

The Feeling of Familiarity of Music and Odors: The Same Neural Signature?

Jane Plailly, Barbara Tillmann and Jean-Pierre Royet

Neurosciences & Systèmes Sensoriels, Université Claude Bernard Lyon 1, UMR CNRS 5020, IFR 19, Institut Fédératif des Neurosciences de Lyon, 69366 Lyon cedex 07, France

The feeling of familiarity can be triggered by stimuli from all sensory modalities, suggesting a multimodal nature of its neural bases. In the present experiment, we investigated this hypothesis by studying the neural bases of familiarity processing of odors and music. In particular, we focused on familiarity referring to the participants' life experience. Items were classified as familiar or unfamiliar based on participants' individual responses, and activation patterns evoked by familiar items were compared with those evoked by unfamiliar items. For the feeling of familiarity, a bimodal activation pattern was observed in the left hemisphere, specifically the superior and inferior frontal gyri, the precuneus, the angular gyrus, the parahippocampal gyrus, and the hippocampus. Together with previously reported data on verbal items, visual items, and auditory items other than music, this outcome suggests a multimodal neural system of the feeling of familiarity. The feeling of unfamiliarity was related to a smaller bimodal activation pattern mainly located in the right insula and likely related to the detection of novelty.

Keywords: feeling of unfamiliarity, fMRI, multimodality, novelty recognition memory

Introduction

Someone walking in the street listens to a tune that seems familiar but cannot immediately recollect anything about it. Someone entering a room perceives an odor but cannot recover the place where it was previously experienced, the date, or the identity of this odor. The feeling of familiarity is a long-term recognition memory process referring to a subjective state of awareness based on judgments of the item's prior occurrence. It involves the recognition of the item's perceptual features and eventually of conceptual or semantic features, without the confirmatory conscious recollection of contextual information and/or without identification. This feeling can be evoked by items coming from all sensory modalities but seems nevertheless to be identical. What are the neural substrates of this feeling? Are they the same regardless of the triggering modality?

Because everyday experiences unfold in multiple modalities, it is currently accepted that the establishment of a durable experience record and its associative incorporation into an existing knowledge base imply multimodal integration (Mesulam 1998). Numerous experiments suggest that entire or partial recall of this knowledge activates the same brain regions whatever the modality of the triggering item. For example, semantic tasks based on visual items activate a distributed neural system shared by words and pictures, including left occipital, temporal, and inferior frontal cortices (Vandenberghe et al. 1996). Categorization tasks based on visual and auditory objects (i.e., pictures and environmental sounds) activate bilateral

inferior frontal gyrus (IFG), suggesting these areas are possible sites for the integration of multimodal object representations in semantic memory (Adams and Janata 2002). Beyond semantic processing, it has also been established that working memory processes for olfactory and visual items share the same neural bases in the prefrontal cortex (Dade et al. 2001) and that hedonicity judgments of auditory, olfactory, or visual items activate the same regions of the orbitofrontal cortex, the temporal pole, and the superior frontal gyrus (SFG) (Royet et al. 2000). Along the same lines, a hypothesis could be made that the feeling of familiarity, which can be triggered by different sensory modalities, is related to the activation of multimodal brain regions. Curran and Dien (2003) were the first to propose the notion of an “amodal familiarity process.” Comparing the neural bases of recognition memory for words presented either visually or auditorily, they reported that midfrontal-evoked potentials related to familiarity processing were not affected by the modality of the item. However, because both the auditory and visual items consisted of words referring to the same knowledge (the word meaning, orthography, pronunciation, etc.), the data did not allow for conclusions as to whether observed brain responses were specifically related to the processing of familiarity. Moreover, this experiment did not distinguish neural bases related to the feeling of familiarity from those related to the feeling of unfamiliarity.

The purpose of our present experiment was to test the hypothesis of the multimodal nature of the familiarity processing network by investigating the neural correlates underlying the feeling of familiarity and the feeling of unfamiliarity evoked by items of 2 modalities: odors and musical excerpts. To allow for direct comparison, odors and musical excerpts were delivered to each participant in the same scanning session. Participants were instructed to make familiarity judgments of both item categories based on their life experiences (i.e., does this odor/musical excerpt seem familiar to you?), avoiding the need for an initial experimental encoding phase. To refer most accurately to each participant's experience, classification of the items as familiar or unfamiliar was done based on the judgments made during the scanning session. On the basis of previous data sets acquired separately for odors (Royet et al. 1999, 2001; Plailly et al. 2005) and music (Platel et al. 1997, 2003), we expected that the neural signature of the feeling of familiarity for both item categories would include increased activation in IFG, cingulate gyrus (CG), and inferior parietal regions. We also analyzed activation in the hippocampus (Hip) and parahippocampal gyrus (pHip) because activation in these regions has been debated in the context of familiarity (Strange et al. 1999, 2005; Maril et al. 2003; Eldridge et al. 2005; Yonelinas et al. 2005).

Materials and Methods

Participants

Thirteen right-handed men (mean age 24.54 ± 2.44 years) without known olfactory or auditory impairments, rhinal disorders (colds, active allergies, history of nasal/sinus surgery, or asthma), neurological disease, ferrous implants (e.g., pacemakers, cochlear implants), or claustrophobia participated in this experiment. The number of years of formal musical training of each participant ranged from 0 to 4 (mean of 1.15 ± 1.68). Participation required a medical screening and written informed consent. The study was approved by the local Institutional Review Board and conducted according to French regulations on biomedical experiments with healthy volunteers.

Olfactory Stimuli

Forty-eight odorants were used in the functional magnetic resonance imaging (fMRI) scanning session, 24 familiar and 24 unfamiliar (determined a priori, see Supplementary Materials, Table1). To maximize differences in familiarity scores while minimizing intensity and hedonicity differences between familiar and unfamiliar items, these odorants were selected from a behavioral pretest. Sixteen male participants (mean age: 27.25 ± 2.89 years) judged the intensity, hedonicity, and familiarity of 84 odorants, presented in random order, using 11-point (from 0 to 10) subjective rating scales (indicating from weak to strong, unpleasant to pleasant, and unfamiliar to familiar, respectively). On the familiarity scale, the 24 familiar odorants selected from the pretest showed average ratings of 6.74 ± 0.75 and for the 24 unfamiliar odorants 4.32 ± 0.70 ($t_{46} = 11.49$, $P < 0.0001$). The odorants of the 2 groups differed slightly in averaged ratings of intensity (5.66 ± 0.68 for familiar and 5.20 ± 0.84 for unfamiliar odorants [$t_{46} = 2.09$, $P = 0.042$]) and more strongly on averaged ratings of hedonicity (5.88 ± 0.82 for familiar and 4.61 ± 0.87 for unfamiliar odorants [$t_{46} = 5.21$, $P < 0.0001$]). The strong, well-known link between familiarity, intensity, and hedonicity judgments of odorants (e.g., Distel et al. 1999; Royet et al. 1999; Sulmont et al. 2002) was reflected in the correlation between familiarity and intensity judgments ($r_{82} = 0.75$, $P < 0.0001$) and between familiarity and hedonicity judgments ($r_{82} = 0.54$, $P < 0.0001$) evaluated from the entire set of pretest odorants. In both the pretest and scanning sessions, odorants were diluted to a concentration of 10% using mineral oil (Sigma Aldrich, Saint-Quentin Fallavier, France). For presentation, 5 mL of this solution was absorbed by compressed polypropylene filaments inside of 100 mL white polyethylene squeeze bottles with a dropper (Osi, Maurepas, France).

Musical Stimuli

Forty-eight musical excerpts were used in the fMRI scanning session, 24 familiar and 24 unfamiliar (determined a priori, see Supplementary Materials, Table2). The musical excerpts consisted of instrumental music without voice or associated texts. They were taken from commercial CD recordings and covered a wide range of instrumentations (e.g., piano, violin, chamber music, orchestra) and composers (e.g., Bach, Strauss, Vivaldi), though with the majority belonging to classical music. To maximize differences in familiarity while maintaining similarity in emotional expressivity and dynamics, these musical excerpts were selected on the basis of a behavioral pretest. We further aimed for similar instrumentations in familiar and unfamiliar groups as well as some overlap in composers. Eighteen male participants (mean age 28.2 ± 3.13 years; number of years of instruction on a musical instrument ranged from 0 to 6, with a mean of 0.89 ± 1.64) judged the familiarity, emotional expressivity, and dynamics of 162 musical excerpts, presented in random order, using 11-point (from 0 to 10) subjective rating scales (indicating from unfamiliar to familiar, negative to positive, and calm to agitated, respectively). On the familiarity scale, the 24 familiar excerpts selected from the pretest showed average ratings of 9.07 ± 0.73 and the 24 unfamiliar excerpts 2.24 ± 0.22 ($t_{46} = 43.75$, $P < 0.0001$). The excerpts of these 2 groups did not differ significantly in averaged ratings of emotional expressivity (5.55 ± 1.62 for familiar and 5.06 ± 0.95 for unfamiliar excerpts) or of dynamics (6.47 ± 1.39 for familiar and 5.71 ± 1.40 for unfamiliar excerpts). Excerpts of familiar and unfamiliar groups had a mean duration of 6.5 s (from 3.9 to 7.8 for familiar and 4.1 to 8.0 for unfamiliar).

Stimulation and Recording Materials

Odorants were presented using an airflow olfactometer, which allowed for synchronization of stimulation with breathing (Vigouroux et al. 2005). The stimulation equipment consisted of 2 modules: the electronic part of the olfactometer was positioned outside the magnet room, and the nonferrous (Duralumin®) air-dilution injection head was placed in the stray field of the magnet. Compressed air (10 L/min) was pumped into the olfactometer and delivered continuously through a standard anesthesia mask positioned on the participant's face. At the beginning of an inspiration, one odorant was injected into the olfactometer by squeezing the odor bottle into the injection head, which carried the odorant to the mask. The stimulation times (i.e., the start of the injection) were transmitted outside the magnetically shielded room by optical fibers to analog-to-digital converters powered by nickel-cadmium batteries. Breathing was recorded by a PVC foot bellows (Herga Electric Limited, Suffolk, UK) held on the participant's stomach with a cotton belt. Breathing data and signals of stimulation were recorded online (100 Hz sampling rate) using a computer equipped with a digital acquisition board DAQCard-500 (National Instruments, Austin, TX). LabVIEW software (National Instruments, Austin, TX, USA) was used to acquire, store, and read data. Data analysis was performed with the WinDaq Waveform Browser 1.91 software (DataQ Instruments, Akron, OH).

The musical excerpts were presented monophonically in CD quality (44.1 kHz, 16 bits) with equalized root-mean-square power. They were presented at a comfortable loudness level using LabVIEW piloting stimulus presentation software via the audio material MR-CONFON (www.mr-confon.de): analog/optical converter, amplifier, and electrodynamic headphones HP-SI01.

Participants rated familiarity by using a 2-button box, which provided transistor-transistor logic signals to a National Instruments (www.ni.com) numeric I/O card (PCI-6527). The nature of the response was recorded using a specific module written in LabVIEW, reading hardware occurrences sent by the 6527 card.

Experimental Procedure

The 48 odorants and 48 musical excerpts were presented in 2 functional runs of eight 90-s blocks (Fig. 1). Each run consisted of 4 olfaction and 4 music blocks. Each block was composed of 6 items with an interitem interval of approximately 15 s for the olfaction condition (depending on the participant's respiration) and 15 ± 0.70 s for the music condition. In each block, 3 items were familiar and 3 items were unfamiliar, as defined by the pretests (see Olfactory Stimuli and Musical Stimuli). The blocks were presented in pairs consisting of an olfaction block and a music block. Half of the pairs started with odors and the other half with musical excerpts. The order of modalities in the pairs and the order of familiar and unfamiliar items in each modality were counterbalanced in a pseudorandomized order over runs and participants. A baseline period of 36 s (B) was inserted between pairs.

For both olfaction and music conditions, participants were asked to rate whether the item was familiar or unfamiliar by pressing one of 2 buttons with the right hand. For half of the participants, "yes" and "no" responses were obtained with the index and the middle fingers, respectively. For the other half, the meaning of response buttons was reversed. During the B period, no stimulation occurred and participants were instructed to rest.

General instructions were provided to participants outside the scanner. During the functional runs, each pair was introduced by a verbal auditory cue 6.17 s prior to its beginning (first, second, third, fourth), and the modality of each block was announced 4.17 s prior to its beginning (Music, Odor). The end of each pair was indicated by a white noise lasting 250 ms. Verbal cues were recorded with the French voice in the demonstration version of the text-to-speech software Bright-Speech 1.2 (www.babeltech.com/Demos.php) and the noise burst with SoundEdit 16 software. Participants wore earplugs to protect from the scanner noise and kept their eyes closed during scanning. Prior to scanning, participants were trained to breathe regularly and to detect odors during inspiration while avoiding sniffing.

Imaging Parameters

Images were acquired using a 3-T whole-body imager MEDSPEC 30/80 AVANCE (Bruker®, Ettlingen, Germany), equipped with a circular

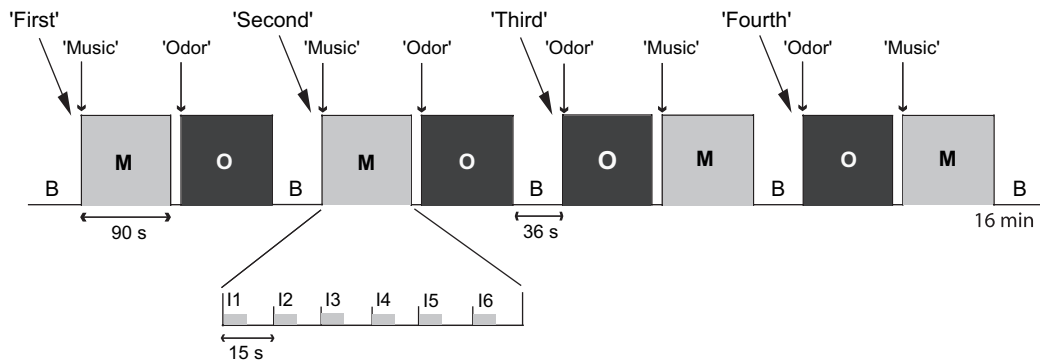


Figure 1. Experimental design. Schematic representation of the time course of the experimental session illustrated with one functional run including 8 blocks of 90 s. The blocks of olfactory conditions (O) and musical conditions (M) were presented in pairs. Each pair was introduced by a verbal cue (first, second, third, fourth), and the modality of each block was announced (Music, Odor). The second line of the schema represents the details of a block for which 6 items (from I1 to I6) were delivered approximately every 15 s. B indicates the baseline period of 36 s.

polarized head coil. Functional imaging was performed first, using a T_2^* -weighted echo-planar sequence at 30 interleaved 3-mm-thick axial slices with a 0.5-mm gap (time repetition = 2500 ms, time echo = 35 ms, flip angle = 80° , field of view = 19.2×19.2 cm, 64×64 matrix of $3 \times 3 \times 3.5$ mm voxels). Afterward a high-resolution structural T_1 -weighted anatomical image (inversion-recovery 3D gradient echo sequence, $1 \times 0.898 \times 1.42$ mm parallel to the bicommissural plane), covering the whole brain, was acquired.

The fMRI Data Preprocessing and Statistical Analyses

Data were preprocessed and analyzed with statistical parametrical mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK) (Friston, Ashburner, et al. 1995). The first 5 volumes of each functional run were discarded to allow for T_2^* equilibration effects. Slices of each remaining volume were slice-timing corrected. Volumes were realigned to the acquired median volume. Images were spatially normalized (Friston, Holmes, et al. 1995) to the Montreal Neurological Institute (MNI) standard brain and smoothed with a $6 \times 6 \times 7$ -mm full width half maximum isotropic Gaussian kernel.

Preprocessed data of each participant were analyzed with the standard general linear model (GLM) approach of SPM2 using boxcar predictors convolved with the canonical hemodynamic response function (Friston et al. 1998). A high-pass filter (cutoff frequency of 1/120 Hz) eliminated instrumental and physiological low-frequency signal variations. Each item was categorized as familiar or unfamiliar on the basis of participants' responses acquired during the scanning session. Four t contrast maps were calculated by comparing familiar (F) and unfamiliar (uF) items to each other for olfaction (O) and music (M) conditions (contrasts FO - uFO, uFO - FO, FM - uFM, and uFM - FM). Random effects 1-sample t -test analyses were applied to extrapolate statistical inferences into the healthy population. This 2-stage analysis (second-order analysis) accounted for intraparticipant (scan-to-scan) variance and between-participant variance. At the group level, 4 voxel-by-voxel single-sample t -tests were performed to test whether each contrast differed significantly from zero.

In a second step, analyses were performed to dissociate areas activated in both modalities (modality independent) from activations specific to each modality (modality specific). Contrast images of the four 1-sample t -tests were transformed into true-false maps of significant and nonsignificant voxels (using the threshold of $P < 0.01$ uncorrected, a $Z \geq 3.00$, and an extent threshold of more than 5 adjacent activated voxels). For the modality-independent analyses, voxels of these maps with "true" values in both modalities were considered as being part of the conjunction maps (i.e., with one map for F minus uF and one for uF minus F). For the modality-specific analyses, these true-false maps served as masks for each modality. Four RFX paired t -tests compared the 2 modalities for either familiarity-specific or unfamiliarity-specific activations. In other words, the analysis [(FO - uFO) - (FM - uFM)] masked with (FO - uFO) allowed for identification of activation patterns specific to the feeling of familiarity of odors; the analysis [(uFO - FO) - (uFM -

FM)] masked with (uFO - FO) allowed for identification of activation patterns specific to the feeling of unfamiliarity of odors; the analysis [(FM - uFM) - (FO - uFO)] masked with (FM - uFM) allowed for identification of activation patterns specific to the feeling of familiarity of musical excerpts; and the analysis [(uFM - FM) - (uFO - FO)] masked with (uFM - FM) allowed for identification of activation patterns specific to the feeling of unfamiliarity of musical excerpts. Duvernoy's (1991) and Mai's (1997) anatomical atlases were used to localize and describe anatomical regions of activation. Activated areas were indicated using the MNI coordinate system. Only results from the second-step analysis were reported (Tables 1 and 2, Figs 2 and 3).

The MarsBar SPM toolbox (<http://marsbar.sourceforge.net>) was used to perform statistical analyses of regions of interest (ROIs) on the left and right Hip and pHip (anatomically defined, Anatomical Automatic Labeling ROI library) for the modality-independent analysis of F minus uF. It was also used to define functional ROIs on the basis of the bimodal activation clusters for both the F - uF and uF - F comparisons and to extract the mean percent signal change of each of these functional ROIs for FO, uFO, FM, and uFM conditions in all participants. With the MarsBar SPM toolbox, percent signal change in an ROI is defined as the maximum height of the time course of an estimated single event for a specific condition, divided by the average signal across the time course of the session within this ROI, and multiplied by 100. The average signal used in this calculation is based on all conditions and is identified as the beta value for the mean column of the regression analysis. Thus, a percent signal change less than zero does not correspond to a deactivation because it is measured in relation to the mean signal within the ROI, and not in relation to the resting baseline. In our experiment, the percent signal change was measured for each session, and the average across the 2 sessions was calculated.

Results

Behavioral Data

For odors and musical excerpts, items were classified as familiar and unfamiliar for each participant on the basis of her/his behavioral responses. The numbers of items judged as familiar and unfamiliar in the scanning session were 26.2 ± 7.9 and 20.6 ± 7.7 for odors and 25.1 ± 3.6 and 22.9 ± 3.7 for musical excerpts. The numbers of items judged as familiar and unfamiliar were identical for musical excerpts ($\chi^2 = 13.22$, $P = 0.354$), but not for odors ($\chi^2 = 62.12$, $P < 0.0001$). No significant difference in the numbers of items was observed between odors and musical excerpts for familiar ($\chi^2 = 10.83$, $P = 0.544$) and unfamiliar ($\chi^2 = 17.18$, $P = 0.124$) items.

To investigate the consistency of the classification of each item as familiar or unfamiliar, we compared the classifications

Table 1

Brain regions with significant differences in both modalities (Bimodal) or specific to olfaction modality (Olfaction) and specific to music modality (Music) when comparing Familiar minus Unfamiliar items

Bimodal						Olfaction						Music					
Area	k	Z	x	y	z	Area	k	Z	x	y	z	Area	k	Z	x	y	z
Frontal						Frontal						Frontal					
SFG/CS	59	4.67	-6	54	-4	CG	6	3.22	12	39	7	SFG	11	3.40	-3	60	4
SFG/MFG	21	4.16	-21	21	56							MFG	26	4.26	-33	12	53
SFS	49	4.15	-6	48	39							MFG		3.45	-27	6	49
SFG		3.40	-6	36	39							Precentral g	7	3.14	-33	-3	42
SFG		3.27	-3	39	35							Temporal					
IFG	7	3.44	-39	9	35							STS	10	3.93	-45	-75	28
Lateral orbital g/IFG, pars orbitalis	31	3.19	-51	30	0							STS	9	3.81	-54	-21	-11
IFG, pars orbitalis		3.02	-51	27	11							STS	15	3.67	-51	-57	11
Parieto-occipital						Temporal						Parietal					
AG	52	4.48	-39	-72	39	Short insular g	6	3.36	-36	-15	14	CG, post part	13	3.60	-3	-39	39
Mid occipital g, sup part		3.59	-39	-63	25							SMG	6	3.45	-60	-45	35
Mid occipital g, sup part		3.20	-51	-60	21							SMG	6	3.21	-45	-48	35
Mid occipital g, sup part		3.04	-48	-63	18							AG	9	3.02	48	-60	18
PCu	79	4.01	-3	-63	28												

Note: k, cluster of voxels size; Z, Z value; x, y, z, MNI coordinates in left-right (x), posterior-anterior (y), and inferior-superior (z) planes; g, gyrus; mid, middle; post, posterior; sulc, sulcus; sup, superior.

Table 2

Brain regions with significant differences in both modalities (Bimodal) or specific to olfaction modality (Olfaction) and specific to music modality (Music) when comparing Unfamiliar minus Familiar items

Bimodal						Olfaction						Music					
Area	k	Z	x	y	z	Area	k	Z	X	Y	Z	Area	k	Z	X	Y	Z
Temporal						Frontal						Frontal					
Ins	7	3.25	30	24	7	SFG	13	3.69	27	21	46	SFG	17	3.49	12	24	35
												Central sulc	31	4.28	-48	-24	46
												Sup precentral sulc	17	3.86	-27	-18	56
Parietal						Parietal						Parietal					
						SMG	15	3.56	60	-39	32	Parietal operculum	14	3.44	-39	-21	18
						SMG	6	3.45	63	-51	25	SMG	6	3.05	39	-39	32

Note: k, cluster of voxels size; Z, Z value; x, y, z, MNI coordinates in left-right (x), posterior-anterior (y), and inferior-superior (z) planes; Ins, insula; sulc, sulcus; sup, superior.

made by participants in the fMRI scanner with those previously obtained in the behavioral test. For odors, $74.0 \pm 15.0\%$ of items preselected as familiar on the basis of the pretest were judged as familiar during scanning and $62.2 \pm 19.0\%$ of preselected unfamiliar items were judged as unfamiliar during scanning. For musical excerpts, these data were $94.9 \pm 11.7\%$ and $90.4 \pm 9.4\%$, respectively.

Neuroimaging Data

The Feeling of Familiarity

A bimodal neural system was activated during the feeling of familiarity. For both odors and musical excerpts, the processing of familiar items (in comparison with unfamiliar items) activated left frontal and parieto-occipital areas (Table 1, Fig. 2). Three different regions in the SFG were activated: an anterior ventral one leading to the cingulate sulcus (CS), an anterior dorsal one bordering the superior frontal sulcus (SFS), and a more posterior dorsal one overlapping the middle frontal gyrus (MFG). Both the dorsal portion and the pars orbitalis (bordering the lateral orbital gyrus ventrally) of the IFG were also activated. The parieto-

occipital areas of the bimodal familiarity activation pattern involved 2 clusters: one centered on the angular gyrus (AG) leading to the superior part of the middle occipital gyrus and one centered on the precuneus (PCu) and leading to the lingual gyrus. The left Hip ROI ($t = 3.76$, corrected $P < 0.01$) and the left pHip ROI ($t = 3.73$, corrected $P < 0.01$) were significantly activated during the feeling of familiarity.

For each of the 7 bimodal activation clusters (Table 1), percent signal changes (Figure 2) were analyzed using a 2×2 analysis of variance (ANOVA) with Modality (olfaction, music) and Familiarity (familiar, unfamiliar) as within-participant factors. The main effect of Familiarity was significant for the clusters centered on the SFG/CS ($F_{1,12} = 48.35$, $P < 0.0001$), the SFG/SFS ($F_{1,12} = 69.98$, $P < 0.0001$), the SFG/MFG ($F_{1,12} = 34.51$, $P < 0.0001$), the dorsal and ventral parts of the IFG ($F_{1,12} = 25.65$, $P < 0.001$ and $F_{1,12} = 58.35$, $P < 0.0001$, respectively), the AG ($F_{1,12} = 107.20$, $P < 0.0001$), and the PCu ($F_{1,12} = 44.05$, $P < 0.0001$). The main effect of Modality was significant only for the clusters centered on the AG and PCu ($F_{1,12} = 23.11$, $P < 0.001$ and $F_{1,12} = 8.19$, $P < 0.05$, respectively). For all clusters, the interaction between Modality and Familiarity was not significant.

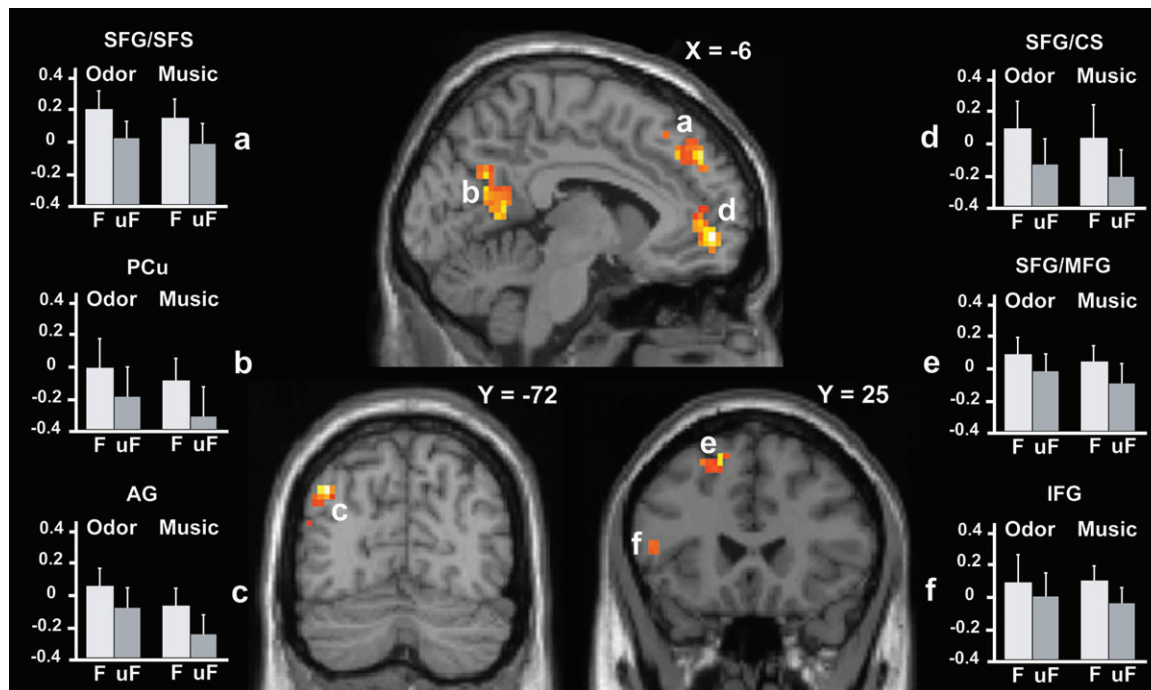


Figure 2. Bimodal brain activations evoked by the feeling of familiarity for odors and music. Significant activation was observed in the (a) SFG bordering the SFS ($-6, 48, 39$), (b) PCu ($-3, -63, 28$), (c) AG ($-39, -72, 39$), (d) SFG bordering the CS ($-6, 54, -4$), (e) SFG/MFG ($-21, 21, 56$), and (f) ventral part of the IFG ($-50, 30, 0$). Activations are superimposed on coronal and sagittal sections from the standard MNI brain using neurological convention (Right is right). For each cluster of activation, the percent signal change (mean \pm standard deviation) is indicated for the feeling of familiarity (F) and the feeling of unfamiliarity (uF) for odors and music.

In addition to the bimodal activation pattern for the feeling of familiarity, modality-specific activations were observed for both odors and musical excerpts. For odors, the modality-specific activation consisted of the left short insular gyrus and the right anterior CG (Table 1). Activation of the anteroventral part of the right medial frontal gyrus (neighboring the anterior CG) was previously observed in odor familiarity judgments (Royet et al. 1999). However, given that anterior CG activation has been previously shown to be associated with pleasantness ratings of odors (Royet et al. 2001; Rolls et al. 2003) and that, in the behavioral pretest, familiar odors were judged as being more pleasant than unfamiliar odors, this activation could be also related to pleasantness processing rather than to familiarity processing. For music, the modality-specific activation included areas in the frontal lobe (the left SFG and MFG, and the left precentral gyrus), the temporal lobe (the superior temporal sulcus [STS]), and the parietal lobe (the posterior part of the CG, the right AG, and the left supramarginal gyrus [SMG] laterally and medially; Table 1). Significant activation in middle and posterior regions of the left STS has also been activated during spontaneous auditory imagery of familiar musical excerpts (Kraemer et al. 2005). Increased activation in the posterior CG could be related to the retrieval of music-related memories because it has been observed in the retrieval of autobiographic memories (Maddock et al. 2001; Piefke and Fink 2005). Several of the music-specific activations were situated closely to regions of the bimodal activation pattern (left SFG, MFG, precentral gyrus, and AG) and might be related to the fact that overall stronger activation has been observed in the music than in the olfaction modality. This observation can be linked to our behavioral pretest showing a more pronounced distinction between familiar and unfamiliar items for musical excerpts than for odors and to the stronger interparticipant agreement for musical

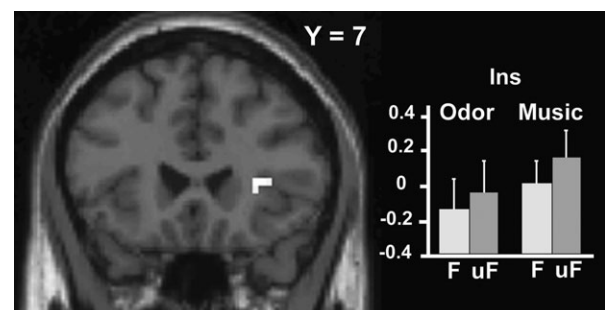


Figure 3. Bimodal brain activation evoked by the feeling of unfamiliarity for odors and music. Significant activation in the anterior ventral insula (Ins; $30, 24, 7$) is superimposed on a coronal section from the standard MNI brain using neurological convention (Right is right). The percent signal change (mean \pm standard deviation) is indicated for the feeling of familiarity (F) and the feeling of unfamiliarity (uF) for odors and music.

excerpts than for odors during scanning. This difference between modalities was also reflected in participants' informal comments after the experiment: they indicated that differentiating familiar from unfamiliar items was more evident for musical excerpts than for odors.

The Feeling of Unfamiliarity

For both odors and musical excerpts, the processing of unfamiliar items (in comparison with familiar items) evoked significant activation only in the right anterior insula (Ins) (Table 2, Fig. 3). Percent signal change of this cluster was analyzed by a 2×2 ANOVA with Modality and Familiarity as within-participant factors. The main effects of Familiarity ($F_{1,12} = 38.03, P < 0.0001$) and Modality ($F_{1,12} = 10.49, P < 0.01$) were significant, but not their interaction.

Beyond this bimodal cluster, the feeling of unfamiliarity evoked additional activation in the right SFG and SMG, with

slightly distinct subregions depending on the modality (Table 2). Coordinates of maximum activation were situated more laterally for odors ($x = 27$ and $x = 60$, respectively) than for music ($x = 12$ and $x = 39$, respectively). For the perception of unfamiliar odors, Savic and Berglund (2004) reported specific activation solely in the right medial SMG. Further modality-specific activation was only observed for musical excerpts and was situated in the left central and superior precentral sulci and the left parietal operculum.

Discussion

The goal of this experiment was to investigate whether familiarity processing, with its 2 components (feeling of familiarity and feeling of unfamiliarity), involves the activation of multimodal neural bases. In addition to modality-specific activations, our findings showed that the neural substrates underlying the feeling of familiarity evoked by odors and music overlap within an extensive bimodal neural system that included the SFG, IFG, AG, PCu, Hip, and pHip in the left hemisphere. The comparison of this outcome with previous data obtained for other modalities suggests the existence of a multimodal neural system engaged in the feeling of familiarity, regardless of the triggering modality. For the feeling of unfamiliarity evoked by both odors and music, we observed bimodal activation mainly in the right Ins that could be related to the detection of the novelty of the items.

The Left Hemispheric Feeling of Familiarity

The feeling of familiarity evoked a bimodal activation pattern entirely located in the left hemisphere. Subsets of the regions composing the bimodal activation pattern (i.e., SFG/CS, SFG/SFS, ventral IFG, AG, and PCu) have been reported, in the left hemisphere, to be involved in the familiarity processing of odors (Royet et al. 1999, 2001; Savic and Berglund 2004; Plailly et al. 2005) and music (Platel et al. 1997, 2003). The Hip and pHip have been previously activated in odor familiarity judgments, but in the right hemisphere (Plailly et al. 2005). The importance of the left hemisphere for the processing of familiar items has been shown using musical excerpts in neuropsychological cases and neuroimaging studies (Eustache et al. 1990; Platel et al. 1997, 2003; Ayotte et al. 2000). For odors, although the passive perception of familiar items involved both hemispheres, prefrontal activation was strictly left sided and was positively correlated with familiarity ratings (Savic and Berglund 2004).

The ventral part of the left IFG has been observed in semantic retrieval (Greenberg et al. 2005) and in the selection and integration of semantic information in a modality-independent manner (e.g., Homae et al. 2002; Moss et al. 2005). Our observed IFG activation in the feeling of familiarity evoked by odors and music suggests the activation of semantic memory systems, independent of the modality of the triggering stimulus. The left hemisphere localization of this activation can be interpreted in the framework of the hemispheric encoding/retrieval asymmetry model (Tulving et al. 1994). According to this model, the left prefrontal cortex has a preferential role in the recall of semantic information and in the encoding of episodic material, whereas the right prefrontal cortex operates preferentially in the recall of episodic information.

A Multimodal Neural System of the Feeling of Familiarity

Neural substrates of recognition memory processes have been studied with 2 experimental approaches. One of them (used in our experiment) investigates recognition memory referring to

autobiographical events or general knowledge of the world (Platel et al. 1997, 2003; Gorno-Tempini et al. 1998; Royet et al. 1999, 2001; Nakamura et al. 2001; Shah et al. 2001; Plailly et al. 2005). The other, more frequently used, approach investigates recognition memory referring to items encountered in the experimental session (Henson et al. 1999; Wheeler and Buckner 2004; Eldridge et al. 2005; Yonelinas et al. 2005; Daselaar et al. 2006; Montaldi et al. 2006). In contrast to verbal stimuli or images constructed for the experiment, the use of music and odors, as well as faces and voices, allows for investigation of familiarity processing in reference to long-term memory as it happens in everyday life, without requiring an experimental encoding phase.

A careful comparison of neural correlates involved in memory processes studied with both experimental approaches (i.e., familiarity referring to either life or laboratory experience) reveals at least partial overlap of the neural correlates across sensory modalities. Parts of the neural system activated during the feeling of familiarity of odors and music (i.e., left SFG/CS, SFG/SFS, SFG/MFG, ventral IFG, AG, and PCu) have also been shown during the processing of familiar faces and voices in studies referring to participants' life experience (Gorno-Tempini et al. 1998; Leveroni et al. 2000; Nakamura et al. 2001; Shah et al. 2001; Kosaka et al. 2003; Paller et al. 2003; Kriegstein and Giraud 2004) and during the processing of pictures or verbal items (presented visually) referring to recent laboratory experience. Similarly, the subregion of the Hip ($y = -19$) that was activated in the feeling of familiarity of odors and music was very close to the subregion ($y = -20$) identified by Strange et al. (1999, 2005) during familiarity judgments of pictures, geometrical figures, and visually presented verbal items.

The overlap between the neural substrates involved in familiarity processing of odors, music, faces, voices, words, and pictures, whether these processes refer to life or laboratory experiences of participants, leads to the view that a multimodal, rather than a bimodal, neural system underlies the feeling of familiarity. This finding could be related to the specificity of the feeling of familiarity, a feeling that remains similar regardless of the triggering item's modality.

Distinction between Familiarity and Recollection Processes

According to the "dual-process theory" proposed by Mandler (1980), recognition memory involves processes related not only to familiarity but also to recollection (for review, see Gardiner et al. 2002; Yonelinas 2002). According to this theory, familiarity and recollection share some neural bases but also have specific neural bases. Although the resolution of recognition memory into familiarity and recollection processes is currently the prevailing theory, the "signal detection theory" (Donaldson 1996; Dunn 2004) suggests that experiences of familiarity and recollection reflect different subjective response criteria along a recognition response continuum: items lying above a decision criterion lead to recollection and those lying below this criterion lead to a feeling of familiarity. According to this second theory, familiarity and recollection share the same neural bases, but they differ in the extent and/or strength of activation.

In the present experiment, some of the regions of the bimodal activation pattern related to the feeling of familiarity (SFG/SFS, SFG/MFG, ventral IFG, AG, PCu, Hip, and pHip) were previously found to be activated not only in familiarity judgments but also in recollection of pictures and visually

presented verbal items (Henson et al. 1999; Eldridge et al. 2000, 2005; Konishi et al. 2000; Donaldson et al. 2001; Yonelinas et al. 2002, 2005; Maril et al. 2003; Ranganath et al. 2004; Wheeler and Buckner 2004; Woodruff et al. 2005). These overlapping findings can be interpreted within the framework of the signal detection theory, notably that these brain regions are involved in both familiarity and recollection processes. However, the dual-process theory proposes 2 alternative hypotheses for the interpretation of these results. First, the 2 processes might involve different specialized regions in these relatively large areas. For example, Wheeler and Buckner (2004) showed for the parietal cortex (comparable with the AG in our experiment) some dissociation across regions; a lateral part responded specifically to recollection, whereas a more medial part responded to both recollection and familiarity judgments. Second, participants might employ both types of recognition memory processes, even if not requested by the task. In our experiment, functional data were analyzed for approximately 6 s for each item. This duration seems to be sufficiently long for participants to gather more information about the item (i.e., eventually leading to recollection) or to evoke specific memories. Recently, Yonelinas et al. (2005) used an elaborate experimental design to study neural correlates specifically related to either familiarity or recollection. Based on their data pattern, we propose the following post hoc separation of our functional data: the left SFG/SFS, ventral IFG, and AG might be involved in the feeling of familiarity, whereas the left SFG/CS and Hip might participate in recollection. Further investigations are needed to examine this assumption and extend the dissociation of areas observed by Yonelinas et al. (2005) to both olfaction and music.

The Feeling of Unfamiliarity

The feeling of unfamiliarity of odors and music was related to the bimodal activation of the right anterior Ins. This outcome corroborates previous findings showing that the feeling of unfamiliarity evoked only a small activation pattern in comparison with the feeling of familiarity (Platel et al. 2003; Savic and Berglund 2004; Yonelinas et al. 2005). One could argue that the feeling of unfamiliarity refers to the absence of feeling of familiarity. However, because the processing of the items' unfamiliarity activated the same brain area whatever the item modality, our results suggest the existence of neural processes specific to the feeling of unfamiliarity. In addition, from our data based on the modality-specific activation, we hypothesize that the bimodal neural bases of the feeling of unfamiliarity also include the right SFG and SMG. For both modalities, activation occurred in these 2 additional regions, although they were situated more laterally for odors than for music.

The feeling of unfamiliarity might be associated with the impression of novelty, which is felt when participants are confronted with items that have not been previously encountered (i.e., "new" items). Functional imaging studies investigating the signal related to new minus old (i.e., previously encountered) items consistently reported, among other regions, activation in the entorhinal cortex (Henson et al. 2003; Daselaar et al. 2006; Fernandez and Tendolkar 2006). In our experiment, the absence of entorhinal cortex activation during the feeling of unfamiliarity might be related to signal dropout in lower temporal regions. However, novelty judgments, as implemented in these recognition memory experiments, require the comparison with items perceived first in an encoding phase in the same experimental session (i.e., occurring a short time ago). In our

experiment, the requested judgments (i.e., familiar/unfamiliar) referred to participants' entire life experience. The difference in the time frames for the unfamiliarity judgments might cause differences in participants' confidence of their given responses, which then might be reflected in changes in neural activation patterns (such as the missing entorhinal activation).

Novelty processing has also been studied using the oddball paradigm, which requires the detection of infrequent items among a stream of frequent items. Using such a procedure, experiments have shown that the novelty of visual, auditory, and tactile oddball items activated a neural system that included the right anterior Ins and SMG (McCarthy et al. 1997; Menon et al. 1997; Linden et al. 1999; Ardekani et al. 2002; Downar et al. 2002), areas that were also activated in the present experiment for unfamiliar odors and music. These data sets, together with our findings, suggest that the feeling of unfamiliarity and the decision of novelty could be described as 2 components of the same nonrecognition process. Further experiments are needed to test whether the feeling of unfamiliarity and decision of novelty related to "nonrecognition" equate to the feeling of familiarity and recollection related to "recognition."

Conclusion

In summary, our results show that the feeling of familiarity of odors and music activates common neural bases located in the left hemisphere, which partly involve brain regions previously described for semantic processing and recognition memory. The overlap between the neural substrates of familiarity processing of odors and music with those of the familiarity processing of several other types of stimuli (i.e., faces, voices, pictures, and verbal items) further suggests a multimodal neural network underlying the feeling of familiarity. The observed bimodal neural bases related to the feeling of unfamiliarity suggest the existence of neural processes specific to this feeling, which advance the idea that the feeling of unfamiliarity and the detection of novelty are components of a nonrecognition process.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>.

Notes

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Address correspondence to Jane Plailly, Neurosciences & Systèmes Sensoriels, UMR CNRS 5020, Université Claude Bernard Lyon 1, 50 avenue Tony Garnier, 69366 Lyon cedex 07, France. Email: plailly@olfac.univ-lyon1.fr.

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