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Location of the polysensory zone in the precentral gyrus of anesthetized monkeys

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Abstract Neurons in the premotor cortex of macaques respond to tactile, visual and auditory stimuli. The distribution of these responses was studied in five anesthetized monkeys. In each monkey, multiunit activity was studied at a grid of locations across the precentral gyrus. A cluster of sites with polysensory responses was found posterior to the genu of the arcuate sulcus. Tactile and visual responses were represented in all five monkeys, while auditory responses were rarer and found in only two monkeys. This polysensory zone (PZ) was located in the caudal part of premotor cortex. It varied in extent among the monkeys. It was mainly ventral to the genu of the arcuate, in the dorsal and caudal part of the ventral premotor cortex (PMv). In some monkeys it extended more dorsally, into the caudal part of dorsal premotor cortex (PMd). Sensory responses were almost never found in the rostral part of PMd. We suggest that the polysensory zone may contribute to the guidance of movement on the basis of tactile, visual and auditory signals.

Key words Bimodal · Trimodal · Premotor · Sensorimotor · Visuomotor

Introduction

Neurons in premotor cortex of the macaque brain respond to tactile, visual and auditory stimuli (Rizzolatti et al. 1981; Gentilucci et al. 1988; Fogassi et al. 1996; Graziano et al. 1997, 1999). These responses can be found even when the monkey is not trained to react to the stimuli, and they are still present when the monkey is anesthetized. Some neurons respond only to tactile stimuli, while others are bimodal, both visual and tactile. A smaller proportion of neurons are trimodal, responding to visual, tactile and auditory stimuli (Graziano et al.

1999). Almost all of these sensory responses emphasize the space on or near the monkey's body. The bimodal, visual-tactile neurons respond to a touch on the arm or face and also to the sight of objects in the space near the tactile receptive field, within about 20 cm (Rizzolatti et al. 1981; Gentilucci et al. 1988; Fogassi et al. 1996; Graziano et al. 1997). The auditory responses are usually strongest to sounds generated near the body, regardless of the amplitude of the sound (Graziano et al. 1999).

The function of these sensory responses in motor and premotor cortex is unknown. One possibility is that they help to guide movement of the head and limbs in relation to nearby objects. In support of this view, some neurons have both sensory and motor properties and could therefore serve as a sensorimotor link (Gentilucci et al. 1988; Graziano et al. 1997).

The distribution of these sensory responses within the precentral gyrus is not clear. Rizzolatti and colleagues (1981) first described bimodal, tactile and visual neurons in the ventral part of premotor cortex (PMv), below the spur of the arcuate sulcus. Dorsal premotor cortex (PMd) has not been as thoroughly tested for responses to stimuli in the space near the body, although at least one study found bimodal, visual-tactile neurons in the caudal part of PMd (Fogassi et al. 1999). No single study has tested the distribution of multimodal neurons across the entire precentral gyrus.

Almost all of the studies described above involved awake animals, in which a few neurons were tested each day over a period of months or years. Under these conditions, it is difficult to map a large region of cortex systematically and to reconstruct the location of all electrode penetrations. The anesthetized preparation is better suited to the systematic mapping of a large expanse of cortex, for several reasons. First, the dura can be reflected. The sulcal pattern varies between monkeys, but with the brain exposed it is possible to ensure that the region of interest is correctly located and fully mapped and that the locations of the electrode penetrations relative to the sulci are accurately measured. Second, a large region of cortex such as the precentral gyrus can be mapped completely in

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one monkey in one 24-h session. This approach avoids any day-to-day inadvertent changes in the calibration of the micromanipulator, in the location of the brain areas as the cortex under the craniotomy gradually shrinks, and any learning-dependent or damage-induced changes in the map itself. The limitation of the anesthetized preparation, however, is that task-related responses cannot be studied. Only the responses to passively presented visual, tactile and auditory stimuli can be tested.

In this experiment we mapped the precentral gyrus in five anesthetized monkeys. The main finding is that each monkey had a polysensory region, in which the multiunit activity responded to tactile, visual, and sometimes auditory stimuli. We refer to this area as the polysensory zone (PZ). The PZ varied greatly in size and location among the five monkeys, but was always associated with the representation of the arm and face. In previous papers we and others described polysensory responses in the ventral part of premotor cortex, area PMv (Rizzolatti et al. 1981; Gentilucci et al. 1988; Fogassi et al. 1996; Graziano et al. 1997, 1999). The current data further specify the location of these polysensory responses, and show that much of PMv is not polysensory.

Materials and methods

Neuronal responses in the precentral gyrus were studied in five *Macaca fascicularis* monkeys (2.5–6.5 kg). All husbandry, surgical, and behavioral procedures were approved by the Princeton University Institutional Animal Care and Use Committee and the consultant veterinarian and were in accordance with NIH and USDA guidelines.

Surgery

For each monkey, an initial surgical operation was performed with the animal under isoflurane anesthesia and strict aseptic conditions, during which the top of the skull was gently cleared of skin and muscle, surgical screws were fixed into the bone, and the exposed bone was covered with a layer of dental acrylic approximately 1 cm thick. A stainless steel recording chamber 5.5 cm in diameter was embedded in the acrylic over the left frontal lobe. A steel bolt for holding the head was also imbedded in the acrylic. A craniotomy was made inside the recording chamber to expose the dura over the precentral sulcus. After surgery the monkey was given a daily intramuscular injection of antibiotic (Baytril, 2.5 mg/kg) and a twice daily injection of analgesic (buprenorphine 0.01 mg/kg) for the next several days. Two to 7 days later, the animal was anesthetized again for the terminal recording experiment.

Recording procedures

At the beginning of each recording session, the animal was given a restraining dose of ketamine hydrochloride (10 mg/kg) with acepromazine (0.4 mg/kg) injected intramuscularly. After being removed from the home cage, the animal was then given an intramuscular injection of atropine sulfate (0.15 mg/kg) to reduce mucosal secretions, of the antibiotic Baytril (2.5 mg/kg), and of dexamethasone (0.8 mg/kg) to reduce the swelling of the brain. The animal was then intubated with a pediatric tracheal tube and given a 2:1 mixture of nitrous oxide and oxygen, to which 1–3% isoflurane was added. The head was then fixed into a stereotaxic frame by means of the head bolt. The animal rested on heated pads. Tem-

perature was monitored through a rectal probe, EKG was monitored through skin electrodes, and expired CO₂ was monitored with a capnograph. Throughout the experiment, these vital signs were recorded every 15 min.

Under sterile conditions, the recording chamber was opened and flushed with warm sterile saline. In some monkeys, the dura was removed over the precentral gyrus at the start of the experiment and the brain was covered in warm mineral oil. In other animals, the pattern of sulci could be seen through the dura, and the dura was left intact until the end of the experiment, at which time it was opened to measure precisely the locations of the sulci.

After all cleaning, cutting or removal of the dura, the isoflurane was turned off and the animal was maintained under 2:1 nitrous oxide and oxygen. No surgery or potentially painful procedures were performed without the isoflurane. The animal was immobilized with a continuous intramuscular infusion (0.03 mg/kg/h) of pancuronium bromide (Pavulon), and was artificially respired. The pupils were dilated with cyclopentolate (1%) and the corneas were covered with 60-diopter contact lenses.

A micromanipulator was fixed to one rail of the stereotaxic frame and used to position a stainless steel guide cannula (an 18-g needle) through which a varnish-coated tungsten microelectrode (Frederick Haer Inc., impedance 0.5–5 MW) could be advanced. Using the tip of the electrode, we measured the locations of the arcuate and central sulci at regular intervals in order to construct maps of the surface of the brain. In four of the five monkeys, the electrode was tilted 30° to the monkey's left from the sagittal plane. In this way, the electrode was approximately normal to the cortical surface of the left hemisphere. In monkey 3, the electrode was in the sagittal plane. For this monkey, in order to plot the data, the medial-lateral positions of the electrode penetrations were scaled by the cosine of 30° such that the resulting map was comparable to the maps from the other monkeys.

For monkeys in which we recorded through the dura, the guard tube was lowered until it was seen to pierce the dura, and then the electrode was advanced from the guard tube into the brain. In monkeys in which the dura was removed before recording, the guard tube was lowered until it touched the surface of the brain and then the electrode was advanced into the brain. Neuronal activity was monitored over a loud speaker and on an oscilloscope. The depth at which the electrode first encountered neurons was noted, and then the electrode was advanced another 0.3–0.5 mm and the neuronal activity was tested for visual, tactile and auditory responsiveness. Sometimes individual neurons were isolated; but for purposes of this experiment, to best determine the response properties at a particular cortical site, we usually studied the multiunit activity of neurons surrounding the electrode tip. On each electrode penetration, we studied the neuronal responses at one to four different depths. The electrode was never advanced more than 1.5 mm into the cortex, to insure that each site tested along the penetration was at approximately the same location in the cortical sheet as the entry point of the electrode into the cortex. On any one electrode penetration, we always found the same response characteristics at different depths. To avoid any order effects, we placed electrode penetrations in a scattered fashion, each penetration far from the previous one, never testing two adjacent points consecutively.

Responses to stimuli were assessed subjectively, by listening to the multiunit activity over a loudspeaker. Somatosensory responsiveness was studied using manual palpation, manipulation of joints, gentle pressure, and stroking with cotton swabs. Somatosensory receptive fields were plotted by repeated presentation of the most effective of these stimuli. Visual responsiveness was tested with objects presented on a wand. To separate visual responses from tactile responses on the face, we also tested tactile responses in the dark. In previous experiments, we found that visual stimuli projected on a screen do not activate these neurons (Graziano et al. 1997). The reason for this lack of response to two-dimensional objects on a screen is not known, but there are many differences between real objects in the space near the monkey and flat shapes on a screen. For example, real objects contain a greater diversity of visual cues for distance.

Auditory responsiveness was tested with a hand-held device that produced an approximately square-wave pulse. At a distance of 20 cm, the sound pressure level was 75 dB. We also tested with claps, voice, and the sound of gloved fingers rubbing against each other. In a previous experiment, we found that these stimuli are effective when presented close to the monkey's head (Graziano et al. 1999); therefore in the present experiment we presented them just behind the head, or just in front of the head in the dark, within about 20 cm.

During each recording session, 30–100 electrode penetrations were made in the precentral gyrus over approximately 24 h. At the end of the recording session, the location of the sulci was measured again at 10–20 sites with the tip of the electrode to confirm the previous measurements. The monkey was then given an overdose of sodium pentobarbital and perfused through the heart with 4% paraformaldehyde to preserve the brain.

Results

Monkey 1

Figure 1 shows the map of the precentral gyrus obtained from monkey 1. The coordinates of the arcuate, principal and central sulci were measured at regular intervals with the tip of the electrode prior to recording from the cortex. Each dot shows the entry point of an electrode penetration.

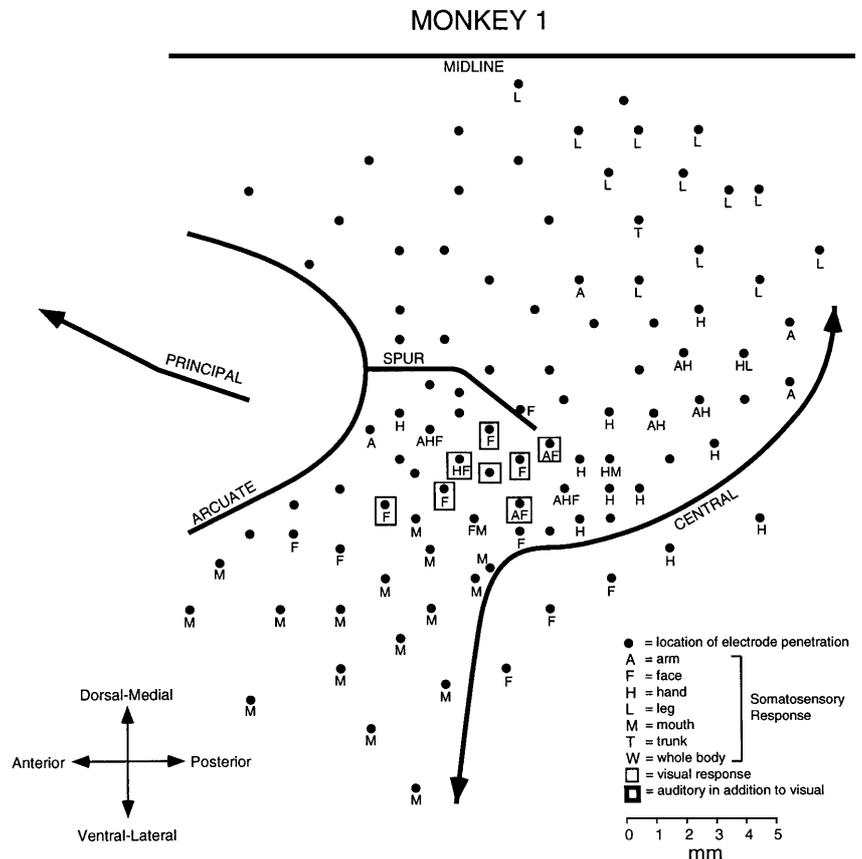
The region dorsal to the arcuate sulcus and its spur did not respond to tactile, visual or auditory stimuli.

Posterior and ventral to this unresponsive zone, along the central sulcus, we found a map of the body, arranged from the leg and foot representation in the upper right

(penetrations labeled “L”), to a representation of the inside of the mouth, in the lower left (labeled “M”). This strip of cortex responsive to somatosensory stimuli is 5–10 mm wide and runs the whole length of the central sulcus. The body representation is not well segregated. Although there is a general progression from the leg at top, to the arm, to the face, and finally to the inside of the mouth at bottom, there is also considerable overlap between body parts. In particular, there is overlap between the face and the mouth representations and also between the face, arm, and hand representations. In this monkey, the central sulcus has an especially sharp bend and runs almost horizontally for about 5 mm. The body map also bends in order to follow the central sulcus. As a result, the face representation is partly anterior to the arm and hand representation, rather than ventral to it. This quirk in the map of monkey 1 underscores the point that the same functional areas can be in different locations in different monkeys.

The somatosensory responses were sometimes tactile and sometimes related to manipulation of the joints. These somatosensory submodalities were intermingled and followed no discernible pattern. We often found tactile and joint-related responses at the same site. When the response was on the fingers, it was difficult to separate touch from joint movement, since even a light touch caused the fingers to move slightly. Most somatosensory responses were contralateral (50%) or bilateral (45%) and a small number were purely ipsilateral (5%).

Fig. 1 Map of electrode penetrations between the central sulcus, the arcuate sulcus, and the midline of the brain in monkey 1. *Unlabeled dots* indicate unresponsive penetrations. The cortex dorsal to the arcuate sulcus was unresponsive. The cortex along the central sulcus was somatotopically mapped, from the leg *at top* to the mouth *at bottom*. The polysensory, visual-tactile area was located in the middle of the body map. Five penetrations were located posterior to the central sulcus, in primary somatosensory cortex



In the center of the body map, in the representation of the face and also in the region of overlap between the face and the arm, the neurons responded to visual stimuli (rectangles around penetration sites) in addition to somatosensory stimuli. This small, relatively discrete zone of polysensory responses, in this monkey, lies just beneath the spur of the arcuate. It is this region that we call the PZ. The bimodal responses found in this region match the responses described in previous reports (Rizzolatti et al. 1981; Gentilucci et al. 1988; Fogassi et al. 1996; Graziano et al. 1997). The neurons responded to a light touch on the face, arms, or both, and also to the sight of objects in the space near the tactile receptive field. Objects farther than about 20 cm from the body did not give consistent responses. One site had a visual response but no detectable somatosensory response. The visual response at this location was similar to the responses found at the other locations, in that it was best for objects near the body. We did not find any trimodal, visual-tactile-auditory responses in this monkey. Auditory responses were rare in the five monkeys and tended to have a patchy distribution.

In previous experiments on the polymodal neurons in premotor cortex, the leg representation was not studied (Rizzolatti et al. 1981; Gentilucci et al. 1988; Fogassi et al. 1996; Graziano et al. 1997, 1999). Thus, prior to this experiment, we did not know whether visual or auditory responses would be found in the leg representation. As shown in Fig. 1, the polymodal responses did not extend into the leg representation in this monkey. The leg representation was somatosensory only. During most of the experiment the monkey was arranged on the table in a "sphinx" posture, with its forearms and hands in view. The torso, legs and tail were not in view. Was the lack of visual response in the leg representation caused by the legs being placed out of view? To answer this question, we rearranged the monkey's body such that the back curled to the left and the hips, legs and tail were in front of the monkey within its view. We then tested nine different sites that responded to somatosensory stimuli on the feet and legs. None of these sites responded to visual stimuli. Note that much of the arm and hand representation was also unresponsive to visual stimuli, even though the arms and hands were always in view.

Between the PZ and the central sulcus we found a thin strip of cortex that responded to somatosensory but not to visual stimuli. Following the suggestion of Gentilucci et al. (1988), we hypothesize that this non-visual strip of cortex adjacent to the central sulcus corresponds to primary motor cortex.

Between the PZ and the lower limb of the arcuate, just beneath the spur, we found somatosensory responses on the hand and arm.

We also made five penetrations posterior to the central sulcus in primary somatosensory cortex. We found small tactile receptive fields on individual digits of the hand and on portions of the face, matching the expected somatotopy.

Monkey 2

Figure 2 shows the result for monkey 2. This monkey shows approximately the same pattern as monkey 1. A relatively unresponsive region lies dorsal to the arcuate sulcus. Almost all penetrations in this region are unresponsive; and likewise almost all unresponsive penetrations are in this area. Posterior to the unresponsive zone, a map of the body runs along the precentral gyrus from the leg in the dorsal part of the gyrus, through the hand and arm, then to the face, and finally to the mouth in the ventral part of the gyrus. There is considerable overlap between the different body parts. For example, tactile responses on the face are found ventrally in the mouth area, and tactile responses over the entire body (labeled "W"), including the face and the inside of the mouth, are found dorsally in the leg area.

The bimodal, visual-tactile responses are clustered just posterior to the arcuate sulcus, in the representation of the face and the arm. In this monkey the bimodal responses are more scattered than in the previous monkey. Although they cluster mainly in one location, isolated bimodal sites are found more ventrally and dorsally than in monkey 1. Three sites were trimodal (thickened rectangles around penetration sites). At these sites, the tactile receptive fields included the back of the head. The neurons responded to visual stimuli in the peripheral part of visual space near the tactile receptive field, and also to

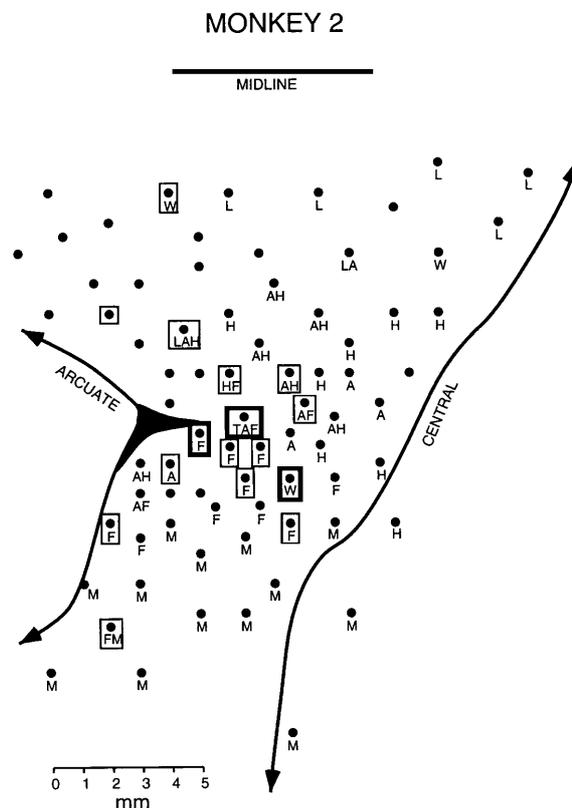


Fig. 2 Map of electrode penetrations in monkey 2. See Fig. 1 for symbol key

clicks made near the tactile receptive field within about 20 cm of the head.

As in the previous monkey, the PZ in this monkey does not extend to the central sulcus. There is a narrow strip of cortex along the central sulcus that has somatosensory responses but not visual responses. This strip may correspond to primary motor cortex. Also, just posterior to the lower limb of the arcuate and ventral to the spur, we found a small region that represents the arm and hand. Posterior to the central sulcus, in primary somatosensory cortex, we found the expected small tactile receptive fields on the hand and in the mouth.

Monkey 3

Figure 3 shows the result for monkey 3. This monkey follows the same pattern as the previous two. An unresponsive zone lies above the arcuate, a map of the body runs along the central sulcus, and a zone of cortex in the middle of this map is polysensory, both tactile and visual. In this monkey, the PZ is small and relatively ventral. Dorsal to it are a number of sites with tactile responses on the arm, hand and face but no accompanying visual responses.

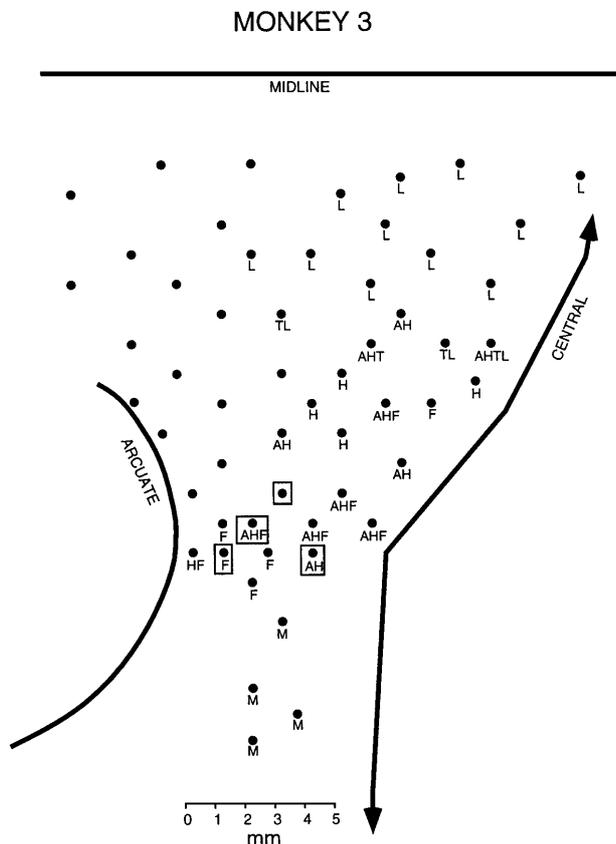


Fig. 3 Map of electrode penetrations in monkey 3. See Fig. 1 for symbol key

Monkey 4

Figure 4 shows the result for monkey 4. In this monkey, the body map is especially poorly organized. Although the legs are represented dorsally and the mouth mainly (although not exclusively) ventrally, the separation between the arm, hand and face representations is not apparent. Bimodal responses were found throughout this intermingled arm and face representation. This monkey is so different from the others that it demonstrates just how extreme the variability in the precentral gyrus can be. However, despite this deviation from normal, the pattern of results in this monkey is still comparable to that in the other four monkeys. There is a body map, albeit crude, and the polysensory responses are in the face and arm portion of the map.

Trimodal, visual-tactile-auditory responses were found at two locations in this monkey, as shown by the thickened boxes in Fig. 4.

Monkey 5

Figure 5 shows the result for monkey 5. Only the ventral part of the precentral gyrus was mapped. The somatotopic organization is unusually clear in this monkey. From the bottom to the top, the mapped area progresses from a representation of the mouth, to a region of overlap between the mouth and the face, to a representation of the face, to a region of overlap between the face and the arm and hand, and finally to a representation of the arm and hand. That is, the transitions from one body part to the

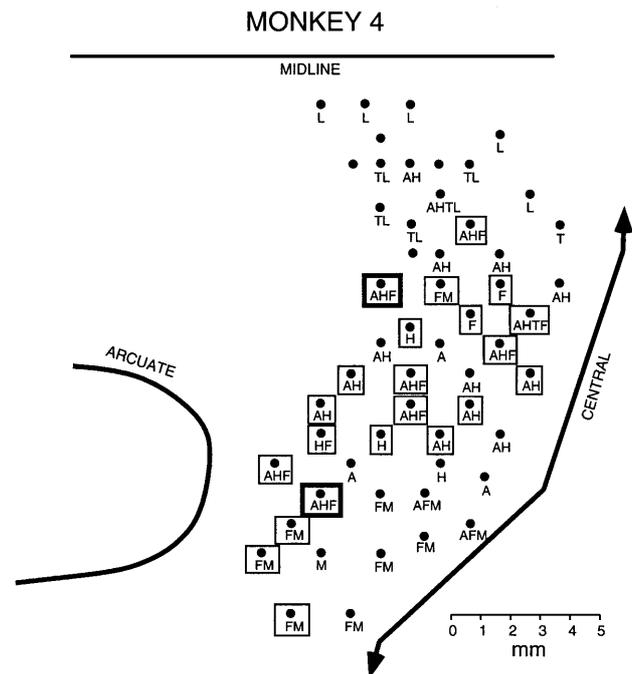


Fig. 4 Map of electrode penetrations in monkey 4. See Fig. 1 for symbol key

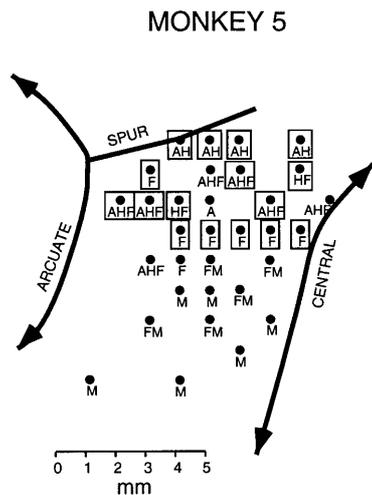


Fig. 5 Map of electrode penetrations in monkey 5. See Fig. 1 for symbol key

next are exceptionally clear. The degree to which the precentral gyrus is somatotopically organized, therefore, can vary considerably from monkey to monkey.

In this monkey, visual responses were found throughout the face and arm representations. The polysensory zone extended from the central sulcus to the arcuate sulcus. In the four monkeys described above, we found a thin strip of cortex between the PZ and the central sulcus that responded to somatosensory but not to visual stimuli. We hypothesized that this non-visual strip of cortex may correspond to primary motor cortex. If such a strip of cortex existed in monkey 5, it must have been so thin that it lay in the anterior bank of the sulcus itself.

Group data

In total, 66 cortical sites responded to visual stimuli. Of these, three were purely visual and had no accompanying tactile response. Of the remaining 63 sites, all had a tactile receptive field that included the face ($N=24$, 38%), the arm ($N=15$, 24%) or both ($N=24$, 38%). In no case was a visual response found in association with a tactile receptive field confined to the trunk, the leg, the foot or the inside of the mouth. That is, the polysensory responses are associated with the face and arm representation.

We found trimodal, auditory-visual-tactile responses in only two of the five monkeys, and at only five cortical sites. The auditory input appears to be patchy and much less extensive than the visual input.

Discussion

In this experiment, multiunit responses were studied. Single neurons were studied only occasionally. Therefore, the data do not indicate whether individual neurons had convergent input from multiple sensory modalities.

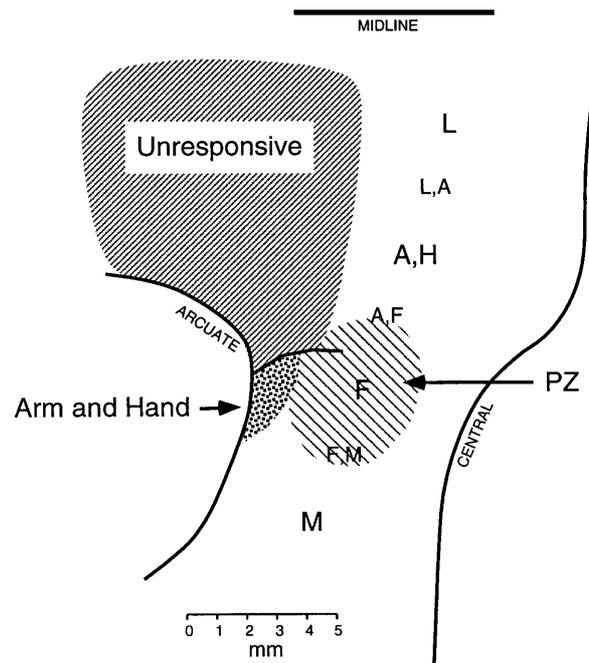


Fig. 6 Summary of the spatial organization of tactile, visual and auditory responses in the precentral gyrus, based on the five experimental monkeys shown in Figs. 1, 2, 3, 4, and 5. Dorsal to the arcuate sulcus, the cortex was mostly unresponsive. Beneath the spur of the arcuate the hand and arm were represented. Along the precentral gyrus the cortex was somatotopically organized, progressing from dorsal to ventral through the leg (*L*), the arm and hand (*A, H*), the face (*F*), and finally the mouth (*M*). These different regions in the map overlapped more in some monkeys than in others. In the center of the map, in the face representation and part of the arm representation, the neurons also often responded to visual stimuli, and sometimes to auditory stimuli, presented in the space near the monkey's body. This zone is labeled PZ (polysensory zone). The PZ varied in size between monkeys. Between the PZ and the central sulcus a thin zone of cortex responded to somatosensory stimuli but not to visual or auditory stimuli. This area may correspond to primary motor cortex

The multimodal properties of individual neurons in pre-motor cortex have been extensively studied in previous experiments (Rizzolatti et al. 1981; Gentilucci et al. 1988; Fogassi et al. 1996; Graziano et al. 1997, 1999). The present experiment, in contrast, focussed exclusively on the distribution across the cortical surface of the visual, tactile and auditory responses.

Figure 6 is a summary of the results from the five monkeys. One of the most striking findings of this experiment is the variation among monkeys. Although all monkeys followed the same general pattern, they differed in the location and relative sizes of functional sub-regions. Therefore the summary is not an accurate topographic guide to any individual monkey.

Unresponsive zone in dorsal premotor cortex

We found that a region in the dorsal part of premotor cortex was unresponsive to passively presented sensory

stimuli. Recently, PMd was subdivided into a rostral part, PMDr, and a caudal part, PMDc (Wise et al. 1997). The two parts have somewhat different cytoarchitecture, connections and single neuron properties (Barbas and Pandya 1987; Johnson et al. 1996; Fogassi et al. 1999). The large unresponsive zone that we found in the present experiment appears to match, roughly, PMDr. In previous experiments on awake monkeys, neurons in this area responded during the performance of trained visuomotor tasks (Johnson et al. 1996; Wise et al. 1997). The area may have been unresponsive in our experiment because the monkey was not awake performing a task.

Hand representation in ventral premotor cortex

Just beneath the spur of the arcuate, anterior to the polysensory zone, we found a small representation of the arm and hand. This result corroborates the findings of Rizzolatti and colleagues (Rizzolatti et al. 1988; Murata et al. 1997), who found a representation of the arm and hand in roughly the same region, an area they termed F5 (Matelli et al. 1985).

Precentral polysensory zone (PZ)

We found a map of the body along the precentral gyrus, from a leg representation dorsally to a mouth representation ventrally. This map roughly matched the results of others (e.g., Woolsey et al. 1952; Kwan et al. 1978; Muakkassa and Strick 1979; Godschalk et al. 1984; Kurata 1989; Fogassi et al. 1999). In the middle of the body map, in all five monkeys, we found a polysensory zone that responded to tactile, visual and sometimes auditory stimuli. This polysensory zone was located in the face representation, the arm and hand representation, and the overlap between the two. In some monkeys, it was small and ventral to the spur of the arcuate. However, in other monkeys it extended more dorsally, above the spur of the arcuate, and in one case extended as much as 9 mm dorsal to the genu of the arcuate.

This variation in the location and size of the PZ seems to be related to the variation in the somatotopic map itself. In some monkeys, the map was relatively well organized. Different body parts were represented in different regions, although the regions overlapped. In other monkeys, the map was so disorganized that it could hardly be recognized as such. The extent and location of the face and arm representation therefore varied among monkeys. The presence of polysensory responses in the face and arm representation, however, was a constant across all five monkeys.

The variation in the somatotopy that we found agrees with previous findings. Sanes et al. (1995) found that the motor map in humans did not always have a clear somatotopic organization. They suggested that the map was organized along functional lines; that is, different body parts might be represented at the same cortical site

because they were used together during coordinated movements. Wu and Kaas (1999) recently found that the somatotopic map in the motor cortex of monkeys changes after amputation of a limb. Variation in the location, size and organization of cortical areas is common, even outside the motor system. Primary somatosensory cortex can change with experience, resulting in large differences between animals (Kaas 1991); and even the borders of visual areas in the occipital lobe show enormous differences between monkeys (Gattass et al. 1988). These findings indicate that a cortical area, such as the PZ, must be located functionally in each monkey before it can be studied. Perhaps some of the conflicting results on the visual and spatial properties of neurons in premotor cortex are related to this variation in the location of the PZ.

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