Responses to Auditory Stimuli in Macaque Lateral Intraparietal Area I. Effects of Training

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Grunewald, Alexander, Jennifer F. Linden, and Richard A. Andersen. Responses to auditory stimuli in macaque lateral intraparietal area. I. Effects of training. *J. Neurophysiol.* 82: 330–342, 1999. The lateral intraparietal area (LIP) of macaques has been considered unresponsive to auditory stimulation. Recent reports, however, indicate that neurons in this area respond to auditory stimuli in the context of an auditory-saccade task. Is this difference in auditory responsiveness of LIP due to auditory-saccade training? To address this issue, LIP responses in two monkeys were recorded at two different times: before and after auditory-saccade training. Before auditory-saccade training, the animals had never been trained on any auditory task, but had been trained on visual tasks. In both sets of experiments, activity of LIP neurons was recorded while auditory and visual stimuli were presented and the animals were fixating. Before training, 172 LIP neurons were recorded. Among these, the number of cells responding to auditory stimuli did not reach significance, whereas about one-half of the cells responded to visual stimuli. An information theory analysis confirmed that no information about auditory stimulus location was available in LIP neurons in the experiments before training. After training, activity from 160 cells was recorded. These experiments showed that 12% of cells in area LIP responded to auditory stimuli, whereas the proportion of cells responding to visual stimuli remained about the same as before training. The information theory analysis confirmed that, after training, information about auditory stimulus location was available in LIP neurons. Auditory-saccade training therefore generated responsiveness to auditory stimuli de novo in LIP neurons. Thus some LIP cells become active for auditory stimuli in a passive fixation task, once the animals have learned that these stimuli are important for oculomotor behavior.

INTRODUCTION

Most behaviors require some kind of sensorimotor transformation: information is acquired by a sensory modality, and, based on that information, motor acts are executed. To understand how the brain is involved in behavior, it is important to understand how sensorimotor transformations take place. At the sensory end, information must be acquired through sensory transduction and then processed to extract location information. At the motor end, movement output must be generated through the coordinated activation of muscles. In between these two extremes, several other steps necessary for sensorimotor transformation can be identified. For example, the sensory stimulus is assigned significance for a particular behavior, a decision or plan is made to execute a movement, and a coordinate transformation occurs.

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Research during the last several decades has shown that the posterior parietal cortex (PPC) plays a crucial role in this intermediate level of sensorimotor transformation (for review, see Andersen et al. 1997). Recent studies are beginning to examine the exact nature of this sensorimotor transformation process, in particular the involvement of PPC in attention (Gottlieb et al. 1998), decision making (Shadlen and Newsome 1996), movement planning (Snyder et al. 1997), and coordinate transformation (Andersen et al. 1993).

The present article focuses on the lateral intraparietal area (LIP), which lies within the PPC and was originally defined by its characteristic connections to visual extrastriate and oculomotor areas (Andersen et al. 1985a). Area LIP responds during visual stimulation (Blatt et al. 1990), appears to be involved in coordinate transformation (Andersen et al. 1985b; Brotchie et al. 1995; Stricanne et al. 1996), participates in the planning of movements (Bracewell et al. 1996; Mazzoni et al. 1996b), and responds preferentially for eye movements rather than arm movements (Snyder et al. 1997). Thus LIP plays an important role in the sensorimotor transformations necessary for planning eye movements.

Previous descriptions noted that area 7 (at the time area 7 included area LIP) in PPC is not responsive to auditory stimulation (Hyvärinen 1982; Koch and Fuster 1989; Mountcastle et al. 1975). In contrast, more recent studies have shown that neurons in LIP do respond to auditory stimuli in the context of an auditory-saccade task (Mazzoni et al. 1996a; Stricanne et al. 1996). Specifically, when monkeys were trained to memorize the location of an auditory stimulus and to make a saccade to that location on cue after a short delay (perform an *auditory memory saccade*), neural responses were found during the movement, during the delay, and most surprisingly, during the stimulus presentation. The presence of auditory responses during the stimulus presentation suggests that auditory responses in LIP might be sensory in nature, an interpretation that is further supported by their short latencies (Mazzoni et al. 1996a). Thus the recent reports seem to contradict earlier studies.

There are four ways in which this apparent discrepancy could be explained. First, it is possible that early studies failed to detect auditory responses in LIP, because the search for such responses was not carried out in a systematic fashion. Second, auditory-saccade training may recruit LIP neurons to respond to auditory stimuli. Third, the task that the monkey is performing may determine whether LIP neurons respond to auditory stimuli. Finally, both training and task may affect LIP responses to auditory stimuli. This fourth possibility stands in

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contrast to the two previous possibilities, where either only training affects neural responses without any influence on responses due to behavioral modification (possibility 2), or only behavioral modulation affects neural responses, without any influence of training (possibility 3). The present study explores the first two possibilities: the animal is performing the same fixation behavior, but recordings are made before and after auditory-saccade training. The companion paper examines how auditory and visual responses in area LIP after auditory-saccade training are affected by the task the animal is performing, comparing responses in a fixation-only task with responses during an auditory-saccade task (Linden et al. 1999). Taken together, these studies show that, before training, no responses to auditory stimuli are present in LIP, and that both training and task have a strong effect on auditory responsiveness of area LIP. Preliminary reports of the present results have been published previously in abstract form (Linden et al. 1996, 1997).

METHODS

Animals and animal care

Two male rhesus monkeys (*Macaca mulatta*) were used in the experiments. Neither had participated in any previous auditory experiments. *Monkey B* was 6 yr old at the beginning of the experiments described in the present study. He had been previously used in another study involving visually guided eye movements. At the conclusion of the experiments, he was overdosed with pentobarbital, and histology was performed. *Monkey Y* had not been used in any earlier experiments, and he is still a subject in experimental research.

Experimental setup

All experiments and behavioral training sessions were conducted in complete darkness, in a double-walled sound-attenuating anechoic chamber (Industrial Acoustics Company). The walls of the chamber attenuated external sounds above 200 Hz by at least 60 dB, and the interior of the chamber qualified as anechoic for sounds between 200 Hz and 16 kHz [inverse-square-law test deviations from theoretical free-field conditions of $<$1.0 dB in 500-Hz to 8-kHz frequency range and $<$1.5 dB in 200-Hz to 16-kHz frequency range (see Schmitt 1983 for further explanation)]. While inside the chamber, the monkeys were monitored continuously with an infrared camera and a microphone. The monkeys' primate chair was mounted inside a frame of 90-cm-diam magnetic coils used to measure eye movements (see *Recording procedures*).

Two fixed grids of speakers and light-emitting diodes (LEDs) were used to present auditory and visual stimuli. An LED was mounted at the center of each speaker in the grids. In the earliest experiments a hexagonal grid was used; this grid was replaced with an improved rectangular grid in later experiments. The hexagonal grid was made up of 19 speaker/LED devices arranged hexagonally, such that the center-to-center separation of the devices was 12°. The center of the grid coincided roughly with the straight-ahead eye position of the monkeys. The rectangular grid was concave and consisted of 25 speaker/LED devices, with a center-to-center spacing of 8°. Both grids were placed ~80 cm from the monkey's head. Each LED subtended 0.4° of visual angle, and the luminance of the LEDs was ~70 cd/m^2. Both the magnetic coil frame and the stimulus array were padded with sound-absorbing acoustical foam (Sonex) to dampen echoes from their surfaces.

Free-field auditory stimuli were 500-ms bursts of band-limited noise (5–10 kHz, 5-ms rise/fall times, 70 dB SPL). This noise band was chosen because macaque monkeys have been reported to localize 5- to 10-kHz bandlimited noise well in azimuth (Brown et al. 1980), and because the frequency responses of the speakers were relatively flat (±10 dB SPL) within this range. In the recording experiments before the animals had been trained to perform auditory saccades, the speakers sounded about the same, but their responses had not been equalized. For saccade training and posttraining recordings, the input to each speaker was adjusted to equalize the output amplitude spectrum to within 2 dB of 70 dB SPL within the 5- to 10-kHz frequency band, as measured at the location where the monkey's head would be during an experiment. This equalization was performed to ensure that the monkeys were performing a localization task, rather than a spectral recognition task, when they were instructed to perform eye movements. The companion paper addresses the localization task in greater detail (Linden et al. 1999).

Surgical procedures

All surgical and animal care procedures were in accordance with National Institutes of Health guidelines and were approved by the California Institute of Technology Institutional Animal Care and Use Committee. All surgeries were performed under sterile conditions, using general anesthesia (10 mg/kg pentobarbital sodium intravenously). Heart rate, respiration rate, and temperature were monitored throughout each surgery. First, a stainless steel head post and a dental acrylic head cap were implanted onto the skull of each animal. In the same procedure, a scleral search coil was implanted to monitor eye movements (Judge et al. 1980). Analgesics and systemic antibiotics were administered for several days after surgery. After each surgery, the animals were allowed to recover for at least 1 wk before any behavioral training began. After recovery, the animals were trained to fixate and then to perform the pretraining task. Because fixation of a visual target involves a visual saccade to acquire the target, the animals were implicitly trained to perform visually guided eye movements. Once the animals performed the fixation task with sufficient accuracy (~95% success rate), a craniotomy was performed in a second surgery and a stainless steel recording chamber was mounted over PPC normal to the skull surface (stereotaxic coordinates at center: 6 mm posterior, 12 mm lateral). The chamber was implanted over the left hemisphere in *monkey B*, and over the right hemisphere in *monkey Y*. Different hemispheres were used in the two animals to detect any brain lateralization, but none was found.

Recording procedures

During training and recording, each monkey sat in a primate chair facing the stimulus grid. Electrodes were advanced into the brain with a hydraulic microdrive (Frederick Haer). To ensure that recordings were from LIP, rather than area 7a, which lies on the surface, the electrode was advanced into the sulcus (2,500–3,000 μm below the presumed dura) at the start of each recording session.

Single-unit extracellular recording was performed using tungsten microelectrodes. Electrode impedances were typically 0.5–2.0 MΩ at 1 kHz. A guide tube protected the electrode during penetration of the dura and served as the reference input for the differential microelectrode amplifier. The electrode signal was amplified by a factor of 2×10^5, band-pass filtered (Krohn-Hite) between 600 Hz and 5 kHz, and monitored continuously on an oscilloscope and audio monitor. Single units were isolated using a variable-delay voltage-time window discriminator (Tucker-Davis Technologies), and times of spike occurrence were recorded with 1-ms accuracy.

Eye position was monitored using the scleral search coil technique (Judge et al. 1980) and was sampled at 1 kHz. Each behavioral training or recording session began with an eye position calibration, during which the animal fixated visual stimuli at various locations on the stimulus grid. Eye position measurements could be made with high precision (±0.1°).

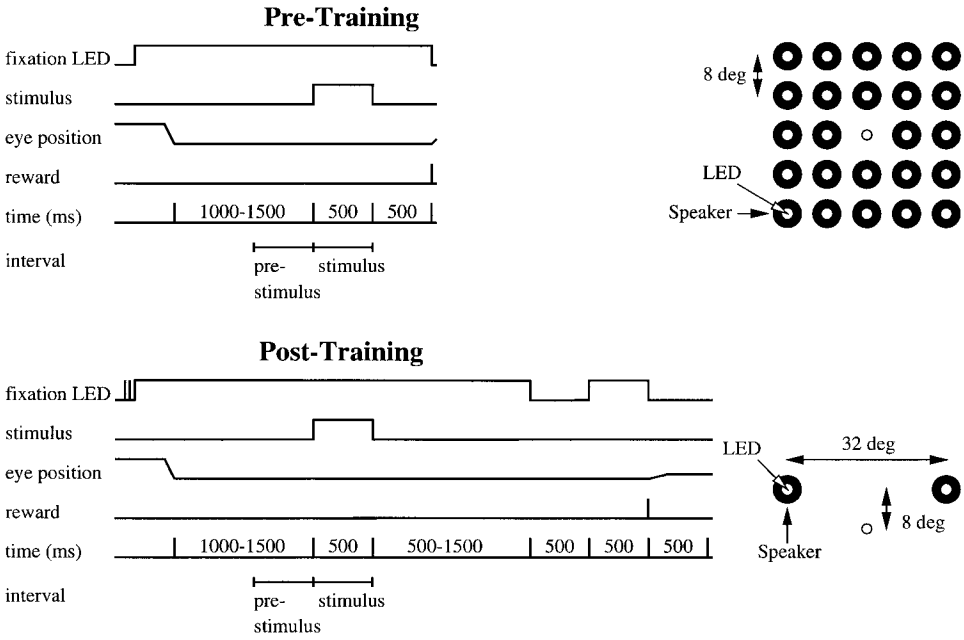

FIG. 1. *Left*: tasks used for recording and training. *Right*: speaker/light-emitting diode (LED) grids used pre- and posttraining. In both the pre- and posttraining experiments, monkeys were required to fixate during the stimulus interval, and for at least 500 ms after stimulus offset. For posttraining experiments, a period in which the monkeys had to fixate in darkness was added to the fixation task, to ensure that monkeys were not performing late saccades (see text).

Behavioral paradigms

Each animal participated in three behavioral phases. The first phase is referred to as the pretraining phase (before auditory-saccade training). The second phase is called the training phase (during auditory-saccade training), and the third phase is termed the posttraining phase (after auditory-saccade training). Note that even in the pretraining experiments the monkeys were not completely naive, because they were familiar with fixation and visual saccade tasks that were used for eye position calibration measurements. Thus the behavioral phase name designates the animal's training with respect to auditory saccades alone. In all experiments, auditory and visual trials were randomly interleaved.

Pretraining

During the first set of experiments, the animals were required to hold their eye position within a square of width 6° (earlier experiments) or a circle of diameter 4–6° (later experiments) centered on the central LED in the hexagonal or rectangular grid, while auditory or visual stimuli were briefly presented at other locations in the grid. In each trial, the monkeys acquired fixation, held fixation for 1,000–1,500 ms until an auditory or visual stimulus appeared, continued holding fixation during the 500-ms stimulus presentation period, and then maintained fixation for another 500 ms after stimulus offset. This task is illustrated in Fig. 1. If the animals succeeded in this task, they were rewarded with a small quantity of water or juice.

Training (auditory saccades)

Once the pretraining experiments had been completed, the animals were trained to perform saccades to auditory targets. During training and in the subsequent experiments, only the rectangular grid was used. Two targets were employed: 8° above the fixation point, and either 16° to the left or to the right. Surprisingly, the auditory-saccade task was not easy for the monkeys to learn. Because initial attempts to train the animals without the use of visual feedback were not successful, the monkeys were trained by presenting an auditory target, requiring the animals to complete a saccade to the auditory target in darkness, and then presenting a visual stimulus at the target location and requiring a corrective saccade. The visual feedback stimulus never appeared simultaneously with the auditory stimulus. Eye movements to auditory targets were deemed to have sufficient accuracy if they ended within a circular window of radius 16° around the target. A reward was administered if the auditory saccade was accurate, and if the subsequent corrective saccade was also accurate. The visual feedback stimulus was gradually moved further back in time, so that eventually it appeared 500 ms after the animals had acquired the auditory target window. In all trials, however, a visual feedback stimulus appeared at the end of the trial. This procedure was continued even during the recording sessions.

Monkey B took 7 mo to learn to perform eye movements to four targets spaced in azimuth. However, the accuracy of the eye movements was not very high (about ±12°), so for the recording experiments only two targets were used. *Monkey Y* took 5 mo to learn to make auditory saccades to nine targets, with the same accuracy. To maintain consistency across the two animals, the same two target locations were employed for both animals during the recording experiments.

Once the animals had learned to perform auditory saccades to these two stimulus locations with acceptance windows of diameter <24° and with a success rate exceeding 80%, auditory and visual memory-saccade training began. In the memory-saccade task, the monkeys were required to maintain fixation through presentation of an auditory or visual stimulus at one of the target locations, and then to continue fixating for a delay period after stimulus offset. Once the fixation light had been extinguished, the animals had to make a saccade to the remembered location of the auditory or visual stimulus. On successful completion, they were rewarded. Both monkeys learned the memory-saccade paradigm for auditory stimuli in a single day, but training of visual memory-saccades required a few days.

Posttraining

After the animals had learned the memory-saccade task, they were trained to perform a modified fixation task similar to the one they had performed in the pretraining phase. In the modified fixation task, the fixation LED flashed twice before staying on. This flash sequence indicated to the animals that a fixation trial was about to occur (rather than a memory-saccade trial). Once the fixation LED stopped blinking, the animals had to acquire the fixation LED and hold their eye position within a circle of diameter 4–6°. After a variable interval (1,000–1,500 ms), either an auditory or a visual stimulus appeared at one of the locations used in the memory-saccade task. As in the

training phase, two targets were employed, 8° above the fixation point and either 16° to the left or 16° to the right. Following disappearance of the stimulus, the fixation LED remained on for 500–1,500 ms, and the monkeys continued fixating. Then the LED was extinguished, but the monkeys had to maintain fixation at the same location in darkness for 500 ms. Continued fixation was required to ensure the monkeys were truly performing the fixation task, and not making delayed saccades. Finally the fixation LED reappeared, and if the monkeys continued fixating for 500 ms they were rewarded with a drop of water or juice. Eye position was monitored for at least 500 ms following the reward, again to ensure that the monkeys did not perform very late saccades to the stimulus locations. Blocks of trials in which the animals performed the fixation task were alternated with blocks of trials in which they performed the memory-saccade task, which is described in the companion paper (Linden et al. 1999).

Recording site search strategy

Neural data were recorded in only two of the three behavioral phases: the pretraining phase and the posttraining phase.

PRETRAINING. While the animals were performing the fixation task described for the pretraining behavioral paradigm, the electrode was advanced until a cell could be isolated. Any cell that was encountered, and that could be kept isolated long enough to characterize, is included in the analysis in the present study. In other words, there was no bias in the search strategy that might have favored finding cells with auditory or visual responses.

POSTTRAINING. In the posttraining experiments, a different search strategy was used. While the electrode was advanced in search of neurons, the monkeys were performing the auditory and visual memory-saccade task. Data were recorded from any isolated cell that appeared to exhibit a response during any period of auditory or visual memory-saccade trials. Thus there were two differences between the pre- and posttraining search strategies: the task the animals were performing during search and the selection criteria. The posttraining search strategy resulted in a bias favoring neurons that responded during the memory-saccade task. In our estimation and according to our analyses and controls, the results are not affected by these differences. This issue is further addressed in RESULTS and in DISCUSSION.

Analysis

All analyses of neural data were based on firing rates (spikes/s or Hz) over a 500-ms interval. Two intervals were analyzed. The prestimulus period started 500 ms before stimulus onset and ended at stimulus onset. The stimulus period started at stimulus onset and ended at stimulus offset. To evaluate whether a neuron exhibited spatial tuning, a Kruskal-Wallis test (nonparametric ANOVA) of firing rate during the stimulus period versus location was performed. This is an appropriate measure of responsiveness, because it allows us to rule out spatially nonspecific responses that might occur due to general arousal effects. Separate analyses that compared stimulus and prestimulus period responses at each location were also carried out and yielded the same trends. In addition, to detect any untuned responses, the location means of stimulus period responses were pooled and compared with prestimulus location means. This analysis showed no conclusive trends for pretraining data or posttraining data. A significance level of 0.05 was employed throughout, and all statistical tests were two-tailed.

To study response properties across the population of neurons, the information that was carried by the neurons about stimulus location was quantified. Unlike the spatial tuning analysis, which merely categorizes cells as tuned or not, the information theoretic analysis quantifies the degree of spatial tuning. The distribution of this quantity can then be used to summarize the population behavior. The noise level in a neuron's response was estimated by taking the standard deviation of the firing rate during the 500-ms prestimulus period. The standard deviation was used as the binwidth in subsequent calculations to obtain a conservative estimate of the information content (Gnadt and Breznen 1996). The firing rates were binned to form two matrices (one for each modality); firing rate bins constituted one dimension of each matrix, and stimulus position the other dimension. The matrices were normalized to estimate joint probability densities. The matrices were also used to estimate marginal probability densities. The information carried by a neuron about stimulus location was then given as the mutual information between stimulus location and firing rate

$$I = \sum_{s} \sum_{r} P(s, r) \log_2 \frac{P(s, r)}{P(s)P(r)}$$

where s is the index of each stimulus, r is the index of the firing rate bin, $P(s, r)$ is the joint probability, and $P(s)$ and $P(r)$ are the marginal probabilities (Rolls and Tovee 1995).

Direct comparison of the stimulus location information available in LIP responses before and after training is not possible, because there is a greater amount of location information available in the stimulus in pretraining experiments than in posttraining experiments due to the greater number of locations tested (18/24 locations vs. 2 locations). The information present in the stimulus period has to be measured relative to a reference level of information instead. To obtain a reference level of location information for each cell, the mutual information was recalculated after all the trial conditions had been shuffled to destroy any correspondence between stimulus location and firing rate. This procedure was repeated 100 times for each cell, and the median mutual information for shuffled data was used as the reference information for that cell. When this reference level is subtracted from the original information, the null hypothesis, that no

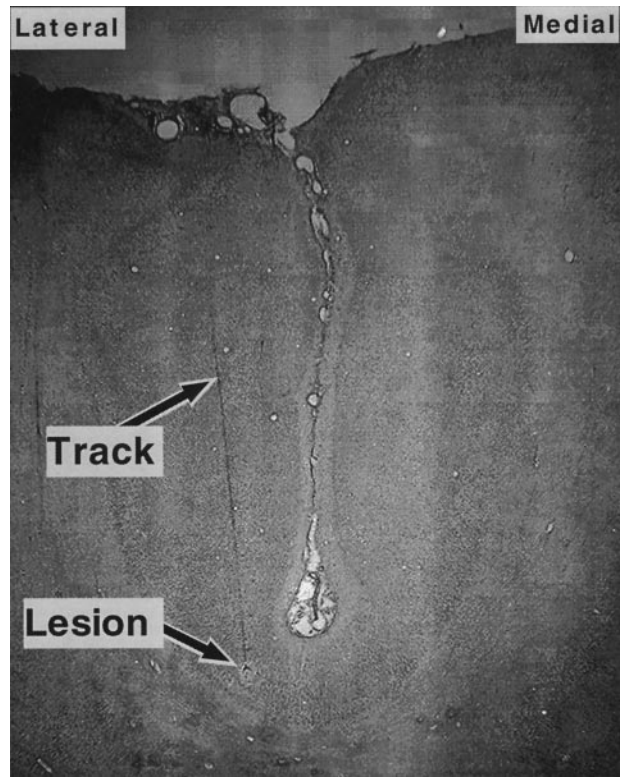

FIG. 2. Nissl-stained section of the intraparietal sulcus from the left hemisphere of *monkey B*. Left is the lateral aspect. The electrode track in which an electrolytic lesion was made is visible on the lateral bank of the sulcus. At the end of the track the lesion site is visible. The lesion is at least 2 mm deeper than the deepest cells that were recorded.

location information about the stimulus was available, can be evaluated. Because the same trials go into the calculation of original information and shuffled information, this analysis is not subject to overestimation due to use of inappropriately small bins.

Histology

After the recordings in *monkey B* were completed, two electrolytic lesions, one shallow (2 mm below dura) and one deep (10 mm below dura), were placed in each of two electrode tracks. On the next day the animal was overdosed with pentobarbital sodium (50 mg/kg) and then perfused with a 10% formaldehyde solution. The brain was extracted and sectioned in 50-μm sections using a freezing microtome, and sections were stained with cresyl violet. Histological examination of the electrolytic lesion sites confirmed that recordings had been made in the lateral bank of the intraparietal sulcus. Figure 2 shows a photomicrograph of a section that includes one of the lesion sites and electrode tracks. Note that only the deep lesion is visible. All cells were recorded at least 2 mm shallower than the site of this lesion.

RESULTS

Database

In the pretraining experiments, 77 neurons were recorded in *monkey B*, and 95 neurons in *monkey Y*, for a total of 172 neurons. In the posttraining experiments, 99 neurons were recorded in *monkey B*, and 61 neurons in *monkey Y*, for a total of 160 neurons. All results are pooled for the two monkeys, because all trends existed and reached significance in each monkey individually.

Main results

PRETRAINING. In the pretraining experiments, very few cells were encountered that had an auditory response. A cell that was recorded before training is shown in Fig. 3. This cell exhibits no auditory response for any stimulus on the grid and has no significant auditory spatial tuning (Kruskal-Wallis test, $P > 0.3$). On the other hand, this cell has a strong response to visual stimulation and strong visual spatial tuning ($P < 0.001$).

Before training, only 6 of 172 (3%) neurons exhibited significant spatial tuning for auditory stimuli, whereas 78 of 172 (45%) of the cells exhibited spatial tuning for visual stimuli, usually contralateral to the recording chamber. The binomial test, which measures how likely an observed proportion is (i.e., 6/172), given an expected proportion (i.e., the false positive rate of 5%), confirmed that the number of cells with auditory spatial tuning did not differ significantly from the number expected by chance ($P > 0.5$). The proportions of neurons with spatial tuning are shown in Fig. 4 for both auditory and visual modalities.

Inspection of responses from the six cells that showed significant auditory spatial tuning confirmed that even these cells did not have obvious auditory responses. Figure 5 shows the histogram for the cell with the smallest P value in the test of spatial tuning; however, even for this cell, there is no obvious response to auditory stimuli.

To further quantify the spatial selectivity of LIP responses to auditory and visual stimuli, the amount of information carried by the spike rate about stimulus location was determined. For comparison, the location information present in the shuffled response was also quantified; for details see METHODS. On a cell-by-cell basis, the amount of location information present during original trials was compared with the location information present in shuffled trials. Histograms of these cell-by-cell differences are shown in Fig. 6. For auditory stimuli there was no significant difference between the amount of location information carried in original and in shuffled trials (Wilcoxon signed-rank test, $P > 0.6$), but for visual stimuli this difference was significant ($P < 0.001$). Thus, before training, the firing rates of LIP neurons did not convey any information about the location of auditory stimuli, whereas they did represent information about the location of visual stimuli.

POSTTRAINING. In the posttraining experiments, some neurons exhibited very brisk responses during auditory stimulation while the monkeys were performing the modified fixation task. Figure 7 shows such a neuron. In addition, many cells had visual responses, usually contralateral to the recording chamber.

Across the population, ~12% (19/160) of cells had spatially tuned responses during auditory stimulation. One-half (46%; 73/160) the cells exhibited spatial tuning during visual stimulation. These proportions are illustrated in Fig. 4. The percentage of cells exhibiting auditory spatial tuning is significantly greater than the expected false positive level, as determined by the binomial test ($P < 0.001$).

On a cell-by-cell basis, the difference in information carried about the stimulus location between original and shuffled trials is shown in Fig. 6. There was a significant difference for auditory trials (Wilcoxon signed-rank test, $P < 0.001$), indicating that the firing rate during the stimulus period contained information about the stimulus location. Similarly, for visual trials, the amount of location information during original trials was higher than the amount of location information during shuffled trials ($P < 0.001$). Thus, after training, information about the stimulus location was present during both auditory and visual trials across the population of neurons recorded.

COMPARISON BETWEEN PRE- AND POSTTRAINING. A statistical comparison of the proportion of cells with spatial tuning in the pretraining and posttraining experiments was carried out using the Fisher-Irwin test. This test determines whether two proportions are likely to have been sampled from the same distribution. This analysis showed a significant difference for the proportion of cells with auditory spatial tuning before and after training (Fisher-Irwin test, $P < 0.01$), whereas there was no difference for visual spatial tuning ($P > 0.5$). This result is illustrated in Fig. 4.

Because 18 or 24 locations were examined in the pretraining experiments and only 2 locations in the posttraining experiments, a direct comparison of the location information available before and after training is not possible. However, it is appropriate to ask whether there was a significant difference between the amount of location information carried in the original responses, and the amount of location information carried in the responses after trials had been shuffled to destroy any correspondence between stimulus location and firing rate. As mentioned before, there was no difference in the pretraining auditory data on a cell-by-cell basis (Wilcoxon signed-rank test, $P > 0.6$), whereas there was a significant difference in the posttraining auditory data set ($P < 0.001$). Thus the information theory analysis confirms that before training no information about the location of auditory stimuli was represented in LIP activities, whereas after training auditory location information was represented.

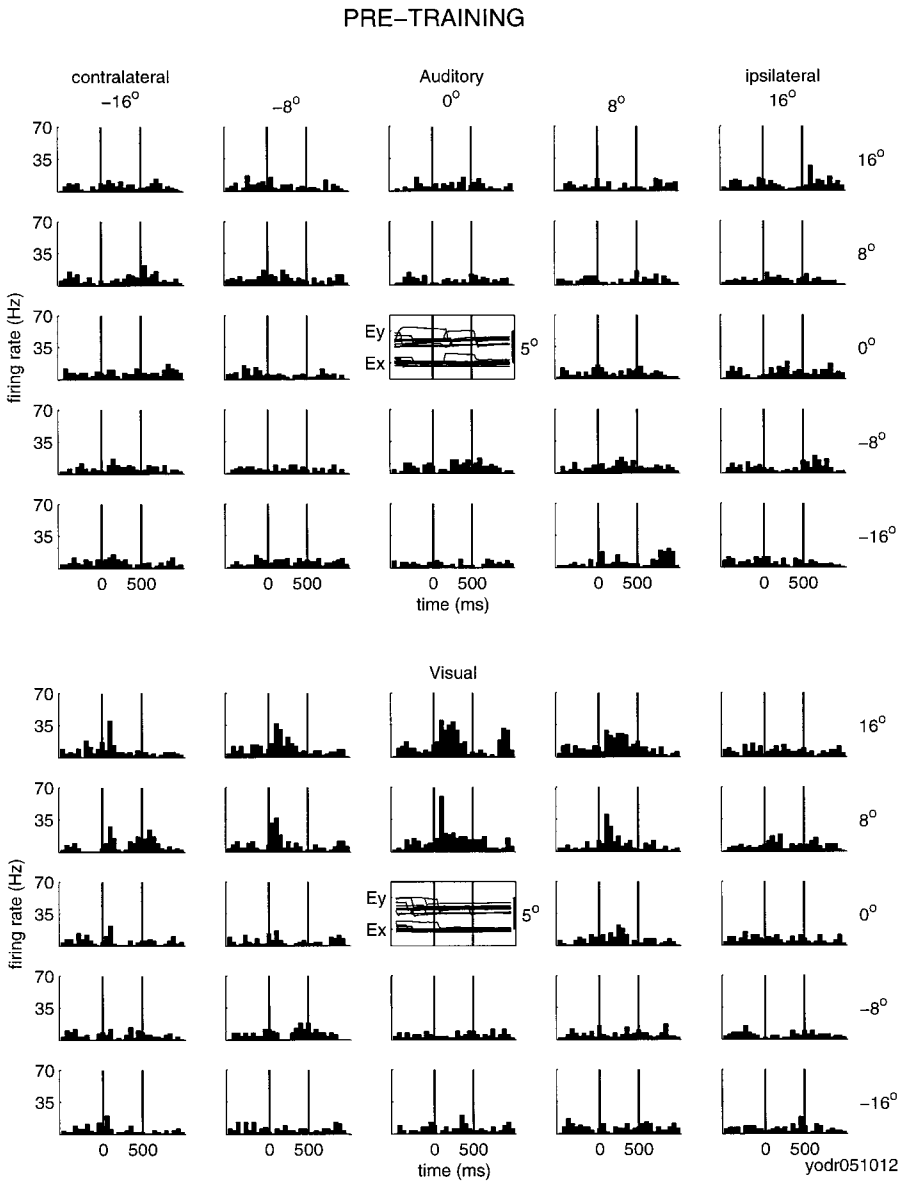

FIG. 3. Cell recorded in the pretraining experiments. *Top*: responses to auditory stimuli. *Bottom*: responses to visual stimuli. Each plot corresponds to the location of the stimulus on the rectangular grid. Plot in the middle of each grid shows representative eye movements recorded for trials in which a stimulus was presented at location (0, 16). At all other locations a peristimulus firing rate histogram is plotted; firing rates are indicated in Hz (spikes/s) and the *x*-axis is time. The 2 bold vertical lines in each plot bracket the period when the stimulus was present. Ex and Ey refer to horizontal and vertical eye positions, respectively.

Control analyses

CONTROL FOR SEARCH BIAS. After training, the search procedure was slightly different, as outlined in METHODS. It is possible that this difference could account for the apparent increase in the responsiveness of LIP to auditory stimuli after training. Two factors argue against this explanation.

First, it is possible to restrict the analysis of the posttraining data to neurons that exhibited a visual response, and to identify the proportion of neurons that had responses to auditory stimuli in that subsample. In other words, we can introduce an artificial post hoc search bias whereby only cells that have visual responses are studied. Of the cells recorded before training, 78 exhibited visual spatial tuning, and of these only 2 had auditory spatial tuning. In contrast, after training, 73 cells exhibited visual spatial tuning, and of these 13 had auditory spatial tuning. This difference (2/78 vs. 13/73) is significant when tested with a two-tailed Fisher-Irwin test ($P < 0.005$), thus indicating that in this limited sample there were more responses to auditory stimuli after training than before. Although not conclusive, this analysis suggests that over the population the number of cells that exhibit responses to auditory stimuli increased due to training.

Second, an additional 33 cells were recorded in *monkey Y*, to control for the different search biases before and after training. In this control experiment the search task was the fixation task, and data were collected from every cell that was isolated. Thus cells were selected in the same way as in the pretraining experiments. Of this sample, 12% (4/33) had significant auditory spatial tuning, a significantly higher percentage than the expected false positive rate (binomial test, $P < 0.05$). Thus search bias is an unlikely explanation for the increased number of responses to auditory stimuli found after training.

CONTROL FOR DIFFERENT GRIDS. Before training, two different grids were employed, one hexagonal and one rectangular (see METHODS). The majority of cells in *monkey B* were recorded using the hexagonal grid, whereas all of the cells in *monkey Y* were recorded using the rectangular grid. The proportion of cells with auditory spatial tuning was about the same for both

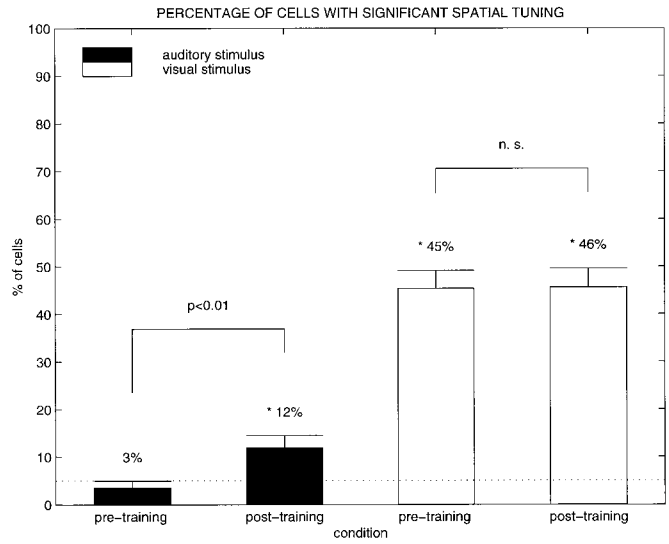

FIG. 4. Proportions of cells that exhibited significant spatial tuning for auditory and visual stimuli in pre- and posttraining experiments. Error bars denote standard deviation estimated using the observed response percentage. Dotted line indicates the expected false positive level, and asterisks mark proportions that are significantly different from the expected false positive level (binomial test). Brackets indicate populations that were compared, probabilities above brackets indicate significance level (or failure to reach significance) in pairwise comparison (Fisher-Irwin test).

grids (3%), and no more than expected by chance for either grid (binomial test, $P > 0.2$). The proportion of cells with visual spatial tuning was 59% for the hexagonal grid and 37% for the rectangular grid.

As noted in METHODS, in the pretraining experiments the frequency spectra of the speakers were not matched, whereas in the posttraining experiments they were matched. It is unlikely that this difference contributed to the increase in LIP responsiveness in the posttraining experiments, because matching made the auditory stimuli even more uniform across the grid. If anything, matching should have reduced, not increased, variation in responses across locations, and hence should have reduced the apparent spatial tuning of LIP neurons.

CONTROL FOR NUMBER OF LOCATIONS/SAMPLES. In the pretraining experiments, the number of stimulus locations was considerably higher than in the posttraining experiments. To equalize the two data sets, data from the pretraining experiments were restricted to the two locations that were used posttraining (or the 2 closest locations for cells recorded using the hexagonal grid). The spatial tuning analysis was repeated using only those two locations from the pretraining data, thereby allowing a direct comparison of pre- and posttraining analyses. Only 2% of cells in this restricted data set exhibited responses to auditory stimuli before training. A comparison between the restricted pretraining dataset and the posttraining data showed that there was a significant increase in the proportion of cells exhibiting responses to auditory stimuli (Fisher-Irwin test, $P < 0.001$). Thus it is unlikely that the apparent effect of training is an artifact of spatial undersampling in the posttraining experiments.

Because many more stimulus locations were used in pretraining than in posttraining experiments, the number of repetitions per location tended to be lower pretraining (between 5 and 10) than posttraining (between 10 and 20). The power of a test is increased both by the number of conditions, and by the number of samples. Because there were more locations and fewer samples per location in pretraining experiments, it is conceivable that the power of the Kruskal-Wallis test might have been lower pretraining than posttraining. Such a difference in power would make responsive cells less likely to be detected in pretraining experiments. This scenario seems unlikely, because any power difference should have affected the visual responses too, and the proportion of neurons with significant visual spatial tuning was about the same pre- and posttraining. However, to address this issue more directly, the power was estimated in a Monte Carlo simulation (see APPENDIX for details). The power of the Kruskal-Wallis test to detect comparable differences was 77% before training, and 46% after training, indicating that the larger number of locations used in the pretraining experiments outweighs the smaller number of repetitions. Thus the absence of responses to auditory stimuli before training is not due to lower statistical power before training. In fact this power analysis suggests that responses to auditory stimuli were less likely to be detected in the posttraining experiments; in other words, the analysis of the proportion of cells that respond to auditory stimuli in the posttraining experiments likely underestimates the true proportion.

CONTROL FOR POSTREWARD EYE MOVEMENTS. Given that responses to auditory stimuli are more prevalent in a saccade task than in a fixation task (Linden et al. 1999), it is possible that responses to auditory stimuli might appear in fixation trials if the monkeys were performing very late saccades to the stimulus locations in the posttraining experiments. If this were the case, then the apparent increase in auditory responsiveness of LIP after training might be due to eye movements, not due to training. To address this concern, eye position was recorded for at least 500 ms after the reward, without any behavioral constraint on the monkey. Saccades during this period were detected using velocity criteria, and the eye position after the first saccade was extracted. If no saccade occurred, the eye position at the end of the trial was used. Figure 8 shows these eye positions for the trials collected from the cell shown in Fig. 7. The monkey did not continue fixating, but tended to make an eye movement up and to the right, presumably toward his default eye position. A similar analysis was performed for all recordings that showed significant auditory spatial tuning in the posttraining experiments. For not a single neuron with auditory spatial tuning did postreward eye positions differ depending on the location of the stimulus (Kolmogorov-Smirnov test separately for the horizontal and the vertical dimensions). In other words, it is very unlikely that late, goal-directed saccades are an explanation for the increased responsiveness of area LIP after training.

CONTROL FOR PENETRATION LOCATIONS. To check that the recordings were made from the same locations before and after training, penetration maps were constructed. Figure 9 shows the types of responses that were associated with each site. Most sites were penetrated at least 10 times pretraining. As a result, especially in *monkey B*, many penetration sites in the center of the chamber that had been visually responsive in the pretraining experiments did not respond visually in the posttraining experiments, probably due to tissue damage. Nevertheless, the pre- and posttraining maps largely overlap, and the locations of most responses suggest that the recordings stem from the same

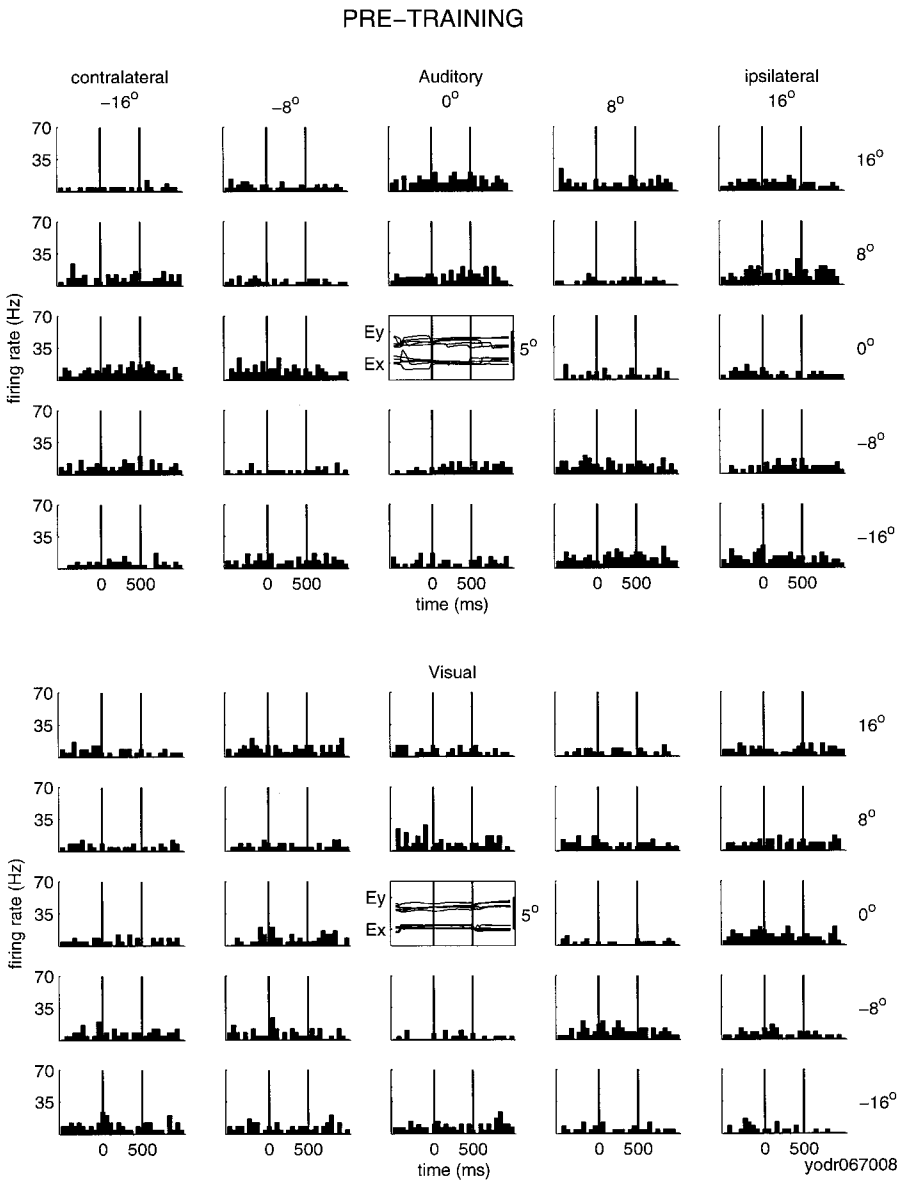

FIG. 5. Cell with the most significant auditory spatial tuning (Kruskal-Wallis test, $P = 0.0008$) from the pretraining experiments. No obvious response is discernible. All conventions are as in Fig. 3. This cell did not exhibit an untuned response (derived by pooling across all locations) for auditory stimuli, but had a weak untuned response for visual stimuli.

brain location. The map also shows the approximate location of the brain section shown in Fig. 2, and the location of the electrolytic lesion visible in that section.

DISCUSSION

Changes due to auditory-saccade training

The key finding of the present study is that auditory-saccade training increases responsiveness of LIP to auditory stimuli. This result was established by two independent methods. In the first method, each cell was categorized as exhibiting significant or no significant spatial tuning, and the proportion of neurons with significant tuning was determined. In the second method, the amount of information about stimulus location available across the population of cells was estimated. The two methods obtain their results differently but arrived at the same conclusion. There are, however, several confounds that need to be ruled out, before the effect of training can be viewed as established.

First, it is possible that the search method, and the criteria by which neurons were selected for further recording, biased the results in such a way as to inflate the number of cells that exhibited spatial tuning and location information after training. As discussed in RESULTS, several lines of reasoning, and a control experiment, argue against this interpretation.

Second, the apparent effect of training might be due to the limitation to a smaller grid in the posttraining task. Because this difference would have made responses more difficult to detect in the posttraining phase, and because the power of the Kruskal-Wallis test was actually higher before training, this is an unlikely explanation for the training effect.

Third, in light of the data from the companion paper (Linden et al. 1999), the task that monkeys are performing appears to have a strong impact on the auditory responsiveness of LIP neurons. In posttraining experiments, blocks of trials in which the monkeys performed the modified fixation task were alternated with blocks in which they performed memory saccades; therefore it is possible that the animals were making saccades

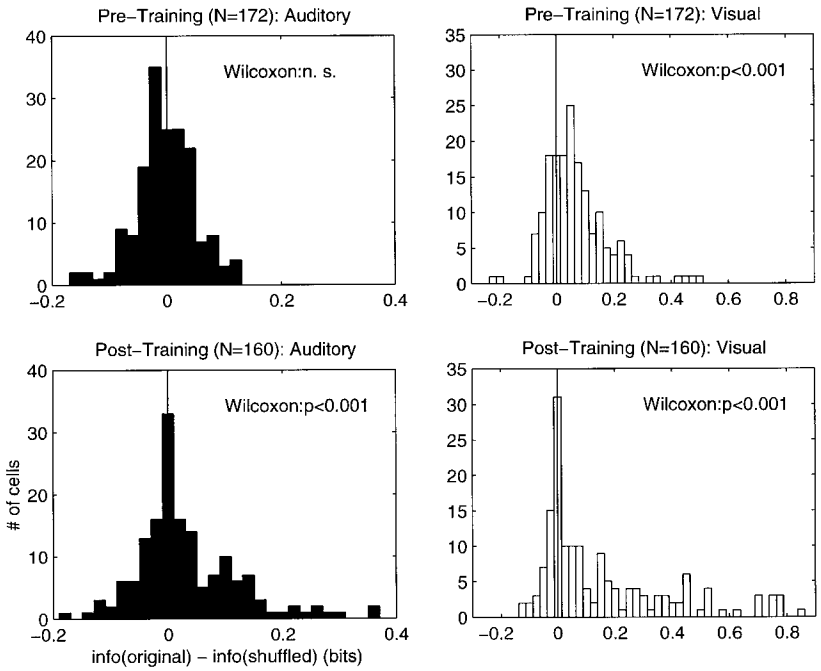

FIG. 6. Histograms of location information carried by lateral intraparietal area (LIP) neurons. Vertical line in each plot indicates no information difference between original trials and shuffled trials. *Left*: location information present in LIP responses for auditory stimuli. *Right*: location information for visual stimuli. *Top*: location information in the pretraining experiments. *Bottom*: location information in the posttraining experiments. A significant *P* value in the Wilcoxon test indicates that location information was present in original but not shuffled trials (difference histogram skewed away from zero).

after receiving a reward in the fixation task. However, as shown in RESULTS, the eye positions in the fixation task following the first eye movements after the reward was administered did not differ depending on the stimulus location. Thus goal-directed, postreward eye movements are an unlikely explanation for the posttraining responsiveness of LIP to auditory stimuli.

Finally, it is possible that the pre- and posttraining recordings were made from different areas, and that in fact the comparison is not valid. This is an issue because the pretraining and posttraining experiments spanned ~2 yr, during which brain and skull growth might have affected the position of cortical areas. In as much as the brain remains more or less at the same location relative to the recording chamber over an extended period of time, the penetration maps in RESULTS show that the recording locations pre- and posttraining overlap substantially. Thus shifts in penetration locations are an unlikely explanation for the effect of training.

In summary, we conclude that the responsiveness of LIP neurons to auditory stimuli in a fixation task changed as a consequence of training animals to perform auditory saccades. Thus one resolution to the discrepancy between earlier studies that reported no auditory responses in LIP (Hyvärinen 1982; Koch and Fuster 1989; Mountcastle et al. 1975) and later studies that did find auditory responses in LIP (Mazzoni et al. 1996a; Stricanne et al. 1996) is that in the former studies the

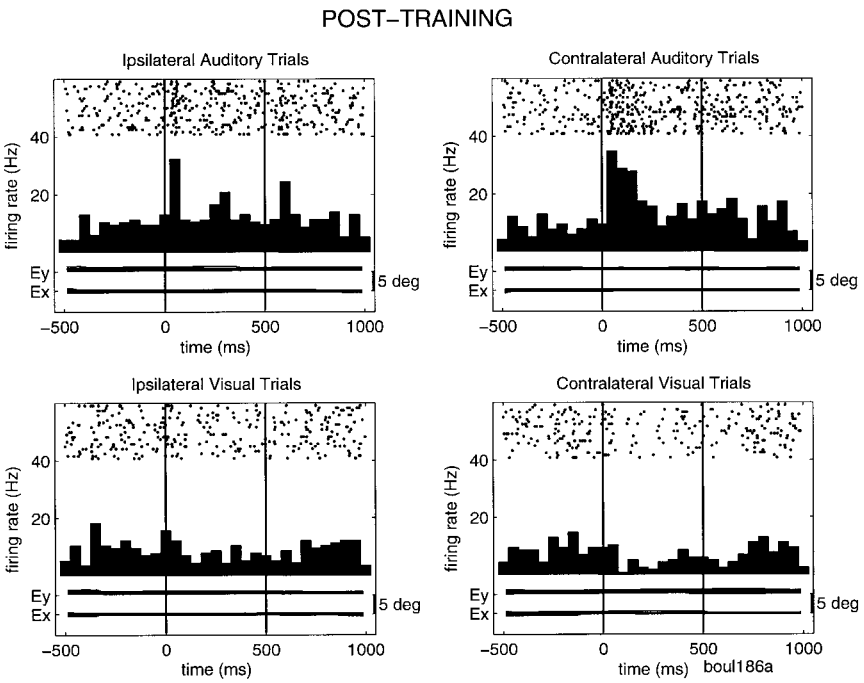

FIG. 7. Cell recorded in the posttraining experiments. This neuron exhibited a response during the presentation of an auditory stimulus. *Top row*: auditory trials. *Bottom row*: visual trials. *Left* and *right columns*: stimulus locations ipsi- or contralateral to the recording chamber, respectively. The top portion in each plot is a spike raster, aligned on stimulus onset. The middle portion is a peristimulus firing rate histogram (firing rates are indicated in Hz), and at the bottom Ex and Ey refer to horizontal and vertical eye positions, respectively. The *x*-axis is time. The 2 bold vertical lines bracket the period when the stimulus was present.

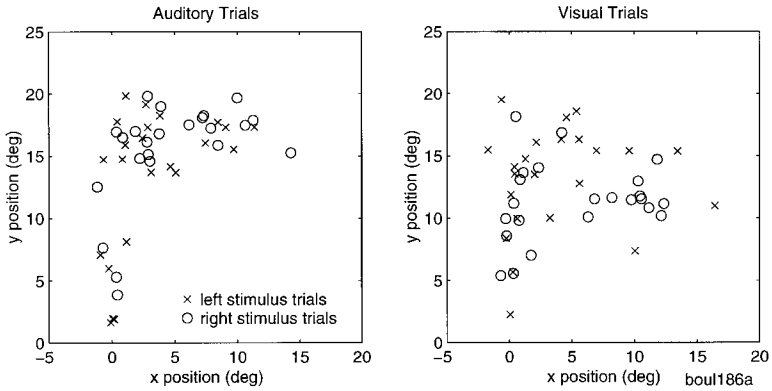

FIG. 8. Eye position after the 1st postreward saccade for trials collected in the same posttraining recording session as the data shown in Fig. 7. *Left*: auditory trials. *Right*: visual trials. ×, trials in which the stimulus was to the left of fixation. ○, trials in which the stimulus was to the right of fixation. The difference between the 2 distributions did not reach significance in either case (1-dimensional Kolmogorov-Smirnov test along the horizontal dimension, $P > 0.5$ for auditory and visual trials).

monkeys had not been trained to perform auditory saccades, whereas in the latter studies they had been. In the INTRODUCTION four detailed possibilities had been proposed to resolve the discrepancy between earlier and later studies. The first possibility was that auditory responses do exist in LIP and had been missed in earlier studies. The second possibility was that auditory-saccade training induces responses to auditory stimuli in LIP. The third possibility was that the task an animal is performing affects the auditory responsiveness of LIP. Finally, the fourth possibility was that both training and task affect neural responses to auditory stimuli in LIP. The present results support possibilities 2 and 4. In light of the results of the companion paper (Linden et al. 1999), which shows that responses to auditory stimuli in LIP are modulated by behavioral task, the fourth possibility (that responses to auditory stimuli in LIP are affected both by training and by the task the animal is performing) is the correct explanation.

The present study is the first report showing emergence of responses to auditory stimuli de novo in PPC after saccade training. Similar training-induced increases of responsiveness have been reported in area 3a following tactile discrimination training (Recanzone et al. 1992), and the appearance of neural selectivity after visual search training has been reported in the frontal eye fields (FEF) (Bichot et al. 1996).

Interpretation of the effect of training

An important issue that ought to be addressed concerns how the effect of training arises. Possible causes for the effect of training can be described at two different levels: a cognitive level and a mechanistic level.

COGNITIVE LEVEL. The dependence of LIP responses to auditory stimuli on training suggests that these responses cannot really be termed "sensory auditory" responses. Rather, these responses are contingent on the monkey being trained on an auditory-saccade task. How do responses to auditory stimuli emerge through training? Four cognitive-level explanations will be considered.

First, it is possible that the emergence of responses to auditory stimuli reflects an attentional change in the animals. It is likely that the monkeys were ignoring the auditory stimuli before training. On the other hand, after auditory-saccade training, the animals may have been paying some attention to the stimuli even though the task does not require the animals to

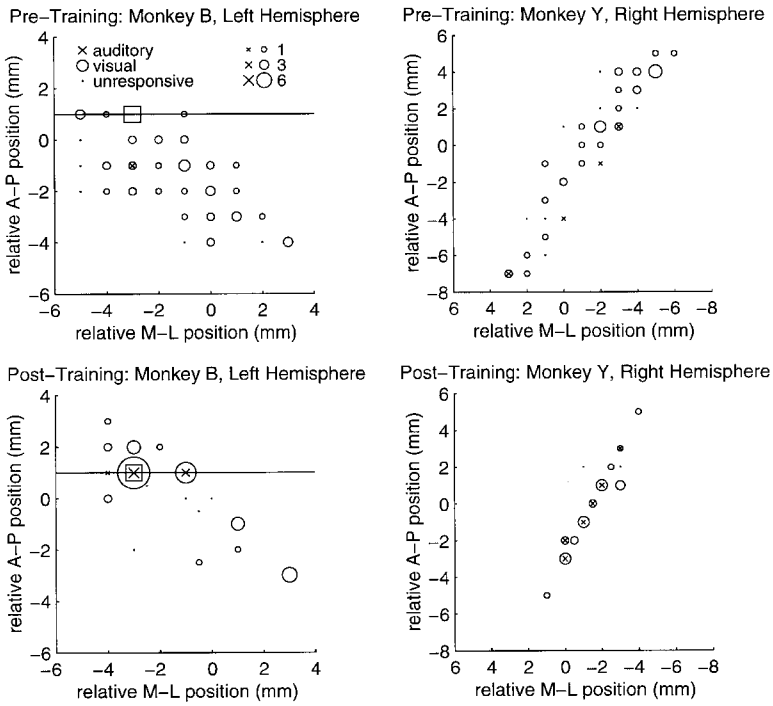

FIG. 9. Penetrations made in each chamber pre- and posttraining in the 2 monkeys. The size of the symbol at each location is scaled to indicate how many cells had a significant response to auditory (×) or visual (○) stimuli. ·, sites at which neither auditory nor visual cells were encountered. Horizontal line in the plot for *monkey B* indicates the position of the brain section shown in Fig. 2. □, site of the electrolytic lesion.

attend to the stimuli. Indeed, other investigators have suggested that LIP signals reflect the allocation of attentional resources (Colby et al. 1996; Gottlieb et al. 1998).

Alternatively, it is possible that the emergence of responses to auditory stimuli reflects a change of intention vis à vis auditory stimuli. Before training, the auditory stimuli were irrelevant as saccade targets, whereas through training they became associated with saccades. It is possible that responses to auditory stimuli in LIP reflect covert plans to make eye movements to auditory stimuli, even when the animal is instructed not to make any eye movements. It has previously been argued that a component of LIP activity codes the intention to make eye movements (Bracewell et al. 1996; Mazzoni et al. 1996b), and that in the absence of actual movements activity in LIP may code the intention but not the execution of eye movements (Snyder et al. 1997). In fact, the eye movement plan can be changed without any movement being executed, and activity in LIP reflects these changes (Snyder et al. 1998). Moreover, LIP activity in response to visual stimuli quickly fades if they are identified as irrelevant in a saccade task (Platt and Glimcher 1997a; Shadlen and Newsome 1996).

A third possibility is situated between the attentional and intentional interpretations, and posits that the activity that appears after training codes the oculomotor significance of the auditory stimuli: the significance of the auditory stimuli as potential saccade targets. In the present experiments the monkeys were trained that auditory stimuli had a new meaning or significance in terms of oculomotor behavior, and as a result these stimuli may have become more represented in LIP. This idea is consistent with the observation that the increased probability of a stimulus as a target for eye movements, or increased reward associated with a particular target, strengthens the representation of that target in LIP (Platt and Glimcher 1997b). This interpretation would also explain the shape selectivity for LIP cells recently reported when animals had been trained to use shape stimuli in an eye movement task (Sereno and Maunsell 1998).

This oculomotor significance idea could be extended to explain why LIP neurons are so responsive to visual stimuli in the fixation task that does not require eye movements, if one assumes that visual stimuli have default oculomotor significance. Similarly, some sounds (e.g., species-specific warning calls, or sounds from behind the animal) may have much higher oculomotor significance than the auditory stimuli used in the present study, and hence might elicit responses to auditory stimuli from LIP even before auditory-saccade training.

If the idea of oculomotor significance is correct, what are we to make of the finding that LIP neurons respond to visual stimuli even in anesthetized monkeys (Blatt et al. 1990)? Similar to LIP, the middle temporal area (area MT) can be activated in the anesthetized monkey (Maunsell and Van Essen 1983), and MT activity has been correlated with motion percepts (Newsome et al. 1989). Thus the occurrence of activation in the anesthetized animal is compatible with the involvement of a particular area in higher cognitive functions in the awake behaving animal.

The fourth interpretation is that compartmentalization and fine distinction between attention, intention, or oculomotor significance is artificial. We have previously argued that the parietal cortex participates in sensory-motor processing, operating as an interface between sensory and motor systems to transform sensation into action (Andersen et al. 1997). Thus LIP has been shown to have both sensory and movement-planning related activity. Attention likewise has been proposed to have evolved from circuits for orienting toward stimuli, and attentional mechanisms may serve the purpose of preparing for action (Kustov and Robinson 1996; Rizzolatti et al. 1994). Moreover, eye movement and attention circuits are largely overlapping in the human cortex (Corbetta et al. 1998), and interconnections and similarities in physiology between LIP and the frontal eye fields (Chafee and Goldman-Rakic 1998) suggest that attention and action planning share similar circuits and may not be modular and separate operations. This fourth possibility would posit that sensory and movement activation should co-occur and that it may not be useful to assign the posttraining auditory activity in LIP to either of the other three interpretations.

The present study cannot distinguish between these four interpretations of responses to auditory stimuli in LIP, because the experiments reported here were not aimed at distinguishing between them. Instead, the experiments were designed to examine why earlier reports did not find auditory responses in LIP, and more recent studies, using animals performing delayed auditory-saccade tasks, did. Future research will be needed to determine which of these possibilities provides the best interpretation of the appearance of responses to auditory stimuli after training.

MECHANISTIC LEVEL. At the mechanistic level, the effect of training that has been observed may be due to the emergence of new connections from an auditory area that is as yet unidentified. Alternatively, it is possible that training unmasks connections that existed all along but were silent. In both cases, different areas may be providing auditory input to LIP. Likely candidate regions in cortex are the temporoparietal area (Tpt), the frontal eye fields (FEF), and the superior temporal polysensory area (STP). A likely subcortical source is the deep layers of the superior colliculus (SC). All of these regions respond to auditory stimuli (Hikosaka et al. 1988; Jay and Sparks 1984; Leinonen et al. 1980; Russo and Bruce 1994). Areas Tpt, FEF, and STP project to LIP directly (Baizer et al. 1991; Blatt et al. 1990; Pandya and Kuypers 1969), whereas the SC projects to LIP via the pulvinar (Asanuma et al. 1985). FEF neurons respond in a fixation task after auditory training (Vaadia et al. 1986). However, it is unclear whether FEF neurons respond to auditory stimuli without auditory-saccade training, or in anesthetized animals. Areas Tpt and STP, on the other hand, have auditory responses in untrained animals (Baylis et al. 1987; Leinonen et al. 1980), and both receive projections from other auditory areas (Pandya and Sanides 1973). Assuming that the areas providing auditory input to LIP respond to auditory stimuli without behavioral training, areas Tpt and STP seem the most likely sources of auditory input to LIP. It is also possible that the SC could be the source of the responses to auditory stimuli we have found in LIP, because the deep layers of SC respond to auditory stimuli in anesthetized monkeys (Cynader and Berman 1972). Further investigation will be necessary to clarify these issues.

As described above, at present it is unknown whether FEF responds to auditory stimuli before auditory-saccade training. In light of the present results in LIP, one wonders to what extent auditory responses in FEF are also due to training, and

to what extent the effect of training we found in LIP may also be reflected in FEF responses, especially because there are strong projections from LIP to FEF (Andersen et al. 1990; Asanuma et al. 1985).

Other effects of training

Watanabe (1992) showed that prefrontal neurons code the associative significance of auditory and visual stimuli. In that study, a cue stimulus indicated to the animal whether a subsequent trial was a reward or a no-reward trial. Cues that indicated a rewarded trial evoked stronger firing in prefrontal neurons. Clearly the cue stimuli were of high significance to the animal, but the cue stimuli informed the animal only of the outcome of the subsequent trial. The training effect that we found in LIP is somewhat different, in that it occurred in the context of eye movements, a context that is likely to be critical to LIP function.

In a different study, Chen and Wise (1995) showed that neurons in the supplementary eye field (SEF) code conditional oculomotor associations between random stimuli and upcoming eye movements. In that study, learning occurred within one session, and thus the neural activity could be studied at the same time as learning took place. It was found that neurons that initially had not responded to novel visual stimuli indicating the direction of an upcoming saccade started responding during training (Chen and Wise 1995), and developed selectivity for the upcoming saccade as the session progressed (Chen and Wise 1996).

It is possible that the effect of training in the present experiments is similar to the training effect found by Chen and Wise. At present it is unclear to what extent the two training paradigms are comparable, because in the present experiments training occurred over a time span of several months, whereas Chen and Wise trained their animals in the course of individual recording sessions, lasting at most several hours. Moreover, Chen and Wise were able to track the change in neural activity as training progressed, whereas in the present experiments we could only compare pre- and posttraining responses.

The present study is the first to demonstrate the emergence de novo of responses to auditory stimuli in PPC due to training. However, more research will be necessary to determine what the best cognitive interpretation of this training effect is, and whether the training effect differs from other forms of training-related neural changes that have been reported.

APPENDIX: POWER ANALYSIS

An estimate of the power of the Kruskal-Wallis test was obtained for the pretraining and the posttraining data separately. In the following, X_{ij} refers to the firing rate at location i in trial j

$$X_i = \frac{1}{n_i} \sum_j X_{ij}$$

refers to the mean firing rate for location i, where n_i denotes the number of trials at location i

$$\bar{X} = \frac{1}{n} \sum_i X_i$$

refers to the mean of the location means, where n denotes the number of locations, and

$$S = \sqrt{\frac{\sum_i (X_i - \bar{X})^2}{n - 1}}$$

refers to the standard deviation of the location means. Similarly, x_{ij}, x_i, and $\bar{x}$ refer to simulated individual trial firing rates, simulated mean firing rates for each location, and simulated mean of location means, respectively.

As the first step in the power analysis, an estimate of detectable dispersion was obtained for each cell with significant visual spatial tuning by calculating the coefficient of variation

$$c_v = \frac{S}{\bar{X}}$$

for visual trials. The mean $\bar{c}_v$ across cells with visual spatial tuning was then calculated. This mean was used to generate simulated cells. Next, location means x_i for simulated auditory trials were randomly generated for each simulated cell from normally distributed samples with mean $\bar{X}$ and standard deviation $\bar{c}_v\bar{X}$, thereby producing simulated location means with a coefficient of variation matching the mean $\bar{c}_v$. Individual simulated firing rates were calculated by shifting the actual firing rates for auditory trials to yield simulated mean firing rates: $x_{ij} = X_{ij} - X_i + x_i$. Thus simulated data were created from individual auditory trials with as much structure as was present in visual trials from cells with significant visual spatial tuning. These simulated firing rates were then subjected to a Kruskal-Wallis test. This procedure was performed once for each cell. The proportion of simulated cells that had significant spatial tuning was taken to be an estimate of the power. This simulation was run 100 times for both pretraining and posttraining data. The estimated power was always larger before training (range: 72–81%) than after training (range: 31–54%). The average estimated power was 77% in the pretraining data, and 46% in the posttraining data.

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