical explanation 3. The mice may have already developed plaques and tangles but these neuroanatomical changes do not, or not yet, affect their olfactory performance and/or their spatial learning and memory capabilities. In humans an olfactory impairment is among the earliest symptoms of Alzheimer's disease (Raquelle 2006). Such an impairment could therefore be expected to occur early in the AD mouse models. However, it is not fully understood if, or how, the neuroanatomical changes in the human brain caused by AD and the observed smell impairment are functionally linked. While humans with AD develop olfactory impairments (Raquelle 2006) the AD model mice used in this study do not necessarily have to develop symptoms in the same way or in the same temporal pattern as humans do. This is exactly why this study is important: to find out how closely the AD induced in model mice resembles the AD found in humans. The genetic manipulation that the AD model mice were subjected to might be sufficient to induce the amyloid plaques and the neurofibrillary tangles that are typical for human AD (Tsuboi 2003), but it might fail to also induce olfactory impairment in the AD model mice.

Humans with Alzheimer's disease develop tangles and plaques in the brain as the disease progresses (Arnold 1991). It is important to note that tangles and plaques have also been demonstrated to develop in the human olfactory bulb. Attems (2006) found large numbers of neurofibrillary tangles and amyloid deposits in 50% of all cases in the olfactory bulbs of patients with definite AD (Braak stages 5 and 6). If the formation of tangles and plaques in the olfactory bulb in humans is the main or at least a contributing cause of olfactory impairment (whether or not this is the case is not known) this may explain the absence of olfactory deficits in the two AD mouse models used here. According to Jackson Laboratory the neuroanatomical changes that develop in the Tau mice in the olfactory bulb do not occur until the mouse is "old". A specific age for the onset of the neuroanatomical changes in the olfactory bulb of the Tau mice is not provided. No information whatsoever with regard to neuroanatomical changes in the olfactory bulb of the Swede mice is provided by Jackson Laboratory. Thus the lack of olfactory impairments observed in the present study might be due to the total lack of or late onset of neuroanatomical changes in the olfactory bulb within the two AD mouse models used here.

Hypothetical explanation 4. Animal models of a human neurodegenerative disease do not necessarily show the same pattern of symptoms as the humans themselves. One example of such a discrepancy is the Parkinson`s disease in animal models. In humans, Parkinson's disease is also accompanied by an olfactory impairment (Hendersson 2003). One can induce typical symptoms of Parkinson's disease in animal models by systemic application of the drug MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin). Animals treated with this drug show an irreversible motor impairment and tremor just like humans, but they do not show an olfactory impairment (Mucignat-Caretta et al., 2009). This illustrates that there might be an important difference between naturally developing neurodegenerative diseases and experimentally induced diseases (whether induced by genetic manipulation or by drug treatment) in how they develop over time and whether or not they show the full array of symptoms that are usually associated with the disease.

Hypothetical explanation 5. The tests used in the present study might not be sensitive enough to detect changes in olfactory performance and/or spatial learning and memory. Although this possibility cannot be ruled out completely, it should be mentioned that among the various methods that are available to test olfactory performance in mice, the operant conditioning of animals in an automated olfactometer (Slotnick 2002) is commonly regarded as the best and most sensitive method that is at hand (Hastings 2003). In the present study the lowest concentration of an odor (1-octanal during month 2) that any of the mice successfully discriminated was 3×10^{-7} ppm. Using the same apparatus and the same odor as in the present study, Laska (2006) demonstrated that CD-1 mice were able to discriminate concentration of 3×10^{-8} ppm, only one log unit from what the mice used in the present study where able to detect.

The study is still ongoing and will hopefully contribute to answering the question whether AD model mice display an olfactory impairment that is typical of human AD. Based on the findings of the present study, the following studies should be performed: testing mice which express the tangles and plaques only in the olfactory bulb or the olfactory cortex would allow to determine where the neuroanatomical changes have to develop in brain areas processing olfactory information to causes the olfactory impairments. Testing mice that develop more plaques and tangles and at an earlier stage in their life would allow to assess the possible

olfactory impairments at an earlier stage and possibly with stronger symptoms that are easier to measure.

6 Acknowledgement

7 References

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