# Dissociated neural representations of intensity and valence in human olfaction

A.K. Anderson[1,2], K. Christoff[2], I. Stappen[3], D. Panitz[2], D. G. Ghahremani[2], G. Glover[4], J.D.E. Gabrieli[2] and N. Sobel[1,5]

[1] *Helen Wills Neuroscience Institute, 349 Mulford Hall, UC Berkeley, Berkeley, California 94720, USA*

[2] *Department of Psychology, Stanford University, 420 Jordan Hall, Stanford, California 94305, USA*

[3] *Institute of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14 A-1090 Vienna, Austria*

[4] *Department of Radiology, Stanford University, 1201 Welch Road, Stanford, California 94305, USA*

[5] *Department of Psychology, 3210 Tolman Hall, UC Berkeley, Berkeley, California 94720, USA*

*Correspondence should be addressed to A.K.A. (adam.k.anderson@stanford.edu) or N.S. (nsobel@socrates.berkeley.edu)*

Published online 21 January 2003; doi:10.1038/nn1001

**Affective experience has been described in terms of two primary dimensions: intensity and valence. In the human brain, it is intrinsically difficult to dissociate the neural coding of these affective dimensions for visual and auditory stimuli, but such dissociation is more readily achieved in olfaction, where intensity and valence can be manipulated independently. Using event-related functional magnetic resonance imaging (fMRI), we found amygdala activation to be associated with intensity, and not valence, of odors. Activity in regions of orbitofrontal cortex, in contrast, were associated with valence independent of intensity. These findings show that distinct olfactory regions subserve the analysis of the degree and quality of olfactory stimulation, suggesting that the affective representations of intensity and valence draw upon dissociable neural substrates.**



Through their distal senses, mammals constantly investigate their environment, and priority in sensory processing is thought to be given to biologically significant stimuli. The amygdala, a heterogeneous structure in the anteromedial temporal lobe, is a primary neural substrate involved in this processing[1,2]. Electrophysiological, lesion and imaging studies have all pointed to an essential role of the amygdala in processing threatening, fearful and highly aversive stimuli[1–6]. The view that the human amygdala is particularly responsive to unpleasant (or 'negatively valenced') events has been recently challenged by findings that the amygdala also responds to pleasant (or 'positively valenced') events[7,8]. Thus, the precise affective dimensions that characterize amygdala encoding in humans remain unclear.

Such indeterminacy of what characterizes amygdala responsiveness is related to the fact that affective space is multidimensional[9,10]. Emotion researchers have long appreciated that emotional responses and stimulus evaluations are primarily characterized by two dimensions: intensity and valence[10]. Although construed as contributing independently to experience[9,10], intensity and valence tend to correlate in at least two ways. First, intensity and valence are often asymmetrically correlated between valences. Negative stimuli (for example, a mutilated body) are typically more intense and arousing than positive scenes (a puppy). Second, intensity and valence are often correlated within a valence. An aversive stimulus (fingernails scratching a chalkboard) typically becomes more unpleasant, or acquires greater negative valence, as it becomes more intense (louder). Indeed, this interaction is so strong that in human experience as well as in empirical study, it is often difficult to dissociate intensity and valence.

Although it is possible to dissociate intensity and valence with standard photographic stimuli, there are complicating interpretational issues associated with using events that differ in semantic content to manipulate these dimensions. Here we took advantage of the unique world of odor where stimulus intensity, which is strongly correlated with subjective and autonomic indices of arousal[11], can be dissociated from stimulus valence[12,13] relatively free of potentially confounding semantic manipulations. This allowed us to ask how these experiential dimensions are represented in the amygdala and associated orbitofrontal cortices—regions that are critically involved in affective[4,14–16] and olfactory processing[4,16–21]. To dissociate the dimensions of intensity and valence, we created four stimuli using two odorants. High- and low-concentration versions of the odorants citral and valeric acid were prepared. Citral smells lemony, fruity and fragrant, and is perceived by most as pleasant[22]. Valeric acid smells sweaty, rancid and sickening and is perceived by most as unpleasant[22]. The concentrations used were selected through a psychophysical pre-study in which the high-concentration citral (citral-high) was rated as similar in intensity to the high-concentration valeric acid (valeric-high), and the low-concentration citral (citral-low) was rated as similar in intensity to the low-concentration valeric acid (valeric-low). Further, an intensity range was selected such that odor valence could be manipulated with relative independence from intensity. Thus, we had

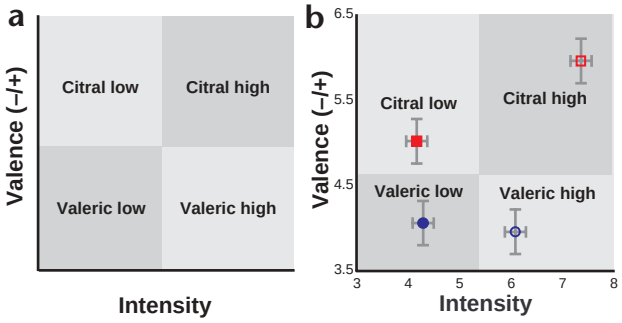


**Fig. 1.** Ideal and observed odor space. The abscissa represents odor intensity. The ordinate represents odor valence, with increasing pleasantness represented as greater magnitudes. (**a**) Odor selections were guided by an attempt to construct an affective space whereby odor intensity and valence were manipulated independently. High and low concentrations of the pleasant-smelling citral and unpleasant-smelling valeric acid were psychophysically pre-selected to represent the four critical design quadrants. (**b**) Subjective intensity and valence estimates obtained after scanning. Horizontal error bars reflect standard error of the mean (s.e.m.) for intensity ratings from 1 (low intensity) to 9 (high intensity) and vertical reflects s.e.m. for valence from 1 (very unpleasant) to 9 (very pleasant). Consistent with the manipulation of odor valence, valeric acid was rated as significantly more unpleasant than citral ($F_{1,15}$ = 25.30, $P$ < 0.0001). Consistent with the manipulation of odor intensity, high-concentration odors were rated as significantly more intense than low-concentration odors ($F_{1,15}$ = 78.45, $P$ < 0.0001). Independent manipulation of intensity and valence was achieved for three of the four design quadrants; this was sufficient to separate neural responses to intensity and valence. Low concentrations of citral and valeric acid were equated for intensity ($F_{1,15}$ = 0.10, $P$ > 0.75), but differed in valence ($F_{1,15}$ = 6.46, $P$ < 0.02); high and low concentrations of valeric differed significantly in intensity ($F_{1,15}$ = 20.31, $P$ < 0.0004), but not in valence ($F_{1,15}$ = 0.08, $P$ > 0.78). High concentrations of citral were rated as more intense ($F_{1,15}$ = 10.25, $P$ < 0.007) than high concentrations of valeric, and more pleasant ($F_{1,15}$ = 7.68, $P$ < 0.01) than low citral. Consistent with their relative independence, there was no significant association between individuals' estimations of odor intensity and valence for both odorants (valeric, $r$ = –0.19, $P$ > 0.27; citral, $r$ = 0.29, $P$ > 0.11).

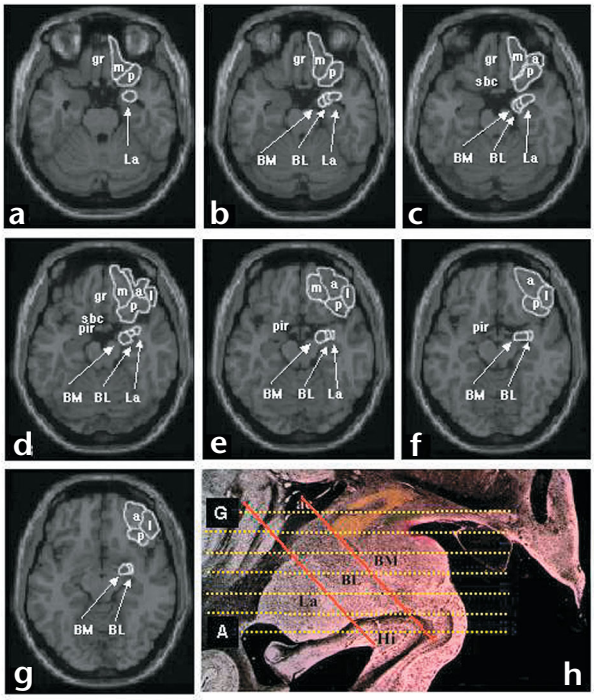


**Fig. 2.** Region of interest (ROI) analysis. Anatomical subdivisions of the amygdala and orbitofrontal cortex were outlined for analysis. Shown here are seven slices of the acquisition that typically contained the ROIs, from the most ventral (**a**) to dorsal (**g**). ROIs were drawn bilaterally (shown unilaterally here) on each participant's anatomical scan (m, medial orbitofrontal; p, posterior orbitofrontal; a, anterior orbitofrontal; BM, basomedial amygdala; BL, basolateral amygdala; La, lateral accessory amygdala). The amygdaloid complex is made up of numerous structures, but these are not separable on the MR image. Thus, we opted for a crude segregation into these three amygdala subregions based on a detailed atlas[24]. (**h**) As can be seen from the cytoarchitecture, there is a coarse inferior–superior organization to the amygdala in oblique bands (red lines), with the La being most inferior, the BM most superior and the BL in-between. Overlaid on the coronal image (from ref. 24) are approximated slices of the current acquisition (yellow dotted lines). As the temporal portion of piriform cortex cannot be distinguished from the anterior end of the amygdala on the MR image, the amygdala ROI was drawn conservatively at this point (slices **d**–**f**).

four conditions: intense-pleasant, intense-unpleasant, unintense-pleasant and unintense-unpleasant. This design allowed for a dissociation of intensity from valence (**Fig. 1a**). We delivered the four stimuli interspersed with a clean-air stimulus in a randomly ordered event-related design to 16 participants, while measuring brain activation with a 3-tesla fMRI scanner. We found that amygdala activation was associated with intensity and not valence of odors. Conversely, distinct regions of orbitofrontal cortex were associated with valence independent of intensity.

## Results

### Intensity coding in the amygdala

First, to measure the response in the amygdala, we structurally outlined this region on each participant's anatomical scan (**Fig. 2**). Then we computed the percent change in the blood oxygen level–dependent (BOLD) signal induced by each of the four odorants as compared to a clean-air baseline. The most critical test of negative valence (rather than intensity) coding in the amygdala is a comparison of a less-intense unpleasant odor with a more-intense pleasant odor. Low-concentration valeric was perceived as far more unpleasant than high-concentration citral (**Fig. 1b**; mean difference from clean air for valeric-low, –1.08; citral-high, 0.81; $F_{1,15}$ = 25.30, $P$ < 0.0001), but valeric-low induced far less amygdala activation than did citral-high (**Fig. 3a** and **b**; right amygdala, $F_{1,285}$ = 33.87, $P$ < 0.0001; left amygdala, $F_{1,285}$ = 24.05, $P$ < 0.0001). By contrast, there was a greater peak response to both high-intensity odorants (valeric-high and citral-high) than to both low-intensity odorants (valeric-low and citral-low) in the right amygdala ($F_{1,285}$ = 48.55, $P$ < 0.0001) and left amygdala ($F_{1,285}$ = 34.13, $P$ < 0.0001). When equated for subjective ratings of intensity, there was no evidence in either the left ($F_{1,285}$ = 0.55, $P$ > 0.45) or right ($F_{1,285}$ = 1.59, $P$ > 0.20) amygdala of a greater response to the unpleasant than the pleasant odorant (low-valeric versus low-citral). Critically, this preferential response to more intense stimulation remained when odors were equated for valence—a greater response was present for valeric-high relative to valeric-low, despite being equally unpleasant in valence (right amygdala, $F_{1,285}$ = 23.89, $P$ < 0.0001; left amygdala, $F_{1,285}$ = 34.13, $P$ < 0.0001). The amygdala response thus reflected the intensity and not the valence of experience.

The amygdala comprises multiple subnuclei with specific olfactory inputs[23], and thus collapsing across these subdivisions

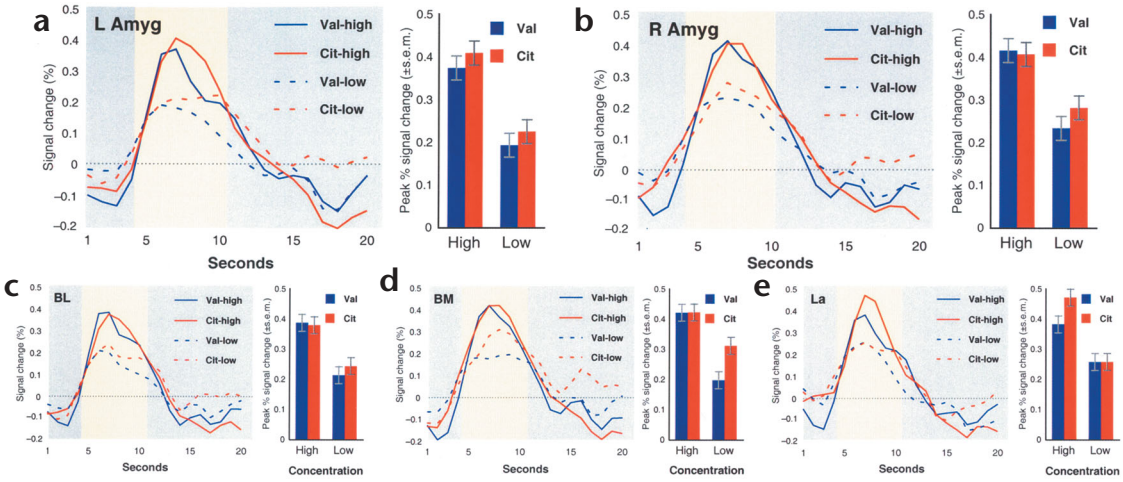


**Fig. 3.** Time course of amygdala BOLD response. Presented are time course (left-hand graphs) and peak hemodynamic responses (right-hand graphs) to the high and low intensity presentations of valeric and citral in the left (**a**) and right (**b**) amygdala. Data also shown for the proposed basolateral (**c**), basomedial (**d**) and lateral accessory (**e**) subdivisions of the amygdala, averaged across both the left and right hemispheres. The time-course ordinate represents percentage signal change, and the abscissa represents time from sniff onset. The peak-response ordinate represents peak percent signal change (± s.e.m.). Mean peak responses are shown from the interval of 4–10 s (cit-low = citral, low intensity; cit-high = citral, high intensity; val-low = valeric, low intensity; val-high = valeric, high intensity).

may have blurred a segregation of intensity and pleasantness coding. In particular, separate subregions might respond selectively to the positive or negative valence of a stimulus, and averaging across these regions would result in the appearance of valence independence. To guard against this possibility, we performed an additional control analysis whereby we coarsely outlined three major subdivisions of the amygdala that were hypothetically resolvable given our functional spatial resolution (**Fig. 2**). We also analyzed the response profiles within these subdivisions. When comparing odors of opposite valence, no subdivision in either the right amygdala (basolateral (BL), $P > 0.86$; basomedial (BM), $P > 0.9$; lateral accessory (La), $P > 0.9$) or left amygdala (BL, $P > 0.9$ ; BM, $P > 0.78$; La, $P > 0.9$) showed a significant trend consistent with the coding of relative unpleasantness (valeric > citral) or pleasantness (citral > valeric) (**Fig. 3c–e**). In contrast, all subdivisions in the right (BL, $P < 0.002$; BM, $P < 0.0001$; La, $P < 0.02$) and left (BM, $P < 0.0002$ ; La, $P < 0.0002$) amygdala showed a significantly greater response for the more intense odorant, with exception of the left BL, which approached significance (BL, $P > 0.07$; all $P$ values were Bonferroni-adjusted for multiple comparisons; **Fig. 3c–e**). As the delineation of subnuclei across subjects was based on a template from one canonical histological image[24], we treat the conclusions regarding specific subdivisions with caution. This control analysis, however, was sufficient to address whether the whole amygdala response profile was characteristic of smaller subdivisions.

## Valence coding in the orbitofrontal cortex

The orbitofrontal cortex has been implicated in affective processing in general[4,14–16] and odor content in particular[4,16–20,25,26]. To address where in the olfactory system valence is encoded outside of the amygdala, we examined odor responses in the orbitofrontal gyri. Anterior, medial, lateral and posterior orbitofrontal gyri were individually delineated on each participant's anatomical scan (**Fig. 2**). The percentage change in signal induced by each of the four odor stimuli was then computed within each region. In contrast with the amygdala, we found distinct orbitofrontal regions that were tuned either to pleasant or unpleasant odor quality rather than intensity. Activation in the right medial orbitofrontal gyrus was greater for pleasant than for unpleasant odors, regardless of intensity (**Fig. 4a**; $F_{1,285} = 12.55$, $P < 0.0005$). In this region, both high and low concentrations of

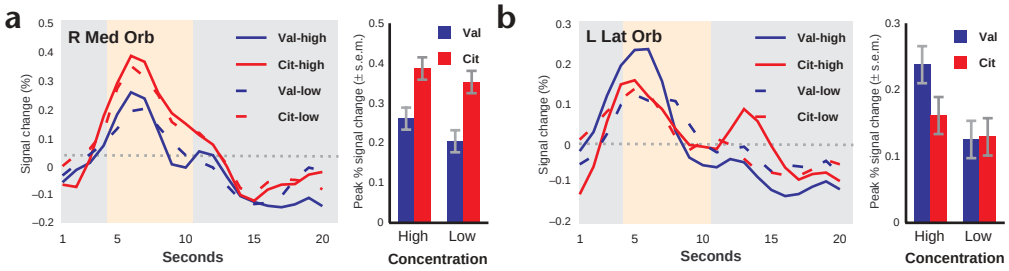


**Fig. 4.** Time course of orbitofrontal BOLD response. Time course (left-hand graph) and peak hemodynamic response (right-hand graph) to the high and low-intensity presentations of valeric and citral in the right medial (**a**) and left lateral (**b**) orbitofrontal cortex. The time-course ordinate represents percent signal change, and the abscissa represents time from sniff onset. The peak response ordinate represents peak percent signal change (± s.e.m.). Mean peak responses are shown from the interval of 4–10 s (cit-low = citral, low intensity; cit-high = citral, high intensity; val-low = valeric, low intensity; val-high = valeric, high intensity).

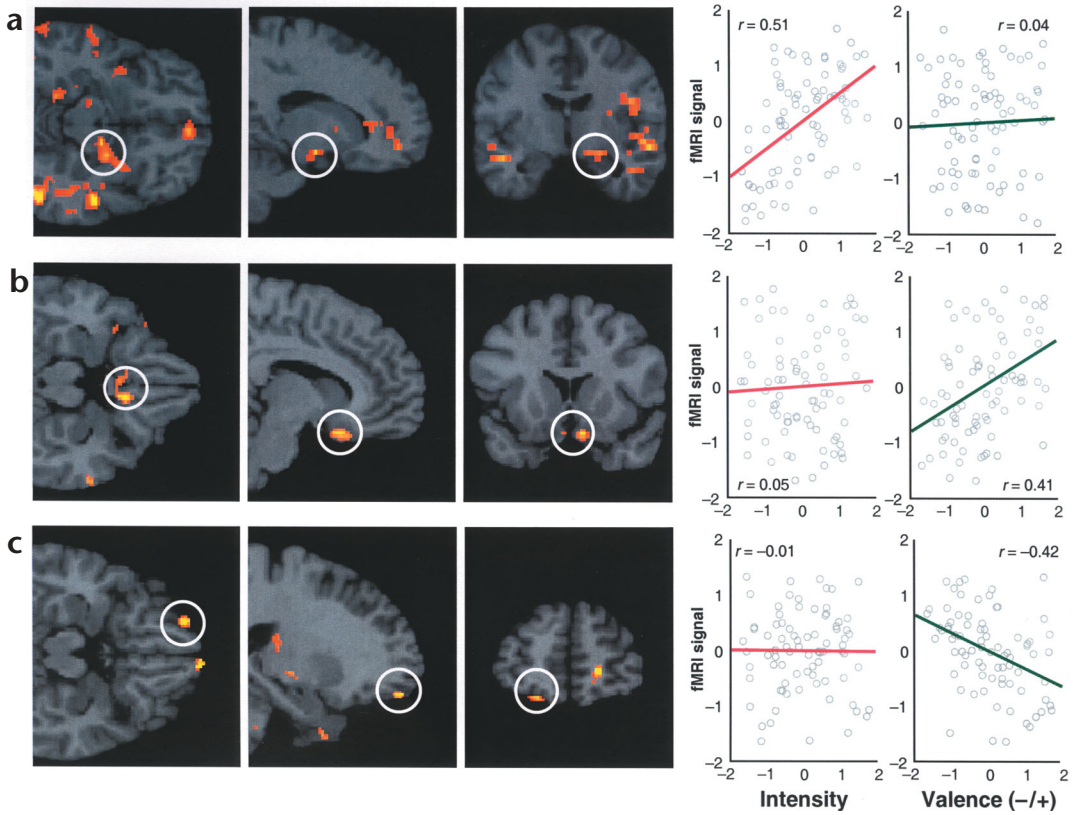


**Fig. 5.** Functional regions of interest (fROI) defined by their correlation with individual differences either in the evaluation of intensity, pleasantness or unpleasantness of the four odor conditions and clean air. Scatter plots depict the degree of association between individuals' fROI signal and valence and intensity evaluations (depicted as circles in standardized units). The ordinate represents fMRI signal, and the abscissa represents either the evaluation of odor intensity or valence for each stimulus condition for each participant. (**a**) A region in the right hemisphere extending from the dorsal amygdala into the piriform cortex was correlated with the evaluation of intensity but not valence. (**b**) A bilateral subcallosal gyrus activation extending into the posteromedial orbitofrontal cortex was correlated with the evaluation of pleasantness but not intensity. (**c**) Left anterior lateral and right anterior medial orbital cortical activations were correlated with the evaluation of unpleasantness but not intensity.

the pleasant-smelling citral induced strong and equal responses ($F_{1,285} = 0.39$, $P > 0.53$), whereas smaller and equal responses ($F_{1,285} = 1.38$, $P > 0.24$) were induced by high and low concentrations of the unpleasant smelling valeric. Critically, this preferential response to pleasant over unpleasant odorants remained when odors were equated for intensity— citral-low induced a greater response than did valeric-low ($F_{1,285} = 7.35$, $P < 0.008$). When data were collapsed across the interval of peak hemodynamic response (4–10 s from sniff onset), an even greater response was present for lower-intensity pleasant stimulation relative to higher intensity unpleasant stimulation ($F_{1,285} = 23.07$, $P < 0.0001$). Activation in the left lateral orbitofrontal cortex showed greater responsiveness to unpleasant than pleasant odors (**Fig. 4b**). This region showed some interaction between intensity and valence, responding more to high-intensity valeric than to high and low citral ($F_{1,285} = 6.98$, $P < 0.009$).

### Correlations with subjective intensity and valence

If the amygdala and the orbitofrontal cortices support the affective dimensions of intensity and valence, respectively, then we would expect activation in those regions to be associated with individual differences in subjective intensity and valence evaluations of odorants. We next functionally defined regions of interest (fROI) by their correlation with participants' judgments of odor intensity and pleasantness. Activation correlated with the intensity judgments in a region extending from the right dorsal amygdala into the piriform cortex (**Fig. 5a**; 46 voxels of maximum height at 16,– 8,–10 ($x$, $y$, $z$ in Talairach coordinates); $F_{1,15} = 20.34$, $P < 0.0005$). Consistent with its association with intensity and not valence, signal from this extended amygdala fROI was significantly correlated with odor intensity ratings ($r = 0.51$, $F_{1,78} = 27.72$, $P < 0.0001$), but not with ratings of odor pleasantness ($r = –0.04$, $F_{1,78} = 0.98$, $P > 0.75$). Activation correlated with pleasantness judgments in the bilateral subcallosal gyrus extending into the right posteromedial orbitofrontal cortex (**Fig. 5b**, 43 voxels; 12,17,–18; $F_{1,15} = 21.43$, $P < 0.0005$). Consistent with its association with pleasantness and not intensity, signal from this fROI was significantly correlated with odor pleasantness ratings ($r = 0.42$, $F_{1,78} = 16.82$, $P < 0.0001$), but not intensity ratings ($r = 0.05$, $F_{1,78} = 0.18$, $P > 0.67$). Activation correlated with odor unpleasantness in the left anterior lateral (20 voxels; –18,51,–19, $F_{1,15} = 15.52$, $P < 0.002$) and right anterior medial (12 voxels; 8,65,–17; $F_{1,15} = 12.81$, $P < 0.003$) orbitofrontal gyri (**Fig. 5c**). Consistent with an association with unpleasantness and not intensity, signal from the lateral and anterior orbital fROI was significantly negatively correlated with odor pleasantness ratings ($r = –0.41$, $F_{1,78} = 15.74$, $P < 0.0002$), but not intensity ratings ($r = 0.01$, $F_{1,78} = 0.10$, $P > 0.99$). Thus, these results are in substantial accordance with the findings from the anatomical ROI analyses.

Brain responses to clean air may offer convergent evidence for the dissociation between intensity and valence coding because clean air represents the lowest point in an intensity scale (zero concentration), but it is the midpoint of an hedonic scale (neutral). If a brain region responds to intensity rather than pleasantness, then it should respond to all odors more than it does to clean air. If a brain region responds to pleasantness rather than intensity, then it should respond more to clean air than to unpleasant odors. Consistent with the intensity response profile of clean air, the dorsal amygdala fROI, which was correlated with intensity judgments, responded more to all odors than to clean air ($F_{1,285} = 545.24$, $P < 0.0001$). In contrast, consistent with the hedonic response profile of clean air, the subcallosal and posteromedial orbitofrontal fROI, which was correlated with pleasantness judgments, responded more to clean air than to high and low-intensity presentations of the unpleasant odorant valeric acid ($F_{1,285} = 28.84$, $P < 0.0001$). This occurred despite a sniff of clean air being judged as far less intense than that of valeric acid ($F_{1,15} = 74.62$, $P < 0.0001$). This deviation from a strict intensity-dependent response suggests this subcallosal region, which has been specifically tied to the susceptibility for depressive symptomatology[27], may represent the subjective experience of pleasure.

## Discussion

Although intensity and valence are often strongly associated in phenomenal experience[9,28], here we provide evidence for a fundamental segregation of their neural representations. This finding is consistent with psychological theories of the underlying structure of emotion, which suggest that emotional experience is the result of activation along independent dimensions of emotional intensity and valence[9,10,29]. Our results suggest the amygdala may represent an intensity dimension, and a constellation of discrete sectors of the orbitofrontal cortex may represent the hedonic dimensions of pleasantness and unpleasantness.

Because of the interactive nature of intensity and valence, it has been difficult to dissociate their neural representations generally, and determining the precise contributions of the amygdala to their coding has been particularly difficult. Previous functional neuroimaging studies have often used complex negative and/or positive visual scenes that differ significantly in perceptual and semantic content to probe amygdala responsiveness[7,30–32]. In such studies, negative scenes (a burn victim) are typically more intense and arousing than positive scenes (a baby). This asymmetry with respect to intensity and unpleasant valence is not restricted to empirical study, but may indeed be a reflection of a naturally occurring covariance in human hedonic responses to the environment[33].

Previous studies in nonhuman animals and humans have shown that the amygdala responds to both unpleasant and pleasant events. Electrophysiological studies have shown that the rat amygdala is important for acquiring both unpleasant and pleasant associations with once-neutral stimulus events[1,2,34]. Neuroimaging studies show that the human amygdala is responsive to both negative and positive sexually provocative scenes[7]. Such bivalent responses could, however, reflect two distinct possibilities: (i) the amygdala codes the valence of experience for both pleasant and unpleasant events or (ii) the amygdala codes the intensity of experience common to both negative and positive events, but not valence itself. Here we show that amygdala response was not altered when valence was manipulated and intensity was held constant. Critically, amygdala response was altered when intensity was manipulated and positive or negative valence held constant. The present findings thus demonstrate that the amygdala response is related specifically to the experiential dimension of intensity, and not the associated dimensions of positive and negative valence of olfactory experience.

This conception of amygdala response is consistent with non-olfactory mediated processing, such as how emotion influences episodic memory formation[8,35,36] and perceptual awareness[37], as well as the ability to appreciate the intensity of emotion expressed in faces and words[38]. The present study, however, focused on olfaction, and thus further studies are needed to examine its implication for other sensory modalities and cognitive processes. For example, there may be a fundamental difference between the mapping of emotional responses to neural events for odors and more semantically rich stimuli such as photographic scenes. One prominent difference is that for odors, increasing physical intensity is strongly associated with increasing intensity of subjective and autonomic emotional response[11], but this same relation does not hold for semantically mediated differences in emotional intensity (for example, the luminance of a complex scene). Furthermore, amygdala valence coding may occur at temporal parameters not addressable with fMRI.

Consistent with the sensory nature of odor intensity, in the olfactory system, initial intensity coding occurs at the levels of the olfactory epithelium and bulb[39] and has been implicated at primary olfactory cortex[40,41], which includes the amygdala[42]. In contrast, our findings suggest that higher-order hedonic differentiation occurs in secondary olfactory regions, which include the orbitofrontal cortices[42]. Thus, the present results suggest a major division of the neural representation of affective space into lower-order intensity and higher-order hedonic components.

Whereas hedonic responses are relatively preserved in patients with amygdala lesions[43], prefrontal damage often significantly impacts hedonic tone[14,44]. Recent studies highlight the critical role of the orbitofrontal regions of the prefrontal cortices in particular[14,45]. Such critical prefrontal contributions to hedonicity dovetail nicely with appraisal theories of human emotion, which emphasize that affective responses are not a simple reflection of the intrinsic quality (positive or negative) of a stimulus, but rather result from interactions among the person, the situational context and the stimulus[46]. Such flexibility of hedonic response is a hallmark of orbitofrontal representations, which are modulated by changes in affective relevance, as in the hungry versus sated state of the perceiver[18]. Thus, unlike the evolutionarily conserved functions of the amygdala, it seems that the malleability of human hedonic experience is characteristic of the more flexible, integrative and evolved functions of the prefrontal cortices.

## Methods

**Subjects.** Participants were eight women and eight men (mean age 21.85 ± 2.63 years). They were all right-handed healthy volunteers that gave informed consent to procedures that were approved by the UC Berkeley and Stanford committees on protection of human subjects. Although not addressed in the present study, gender effects will be important to examine, and they will be presented in a separate article.

**Odor administration and task design.** We used a procedure as previously described in imaging studies of olfaction[19,20]. Odors were delivered in the scanner using an air dilution olfactometer that enabled alternation between odorant and no-odorant conditions every 260 ms and eliminated non-olfactory cues at the time of odorant alternations. The four odorant stimuli and a clean air stimulus were each delivered 30 times in pseudo-random order that controlled for trial history. During the scan, participants were breathing through their mouths only. Every 20 s, participants were instructed (via a projected message) to take one sniff for the duration of the message (1.66 s) and then to indicate if an odorant was present or not by pressing one of two buttons. An in-line pneumatota-

chograph measured nasal flow during the scan to ensure that participants were accurately following instructions. We chose a detection over an intensity/valence estimation task to minimize top-down cognitive processing related to task expectation. Specifically, it has been shown that just the action of odor valence estimation, regardless of odor content, induces a specific pattern of brain activation[47]. To obtain individual intensity/valence estimations, the task was repeated after the scan while the participant was still in the scanner, substituting the detection task with an intensity estimation task: rate from 1 (lowest intensity) to 9 (highest intensity) and valence from 1 (very unpleasant) to 9 (very pleasant). To address the possibility that intensity and valence estimations may have habituated over time[48], we replicated the entire study design on ten additional participants that performed intensity and valence estimations throughout the full duration (50 min without collecting MR data). There was no habituation in intensity ($F_{3,27} < 1$) or valence ($F_{3,27} < 1$) estimates for each of the odorants relative to clean air using this temporal design.

**Odorant selection.** The odorants citral and valeric acid (≥99% purity) were selected through several detailed psychophysical pre-studies conducted on other participants. Although we would have preferred to use pure olfactants for this study, such odorants could not serve to construct the 'ideal' odor space (**Fig. 1a**). The two known pure olfactants vanillin and decanoic acid are not perceived as either intense or unpleasant even when generated as a saturated vapor.

**fMRI data acquisition and analysis.** MR data was obtained with a 3T GE Signa scanner (Waukesha, Wisconsin) using a T2* sensitive spiral sequence (TE = 30, TR = 1 s, 64 × 64 matrix size, 220 FOV, inplane resolution = 3.43 mm, 17 slices, slice thickness = 4 mm). Three factors contributed to signal preservation within the ventral temporal susceptibility regions: spiral sampling of K-space, oblique slice orientation that avoided data acquisition from the air-filled cavities ventral to the ROI (thus minimizing partial voluming) and restricted slice prescription, which allowed greater spatial and temporal sampling from ROIs. Motion correction and minimal spatial smoothing (FWHM = 5 mm) were conducted using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Normalization was later performed only for definition of functional ROIs.

**Anatomical ROIs.** ROIs were defined in each subject's native brain space by a combination of structural and functional features. Structural definition of three broad amygdala subdivisions (lateral, basolateral and basomedial) was determined according to a detailed atlas[24]. Because the actual borders of these subdivisions are not apparent in an MR image, the predicted ratios of these three subdivisions as they occupy the space between the tip of the lateral ventricle and the medioventral border of the brain (semiannular sulcus) (**Fig. 2h**) were overlaid in each subject. Considering the expected individual variation in these structures, these subdivision ROIs should be considered as approximations. Orbitofrontal ROIs were drawn according to standard landmarks (as detailed in ref. 20). Here too, however, the gyral and sulcal landmarks do not fully correspond with underlying cytoarchitecture, and there may be some overlap at the borders of the individual orbitofrontal gyri. ROIs were constrained to voxels that were responsive to odor stimulation with a liberal threshold ($P < 0.5$). Percent signal change was extracted from each ROI first by linear de-trending and low and high pass filtering the raw data, and then by computing deviation from the mean for each voxel across the entire time series. Three-thousand frames (600 per condition) were collected across six scans. Averaging over the 30 repetitions for each trial type, values for each condition by frame relative to no odor were submitted for statistical analysis. The peak responses for each condition, defined by the peristimulus latency between 4–10 s where the group average was maximal, were selected for focused comparisons.

**Functional ROIs.** fROIs were defined by a random effects analysis of activations associated with individual subjects ratings of the intensity and pleasantness across the 16 participants (uncorrected height threshold of $P < 0.005$ and an extent threshold of five contiguous voxels). The resultant intensity, pleasantness and unpleasantness maps were then re-smoothed (FWHM = 6 mm). fROIs defined at the group level were then reverse-normalized and projected back into unnormalized individual brain space. For the purposes of examining the relation of intensity and valence dimensions, the peak of the fit of the canonical hemodynamic response function for each of the four odor conditions, including clean air, were extracted from the fROIs from each individual and submitted to correlational analyses. Separate correlations were then computed for the intensity and valence estimates.

## Acknowledgments

*This work was supported by grants from the Sense of Smell Institute (SOSI), NIH-NIDCD, the Searle Fellowship, an Army MURI, NIMH (MH12829-01) and the McDonnell-Pew Program in Cognitive Neuroscience (20002024). We thank Arak Elite.*

## Competing interests statement

*The authors declare that they have no competing financial interests.*

RECEIVED 10 NOVEMBER; ACCEPTED 23 DECEMBER 2002

1. LeDoux, J.E. Emotion: clues from the brain. *Annu. Rev. Psychol.* **46**, 209–235 (1995).
2. Davis, M. The role of the amygdala in fear and anxiety. *Annu. Rev. Neurosci.* **15**, 353–375 (1992).
3. Royet, J.P. *et al.* Emotional responses to pleasant and unpleasant olfactory, visual, and auditory stimuli: a positron emission tomography study. *J. Neurosci.* **20**, 7752–7759 (2000).
4. Zald, D.H. & Pardo, J.V. Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimulation. *Proc. Natl. Acad. Sci. USA* **94**, 4119–4124 (1997).
5. Morris, J.S. *et al.* A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature* **383**, 812–815 (1996).
6. Breiter, H.C. *et al.* Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* **17**, 875–887 (1996).
7. Hamann, S.B., Ely, T.D., Hoffman, J.M. & Kilts, C.D. Ecstasy and agony: activation of the human amygdala in positive and negative emotion. *Psychol. Sci.* **13**, 135–141 (2002).
8. Hamann, S.B., Ely, T.D., Grafton, S.T. & Kilts, C.D. Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat. Neurosci.* **2**, 289–293 (1999).
9. Lang, P.J., Greenwald, M.K., Bradley, M.M. & Hamm, A.O. Looking at pictures: affective, facial, visceral and behavioral reactions. *Psychophysiology* **30**, 261–273 (1993).
10. Russell, J.A. A circumplex model of affect. *J. Personal. Social Psychol.* 1161–1178 (1980).
11. Bensafi, M. *et al.* Autonomic nervous system responses to odors: the role of pleasantness and arousal. *Chem. Senses* **27**, 703–709 (2002).
12. Doty, R.L. An examination of relationships between the pleasantness, intensity and concentration of 10 odorous stimuli. *Percept. Psychophysiol.* 492–496 (1975).
13. Moskowitz, H.R., Dravnieks, A. & Klarman, L.A. Odor intensity and pleasantness for a diverse set of odorants. *Percept. Psychophysiol.* 122–128 (1976).
14. Davidson, R.J. & Irwin, W. The functional neuroanatomy of emotion and affective style. *Trends Cogn. Sci.* **3**, 11–21 (1999).
15. Price, J.L. Prefrontal cortical networks related to visceral function and mood. *Ann. NY Acad. Sci.* **877**, 383–396 (1999).
16. Zald, D.H., Donndelinger, M.J. & Pardo, J.V. Elucidating dynamic brain interactions with across-subjects correlational analyses of positron emission tomographic data: the functional connectivity of the amygdala and orbitofrontal cortex during olfactory tasks. *J. Cereb. Blood Flow Metab.* **18**, 896–905 (1998).
17. Rolls, E.T. The rules of formation of the olfactory representations found in the orbitofrontal cortex olfactory areas in primates. *Chem. Senses* **26**, 595–604 (2001).
18. O'Doherty, J. *et al.* Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. *Neuroreport* **11**, 893–897 (2000).
19. Sobel, N. *et al.* Sniffing and smelling: separate subsystems in the human olfactory cortex. *Nature* **392**, 282–286 (1998).
20. Sobel, N. *et al.* Time course of odorant-induced activation in the human primary olfactory cortex. *J. Neurophysiol.* **83**, 537–551 (2000).
21. Jones-Gotman, M. *et al.* Contribution of medial versus lateral temporal-lobe structures to human odour identification. *Brain* **120**, 1845–1856 (1997).
22. Dravnieks, A. *Atlas of Odor Character Profiles* (ASTM Press, Pennsylvania, 1985).
23. Zou, Z., Horowitz, L.F., Montmayeur, J.P., Snapper, S. & Buck, L.B. Genetic tracing reveals a stereotyped sensory map in the olfactory cortex. *Nature* **414**, 173–179 (2001).
24. Sakamoto, N. *et al.* The human basal forebrain. Part I. An overview, mini-atlas. in *Handbook of Chemical Neuroanatomy, The Primate Nervous System*

Part III Vol. 15 (eds. Bloom, F., Bjorklund, A. & Hokfelt, T.) 15–56 (Elsevier, Amsterdam, 1999).
25. Zatorre, R.J., Jones-Gotman, M., Evans, A.C. & Meyer, E. Functional localization and lateralization of human olfactory cortex. *Nature* **360**, 339–340 (1992).
26. Savic, I., Gulyas, B., Larsson, M. & Roland, P. Olfactory functions are mediated by parallel and hierarchical processing. *Neuron* **26**, 735–745 (2001).
27. Drevets, W.C. *et al.* Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* **386**, 824–827 (1997).
28. Henion, K.E. Odor pleasantness and intensity: a single dimension? *J. Exp. Psychol.* **90**, 275–279 (1971).
29. Barrett, L.F. & Russell, J.A. The structure of current affect: controversies and emerging consensus. *Curr. Directions Psychol. Sci.* **8**, 10–14 (1999).
30. Irwin, W. *et al.* Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *Neuroreport* **7**, 1765–1769 (1996).
31. Canli, T., Desmond, J.E., Zhao, Z., Glover, G. & Gabrieli, J.D. Hemispheric asymmetry for emotional stimuli detected with fMRI. *Neuroreport* **9**, 3233–3239 (1998).
32. Lane, R.D. *et al.* Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia* **35**, 1437–1444 (1997).
33. Carretie, L., Mercado, F., Tapia, M. & Hinojosa, J.A. Emotion, attention and the 'negativity bias', studied through event-related potentials. *Int. J. Psychophysiol.* **41**, 75–85 (2001).
34. Gallagher, M. The amygdala and associative learning. in *The Amygdala: a Functional Analysis* (ed. Aggleton, J.P.) 311–330 (Oxford Univ. Press, New York, 2000).
35. LaBar, K.S. & Phelps, E.A. Arousal-mediated memory consolidation: role of the medial temporal lobe in humans. *Psychol. Sci.* **9**, 490–493 (1998).
36. Cahill, L. & McGaugh, J.L. Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci.* **21**, 294–299 (1998).
37. Anderson, A.K. & Phelps, E.A. Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature* **411**, 305–309 (2001).
38. Adolphs, R., Russell, J.A. & Tranel, D. A role for the human amygdala in recognizing emotional arousal from unpleasant stimuli. *Psychol. Sci.* **10**, 167–171 (1999).
39. Duchamp-Viret, P., Duchamp, A. & Chaput, M.A. Peripheral odor coding in the rat and frog: quality and intensity specification. *J. Neurosci.* **20**, 2383–2390 (2000).
40. Pause, B.M., Sojka, B. & Ferstl, R. Central processing of odor concentration is a temporal phenomenon as revealed by chemosensory event-related potentials (CSERP). *Chem. Senses* **22**, 9–26 (1997).
41. Wilson, D.A. Binaral interactions in the rat piriform cortex. *J. Neurophysiol.* **78**, 160–169 (1997).
42. Price, J.L. Olfactory system. *in The Human Nervous System* (ed. Paxinos, G.) 979–1001 (Academic, San Diego, 1990).
43. Anderson, A.K. & Phelps, E.A. Is the human amygdala critical for the subjective experience of emotion? Evidence of intact dispositional affect in patients with amygdala lesions. *J. Cogn. Neurosci.* **14**, 709–720 (2002).
44. Robinson, R.G., Kubos, K.L., Starr, L.B., Rao, K. & Price, T.R. Mood disorders in stroke patients. Importance of location of lesion. *Brain* **107**, 81–93 (1984).
45. Bechara, A., Damasio, A.R., Damasio, H. & Anderson, S.W. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* **50**, 7–15 (1994).
46. Lazarus, R.J. *Emotion & Adaptation* (Oxford Univ. Press, New York, 1991).
47. Zatorre, R.J., Jones-Gotman, M. & Rouby, C. Neural mechanisms involved in odor pleasantness and intensity judgments. *Neuroreport* **11**, 2711–2716 (2000).
48. Cain, W.S. & Johnson, F. Jr. Lability of odor pleasantness: influence of mere exposure. *Perception* **7**, 459–465 (1978).