Learning to Name Smells Increases Activity in Heteromodal Semantic Areas

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Abstract: Semantic description of odors is a cognitively demanding task. Learning to name smells is, however, possible with training. This study set out to examine how improvement in olfactory semantic knowledge following training reorganizes the neural representation of smells. First, 19 nonexpert volunteers were trained for 3 days; they were exposed (i) to odorants presented without verbal labels (perceptual learning) and (ii) to other odorants paired with lexicosemantic labels (associative learning). Second, the same participants were tested in a brain imaging study (fMRI) measuring hemodynamic responses to learned odors presented in both the perceptual and associative learning conditions. The lexicosemantic training enhanced the ability to describe smells semantically. Neurally, this change was associated with enhanced activity in a set of heteromodal areas—including superior frontal gyrus—and parietal areas. These findings demonstrate that odor-name associative learning induces recruitment of brain areas involved in the integration and representation of semantic attributes of sensory events. They also offer new insights into the brain plasticity underlying the acquisition of olfactory expertise in lay people. *Hum Brain Mapp* 38:5958–5969, 2017. © 2017 Wiley Periodicals, Inc.

Key words: olfaction; learning; semantic; heteromodal areas

INTRODUCTION

In the olfactory domain, acquisition of knowledge is based on two major types of learning: implicit (or

perceptual) learning, resulting from being merely exposed repeatedly to odors, and associative learning, based on the association of a smell with a nonolfactory stimulus such as a taste, visual, or verbal label. Data from the literature showed that olfactory perception, and in particular odor valence, are modulated by implicit experience. In a study of newborns whose pregnant mothers had consumed an aniseed beverage, Schaal et al. [2000] showed that, after birth, the babies were more attracted to the smell of anise than a control group whose mothers had not consumed the aniseed beverage. In another study, Haller et al. [1999] showed that early exposure to a food influences preferences for this food flavor in adulthood. In addition, it has been shown that exposure to odorant mixtures can alter the perceived quality of the individual components [Stevenson, 2001]. For instance, consuming wine or beer on a daily basis (passive experience) improved the capacity to

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discriminate between wine or beer components [Melcher and Schooler, 2004; Peron and Allen, 1988]. These studies showed that repeated exposure improves odor perception through differentiation of stimulus features, dimensions, or categories. Neurally, a functional brain imaging study showed that one short exposure (3.5 min) to an odorant improved odor discrimination and induced brain plasticity by modulating activity in the piriform cortex and orbitofrontal cortex [Li et al., 2006].

Besides mere exposure, an odor percept can be modified following association with a particular context. Such contextual cues may be nonolfactory, often gustatory stimuli [Barkat et al., 2008; Yeomans, 2006], visual, or verbal labels. Indeed, using an associative learning procedure, Qu et al. [2016] showed that pairing visual stimuli with ambiguous odors induced behavioral changes toward the smells that were associated with neural reorganization in piriform, orbitofrontal, and insular cortices. Regarding verbal labels, lexicosemantic associative learning characterizes professional situations in which odorants are systematically associated to a common vocabulary, allowing both perceptual agreement between learners and robustness for integrating, representing, and retrieving semantic features of smells. For example, perfumers are known not only to acquire systematic knowledge of the chemistry of odorants but also to learn to describe odors semantically on the basis of their olfactory qualities in a shared language [Sezille et al., 2014]. How such olfactory-verbal associative learning reorganizes the representation of smells remains unclear. To date, scientific attempts focused on the effect of verbal labeling on odor (hedonic) perception [Bensafi et al., 2007; Dalton, 1999; Djordjevic et al., 2008; Herz, 2003]. Accordingly, de Araujo et al. [2005] showed that the hedonic meaning of the label (edible: e.g., “cheese”; or not: e.g., “body odor”) assigned to an odor, differentially affected the activation pattern in cingulate gyrus and orbitofrontal cortex, two regions involved in the assignment of value. Moreover, it was shown that presenting the same odorant with two different olfactory labels recruited the cingulate gyrus and the orbitofrontal cortex more strongly when smells were accompanied by semantic information that was related to their source (e.g., “flower” for a rose odor) rather than to “practice” (e.g., “body lotion” for rose odor) [Bensafi et al., 2014]. However, despite this evidence that simultaneous presentation of labels and odorants influences perception and brain activity, very little is known about the way in which the neural representation of odors is affected by olfactory lexicosemantic associative learning.

This study examined this question by combining psychophysical training and brain imaging in the same human subjects. Participants first underwent 3-day training consisting of 3 sessions in which they were exposed to odorants (i) not presented with verbal labels (perceptual learning) or (ii) paired with verbal labels (associative learning). Second, the same participants underwent a functional magnetic resonance imaging (fMRI) study measuring brain activation related to learned odors (presented in both the perceptual

and associative learning conditions) and nonlearned odors. Perceptually, it was assumed that odors previously associated with names would be described semantically using a greater range of lexical features: that is, olfactory description ability should be enhanced more by associative than by perceptual learning. Neurally, it was hypothesized that semantic enrichment for odors in the associative learning condition would be associated with recruitment of a multimodal network of areas integrating and representing semantic features of environmental objects: cingulate gyrus (for its wider involvement in the perception of odors semantically described using complex labeling, see Sezille et al. [2015]), and angular gyrus, anterior temporal lobe, and inferior, middle, and superior frontal gyrus, as past studies showed their involvement in demanding semantic tasks [Bonner et al., 2013; Bonnici et al., 2016; Ferreira et al., 2015; Noonan et al., 2013; Price et al., 2016]. We also considered more typical olfactory areas such as the piriform cortex (for its involvement in coding perceptual and qualitative attributes of smells, see Fournel et al. [2016] and Howard et al. [2009]) and orbitofrontal cortex (as its activity is modulated when odors are perceived concurrently with verbal labels, see de Araujo et al. [2005]; Bensafi et al. [2014]).

MATERIALS AND METHODS

Subjects

The participants were 19 right-handed volunteers (mean $\pm$ SD age 26.56 ± 3.72 years; 10 men and 9 women). They received payment for the time spent in the laboratory. The recording procedure was explained in great detail to the subjects, who provided written consent prior to participation. The study was conducted according to the Declaration of Helsinki and was approved by the institutional review board at the “Technische Universität Dresden.” Detailed medical history combined with endoscopic examination of the nasal cavity and odor perception assessment by the identification test of the “Sniffin’ Sticks” test [Hummel et al., 2007] ascertained that subjects were in good health and had a normal sense of smell (mean $\pm$ SD 14.47 ± 0.77 ; range: 13–16). Note that the psychophysical criteria used to define normal olfactory abilities were an identification score of at least 12 out of 16. Finally, men (mean $\pm$ SD 14.70 ± 0.94) and women (mean $\pm$ SD 14.22 ± 0.44) did not differ in odor identification abilities ($F(1,17) = 1.904$, $P = 0.186$).

Selection of Odorants and Semantic Descriptors

A total of 6 odorants were used, taken from a previous study [Sezille et al., 2014]: methyl anthranilate (CID: 8635): MA; D-carvone (16724): CAR; benzyl acetate (8785): BA; eugenol (3314): EUG; citronellal (7794): CIT; and linalool (6549): LIL (all from Sigma-Aldrich and diluted in propylene glycol). To ensure isointense perception, the odorants were individually diluted to a final concentration (vol/vol)

Figure 1.

Word clouds of semantic descriptions given by perfumers for the 6 selected smells. Word size is proportional to the number of occurrences. [Color figure can be viewed at wileyonlinelibrary.com]

of 1.467%, 13.122%, 12.653%, 1.924%, 1.270%, and 2.164%, respectively, for BA, EUG, MA, CAR, CIT, and LIN. To select the most appropriate verbal labels for each stimulus, we reanalyzed data from 15 perfumers (mean age 34.40 ± 5.18 years; 5 men) from the study by Sezille et al. [2014]. In this experiment, experts were asked to verbally describe each molecule. For each stimulus, we selected the labels most frequently used for three different descriptor categories: “odor source,” “quality,” and “chemical name”; this provided the following labels: CAR: mint, spicy, and carvone; LIN: bergamot, floral, and linalool; EUG: cloves, spicy, and eugenol; BA: jasmine, fruity, and benzyl acetate; MA: flower, spicy, and methyl anthranilate; CIT: lemon-grass, fatty, and citronellal. Figure 1 illustrates these semantic descriptions using “word clouds”; all verbalizations used by the perfumers are included in this word-cloud descriptive analysis.

Stimulus Delivery

Olfactory stimuli were diffused to both nostrils using a computer-controlled olfactometer, allowing application of rectangle-shaped stimuli with controlled stimulus onset at an airflow of 1.5 l/min [Sommer et al., 2012]. During the experiment (both learning and fMRI sessions), participants

were asked to breathe through the mouth, to limit respiratory airflow in the nasal cavity during chemosensory stimulation because previous studies showed that sniffing influenced neural activations in olfactory and nonolfactory areas [Kareken et al., 2004; Sobel et al., 1998]. A Teflon™ nose-piece directed the gaseous stimulus from the olfactometer to the subject’s nose in the MRI room.

Training Sessions

For training purposes, odorants were split into three sets: set 1 comprised MA and CAR, set 2 BA and EUG, and set 3 CIT and LIN. The 3 odorant subgroups did not differ in intensity ($F(2,14) = 0.531$, $P = 0.600$) or pleasantness ($F(2,14) = 1.657$, $P = 0.226$) according to a pilot study (8 volunteers, mean age 19.50 ± 1.31 years; 4 men).

The learning phase was composed of three sessions. In session 1, participants perceived four odors (two sets) (the third set being used as a “nonlearned odors” condition in the subsequent fMRI sessions, see the section “Experimental Procedure and fMRI Experimental Paradigm”) (see Fig. 2a for an illustration of the experimental design for training). Odorant presentation was randomized for each participant and each session. In one odorant set, molecules were perceived without any association (“perceptual learning”),

Figure 2.

Schematic representation of the procedure. (a) Example of the experimental protocol for training for a given participant (task presentation order was randomized for each participant and each session). (b) Experimental protocol used for fMRI sessions (P: perceptual learning; A: associative learning; N: nonlearned odors). [Color figure can be viewed at wileyonlinelibrary.com]

whereas in the other set, they were perceived in association with the three verbal labels ("associative learning"). The comparison of these two conditions ("associative learning" and "perceptual learning") allowed us to examine the effect of learning the verbal labels associated with each odor. Nevertheless, it is important to note that to dissociate the different processes (e.g., attentional, mnemonic, visual, etc.) underlying such olfactory learning, it would have been possible to integrate into our experimental design additional control conditions including nonolfactory stimuli and/or visual stimuli. We have chosen to restrict our design to

these two conditions and not make it more complex to optimize the effects of the learning sessions. However, during the fMRI session (see below), an additional control condition ("nonlearned odors") with new odors was integrated.

Each odorant was presented in 6 ON blocks, in which it was presented for 8 s (eight trials of 1 s of odorant separated by 2 s of air diffusion). For the "associative learning" condition, labels were presented during the ON blocks. As in the fMRI experiment (see the section "Experimental Procedure and fMRI Experimental Paradigm"), between each "ON" block, an "OFF" block of 20 s without any odorant

was interposed. Participants were asked to breathe through the mouth to limit respiratory airflow in the nasal cavity (under the same condition as required in the fMRI scanner). In the “perceptual learning” condition, participants were asked to smell the odorants passively. In the “associative learning” session condition, they were asked to smell each odor while reading and learning the three odor names presented on a sheet in front of them. In both conditions, after smelling each odor in a given subsession (at the end of the 6 ON blocks), participants were asked to rate the intensity, pleasantness, and familiarity of the olfactory stimuli using a scale from 1 to 9 for intensity and familiarity (1: not at all intense/familiar, 9: very intense/familiar), and from -4 to $+4$ for pleasantness (-4 : very unpleasant; $+4$: very pleasant).

Before starting the second session, participants were debriefed and asked to smell each of the 4 odors presented in session 1, and remember whether the odor was presented with or without verbal labels in session 1, and recall the label if possible. Note that during this debriefing session, no performance was measured. Afterward, Session 2 started with procedures containing exactly the same “associative” and “perceptual” learning tasks as in Session 1.

Session 3 took place just before the fMRI session. Here, each odorant was presented in a “perceptual” or “associative” learning session (in one block), to reinforce previous associations. As for Sessions 1 and 2, in the “perceptual learning” condition, participants were asked to passively smell the odor. In the “associative learning” condition, they were asked to smell and read the three proposed odor names.

For the fMRI session, to increase stimulus diversity and avoid any habituation effect, odorants not smelled during the training days (“nonlearned odor” condition) and nonodorized stimuli were included. Therefore, while the main analysis compared the “associative” condition with the “perceptual” condition, the “associative” condition was also compared to the “nonlearned odors” condition (see the section “Data Analysis” for details). An important aspect of our protocol was that the odorant sets were balanced and randomized between participants as a function of learning types; Latin square randomization ensured that Sets 1, 2, and 3 were equally represented between participants in the three fMRI conditions of “perceptual learning,” “associative learning,” and “nonlearned odors.”

Experimental Procedure and fMRI Experimental Paradigm

The study was performed on a 3 T MR scanner (Siemens Magnetom Verio, Germany). The experiment lasted ~60 min (from arrival to departure of the subject) and included 6 sessions: one for each stimulus condition (BA, EUG, MA, CAR, CIT, and LIN). Participants underwent the 6 sessions in random order. Each session in turn comprised 6 on/off-block subsessions. To avoid the adaptation effect that may

occur with long-duration blocks (60 s odor diffusion) (Poellinger et al., 2001), sessions were structured as (i) olfactory “ON” blocks, in which the odorant was presented for only 8 s (eight trials of 1 s of odorant diffusion separated by 2 s of air diffusion) and (ii) nonolfactory “OFF” blocks of the same duration without any odorant stimulation.

The fMRI data were collected in 96 volumes per session with a 33 axial-slice, matrix 2D SE/EP sequence (matrix: 64×64 ; TR: 2,500 ms; TE: 40 ms; FA: 90° ; voxel size: $3 \times 3 \times 3$ mm; FOV: 192). In the 13 min immediately following the functional sessions, a high-resolution T1-weighted brain image (3D GR/IR sequence: TR = 2,180 ms/TE = 3.24 ms/F5: 15° ; voxel size: $0.7/0.7/1$) was acquired.

During scanning, participants were instructed to breathe through the mouth without concomitant nasal airflow (as described above), were not cued for any stimulus presentation, and were not aware of the identity of the stimuli. However, although not asked to make any overt judgment, they were told that they would have to retrieve information about the smells, as they would have to describe them semantically immediately after the functional session and provide perceptual estimates. Thus, after each functional session, participants were asked to identify the odor by describing it qualitatively. Here, no restrictions regarding the numbers of terms recalled were imposed. The number of correct responses was counted for each odorant (ranging from “0” if the participant did not use any of the 3 learned verbal labels to “3” if he/she gave all 3). Participants were also asked to evaluate the stimulus in terms of intensity (on a scale from “1” = “not perceived” to “9” = “extremely intense”), pleasantness (on a scale from “ -4 ” = “extremely unpleasant” to “ $+4$ ” = “extremely pleasant”), and familiarity (on a scale from “1” = “not at all familiar” to “9” = “extremely familiar”) (Fig. 2b).

To take account of a potential effect of intranasal respiration (despite the instruction to breathe through the mouth), nasal breathing was recorded throughout the functional sessions, using an airflow sensor (AWM720, Honeywell, France) connected to a small nasal cannula positioned in each nostril. The physiological signal was amplified and digitally recorded at 100 Hz using LabVIEW software[®]. Inspiratory volume during ON and OFF blocks was calculated for each condition and each participant.

Data Analysis

Statistical analysis used SPM8 software (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). Standard preprocessing was applied: motion correction, co-registration between functional and structural images, normalization in stereotaxic space, and smoothing (by convolving an $8 \times 8 \times 8$ mm³ FWHM Gaussian kernel with fMRI data) to take account of between-subject anatomical variation. The first-level statistical analysis was modeled using a canonical hemodynamic

response function. Three regressors of interest were included in the model: (1) “associative” learning odors (presented during associative learning sessions), (2) “perceptual” learning odors (presented during perceptual learning sessions), and (3) “nonlearned odors” (not presented during learning). Motion parameters were also included in the model as regressors of no interest. As olfactory stimuli were presented in separated sessions, to avoid potential baseline differences across sessions, we modeled the different sessions within the general linear model using dummy regressors.

Finally, for each subject, the contrast of interest consisted in comparing the “associative” condition with the “perceptual” condition (and vice versa). This was complemented by two additional contrasts: the “associative” with the “nonlearned odors” condition (and vice versa), and the “perceptual” with the “nonlearned odors” condition (and vice versa). In the second step, analyses were carried using a standard random-effects model and group activation was assessed using a single-sample *t* test.

Significant activations were identified using cluster-extent-based thresholding. To reduce the rate of false-positive clusters and improve confidence in interpreting specific locations, we followed the recommendations of Woo et al. [2014] using a stringent cluster-defining primary threshold (from $P < 0.0005$ to $P < 0.00005$) and a secondary statistical threshold of $P < 0.05$ corrected for multiple comparisons (family-wise error corrected, FWE). Moreover, at a descriptive level, to avoid misinterpretation of cluster-extent thresholded results, general descriptors rather than specific ones were used (e.g., “inferior frontal gyrus” rather than “triangular part of the inferior frontal gyrus”). All activation coordinates were presented in MNI space.

RESULTS

Effect of Training on Odor Perception

To examine how training influenced odor perception across sessions, an analysis of variance was performed for each rating and condition including sessions as a within-subjects factor (3: Session 1, Session 2, fMRI session). For intensity ratings, results revealed a significant effect of sessions for both “associative learning” condition ($F(2,36) = 4.786$, $P = 0.018$) and “perceptual learning” condition ($F(2,36) = 4.621$, $P = 0.025$) (Fig. 3). These main effects reflected increased intensity from Session 1 to Session 2 in both conditions (“associative learning”: $P = 0.041$; “perceptual learning”: $P = 0.019$) and from Session 1 to the fMRI session in both conditions (“associative learning”: $P = 0.016$; “perceptual learning”: $P = 0.016$). No significant difference was observed between Session 2 and the fMRI session ($P > 0.050$ in all cases). For familiarity ratings, a main effect of sessions was observed in both the “associative learning” condition ($F(2,36) = 8.972$, $P < 0.0001$) and the “perceptual learning” condition ($F(2,36) = 3.698$, $P = 0.042$).

Figure 3.

Odor ratings for (a) intensity, (b) familiarity, and (c) pleasantness for each session of the protocol (S1: first training session; S2: second training session; fMRI: fMRI session) and for each condition (associative learning and perceptual learning). * corresponds to $P < 0.05$ and bars correspond to means $\pm$ standard errors of the mean. [Color figure can be viewed at wileyonlinelibrary.com]

Paired comparisons revealed increased familiarity from Session 1 to Session 2 in the “associative learning” ($P = 0.012$) but not in the “perceptual learning” ($P = 0.100$), and from Session 1 to the fMRI session in both conditions (“associative learning”: $P = 0.0007$; “perceptual learning”: $P = 0.003$). No significant difference was observed between Session 2 and the fMRI session ($P > 0.050$ in all cases). Finally, effects of training on pleasantness ratings were observed neither in the “associative learning” ($F(2,36) = 0.371$, $P = 0.668$) nor in the “perceptual learning” conditions ($F(2,36) = 0.438$, $P = 0.636$).

Figure 4.

Number of correct semantic descriptions in each of the two experimental learning conditions ("associative learning," and "perceptual learning") and in the "nonlearned odors" condition. * corresponds to $P < 0.05$ and bars correspond to mean $\pm$ standard error of the mean. [Color figure can be viewed at wileyonlinelibrary.com]

Odor Perception, Descriptions, and Nasal Respiration During the fMRI Session

Perceptually, statistical analysis revealed no significant difference between conditions in terms of intensity ("associative learning": 6.13 ± 1.77 , "perceptual learning": 5.86 ± 1.47 , "nonlearned odors": 5.65 ± 1.39 , $F(2,36) = 0.743$, $P = 0.454$), pleasantness ("associative learning": 1.57 ± 1.43 , "perceptual learning": 1.18 ± 1.56 , "nonlearned odors": 1.90 ± 1.00 , $F(2,36) = 2.429$, $P = 0.118$), or familiarity ("associative learning": 6.84 ± 1.49 , "perceptual learning": 6.38 ± 1.83 , "nonlearned odors": 6.40 ± 1.63 , $F(2,36) = 0.860$, $P = 0.425$) (Fig. 3).

Regarding odor descriptions, a significant effect of condition was observed for odor naming ability ($F(2,36) = 37.330$, $P < 0.0001$), which was significantly greater in the "associative learning" condition (1.63 ± 0.96 correct labels) compared to the "perceptual learning" (0.25 ± 0.34 ; $P < 0.0001$) and "nonlearned odors" condition (0.18 ± 0.24 ; $P < 0.0001$) (Fig. 4).

Finally, statistical analysis of nasal respiration data found no main effects of condition ($F(2,36) = 0.493$, $P = 0.596$) ("associative learning": 412.72 (AU) ± 376.40 , "perceptual learning": 431.63 ± 364.31 , "nonlearned odors": 443.37 ± 397.60).

Brain Activations During the fMRI Session

Neurally, when the activation was compared between the "associative learning" and "perceptual learning" conditions, significant activations were observed in a neural network including a cluster in angular gyrus and supramarginal gyrus ($-54, -48, 52$, $t = 6.19$, $P(\text{FWE}) = 0.001$), and superior frontal gyrus (SFG) ($6, 34, 40$; $t = 5.98$, $P(\text{FWE}) = 0.002$)

(Fig. 5 and Table I). The converse contrast, on the other hand, did not show any significant activation.

Interestingly, similar activity was also seen when the "associative learning" condition was compared to the "nonlearned odors" condition. This contrast revealed activity in the angular gyrus and supramarginal gyrus ($50, -46, 46$, $t = 5.34$, $P(\text{FWE}) = 0.008$), and SFG ($14, 28, 40$; $t = 4.87$, $P(\text{FWE}) = 0.004$) (Table II). The converse contrast, on the other hand, did not show any significant activation. Finally, direct analyses comparing the "perceptual learning" and "nonlearned odors" conditions (and vice versa) did not reveal any significant activation. Note that the two significant contrasts ("associative" vs "perceptual" conditions; "associative" vs "nonlearned" condition) did not activate the same hemisphere in angular gyrus: left hemispheric angular gyrus activation for the "associative" versus "perceptual" contrast and right hemisphere angular gyrus activation for the "associative" versus "nonlearned" contrast. However, when only uncorrected P values were considered without applying the cluster extent threshold correction, we found activation in right angular gyrus in the "associative" versus "perceptual" contrast ($58, -50, 50$; $t = 5.4647$, $P = 0.00001$) and in the left angular gyrus in the "associative" versus "nonlearned" contrast ($-54, -52, 52$; $t = 4.8580$, $P = 0.00006$).

An important aspect of our findings was the large inter-individual variation in semantic description of odors following associative learning. Whereas some individuals benefited greatly from training, others had only minor improvement if any, as shown by the difference between the number of correctly described qualities in the "associative learning" versus the "perceptual learning" condition (Fig. 6a). We therefore investigated whether interindividual variation was associated with differential recruitment of brain areas showing significant activation following associative learning. Mean percentage signal change within each significant cluster (in the "associative learning" vs "perceptual learning" contrast) was correlated with individual performance in the olfactory semantic description task (i.e., difference in number of correctly described qualities in the "associative learning" vs "perceptual learning" condition). Results revealed a significant positive relationship in the SFG ($-2, 24, 46$) when the "associative" condition was compared to the "perceptual" condition ($r(17) = 0.468$, $P = 0.043$), indicating that "strong" learners deployed more neural resources in this area (Fig. 6b). As previous studies reported gender effects on both odor identification abilities and neural responses to odors [Doty and Cameron, 2009], we conducted a complementary analysis to test whether the above interindividual variation in both odor naming and SFG activation differed as a function of gender. Results revealed no differences in odor verbalization ("associative learning" vs "perceptual learning" condition) between women (mean $\pm$ SD 1.55 ± 0.68) and men (1.22 ± 1.13) ($F(1,17) = 0.576$, $P = 0.458$). Moreover, no significant effect

Figure 5.

fMRI activation in the “associative learning” versus “perceptual learning” conditions. Significant activation was seen in the angular gyrus and supramarginal gyrus, and superior frontal gyrus extending to the cingulate gyrus, accompanied by mean percentage signal change for the three conditions in significant clusters

(A: associative learning condition; N: non-learned condition; P: perceptual learning condition). Bars correspond to mean $\pm$ standard error of the mean. The color scale indicates statistical t values. [Color figure can be viewed at wileyonlinelibrary.com]

of gender on SFG activation was observed (mean $\pm$ SD: women, 0.27 ± 0.17 ; men, 0.24 ± 0.19 ; $F(1,17) = 0.060$, $P = 0.809$).

DISCUSSION

This study showed that learning to associate a specific smell with lexicosemantic features induces greater increase in the ability to describe odors than training without

verbal association. This improvement in odor lexicosemantic retrieval was associated with increased activity in a network of heteromodal brain regions including superior frontal gyrus and parietal areas (angular gyrus and supramarginal gyrus). No such increase in activity was seen in more typical olfactory areas such as the piriform cortex or orbitofrontal cortex.

Superior frontal gyrus activations in response to olfactory stimuli are not rare [Frasnelli et al., 2012; Royet et al., 1999; Zou et al., 2016], and the literature in the field

TABLE I. Hemodynamic activation following perception of odors previously paired with verbal labels (“associative learning” condition) versus paired without verbal labels (“perceptual learning” condition)

Areas	Cluster level			Peak level		MNI coordinates		
	P (FWE-corr)	equivk	P (unc)	T	P (unc)	X	Y	Z
Angular gyrus/supramarginal gyrus	0.001	80	0.0003	6.19	0.0000	−54	−48	52
				5.7643	0.0000	−46	−48	40
Superior frontal gyrus	0.002	73	0.0005	5.9897	0.0000	6	34	40
				5.4791	0.0000	−2	24	46
				5.2498	0.0000	6	22	48

TABLE II. Hemodynamic activation following perception of odors previously paired with verbal labels (“associative learning” condition) versus odors not presented during the learning session (“nonlearned odors” condition)

Areas	Cluster level			Peak level		MNI coordinates		
	<i>P</i> (FWE-corr)	equivk	<i>P</i> (unc)	<i>T</i>	<i>P</i> (unc)	X	Y	Z
Angular gyrus/supramarginal gyrus	0.008	179	0.0005	5.3427 4.3711	0.0000 0.0001	50 46	−46 −60	46 46
Superior frontal gyrus	0.004	205	0.0002	4.8711 4.8203 4.6364	0.0000 0.0000 0.0001	14 8 4	28 32 26	40 50 46

highlights a role of this area in cognitive and verbal processing related to odors. For example, a previous study of odor processing in humans showed that reading olfaction-related words induced activation in the superior frontal gyrus (although labeled as cingulate gyrus in this article) [González et al., 2006]. Another study revealed that activity in the cingulate cortex (bordering the lower part of the superior frontal gyrus) in response to odorants was greater when the smell was labeled with its source (e.g., “smell of rose”) rather than a so-called “practice label” (e.g., “body lotion”) [Bensafi et al., 2014]. Finally, activity in the dorsal anterior cingulate gyrus and bordering the superior frontal gyrus was shown to increase as a function of the semantic richness of odors: smells described with more semantic qualities activated this area more than smells described with few semantic qualities [Sezille et al., 2015].

Interestingly, the concept of semantic richness has been well studied in the visual modality. It was shown that increased semantic richness was associated with increased activity in left angular gyrus [Ferreira et al., 2015]. The angular gyrus plays a prominent functional role in the

integration of lexical-semantic information [Bonner et al., 2013; Price et al., 2016], and is also considered to play a distinct role in semantic retrieval [Bonnici et al., 2016]. Similar to Ferreira et al. [2015], this study showed that this area was significantly more activated by odorants previously paired with names, and by odors more accurately described semantically. This result strengthens the notion that the angular gyrus may be one component of a multi-modal network involved in the retrieval of semantic attributes of sensory events, including smells. Van Ettinger-Veenstra et al. [2016] showed that activity in this area is also influenced by interindividual variation: participants with greater language ability showed greater activation in the left angular gyrus during a semantic task.

Although the correlation between individual performance on the olfactory semantic description task and hemodynamic activity in this area was not significant in this study, a correlation did emerge in the superior frontal gyrus, another heteromodal area. Whereas some participants benefited greatly from training, others showed only minor enhancement of their olfactory semantic description

Figure 6.

Interindividual variation in semantic description of odors as a function of brain activity. (a) Some individuals on the right side of histogram benefited from semantic training, whereas those on the left side did not. (b) Mean percentage signal change in the superior frontal gyrus (6, 34, 40) (“associative” vs “perceptual”

contrast) correlated positively with correct answers on the olfactory semantic description task (“associative” vs “perceptual” conditions). [Color figure can be viewed at wileyonlinelibrary.com]

ability. This variation was also reflected at the neural level: individuals with greater learning ability deployed more neuronal resources in the superior frontal gyrus. This finding is in agreement with recent neuroimaging findings showing that highly skilled individuals performed better on an artificial grammar learning task than moderately skilled subjects and, during the task, deployed more neural resources in the angular/supramarginal gyrus, middle and superior frontal gyrus, and cingulate gyrus [Kepinska et al., 2016]. Beside our correlational analysis, at group level, the superior frontal gyrus was more activated during the perception of odors that were more accurately semantically described. This activation may reflect different levels of information processing, including olfactory, visual, attentional, and working memory processing. First, it may reflect search for the name of the odor source, as the left superior frontal gyrus was seen to be activated during an odor identification task [Frasnelli et al., 2012]. Second, it may reflect retrieval of semantic information, as this area was shown to be involved in odor familiarity evaluation [Royet et al., 1999]. Third, the superior frontal gyrus [du Boisgueheneuc et al., 2006] is involved in working memory, which was certainly involved in our task as participants had to keep the semantic labels associated with the odors in memory and to be able to retrieve them after the functional scans. The experimental design used in this study unfortunately does not allow us to disentangle the respective contribution of each of these factors on neuronal activities. Future studies including an additional condition where odors would be learned in association with pictorial stimuli (vs verbal in our case) could help in distinguishing the respective role of visual imagery, attention, and memory on the activity evoked in the SFG or the angular gyrus.

While this study provides evidence that odor-name-associative learning induces neural reorganization in heteromodal semantic areas, some results require discussion. First, one question that may be raised is whether the current results are specific to odor learning or whether they could be expected for different sensory modalities. Our design, because it did not include a nonolfactory control task, does not allow addressing this question. However, as typical olfactory areas were not recruited after learning while a network of heteromodal brain regions was, it is very likely that the present findings are nonspecific to the olfactory modality. Second, a potential issue regarding our study design concerns the fact that we measured brain activity only after training, whereas measuring fMRI activity before the learning session would also have been an interesting option, allowing to trace changes over time of neural activity within experimental task (“associative,” “perceptual,” and “nonlearned”). However, the main reason why we chose to compare experimental tasks only after training was that in the case of “nonlearned” odors, this category of smells would have been perceived in a “pretraining” fMRI session, and thus would not be “new” to the participants in a “post-training” fMRI session. Third,

odors previously paired with words were more accurately semantically described, but were not more familiar than the “nonlearned odors” presented for the first time during the scanning session. One factor that could explain this lack of greater familiarity is that all the selected odors (including the nonlearned ones) may actually have been relatively known but still not easy for nonexperts to put a name on. This effect is well-known as the “tip-of-the-nose” effect: knowing an odor but being unable to name it [Lawless and Engen, 1977]. Odor-name associative learning broke the tip-of-the-nose effect by increasing access to lexicosemantic representation. Fourth, the reason why no significant differences in brain activity were observed between the “perceptual learning” and “nonlearned odors” conditions is unclear. No hypothesis was made *a priori* on brain activations induced by “nonlearned odors,” and one might expect activations in frontal and occipital areas as shown by Hawco and Lepage [2014] for stimulus and semantic novelty. Moreover, as a previous study by Li et al. [2006] showed that perceptual learning enhanced piriform cortex activity, greater activation might be expected in this area following “perceptual learning,” but this was not in fact the case. Absence of primary cortex activity is not rare in fMRI studies involving olfactory stimuli, and many factors may explain this, including susceptibility artifacts and, importantly, top-down modulation (see Bensafi [2012] for a review). Savic et al. [2000] did not observe any activation in the piriform cortex when participants had to evaluate and discriminate the quality of the smells, whereas there was activation when they were asked to smell the same odors passively. Moreover, Kareken et al. [2003] showed piriform activity when participants had to detect the odors but not when they had to identify them. In the same vein, in our experimental task, although participants were not asked to perform any motor task, they tried to retrieve semantic and affective information about the odors during the scanning session. Fifth, the question why similar activations were observed when contrasting the “associative learning” versus “nonlearned” conditions and the “associative learning” versus “perceptual learning” conditions remains unanswered. One assumption may be that the magnitude of the effect of associative learning is greater than that of the two others conditions. It involves associative and semantic areas that may modulate sensory areas through top-down command, possibly explaining why the activity of these areas (SFG and parietal areas) is seen in both contrasts. We acknowledge however that this assumption remains speculative at this stage and deserves further examination in the future.

Another question that may be raised is whether there were individual differences in the participants’ initial abilities in terms of working memory or verbal fluency and whether this could have influenced odor description level during training. Although our protocol did not include such neuropsychological evaluations and as such, cannot answer this question, we ensured that participants had

sufficient semantic and verbal abilities to satisfactorily identify the odors in the identification section of the Sniffin' Sticks test. Also, to examine whether or not the participants' general abilities to identify odors influenced the extent to which they benefitted from the effect of learning, we split the participants into two groups: those with an odor identification score between 13 and 14 (/16; $n = 11$) and those with a score between 15 and 16 (/16; $n = 8$). No significant differences were found between these two groups in the descriptions of odors during the associative ($F(1,17) = 0.197$, $P = 0.663$), perceptual ($F(1,17) = 0.443$, $P = 0.515$) and non-learned ($F(1,17) = 0.973$, $P = 0.338$) conditions.

In conclusion, despite growing behavioral evidence for improvement of semantic description of smells with training, especially in expert subjects, very little has been known about its neural underpinnings. In addition, beneficial effects of semantic training for nonexperts remained elusive. This study set out to examine this question and found that, for nonexperts, learning to name smells engaged more neuronal resources in semantic heteromodal areas. The main theoretical implication of these findings is that they support the view that binding information from different sensory inputs with semantic knowledge involves convergence zones or "hubs" [Damasio, 1989], in which parietal and frontal areas play a significant role. Although our study extended this model to the olfactory modality and opens up new perspectives in the brain plasticity underlying acquisition of olfactory expertise by nonexperts, the exact specific contribution of each of the parietal and frontal areas identified in binding olfactory and semantic information is still unclear and deserves further investigation. In particular, future studies should set out to provide functional or causal evidence of the role of these heteromodal areas in both integration of odor semantic information during training and retrieval of olfactory semantic information during recognition.

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