Smell-based memory training: Evidence of olfactory learning and transfer to the visual domain

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Smell-based memory training: Evidence of olfactory learning and transfer to the visual domain

Abstract: Human and non-human animal research converge to suggest that the sense of smell, olfaction, has a high level of plasticity and is intimately associated with visual-spatial orientation and memory encoding networks. We investigated whether olfactory memory training would lead to transfer to an untrained visual memory task, as well as untrained olfactory tasks. We devised a memory intervention to compare transfer effects generated by olfactory and non-olfactory (visual) memory training. Adult participants were randomly assigned to daily memory training for about 40 days with either olfactory or visual tasks, that had a similar difficulty level. Results showed that while visual training did not produce transfer to the olfactory memory task, olfactory training produced transfer to the untrained visual memory task. Olfactory training also improved participants' performance on odor discrimination and naming tasks, such that they reached the same performance level as a high-performing group of wine professionals. Our results indicate that the olfactory system is highly responsive to training, and we speculate that the sense of smell may facilitate transfer of learning to other sensory domains. Further research is however needed in order to replicate and extend our findings.

Public Significance Statement: This study suggests that olfaction, the sense of smell, might be helpful in memory training, as olfactory-based memory training benefitted visual memory task performance. Olfactory-based training also led to improvement in some olfactory abilities, such that novices, following training, achieved the same level of performance as wine professionals.

Keywords: Smell, olfactory disorders, odorants, memory, spatial learning

Introduction

Olfaction, the sense of smell, is highly associated with learning, and some studies suggest that olfactory sensory abilities even play a role in visual memory performance. For example, odor discrimination training leads to visuo-spatial learning enhancement in rats (Zelcer et al., 2006). Conversely, an ablation of the olfactory bulb impairs visuo-spatial learning in rats (van Rijzingen et al., 1995). The present study focuses on whether olfactory-based memory training in adult human participants would have positive effects both on visual memory and olfactory perceptual task performance. The olfactory system is characterized by a high level of biological and functional plasticity (Fletcher, 2012; Kass et al., 2013; Li et al., 2008). For example, healthy adult humans might improve olfactory performance merely by means of repeated olfactory stimulation (Mainland et al., 2002), and to our knowledge, no analogous effects have been reported in the visual system. Olfactory abilities are highly trainable (Damm et al., 2014; Hummel et al., 2009; Morquecho-Campos et al., 2019). Olfactory experts (e.g. perfumers and wine tasters) perform better than non-experts on olfactory assessments (Royet et al., 2013) and their expertise is correlated with structural reorganizations in memory-associated brain areas (Delon-Martin et al., 2013). A preliminary study, while lacking a matched control group, indicated that odor-based spatial memory training might benefit performance on related visual cognitive tasks (Olofsson et al., 2017). Memory transfer is often studied using visual, and in some cases auditory tasks, and results indicate that while some studies have yielded promising results (e.g. Mahncke et al., 2006; Bergman-Nutley & Klingberg 2014), others show no transfer (Owen et al., 2010), or only to tasks that are very similar to the trained task, such that the overall pattern of results remain mixed (Lindenberger et al., 2017; Melby-Lervåg et al., 2016; Teixeira-Santos et al., 2019). Transfer across sensory systems are rarely assessed (see e.g. Zelinski, 2009, for review). Previous studies

investigated whether visual working memory training transfers to improved performance on a similar auditory working memory task, but results are not conclusive (Buschkuhl et al., 2014; Schneiders et al., 2011). As the usefulness of some visual-based cognitive training interventions has been questioned on methodological grounds (Simons et al., 2016), new methods for establishing transfer of learning are warranted. To our knowledge, differences in cross-sensory transfer has never been systematically addressed using olfaction. Olfaction, with its combination of high levels of plasticity and its close integration with memory encoding regions, might provide a vehicle for transfer effects. This study aimed to test the hypothesis, based on the evidence reviewed above (pronounced olfactory plasticity and transfer effects), that memory training in the olfactory system would lead to significant transfer to a visual task, as well as to non-trained olfactory tasks. We further hypothesized, based on the indirect evidence reviewed above (modest transfer within the visual cognitive domain and lack of evidence of visual transfer to olfactory tasks) that transfer from visual training to olfactory tasks would be less pronounced. To address this hypothesis, we devised two spatial learning board games where olfactory and visual objects were located and matched. Such tasks are known to engage memory encoding networks (Kunz et al., 2015; Rasch et al., 2007) and we used them to establish training-related gain and transfer.

Materials and methods

Participants

This study was approved by the Swedish Ethics Review Authority (2014/621-31/1) and complied with the Declaration of Helsinki for Medical Research involving Human Subjects. Participants (n=106; age 18-50 years) were recruited to olfactory and visual memory training conditions by means of advertising, mainly through a designated website for research study advertisements.

Exclusion criteria were neurologic or psychiatric disorders, colds, allergies or breathing problems, and olfactory or uncorrected visual impairments. Participants were randomly assigned to either olfactory memory (OM) or visual memory (VM) training groups, and were tested by trained research assistants who were blind to the participants' training. Participants were compensated monetarily after completion of the training program. Seventy-two participants completed training, pre-test and post-test; 41 with the olfactory memory task (OM) and 31 with the visual memory task (VM). The effective sample is higher than, or similar to, several other studies on this topic, which should provide a sufficient power to detect effects (e.g. Hummel et al., 2009; Altundag et al., 2015). Twenty-eight participants did not complete memory training or deviated from the training protocol (17 OM, 11 VM; the OM training was slightly more vulnerable to disruptions from cold and flu). Additionally, 6 participants were excluded due to technical or experimenter errors during initial testing. The current dataset with 72 participants includes participants which were recruited to a study that was originally conceived as a follow-up, where participants were randomized to identical olfactory and visual training conditions and identical pre- and post-test tasks. The second study, which also included two other training conditions and a novel set of criterion tasks, was scaled down midway through data collection for practical reasons, starting with the visual condition. The data from the follow-up study (11 VM, 20 OM) were instead aggregated with the original study data to achieve more reliable outcomes, which explains the lower number of participants in the visual condition (see online supplemental materials for data). Post-hoc exploration indicated that original vs. follow-up datasets showed similar results.

116 *Wine professionals*

117 To provide a point of reference for the hypothesized training-related olfactory improvement in the
118 OM group, we additionally recruited 15 wine professionals for testing with the Sniffin' Sticks
119 battery. They were recruited through a professional network email list and were currently active
120 as wine panelists, wine tasting course leaders, wine importers or wine journalists (see
121 supplementary materials for descriptive and performance data). Even though the professionals had
122 a higher mean age than participants in the training groups, we decided it was more important to
123 have professionals with many years of experience as a bench-mark for olfactory expert
124 performance (Delon-Martin et al., 2013); rather than striving for an age-matched group of young,
125 but less experienced, olfactory experts (e.g. enology students).

126

127 *Training tasks*

128 The olfactory memory game (OM) included 24 tin cans, containing 12 different kinds of
129 commercially available flavored teas to make up 12 stimulus pairs (see supplementary materials).
130 Two parallel, non-overlapping sets were created to make the olfactory and visual games more
131 challenging and to involve a larger number of stimuli during the training period, a feature we hoped
132 would help us achieve generalized learning and avoid minimize unknown sources of bias driven
133 by individual stimuli. Prior work in patients with olfactory loss has shown better results from
134 olfactory training when odors are changed during training (Altundag et al., 2015). Odors were
135 placed in white cotton bags to prevent visual identification. The cans were randomly distributed
136 on a board that included 24 squares arranged in a 6-by-4 grid. On each trial, the player sampled
137 two tin cans of choice and compared their content. Upon detecting a match, the matched items
138 were removed from the board. Performance was measured as the number of trials required to empty

the board, with fewer trials indicating higher performance. Trial number was also used to compare the difficulty of the two tasks. In order to establish accurate performance logs, each tin can was marked underneath with a barcode that was unique to each can, but mirror-inverted for the can holding the matching stimulus (see supplementary materials). Thus, participants could easily verify a match by turning two cans upside down and holding the barcodes opposite each other. However, the mirror-reversed barcodes were not visible while playing, and participants were instructed to only use them to confirm a perceived match, limiting exposure to the barcodes mostly to trials where the cans were immediately removed from the board. Barcodes were thus unlikely to influence memory performance, since they could not be used as a memory cue for the matching task (see supplementary materials).

A visual memory (VM) game was devised as a control task. Two parallel, non-overlapping sets were constructed. In each set, 12 different language symbols were obtained from Korean and Mandarin Chinese languages, and placed inside the 24 tin cans (see supplementary materials). The two training tasks were similar in all aspects except the engagement of odors vs. visual objects and they were carried out in a similar way. The symbols were unfamiliar to our Swedish participants.

Procedure

Completion of the study required training for about 40 days at home (one training session completed each day, average training time was 10 minutes) and pre-training and post-training laboratory assessment. In cases when participants were unable to complete training on a given day, they were instructed to train twice the following day(s) such that their total number of training sessions were kept constant. Post-training assessments were scheduled after at least 38

days of training and at about 40 days (see Table 1 for details), and participants continued training until the day of return. During the laboratory assessments, participants completed tests with the OM and VM tasks as well tests of olfactory function. During training, participants trained with only one type of game, but alternated between the parallel sets every 5 days.

The games were played individually. Participants were instructed to place all the cans on the game board in a random order and play the game by sampling two cans on each trial, removing the cans if they were matching. Each trial was documented on a scoring sheet as “matching” or “non-matching”. After a minimum of 38 training days, participants returned for the second laboratory assessment. Participants that could not return at 38-40 days from their pre-assessment were either instructed to continue training for a few more days until they were available for laboratory testing or, if this was not possible, considered as drop-outs.

Pre-post testing. Pre-training and post-training sessions followed the same procedure and consisted of standardized tests of olfactory ability and assessments of the participants performance in the olfactory and visual memory games. First, the standardized “Sniffin’ Sticks” were used to assess olfactory abilities (see Hummel et al., 1997, 2007; Kobal et al., 1996, for details). Olfactory threshold (for n-butanol) and discrimination assessments were completed in exact accordance to established protocols, and odor sets were replaced within their expiry date. In threshold testing, the experimenter presents the participant with three odorous pens, only one of which contains an odor (n-butanol), and the participant selects the odorous pen in a forced-choice procedure. Across trials, the concentration of the odor stimulus varied as a function of performance, and a threshold value of up to 16 was eventually established. In discrimination

testing, three pens are similarly presented, two of which has the same smell and the third has a different smell, and the participant selects the deviating smell in a forced choice procedure. Discrimination ability is established as a sum score across 16 trials. For naming and identification assessments, participants were presented with familiar odors, and were first asked to name it without cues; these answers provided the basis for calculating odor naming accuracy scores (naming is not part of the standard Sniffin' Sticks assessment, but is often added to identification assessments to provide complementary information, see e.g. Olofsson et al., 2013). Irrespective of the naming response, odor identification was then assessed by providing four odor name alternatives (one of which was correct) in a forced-choice task. To avoid test-retest effects on the olfactory identification and naming tests, we used an extended version of the Sniffin' Sticks set that contained 32 odors, which were divided into two non-overlapping sets of 16 (8 odors from the original Sniffin' Sticks set and 8 odors from its extension set), for unique use at test and re-test, respectively. The use of each of the two alternate sets at pre-test and post-test was randomized for each individual to minimize trivial test-retest effects in the identification and naming tasks. Scores on olfactory tasks could range from 0 (min) to 16 (max). Participants were not given any corrective feedback. We hypothesized all four tests would potentially be improved only by olfactory training, resulting in interactions between time and group.

Participants' performance in the training games was assessed. Assessment order (olfactory memory first versus visual memory game first) was randomized across participants. The experimenter instructed the participant in how to play the memory games and how to document performance (number of trials) into the accompanying spreadsheet according to the same procedure as training at home. After verifying that the participant had understood the instructions

correctly by letting the participant play and document two test trials under supervision, the test leader left the room and returned once the participant was finished with the game. After completion, the test leader controlled that the participant had found and grouped all matching cans correctly and that the spreadsheets were correctly documented.

Questionnaires. Before the first and the second testing session, participants filled out an online questionnaire at home that assessed background variables such as level of education, age, gender, and self-rated health, memory, and olfaction. At the post-training session, subjects rated their motivation retrospectively for the first and last weeks of training, how demanding they perceived the game to be, and how much they enjoyed playing the game, on scales ranging from 1 (min) to 10 (max).

Data Analysis. To provide an assessment of ceiling-level performance in the memory games, we simulated the performance of a group of 10000 "virtual experts" that explored the stimulus set randomly but with optimal perception and memory of the objects encountered at all previous trials such that performance was optimized. Although variance occurred as a function of random localization of game items on the game board, and the random exploration of novel items, a player with perfect memory would need an average of 18.9 trials (SD = 0.83; code available upon request). Assessment of performance differences due to training was established using t-tests and ANOVAs where appropriate.

Results

Demographics, olfactory performance and self-rated variables. Descriptive data are presented in Table 1. T-tests indicated that groups were not different with regards to age ($t(1,70) = 0.967, p = .337$, Hedges's $g = 0.228$) and education ($t(1,70) = 0.473, p = 0.639$, Hedges's $g = 0.118$), and a pearson chi-square test indicated no difference in sex distribution ($X^2 = 0.212, p = 0.625$, $\phi = 0.054$). The two groups did not differ in terms of baseline performance on any olfactory task (all $ps > 0.145$). All participants were enrolled in the study for at least 38 days of training. The number of days in the study varied somewhat among participants due to their availability for post-training lab testing (see Table 1) but an independent t-test on all participants, except 3 for which these data were lost, indicated groups did not differ in this regard ($t(1,67) = 0.540, p = 0.591$, Hedges's $g = 0.125$). We ran ANOVAS to investigate effects of time (pre- vs. post-training) on olfactory control tests and self-reported variables. Odor threshold and identification scores did not differ statistically between groups or as a function of time, nor were there any significant interactions (all $ps > 0.145$). Increased performance from pre-test to post-test was observed in odor naming ($F(1,68) = 5.363, p = 0.023, \eta_p^2 = 0.071$) and discrimination ($F(1,68) = 4.245, p = 0.043, \eta_p^2 = 0.057$), but these effects were qualified by interactions between time and group, both for naming ($F(1,68) = 7.835, p = 0.007, \eta_p^2 = 0.101$) and for discrimination ($F(1,68) = 23.197, p < 0.001, \eta_p^2 = 0.249$); these interactions warranted follow-up ANOVAs targeting each group. These analyses showed training-related effects were present only in the OM group (discrimination $F(1,40) = 25.333, p < 0.001, \eta_p^2 = 0.388$; naming $F(1,40) = 21.681, p < 0.001, \eta_p^2 = 0.352$) but not in the visual group (discrimination $F(1,30) = 3.755, p = 0.062, \eta_p^2 = 0.111$; naming $F(1,30) = 0.073, p = 0.788, \eta_p^2 = 0.002$). Self-rated motivation and enjoyment was initially high in both groups, but declined to moderate levels during the training period, a decline that was significant for motivation ($F(1,70) = 29.8, p < 0.001, \eta_p^2 = 0.299$) and enjoyment

253 (F(1,70) = 37.9, $p < 0.001$, $\eta_p^2 = 0.351$), but did not differ for the two groups (no main or
254 interaction effects involving group, all $ps < 0.088$). Perceived difficulty of the tasks was
255 moderate, similar across the training groups and remained stable during the training period (all
256 $ps > 0.070$).

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Table 1. Mean demographic, Sniffin' sticks and questionnaire data for the olfactory and visual training groups at pre- and at post-test.

	Pre-assessment		Post-assessment	
	Olfactory group	Visual group	Olfactory group	Visual group
Age (+SD)	25.6 (5.0)	27.0 (7.5)	-	-
n (% female)	41 (66)	31 (71)	-	-
Education years (+SD)	14.3 (1.7)	14.6 (2.7)	-	-
Days until post-test (+SD)	-	-	42.7(5.9)	43.4 (4.1)
Odor threshold (+SD)	11.2 (3.3)	10.8 (2.8)	11.6(3.3)	10.8 (2.8)
Odor discrimination (+SD)	12.3 (2.1)	12.9 (1.8)	13.9 (1.7)	12.3 (1.7)
Odor identification (+SD)	12.5 2.0)	12.4 (1.7)	12.9 (2.0)	12.8 (2.3)
Odor naming (+SD)	5.4 (1.9)	6.2 (2.8)	7.1 (2.4)	6.0 (2.4)
Odor memory task (+SD)	38.1 (10.8)	40.1 (10.5)	28.3 (7.3)	38.5 (9.6)
Visual memory task (+SD)	33.8 (10.3)	37.9 (8.8)	26.5 (7.2)	24.4 (6.7)
Self-rated motivation (1-10)	7.5 (1.9)	7.1 (2.3)	5.9 (2.4)	5.9 (2.2)
Self-rated enjoyment of task (1-10)	7.5 (1.8)	7.0 (1.9)	5.1(2.2)	5.7 (2.5)
Perceived difficulty of task (1-10)	4.7 (2.9)	4.4 (2.4)	4.8 (2.4)	3.5 (1.9)

SD = Standard Deviation; n = sample size.

Memory game performance. Mean performance scores in the training games for each training group at pre- and post-assessment are summarized in Table 1. Participants did not differ significantly in baseline performance in the olfactory ($t(70) = 0.76, p = 0.452$; Hedges's $g = 0.18$) or visual memory game ($t(70) = 1.80, p = 0.077$; Hedges's $g = 0.42$). Data from the participants' training logs suggested that the two training conditions were equally difficult across the training period. Mean trials over the training period was 28.8 (SD = 6.2) for the olfactory and 27.5 (SD = 7.0) for the visual training game. This difference was not statistically significant

($t(70) = 0.83, p = 0.412$; Hedges's $g = 0.20$). As expected, performance increases on assigned game tasks were observed when comparing pre-training and post-training scores in both the OM ($t(40) = 6.02, p < 0.001$, Cohen's $d = 0.94$), and the VM group ($t(30) = 10.80, p < 0.001$, Cohen's $d = 1.94$). However, the magnitude of the pre-post performance increases for the assigned game was not significantly different across training groups ($t(70) = -1.69, p = 0.095$, Hedges's $g = -0.38$). On average, neither of the training groups approached the ceiling level of the "virtual experts" (mean trials = 18.9; SD = 0.83; Fig. 2).

The results of a two-factor mixed-design ANOVA showed significant interaction effects between time (pre- vs. post-training) and training modality (odor vs. visual) for both the OM ($F(1,40) = 23.8, p < 0.001, \eta_p^2 = 0.254$) and the VM task ($F(1,40) = 7.71, p = 0.007, \eta_p^2 = 0.099$). These within-subject effects indicate that as expected, the largest performance increases were observed in the game tasks that the participants trained.

To test whether the training regimes differed in associated performance gains, we first investigated between-subject effects of training modality (odor vs. visual) and time (pre- vs. post-training) on the OM and VM task performances, separately. Results for the OM task yielded significant interaction effects of time and training modality ($F(1,40) = 9.59, p = 0.003, \eta_p^2 = 0.12$) but this was not the case for the VM task ($F(1,40) = 0.44, p = 0.510, \eta_p^2 = 0.006$), showing that performance gains were significantly different across groups for the OM game while performance gains were not significantly different across groups for the VM game. The results indicate that olfactory training led to a performance increase in both the olfactory and the visual game, while visual training only led to a performance increase in the visual game.

Figure 1 (A-B). Panel plots of individual game performance measured as trials needed to complete the memory task during the training period for the olfactory training group (A) and visual training group (B). Ceiling level was established by data-simulated “virtual experts” (black solid line).

Figure 2 (A-B). Average change (blue line) in task performance (trials) estimated as a quadratic function of days of training for the olfactory training group (A) and visual training group (B) with 95% CIs. Ceiling level was established by data-simulated “virtual experts” (black solid line).

Indeed, post hoc comparisons with t-tests showed that OM training resulted in improved VM performance ($t(40) = 4.42$, $p < 0.001$, Cohen's $d = 0.69$), but VM training did not result in improved OM performance ($t(30) = 0.97$, $p = 0.339$, Cohen's $d = 0.17$), suggesting that transfer was asymmetrical. Of key importance for our main *a priori* hypothesis, transfer gain for the OM group in the visual memory task was larger than the corresponding transfer gain for the VM group in the odor memory task, ($t(70) = 2.444$, $p < 0.017$, Hedges's $g = 0.65$; Fig. 3A-B). These analyses showed that for the OM training group, the transfer gain on the visual memory task was in fact similar to the training gain in the odor task. Results thus indicate a one-sided transfer of learning from the OM to the VM task.

Figure 3 (A – B) Boxplots of performance (trials needed) on olfactory memory (OM) and visual memory (VM) tasks at pre-training (white boxes) and post-training (grey boxes) for the two training groups, and score on the olfactory control tasks, (C) odor discrimination, (D) odor naming, (E) odor identification, and (F) butanol odor threshold. Results are shown for the visual memory training group and olfactory memory training group and for olfactory professionals (Pro; pink boxes). Boxplots are displayed separately for pre-training (white boxes) and post-training (grey boxes), with the exception of professionals who did not participate in training or post-training assessment. The boxes indicate the 25, 50 (median), and 75 percentiles of the distribution (lower, middle, and upper horizontal lines of the box). The upper hinges indicate the maximum value of the variable located within a distance of 1.5 times the inter-quartile range above the 75-percentile. The lower hinges indicate the corresponding distance to the 25-percentile value. Circles indicate values outside these hinges (outliers). The means and 95% confidence intervals (dots and error bars in blue) are superimposed on the boxplots.

Olfactory baseline performance. Independent samples t-tests showed that baseline performance levels were similar for the two training groups in all olfactory tasks ($ps > 0.173$, Hedges's $g < 0.32$) and memory games ($ps > 0.077$; Fig. 3). Baseline performances on the olfactory control tasks in the OM group were not significantly correlated with baseline OM game score ($ps > 0.251$, Hedges's $g < 0.42$). The results suggest that the two groups were well matched, and that initial OM game performance did not depend on varying olfactory acuity.

Follow-up analyses in the OM group revealed no relationship between baseline performances on the olfactory tasks and training-related increase in the OM game ($ps > 0.247$), suggesting that OM gains did not depend on baseline olfactory acuity. Transfer from olfactory training to the VM game were also not associated with baseline olfactory test scores ($ps > 0.116$).

Comparison to wine professionals. When comparing wine professionals to the pre-training OM group, wine professionals performed better on the odor threshold ($t(54) = 2.285, p = 0.026$, Hedges's $g = 0.68$) and odor discrimination tasks ($t(54) = 2.320, p = 0.02$, Hedges's $g = 0.69$) but not on the odor identification ($t(54) = 0.905, p = 0.369$, Hedges's $g = 0.27$) or odor naming tasks ($t(54) = 0.1864, p = 0.068$, Hedges's $g = 0.55$), although the latter was close to the significance threshold. Following OM training, however, performance was similar to the professionals in all olfactory tasks, including odor naming ($t(54) = 0.819, p = 0.416$, Hedges's $g = 0.24$) and odor discrimination ($t(54) = 0.407, p = 0.685$, Hedges's $g = 0.12$), odor threshold ($t(54) = 1.878, p = 0.066$, Hedges's $g = 0.56$), and odor identification ($t(54) = 0.182, p = 0.856$, Hedges's $g = 0.05$). In contrast, and as expected, the VM group post-training still performed more poorly compared to the professionals on odor threshold ($t(44) = 2.881, p = 0.006$, Hedges's $g = 0.89$) and odor discrimination ($t(44) = 2.536, p = 0.015$, Hedges's $g = 0.78$), but not odor identification ($t(44) = 0.0362, p = 0.719$; Hedges's $g = 0.11$) or odor naming ($t(44) = 0.723, p = 0.473$, Hedges's $g = 0.22$).

Discussion

Olfaction is well integrated with the neural systems supporting memory encoding, but the role of smell-based interventions to enhance memory functions is unexplored. Our main result show that engaging the olfactory system in a memory training task was associated with a transfer effect to a similar visual memory task, as well as to untrained olfactory tasks. In contrast, participants who trained with the visual memory task did not show any improvements on the olfactory memory task. The transfer effects were observed in olfactory training, but not in visual training, even though task difficulty and learning rates were comparable for the two training tasks. Based on

our results, we speculate that memory training that engages the olfactory system might promote cross-sensory transfer to a larger extent than is the case for the visual system (which is the dominant model for cognitive interventions). Our results also emphasize that training-related transfer is often unrelated to the magnitude of gains in the trained task (Bjork, 2018).

Further investigations are needed before definitive conclusions can be drawn about the usefulness of olfactory-based cognitive training. It is unclear if it was the multisensory nature of the memory tasks, or unknown differences in cognitive demands, rather than the engagement of olfaction per se, that produced transfer. While this interpretation cannot be ruled out in the present data and should be the focus of further experiments, it should be noted that each training task used one type of sensory stimulus, visual objects and odors, respectively, that was absent in the other. Thus, we view the sensory complexity as comparable across the two conditions, but to conclusively establish this notion, further experimentation is needed where multisensory complexity of the training tasks is manipulated.

Assuming that olfaction indeed promotes cross-sensory cognitive transfer, the mechanisms are unknown, but previous research in visual cognitive training provide clues that help us speculate about its cause. In visual working memory training, the overlapping neural substrates of the trained and transfer tasks is a key determinant of transfer (Dahlin et al., 2008). Thus, the present observation of "asymmetric transfer", from olfactory memory training to visual memory gain, but not vice versa, might indicate that olfactory input provides a relatively unmediated input to the mediotemporal memory encoding regions (Zelano et al., 2016), whereas the visual system involves extensive prior processing in many intermediate cortical regions (Felleman & Van

Essen, 1991). From the perspective that these additional processing stages act as information filters, visual processing networks will generate a sparse output (Solomon & Pelli, 1994). By this logic, we speculate that the relatively unfiltered olfactory input to the memory encoding regions (see e.g. Olofsson & Gottfried, 2015) might potentiate transfer effects due to an increased overlap with memory encoding neural networks. We acknowledge that future studies are needed in order to clarify the behavioral and neuronal mechanisms that might explain transfer from olfactory to non-olfactory tasks. Future studies should also investigate whether these effects replicate and generalize to other forms of olfactory-based cognitive training. Of particular interest is the development of digital olfactory technologies that enable online monitoring of olfactory performance and adjusting difficulty levels along with performance gains, etc (see e.g. Niedenthal et al., 2019).

In this work, we satisfied several key criteria that are rarely met in cognitive intervention studies (Simons et al., 2016). First, we established a very high level of similarity between the task format of our interventions, as they differed only in the sensory channels that were stimulated, and not the spatial memory format. Second, we were able to monitor performance during training, a rare feature in olfactory-based interventions (Pekala et al., 2016). Our data from the training period ruled out the possibility that trivial retest effects could account for our enhanced learning of the visual task in the OM group; indeed, day-by-day learning rates were on average very small and could not generate strong test-retest effects. Third, we compared results with those obtained from both “virtual experts” with optimal performance (in game tasks), and wine professionals (in olfactory perception tasks), to establish points of reference for training. These features helped support our interpretation that olfactory-based memory training produces substantial transfer

effects. Future work is needed to elucidate whether odor-based memory transfer effects might be sustained for several months, as are reported in some visual training studies (Constantinidis & Klingberg, 2016; Sandberg & Stigsdotter Neely, 2016). Future work should also address how olfactory memory training might produce transfer effects onto untrained tasks that shares neither the sensory modality, nor the task format of the training task (i.e. “far transfer”). Given the present results, odor-based cognitive training might be expected to produce enhanced transfer compared to visual-based training.

We hope that the results of our study will stimulate further research on odor-based cognitive interventions. Such interventions could be useful in older individuals, since olfactory impairments constitute early markers for age-related cognitive impairment and dementia (Devanand et al., 2015; Olofsson et al., 2009; Stanciu et al., 2014). It remains to be seen whether odor learning interventions will permit transfer to non-olfactory cognition in older individuals, but such studies are warranted given the devastating impact of memory loss and dementia in the aging population (Wimo et al., 2013).

Conflict of Interest: None declared.

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Supplementary materials.

Supplementary Figure 1 (A-I). Memory training equipment. A. Participants were provided with a game board, showing the placement of the cans, and two parallel sets of either olfactory or visual memory games (one of which is shown inside its cardboard box). Participants were also provided with a booklet with detailed instructions for daily training and a booklet where they logged their performance on a trial-by-trial basis (in Swedish, not shown here) B. The placement of the cans during training onset. C. Open cans in the olfactory task. Each can includes a tea bag

with content for odor-based training. Participants only opened two cans for sampling on each trial, so this display serves only to illustrate the content of the cans in the olfactory task. D. Open cans in the visual task. Each can includes a Mandarin Chinese or Korean language symbol for visual-based training. Participants only opened two cans for sampling on each trial, so this display serves only to illustrate the content of the can in the visual task. E. Example of barcodes that are located under the cans and used for confirming whether two sampled cans are matching or not. Due to the mirror-reversed design of the barcodes for matching cans, each of the 24 cans has an unique barcode pattern when viewed individually (irrespective of whether they are matching or not). F. Example of barcodes for a matching pair. When facing each other, barcodes align, confirming that the stimuli are matching. Upon confirming a match with barcodes, the cans are removed from the board. G. Example of barcodes for a non-matching pair. When viewed individually, it is difficult to imagine what the matching barcode would look like (as there are 12 pairs per set and no individual bar code is identical to another). H. When facing each other, barcodes do not align, confirming the stimuli are not matching. The cans are returned to the board. I. Overview of all barcodes (cans turned upside down and aligned). Participants are instructed to only view barcodes when encountering a perceived match. This ensures minimal exposure to barcodes during training, and as the cans are removed when a match is encountered, the barcodes are not useful as memory cues.

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Supplementary Table 1. Demographic and performance data on Sniffin' Sticks assessments for wine professionals.

Expert	Age	Gender	Expertise	Experience (years)	Odor Threshold	Odor Discrimination	Odor Identification	Odor Naming
1	49	M	Wine tasting course leader	17	15	14	14	11
2	54	F	Wine journalist	14	16	15	14	7
3	48	F	Wine taster	10	16	14	12	8
4	39	M	Wine importer	3	12	15	15	8
5	31	M	Sommelier	13	13	16	13	9
6	48	F	Sommelier	9	15	13	13	8
7	46	F	Sommelier	6	16	15	12	5
8	31	F	Wine taster	3	8	11	13	7
9	65	M	Wine importer	20	13	16	13	5
10	56	M	Wine taster	13	8	13	12	5
11	36	M	Wine taster	8	13	12	13	5
12	56	F	Wine taster	13	16	16	15	7
13	45	M	Wine importer	3	16	13	13	7
14	62	M	Wine journalist	6	9	11	11	3
15	54	F	Wine journalist	6	15	11	12	3
Mean (SD)	48 (10.36)	46.7 % F	-	9.6 (5.28)	13.4 (2.95)	13.67 (1.84)	13 (1.13)	6.53 (2.2)

M = Male; F = Female; SD = Standard Deviation.

References

- Altundag, A., Cayonu, M., Kayabasoglu, G., Salihoglu, M., Tekeli, H., Saglam, O., & Hummel, T. (2015). Modified olfactory training in patients with postinfectious olfactory loss. *The Laryngoscope*, 125(8), 1763–1766. <https://doi.org/10.1002/lary.25245>
- Bergman-Nutley, S., & Klingberg, T. (2014). Effect of working memory training on working memory, arithmetic and following instructions. *Psychological Research*, 78(6), 869–877. <https://doi.org/10.1007/s00426-014-0614-0>
- Bjork, R. A. (2018). Being Suspicious of the Sense of Ease and Undeterred by the Sense of Difficulty: Looking Back at Schmidt and Bjork (1992). *Perspectives on Psychological Science: A Journal of the Association for Psychological Science*, 13(2), 146–148. <https://doi.org/10.1177/1745691617690642>
- Buschkuehl, M., Hernandez-Garcia, L., Jaeggi, S. M., Bernard, J. A., & Jonides, J. (2014). Neural effects of short-term training on working memory. *Cognitive, Affective & Behavioral Neuroscience*, 14(1), 147–160. <https://doi.org/10.3758/s13415-013-0244-9>
- Constantinidis, C., & Klingberg, T. (2016). The neuroscience of working memory capacity and training. *Nature Reviews. Neuroscience*, 17(7), 438–449. <https://doi.org/10.1038/nrn.2016.43>
- Dahlin, E., Neely, A. S., Larsson, A., Bäckman, L., & Nyberg, L. (2008). Transfer of learning after updating training mediated by the striatum. *Science (New York, N.Y.)*, 320(5882), 1510–1512. <https://doi.org/10.1126/science.1155466>
- Damm, M., Pikart, L. K., Reimann, H., Burkert, S., Göktas, Ö., Haxel, B., Frey, S., Charalampakis, I., Beule, A., Renner, B., Hummel, T., & Hüttenbrink, K.-B. (2014). Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. *The Laryngoscope*, 124(4), 826–831. <https://doi.org/10.1002/lary.24340>
- Delon-Martin, C., Plailly, J., Fonlupt, P., Veyrac, A., & Royet, J.-P. (2013). Perfumers' expertise induces structural reorganization in olfactory brain regions. *NeuroImage*, 68, 55–62. <https://doi.org/10.1016/j.neuroimage.2012.11.044>
- Devanand, D. P., Lee, S., Manly, J., Andrews, H., Schupf, N., Doty, R. L., Stern, Y., Zahodne, L. B., Louis, E. D., & Mayeux, R. (2015). Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. *Neurology*, 84(2), 182–189. <https://doi.org/10.1212/WNL.0000000000001132>
- Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex (New York, N.Y.: 1991)*, 1(1), 1–47. <https://doi.org/10.1093/cercor/1.1.1>
- Fletcher, M. L. (2012). Olfactory aversive conditioning alters olfactory bulb mitral/tufted cell glomerular odor responses. *Frontiers in Systems Neuroscience*, 6, 16. <https://doi.org/10.3389/fnsys.2012.00016>
- Hummel, T., Kobal, G., Gudziol, H., & Mackay-Sim, A. (2007). Normative data for the “Sniffin” Sticks including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects.” *European Archives of Oto-Rhino-Laryngology*, 264(3), 237–243. <https://doi.org/10.1007/s00405-006-0173-0>
- Hummel, T., Sekinger, B., Wolf, S. R., Pauli, E., & Kobal, G. (1997). “Sniffin” sticks: olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chemical Senses*, 22(1), 39–52.

- 517 Hummel, Thomas, Rissom, K., Reden, J., Hähner, A., Weidenbecher, M., & Hüttenbrink, K.-B.
 518 (2009). Effects of olfactory training in patients with olfactory loss. *The Laryngoscope*, 119(3),
 519 496–499. <https://doi.org/10.1002/lary.20101>
- 520 Kass, M. D., Rosenthal, M. C., Pottackal, J., & McGann, J. P. (2013). Fear learning enhances
 521 neural responses to threat-predictive sensory stimuli. *Science (New York, N.Y.)*, 342(6164),
 522 1389–1392. <https://doi.org/10.1126/science.1244916>
- 523 Kobal, G., Hummel, T., Sekinger, B., Barz, S., Roscher, S., & Wolf, S. (1996). “Sniffin” sticks”:
 524 screening of olfactory performance.” *Rhinology*, 34(4), 222–226.
- 525 Kunz, L., Schröder, T. N., Lee, H., Montag, C., Lachmann, B., Sariyska, R., Reuter, M.,
 526 Stirnberg, R., Stöcker, T., Messing-Floeter, P. C., Fell, J., Doeller, C. F., & Axmacher, N.
 527 (2015). Reduced grid-cell-like representations in adults at genetic risk for Alzheimer’s disease.
 528 *Science (New York, N.Y.)*, 350(6259), 430–433. <https://doi.org/10.1126/science.aac8128>
- 529 Li, W., Howard, J. D., Parrish, T. B., & Gottfried, J. A. (2008). Aversive learning enhances
 530 perceptual and cortical discrimination of indiscriminable odor cues. *Science*, 319(5871), 1842–
 531 1845. <https://doi.org/10.1126/science.1152837>
- 532 Lindenberger, U., Wenger, E., & Lövdén, M. (2017). Towards a stronger science of human
 533 plasticity. *Nature Reviews Neuroscience*, 18(5), 261–262. <https://doi.org/10.1038/nrn.2017.44>
- 534 Mainland, J. D., Bremner, E. A., Young, N., Johnson, B. N., Khan, R. M., Bensafi, M., & Sobel,
 535 N. (2002). Olfactory plasticity: one nostril knows what the other learns. *Nature*, 419(6909), 802.
 536 <https://doi.org/10.1038/419802a>
- 537 Mahncke, H. W., Connor, B. B., Appelman, J., Ahsanuddin, O. N., Hardy, J. L., Wood, R. A.,
 538 Joyce, N. M., Boniske, T., Atkins, S. M., & Merzenich, M. M. (2006). Memory enhancement in
 539 healthy older adults using a brain plasticity-based training program: a randomized, controlled
 540 study. *Proceedings of the National Academy of Sciences of the United States of America*,
 541 103(33), 12523–12528. <https://doi.org/10.1073/pnas.0605194103>
- 542 Melby-Lervåg, M., Redick, T. S., & Hulme, C. (2016). Working Memory Training Does Not
 543 Improve Performance on Measures of Intelligence or Other Measures of “Far Transfer”:
 544 Evidence From a Meta-Analytic Review. *Perspectives on Psychological Science: A Journal of*
 545 *the Association for Psychological Science*, 11(4), 512–534.
 546 <https://doi.org/10.1177/1745691616635612>
- 547 Morquecho-Campos, P., Larsson, M., Boesveldt, S., & Olofsson, J. K. (2019). Achieving
 548 Olfactory Expertise: Training for Transfer in Odor Identification. *Chemical Senses*, 44(3), 197–
 549 203. <https://doi.org/10.1093/chemse/bjz007>
- 550 Niedenthal, S., Lundén, P., Ehrndal, M., & Olofsson, J. K. (2019) A Handheld Olfactory Display
 551 For Smell-Enabled VR Games, 2019 IEEE International Symposium on Olfaction and Electronic
 552 Nose (ISOEN), Fukuoka, Japan, 1-4. <https://doi.org/10.1109/ISOEN.2019.8823162>.
- 553 Olofsson, J. K., & Gottfried, J. A. (2015). The muted sense: neurocognitive limitations of
 554 olfactory language. *Trends in Cognitive Sciences*, 19(6), 314–321.
 555 <https://doi.org/10.1016/j.tics.2015.04.007>
- 556 Olofsson, J. K., Niedenthal, S., Ehrndal, M., Zakrzewska, M., Wartel, A., & Larsson, M. (2017).
 557 Beyond Smell-O-Vision: Possibilities for Smell-Based Digital Media. *Simulation & Gaming*,
 558 48(4), 455–479. <https://doi.org/10.1177/1046878117702184>
- 559 Olofsson, J. K., Rogalski, E., Harrison, T., Mesulam, M.-M., Gottfried, J. A. (2013). A cortical
 560 pathway to olfactory naming: evidence from primary progressive aphasia, *Brain*, 136(4), 1245–
 561 1259. <https://doi.org/10.1093/brain/awt019>
- 562 Olofsson, J. K., Rönnlund, M., Nordin, S., Nyberg, L., Nilsson, L.-G., & Larsson, M. (2009).

563 Odor identification deficit as a predictor of five-year global cognitive change: interactive effects
 564 with age and ApoE-epsilon4. *Behavior Genetics*, 39(5), 496–503.
 565 <https://doi.org/10.1007/s10519-009-9289-5>
 566 Owen, A. M., Hampshire, A., Grahn, J. A., Stenton, R., Dajani, S., Burns, A. S., Howard, R. J.,
 567 & Ballard, C. G. (2010). Putting brain training to the test. *Nature*, 465(7299), 775–778.
 568 <https://doi.org/10.1038/nature09042>
 569 Pekala, K., Chandra, R. K., & Turner, J. H. (2016). Efficacy of olfactory training in patients with
 570 olfactory loss: a systematic review and meta-analysis. *International Forum of Allergy &*
 571 *Rhinology*, 6(3), 299–307. <https://doi.org/10.1002/alr.21669>
 572 Rasch, B., Büchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-wave sleep prompt
 573 declarative memory consolidation. *Science (New York, N.Y.)*, 315(5817), 1426–1429.
 574 <https://doi.org/10.1126/science.1138581>
 575 Royet, J.-P., Plailly, J., Saive, A.-L., Veyrac, A., & Delon-Martin, C. (2013). The impact of
 576 expertise in olfaction. *Frontiers in Psychology*, 4, 928. <https://doi.org/10.3389/fpsyg.2013.00928>
 577 Sandberg, P., & Stigsdotter Neely, A. (2016). Long-term effects of executive process training in
 578 young and old adults. *Neuropsychological Rehabilitation*, 26(5–6), 761–782.
 579 <https://doi.org/10.1080/09602011.2015.1108205>
 580 Schneiders, J. A., Opitz, B., Krick, C. M., & Mecklinger, A. (2011). Separating intra-modal and
 581 across-modal training effects in visual working memory: an fMRI investigation. *Cerebral Cortex*
 582 *(New York, N.Y.: 1991)*, 21(11), 2555–2564. <https://doi.org/10.1093/cercor/bhr037>
 583 Simons, D. J., Boot, W. R., Charness, N., Gathercole, S. E., Chabris, C. F., Hambrick, D. Z., &
 584 Stine-Morrow, E. A. L. (2016). Do “Brain-Training” Programs Work? *Psychological Science in*
 585 *the Public Interest*, 17(3), 103–186. <https://doi.org/10.1177/1529100616661983>
 586 Solomon, J. A., & Pelli, D. G. (1994). The visual filter mediating letter identification. *Nature*,
 587 369(6479), 395–397. <https://doi.org/10.1038/369395a0>
 588 Stanciu, I., Larsson, M., Nordin, S., Adolfsson, R., Nilsson, L.-G., & Olofsson, J. K. (2014).
 589 Olfactory impairment and subjective olfactory complaints independently predict conversion to
 590 dementia: a longitudinal, population-based study. *Journal of the International*
 591 *Neuropsychological Society*, 20(2), 209–217. <https://doi.org/10.1017/S1355617713001409>
 592 Teixeira-Santos, A. C., Moreira, C. S., Magalhães, R., Magalhães, C., Pereira, D. R., Leite, J.,
 593 Carvalho, S., & Sampaio, A. (2019). Reviewing working memory training gains in healthy older
 594 adults: A meta-analytic review of transfer for cognitive outcomes. *Neuroscience and*
 595 *Biobehavioral Reviews*, 103, 163–177. <https://doi.org/10.1016/j.neubiorev.2019.05.009>
 596 van Rijzingen, I. M., Gispen, W. H., & Spruijt, B. M. (1995). Olfactory bulbectomy temporarily
 597 impairs Morris maze performance: an ACTH(4-9) analog accelerates return of function.
 598 *Physiology & Behavior*, 58(1), 147–152.
 599 Wimo, A., Jönsson, L., Bond, J., Prince, M., Winblad, B., & Alzheimer Disease International.
 600 (2013). The worldwide economic impact of dementia 2010. *Alzheimer's & Dementia: The*
 601 *Journal of the Alzheimer's Association*, 9(1), 1-11.e3. <https://doi.org/10.1016/j.jalz.2012.11.006>
 602 Zelano, C., Jiang, H., Zhou, G., Arora, N., Schuele, S., Rosenow, J., & Gottfried, J. A. (2016).
 603 Nasal Respiration Entrain Human Limbic Oscillations and Modulates Cognitive Function. *The*
 604 *Journal of Neuroscience*, 36(49), 12448–12467. [https://doi.org/10.1523/JNEUROSCI.2586-](https://doi.org/10.1523/JNEUROSCI.2586-16.2016)
 605 16.2016
 606 Zelcer, I., Cohen, H., Richter-Levin, G., Lebiosn, T., Grossberger, T., & Barkai, E. (2006). A
 607 cellular correlate of learning-induced metaplasticity in the hippocampus. *Cerebral Cortex (New*
 608 *York, N.Y.: 1991)*, 16(4), 460–468. <https://doi.org/10.1093/cercor/bhi125>

609 Zelinski, E. M. (2009). Far transfer in cognitive training of older adults. *Restorative Neurology*
610 *and Neuroscience*, 27(5), 455-471. <https://doi.org/10.3233/RNN-2009-0495>
611

612