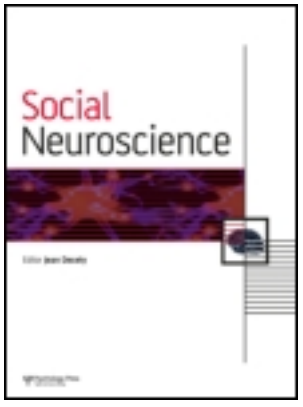

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Smelling odors, understanding actions

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Previous evidence indicates that we understand others' actions not only by perceiving their visual features but also by their sound. This raises the possibility that brain regions responsible for action understanding respond to cues coming from different sensory modalities. Yet no studies, to date, have examined if this extends to olfaction. Here we addressed this issue by using functional magnetic resonance imaging. We searched for brain activity related to the observation of an action executed towards an object that was smelled rather than seen. The results show that temporal, parietal, and frontal areas were activated when individuals observed a hand grasping a smelled object. This activity differed from that evoked during the observation of a mimed grasp. Furthermore, superadditive activity was revealed when the action target-object was both seen and smelled. Together these findings indicate the influence of olfaction on action understanding and its contribution to multimodal action representations.

Keywords: Action; Olfaction; Odor; Multisensory integration; Functional MRI.

INTRODUCTION

Neurophysiological research on neural processing underlying the understanding of others' actions has revealed activity within a network of brain regions including the premotor cortex, the primary motor and somatosensory cortices, several parietal areas, and the posterior temporal-occipital cortex (Evangeliou, Raos, Galletti, & Savaki, 2009; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Peeters et al., 2009; Puce & Perret, 2003; Raos, Evangeliou, & Savaki, 2004, 2007). This motor circuitry, termed the action observation system (AOS), enables the representation of the visual features characterizing the observed action (Keysers & Perret, 2004; Rizzolatti, Fogassi, & Gallese, 2001). For instance, when a monkey observes a human model grasping an object, the AOS exhibits a differential level of activity depending on the nature of both the visual object (e.g., edible vs. non edible; Fogassi et al., 2005) and the acting model (e.g., an entire model vs. an arm/hand ensemble; Nelissen, Luppino, Vanduffel, Rizzolatti, & Orban, 2005). Furthermore, activity within this system appears to be modulated by the interaction between the target object and the moving

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effector. Responses in the monkey AOS differ depending on whether the monkey observes a human hand performing a proper grasp or observes a mimed grasp (Nelissen et al., 2005; Umiltà et al., 2001).

A recent advance in the characterization of the AOS is the demonstration that most of this system is multimodal. It responds to action-related information conveyed not only via vision, but also via audition (Keysers et al., 2003; Kohler et al., 2002). When a monkey hears the sound generated by a hand contacting an object (e.g., hands breaking a peanut), the AOS is activated as if the hand–object interaction were "seen" (Kohler et al., 2002). Importantly, the level of activation within the AOS varies depending on the type of heard actions (Keysers et al., 2003; Kohler et al., 2002). Hearing the sound of a hand grasping a ring elicited less AOS activity than hearing the sound generated by the two hands breaking a peanut (Kohler et al., 2002).

Neuroimaging evidence suggests that an AOS, similar to that of the monkey in many respects, may also exist in humans (Avikainen, Forss, & Hari, 2002; Buccino et al., 2001, 2004; Decety et al., 1997; Gazzola, Aziz-Zadeh, & Keysers, 2006; Gazzola & Keysers, 2009; Gazzola, Rizzolatti, Wicker, & Keysers, 2007; Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Grèzes, Armony, Rowe, & Passingham, 2003; Grosbras & Paus, 2006; Hari et al., 1998; Peeters et al., 2009; Perani et al., 2001; Turella, Erb, Grodd, & Castiello, 2009). The human AOS can discriminate the features of an agent performing the observed action (e.g., robotic vs. biological agents) (Tai, Scherfler, Brooks, Sawamoto, & Castiello, 2004), the features of the object grasped by another person (e.g., cookie vs. disk) (Hamilton & Grafton, 2006) and the visual elements characterizing a motor sequence that brings a specific goal (Hamilton & Grafton, 2008; Majdandžić, Bekkering, van Schie, & Toni, 2009). Furthermore, the analogy between human and monkey AOS is strengthened by the revelation that the human AOS is also multimodal in nature. Some evidence now suggests that the human AOS is engaged when a person hears, for example, the sound of somebody's hands ripping a paper sheet (Aziz-Zadeh, Iacoboni, Zaidel, Wilson, & Mazziotta, 2004; Gazzola et al., 2006; Etzel, Gazzola, & Keysers, 2008). And, when both visual and auditory information related to another individual's action is available, the recognition of the perceived action is enhanced (Keysers et al., 2003).

The demonstration of multimodal aspects characterizing the AOS makes it possible that information coming from sensory modalities other than vision and audition is processed and integrated within the AOS. In this respect, preliminary investigations have focused on the contribution that the sense of smell might have on representing others' behavior (Prehn-Kristensen et al., 2009; Rossi et al., 2008; Wicker et al., 2003). For instance, Rossi et al. (2008) asked participants to look at a model grasping a piece of food in the presence of the odor associated with that edible target. At that time transcranical magnetic stimulation (TMS) was delivered on the "hand" sector of the primary motor cortex (M1). The main result was that the amplitude of motor evoked potentials (MEPs) increased when the odor was delivered. This finding indicates that the olfactory component of others' actions enhances excitability of M1. On this basis, one might be tempted to infer that olfactory information enters the observer's AOS enabling action understanding. However, before this conclusion can be fully accepted, some important issues might be considered. First, TMS does not allow localization of the brain structures underlying MEPs facilitation (Fadiga, Craighero, & Olivier, 2005). Therefore, evidence for the representation of an action embedding olfactory information (i.e., olfactomotor information) within the AOS needs to be demonstrated. Second, even assuming that via TMS it would be possible to demonstrate that the AOS represents olfactomotor information, this would not be sufficient to document that olfactory cues play an effective role in action understanding. In addition, specific evidence that the AOS can differentiate across similar actions on the basis of olfactory information should be provided. To address these questions here we performed a functional magnetic resonance imaging (fMRI) study in which olfactory information was delivered during the observation of different hand actions.

MATERIALS AND METHODS

Participants

In accordance with the declaration of Helsinki, informed consent was obtained from 15 healthy, right-handed volunteers (8 females; mean age 26, age range 22–33). Handedness was assessed with the Edinburgh inventory (Oldfield, 1971). All participants reported normal olfaction, no history of olfactory dysfunction, and normal or corrected-to-normal vision in a confidential report. The experiment was conducted with approval from the local ethical committee.

Stimuli and experimental conditions

The experimental stimuli consisted of video-clips (Audio Video Interleave format, 25 frames/s, resolution 400 × 300 pixels; duration 3 s) representing a human right hand together with an object. For the entire duration of the movie either odorized or odorless air was delivered. The task for participants was to observe the presented video-clips.

There were eight experimental conditions, as follows.

1. A *Grasping Visual* (GV) condition, in which participants observed the hand grasping either a large or a small object in the absence of odor (refer to "Visual objects" and "GV" in Figure 1).
2. A *Static Visual* (SV) condition, in which participants observed the hand resting alongside one of the four visual objects presented in Figure 1 ("Visual objects"), in a prone position, with the palm towards the working surface in the absence of odor ("SV").
3. A *Grasping Olfactory* (GO) condition in which participants observed a hand grasping an object as for the GV condition, but the object was hidden behind a brown-colored partition. During the observation of the video-clip an odor associated with the hidden object was delivered ("GO" in Figure 1; the boxes within the panel indicate the presence of an odor).
4. A *Static Olfactory* (SO) condition, in which participants observed a stationary hand as for the SV condition, but the object was hidden behind a brown-colored partition. During the observation of the video-clip an odor associated with the hidden object was delivered (refer to "SO" in Figure 1; the boxes within the panel indicate the presence of an odor).
5. A *Grasping Visual-Olfactory* (GVO) condition, in which participants observed video-clips identical to those utilized for the GV condition except that during the observation of the video-clip an odor associated with the visual object was also delivered ("GVO" in Figure 1; the boxes within the panel indicate the presence of an odor).
6. A *Static Visual-Olfactory* (SVO) condition, in which participants observed video-clips identical to those utilized for the SV condition except that during the observation of the video-clip an odor associated with the visual object was also delivered ("SVO" in Figure 1; the boxes within the panel indicate the presence of an odor).
7. A *Grasping* (G) condition, in which participants observed video-clips identical to those utilized for the GO condition except that during the observation of the video-clip no odor was delivered ("G" in Figure 1). Therefore, participants were presented with mimed hand grasp movements, i.e., hand grasping movements without a real end-goal.
8. A *Static* (S) condition, in which participants observed video-clips identical to those utilized for the SO condition except that during the observation of the video-clip no odor was delivered ("S" in Figure 1).

Participants' point of view within the scanner was also considered. Therefore, in half of the video-clips the hand entered the scene from the left, whereas in the other half the hand entered the scene from the right side (panels from "GV" to "S" in Figure 1). This resulted in a total of eight different experimental stimuli (i.e., four different objects by two different hand positions) per condition. This set of experimental stimuli was repeated four times within each condition (i.e., 32 stimuli corresponding to 32 experimental trials were administered).

Apparatus

All the experimental stimuli were presented by using the software Presentation (Neurobehavioral Systems, Albany, CA, www.neuro-bs.com) which ensured synchronization with the MR scanner. An LCD computer-controlled projector (NEC, resolution 1024 × 768, refresh rate 60 Hz) was employed to present the movies in color at the centre of a screen positioned outside the bore of the magnet. The stimulus was viewed by the participants through a mirror mounted on the head coil. When projected onto the mirror, the movies were 26.8 cm wide × 20.1 cm high and subtended visual angles of 20° × 15°. An MRI-compatible, custom-built computer-controlled olfactometer with eight channels (Department of Experimental Psychology, University of Oxford, UK) was used to administer olfactory stimuli. The olfactometer was capable of rapid delivery of discrete odor pulses in the absence of tactile, thermal, or auditory variation. Each odor generator consisted of a glass boat containing one of four odor solutions. The odor solutions of strawberry, almond, orange, and apple were obtained mixing 6000 ml of propylene glycol and 180 ml (3%), 60 ml (1%), 420 ml (7%), and 45 ml (0.75%) of the specific odorant compound, respectively (Cerizza, Milan, Italy). These odor solutions were adopted because they generated odors that were judged to have equal intensity, hedonic tone, and familiarity in

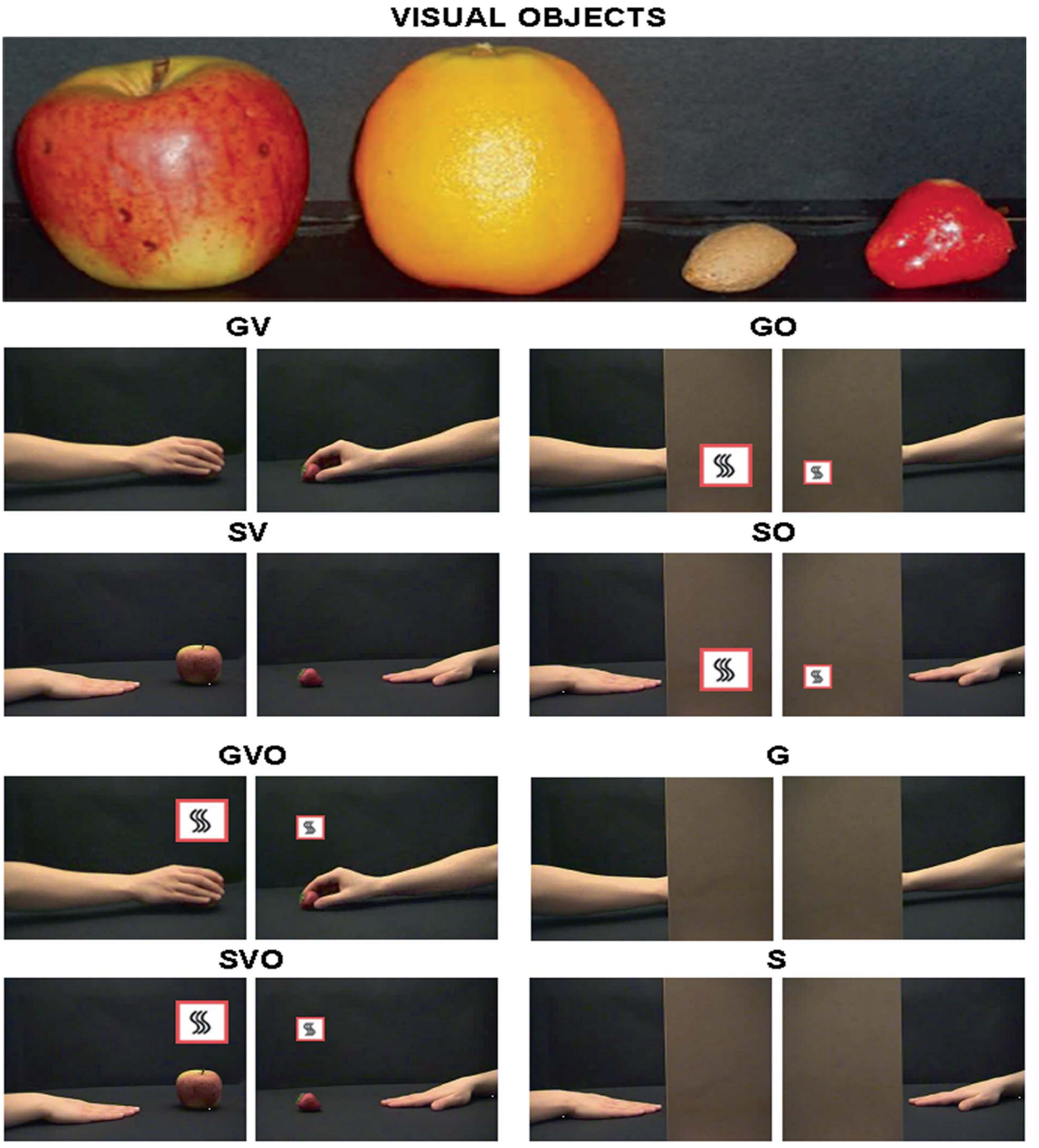

Figure 1. Graphical representation of the stimuli and the experimental conditions. Visual objects: an apple and an orange were considered as the large visual objects, whereas an almond and a strawberry were considered as the small visual objects. *Grasping Visual* (GV) condition: a whole hand grasp (WHG) for the large visual object (left) and a precision grip (PG) for the small visual object (right). *Static Visual* (SV) condition: a hand resting nearby a large visual object (left) and a small visual object (right). *Grasping Olfactory* (GO) condition: a hand grasping either a large object (left) or a small object (right) hidden behind a partition in the presence of an odor associated with the object. *Static Olfactory* (SO) condition: a hand resting alongside either a large object (left) and a small object (right) hidden behind a partition in the presence of the odor associated with the object. *Grasping Visual-Olfactory* (GVO) condition: a hand grasping either a large visual object (left) and a small visual object (right) in the presence of the odor associated with the object. *Static Visual-Olfactory* (SVO) condition: a hand resting alongside a large visual object (left) and a small visual object (right) in the presence of the odor associated with that object. *Grasping* (G) condition: a hand grasping either a large object (left) or a small object (right) hidden behind the partition. *Static* (S) condition: a hand resting alongside either a large object (left) and a small object (right) hidden behind the partition. The boxes with red perimeters indicate the presence of an odor. The size of the boxes represents the size of the object evoked by the odor. The larger boxes indicate large objects. The smaller boxes indicate small objects. The boxes are presented in the figure for clarification purposes. Video-clips which were administered during the experiment did not include the boxes.

previous investigations (Tubaldi, Ansuini, Demattè, Tirindelli, & Castiello, 2008a; Tubaldi, Ansuini, Tirindelli, & Castiello, 2008b). A fifth glass boat containing propylene glycol was used for the delivery of odorless air. The air passed over the odor solutions and the propylene glycol at a flow rate of 8 l/min and was delivered on both nostrils to subjects via Teflon tubing to a facial mask (Tubaldi et al., 2008a, 2008b).

Activation paradigm

During the experiment participants lay supine in the scanner and observed all the displayed movies either in the absence or in the presence of an odor. An experimental trial consisted of a single event (i.e., a movie while odorized or odorless air was delivered) that lasted 3 s. The time between the trial offset and the onset of the next trial (interstimulus interval, ISI) was 10,500 ms. If an odor was delivered, an ISI of 10,500 ms allowed recovery from any odor adaptation (Hummel, Knecht, & Kobal, 1996). During ISI, a black fixation cross on a blank screen was presented and odorless air was delivered. For each experimental condition, 32 trials were administered. Trial order was fully randomized, except that in order to minimize the effects of stimulus repetition and odor habituation the object (or the odor associated with the hidden object) differed in every trial with respect to that administered in the previous trial (Gottfried & Dolan, 2003). The experiment consisted of four functional runs. Within each of these functional runs, two of the eight experimental conditions were presented. Specifically, trials for the GV condition and trials for the SV condition were randomly presented within a first functional run (i.e., visual run). A second functional run consisted of trials representing the GO condition and the SO condition (i.e., olfactory run). A third functional run included trials related to the GVO and the SVO conditions (i.e., visual-olfactory run). Finally, trials for the G and the S conditions were randomly presented within a fourth functional run (i.e., mimed run). Each functional run lasted 882 s, and started and ended with 8-s and 10.5-s rest periods respectively, each consisting of a black fixation cross on a blank screen. Consecutive functional runs were intermingled with a 5-min break during which no kind of stimulation was delivered. By administering two conditions per run, we ensured that signal related to the contrasts GV – SV, GO – SO, GVO – SVO, and G – S spanned frequency bands above the cut-off selected for the high-pass filter (see "Data analyses" section). For the visual run, the olfactory run, and the visual-olfactory run, six different presentation orders were possible. In this respect, we counterbalanced the presentation order across participants: At least two participants were presented with each order. Data for the G and the S conditions (i.e., the mimed run) were always collected first to avoid representation of an action-target object via motor imagery on the basis of previously perceived goal-directed actions (Decety & Grèzes, 2006). Within each functional run, there was a variable delay of 0–1500–1000–500 ms between trial onset and TR onset for each condition (Figure 2). With respect to TR onset, 8 of the 32 trials were shifted 0 ms, 8 were shifted 1500 ms, 8 were shifted 1000 ms and 8 were shifted 500 ms (Figure 2). Such a distribution allowed us to detect the entire evolution of the hemodynamic response associated with an experimental condition with a 500-ms time resolution (when assuming that the evoked hemodynamic response conforms to the canonical hemodynamic response function implemented in SPM 5; Wellcome Department of Cognitive Neurology, London, www.fil.ion.ucl.ac.uk/spm).

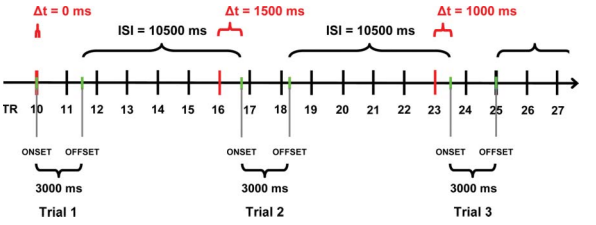

Figure 2. Graphical representation of the experimental timing. Trial 1 was presented after nine TRs (i.e., 18,000 ms) from the beginning of the functional run. Trial 1 onset was shifted 0 ms with respect to the onset of TR 10 (Δt = 0 ms). Following the implementation of a 10,500 ms ISI, the onset for Trial 2 resulted shifted 1500 ms with respect to the onset for TR 16 (Δt = 1500 ms). Then, the 10,500 ms-ISI determined a shift in the onset for Trial 3 by 1000 ms with respect to the onset for TR 23 (Δt = 1000 ms). The onset for Trial 4 was shifted 500 ms with respect to the onset for TR 30 (for the sake of brevity, the occurrence of Trial 4 has not been illustrated). Each temporal shift between trial onset and TR onset (Δt = 0–1500–1000–500 ms) was repeated eight times during the entire functional run for a total of 32 trials.

Image acquisition

Gradient echo, T2*-weighted echoplanar images (EPIs) with blood-oxygen-level-dependent (BOLD) contrast were acquired on a 3 T Siemens Magnetom Trio MRI scanner equipped with a 12-channel head array radio-frequency coil. EPI datasets with whole brain coverage (32 transversal slices; 3 × 3 × 3.5 mm voxel size; 0.7 mm gap) were collected in interleaved fashion every 2000 ms with the following parameters:

field-of-view, 192 × 192 mm; in-plan resolution 64 × 64 voxels; echo time, 33 ms; bandwidth, 2442 Hz/Px. For each functional run, a total of 441 volumes were collected, minus 5 "dummy" volumes to permit T1 equilibration. In addition, high-resolution T1-weighted images (anatomical scans) were acquired for each participant (MP-RAGE, 160 sagittal slices, in-plane resolution 224 × 256 voxels, 1 mm isotropic voxels, TR = 2300 ms, TE = 3 ms).

Odor recognition task and paced-breathing session

In order to ensure that participants were able to identify each of the four delivered odors (i.e., orange, apple, strawberry, and almond), we asked to participants to perform an odor recognition task. Before entering within the scanner, volunteers were presented with the four visual objects (see "Visual objects" in Figure 1). Then, an odor was presented for 2 s and participants were instructed to indicate the object associated with that odor. The odors were delivered by using the olfactometer employed as to administer olfactory stimulation within the MR scanner. A total of eight trials (two for each type of odor) were presented in randomized order. When performing the task, participants showed no errors.

Before the initiation of each functional run, participants took part in a paced-breathing session. During this session, participants were trained to synchronize their breathing cycle according to the rhythm with which odor would have been delivered during the fMRI experiment. They performed 15 paced air inhalations within one training block lasting 210 s (for technical details see Tabert et al., 2007). This ensured that odor administration during the fMRI experiment was always synchronized with the participants' inhalation phase and that the sampling of the delivered odor was uniform across scans and participants. Furthermore, visual inspection of the participants' breathing patterns (i.e., respiration rate) during the fMRI experiment revealed no differences across the experimental runs in which an odor was delivered (i.e., olfactory run and visual-olfactory run) and those in which no odor was administered (i.e., visual run and mimed run).

Data analyses

MRI data were analyzed using SPM 5 software, implemented in Matlab 7.0 (Mathworks, Natick, MA). First, EPI images were realigned to the first functional volume of each run in order to correct for any head movement occurring within the run. Second, high-quality T1 images were co-registered to the mean EPI image and segmented. The coregistered gray matter segment was normalized onto the grey matter template (available in the SPM 5 "apriori" directory), and the resulting normalization parameters applied to all EPI images (re-sampled voxels at 2 × 2 × 2 mm). The T1 image was also normalized to the MNI space using the same parameters, keeping the original resolution of 1 × 1 × 1 mm. Finally, EPI data were spatially smoothed adopting an 8-mm full-width-at-half-maximum Gaussian kernel. The event-related functional data were analyzed using the general linear model (Friston et al., 1995). Eight regressors of interest were defined based on the timing of presentation for each experimental condition (duration = 3 s). These functions were convolved with a canonical hemodynamic response function. Subject-specific movement parameters were included to account for translation and rotation along the three possible dimensions as measured during the realignment stage. A high-pass filter (cut-off, 128 s) was also applied to remove low-frequency drifts in signal. The parameter estimates for each regressor were calculated for all brain voxels (i.e., beta images were computed). Then beta images referring to the GV, the GO, the GVO, and the G conditions and to the four corresponding control conditions (i.e., the SV, the SO, the SVO, and the S conditions) were extracted for each subject and then entered into a 2 × 4 flexible factorial design. The two within-subjects factors were "Hand" (*Grasping*/*Static*) and "Object" (*Visual*/*Olfactory*/*Visual-Olfactory*/*Absent*). A third factor of no interest was also modeled, i.e., the effect of subjects.

The hypotheses underlying the present study were concerned with the possibility that the AOS represented olfactomotor information (either in isolation or in combination with visuomotor information) and used the olfactory component of this information for action discrimination. Therefore, testing for these hypotheses was confined to the relevant neural system, i.e., the AOS. We localized the AOS concerned with visuomotor information by performing the contrast [GV – SV] at whole brain level [intensity threshold, p = .015 FDR corrected; cluster-extent threshold = 15 voxels] (Friston, Rotshein, Geng, Sterzer, & Henson, 2006; Friston & Henson, 2006; Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). Then, by using Marsbar SPM Toolbox (Brett, Anton, Valabregue, & Poline, 2002), the beta value corresponding to each control condition (i.e., SV, SO, SVO, and S) and each experimental condition (i.e., GV, GO, GVO, and G) was extracted for each participant from

the peak-voxel of each identified AOS area. Next, by subtracting the averaged beta values across participants for each control condition from the averaged beta values across participants for the corresponding experimental condition, activation values GV – SV, GO – SO, GVO – SO, and G – S were computed. Experimental hypotheses were verified by performing statistical comparisons on these activation values (Friston et al., 2006; Kilner, Neal, Weiskopf, Friston, & Frith, 2009; Saxe, Brett, & Kanwisher, 2006).

First, to evaluate whether the AOS represented olfactomotor information, we tested for a greater activation for the GO condition compared to the SO condition [GO – SO, intensity threshold, $p = .05$].

Second, to ascertain whether or not visuomotor and olfactomotor information integrated within the AOS, we first tested whether there was a greater activation for the GVO condition compared to the SVO condition [GVO – SVO, intensity threshold, $p = .05$]. Next, we evaluated whether such activation was greater than the sum of the activations for the GV and the GO conditions (Beauchamp, 2005a; Laurienti, Perrault, Stanford, Wallace, & Stein, 2005). In estimating this superadditive model, the activation [G – S] was added to the activation [GVO – SVO]. This resulted in the interaction contrast: [(GVO – SVO) + (G – S)] – [(GV – SV) + (GO – SO)], intensity threshold, $p = .05$.

Third, we assessed whether two similar actions could be differentiated within the AOS on the basis of olfactory information. To this end, we first tested whether the activation for the G condition was greater than activation for the S condition [G – S, intensity threshold, $p = .05$] within the AOS areas already exhibiting greater activation for the GO than for the SO condition. Following this, we tested whether the extent of activation when comparing the G with the S condition was different to the extent of activation observed when comparing the GO with the SO condition. This resulted in the interaction contrast: [G – S] – [GO – SO], intensity threshold, $p = .05$. If the interaction contrast is significant, then differential activation can solely be ascribed to the olfactory information signaling the target-object. This is because both the amount and the type of perceived movement (e.g., hand shaping and trajectory, digits' opening and closing) is identical for the compared actions. A *t*-test was performed for each contrast.

Finally, we assessed whether both the primary and the secondary olfactory cortices were recruited during the smelling of an odor. To this end, we performed the contrast [GO + SO] – [GV + SV] within such regions [intensity threshold, $p = .015$ FDR corrected; cluster-extent threshold = 15 voxels]. To establish the localization of the primary olfactory cortex, we considered the MNI coordinates of peak-voxel reported in previous imaging studies in which: (a) the neural characterization of basic olfactory processing was the central aim; (b) odor-evoked activity was not complicated by the use of aversive odorants; and (c) subjects were not asked to make any cognitive olfactory judgments (other than odor detection) during scanning. On the basis of such criteria data from four brain imaging studies (Gottfried, Deichmann, Winston, & Dolan, 2002; Gottfried, Winston, & Dolan, 2006; Poellinger et al., 2001; Zatorre, Jones-Gotman, Evans, & Meyer, 1992) were considered. A total of 12 coordinates were identified, including 9 for the left hemisphere and 8 for the right hemisphere. All of these studies reported significant bilateral activation. Voxel coordinate mean together with the standard error was computed separately for the right and the left hemisphere. The results indicated that the left and the right primary olfactory cortices were localized in the MNI space at ($x = –24 \pm 2$ mm, $y = 1 \pm 1$ mm, $z = –17 \pm 4$ mm) and at ($x = 21 \pm 1$ mm, $y = 5 \pm 2$ mm, $z = –15 \pm 4$ mm), respectively. From an anatomical perspective, neural loci associated with these coordinates were located within the piriform cortex, alongside the dorsal-medial surface of the temporal lobe at the level of the fronto-temporal junction. To establish the localization of the secondary olfactory cortex we used data from a meta-analysis performed by Gottfried & Zald (2005). According to these authors, the left and the right secondary olfactory cortex are located within the orbital surface of the frontal lobe at ($x = –21$ mm, $y = 31$ mm, $z = –16$ mm) and at ($x = 24$ mm, $y = 34$ mm, z = –12 mm), respectively (Talairach coordinates). By applying the Matthew Brett's "tal2mni" function (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/tal2mni.m) to the Talairach coordinates we obtained the corresponding MNI coordinates for the left and the right secondary olfactory cortex: ($x = –21$ mm, $y = 33$ mm, $z = –17$ mm), and ($x = 24$ mm, $y = 35$ mm, $z = –12$ mm), respectively. By using WFU_PickAtlas (an SPM 5 extension available at www.fmri.wfubmc.edu/cms/software) we built four spheres (radius = 10 mm) and centered each sphere on each set of MNI coordinates. The four spheres were joined to compose an individual brain mask. The brain volume which was included within the mask represented the search volume for the contrast [GO + SO] – [GV + SV].

Localization

Anatomical details of significant signal changes were obtained by superimposing the SPM{*t*} maps resulting from the contrasts [GV – SV] and [GO + SO] – [GV +

SV] on the T1 canonical MNI template image. Results were also checked against normalized structural images of each participant. For the purpose of additional anatomical precision, the SPM{t} map was overlaid on a surface based-representation of the MNI canonical brain using the SPM surfrend toolbox (written by I. Kahn; http://spmsurfrend.sourceforge.net). The surface-based representation was then rendered using FreeSurfer (CorTechs Labs, Charlestown, MA) (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). We used two atlases as general neuroanatomical references (Duvernoi, 1999; Mai, Assheuer, & Paxinos, 2004). Further, the SPM Anatomy Toolbox 1.6 (Eickhoff et al., 2005) based on three-dimensional probabilistic cytoarchitectonic maps was used to determine the cytoarchitectonic probability (where available) of peak activity voxels. For the premotor cortexes we also ascertained the position of the activation clusters and peaks from a meta-analysis by Mayka, Corcos, Leurgans, and Vaillancourt (2006). Activation peaks were reported in MNI coordinates.

RESULTS

Identification of the AOS concerned with visuomotor information

The comparison [GV – SV] showed that perception of a hand grasping a visual object (i.e., visuomotor information) activated a network of brain regions distributed across the temporal, the parietal, and the frontal lobes (Table 1 and Figure 3A). With respect to the temporal lobe, significant activation was revealed within both the right and the left middle temporal cortex (MTc) (Table 1 and Figures 3B, 3C). When considering the superior parietal cortex (SPc), significant activation was found within both the right and the left primary somatosensory area (Table 1 and Figures 3D, 3E). Furthermore, significant activation was found within the sector PFcm of both the right and the left inferior parietal cortex (IPc) (Table 1 and Figures 3F, 3G). Parietal activity within the left sector PFcm spread within the intraparietal sulcus (IPS) (Table 1). Significant activation was also detected within the sector PFt of the left IPc (Table 1 and Figure 3H). When considering the frontal lobe, significant activation was found within both the right and the left premotor dorsal cortex (PMdc) (Table 1 and Figures 3I, 3J). Finally, significant activation was found within the right premotor ventral cortex (PMvc) (Table 1 and Figure 3K).

Representation of olfactomotor information within the AOS

The comparison [GO – SO] showed that perception of a hand grasping an object signaled via olfaction (i.e., olfactomotor information) activated a subset of the

TABLE 1
Anatomical localization of the activation peaks as revealed by the contrast *Grasping Visual* (GV) condition – *Static Visual* (SV) condition

Brain region	*x*	*y*	*z*[a]	*Probabilistic cytoarchitecture*	*Peak t*	*p value*[b]
Temporal lobe						
Right middle temporal cortex	48	–66	4	MT/V5 (50%)	8.52	<.001
Left middle temporal cortex	–46	–70	8	MT/V5 (30%)	9.06	<.001
Parietal lobe						
Right superior parietal cortex						
Primary somatosensory area	32	–48	58	BA 2 (60%)	5.47	<.001
Left superior parietal cortex						
Primary somatosensory area	–34	–44	60	BA 2 (50%)	6.51	<.001
Right inferior parietal cortex	56	–36	22	PF_{cm} (60%)	5.87	<.001
Left inferior parietal cortex	–48	–38	26	PF_{cm} (50%) hIP2 (10%)	4.94	<.001
Left inferior parietal cortex	–48	–24	36	PF_{t} (60%)	4.53	<.001
Frontal lobe						
Right dorsal premotor cortex	42	–4	54	BA 6 (40%)	3.92	<.01
Left dorsal premotor cortex	–48	–4	48	BA 6 (100%)	4.56	<.001
Right ventral premotor cortex	58	4	40	BA 6 (60%)	4.18	<.01

Notes: [a]MNI coordinates (mm). [b]FDR-corrected for whole-brain volume. PF_{cm}, ventral part of the anterior inferior parietal lobule; PF_{t}, dorsal part of the anterior inferior parietal lobule; hIP2, human intraparietal area 2 (Caspers et al., 2008).

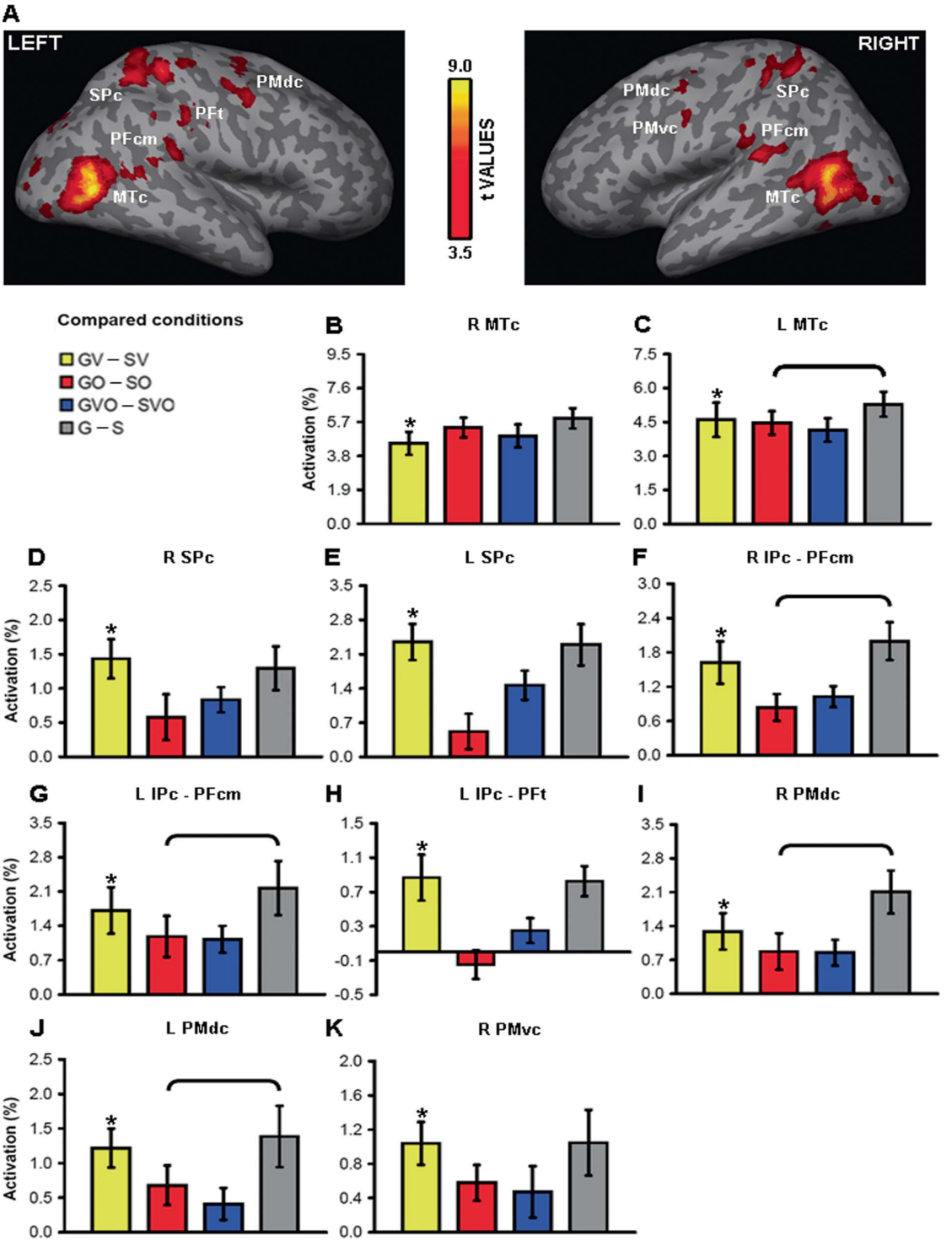

Figure 3. Functional modulation of the AOS activity depending on the nature of sensorimotor information. (A) SPM {*t*} map resulting from the contrast GV – SV rendered onto the MNI canonical brain. (B–K) Size of the activation for the GV (yellow bars), the GO (red bars), the GVO (blue bars), and the G (gray bars) conditions with respect to the SV, the SO, the SVO, and the S conditions, respectively, as measured at the peak-voxel level within (B, C) the right and the left middle temporal cortex (R MTc and L MTc, respectively), (D, E) the right and the left superior parietal cortex (R SPc and L SPc, respectively), (F, G) the sector PFcm of the right and the left inferior parietal cortex (R IPc – PFcm and L IPc – PFcm, respectively), (H) the sector PFt of the left inferior parietal cortex (L IPc – PFt), (I, J) the right and the left premotor dorsal cortex (R PMdc and L PMdc, respectively), and (K) the right premotor ventral cortex (R PMvc). Error bars represent standard errors of the activations. Asterisks indicate the statistically significant results obtained from the contrast [GV – SV] performed at whole brain level.

cerebral areas identified for visuomotor information (Figures 3B–3K). Specifically, perceiving olfactomotor information brought a significant activation within the bilateral MTc (*right side:* $t = 9.32$, $p < .001$; *left side:* $t = 8.36$, $p < .001$) (Figures 3B, 3C). When considering the parietal lobe, no significant activation was found within the bilateral SPc (*right side:* $t = 1.67$, $p > .05$; *left side:* $t = 1.39$, $p > .05$) (Figures 3D, 3E). Significant activation was found within the sector PFcm of the bilateral IPc (*right side:* $t = 3.47$, $p < .01$; *left side:* $t = 2.73$, $p < .01$) (Figures 3F, 3G). Finally, no significant activation was found within the sector PFt of the left IPc ($t = –0.84$, $p > .05$) (Figure 3H). With respect to the frontal lobe, significant activation was found within the bilateral PMdc (*right side:* $t = 2.25$, $p < .05$; *left side:* $t = 2.31$, $p < .05$, respectively) (Figures 3I, 3J). Significant activation was also found within the right PMvc ($t = 2.69$, $p < .01$) (Figure 3K).

Integration of visuomotor and olfactomotor information within the AOS

The comparison [GVO – SVO] showed that perceiving a hand grasping an object signaled via both vision and olfaction, i.e., visuo-olfactomotor information, determined significant activation within the bilateral MTc (*right side:* $t = 7.44$, $p < .001$; *left side:* $t = 7.75$, $p < .001$) (Figures 3B, 3C), the bilateral SPc (*right side:* $t = 4.39$, $p < .001$; *left side:* $t = 4.77$, $p < .001$) (Figures 3D, 3E), and the sector PFcm of the bilateral IPc (*right side:* $t = 5.47$, $p < .001$; *left side:* $t = 3.69$, $p < .001$) (Figures 3F, 3G). With respect to the sector PFt of the left IPc, no significant activation was found ($t = 1.69$, $p > .05$) (Figure 3H). Significant activation was also found for the bilateral PMdc (*right side:* $t = 3.07$, $p < .01$; *left side:* $t = 1.73$, $p < .05$) (Figures 3I, 3J). Activation was not significant within the right PMvc ($t = 1.52$, $p > .05$) (Figure 3K). Furthermore, the superadditive model [(GVO – SVO) + (G – S)] – [(GV – SV) + (GO – SO)] accounted for the activation elicited by perception of visuo-olfactomotor information within both the right MTc and the left SPc (Table 2).

Representation of olfactory information within the AOS

The comparison [G – S] showed that the perception of a mimed grasp determined significant activation within the areas of the AOS that were also activated for olfactomotor information (Figures 3B–3K). Specifically, significant activation was found within the bilateral MTc (*right side:* $t = 10.08$, $p < .001$; *left side:* $t = 9.32$, $p < .001$) (Figures 3B, 3C), the sector PFcm of the bilateral IPc (*right side:* $t = 5.84$, $p < .001$; *left side:* $t = 3.82$, $p < .001$) (Figures 3F, 3G), and the bilateral PMdc (*right side:* $t = 4.59$, $p < .001$; *left side:* $t = 3.03$, $p < .01$) (Figures 3I, 3J). Significant activation was also found within the right PMvc ($t = 2.64$, $p < .01$) (Figure 3K). Crucially, the interaction contrast [G – S] – [GO – SO] indicated that activation for the perception of olfactomotor information differed with respect to that obtained while perceiving a mimed grasp. Specifically, significant differential activation was found within the left MTc ($t = 1.96$, $p < .05$) (Figure 3C), the sector PFcm of the bilateral IPc (*right side:* $t = 3.09$, $p < .05$; *left side:* $t = 2.35$, $p < .05$) (Figures 3F, 3G), and the bilateral PMdc (*right side:* $t = 3.40$, $p < .01$; *left side:* $t = 1.83$, $p < .05$) (Figures 3I, 3J). No significant differential activation was found for the right MTc ($t = 1.65$, $p > .05$) (Figure 3B) and the right PMvc ($t = 1.12$, $p > .05$) (Figure 3K).

TABLE 2
Neural sites of integration between visuomtor and olfactomotor information

Brain regions	*Probabilistic cytoarchitecture*	*Averaged activation (%)*[a]	*t value*	*p value*
Temporal lobe				
Right middle temporal cortex	MT/V5 (50%)	0.93 (0.50)	1.85	<.05
Parietal lobe				
Left superior parietal cortex	BA 2 (50%)	0.90 (0.44)	2.01	<.05

Notes: Averaged activation across participants for the superadditive model is reported. Standard errors are shown in parentheses. Statistical assessment for the superadditive model [(GVO – SVO) + (G – S)] – [(GV – SV) + (GO – SO)] is also presented. [a]Superadditive combination of betas as measured at the peak voxel revealed by the contrast [GV – SV]. GVO, *Grasping Visual-Olfactory* condition; SVO, *Static Visual-Olfactory* condition; G, *Grasping* condition; S, *Static* condition; GV, *Grasping Visual* condition; SV, *Static Visual* condition; GO, *Grasping Olfactory* condition; SO, *Static Olfactory* condition.

TABLE 3
Anatomical localization of the activation peaks as revealed by the contrast [*Grasping Olfactory* condition (GO) + *Static Olfactory* condition (SO)] – [*Grasping Visual* condition (GV) + *Static Visual* condition (SV)]

Brain regions	*x*	*y*	*z*[a]	*Peak t*	*p value*[b]
Piriform cortex					
Left primary olfactory cortex	–28	2	–16	7.16	<.001
Right primary olfactory cortex	22	0	–12	6.35	<.001
Orbitofrontal cortex					
Left secondary olfactory cortex	–28	32	–12	4.89	<.001
Right secondary olfactory cortex	30	30	–10	4.43	<.001

Notes: [a]MNI coordinates (mm). [b]FDR-corrected for search-brain volume.

Representation of olfactory information within the olfactory areas

In agreement with previous neuroimaging investigations (Gottfried et al., 2002, 2006; Gottfried & Zald, 2005; Poellinger et al., 2001; Zatorre et al., 1992), the comparison [GO + SO] – [GV + SV] showed that the smelling of an odor activated bilaterally both the primary and the secondary olfactory cortices (Table 3 and Figure 4).

DISCUSSION

The present experiment investigated the impact of olfactory information embedded in others' actions on the AOS, a network of brain areas thought to be responsible for action understanding (Goldman & Sebanz, 2005; Raos et al., 2007). The results obtained demonstrate that olfactory cues are pivotal in determining neurofunctional modulation within such system.

The contribution of olfaction to action understanding

We show that the perception of a motor interaction involving a hand in contact with an "olfactory" object has the potential to increase activity within the bilateral MTc, the sector PFcm of the bilateral IPc, the bilateral PMdc, and the right PMvc. This provides compelling evidence that the AOS is able to build up representations of others' action embedding sensory cues conveyed via olfaction (Rossi et al., 2008). Furthermore, we reveal that for a subset of these brain areas the level of activity for a hand grasping an "olfactory" object was less than for a mimed grasp (i.e., G condition). Therefore, the AOS can also differentiate between actions on the basis of olfactory information.

A similar pattern of activation for the premotor and the inferior parietal cortices (sector PFcm) together with the intraparietal sulcus has previously been documented for the observation of a hand grasping a visual object with respect to the observation of a hand mimicking a grasp movement (Grèzes et al., 2003). Our findings confirm and extend the notion that a proper grasp and an identical non-object-related movement are represented within the same network of temporal, parietal, and frontal areas. Noticeably, direct knowledge of what another individual is doing would reflect on the functional responses of this network (Thioux, Gazzola, & Keysers, 2008). Therefore, similarly to vision, the sense of smell might convey useful sensory information for understanding whether the perceived action is transitive (i.e., grasping an object) or intransitive (i.e., pretending to grasp an object). The fact that the AOS was more engaged for a mimed than for a proper grasp might suggest that although a similar network mediates the representation for both types of action, the neural responses differentiate these two types of action. Representation of a mimed grasp could be more complex and demanding than representation of a proper grasp, and might imply the retrieval of the representation for a type of proper grasp which more closely match the mimed grasp (Villarreal et al., 2008). This process, in turn, might require the implementation of an image of the object that is based on movement cues (e.g., hand shaping) as if the perceived action was transitive (Villarreal et al., 2008). Conversely, the representation of a proper grasp would not be mediated by retrieval of a transitive action to which the perceived action is to be matched, nor by "object imagery." Therefore, higher activity for a mimed than for a proper grasp would reflect the unusual nature of the perceived action and the richness of the observer's own sensorimotor experience.

However, before such a conclusion can be accepted, there is an important issue that must be addressed. The higher activity for a mimed grasp (i.e., G – S) than for a proper grasp on an olfactory object (i.e., GO – SO) might be simply due to an attentional effect. In this respect, olfactory stimulation might distract participants from viewing the video clips for the GO and the SO condition. This, in turn, would cause a reduction of activity within the AOS areas. This explanation, however, is unlikely given that a similar pattern of results emerges when the object is coded

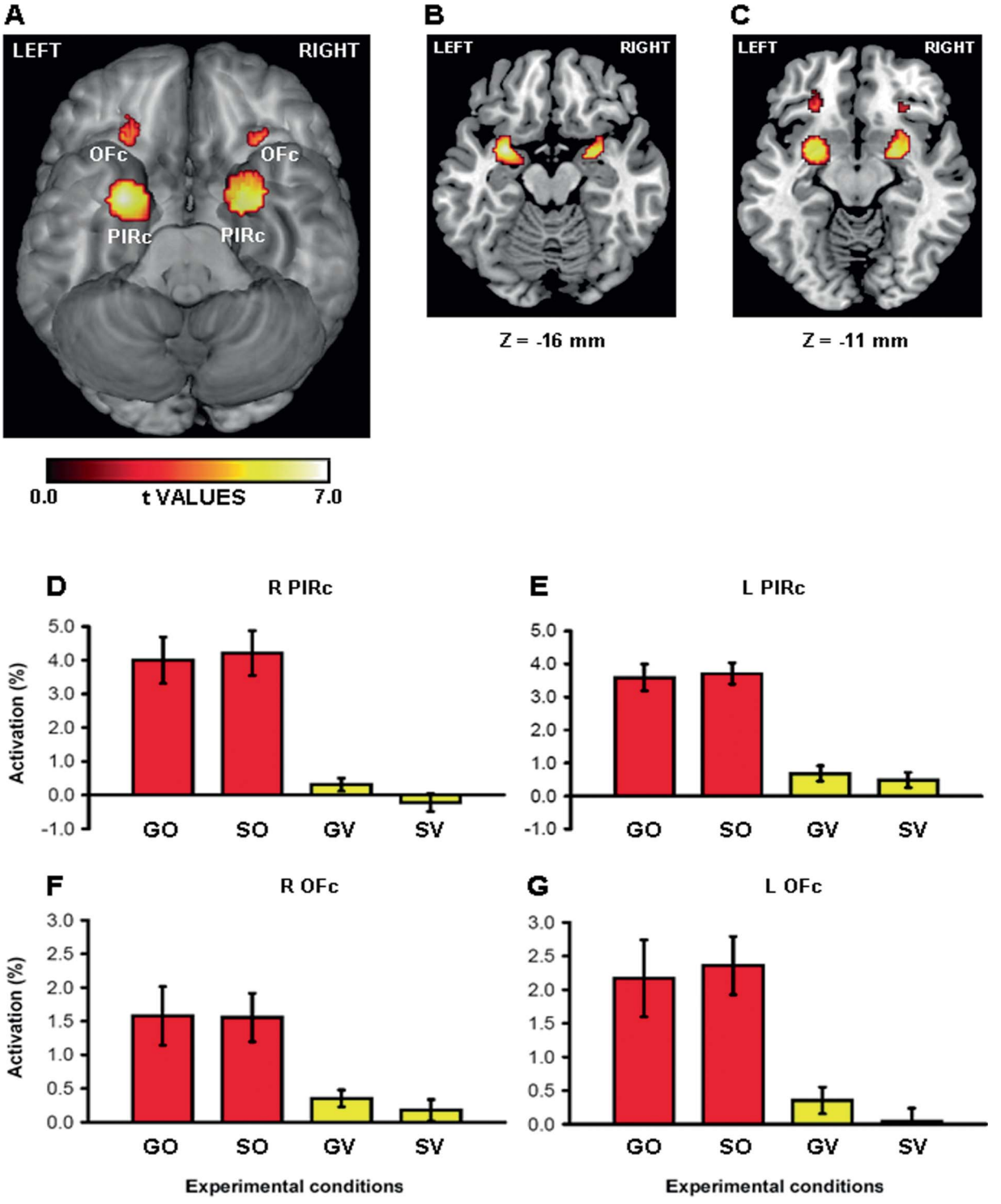

Figure 4. Activation within the bilateral piriform cortex (PIRc) and the bilateral orbitofrontal cortex (OFc) during the smelling of an odor. (A) SPM {*t*} map resulting from the contrast [GO + SO] – [GV + SV] rendered onto a ventral view of the MNI canonical brain. (B) Activation foci within the right and the left PIRc as revealed by the horizontal section at z = –16 mm. (C) A horizontal section at *z* = –11 mm also show the activation foci within the right and the left OFc. (D–G) Size of the activation for the experimental conditions in which an odor was delivered (the GO and the SO condition; red bars) and no odor was administered (the GV and the SV condition; yellow bars) as measured at the peak–voxel level within (D, E) the right and the left PIRc (R PIRc and L PIRc, respectively) and (F, G) the right and the left OFc (R OFc and L OFc, respectively). Note that in Panel A a phantom view for the activation foci within the PIRc has been adopted. Although the activation foci appear on the dorsal surface of the temporal lobe, they are actually located within the dorsal-medial surface of the temporal lobe.

via vision. For instance, we found higher activity for a mimed grasp (i.e., G – S) than for a proper grasp on a visual object (i.e., GV – SV) within the right PMdc ($t = 2.80$, $p < .05$) (Figure 3I). In such circumstances, no odour was present, therefore no distraction might have occurred. This suggests that the lower activity elicited by the viewing of a proper grasp, when the object is signaled via olfaction, might be attributed to the olfactory information cueing the action target-object.

A point worth mentioning is that action discrimination (i.e., GO condition vs. G condition) did not occur within the right PMvc. This area responded similarly to olfactomotor information and a mimed grasp. It is possible that at this level there is a distinct type of analysis of others' action. That is, the PMvc might be sensitive to how an individual performs an action, disregarding the goal and the intended effects of the action (Thioux et al., 2008). At this level, olfactory information, which signals the presence/absence of the target-object, would not be coded. Continuing on this analysis, because actions to grasp an "olfactory" object and to mime a grasp movement were performed in a similar fashion, the representation of a proper grasp and a mimed grasp would not elicit discernible activity. A number of fMRI studies support this proposal (Buccino et al., 2001; Lui et al., 2008; Sakreida, Schubotz, Wolfensteller, & von Cramon, 2005; Wheaton, Thompson, Syngeniotis, Abbott, & Puce, 2004). Specifically, perception of both goal-directed action and mimes of the same action without a visual object increased activity within the bilateral premotor cortex, with activity occurring within different sectors of the premotor cortex depending on the moving effector (hand, mouth, and foot; Buccino et al., 2001).

A further issue that needs to be discussed concerns how olfaction compares in terms of functions with vision in humans. It is well known that olfaction provides us with detailed information about the world beyond our body surface (Stockhorst & Pietrowsky, 2004) and to recognize individuals, objects, and events within the environment (Stevenson & Wilson, 2007) as well as vision does (Ullman, 1996). Furthermore, recent evidence indicates that a similar parallelism between vision and olfaction might apply for action guidance (Castiello, Zucco, Parma, Ansuini, & Tirindelli, 2006; Tubaldi et al., 2008a). For instance, as viewing a fruit elicits action planning, smelling the odor of a fruit triggers the planning of a grasp suited for interacting with that fruit (Castiello et al., 2006; Tubaldi et al., 2008a). And, when the type of grip evoked by the odor does not coincide with that for the to-be-grasped fruit, interference effects are evident on hand kinematics (Tubaldi et al., 2008b). Here we go a step further by revealing that these parallel qualities across modalities are also evident at the level of action understanding. Olfaction, like vision, has the ability to code information regarding others' actions in a format that is fully manageable by the AOS.

Integration of visuomotor information with olfactomotor information

Some studies in monkeys uncovered that the premotor cortex discharged when the animal either saw a hand acting on a visual target-object (i.e., visuomotor information) or heard the sound related to such interaction (i.e., audiomotor information) (Kohler et al., 2002; Keysers et al., 2003). Importantly, the contributions of visuomotor and audiomotor information to the neuronal population activity were not independent, and when both pieces of sensorimotor information were available, the representation of another individual's action was optimal (Keysers et al., 2003). Subsequent investigations seemed to suggest that a similar integration mechanism might operate in humans (Etzel et al., 2008; Gazzola et al., 2006). Here we crucially extend the boundaries of the (multi)sensory motor territory within which this process occurs by demonstrating the contribution of the olfactory cues embedded into others' actions. The present findings show that the AOS responded when visuomotor and olfactomotor information co-occurred (i.e., the GVO condition). This indicates that the two kinds of sensorimotor information are processed in concert, raising the possibility that an integration mechanism operates within the AOS. Evidence supporting this comes from our finding that both the right MTc and the left SPc exhibited a superadditive activation pattern when visuomotor information and olfactomotor information were presented simultaneously (i.e., the GVO condition). The sum of the functional responses for each type of sensorimotor input (i.e., the GV and the GO conditions) did not predict the level of activity evoked by the condition in which both visuomotor information and olfactomotor information were present. Therefore, when visuomotor information and olfactomotor information were both available some form of interaction occurred, and the level of activity reflected a new visuo-olfactomotor product, synthesized from visuomotor and olfactomotor information. Along these lines, our results suggest that the fusion of visuomotor and olfactomotor information may increase the likelihood of identifying others' actions or speed up action recognition (Bonaiuto, Rosta, & Arbib, 2007; Oztop & Arbib, 2002).

When considering AOS activity in greater detail, it emerges that the two integrative areas (the right MTc and the left SPc) fall within two distinct functional categories. The right MTc not only exhibited a superadditive pattern for visuo-olfactomotor information, but also responded to both visuomotor and olfactomotor information when presented in isolation. Therefore, any evidence of action, be it visuomotor or olfactomotor, was sufficient *per se* to elicit a full-blown representation of the action. In this view, superadditive activity for visuo-olfactomotor information would indicate the combination of two originally distinct representations, each based on specific types of sensorimotor information. The left SPc was sensitive to visuomotor information, but it was not responsive to olfactomotor information. Therefore it is unlikely that superadditive activity indicates the combination of visuomotor and olfactomotor action representation. In this respect, we suggest that the left SPc represents other people's action based on visuomotor information, and information conveyed via olfaction enriches such representation. Superadditive activity would reflect this process of sensorimotor enrichment.

Two further points regarding the present findings should be noted. First, they make a novel contribution to the mapping of convergence zones within the primate brain, which might allow for the integration of signals from different senses. Previous cell recordings, tracing work, and neuroimaging studies (Stein & Stanford, 2008; Driver & Noesselt, 2008) strongly indicate that the parietal cortex receives converging feedforward projections from visual, auditory, and somatosensory areas to merge incoming information for object recognition and attentional orienting. In this connection, we show that the synergy among percepts also involves olfactomotor and visuomotor information and, most importantly, such synergy contributes to a meaningful representation of ecologically relevant actions. Second, superadditive activity was found within the MTc. Recent neuroimaging investigations have shown that motion cues conveyed via different sensory modalities are represented within the MTc (Bartels, Logothetis, & Moutoussis, 2008; Born & Bradley, 2005; Hagen et al., 2002; Alink, Singer, & Muckli, 2008; Scheef et al., 2009). Furthermore, the MTc is able to integrate visual, auditory, and tactile motion cues in order to stabilize and enhance motion perception (Beauchamp, 2005b). Visuomotor and olfactomotor information can be regarded as complex patterns that specify the motion of the reach-to-grasp toward the object. Therefore, the finding that these patterns do integrate confirms the role of the middle temporal cortex in multimodal motion integration, and extends it to the olfactory domain.

A final point is concerned with the locus within which visuomotor information and olfactomotor information integrate. Previous evidence indicates that when the task is to perceive the odor of a visible object, then olfactory and visual information are integrated within multisensory centers subserving object recognition, namely the orbitofrontal cortex (Gottfried & Dolan, 2003; Österbauer et al., 2005). However, when the task is to localize the source of the odor, olfactory information is encoded within the superior temporal gyrus, an area within which multimodal spatial maps are represented (Porter, Anand, Johnson, Khan, & Sobel, 2005). Here we add to this literature by demonstrating that when the task requires observation of a goal-directed action, visual-olfactory binding occurs within the various components of the AOS. Hence we provide further evidence for the notion that the main determinant for assigning the locus of sensorimotor integration is the nature of the task.

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