Face-selective Neurons During Passive Viewing and Working Memory Performance of Rhesus Monkeys: Evidence for Intrinsic Specialization of Neuronal Coding

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The functional organization of prefrontal cortex (PFC) is a central issue in cognitive neuroscience. Previous physiological investigations have often failed to reveal specialization within the PFC. However, these studies have generally not been designed to examine this issue. Methodological issues such as statistical criteria for specificity, the number of neurons sampled, the extent of cortex sampled, and the number, location and nature of the stimuli used are among the variables that need to be considered in evaluating the results of studies on functional localization. In the present study, we have examined neurons in macaque monkeys trained to fixate while viewing visual stimuli, including faces, or to use them as memoranda on a working memory task. Visual responses of over 1500 neurons were recorded throughout a wide expanse of the PFC (areas 12, 9, 46, 8 and 45). Neurons were considered selective for faces if the best response to a face was over twice as strong as that to any of a wide variety of non-face stimuli. Full electrode track reconstructions in three monkeys revealed in each that neurons which met this criterion were concentrated almost exclusively in three distinct subregions within the projection region of the temporal lobe visual areas. We further show that for all neurons, the most visually selective neurons (for faces, objects or color patterns) were also the most concentrated in the temporal lobe recipient PFC. Similar face selectivity, regional specialization, and delay or delay-like activity were observed in monkeys whether trained on memory tasks or not, which suggests that these are naturally occurring properties of prefrontal neurons. These results confirm neuronal and regional specialization for information processing in PFC and elucidate how heretofore unexamined experimental variables have a strong influence on the detection of regional specialization.

Introduction

The issue of functional specialization in the prefrontal cortex (PFC) has recently gained renewed attention both by primate neurophysiologists and cognitive neuroscientists using imaging techniques in human subjects. Views of the functional architecture of the PFC range from a high degree of equipotentiality of neurons with respect to the information they process (Rao *et al.*, 1997) to a high degree of regional specificity based on anatomical constraints (Wilson *et al.*, 1993). The resolution of these issues has implications for cognitive concepts such as the existence and nature of a 'central executive' area in the PFC (Baddeley, 1983). Single unit recording studies in non-human primates have the capability to address these issues with the highest temporal and spatial resolution available in brain–behavior research. Nevertheless, the findings of such work have led to some divergent conclusions. The results of Rao *et al.* (Rao *et al.*, 1997) have been widely interpreted as evidence for a low degree of localization of spatial and non-spatial content in PFC. On the other hand, our recent finding that prefrontal neurons responding selectively to pictures of faces are restricted to a specific region in PFC indicates a high degree of both areal and cellular specificity (Ó Scalaidhe *et al.*, 1997) [see also Pigarev (Pigarev, 1979)]. This is consistent with the locus of anatomical inputs from the temporal lobe areas which also contain face and object selective neurons (Kuypers *et al.*, 1965; Jones and Powell, 1970; Chavis and Pandya, 1976; Jacobsen and Trojenowski, 1977; Kawamura and Naito, 1984; Shiwa, 1987; Barbas, 1988; Seltzer and Pandya, 1989; Ungerleider *et al.*, 1989; Distler *et al.*, 1993; Bates *et al.*, 1994; Rodman, 1994; Webster *et al.* 1994; Bullier *et al.*, 1996).

In view of the current interest and debate concerning the functional architecture of PFC, the present report provides in full the evidence for face-specific processing within the inferior PFC in the macaque monkey. One of the monkeys was trained merely to visually fixate and viewed the stimuli passively while two other monkeys were additionally trained on a working memory task in which faces served as memoranda. If, as has been suggested (Rao *et al.*, 1997) [see Iarovici (Iarovici, 1997)], the regional specialization in PFC that has been observed (Wilson *et al.*, 1993; Ó Scalaidhe *et al.*, 1997) is the result of training on memory tasks, then regional specialization should not exist in an animal only trained to fixate. By contrast, regional specialization in a monkey only trained to fixate would indicate that PFC is intrinsically specialized based on its pattern of anatomical inputs (Goldman-Rakic *et al.*, 1999).

This report describes the properties and anatomical localization of face-selective neurons under both passive viewing conditions and in a working memory task, and investigates the issue of which methodological factors are important for observing regional specialization in PFC. We attribute the specificity in our data to the use of ethologically significant stimuli, to the high criteria employed to categorize neuronal selectivity, and to systematic recording of neurons over a wide territory spanning several cytoarchitectonic areas. A preliminary report of these findings has been published (Ó Scalaidhe *et al.*, 1997).

Materials and Methods

Subjects

Three macaque monkeys (*Macaca mulatta*), one male (LN) and two female (NA, GR), were used in these experiments. All three monkeys were trained to fixate and view pictorial representations of faces and other stimuli passively while two of the monkeys (LN and NA) were further trained on a working memory task (see below). These monkeys will be referred to as WM-naive and WM-trained monkeys respectively. They ranged in weight between 5.0 and 9.5 kg. All training, surgery and housing procedures were performed in accordance with guidelines set by the National Institutes of Health and the Society for Neuroscience. All protocols were approved by the Yale University Animal Care and Use Committee and were developed and carried out in coordination with a consulting veterinarian.

Surgical Methods

Prior to any surgery or training, the monkeys were adapted to handling and to sitting in a primate chair. The monkeys were then implanted with a head bolt and a scleral eye coil for measuring eye position. A 2.0 cm diameter recording chamber was placed over the PFC based on stereotaxic coordinates from a cortical atlas and the location of skull landmarks. Surgery was performed under sodium pentobarbital anesthesia using standard sterile procedures. The eye coil surgery was derived from the procedure described by Judge *et al.* (Judge *et al.*, 1980). To stabilize the animal's head during behavioral procedures a head bolt was implanted onto the skull with skull screws covered by dental cement. Following recovery from the eye coil surgery, the animals were put on a controlled drinking schedule and began training. When training was completed an additional surgery was performed using the same techniques to remove the skull within the recording chamber for access to the recording sites.

Apparatus and Visual Stimuli

During training the monkeys sat in a primate chair with their head held in position by the implanted head bolt. The animals faced a color video monitor in a sound attenuating room. The fixation stimulus was a 0.5° spot on the video monitor. For all tasks, eye position was measured to within 0.5° accuracy by a magnetic search coil apparatus (CNC Engineering, Seattle, WA). A Digital Equipment Corporation PDP-11 computer monitored eye position, controlled stimulus presentation via an IBM-compatible PC, controlled reinforcement contingencies, and collected electrophysiological, performance and eye movement data. Visual stimuli were digitized video images presented on a color monitor using a color graphics card (Targa) with 640 × 400 pixel resolution and 16 bit color resolution.

Visual Task

All three monkeys were first trained to fixate within 2.0° of the fixation stimulus for 2000 ms to receive a liquid reward (apple juice). For the VIS task, the monkeys were required to maintain fixation throughout a trial. If the monkey failed to maintain fixation, the fixation light was extinguished, the reward was withheld and a 1 s time-out was added to the intertrial interval (ITI). A trial consisted of: fixation of a centrally presented fixation point for 0.5 s, 1.0 s of visual stimulus presentation, followed by an additional 0.5 s of fixation (Fig. 1*A*). Visual stimuli consisted of 40 standard sets of visual stimuli, each consisting of seven stimuli: one face, one monochromatic colored rectangle and five objects. Faces were either human or rhesus monkeys and the objects were typically laboratory equipment or other miscellaneous objects. Additional sets of stimuli contained: objects, monkey faces and colored rectangles; monkey faces varying in identity, expression and profile; pictures of monkey faces scrambled; stimuli of emotional significance (e.g. snakes, leather handling gloves, a spider and a human hand); stimuli of motivational significance to the monkeys (such as monkey chow and an apple); spots of light and other common 'laboratory' stimuli such as oriented lines; stimuli at different retinal locations; and stimuli varying in size, color versus black and white, and normal view versus inverted. Visual stimuli typically subtended 8–10° of visual angle.

Visual Memory Task

Two monkeys (LN and NA) were also trained on a variant of the oculomotor delayed response (ODR) task that required them to make a leftward or rightward saccade of 13° based on the presentation of a centrally presented pattern or face or a peripherally presented spot of light in the appropriate spatial location. Monkeys were trained by successive approximation to make delayed saccades in response to stimuli that signaled leftward or rightward eye movements. Monkeys first foveated the central fixation point for 0.5 s. A visual cue indicating the direction of the appropriate saccade was then presented for 0.5 s, followed by a delay of 2.5 s in which the monkey was required to maintain fixation, and finally the offset of the fixation point signaled the animal to make either a leftward or rightward saccade based on the identity or location of the cue (Fig. 1*B*). Monkeys were typically tested with: two monochromatic color stimuli (blue, yellow; centrally presented, subtending 3°), two colored pattern stimuli (centrally presented subtending 3°), two peripherally presented spatial cues, each subtending 0.5° at 13° (left or right) eccentricity, and one monkey (LN) was also tested with two face stimuli (centrally presented, subtending 8°). For each of the aforementioned pairs of stimuli, one indicated a leftward saccade of 13°

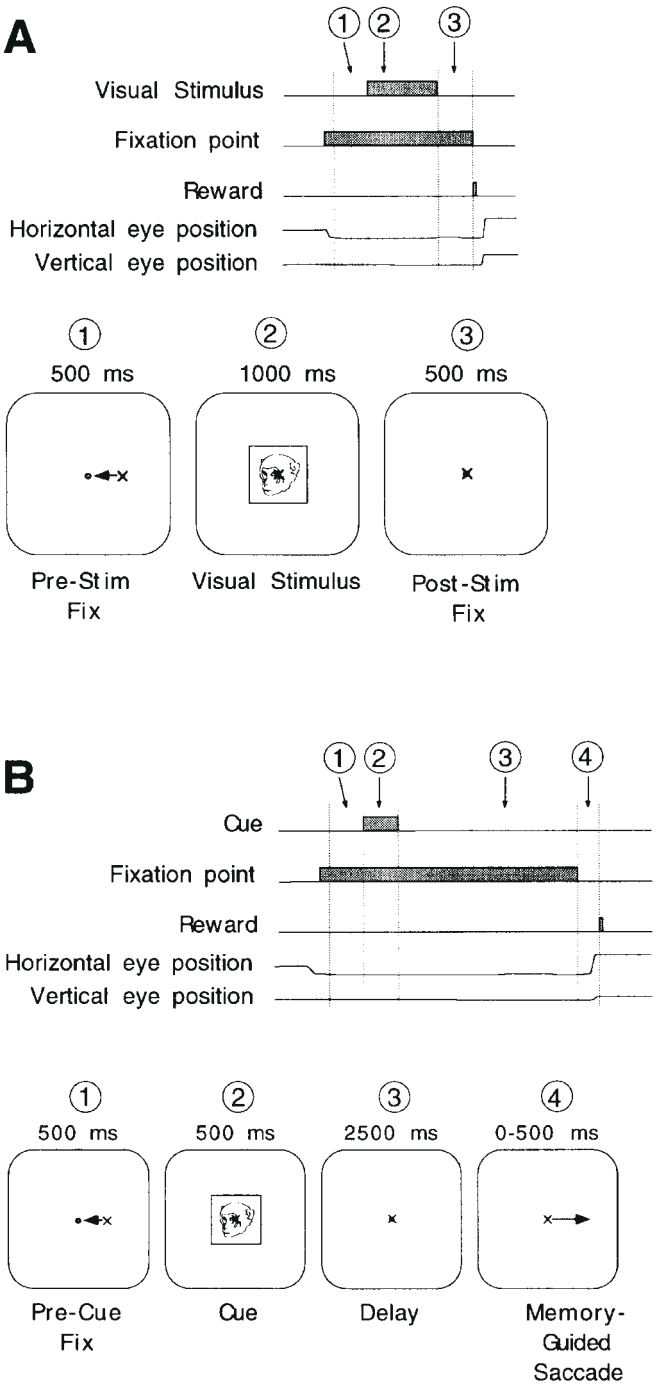

Figure 1. The visual and memory tasks. (*A*) Timing of events in the visual task (VIS): first the fixation point appears and the monkey foveates the fixation point (1); after 500 ms the visual stimulus appears, the monkey maintains fixation for 1.0 s (2), the visual stimulus disappears, the monkey maintains fixation for 500 ms (3) and finally receives apple juice. (*B*) Timing of events in the oculomotor memory task (ODR): first the fixation point appears and the monkey foveates it (1); after 500 ms the visual cue appears (2), 500 ms later the cue disappears and the monkey maintains fixation for a 2.5 s delay period (3), then the fixation point disappears, and finally the monkey makes a saccade (4) based either on the identity or spatial location of the visual stimulus and receives apple juice.

and the other indicated a rightward saccade of 13°. In all tasks, correct responses were rewarded with apple juice.

Other Tasks

Neurons were occasionally tested with additional tasks to determine if they responded to components of the visual and/or the delay tasks. A visual fixation task simply required the monkey to maintain fixation for 2.0 s (the entire length of fixation required in the VIS task). This allowed classification of most non-selective responses as fixation responses. Similarly, a saccade task (SAC) required the monkey to maintain fixation for 3.0 s and then make a saccade to a spot of light which appeared at one of eight locations separated by 45° at 13° from the fixation point. This task required the same eye movements as did the delay task but without a memory requirement. An oculomotor delayed response task with eight spatial cues as in the SAC task was used to test visual, mnemonic and saccadic responses to peripheral spatial stimuli. A small number of neurons that appeared to have reward or auditory related responses were tested with tasks that simply presented auditory stimuli, reward or the sound of the reward pump without a behavioral contingency.

Experimental Procedure

An important aspect of the experimental procedure used in this study is that, by testing every isolated neuron, it enabled derivation of an unbiased estimate of the percentage of neurons showing selectivity in each region of the PFC. Every isolated unit was tested, typically for 8–10 trials per stimulus, on the VIS task and/or on the ODR task. In two of the three monkeys (LN and GR) neurons which appeared to respond to faces were tested extensively with additional sets of stimuli, both to ascertain whether the cell was selective for faces and to determine the properties of the neuron. Typically these neurons were tested exhaustively unless it either became obvious that the neuron was not selective for faces or the neuron was no longer well isolated from the activity of other neurons. The third monkey (NA) was tested only on the standard VIS and ODR tasks. Monkeys were run 5 days a week and daily sessions lasted until the animal completed 700–1000 correct trials (3–4 h). Electrode penetrations were usually located in different parts of the PFC on successive days. Occasionally an electrode penetration site was revisited to help determine the laminar and topographic regularity of the neuronal responses. To prevent biasing of the recording sample, penetrations were repeated at locations where unresponsive neurons were found as well as at sites with responsive neurons. There was no significant difference in the number of penetrations at anterior-posterior site locations with (mean = 2.46) and without (mean = 1.44) face-selective neurons ($P = 0.25$; two tailed *t*-test for independent observations).

Data Analysis

Analysis of variance was used to compare neuronal responses for each stimulus within the pretrial, fixation, visual stimulus and post-stimulus periods. The mean firing rate was calculated for five time intervals for the VIS task: 1 s during the ITI preceding the onset of the fixation point, 400 ms starting 100 ms after visual fixation, 200 ms beginning 100 ms after presentation of the visual stimulus (corresponding to a phasic response), 900 ms from 100 ms after onset of the visual stimulus (corresponding to a tonic response), and 2000 ms starting 100 ms after offset of the visual stimulus (corresponding to a sustained off response) . Similarly, time windows were established for the pretrial, cue, delay and response periods of the ODR task. The firing rates identified by trial number, stimulus and time window were imported (using MicroSoft™ Excel™; Redmond, WA) into a statistics package (Systat™; Chicago, IL) using custom-designed batch files and macros. An analysis of variance (ANOVA) was then performed using stimulus as a factor and time window as a factor with repeated measures. We chose to analyze the data in this fashion rather than by using a standard two-way ANOVA (with stimulus and time window as the factors) because the repeated-measures test is less susceptible to intertrial variation in the neurons' intrinsic firing rate (due to unknown extra-experimental variables). Only neurons with a significant main effect of stimulus or a significant interaction between stimulus and time window at a level of $P < 0.05$ were considered selectively responsive on the task. Using the criteria of Rolls and colleagues (Perrett *et al.*, 1982; Baylis *et al.*, 1987; Hasselmo *et al.*, 1989), cells that had a response magnitude to the best face stimulus that was over twice as strong as the best response to a non-face stimulus were considered to be face selective.

In addition to the quantitative analysis, all neuronal data was printed out as trial-by-trial rasters and averaged spike density functions (SDFs) and visually inspected. The neurons' responsiveness was qualitatively evaluated, blind with respect to neuron location, on a scale of 0–5 (0 = unresponsive, 1 = ambiguous, 2 = weakly selective, 3 = moderately selective, 4 = strongly selective, 5 = very strongly selective). Ratings of 0 or 1 were considered unresponsive, ratings of 2 or 3 were considered moderately selective and ratings of 4 or 5 were considered strongly selective. Agreement between the quantitative and qualitative methods was excellent, largely because of the stringent response magnitude criteria used to determine face selectivity (see above). Therefore, quantitative measures are used to evaluate responsiveness in this report and all responses are based on significant comparisons at the level of $P < 0.05$. A small number of neurons (<5%) with very low firing rates had no firing in one or more cells of the ANOVAs and therefore could not be quantitatively analyzed. Visual inspection of the rasters and SDFs showed that these neurons were almost always unresponsive and were never face selective.

When neurons were determined to be face selective a number of comparisons were made to determine various aspects of the neuron's behavior. The latency of the cell was determined by convolving the activity of the neurons activity across trials with a Gaussian function. This essentially replaced each action potential with a Gaussian curve with a standard deviation of 30 ms, yielding a continuous SDF. The latency of the best response was determined by the method of MacPherson and Aldridge (MacPherson and Aldridge, 1979), i.e. by calculating 95% confidence intervals for a 1 s control period in the ITI, determining the time (at least 50 ms after stimulus presentation) at which the SDF first crossed the upper or lower 95% confidence interval, and determining the midpoint between the first crossing of the confidence interval and the first peak in the response. For deriving a response window, the end of the response was either the time of stimulus offset or the time that the response returned to below (or above) the 95% confidence interval for at least 100 ms. This quantitatively derived response window from the best response was then used for all further calculations of selectivity and other comparisons of responses to different stimuli.

To quantify the extent to which individual face-selective cells were tuned, we developed the following measure of stimulus selectivity: the mean deviation from the maximum response. This measure satisfies one boundary condition and a number of other features of selectivity. The function has the following form:

$$\begin{aligned} S(x_{\max}, x_2, x_3, \ldots, x_n) &= \frac{(x_{\max} - x_2)}{n} + \frac{(x_{\max} - x_3)}{n} + \cdots + \frac{(x_{\max} - x_n)}{n} \\ &= \frac{1}{n}\sum_{i=1}^{n}(x_{\max} - x_i) \\ &= x_{\max} - \frac{\sum_{i=1}^{n} x_i}{n} \end{aligned}$$

where x_i is the response (the difference between the average firing rate to stimulus i and the average pretrial baseline firing rate for stimulus i) to the ith stimulus, $x_{\max} = x_1$ is the largest response, and n is the number of stimuli that the neuron was tested with. It can be seen that for a completely non-selective neuron, $x_{\max} = x_i$ and $S = 0.0$. By contrast, if the neuron only responds to one stimulus out of an infinite number of stimuli (a 'grandmother cell'), $x_i \neq x_{\max} = 0.0$ and the limit of S as the number of stimuli approaches infinity is the largest response. Consistent with an intuitive understanding of neuronal selectivity, larger differences between the maximal response and the other responses result in larger values of S, increasing numbers of stimuli tested result in asymptotically increasing values of S, and inhibition to some stimuli and excitation to others results in a greater value than excitatory responses to the same stimuli and no response to other stimuli. Finally, S is denominated in spikes per second and makes no assumption about the distribution of response magnitudes.

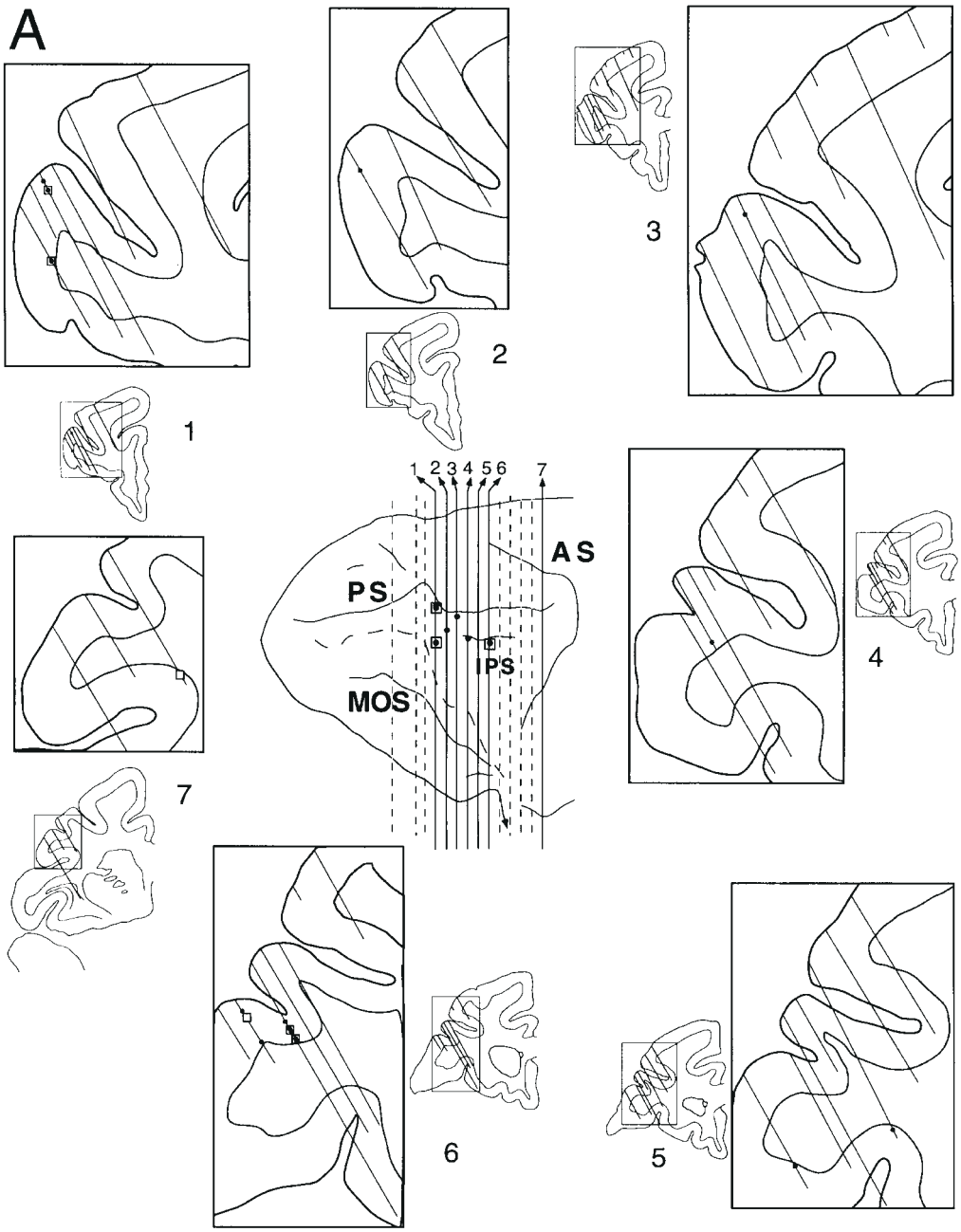

Figure 2*A*

Histology

At the conclusion of experimentation, the monkeys were deeply anesthetized with an overdose of sodium pentobarbitol and perfused through the heart with saline followed by 2% gluteraldehyde with 0.5% formalin followed by several sucrose washes. The brains were then infiltrated with 30% sucrose, blocked and sectioned in the coronal plane at 50 μm on a freezing microtome. A series of coronal sections through the recording area were stained with cresyl violet.

The location of each face-selective neuron was drawn on a tracing of the appropriate section through the monkey's brain. Because it was not possible to find every electrode penetration over the course of many months of recording, indirect means were used to determine to location of most face-selective neurons. The shrinkage of the tissue was calculated based on the location of sections containing marking lesions made at specific anterior–posterior locations and cortical depths during the last recording sessions. Using this factor in conjunction with the location of identified electrode penetrations, the appropriate section was determined and the cell's location was then found. Reference to the recording databook was made to ensure that the pattern of cortex, white matter and sulci encountered during the recording session matched the identified section, and the angle of electrode penetration was confirmed by reference to X-rays made during the recording sessions. A lateral reconstruction was created from the histological sections and the sections with electrode tracks were drawn on the lateral reconstruction.

Results

Subregional Specialization

Face-selective neurons were concentrated within subregions of the PFC that receive temporal lobe afferents. There were two concentrations of face-selective neurons within the inferior

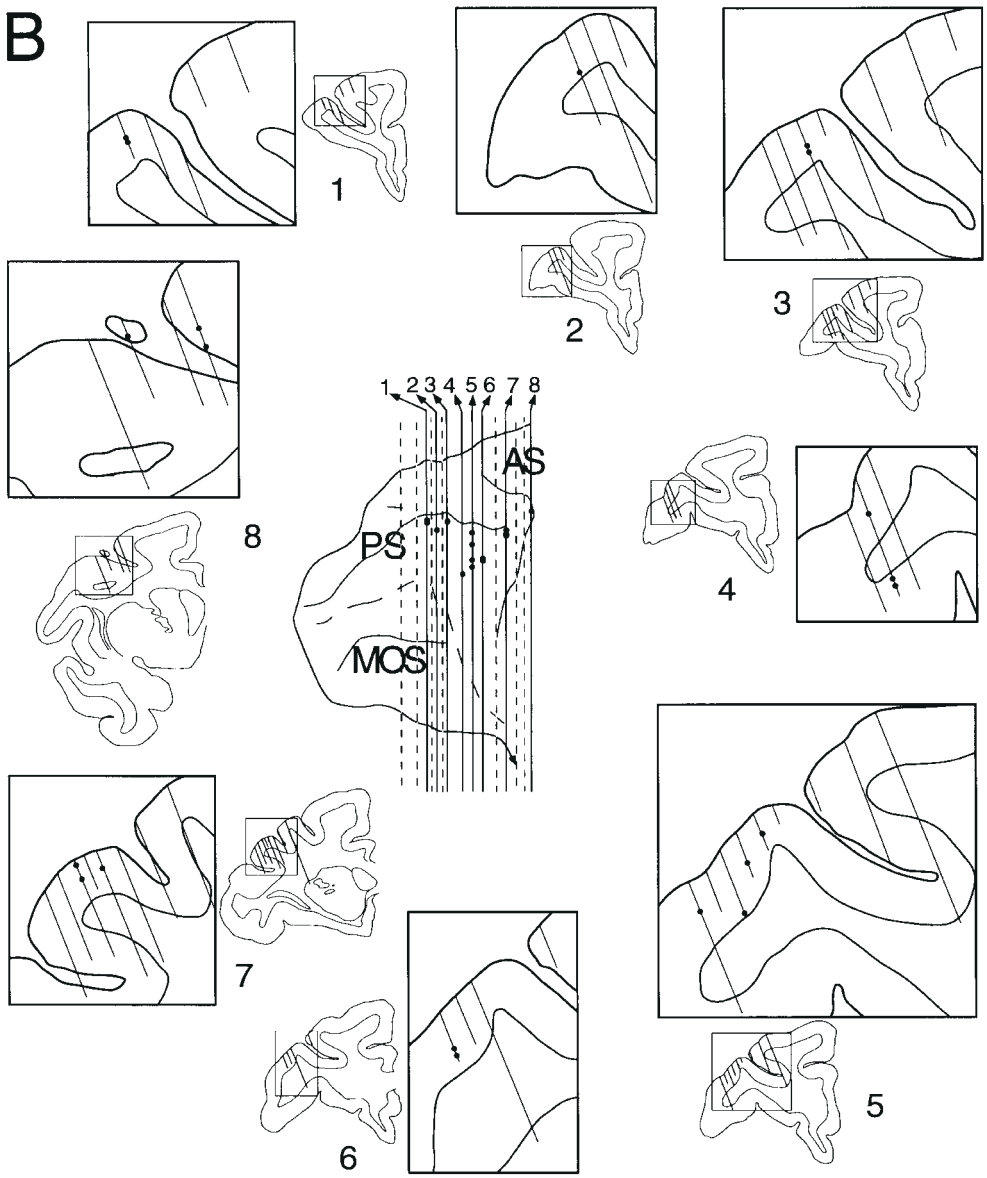

Figure 2*B*

frontal convexity (IFC): one just below the principal sulcus immediately behind its anterior–posterior midpoint (see Fig. 2*A*, sections 1–3; 2*B*, sections 1–3) and one in the small sulcus ventral to the principal sulcus and anterior to the lower limb of the arcuate sulcus (Fig. 2*A*, sections 4,6; 2*C*, sections 1,2). This sulcus is not seen in all monkeys (e.g. monkey GR, Fig. 2*B*) but the concentration of face-selective neurons is present in the same region in the absence of a sulcus (Fig. 2*B*; sections 4–6). Probably because of its small size and variable nature this sulcus is often not depicted in atlases. It has been described (Connolly, 1936, p. 334) as a lateral extension of the lateral orbital sulcus (a.k.a. the fronto-orbital sulcus). Because, in our experience, this sulcus is neither continuous with the lateral orbital sulcus nor with the orbital surface, we refer to it as the inferior prefrontal sulcus. There appears be a third subregion with a high concentration of face-selective neurons, in the lateral orbital cortex (Fig. 2*A*, section 5; 2*B*, section 4) at the anterior–posterior level of the inferior prefrontal sulcus; however, more recording in orbital cortex would be necessary to confirm this possibility.

A total of 44 neurons were selective for the sight of faces. Face-selective neurons constituted ~5% of the neurons in the IFC (37/779) of both the monkeys that were trained on working memory tasks (LN = 13/186, NA = 9/437) and the monkey that learned only to fixate (GR = 15/156). Few face-selective neurons were encountered in the lateral orbital sulcus, but their proportion was remarkably similar (LN = 2/46, GR = 2/43; see Fig. 3). The lower percentage of face-selective neurons in monkey NA was probably due to the fact that this animal was tested with only one set of visual stimuli per neuron. Many other cells (approximately one-third) in the IFC responded selectively to visual stimuli but were not face selective. A smaller proportion of neurons in the arcuate sulcus (1.5%; 3/205) also showed face selectivity. No neurons were selective for faces in the principal sulcus (0/480; LN = 0/110, GR = 0/159; NA = 0/211) or the superior prefrontal convexity (0/180: LN = 0/88, GR = 0/37, NA = 0/55) in either the WM-trained (LN, NA) or WM-naive (GR)

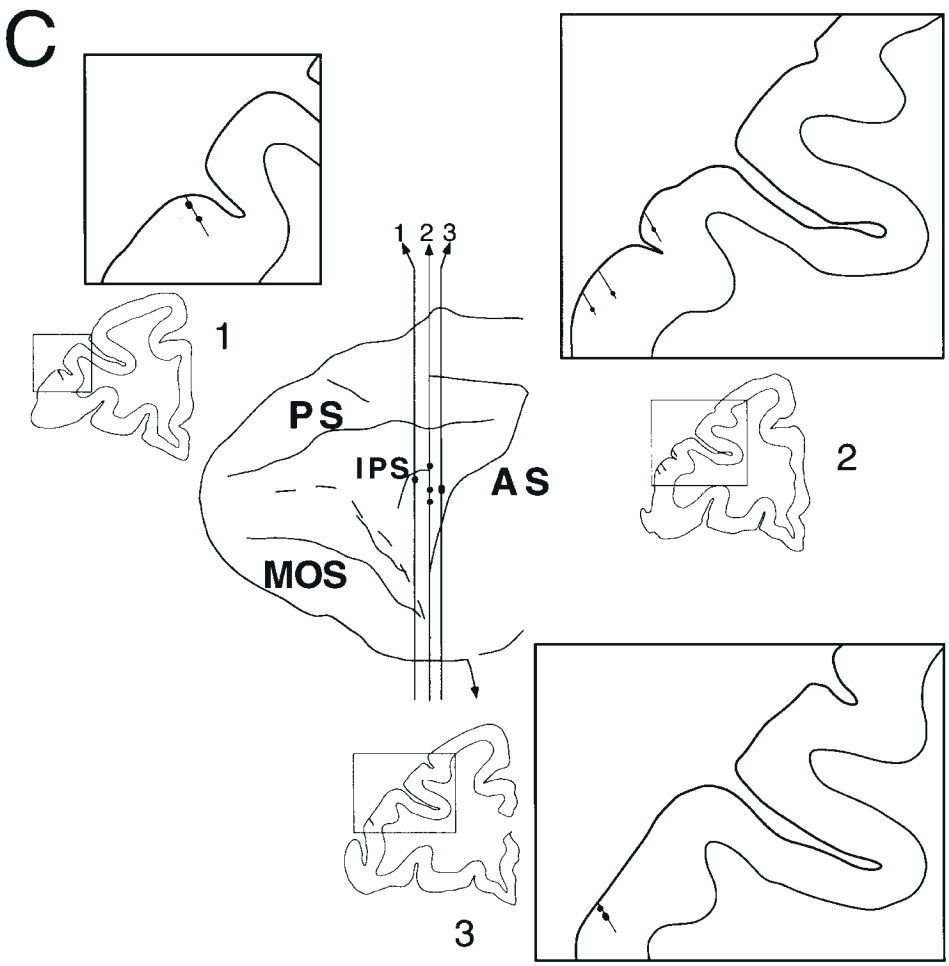

Figure 2. The locations of face-selective neurons for monkeys LN (*A*), GR (*B*) and NA (*C*). The location of neurons with face-selective visual responses are indicated on individual sections through the PFC by filled circles and the locations of neurons with delay activity selective for faces (in monkey LN) are indicated by shaded squares. All electrode penetrations corresponding to the sections are indicated in (*A*) and (*B*). The location of the individual sections is indicated on lateral reconstructions of the PFC. Dashed lines through the lateral view in (*A*) and (*B*) indicate sections where no face-selective neurons were encountered. Only penetrations and sections with face-selective neurons are shown in (*C*). Some neurons cannot be seen in the lateral view because they are buried in the IPS or lie on the orbital surface. The dashed line in the lateral reconstruction indicates the ventral boundary of the inferior prefrontal gyrus. Abbreviations: MOS, medial orbital sulcus; IPS, inferior prefrontal sulcus; AS, arcuate sulcus; PS, principle sulcus.

animals. As would be expected from the total lack of face-selective neurons in these areas, the distribution of face-selective neurons was highly non-random (χ^2, $P = 4.8 \times 10^{-7}$). Although there was no significant difference between the number of electrode penetrations at anterior–posterior sites with or without face-selective neurons (see Materials and Methods) there was some oversampling of sites with face-selective locations (mean number of penetrations = 2.46 versus 1.44). Accordingly, the best unbiased estimate of the incidence of face selectivity is the median percentage for each region (across monkeys) multiplied by 0.59 (1.44 divided by 2.46). This yields an estimate of 4% of the IFC neurons, 3% of the orbital neurons and 1% of the arcuate neurons being face selective. Throughout the PFC, 1733 units (LN = 442, GR = 588, NA = 703) were tested with visual stimuli, including faces. In addition, in one monkey (LN), 300 neurons were tested using faces as memoranda in a working memory task. Similar to the face-selective visual responses, 83% (5/6) of the face-specific delay neurons were in the IFC and one was in the lower limb of the arcuate sulcus adjacent to the IFC (see Fig. 2*A*). Of the 56 neurons recorded in the principal sulcus and 81 in the superior frontal convexity, none were selective for faces on the memory task.

Factors Related to Regional Specialization

The unprecedented magnitude of regional specialization in PFC shown by the face-selective neurons led to the question of how strongly selective the face-selective neurons are compared to neurons that were visually selective for pictures of objects and color patterns. Figure 4 shows the proportion of neurons with face-selective responses with one-way ANOVA (on the entire cue presentation period) P levels of: $P < 0.0001$, $0.0001 \leq P < 0.001$, $0.001 \leq P < 0.01$, $0.01 \leq P < 0.05$ and $P \geq 0.05$. The proportion of neurons that were face selective increased with increasing selectivity (by ANOVA) until nearly 20% of the neurons with the most selective responses ($P < 0.0001$) were face selective. This, along with the nearly absolute regional localization of the face-selective neurons, led to examining whether face-selective neurons show an unusual amount of regional specialization because there is something special about faces, or whether highly selective neurons in general are more localized to the areas that get anatomical input from the temporal lobe.

To investigate the role of response selectivity in the degree of regional specialization, all recorded neurons were classified into three groups: unresponsive, moderately and strongly selective (see Materials and Methods for details). The ratio of neurons

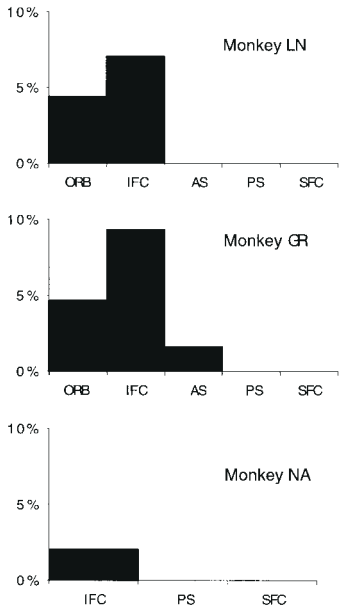

Figure 3. The percentage of face-selective neurons in each prefrontal region for each animal (no neurons were recorded in the orbital or arcuate cortex of monkey NA). Abbreviations: ORB, lateral orbital cortex; IFC, inferior prefrontal convexity ; AS, arcuate sulcus; PS, principle sulcus, SFC, superior prefrontal convexity (above PS and anterior to AS).

meeting the selectivity criteria to the number of neurons expected to meet the criteria (assuming they are randomly distributed) for the IFC and the rest of the PFC is shown on the ordinate. For example, if throughout the entire PFC there were n neurons recorded and x met the criteria for a strong response, one would expect x/n multiplied by the number of neurons recorded to have 'strong' responses in the IFC if the strongly responsive neurons are randomly distributed. If neurons were randomly distributed with respect to how strongly selective they are, the data points in Figure 5 would all be 1.0 and the lines would be flat. As shown in Figure 5, however, as response strength criteria became stricter, the proportion of visually selective neurons in the IFC increased monotonically. The increasing amount of regional specialization observed with more stringent response criteria holds for both qualitative (Fig. 5*A*,*C*) and quantitative analyses (Fig. 5*B*,*D*) and regardless of whether face-selective neurons are included in the sample of visually selective neurons (Fig. 5*A*,*B*) or not (Fig. 5*C*,*D*). Thus, increasingly strict selectivity criteria yield greater observed regional specialization. Conversely, classification of weak responses as selective will result in seeing less regional specialization. This suggests that there is both something special about faces (they are especially effective stimuli) and that highly selective neurons, whether they are selective for faces or objects, tend to be highly concentrated in the areas of the PFC that get temporal lobe input.

Given the complex functional architecture of PFC and the relatively small proportion of neurons that show face selectivity, the location and selectivity of the face-selective neurons were compared with the set of neurons that showed spurious selective 'responses' in the pretrial period. Thus we searched the database of two monkeys (LN and GR) for neurons that exhibited a significant response in the pretrial period, such that the response in the pretrial period prior to presentation of the *best face* was at least twice as large as the best response in the pretrial

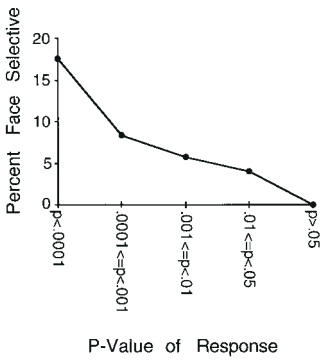

Figure 4. The proportion of all inferior prefrontal convexity neurons that are face selective for varying response strengths as measured by analysis of variance *P* values. As response criteria became stricter, the proportion of neurons with face-selective responses increased.

period prior to the presentation of the best *non-face*. Because stimuli were randomly presented, any such 'responses' would address the likelihood that face-selective responses could represent statistical artifact. No neurons were found to meet these criteria, suggesting that the criteria employed for face selectivity are essentially sound and resistant to type 1 errors. Even relaxing these criteria for 'selectivity' in the pretrial period to simply require significance on both the repeated measures ANOVA and the one-way ANOVA for the pretrial period, corresponding to our criteria for a selective *visual* response, these spurious 'responses' were evenly distributed throughout the PFC (Fig. 6*A*). Also, unlike face-selective neurons, which had a mean absolute *S* value (see Materials and Methods) of 16.0, the *S* values for these neurons were clustered close to zero and were thus much less selective than the face-selective neurons ($P = 7.5 \times 10^{-8}$, two tailed *t*-test for unpaired observations). We also compared the *P* values from the respective ANOVAs of the face-selective neurons with neurons showing spurious pretrial 'responses' (see Fig. 6*B*,*C*). As might be expected from their selectivity indices, the *P* values for the face-selective neurons were much smaller than for the pretrial 'selective' neurons. Therefore, when pretrial activity is tested with the same criteria used to find face-selective neurons none are found, and when relaxed criteria are used to simulate statistical artifacts these neurons, unlike face-selective neurons, are evenly distributed throughout the PFC and have weaker selectivity than do the face-selective neurons.

Magnitude of Selectivity and Temporal Response Characteristics

The face-selective neuron shown in Figure 7*A* displayed a vigorous response to three of the faces and little or no response to the other faces or to a variety of non-face stimuli. This neuron was tested with >50 pictures of faces and other stimuli. Figure 7*B* shows a different face-selective neuron that responded strongly to a number of face stimuli but was also unresponsive or only weakly responsive to >30 non-face stimuli. These neurons represent the extremes of a continuum which ranges from neurons that are highly selective for specific faces to neurons that show strong responses to a wide variety of faces. Similar findings were obtained in all three monkeys, whether trained on a memory task or not. The selectivity of the face-selective neurons was quantified using the mean deviation from the maximal response (*S*, see Materials and Methods) as a measure of face selectivity. Both inhibitory and excitatory responses were

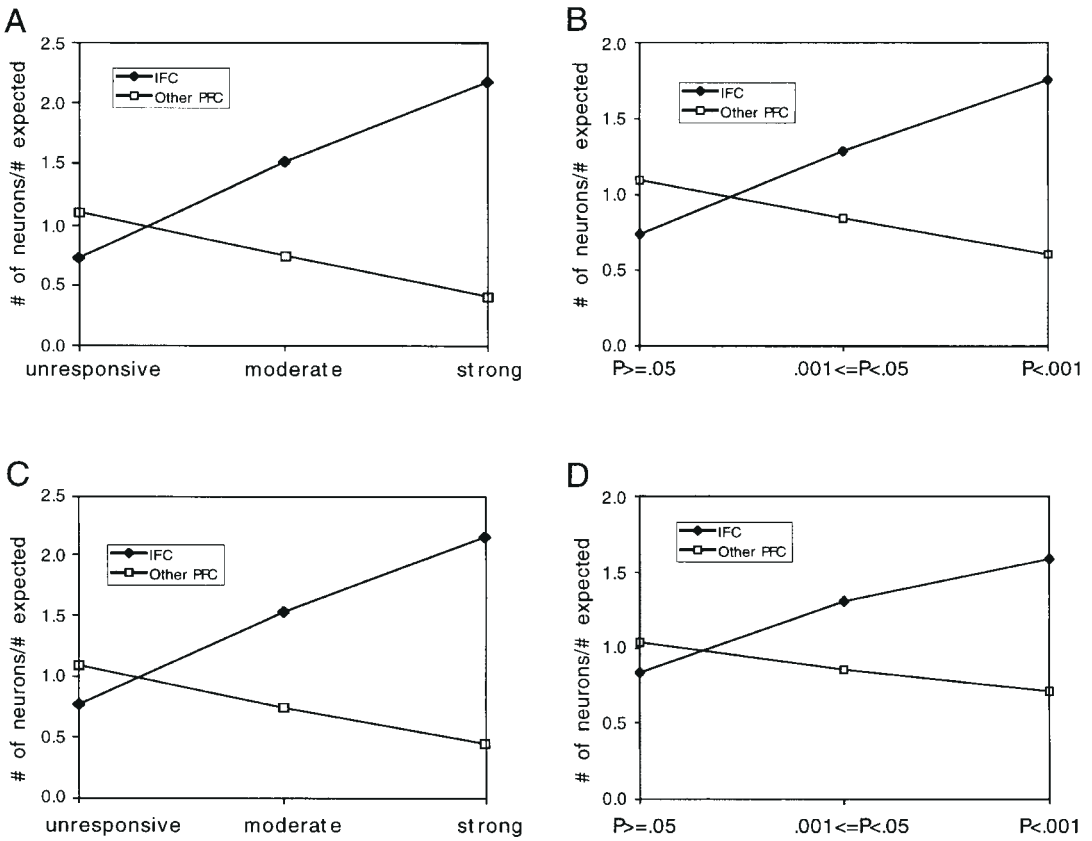

Figure 5. Regional specialization as a function of selectivity criteria. The number of visually selective neurons divided by the number of selective neurons expected (assuming a random distribution) in the IFC and the rest of PFC is shown on the ordinate and magnitude of selectivity is shown on the abscissa (see text). The amount of regional specialization observed increases monotonically with increasingly high response criteria. (*A*) All neurons recorded, response strength assessed qualitatively (see Materials and Methods). (*B*) All neurons recorded, response strength assessed by ANOVA. (*C*) All neurons recorded, response strength assessed qualitatively. (*D*) All neurons except face-selective neurons, response strength assessed by ANOVA.

observed but excitatory face-selective neurons were more frequent (38 versus 6) and more strongly selective (mean S = 17.1 versus –9.0) than the inhibitory neurons (Fig. 7*c*). The mean absolute value of S was 16.0, indicating that the average face cell's best response to a face averaged 16 spikes/s more (or less) than its response to all other stimuli. The visual responses to faces as cues in the delay task (see below) were compared to the response to the same stimuli used in the VIS task. There was no effect of task on the strength of the visual response (P = 0.98, two tailed t-test for paired observations).

Face-selective neurons had relatively long latencies and showed a variety of temporal patterns in their responses. The mean latency of the best face-selective response was 138 ms (Fig. 8*A*) and the mean pretrial spontaneous activity was 6.8 spikes/s. Face-selective neurons in the region of the inferior prefrontal sulcus had more spontaneous activity than neurons just below the principal sulcus (7.8 versus 3.7 spikes/s; P = 0.04, two-tailed t-test for independent observations). Just under half (20/44) of the face-selective neurons responded phasically, i.e. their responses returned to below (or above) the 95% confidence interval of pretrial activity before the end of the stimulus period (Fig. 8*B*, see Materials and Methods). Approximately one-third (13/44) of the neurons had tonic activity throughout the stimulus period and five neurons responded with a phasic burst of spikes followed by tonic activity. Some neurons responded with phasic activity to certain stimuli and phasic and tonic activity to others and were classified on the basis of their best response. Finally, six neurons exhibited post-stimulus activity beginning with the offset of the visual stimulus (see below).

Responses to Scrambled Faces and Other Control Stimuli

To determine whether face-selective neurons were responding based on the local features of face stimuli, we compared their responses to pictures of faces and to the same faces cut into 7–11 rectangles and scrambled (Fig. 9*A*). Elements of the faces such as teeth and eyes could still be seen in these stimuli but these stimuli did not evoke an immediate impression of a face. Because the stimuli were not otherwise manipulated, the internal color and texture were identical to the veridical faces. Despite the similarity of the local stimulus features, the neuronal responses of face-selective neurons were typically greatly attenuated and commonly non-existent to the scrambled faces (P = 0.000017, two-tailed t-test for paired observations; see Fig. 9*B*).

Face-selective neurons were tested for their responsiveness to stimuli based on familiarity, emotional or motivational significance. None of the neurons that were selective for pictures of faces showed similar responses to other stimuli with strong motivational or emotional significance such as pictures of food, leather handling gloves, snakes, etc. Face-selective neurons also did not respond selectively to highly familiar non-face stimuli, suggesting that mere familiarity was not the critical feature in the responses to faces. Figure 10 shows the mean response of the face-selective neurons to faces, emotionally significant stimuli

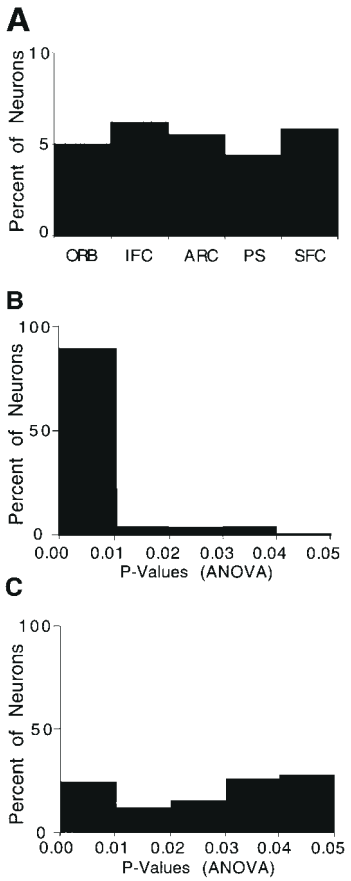

Figure 6. (*A*) Cortical distribution of spurious selective responses. Note that these neurons were evenly distributed throughout the PFC. (*B*) *P*-values for face-selective neurons. The percentage of neurons is shown on the ordinate and the *P*-values are shown on the abscissa. (*C*) *P*-values for spurious 'selective' responses.

(handling gloves, insects, a snake, etc.), motivationally significant stimuli (an apple, monkey chow, etc.), neutral objects (electrical connectors, toys, etc.), peripherally presented spots of light, monochromatic color fields and common psychophysical stimuli such as oriented lines. Despite the fact that face-selective neurons do not respond well to all faces (see Fig. 7), there was a highly significant effect of stimulus class (ANOVA; $P < 10^{-9}$). In fact, specific comparisons revealed that the only significant difference due to stimulus class was between faces and other stimuli ($P = 0.000013$; Tukey HSD), indicating that if motivational or emotional significance of the stimuli was a factor in the responses to faces, it was a weak influence. To determine the relative importance of facial expression and monkey identity, eight face-selective neurons were tested with six pictures of faces varying in monkey identity (two monkeys) and facial expression (passive, threatening and yawning). Neurons did not code for monkey and facial expression in an either/or fashion (two-way ANOVA). Specifically, seven neurons showed an effect of monkey, five neurons had an effect of expression and five neurons had an interaction of monkey and expression.

In order to further assess whether the selective responses were a result of local features particular to certain face stimuli, 6 face-selective neurons and 15 visually selective neurons were tested with the same sets of 10 stimuli inverted, converted to black and white, and decreased in size to 3°. The selectivity of the face-selective neurons was not affected by these manipulations (ANOVA; $P = 0.568$). There was a tendency for the inverted and smaller stimuli to elicit less selective responses from the visually selective neurons, but this also was not statistically significant (ANOVA; $P = 0.072$). Stimuli were also ranked based on their response magnitude (spikes per second over baseline) to the original (unmanipulated) set of stimuli and the responses were then normalized by dividing all responses by the best response to an unmanipulated stimulus. Response magnitude was strongly correlated with stimulus identity independent of these perturbations both for the face-selective (Pearson $r = -0.877$, Bonferroni $P < 10^{-9)}$ and visually selective neurons (Pearson $r = -0.742$, Bonferroni $P = 4.5 \times 10^{-8)}$ and did not vary significantly in relation to the stimulus manipulation (Fig. 11). Therefore, face-selective neurons showed considerable invariance with respect to changes in stimulus orientation, size and color versus black and white.

Receptive Field Organization

Stimulus identity is attained under natural conditions after first foveating an object, face or text. To investigate the receptive fields of the neurons, 11 face cells were tested with their optimal stimulus at nine locations: centrally and at eight locations 13° from the fixation point. Neurons responded best to foveal stimulation (Fig. 12*A*; ANOVA; $P = 0.0099$). Although responses to peripheral stimuli often occurred, especially contralateral to the recording electrode, these tended to be weaker than the responses to foveal stimulation. A subset of these face-selective neurons were also tested with peripheral presentation of 0.5° spots of light. In this case, although there occasionally were statistically detectable responses to these peripheral spatial stimuli, their response was even less than to peripherally presented faces ($P = 6.6 \times 10^{-7}$, two-tailed *t*-test for paired observations; see Fig. 12*B*). Therefore, the response to peripherally presented faces, while less than that to centrally presented faces, was considerably larger than the response to peripherally presented spots of light.

Selective Delay Responses

A major role of the PFC appears to be holding information 'on line' (Goldman-Rakic, 1987). Accordingly, 300 neurons were tested on a memory task that required the monkey to respond on the basis of visual cues presented 2.5 s previously. Eleven cells showed selectivity for one of two faces employed as stimuli in the delay task: nine neurons displayed selective visual responses, six displayed delay activity selective for one of the faces and four neurons had both visual and delay-related responses. Face-specific delay period activity could not be due to the direction of the upcoming saccade because other stimuli (see Materials and Methods) indicating the same saccade did not elicit delay period responses (other neurons concentrated in the arcuate sulcus did reflect the impending direction of movement). The preponderance of visual activity over delay activity was also typical of IFC neurons with object-selective responses (F.A.W. Wilson, S.P. Ó Scalaidhe and P.S. Goldman-Rakic, unpublished results). The mean absolute value of *S* during the delay period for neurons with face-selective delay activity (see below) was 6.1 spikes/s. Thus the face-selective visual responses (mean $|S| = 16.0$) were considerably more selective than the delay period activity (two-tailed *t*-test for independent observations, $P = 0.0001$) probably due to the face-selective responses during presentation of the face being stronger (more spikes per second) than during the delay period.

Two types of delay activity selective for the face stimuli were

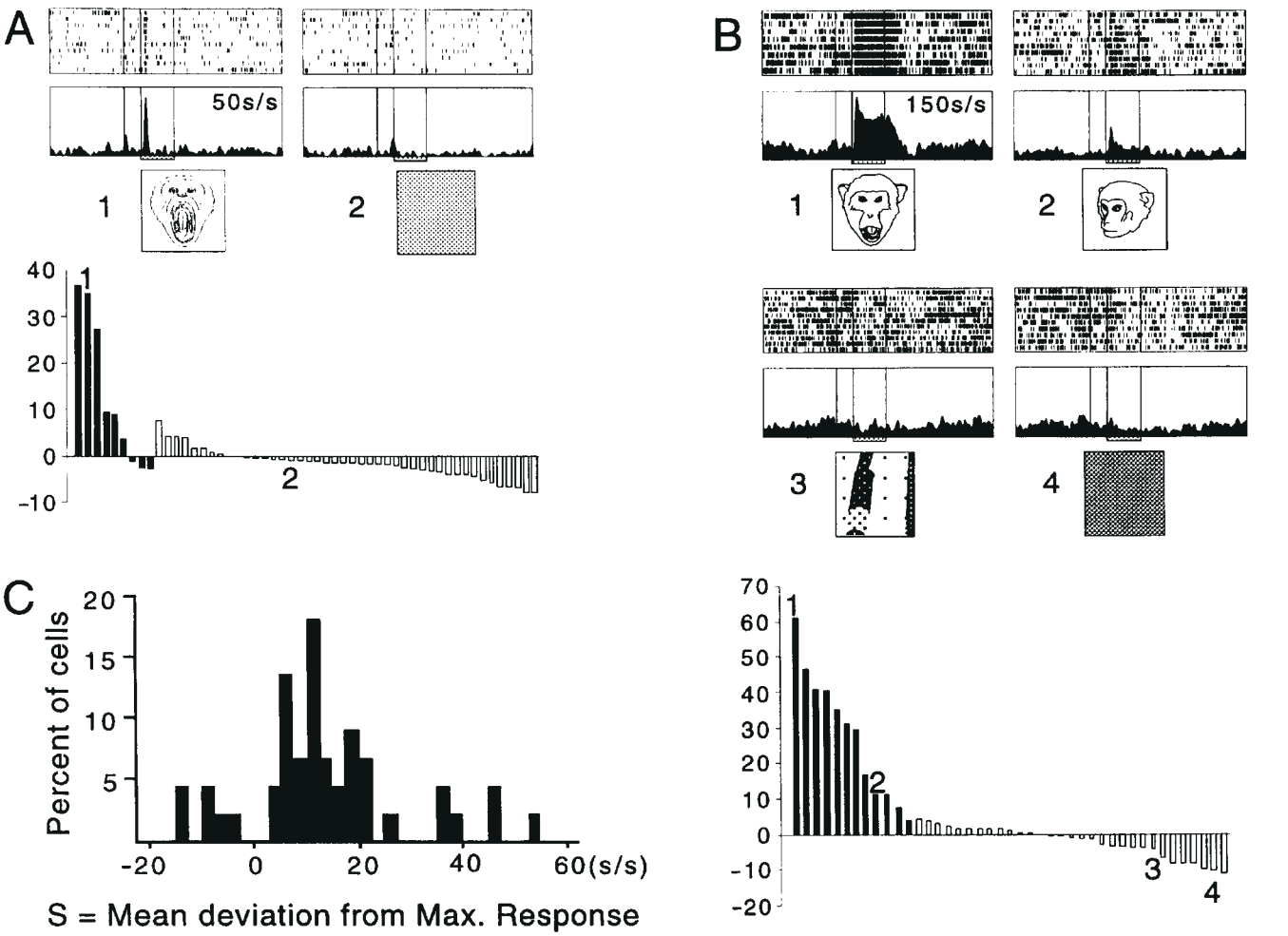

Figure 7. Face-selective responses. (*A*) Trial-by-trial rasters and summed spike density functions (SDFs) of one face-selective cell to a representative subset of the faces and objects with which it was tested. For both rasters and SDFs the first vertical line denotes the animal's foveation of the fixation point, the second vertical line indicates stimulus onset and the third vertical line indicates stimulus offset. The bar underneath the SDFs indicates the duration of the stimulus. The actual stimuli were color images presented on a computer monitor (see Materials and Methods). The full height of the SDF frames is 50 spikes/s. The bar graph shows the response in spikes per second over baseline to faces (dark bars) and non-faces (white bars). The numbers on the bar graph correspond to the rasters and spike density functions for the stimuli shown. This cell showed a response that was specific to three of the faces tested. (*B*) Trial-by-trial rasters and SDFs of another face-selective cell to a representative subset of the faces and objects with which it was tested. The conventions are as in (*A*), except that the full height of the SDF frame is 150 spikes/s. This cell showed a strong response to a variety of faces but little or no response to non-faces. (*C*) The selectivity of the face-selective cells as assessed by the mean deviation from the maximal response (*S*). The index of selectivity, *S*, is shown on the abscissa; neurons with excitatory responses yielded positive values and neurons with inhibitory responses yielded negative values. The proportion of cells and the number of cells are shown on the ordinate. The mean value of *S* for excitatory neurons was 17.1 and for inhibitory neurons 9.0.

observed: 'onset' responses which were triggered by a stimulus but persisted into the delay and an 'offset' type of response which began only after the stimulus disappeared. 'Onset' type delay activity is illustrated in Figure 13*A*; this neuron, located just over the lip of the anterior bank of the arcuate sulcus, also had post-saccadic activity related to the direction of the eye movement, consistent with the blending of visual and movement selectivity that was observed in the PFC within and anterior to the lower limb of the arcuate sulcus. Figure 13*B* shows an example of 'offset' delay activity; in this case a cell that had selective delay period activity for one of the faces in the absence of a visual response. Four neurons had 'onset' type delay activity and two neurons had 'offset' type delay activity. It is important to note that no neurons with face-selective delay activity had delay period activity on the spatial ODR task.

The capacity for post-stimulus responsivity of face-selective cells was also revealed by analysis of neuronal activity expressed in the VIS task. We observed two types of post-stimulus face-selective activity that mirrored the two types of delay activity seen on the ODR task. The 'onset' type of post-stimulus face-selective visual responses were triggered by the stimulus but persisted from 200 to 1500 ms after its offset. Figure 14*A* shows an example of a neuron with an inhibitory face-selective response that persisted after the offset of the visual stimulus (indicated by the third vertical line in the rastergram and SDF) until beyond the end of the trial (indicated by the fourth vertical line). Of particular interest, this type of response occurred both in the monkeys trained on the delay task (LN and NA) and in the monkey trained only on the VIS task (GR). Like the 'onset' type of delay activity, the response of these neurons typically tapered off by 1000 ms after offset of the visual stimulus. This type of prolonged visual activity was very common in the face-selective neurons: of the 18 neurons with tonic responses, 15 (83%) showed prolonged visual activity for >200 ms after stimulus offset.

Because 'offset' delay activity consists of a face-selective delay

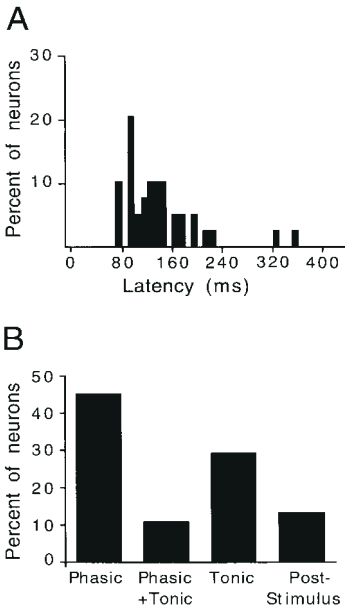

Figure 8. Temporal characteristics of face-selective neurons. (*A*) Latency of face-selective responses. The percentage of neurons is shown on the ordinate and their latency is shown on the abscissa. (*B*) Time course of face-selective responses. Neurons were classified as having either phasic responses, a phasic burst followed by maintained tonic activity, tonic activity throughout the presentation of the visual stimulus, or selective activity beginning after termination of the visual stimulus.

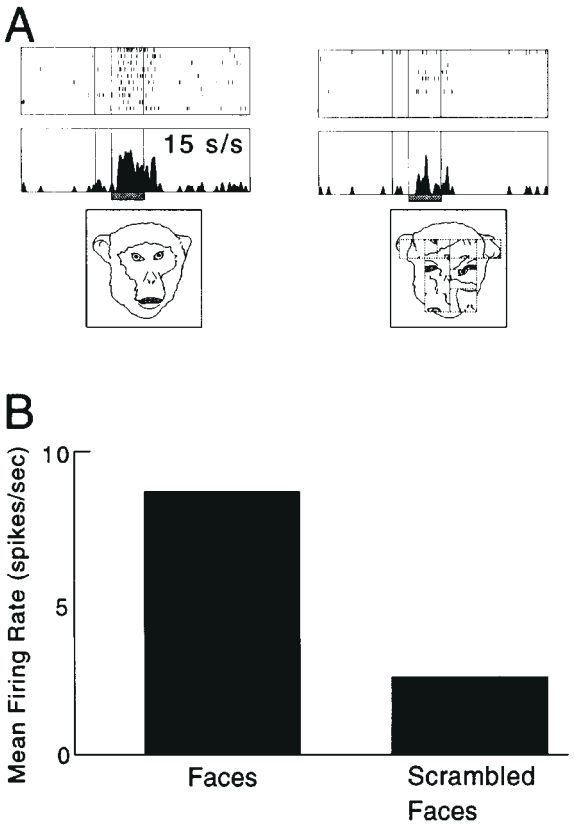

Figure 9. (*A*) The mean response of a face-selective neurons to a face and to the same face scrambled. Conventions are as in Figure 7. The response was eliminated by scrambling the face stimulus. (*B*) The mean response of all face-selective neurons tested to faces and to the same faces scrambled. The response to faces was significantly greater than scrambled faces ($n = 23$; two-tailed t-test for paired observations, $P = 0.00002$).

period activity in the absence of a visual response during stimulus presentation, this would at first seem unlikely to be observed on the VIS task, especially in an animal that had not been trained on a memory task. An unexpected finding, therefore, was that prolonged face-selective 'offset' responses occurred after the offset of a visual stimulus and lasted into the ITI. For example, the neuron shown in Figure 14*B* increased its firing rate immediately after stimulus offset and continued to respond throughout the ITI in a manner strikingly similar to the delay activity seen in Figure 13*B*. Monitoring of eye movements with the eye position display and the monkey via a video camera revealed that the firing of these neurons was not related to eye movements or to any other observable behavior particular to the offset of the face stimuli. Finally, although the sample of neurons with face-specific delay activity is small, the ratio of 'onset' type visual responses to all post-stimulus responses (15/21 = 71%) and the ratio of 'offset' type visual responses to all post-stimulus responses (6/21 = 29%) is strikingly similar to the ratio of 'onset' delay responses to all delay responses (4/6 = 67%) and the ratio of 'offset' delay responses to all delay responses (2/6 = 33%) respectively.

Discussion

The striking similarity of the face-selective PFC neurons to those previously reported in the inferior temporal cortex demonstrates that they are components of a cortical network dedicated to the same domain of information processing. These neurons were organized into subregions, providing further evidence that the PFC contains multiple specialized regions based on its connections with higher sensory areas. These findings, both in animals trained on a working memory task and in animals naive to this task, suggest that specialization of function in PFC is a naturally occurring property rather than the result of training. Finally, the unambiguous regional specialization seen in this study may explain why previous studies of PFC have failed to reveal its modular organization.

Face-selective Neurons in the Prefrontal and Temporal Cortices

Consistent with the adaptive significance of faces for macaques, beginning with the work of Gross and colleagues (Gross *et al.*, 1972), the existence of face-selective neurons in the temporal lobe of non-human primates has been repeatedly confirmed (Perrett *et al.* 1982; Baylis *et al.* 1985, 1987; Rolls and Baylis 1986; Yamane *et al.*, 1988; Tanaka *et al.* 1991). The responses of the PFC neurons identified here, like face-selective neurons of the temporal lobe, appeared to be triggered by faces rather than by ancillary stimulus characteristics. As in the temporal lobe (Bruce *et al.*, 1981; Perret *et al.*, 1982; Desimone *et al.*, 1984; Baylis *et al.*, 1985; Rolls and Baylis, 1986; Tanaka *et al.*, 1991), a wide variety of control stimuli failed to drive the neurons. Like inferior temporal cortex (IT) (Young and Yamane, 1992; Rolls and Tovee, 1995), these neurons were also selective within the class of faces despite their common features. They also responded with similar specificity to faces whether they were inverted, monochromatic or reduced in size, resembling the responses of face- and object-selective neurons in the inferior temporal gyrus (Sato *et al.*, 1980; Perret *et al.*, 1982, 1988; Schwartz *et al.*, 1983; Desimone *et al.*, 1984; Rolls and Baylis, 1986; Hasselmo *et al.*, 1989; Lueschow *et al.*, 1994). Further, the responses to scrambled faces were greatly diminished compared to the responses to intact faces, a characteristic of temporal lobe

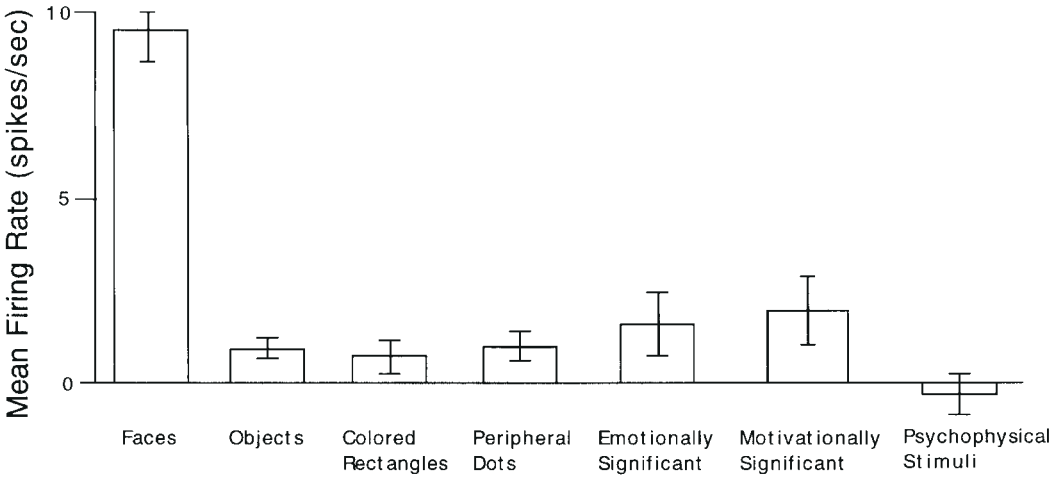

Figure 10. The mean response of face-selective neurons to faces, objects (e.g. electrical connectors, toys), monochromatic color rectangles, peripheral spots of light, emotionally significant objects (e.g. handling gloves, insects, snakes), motivationally significant stimuli (e.g. monkey chow, apples) and psychophysical stimuli (e.g. oriented lines, Fourier descriptors). There was a significantly greater response to faces than to any other stimuli (Tukey HSD; $P < 0.00005$). There were no significant differences between the other classes of stimuli.

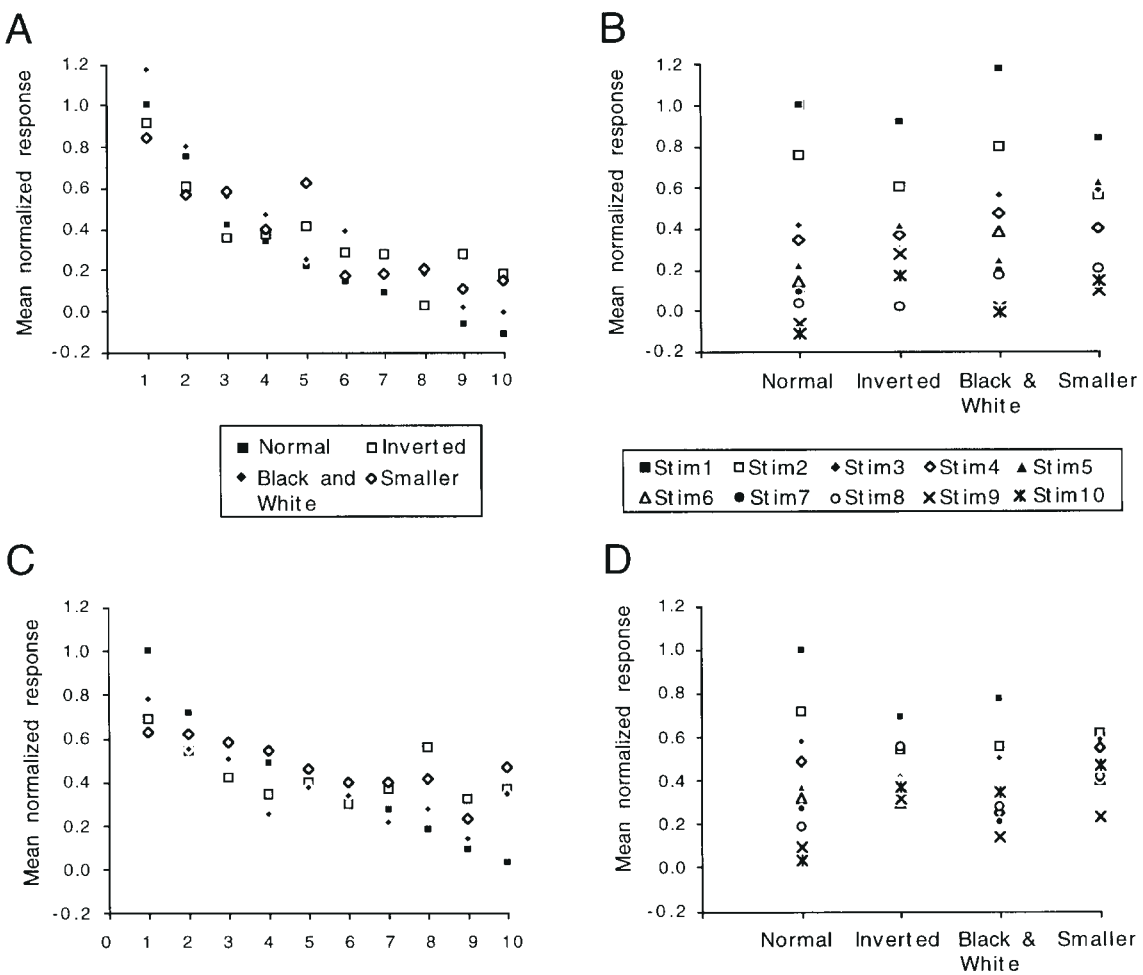

Figure 11. The effect of inversion, removal of color and changes in size on response selectivity. Faces and a variety of other stimuli were employed as stimuli. The effect of stimulus identity (stimulus 1–10) is shown for face-selective (*A*) and visually selective neurons (*C*) by the magnitude of each response divided by the best response to an unmanipulated stimulus on the ordinate and the stimulus identity on the abscissa. Stimuli are ranked from 1 to 10 based on the magnitude of their response to the normal stimuli. Stimulus identity was strongly correlated with the magnitude of the response across all manipulations for both face-selective (Pearson moment correlation, $r = -0.877$; Bonferroni $P < 10^{-9}$) and visually selective neurons (Pearson moment correlation, $r = -0.741$; Bonferroni $P = 4.5 \times 10^{-8}$). By contrast there was no significant correlation between stimulus manipulation (inversion, removal of color and decrease in size) and magnitude of response for either face-selective (*B*; Pearson moment correlation, $r = 0.132$; Bonferroni $P = 0.418$) or visually selective neurons (*D*; Pearson moment correlation, $r = 0.074$; Bonferroni $P = 0.649$).

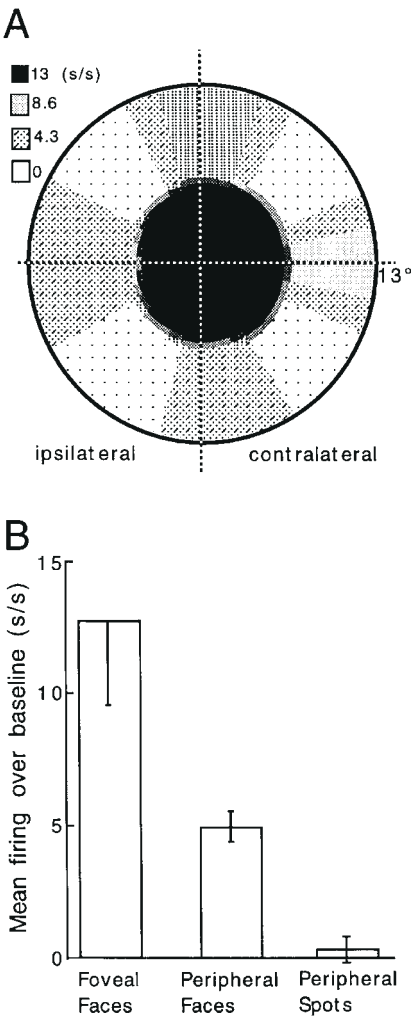

Figure 12. (*A*) Averaged responses of all face-selective neurons tested for receptive field size indicated by shading. Cells were tested with nine stimulus locations: one at the fovea and eight in a ring 13° from the fixation point separated by 45°. The center of the circle represents the response at the fovea and the circle itself represents the eccentricity of the other eight stimuli (13°). Note that the best response was to foveal stimulation with individual neurons also responding to other stimuli, especially contralateral to the recording electrode. (*B*) Averaged responses of face-selective neurons to foveally and peripherally presented faces and to peripherally presented spots of light. The response to peripheral faces was significantly stronger than to the spots of light ($P = 6.6 \times 10^{-7}$; two-tailed *t*-test for paired observations).

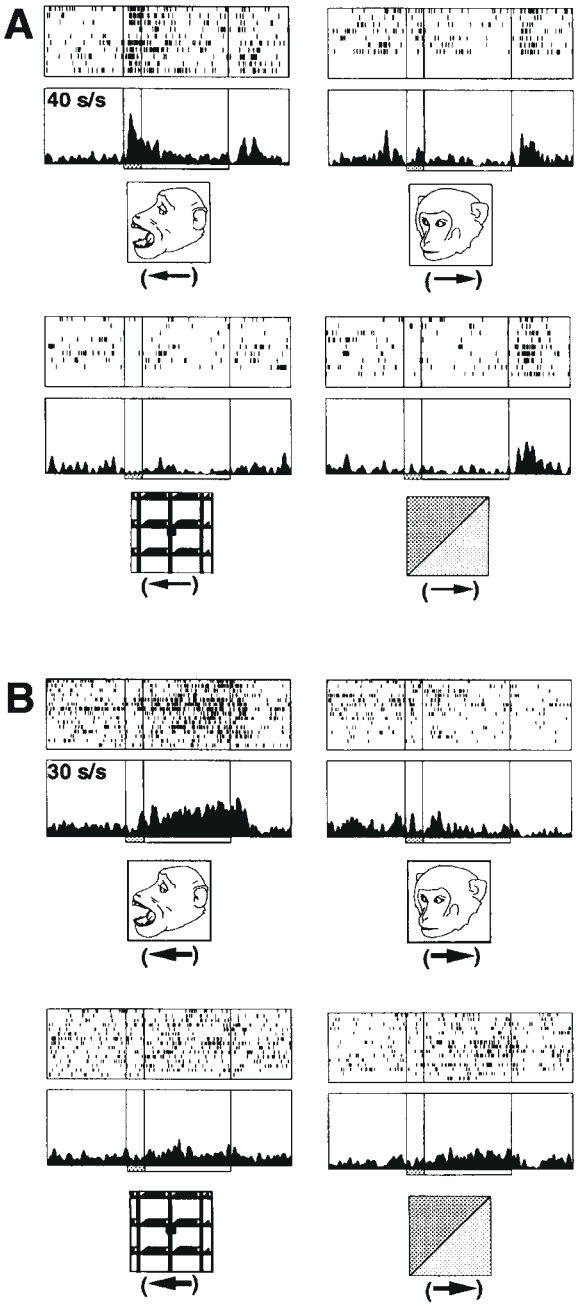

Figure 13. Two types of delay activity. (*A*) Trial-by-trial rasters and SDFs from a cell with 'onset' delay activity on the oculomotor delayed-response task. The first vertical line denotes the presentation of the visual cue, the second vertical line indicates stimulus offset and the beginning of the delay period, and the third vertical line indicates the end of the delay period and the signal to respond. The duration of the visual cue (0.5 s) is indicated by the dark shaded bar under the spike density function, and the delay period (2.5 s) is indicated by the white bar. Line drawings below the SDFs represent the stimuli and arrows indicate the saccade direction at the end of the delay period. This neuron had a visual response to a face which then persisted into the delay period. There was no visual or delay response to the color patterns shown or to four other cue stimuli (data not shown). (*B*) Trial-by-trial rasters and summed histograms from one cell with 'offset' delay activity on the oculomotor delayed response task. Conventions are as in (*A*). This neuron had a response selective for one of the faces in the delay period which began with the offset of the face. As in (*A*) there was no visual or delay response to the color patterns shown or to four other cue stimuli (data not shown).

face-selective neurons (Perret *et al.*, 1982, 1988; Desimone *et al.*, 1984). Also, the face-selective neurons in the PFC did not respond similarly to highly familiar emotionally or motivationally significant stimuli such as handling gloves or food. The latency of face-selective responses (mean = 136 ms) was quite similar to that of responses in IT (140 ms) (Rodman *et al.*, 1993). The similarity of IT and IFC neurons resembles the results of a recent study showing the similarity between neural responses in parietal area LIP and prefrontal area 8 (Chafee and Goldman-Rakic, 1998). One difference between the IFC and IT is that the incidence of face selectivity appears to be somewhat lower in the prefrontal convexity (~5%) than in the temporal lobe (5–20%) (Perrett *et al.*, 1982; Yamane *et al.*, 1988; Tanaka *et al.*, 1991; Desimone *et al.*, 1984; Baylis *et al.*, 1987). Similarly, 30–40% of neurons in the IFC have selective visual responses (F.A.W. Wilson, S.P. Ó Scalaidhe and P.S. Goldman-Rakic, unpublished observations) compared to 60–80% in IT (Rodman *et al.*, 1993). Consistent with these results, recent human ERP recordings have shown face-specific potentials, smaller than those seen

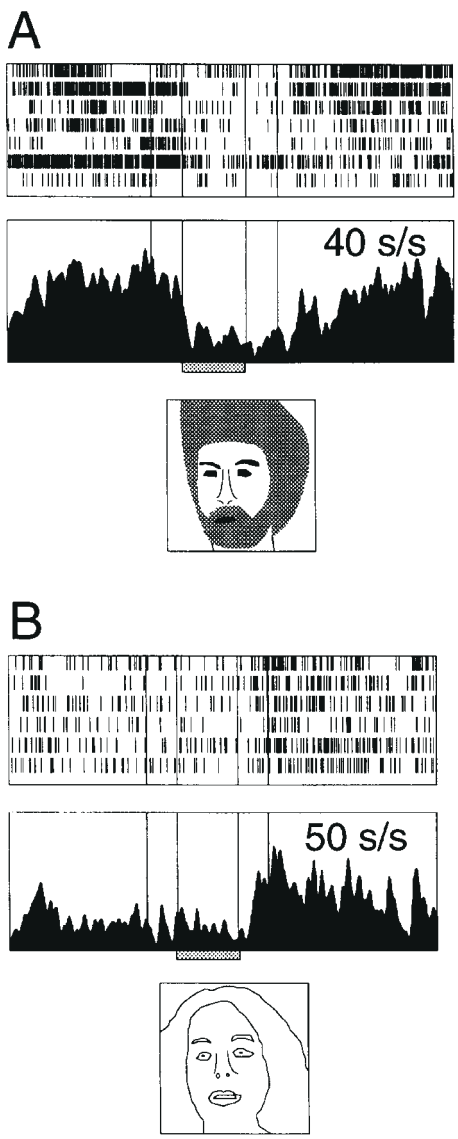

Figure 14. Two types of post-stimulus responses. (*A*) An example of a neuron with an inhibitory visual response that persists after the offset of the visual stimulus homologous to 'onset' delay activity. As in Figure 7 the first vertical line indicates visual fixation, the second vertical line indicates onset of the visual stimulus, and the third vertical line indicates the offset of the visual stimulus. The final vertical line indicates the offset of the fixation point and delivery of juice. The stimulus duration is indicated by a bar under the SDF and the scale of the SDFs are indicated to their right. (*B*) A neuron with face-selective post-stimulus activity in the absence of a visual response, homologous to 'offset' delay activity. Conventions are as in (*A*). There was a strong and lasting post-stimulus response to the face and not to any of the other stimuli. This activity continued throughout the ITI and was not related to eye movements or to any other observable behavior that followed the face stimulus during the post-trial period. These type of responses were seen in monkey GR (both examples shown) who was not trained on the memory tasks as well as the two monkeys trained on the memory task (LN and NA).

in fusiform gyrus, restricted to inferior PFC (Allison *et al.*, 1999). Altogether these findings reveal that the face-selective responses, like responses in the IFC in general, are more similar to those of the temporal lobe than they are to those of dorsal PFC, suggesting not only that the IFC contains neurons that are part of a transcortical network that is specific for face processing, but that face and spatial processing are segregated in the PFC.

Receptive Field Properties

A hallmark of visual receptive fields in IT is that they are most responsive to foveal stimulation (Gross *et al.*, 1972; Desimone and Gross, 1979; Rodman *et al.*, 1993). The face-selective neurons in the IFC also responded best to foveal stimulation. Although we did not attempt to precisely map receptive fields in the PFC, they were clearly often large and bilateral, as in IT (Gross *et al.*, 1972; Desimone and Gross, 1979; Desimone *et al.*, 1984; Rodman *et al.*, 1993). Suzuki and Azuma (Suzuki and Azuma, 1983) also found that neurons anterior to the arcuate sulcus and ventral to the principal sulcus have large receptive fields that include the fovea. A recent study of PFC described non-foveal receptive fields in the IFC during the delay period of a memory task (Rainer *et al.*, 1998). The difference between these results and ours may be due to the training of the monkeys in the Rainer *et al.* study; this study used the same 2–5 stimuli over months of experience and required the monkeys to identify the stimuli without looking at them. It would be interesting to test neurons in the same monkeys under more natural conditions before training on such tasks to determine if plasticity in response to unusual task demands can produce this magnitude of receptive field change.

Responses in the face-selective neurons were sometimes evoked by peripheral spots of light, although these were invariably weaker than those to faces. Therefore, like neurons in the temporal lobe, face-selective IFC neurons respond best to complex stimuli presented at the fovea, less well to peripherally presented complex stimuli, and least of all to peripherally presented spots of light. These results emphasize an important aspect of identity processing in the visual system – that the identity-selective regions have both specificity for identity and an emphasis on central vision, consistent with how, under natural conditions, primates foveate objects of interest to identify them.

Relationship Between Perception and Working Memory

Face-selective delay neurons were found to be located exclusively in the same areas that face-selective visual responses were found. This finding constitutes evidence that face-selective delay period activity arises directly from neurons receiving submodality-specific sensory input from the temporal lobe and/or from neurons locally connected to these cells. Indeed, the prefrontal neurons were equally responsive to the same visual stimuli whether they served as stimuli in a memory task or simply viewed the stimuli while visually fixating, as has been shown in the spatial PFC system (Funahashi *et al.*, 1990). This implies that very similar visual responses seen on the memory task in trained monkeys are also present in untrained animals. More significant is the observation that selective visual activity often continues after the offset of the visual stimulus both in animals trained on memory tasks and in a monkey that was not (Figs 12,13). Further, prolonged delay-like 'onset' and 'offset' post-stimulus activity was observed in all three monkeys in the absence of any behavioral response. These findings suggest that the putative mnemonic activity arises from the same neurons of the IFC that are visually selective in the absence of an explicit memory or movement requirement.

Specialization of Function in PFC

A number of methodological factors are probably responsible for the unprecedented magnitude of regional specialization shown in the current study. First, the use of face stimuli, which are highly spatially constrained, decreased the likelihood that

internal spatial features are responsible for the selectivity of the neurons. By contrast, at least some of the object-selective neurons, observed by us and others, may be responding based on incidental stimulus attributes unrelated to their identity. For example, unlike face-selective neurons, some 'object-selective' neurons may respond selectively based on internal spatial characteristics. Second, perhaps due to their ecological significance, faces proved to be highly effective for eliciting selective responses from IFC neurons. As shown by the increasing level of regional specialization seen with increasingly strict response criteria (Fig. 5), only using highly effective stimuli will reveal the full degree of regional specialization present in an area. It is perhaps significant that the imaging studies of the inferior PFC that have observed regional specialization based on visual stimulus modality have used faces as visual stimuli (Courtney *et al.*, 1996; Haxby *et al.*, 1996). Third, in the present study every neuron was sampled without regard for whether it appeared responsive based on cursory testing. By not preselecting the neurons recorded from (and obtaining artificially high percentages of responsive neurons in all areas) an unbiased estimate of the percentage of face-selective neurons in each area was obtained. Fourth, the use of rigorous statistical criteria to analyze the responses is important for determining functional specialization because any statistical noise will be evenly distributed throughout all areas recorded from and therefore obscure regional specialization (Fig. 6). By using a strict response magnitude criterion in addition to the ANOVA criteria we eliminated the possibility of including neurons with statistically detectable but weak responses. As shown by Figure 5, including large numbers of neurons with weak selectivity in the sample of responsive neurons (e.g. by recording unusually large numbers of trials or using suboptimal stimuli) can obscure the localization of the strongly responsive neurons which are most likely to reflect the function of the cortical region. A similar situation obtains in the visual system. For example, the IT cortex is not thought to be related to the detection of stimulus movement (Ó Scalaidhe *et al.*, 1995), yet a large percentage of neurons (~50%) of IT neurons show (often weakly) selective responses to stimulus movement (Gross *et al.*, 1972; Rocha-Miranda *et al.*, 1975). Thus, the presence of even a fairly high percentage of weakly selective neurons does not necessarily denote a critical function of a cortical area. Fifth, we recorded isolated single neurons. By recording multiple units the likelihood of a 'neuron' responding is increased. The probability of one neuron being selectively responsive out a group of n neurons is: $f(n) = 1 - (1.0 - P)^n$ where $f(n)$ is the probability of a neuron in the group of n neurons being selective and P is the incidence of responsiveness in single neurons. With respect to functional specialization it should be appreciated that *any* source of noise, whether it be due to type 1 statistical errors, sampling bias, inclusion of weakly selective (and probably at best incidentally task related) neurons, recording multiple neurons or histological localization errors, will mitigate against finding regional specialization.

It has recently been suggested that the regional specialization observed in PFC (Wilson *et al.*, 1993) is a result of training on specific tasks (Rao *et al.*, 1997) [see Iarovici (Iarovici, 1997)]. The present results strongly argue against this conjecture since there was at least as much regional specialization observed when monkeys simply viewed visual stimuli as when they performed memory tasks. Further, there was as much regional specialization for processing of faces in a monkey that was never trained on a memory task as there was in the two monkeys that were trained on memory tasks (Fig. 2). Finally, the existence of post-stimulus activity, similar to delay activity, in a monkey never trained on a memory task (see Fig. 14) strongly suggests that learning and/or performance of memory tasks is unnecessary for the observation of either delay-like activity or regional specialization.

Function of Face-selective Neurons in the PFC

The role of IT in object recognition (Gross, 1992) suggests that neurons selective for faces in IT mediate face recognition. Although, to our knowledge, there are no studies of the effects of prefrontal damage on face recognition or discrimination, a number of studies have reported only small and transient impairments on visual discrimination using objects and colors after damage to the IFC (Passingham, 1975; Bachevalier and Mishkin, 1986; Kowalska *et al.*, 1991). Similarly, IFC lesions produce only small and transient impairments on delayed non-matching-to-sample tasks using trial unique stimuli (Kowalska *et al.*, 1991), unlike orbito-frontal lesions (Bachevalier and Mishkin, 1986; Meunier *et al.*, 1997). The lack of effects on visual discrimination and the impairments on working memory tasks (see below) contrasts with the prevalence of visual responses and the relative scarcity and weakness of delay activity. Perhaps any visual function lost due to IFC damage can be compensated for by remaining visual areas such as IT cortex, while the prefrontal contribution to performance of memory tasks is critical.

IFC lesions cause impairments on tasks requiring object alternation (Mishkin and Manning, 1978), delayed object and color matching (Passingham, 1975; Mishkin and Manning, 1978) when small sets of stimuli are employed. A recent study which found only a small and transient impairment on simultaneous color matching and no subsequent impairment on delayed color matching (Rushworth *et al.*, 1997) did not involve removal of the lateral orbital cortex, which contains face- and object-selective neurons. Indeed, removal of the lateral orbital cortex seems to be necessary to see the largest impairments on delayed color- and object-matching tasks (Passingham, 1975; Mishkin and Manning, 1978) consistent with it receiving input from IT (Martin-Elkins and Horel, 1992; Morecraft *et al.*, 1992; Suzuki and Amaral, 1994; Carmichael and Price, 1995). These effects also distinguish the inferior prefrontal areas from the principal sulcus, lesions of which produce small and transient effects on tasks involving memory for objects or object features (Mishkin and Manning, 1978). Like the effects of delay on spatial tasks in the principal sulcus (Goldman *et al.*, 1971), the impairments following IFC lesions are present at very brief delays (Passingham, 1975; Mishkin and Manning, 1978). The impairment at very short delays after both principal sulcal lesions and IFC lesions suggests that monkeys with such lesions perform spatial and object working memory tasks, respectively, in an 'out of sight, out of mind' fashion. An unambiguous test of the function of face-selective neurons, however, awaits: (i) the use of tasks with faces as stimuli, (ii) the use of varying delay lengths and (iii) a complete removal of the PFC from which face-selective neurons have been recorded. Although the definitive lesion study has yet to be performed, the preponderance of evidence suggests that the face-selective cells in the IFC and lateral orbital cortex, rather than playing a critical role in face discrimination or recognition, play a role in working memory for faces analogous to that of other cells in PFC for spatial working memory.

Notes

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