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Neural Responses to Facial Expression and Face Identity in the Monkey Amygdala

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[1]*Department of Physiology, College of Medicine, The University of Arizona, Tucson, Arizona;* [2]*Graduate School of Neurosciences Amsterdam, Faculty of Science, Swammerdam Institute for Life Sciences, Center for Neuroscience, University of Amsterdam, Amsterdam, The Netherlands;* [3]*Helen Wills Neuroscience Institute, University of California–Berkeley, Berkeley; and* [4]*Department of Psychiatry and Behavioral Sciences, The California National Primate Research Center and The Music Intelligence Neural Development Institute, University of California–Davis, Sacramento, California*

Gothard KM, Battaglia FP, Erickson CA, Spitler KM, Amaral DG. Neural responses to facial expression and face identity in the monkey amygdala. *J Neurophysiol* 97: 1671–1683, 2007. First published November 8, 2006; doi:10.1152/jn.00714.2006. The amygdala is purported to play an important role in face processing, yet the specificity of its activation to face stimuli and the relative contribution of identity and expression to its activation are unknown. In the current study, neural activity in the amygdala was recorded as monkeys passively viewed images of monkey faces, human faces, and objects on a computer monitor. Comparable proportions of neurons responded selectively to images from each category. Neural responses to monkey faces were further examined to determine whether face identity or facial expression drove the face-selective responses. The majority of these neurons (64%) responded both to identity and facial expression, suggesting that these parameters are processed jointly in the amygdala. Large fractions of neurons, however, showed pure identity-selective or expression-selective responses. Neurons were selective for a particular facial expression by either increasing or decreasing their firing rate compared with the firing rates elicited by the other expressions. Responses to appeasing faces were often marked by significant decreases of firing rates, whereas responses to threatening faces were strongly associated with increased firing rate. Thus global activation in the amygdala might be larger to threatening faces than to neutral or appeasing faces.

INTRODUCTION

Facial expressions form an essential part of the social and emotional communication repertoire of primates and are processed by a distributed neural network in which the amygdala plays an important role (for a review see Adolphs 2002; Parr et al. 2005). Patients with amygdala damage lose their ability to recognize certain facial expressions (Adolphs et al. 1994) and show poor social judgment (Adolphs et al. 1995; Winston et al. 2002). Likewise, monkeys with amygdala lesions demonstrate abnormal emotional behavior and respond inappropriately to signals exchanged during social interactions (e.g., Aggleton 1993; Brown and Schäfer 1888; Dicks et al. 1968; Emery et al. 2001; Kling and Brothers 1992; Kling and Steklis 1976; Kling et al. 1970; Klüver and Bucy 1939; Prather et al. 2001; Roswold et al. 1954; Thompson 1977). The impairments of social behavior observed in these monkeys might be caused either by a failure to recognize facial expressions or by a failure to recognize the identity and rank of the individuals encountered.

Further support for the role of the amygdala in face processing is provided by neuroimaging studies that demonstrate reliable activation of the amygdala in response to passive viewing of faces in both humans (Breiter et al. 1996; Morris et al. 1996, 1998; Sato et al. 2004; Vuilleumier et al. 2002; Whalen et al. 1998; Wright and Liu 2006) and in monkeys (Logothetis et al. 1999; KL Hoffman, unpublished data). A larger activation of the human amygdala to fearful and angry faces than to neutral or happy faces (for a review see Zald 2003) together with the observation that negative facial affect is the least discernible expression for patients with amygdala damage (Adolphs et al. 1994; Sprengelmeyer et al. 1999; but see Rapcsak 2003) led to the proposal that the amygdala is preferentially involved in processing negative facial expressions and fear-related stimuli in general.

Face selectivity and the proposed processing bias in the amygdala were previously assessed at a neuronal level in both humans (Fried et al. 1997, 2002) and monkeys (Leonard et al. 1985; Nakamura et al. 1992; Sanghera et al. 1979; Wilson and Rolls 1993). Thus far, single-neuron recordings have not confirmed a bias in favor of threatening faces or in favor of aversive stimuli in general (Fuster and Uyeda 1971; Nakamura et al. 1992; Nishijo et al. 1988a,b; Ono et al. 1983; Sanghera et al. 1979). Furthermore, it is unclear whether the face-selective neurons in the monkey amygdala respond to face identity, facial expression, or some other dimension of faces, such as direction of gaze, age, sex, or perceived status of the monkey in the stimulus image.

Neural signals that may contribute to face selectivity in the amygdala originate in multiple areas of the temporal cortex where face-responsive neurons have been found (Bruce et al. 1981; Desimone 1991; Desimone et al. 1984; Gross et al. 1972; Hasselmo et al. 1989; Perrett et al. 1982, 1984; Tsao et al. 2003, 2005; Wang et al. 1996). Neurons in the superior temporal sulcus (STS) and in the polysensory area dorsal to area TE respond mainly to facial expressions and to direction of gaze (Hasselmo et al. 1989; Perrett et al. 1985), whereas neurons in the inferior temporal gyrus are more likely to respond to face identity (Eifuku et al. 2004; Rolls and Tovee 1995a,b; Sugase et al. 1999; Young and Yamane 1992). The

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anatomical convergence of inputs from the STS and TE in the amygdala leads to the hypothesis that these inputs may be further processed in the amygdala, leading to the selection of social responses based on a combination of identity and facial expression.

The present study had two major objectives: *1*) to determine the specificity of neural responses to faces in monkey amygdala, i.e., to investigate whether faces and other complex objects are processed by distinct groups of neurons with stimulus-specific or category-specific responses; and *2*) to determine whether face identity and facial expression are encoded independently or jointly in the firing properties of the face-responsive neurons. The first objective was addressed by recording neural responses to large image sets that contained monkey faces, human faces, and objects. For the second objective, which required independent assessment of the contribution of face identity and facial expression; appeasing, neutral, and aggressive facial expressions from each stimulus monkey were shown to the experimental animals (Gothard et al. 2004). These stimuli allowed a distinction between neurons in the monkey amygdala that respond to *1*) facial expressions regardless of identity, *2*) face identity regardless of expression, or *3*) specific combinations of expression and face identity.

METHODS

Surgical procedures

All surgical procedures were carried out in compliance with National Institutes of Health guidelines and were approved by the IACUC at the University of Arizona. Two adult male rhesus monkeys (*Macaca mulatta*) (monkeys S and H) were surgically prepared for multielectrode recordings from the amygdala using a two-step surgical procedure. For both surgical procedures the monkeys were preanesthetized with ketamine (10–15 mg/kg), administered intramuscularly, and brought to surgical levels of anesthesia with isoflurane (1–1.5%) supplemented with fentanyl (7–10 $\mu g \cdot kg^{-1} \cdot h^{-1}$). During the first procedure, monkeys were implanted with three titanium tripod plates, custom-manufactured by Thomas Recording (Giessen, Germany). Each tripod plate had an elevated center with a threaded screw hole and three flat radial support arms emerging at 120° intervals. The three support arms were 10 mm long, 2 mm wide, and were perforated at the end to accommodate a 2-mm-diameter bone screw. The arms were bent to match the curvature of the skull and affixed to the bone with screws. Two plates were affixed posteriorly, 15 mm lateral from midline and approximately 20 mm posterior from the interaural line. The third plate was affixed straddling the midline 2 cm anterior to the interaural line. The temporalis muscle and the scalp were closed over the plates and the bone was allowed to heal and grow around the plates (about 4–12 mo). Once substantial bone growth had occurred around the screws and the arms of the plates (verified by CT scan), the second procedure was undertaken in which the scalp above the plates was perforated and small threaded head posts (3-mm-diameter shaft, 15-mm length, 5-mm-diameter spherical head) were screwed into the center of each of the tripod plates. The posts served as anchors for a removable stainless steel ring that was secured in a rigid frame during experiments. Such an arrangement distributed the torque generated by head immobilization across the three head posts.

During the second surgical procedure, a recording chamber was secured with bone screws and bone cement to the skull above the amygdala. The chamber was placed at stereotaxic coordinates calculated from a structural MRI carried out before surgery. Magnetic search coils were also implanted in the left eye of one of monkey (S) following standard procedures (Judge et al. 1980; Robinson 1963). After a 10-day recovery period, monkeys were trained to tolerate head immobilization and to fixate on objects presented on a computer monitor. When behavioral training was complete, a 6- to 8-mm-diameter craniotomy was performed within the chamber.

Behavioral training

The monkeys were trained to fixate on a white square that subtended 0.5 degree of visual angle (dva). The eye movements of monkey S were tracked with a resolution of 0.25 dva and were digitized at 500 Hz using an analog eye tracker (DNI, Newark, DE). Eye movements of monkey H were monitored with the infrared eye tracker (Iscan, Burlington, MA) with a resolution of 0.5 dva. Both eye trackers were connected to the CORTEX experimental control system (NIMH-supported freeware from the website: http://www.cortex. salk.edu). When the eyes were fixated for ≥150 ms at the white square, the fixation icon was removed from the monitor and a stimulus image, subtending 12 dva, was displayed. The monkeys were allowed to freely scan the image, with the requirement to maintain gaze within the boundaries of the image. If this requirement was met for the entire duration of the display (500 ms or 1 s) the monkeys received a 0.5- to 1-ml reward droplet. The reward consisted of a paste of mashed granola, rice cereal, and fruit juice or simple fruit juice mixed with applesauce. To disambiguate the effect of the reward from the effect of the stimuli, monkeys received a reward on only 50% of the trials, so that each image was followed an equal number of times by reward or no reward. The duration of the intertrial interval (ITI) was 1 s. When the monkey's eyes moved outside the boundary of the image, the trial was terminated by removing the image from the monitor. Error trials were not rewarded and were followed by a 2-s time-out period. Error trials were excluded from the analysis. To prevent habituation and blunting of the emotional response to face stimuli, the sets of images used for training or used during the period when we searched for neurons in the amygdala did not contain monkey faces or images intended for presentation during neurophysiological recordings.

Stimulus sets

The stimuli were digitized images that subtended 12 × 12° of visual angle and fell into the following categories: *1*) monkey faces, *2*) human faces, and *3*) objects/abstract images. Images of 25 unfamiliar monkeys were selected from an extended library of digitized monkey faces (Gothard et al. 2004). Each monkey was depicted with three facial expressions: an affiliative expression (lipsmack), a neutral expression, and an aggressive expression (open-mouth threat) (Fig. 2). A *lipsmack* is an appeasing expression used by monkeys during a friendly approach, preceding grooming, or as part of a complex of gestures used to beg for food or grooming from other monkeys or from caretakers (Hinde and Rowell 1962; van Hoof 1962). The open-mouth threat is a typical aggressive facial expression. High-ranking monkeys use this expression to threaten lower-ranking individuals, which, in response, display submission or retreat from the threatening monkey (Chevalier-Skolnikoff 1973; Hinde and Rowel 1962; Redican 1975).

Human faces were selected from images of individuals familiar to the subject monkey (caretakers, researchers, veterinary technicians) photographed in their usual attire, often wearing protective masks and goggles (Fig. 2).

The images of objects were of two general types: pictures of objects familiar to the monkeys (laboratory equipment, fruits, food items, toys, and objects used for behavioral enrichment) and pictures of objects unfamiliar to the monkeys (abstract images, pictures of animals, nature scenes, and man-made objects (Fig. 2).

These three classes of images were assembled in different proportions into eight stimulus sets. Six of the eight stimulus sets contained 15 images of monkey faces, five images of human faces, five images of familiar objects, and five images of abstract or unfamiliar objects, totaling 30 images (Fig. 2). The 15 monkey face images depicted five monkeys with a lipsmack, a neutral face, and a threatening face each. In the other two stimulus sets, the ratio of monkey faces, human faces, and objects remained the same (3:1:2, respectively) but the number of images was either eight monkeys or ten monkeys with three expressions each. Each stimulus set contained different monkeys, humans, and objects, with the exception of three humans that appeared in more than one set but in a different photograph (e.g., with or without masks and safety goggles).

Electrodes and electrode delivery system

A custom-built, seven-channel Eckhorn drive, manufactured by Thomas Recording, was used to deliver seven electrodes (80- to 100-μm diameter, tungsten/platinum core, quartz glass coated) to a depth 25–35 mm below the surface of the brain. The drive contains seven precision motors that tense or relax a rubber tube attached to the back of the electrode, advancing or withdrawing the electrode in 1- to 3-μm increments (Eckhorn and Thomas 1993; Mountcastle et al. 1991). The electrodes were delivered into the brain by 30-gauge stainless steel sharp cannulae that penetrate the dura and were advanced into the brain 5 mm. The target coordinates of the amygdaloid nuclei were calculated for each monkey using an MRI-based method developed by Saunders et al. (1990), Rebert et al. (1991), and Zola-Morgan et al. (1991) and adapted to the amygdala by Amaral and colleagues (1992). The electrodes were connected to a headstage amplifier (gain = 20), built into the drive, and from there the signals were directed to a Lynx-8 (Neuralynx, Tucson, AZ) amplifier (gain of 2,000, band-pass 0.6 to 6 kHz). Neural data were digitized at 30 kHz, recorded continuously using a Power 1401 data-acquisition system [Cambridge Electronics Design (CED), Cambridge, UK], and stored on a disk for off-line spike sorting.

Neural recordings

At the beginning of a recording session, the electrode drive was placed in the recording chamber and aimed primarily at the lateral and basal nuclei of the amygdala. For the vast majority of recordings the electrode array was positioned to reach the dorsal and lateral aspects of the amygdala, the target of projections from and to cortical visual areas (Amaral and Price 1984; Amaral et al. 1992), particularly the rostral half of the amygdala where the lateral and basal nuclei are bordered superiorly by the anterior amygdaloid area (AAA) and the substantia innominata (SI); only a few recordings were made from the caudal half of the amygdala where the lateral and basal nuclei lie ventral to the central nucleus. The sharpened cannulae containing the electrodes were advanced through the dura 5 mm into the brain. The electrodes were then advanced at a speed of 30–100 μm/s to a depth associated with the stereotaxic coordinates of the dorsal border of the amygdala. When the electrodes reached the dorsal border of the amygdala, background activity was modulated by the onset and offset of images. The electrodes continued to be advanced in small increments until neural signals with a high signal/noise were observed. Some neurons appeared to be responsive to the fixation icon or images displayed during electrode advancement, although this was not a selection criterion. When the majority of the electrodes registered well-isolated and stable spikes, one of the stimulus sets was displayed and the test stimuli were delivered in repeated blocks that contained the entire sets of images. The recording session continued until the monkey looked 10 to 20 times at each image in a stimulus set.

We used a template-matching algorithm for off-line spike sorting (Spike2, CED). Only well-isolated neurons that could be monitored for at least five presentations of each image in the stimulus set were included in the analysis.

Histological analyses were performed for monkey S. After euthanasia, the calvarium was opened and the head was submerged in 4% phosphate-buffered (pH 7.2) formaldehyde. The block containing the amygdala was sectioned in the coronal plane at 40-μm thickness and two systematic series through the amygdala were mounted on microscopic slides and stained either with the Nissl method to define nuclear boundaries or with the Pearl technique to identify the location of the electrode track.

Monkey H is currently involved in other studies, thus precluding histological confirmation of the electrode tracks. The reconstruction of intraamygdala recording sites based on histological and MRI analysis is shown in Fig. 1.

Data analysis

Analyses were carried out with custom-designed programs in MATLAB (The MathWorks, Natick, MA). Only trials in which the monkey maintained its gaze within the boundary of the stimulus images for the required time were included in the analysis. For each image presentation, two time intervals were considered: a *baseline* interval, 1 s immediately before the onset of the fixation icon, and a *response* interval, beginning 100 ms after stimulus-image onset and ending when the image was removed from the display. Images from the six stimulus sets that contained 30 stimuli were displayed for 500 ms, whereas images from the other two stimulus sets were displayed for 1,000 ms. The onset of the response interval was chosen to exclude nonimage-specific responses to the fixation spot. The numbers of spikes generated by the cell during the response interval, normalized by interval duration, were computed to characterize the response of each cell for each image presentation.

Category selectivity was assessed with one-way ANOVAs with three levels: "Monkey," "Human," and "Object." Significant results are reported based on $P < 0.05$ level, unless stated otherwise. Bonferroni–Dunn post hoc tests (also at $P < 0.05$) were used to determine which category of stimuli for which each cell was selective.

Identity and expression selectivity were assessed using two-way ANOVAs where the two factors were "Identity" (with five, eight, or ten levels depending on the number of monkeys in the stimulus set) and "Expression" (with three levels: Threat, Neutral, and Lipsmack). Selectivity is reported at the $P < 0.05$ level. The same Bonferroni–Dunn post hoc test was used to determine which of the three expressions for which the neuron was selective.

To determine whether the same three categories of stimuli (monkey faces, human faces, and objects) would emerge from the responses of small groups of neurons, a multidimensional scaling (MDS) procedure was applied to the neural data. For each image in a stimulus set, a vector was compiled, containing the normalized average firing rate of all the recorded neurons in response to an image. To avoid excessively weighting cells with high firing rates, the average firing rates were normalized. Cells that did not differentiate among stimuli or had an extremely low discharge rate (i.e., cells for which the SD of the average firing rates across stimuli was <0.3 Hz) were not included in the analysis. Nonmetric MDS (using the Kruskal stress criterion) was applied to the matrix of the Euclidean distances between the resulting population vectors for each stimulus. The first two components of the resulting scaling were retained, to create a two-dimensional representation of the stimulus space (Fig. 3B and Fig. 8D).

RESULTS

In all, 196 neurons were recorded from two monkeys (156 from monkey S and 40 from monkey H) performing a passive viewing task. Based on MRI analysis and stereotaxic electrode placement (see METHODS), we estimate that the recorded neu-
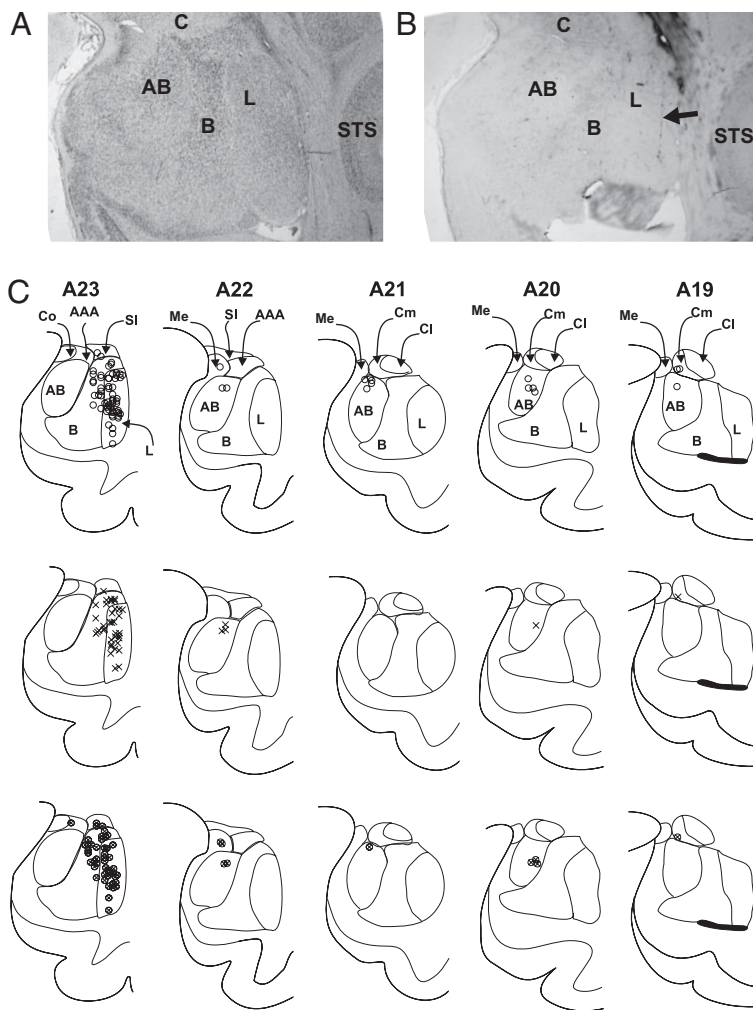
FIG. 1. Histological analysis and magnetic resonance imaging (MRI)–based reconstruction of the electrode tracks in the amygdala. *A*: Nissl-stained (40 μm) coronal section through the amygdala. *B*: adjacent section stained by the Pearl method to demonstrate small hemoglobin deposits associated with microinfarcts attributed to the electrode as it passed through the lateral nucleus of the amygdala (arrow). C, central nucleus; L, lateral nucleus; B, basal nucleus; AB, accessory basal nucleus; STS, superior temporal sulcus. *C*: recording sites for 3 main types of face-selective neurons in 5 consecutive 1-mm-thick sections through the amygdala. Numbers above each section correspond to the distance from the interaural line for each amygdala section. Recording sites for identity-selective neurons are indicated by open circles (*top row* of sections), for expression-selective neurons are indicated by × (*middle row*), and neurons that responded to combination of identity and facial expression indicated by ⊗. Cl, central nucleus lateral division; Cm, central nucleus medial division; Co, cortical nucleus; L, lateral nucleus; B, basal nucleus; AB, accessory basal nucleus; Me, median nucleus; SI, substantia innominata. Most of the neurons were recorded from section A23. No topography was observed for neurons with identity or expression selectivity.

rons were located in the lateral, basal, accessory basal, central, and medial nuclei of the amygdala as well as the anterior amygdaloid area/substantia innominata region overlying the amygdala. Electrode tracks in the amygdala were identified histologically for one monkey (monkey S; Fig. 1, *A* and *B*). Table 1 contains the number of neurons recorded from each nucleus, the ratio of neurons with various response properties in these nuclei, and the average firing rates in each nucleus (baseline firing rate and firing rate in response to the threatening, neutral, and appeasing facial expressions). No difference was found between the nuclei on any of these measures.

Response latency of all visually responsive neurons, regardless of recording site, generally varied between 110 and 140 ms. There were only seven neurons that responded with a latency of 70–100 ms to the fixation icon preceding the stimuli. Responses to the fixation icon were excluded from the analysis because they might be related to an orienting response rather than to the content of the stimulus images.

Category-selective responses

Neural firing rates during stimulus presentation (excluding the first 100 ms after stimulus onset) for three categories of images ("Monkey," "Human," "Object") were compared for each neuron using a one-way ANOVA. Of the 196 neurons, 102 (52%) showed a significant effect of category ($P < 0.05$) (chance level = 9.8 neurons, binomial sign test, z = 30.2, $P < 0.0001$).

A typical stimulus set and examples of category-selective neurons are shown in Fig. 2. The stimulus set (Fig. 2*A*) contained 15 monkey faces (three facial expressions for each of the five monkeys used in this image set), five human faces, and ten objects. Mean ($\pm$SE) firing rate responses to each of the stimuli in this set are shown for three category-selective neurons in Fig. 2, *B–D*. The neuron depicted in Fig. 2*B* discharged with significantly higher rates during the presentation of monkey faces, compared with the presentation of human faces or objects ($P < 0.0001$). This neuron showed particularly robust responses to threatening monkey faces. In contrast, the neuron in Fig. 2*C* responded with significantly higher rates for human faces than for monkeys faces or objects ($P < 0.0001$), whereas the neuron in Fig. 2*D* was selective for objects ($P < 0.0001$), particularly familiar objects (last five bars, Fig. 2*D*). These examples illustrate the remarkable selectivity of some neurons in the amygdala for broad categories of stimuli. A small subset of object-selective neurons (including the example neuron in
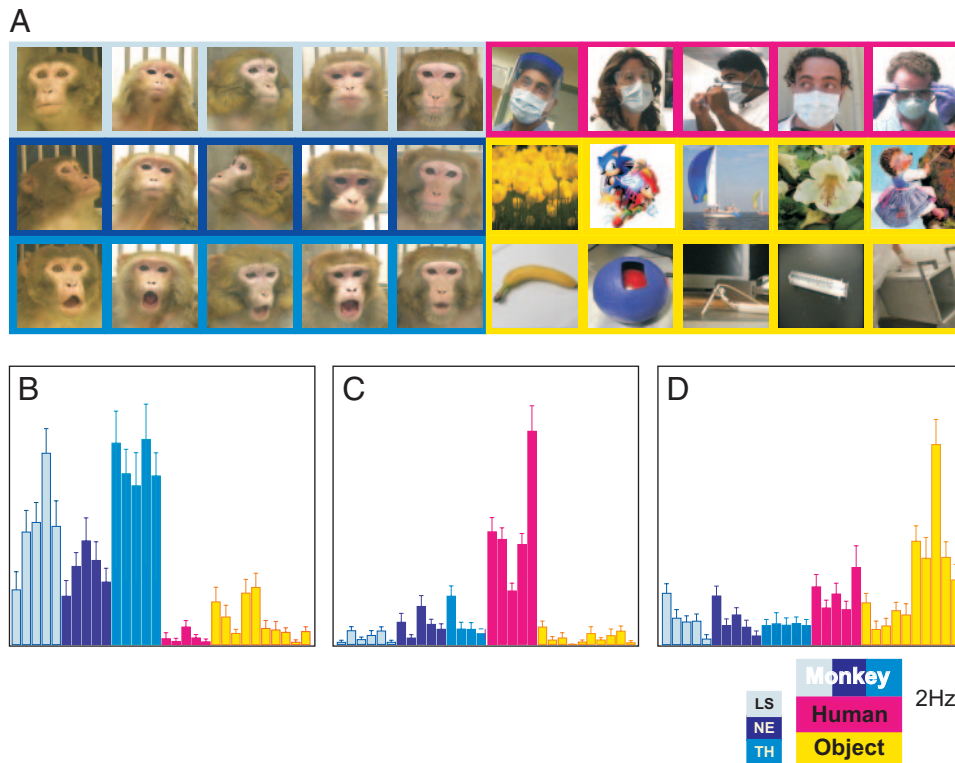
FIG. 2. Stimulus categories and category-selective neurons in the monkey amygdala. *A*: example of a typical stimulus set. Of the 30 images in this stimulus set, 15 images are monkey faces (blue frames, *left*) that show 5 monkeys with 3 facial expressions each: Lipsmack (*top row*, light blue frames), Neutral (*middle row*, navy blue frames), and Threat (*bottom row*); remaining 15 images (*right*) are 5 familiar human faces shown in attire familiar to the experimental monkeys (purple frames) and 10 images of objects, either unfamiliar (*middle row*), or familiar lab objects (*bottom row*). *B*, *C*, and *D*: histograms of the firing rates of 3 neurons from the lateral nucleus of the amygdala that respond to monkey faces (*B*), human faces (*C*), and objects (*D*). Bars represent means ± SE firing rate to each of 30 stimuli during a window of 1,000 ms after stimulus onset. Neuron depicted in *B* showed significantly (*P* < 0.001) elevated firing rates in response to monkey faces (blue bars, color code is the same as in *A*) compared with human faces and objects. Note that this neuron also shows differential responses for facial expressions (*P* = 0.001) with maximal response to threats. Neuron in *C* showed significantly elevated firing rates in response to human faces only (*P* < 0.001). Neuron in *D* showed significantly higher firing rates for objects (*P* < 0.001). Note that the response of this particular neuron is elevated for familiar objects used in the laboratory. Maximum response was made to the reward spout (*middle image, bottom row*).

Fig. 2*D*) appeared to respond differentially to familiar versus unfamiliar stimuli. The number of such neurons, however, was too small and their behavior too inconsistent to draw reliable statistical conclusions.

To determine which category was preferred by each neuron, a post hoc test was performed in which the average firing rate of a neuron for each category was compared with the firing rate for the other two categories combined (Bonferroni–Dunn post hoc test). In this test, a significant differential response to a category can be manifested as either an increase or decrease in firing rate relative to the combined firing rate for the other two categories. This test thus identified the neurons that *differentiated* among categories by responding either with higher or lower firing rates to images from a particular category. Monkey faces elicited differential responses from 83 neurons, human faces from 48 neurons, and objects from 76 neurons (Fig. 3*A*). Many of the 102 neurons differentiated between more than one category of image by increases or decreases of firing rate that were specific for each category. Thus a category-selective neuron could be listed as showing multiple differential responses (e.g., a monkey selective neuron might show increased firing rates for monkey faces compared with human faces and objects *and* decreased firing rate for objects compared with monkey and human faces). Of the 83 neurons selective for images in the "Monkey" category, 32 showed a higher firing rate and 51 showed a lower firing rate for monkey faces than for images from the other two categories. Human faces elicited category-selective responses from 48 neurons (31 with higher and 17 with lower firing rates for humans faces than for the other image categories). Finally, 76 neurons were selective for objects, of which 47 neurons had higher and 29 neurons had lower firing rates for objects than for the other categories of images. When all stimuli are taken together, there was no

significant bias in the overall population of amygdala neurons for responsiveness to any particular category [one-way repeated-measures ANOVA, $F_{(2,194)} = 0.9$, $P > 0.05$].

To determine whether the same three image categories would emerge from the analysis of population responses, an MDS analysis was carried out on all the neurons recorded with the same stimulus set. Figure 3*B* shows the relative distances between 30 images computed from the similarity of the discharge pattern of 22 neurons for each image. In this two-dimensional stimulus space, images of monkey faces are clustered and distributed separately from images of objects and from images of human faces, indicating that neural population activity in the amygdala is different for different categories but comparatively more similar for images within the same category. The larger distribution of distances in stimulus space between categories than within categories of images (Kolmogorov–Smirnov, $P < 0.0001$) is shown in Fig. 3*C*.

An example of a category-selective cell is shown in Fig. 4. This neuron responded weakly to images of monkey faces but showed a robust (60–70 Hz) response to all the objects in the stimulus set. The monkeys shown in Fig. 4 display an appeasing facial expression to illustrate that monkeys and object with positive valence (the banana and the reward spout) do not elicit similar firing rates. The firing rate variation across objects with positive or negative affective significance was smaller than the variation between the categories of faces versus objects.

Response selectivity for facial expression and monkey identity

In addition to the tests for category selectivity, each recorded neuron was further analyzed to determine response selectivity
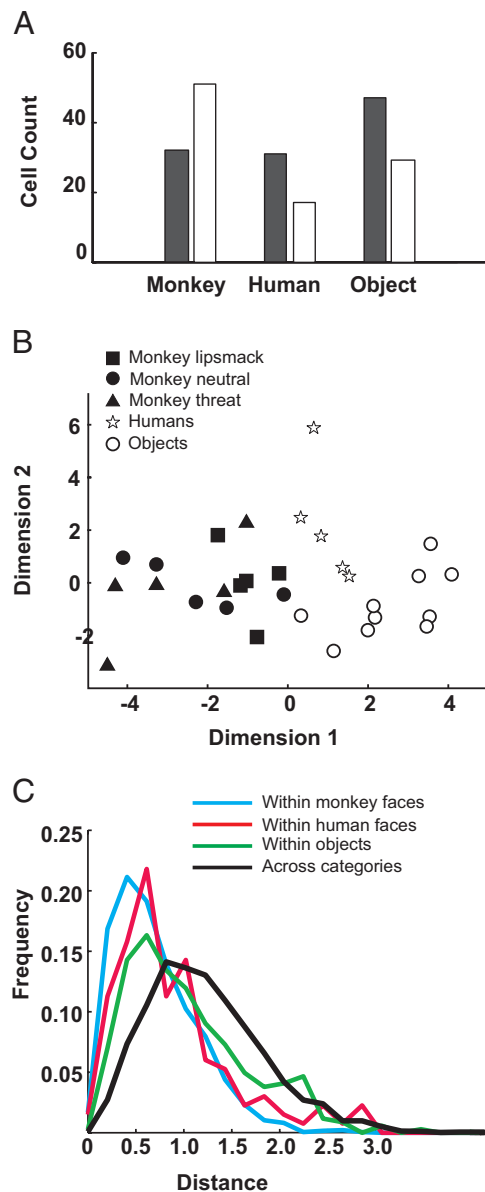
A

B

C

FIG. 3. Category-selective neurons in the monkey amygdala. *A*: distribution of category-selective ($P < 0.05$) cells that had a significantly increased (filled bars) or decreased (empty bars) firing rate for each of the 3 stimulus categories (2-tailed Bonferroni–Dunn post hoc tests; $P < 0.05$). *B*: stimulus space representation calculated by multidimensional scaling (MDS; Kruskal method) based on the firing rate of 22 neurons tested with a set of 30 images including monkey faces (5 monkeys with 3 facial expressions each), human faces, and objects. Clustering and the distances between images indicate the relative similarity in the firing pattern elicited by each image. *C*: frequency histogram of distances in the stimulus space for images between categories (black line) and images within categories (colored lines), from all the experimental sessions. Distances between images from different categories were significantly longer than distances between images from the same category (Kolmogorov–Smirnov $P < 0.0001$).

for monkey facial expression or monkey identity. Two-way ANOVAs were performed where the two factors were *facial expression* (levels: "Threat," "Neutral," "Lipsmack") and *monkey identity* (five, eight, or ten levels depending on the number of individual monkeys depicted in a stimulus set). About half of the neurons (95 of 196, or 48%) responded selectively ($P < 0.05$) to facial expression and or face identity. This number

slightly exceeds the number of cells that showed category selectivity for monkey faces because it includes neurons that responded to only a small fraction of the monkey faces and therefore did not reach significance when analyzed for category selectivity. For example, a neuron that responded with increased firing rate only to lipsmacks may not have been identified as category selective as a result of the modest firing rate for the other two expressions.

Eighty-one neurons (41% of the total) responded selectively to face identity. Only 39 of these responded to face identity regardless of facial expression; the remaining 42 neurons showed a significant interaction between face identity and facial expression. An example of an identity-selective neuron is shown in Fig. 5. This cell responded to all three facial expressions displayed by the first two monkeys (although with considerable difference in firing rate and duration of response) and did not respond to the faces of the other two monkeys. This identity-selective response was not modulated by facial expression [$F(7,562) = 2,487$, $P < 0.0001$].

Forty-eight neurons (24% of the recorded population) responded selectively to a facial expression ($P < 0.05$). Again, more than half of these (30 neurons) exhibited significant interactions between identity and expression. Figure 6 shows an example of a threat-selective neuron that responded exclusively to threatening faces but the firing rates for this neuron varied significantly across threats displayed by different individuals [$F(2,377) = 3,843$, $P < 0.0001$].

The third group of 14 neurons responded only to combinations of identity and facial expressions (i.e., had a significant effect only for the interaction in the ANOVA). In the example shown in Fig. 7, the cell did not respond reliably to identity or facial expression, but rather showed a significant increase in firing rate only to the lipsmack of the first two monkeys and the threat of the other two monkeys [$F(18,207) = 66.09$, $P < 0.0001$].

A significant interaction between facial expression and identity was observed either when neurons responded to particular conjunctions of identity and facial expression (as shown in Fig. 7) or when neural responses selective for one stimulus parameter (expression or identity) were modulated by the other parameter. The neuron shown in Fig. 6 is an example of threat-selective responses modulated by identity.

Overall, the number of responses that showed significant interactions exceeded the number of responses that showed a significant response only for identity or expression. These results are summarized in Fig. 8*A*. Furthermore, 34 neurons showed a significant main effect for both identity and expression (e.g., a neuron responded with higher firing rates to all three facial expression of monkeys 1 and 2 compared with monkeys 3, 4, and 5, but also showed expression selectivity by responding with higher firing rates to the threatening expressions of all five monkeys). Taken together, 64% of the recorded neurons responded to both expression and identity (half of which also showed significant interaction between these factors) indicating that face-selective neurons in the amygdala are more likely to respond to both identity and expression than to only one of these factors.

An additional post hoc analysis (two-tailed Bonferroni–Dunn test) was performed to determine which expression was the most likely to elicit significant changes in firing rates. Differential responses to facial expressions included both in-

TABLE 1. *Comparison of neural responses across the sampled amygdaloid nuclei*

Nc	Count	Category	ID	EXP	ID × EXP	TH	N	LS	TH f.r., Hz	N f.r., Hz	LS f.r., Hz	Baseline f.r., Hz
L	96	51 (53.1%)	42 (43.8%)	24 (25.0%)	25 (26.0%)	13	17	16	3.7 ± 5.4	3.4 ± 5.3	3.3 ± 5.1	2.5 ± 4.5
B	45	22 (48.9%)	16 (35.6%)	14 (31.1%)	18 (40.0%)	5	6	4	1.9 ± 2.7	1.8 ± 2.4	1.9 ± 2.7	1.4 ± 2.0
AB	25	12 (48.9%)	12 (48.0%)	5 (20.0%)	5 (20.0%)	4	3	3	2.9 ± 3.9	3.1 ± 4.4	3.0 ± 4.1	1.8 ± 1.8
C	9	5 (55.6%)	3 (33.3%)	1 (11.1%)	3 (33.3%)	0	0	0	2.0 ± 3.4	2.1 ± 3.6	1.9 ± 3.3	1.9 ± 3.2
M	6	2 (33.3%)	0	0	1 (16.9%)	0	0	1	2.7 ± 1.7	2.7 ± 1.8	3.0 ± 2.1	2.3 ± 1.9
AAA	15	9 (60.0%)	8 (53.3%)	4 (26.7%)	9 (60.0%)	5	1	2	7.2 ± 13.0	7.5 ± 14.1	7.8 ± 14.3	5.3 ± 10.9

Firing rate (f.r.) values are means ± SE. Nc, nucleus; L, lateral; B, basal; AB, accessory basal; C, central; M, medial; AAA, anterior amygdaloid area; ID, neurons that showed a significant main effect of identity; EXP, neurons that showed a significant main effect of expression; ID × EXP, neurons that showed a significant interaction between identity and expression; TH, threat; N, neutral; LS, lipsmack.

creases and decreases of firing rate for a given expression compared with the average firing rate for the other two expressions combined. Of the 48 expression-selective neurons, 21 responded to threats, 11 responded to neutral faces, and 16 responded to appeasing faces. The majority of neurons that responded selectively to threats increased their firing rate (19 of 21) (Fig. 8*C*). Neurons that responded to neutral faces were equally likely to decrease or increase their firing rate. Finally, neurons that responded to lipsmacks were more likely to "select" for lipsmacks by virtue of a lower firing rate compared with the responses to threats and neutral faces combined.

Population analyses

When the entire population of amygdala neurons was considered, the differences in firing rates for threatening (3.3 ± 5.7 Hz), neutral (3.2 ± 5.7 Hz), and lipsmacking (3.2 ± 5.6 Hz) expressions were not significant ($P > 0.05$). When only the expression-selective neurons were considered, however, a small but significant difference was observed (threat: 4.2 ± 4.7; neutral: 3.8 ± 4.8; lipsmack: 3.6 ± 4.5 Hz; repeated-measures ANOVA, $P < 0.01$). This tendency of the expression-selective neurons to respond with higher firing rates to threatening faces is shown in the peristimulus time histogram (PSTH) constructed from all expression-selective neurons in Fig. 8*B*. The firing rates elicited by threatening faces exceeds the firing rates elicited by neutral or appeasing facial expressions for only a limited period of time ranging between 200 and 300 ms after stimulus presentation. This effect arises primarily from neurons recorded from one of the two monkeys (monkey S). Proportions of neurons with different response properties in the two subject monkeys are shown in Table 2.

Figure 8*D* shows the stimulus space for threatening, neutral, and appeasing faces of eight monkeys (32 images) generated by the MDS analysis from the firing pattern of 19 neurons. The images show little clustering along the dimension of facial expression, with the exception of four threatening faces that are set apart from the rest of the images in the lower part of the stimulus space and two appeasing faces that are situated to the left of all the other images. This pattern was observed for one of the eight image sets and the monkeys whose threatening faces landed further from the central cluster did not have common features, such as age, sex, direction of gaze, or social status. These expressions also did not appear more intense than the rest of the expressions in the stimulus set. A more typical example of stimulus space where the spatial distribution of all three facial expressions is overlapping is shown in Fig. 3*B*. Nevertheless, the pattern shown in Fig. 8*D* suggests that a subset of threatening *and* appeasing facial expressions can elicit highly dissimilar patterns of activity in small populations of neurons.

DISCUSSION

Summary

We examined the response properties of amygdala neurons to a large array of images that belong to three main categories: monkey faces, human faces, and objects. The majority of neurons responded differentially to images from these three categories. Neurons that responded to monkey faces were further examined to determine the contribution of face identity and of facial expression to the observed changes in firing rates. We found that the majority of face-selective neurons responded to one or more combinations of identity and expression and only a small fraction of the neurons responded to identity irrespective of expression or expression irrespective of identity. The fraction of threat-specific neurons was not larger than the fraction of neurons that responded to neutral or appeasing faces. However, the global (summed across all expression-selective neurons) neural activity was higher for threatening faces than for neutral or appeasing faces. This effect was observed for only a brief period of time between 120 and 250 ms after stimulus display.
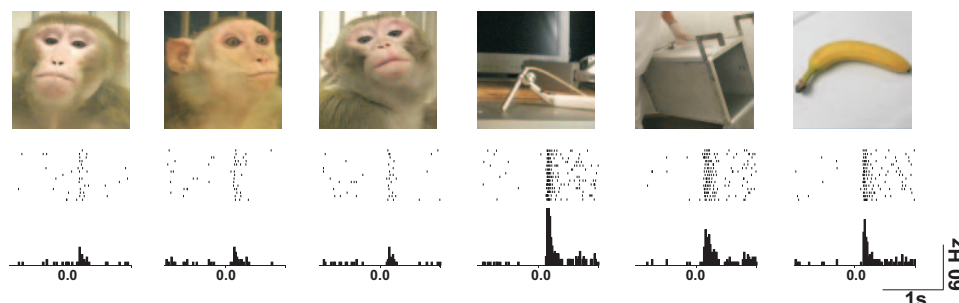

FIG. 4. Example of an object-selective neuron. Example stimuli of monkey faces and objects with the corresponding peristimulus time histograms (PSTHs) (in 20-ms bins) and single-trial spike rasters of a neuron that responded with higher rates to objects than to monkey faces and human faces (not shown).
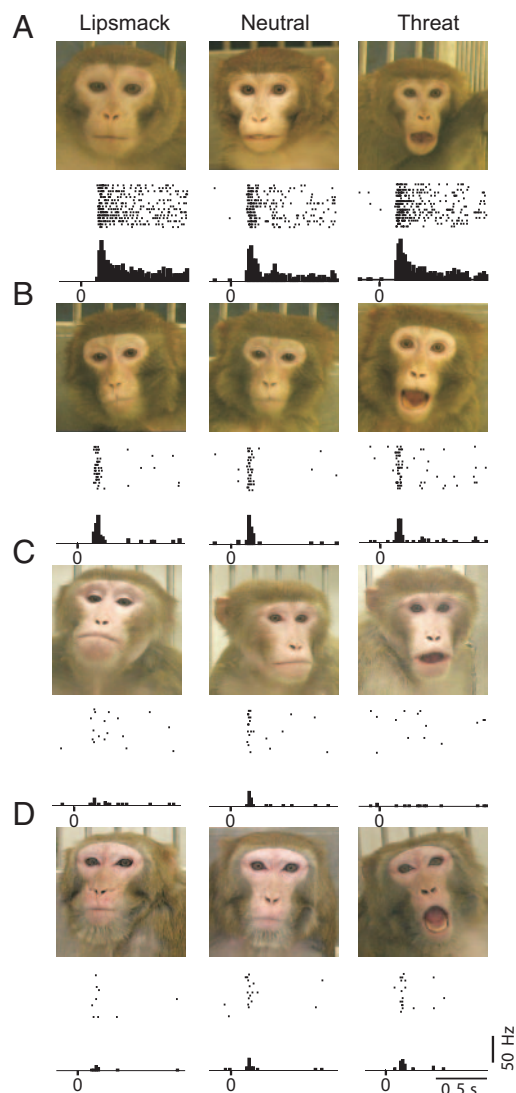
FIG. 5. Example of an identity-selective neuron. Each row of images (*A*, *B*, *C*, and *D*) contains 3 facial expressions displayed by the same monkey (4 of the 8 stimulus images contained in the stimulus set are shown). Below each image are the PSTHs (in 20-ms bins) and single-trial spike rasters of a neuron that responded with a 10-fold increase in firing rate to the faces of the 2 monkeys in the *top 2 rows* (df = 7, F = 268, $P < 0.001$).

Category-selective neurons

The majority of amygdala neurons responded with significantly different firing rates to images of monkey faces, human faces, or objects. However, for the ANOVA, the image categories were predetermined, leaving open the possibility that the effect is dictated by the structure of the stimulus set and the method of analysis (e.g., a neuron that responds to half of the 15 monkey faces, but only to a few human faces and objects might appear category selective for monkey faces). The MDS analysis distinctly classified the stimuli in the same three categories. Comparable clustering patterns were observed for all image sets; i.e., the relative distances between categories were larger than distances within a category (Fig. 3*C*).

In general, no processing bias was observed in favor of conspecific face stimuli. On the contrary, some of the most selective responses were elicited by images with no obvious significance for the monkey (e.g., fractals, junk objects). Sim-

ilar observations by Nishijo et al. (1998a,b) support the hypothesis that the amygdala participates in the representation and evaluation of all the stimuli encountered by an organism.

According to a functional scheme proposed by Paré and colleagues (Collins and Paré 1999; Paré and Smith 1993; Royer et al. 1999; reviewed by Davis and Whalen 2001), the lateral, basal, and accessory basal nuclei of the amygdala, evaluate the emotional valence of stimuli, whereas the central nucleus is the effector for an appropriate behavioral and autonomic response. Neurons in the central nucleus are involved in the initiation of somatic, autonomic, and endocrine responses to emotional stimuli (Kaada 1967; Kapp et al. 1979; Moga and Gray 1985). The central nucleus would thus be activated when the output of the evaluation process that takes place in the basolateral complex signals that the stimuli are emotionally important or require further exploration (Davis and Whalen
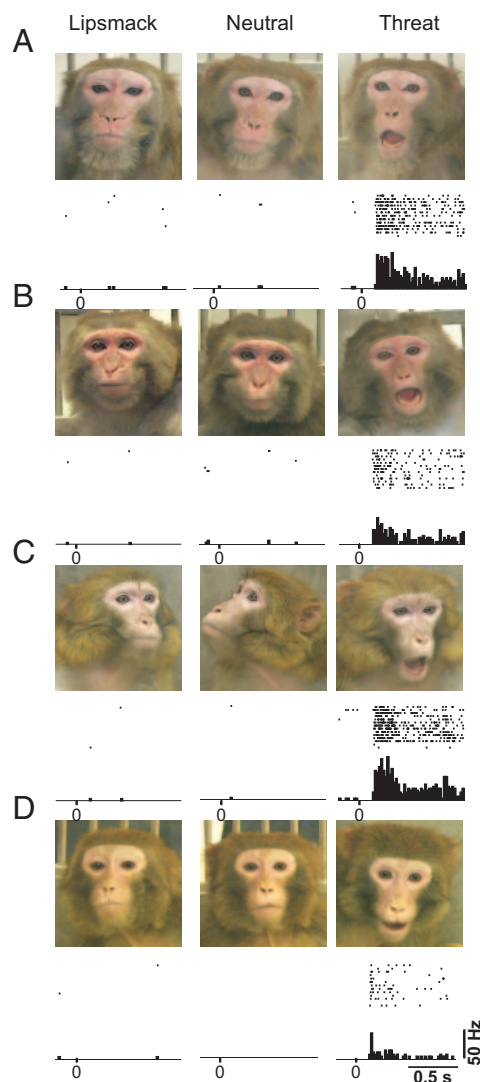

FIG. 6. Example of an expression-selective neuron. Each row of images (*A*, *B*, *C*, and *D*) contains 3 facial expressions displayed by the same monkey (4 of the 10 stimulus images contained in the stimulus set are shown). Below each image are the PSTHs (in 20-ms bins) and single-trial spike rasters of a neuron that fired almost exclusively when threatening faces were presented. 0 indicates the time of stimulus display. Although the firing rate was significantly higher for threats (df = 2, F = 374.8, $P < 0.001$), large variations of response magnitude were observed with monkey identity.
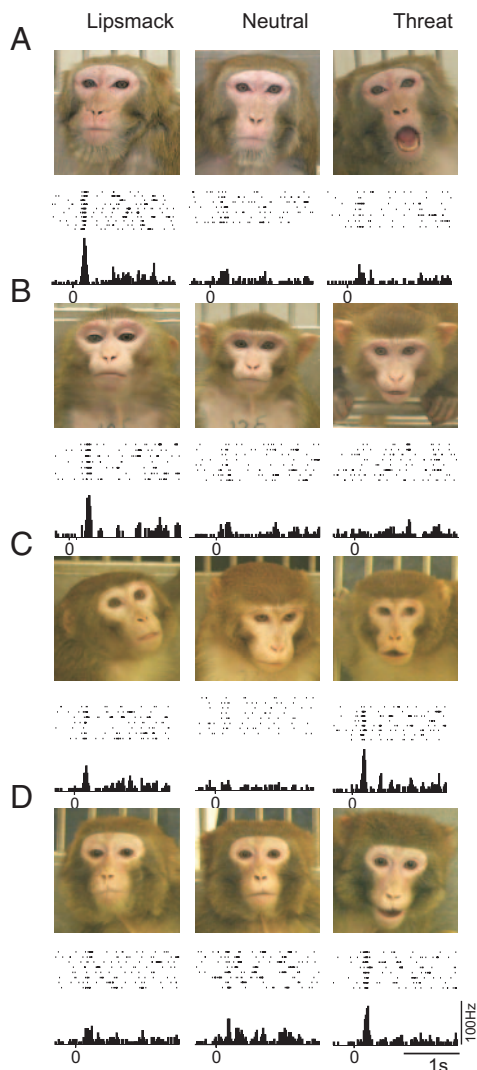
Lipsmack   Neutral   Threat

A
B
C
D

100Hz

0   0   0   1s

FIG. 7. Example of a neuron selective for specific combinations of identity and facial expression. Each row of images (*A*, *B*, *C*, and *D*) contains 3 facial expressions displayed by the same monkey (4 of the 10 stimulus images contained in the stimulus set are shown). Below each image are the PSTHs (in 20-ms bins) and single-trial spike rasters of a neuron that showed elevated firing rates in response to mutually exclusive combinations of identity and expression (df = 18, F = 5.203, $P < 0.001$), i.e., the Lipsmack of the top 2 monkeys and the threatening expression of the bottom 2 monkeys.

2001). The information transfer from the lateral and basal nuclei to the central nuclei is gated by the intercalated neurons that are under prefrontal control (Likhtik et al. 2005; McDonald 1998; Quirk et al. 2003). The intercalated neurons are assumed to block the activation of the central nucleus in response to neutral stimuli or stimuli that do not require immediate action (Davis and Whalen 2001). In this framework, the basal and lateral nuclei, where the evaluation is taking place, are expected to process *all* stimuli, whether emotional or neutral. Our data support this functional scheme. The majority of neurons (167 of 196) reported here were recorded from the lateral, basal, and accessory basal nuclei. It is thus not surprising that images with little or no species-specific significance elicited category-specific or image-specific responses.

Previous single-unit studies in the monkey amygdala also showed neural responses selective for monkey faces (Leonard et al. 1985; Rolls 1984; Sanghera et al. 1979), human faces

(Nakamura et al. 1992; Rolls 1992), images of meaningful objects, such as food items (Nishijo et al. 1989a,b; Ono et al. 1989; Wilson and Rolls 2005), and even to abstract images (Fuster and Uyeda 1971; Paton et al. 1006). These studies emphasized the selectivity of amygdala neurons for individual stimuli rather than for categories of images, although these conclusions are based on responses to relatively few stimuli. We used eight image sets, each containing 30–60 images, that allowed more refined evaluation of response selectivity but also increased the difficulty to control for all the stimulus variables.

The images used in the present study fall short of an ideal stimulus set that should contain negative, neutral, and positive variants of all categories of images. This kind of symmetry in the stimulus set might result in a different type of category and
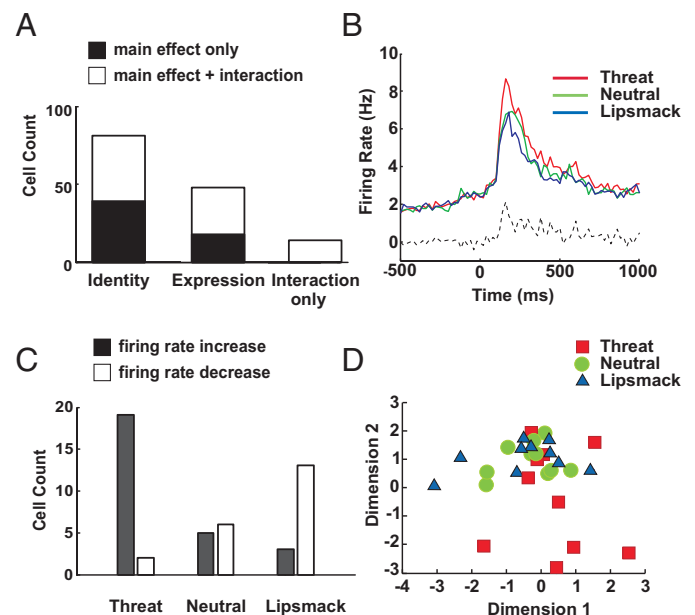

FIG. 8. Basic properties of the expression and identity-selective neurons in the monkey amygdala. *A*: histogram of the number of neurons that had a significant effect in the 2-way ANOVA analysis of identity or expression at the $P < 0.05$ level for monkey identity (1st bar), facial expression (2nd bar), and only an effect of interaction (3rd bar). White portions of the 1st and 2nd bars indicate the percentage of neurons that showed a significant ($P < 0.05$) interaction effect in addition to the main effect. A larger number of neurons showed significant effects of interaction than significant effects only of identity or for expression, indicating that the majority of face-responsive cells in the amygdala respond to combinations of faces and facial expressions. *B*: PSTH aligned on the image presentation of threatening faces (*red trace*), neutral faces (*green trace*), and lipsmacking faces (*blue trace*) averaged over the 48 neurons that showed a significant main effect of expression at the $P < 0.05$ level. Neurons that responded selectively to threatening faces responded with higher firing rates in the 200- to 300-ms period after stimulus presentation ($P < 0.001$) dashed line, difference between Threat, and average of Neutral and Lipsmack. *C*: distribution of the expression-selective ($P < 0.05$) neurons that significantly increased (filled bars) or decreased (empty bars) their firing rate in response to each of the 3 facial expression types (2-tailed Bonferroni–Dunn post hoc tests; $P < 0.05$). Majority of the Threat-selective neurons showed an increased firing rate in response to threats, whereas the majority of the Lipsmack-selective neurons showed a decreased firing rate in response to lipsmacks. *D*: stimulus space for 32 face images (8 monkeys displaying 3 expressions each) calculated from the firing rate of 19 neurons by MDS (Kruskal method). Half of the threatening faces are further from a central cluster of images that contain the faces of all 8 individuals displaying all 3 types of facial expressions, indicating that the population activity in response to threatening faces compared with neutral or appeasing faces is only partially different.

TABLE 2. *Category selectivity and monkey identity/expression-selectivity breakdown for each monkey*

	Monkey S (156 Cells)	Monkey H (40 Cells)	Total (196 Cells)
Effect of category	82 (52.6%)	19 (47.5%)	101 (51.0%)
Category post hocs			
Monkey increased f.r.	25 (16.0%)	7 (17.5%)	32 (16.3%)
Monkey decreased f.r.	42 (26.9%)	9 (22.5%)	51 (26.0%)
Human increased f.r.	24 (15.3%)	7 (17.5%)	31 (15.8%)
Human decreased f.r.	15 (9.6%)	2 (5.0%)	17 (8.7%)
Object increased f.r.	39 (25.0%)	8 (20.0%)	47 (24.0%)
Object decreased f.r.	23 (14.7%)	6 (15.0%)	29 (14.8%)
Effect of expression	42 (26.9%)	6 (15.0%)	48 (24.5%)
Effect of identity	66 (42.3%)	15 (37.5%)	81 (41.3%)
Expression/Identity	52 (33.3%)	9 (22.5%)	61 (31.1%)
Expression post hocs			
Threat increased f.r.	17 (10.9%)	2 (5.0%)	19 (9.7%)
Threat decreased f.r.	2 (1.3%)	0 (0.0%)	2 (1.0%)
Neutral increased f.r.	4 (2.6%)	1 (2.5%)	5 (2.5%)
Neutral decreased f.r.	6 (3.8%)	0 (0.0%)	6 (3.1%)
Lipsmack increased f.r.	3 (1.9%)	0 (0.0%)	3 (1.5%)
Lipsmack decreased f.r.	12 (7.7%)	1 (2.5%)	13 (6.6%)

stimulus selectivity than the observations reported here. However, in designing this study we believed that an entirely balanced set of stimuli was not achievable. In particular, it is difficult to match the affective and social meaning of human and monkey facial expressions. In our stimulus set, the images within each category certainly appear more similar in terms of shape, color, and features than the stimuli between categories. Yet the category-selective neurons showed large variations of firing rates across the images from the same category (see Fig. 2). Consequently, we cannot dismiss the possibility that the category selectivity reported here is accounted for by the shared visual components of stimuli (Fujita et al. 1992; Kobatake and Tanaka 1994; Wang et al. 1996) and not by cognitive *categorization* resulting from experience with the stimuli (Erickson et al. 2000) or task demands (Erickson and Desimone 1999; Logothetis et al. 1995; Miller et al. 1996; Sakai and Miyashita 1991).

The observed neural responses in the amygdala do not seem dramatically different from the responses reported in IT. This is to be expected given that the amygdala receives the processed output of these areas and returns massive feedback projections to these same areas. It was unexpected, however, that images with known emotional valence and objects with no obvious emotional significance are equally likely to elicit strong, stimulus-selective neural responses. One possible cause for this effect is that monkeys performed a passive viewing task where the stimuli were not associated with reinforcers. Stimulus–reinforcer associations were previously shown to broadly facilitate neural responses in the amygdala (Paton et al. 2006; Quirk et al. 1977; Sugase-Miyamoto and Richmond 2005).

Face-selective neurons

The majority (55%) of the neurons in the amygdala responded to monkey face stimuli. This percentage is comparable to previous studies that reported face cells in the amygdala (e.g., Nakamura et al. 1992). Compared with previous studies, however, we independently manipulated face identity and facial expression expecting that facial expressions, especially threatening faces, will be the primary determinant of neural activity. The largest fraction of face-selective neurons (64%) responded to both expression and identity, half of which also showed significant interaction between these factors, suggesting that expression and identity are processed jointly rather than separately in the amygdala. Moreover, the neurons that showed a significant main effect for identity were more numerous than the neurons that showed a significant main effect for expression. Within these classes, the neurons that showed a significant main effect for identity only (no interaction with expression) were also more numerous than the neurons that showed a significant main effect for expressions only, suggesting that the monkey amygdala is equally or more concerned about identity than about facial expression. Indeed, recent fMRI studies in humans reached similar conclusions (Wright and Liu 2006). Overall, the largest population of neurons showed significant interaction between identity and expression. Taken together, these observations suggest that the amygdala can specify unique combinations of individuals and facial expression. The ethological relevance of this observation rests with the fluid dominance hierarchy of macaque troupes where facial expressions gain or lose emotional significance as the displaying monkey ascends or descends in social rank. In this scenario, the identity of the displaying individual might carry as much emotional significance as the expression itself, such as the threatening face of a high-ranking adult is more dangerous than the threatening face of a juvenile.

Previously many important properties of face cells were determined, both in the cortex (in STS: Bruce et al. 1981; Desimone 1991; Desimone et al. 1984; Hasselmo et al. 1989; Perrett et al. 1982; Wang et al. 1996; in TE: Eifuku et al. 2004; Rolls 2000; Rolls and Tovee 1995a; Sugase et al. 1999; Tsao et al. 2003; Young and Yamane 1992) and in the amygdala (Leonard et al. 1985; Nakamura et al. 1992; Sanghera et al. 1979), yet little evidence has been available for either clearly separate or joint processing of facial identity and facial expressions (Calder and Young 2005). Using an image set that contained three monkeys with three expressions each, Hasselmo and colleagues (1989) recorded neural activity from STS and from area TE of the temporal cortex. They found that the majority of neurons in the upper bank of STS responded to facial expression regardless of identity, whereas the neurons in area TE responded to identity regardless of facial expression. Only 6.7% of their sample showed a combined effect of these two factors. In the present study, 64% of the neurons responded to such combinations. Joint processing of expression and identity is further supported by our MDS analysis where the three facial expressions displayed by five to eight monkeys fall in the same cluster (see Fig. 8*D*).

A potential confound for the image-selective responses in the amygdala is that in monkeys, eye movements appear to be different for each facial expression (Gothard et al. 2004). Although the scanpaths show regularities in the amount of time spent exploring each facial feature, there is no evidence for a stereotypical sequence of fixations and saccades. For example, the ratio of time spent looking at the eyes relative to the mouth is approximately 80/20 for lipsmacks and 55/45 for threats, although the targets and the durations of fixations are highly variable. Eye movements start at 200–250 ms after stimulus display and, by visual inspection, scanpaths do not exhibit any fixed temporal structure. The peak in the differential neural response precedes the

onset of the first saccade by 80–120 ms (see Fig. 8*B*). Therefore a simple oculomotor explanation for expression-selective responses can be reasonably excluded. A more detailed analysis of the relationship between eye movements and neural responses in the amygdala might uncover mechanisms by which the amygdala directs attention toward face areas that carry information about emotion (Adolphs et al. 2005).

Differential processing of aggressive and appeasing/neutral facial expressions

In support of the prediction that negative facial expressions elicit stronger responses in the amygdala, we found a small but significant increase in firing rate for threatening faces compared with neutral or appeasing faces. This effect was accounted for by the population of neurons sampled from monkey S. Moreover, the higher population firing rate in response to threatening faces is short lived (restricted to an interval of 120–250 ms after stimulus presentation) compared with the overall response profile to face images (see population histogram in Fig. 8*D*). This small difference could account for some of the neuroimaging results obtained by subtraction analyses. An equivalent subtraction method applied to the data presented here would allow us to propose a higher global output of the amygdala for threatening faces compared with other facial expressions, yet this conclusion would ignore the large fraction of neurons that responded selectively to neutral and appeasing faces (Fitzgerald et al. 2006; Wright and Liu 2006). It thus appears that in the context of a passive viewing task of conspecific facial expressions, threatening faces have a small but distinct advantage of engaging the monkey amygdala. This observation is consistent with conclusions from the majority of primate neurophysiology studies that the primate amygdala evaluates stimuli with both negative and positive valence but draws a sharp difference between them (Fuster and Uyeda 1971; Nakamura et al. 1992; Nishijo et al. 1988; Ono et al. 1983; Paton et al. 2006; Sanghera et al. 1979; Wilson and Rolls 2005).

It thus appears that the monkey amygdala contains neurons that transmit information about a large array of complex visual stimuli and their category membership regardless of emotional or species-specific significance. Concomitantly, the face-selective neurons respond to multiple, socially relevant dimensions of faces with both positive and negative valences.

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