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Sensorimotor Integration in the Precentral Gyrus: Polysensory Neurons and Defensive Movements

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Cooke, Dylan F. and Micael S. A. Graziano. Sensorimotor integration in the precentral gyrus: polysensory neurons and defensive movements. *J Neurophysiol* 91: 1648–1660, 2004. First published October 29, 2003; 10.1152/jn.00955.2003. The precentral gyrus of monkeys contains a polysensory zone in which the neurons respond to tactile, visual, and sometimes auditory stimuli. The tactile receptive fields of the polysensory neurons are usually on the face, arms, or upper torso, and the visual and auditory receptive fields are usually confined to the space near the tactile receptive fields, within about 30 cm of the body. Electrical stimulation of this polysensory zone, even in anesthetized animals, evokes a specific set of movements. The movements resemble those typically used to defend the body from objects that are near, approaching, or touching the skin. In the present study, to determine whether the stimulation-evoked movements represent a normal set of defensive movements, we tested whether they include a distinctive, nonsaccadic, centering movement of the eyes that occurs during defensive reactions. We report that this centering movement of the eyes is evoked by stimulation of sites in the polysensory zone. We also recorded the activity of neurons in the polysensory zone while the monkey made defensive reactions to an air puff on the face. The neurons became active during the defensive movement, and the magnitude of this activity was correlated with the magnitude of the defensive reaction. These results support the hypothesis that the polysensory zone in the precentral gyrus contributes to the control of defensive movements. More generally, the results support the view that the precentral gyrus can control movement at the level of complex sensorimotor tasks.

INTRODUCTION

The precentral gyrus of monkeys contains a restricted zone in which the neurons respond with short latency to tactile, visual, and sometimes auditory stimuli (Fogassi et al. 1996; Gentilucci et al. 1988; Graziano and Gandhi 2000; Graziano et al. 1997, 1999; Rizzolatti et al. 1981). These polysensory neurons were first reported in ventral area 6, or the ventral premotor cortex (PMv), shown in Fig. 1*A* (Graziano et al. 1997; Rizzolatti et al. 1981). Their location was specified further to a posterior part of PMv termed F4, shown in Fig. 1*B* (Gentilucci et al. 1988; Matelli et al. 1985). In a recent mapping study, the polysensory neurons were found to be clustered in the region of the dorsal half of F4 (Fig. 1*C*), although the size and exact location of this polysensory region varies somewhat among monkeys (Graziano and Gandhi 2000). Here we refer to this functionally distinct region in the precentral gyrus as the *polysensory zone* (PZ). A similar polysensory zone may also exist in the human premotor cortex (Bremmer et al. 2001).

Most neurons in PZ respond to tactile and visual stimuli (Fogassi et al. 1996; Gentilucci et al. 1988; Graziano et al. 1997; Rizzolatti et al. 1981). For these bimodal cells, the tactile receptive field is located on the face, shoulder, arm, or upper torso. The visual receptive field extends from the approximate region of the tactile receptive field into the immediately adjacent space (Fig. 1*D*). Typically, the visual receptive field extends 5 to 30 cm from the body; most cells do not respond to more distant stimuli (Graziano et al. 1997). Neurons with a tactile receptive field on the side or back of the head often respond to auditory stimuli near the tactile receptive field, within about 30 cm of the head (Graziano et al. 1999). Thus the neurons in PZ represent the space on and immediately surrounding the body. For most cells, the visual receptive field has the remarkable property that it remains anchored to the tactile receptive field regardless of the position of the monkey's eyes, head, or limbs (Fogassi et al. 1992, 1996; Gentilucci et al. 1983; Graziano 1999; Graziano and Gross 1998; Graziano et al. 1994, 1997). That is, each neuron responds when an object is near, approaches, or touches a specific part of the body surface. These sensory receptive fields anchored to specific parts of the body have been described as "body-part-centered" (Graziano et al. 1997).

The function of the polysensory neurons in the precentral gyrus has been the subject of speculation for 2 decades. The region of cortex in which they are located projects directly to the spinal cord (Dum and Strick 1991), and therefore it might contribute to the sensory guidance of movement (e.g., Graziano et al. 1997; Rizzolatti et al. 1981). To test for possible motor functions, we recently electrically stimulated sites within the PZ and studied the evoked movements (Graziano et al. 2002). In every case, the evoked movements were consistent with avoiding, withdrawing, or protecting the part of the body on which the tactile receptive field was located. These defensive-like movements could be obtained even in monkeys anesthetized with barbiturates and thus did not appear to be reactions to a fictive sensory experience. For some cortical sites in PZ, the neurons responded to tactile stimuli on the side of the head and to visual stimuli near and approaching the tactile receptive field. Stimulation of these sites evoked a constellation of movements including blinking, squinting, flattening the ear against the side of the head, elevating the upper lip, shifting the head away from the sensory receptive fields, shrugging the shoulder, and rapidly lifting the hand into the space near the side of the head as if to block an impending impact. For other cortical sites, the neurons responded to tactile stimuli on the hand and forearm and to visual stimuli near and

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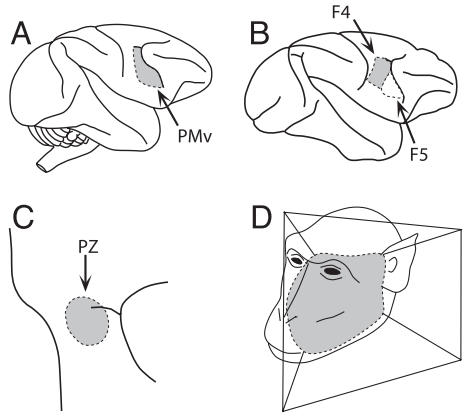


FIG. 1. Polysensory neurons in the precentral gyrus. *A*: ventral premotor cortex (PMv) in which polysensory neurons were found (from Graziano et al. 1997). *B*: polysensory neurons were found to be concentrated in area F4 (Gentilucci et al. 1988; Matelli et al. 1985). *C*: approximate location of the polysensory zone (PZ) as determined in a mapping study by Graziano and Gandhi (2000). *D*: tactile receptive field (shaded) and visual receptive field (boxed area extending from shaded area) of a typical bimodal, visual-tactile neuron in PZ. This neuron was studied in the present experiment; other data from this neuron are shown in Fig. 6*A*.

approaching the hand. Stimulation of these sites evoked a fast withdrawal of the hand to a guarding-like posture behind the back. Stimulation of nonpolysensory sites surrounding area PZ did not result in defensive-like movements. On the basis of these results, we hypothesized that at least one major function of the polysensory neurons in PZ may be to monitor nearby, potentially threatening objects and to coordinate complex movements to protect the body surface from those objects.

Although stimulation of PZ evoked movements that appeared to be defensive, how similar are the evoked movements to actual defensive movements? To answer this question, we tested the reactions of monkeys to a puff of air directed at various locations on the face and body (Cooke and Graziano 2003). We found that the air puff evoked a constellation of movements that matched in detail the movements evoked by stimulation of area PZ. For example, an air puff to the side of the face evoked blinking, squinting, flattening the ear against the side of the head, elevating the upper lip, shifting the head away from the location of the air puff, shrugging the shoulder, and rapidly lifting the hand into the space near the side of the head as if to block an impending impact. An air puff to the hand evoked a fast withdrawal of the hand to a guarding posture behind the back. These findings on the similarity of natural defensive movements to stimulation-evoked movements suggest that stimulation of area PZ may indeed evoke a normal defensive reaction.

One of the most distinctive components of a normal defensive reaction is a movement of the eyes from any initial position toward the center of gaze (Cooke and Graziano 2003). These centering eye movements are slower than normal saccades and begin with a characteristic downward and nasal curve. Such nonsaccadic, centering eye movements may be related to the protective withdrawal of the eye into the orbit, a movement that in primates involves the co-contraction of the extraocular muscles (e.g., Bour et al. 2002; Collewijn et al. 1985; Evinger et al. 1984). Does electrical stimulation of PZ evoke this distinctive, defense-related pattern of eye movements? At least one study reported centering movements of the eye on stimulation of the ventral premotor cortex (PMv) (Fujii et al. 1998). However, whether the studied region matched PZ, and whether the evoked movements matched the pattern for a defensive reaction, are not yet known.

In summary, the neurons in PZ respond to objects near, approaching, or touching the body. Electrical stimulation of PZ, even in anesthetized animals, evokes a stereotyped set of movements similar to a defensive reaction. One component of a defensive reaction, a distinctive centering of the eyes, has not yet been clearly demonstrated on stimulation of PZ.

The purpose of the present study was to further test the possible role of PZ in defensive movements. We focused on 3 issues. First, we replicated our previous finding that stimulation of PZ evokes defensive-like movements. We studied the activity evoked in the orbicularis muscle, a muscle that surrounds the eye and participates in squinting and blinking. In this fashion we were able to quantify previously unstudied aspects of the evoked movements, such as latency and laterality.

Second, we studied the pattern of eye movement evoked by electrical stimulation of sites in PZ. We hypothesized that stimulation should evoke centering eye movements similar to those evoked by a puff of air to the face. Because this type of eye movement is distinctive to defense, demonstrating it on stimulation of PZ would strongly support the interpretation that the evoked movements represent a normal, coordinated defensive reaction.

Third, we recorded the activity of neurons in PZ while applying a puff of air to the monkey's face. Although the air puff was the same on each trial, the neuronal response and the monkey's defensive reaction varied somewhat among trials. We hypothesized that trials with greater neuronal response would be associated with a larger defensive reaction to the air puff.

METHODS

All husbandry, surgical, and behavioral procedures were approved by the Princeton University Institutional Animal Care and Use Committee and the attendant veterinarian and were in accordance with NIH and USDA guidelines. We studied 2 adult male *Macaca fascicularis* (4.5–7.0 kg).

Surgery

For each monkey, an initial surgical operation was performed under isoflurane anesthesia and strict aseptic conditions, during which an acrylic skullcap was fixed to the skull with bone screws. A steel bolt for holding the head and a 2.5-cm-diameter steel chamber for neuronal recording and electrical stimulation were also embedded in the acrylic. The recording chamber was positioned for a vertical approach to the precentral gyrus in the right hemisphere. The well was centered 20 mm anterior and 15 mm lateral to ear-bar zero. A standard scleral coil was implanted in one eye. The leads of the eye coil were threaded under the skin and attached to an electrical connector that was embedded in the acrylic implant, to allow for the recording of eye movement. Each animal recovered from the surgery within 1 wk, but was given an additional 2 wk to allow the skull to grow tightly around the skull screws. In a subsequent procedure, also under deep anesthesia and aseptic conditions, the recording chamber was opened and a hole approximately 5 mm in diameter was drilled through the layer of acrylic and the bone, exposing the dura.

Neuronal recording

During the daily recording sessions, the monkey sat in a Lexan primate chair with the head restrained by the head bolt. A hydraulic microdrive (Narishige) was mounted to the top of the recording chamber. A steel guide cannula (an 18-gauge syringe needle) was lowered through the hole in the skull and into the dura. Then the varnish-coated tungsten microelectrode (Frederick Haer, impedance 0.5–5 MΩ) was advanced from the guide cannula into the brain.

Neuronal activity was initially studied by monitoring the signal on an oscilloscope and 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. Most multimodal neurons in PZ do not respond to visual stimuli projected onto a tangent screen, even when the screen is placed close to the face, within 20 cm (Graziano et al. 1997). Instead they respond best to objects near the animal. Therefore we used real objects, such as a ping-pong ball mounted on the end of a rod, to study visual receptive fields. To ensure that the responses to stimuli close to the body were not caused by inadvertent tactile stimulation, for example by static electricity or air movement, the visual stimuli were also presented while the eyes were covered, while the animal was shielded with a piece of clear Lexan, or under both conditions.

Air-puff trials

After a neuron was tested qualitatively for tactile and visual responses, the cell was then tested quantitatively. Its activity was recorded while an air puff was presented to the monkey's face. At the same time, the monkey's behavior was monitored in 3 ways: by video at 30 frames/s; by an eye coil to measure eye position; and by electromyographic (EMG) recordings from the right and left orbicularis muscles to measure the amount of the facial defensive movement.

An air nozzle directed a 0.5-s stream of air at the monkey's skin from a distance of 5 cm. An electrically actuated valve was connected to the base of the nozzle to control the onset and offset of the air stream. A pressure regulator mounted to a tank of compressed air was used to control the pressure of the air stream. Pressures were typically set between 5 and 30 psi (pounds per square inch). For most experiments, the pressure was set to 15 psi. Two nozzles were used: one directed at the right cheek (ipsilateral to the recording chamber) and one directed at the left cheek (contralateral to the recording chamber). The 2 nozzles were actuated in a pseudorandom schedule with an interpuff interval of 30 s. The monkey performed no task during this experiment. The video record confirmed that the monkeys remained alert and calm during the air-puff trials, with no sign of agitation or distress. The defensive movements involved a brief blink, squint, lifting of the upper lip, folding of the ear against the head, and shrug, matching the results of a previous study (Cooke and Graziano 2003). In the initial trials for each monkey, the defensive reaction included a lifting of the hand toward the space beside the head; this movement of the arm habituated and was not consistently observed in later trials.

Electrical stimulation trials

In some sessions, after recording the activity of neurons during air-puff trials, we then electrically stimulated the cortical site through the same microelectrode. Stimulation was performed on only a small proportion of electrode penetrations, to reduce the possibility of damage to the brain that might compromise the ongoing study of single-neuron–response properties.

Stimulation was applied by an S88 stimulator and 2 SIU6 stimulus isolation units (Grass, West Warwick, RI). Stimulation consisted of a train of pulses presented at 200 Hz. Each pulse had a negative followed by a positive phase, each phase 0.2 ms in duration. Current was measured by the voltage drop across a 1-kΩ resistor in series with the return lead of the stimulus isolation units. For quantification of the evoked movement, the current was usually set between 20 and 50 μA. The duration of each train was set to 500 ms. For some sites we also tested with trains of 100 ms, as described in RESULTS.

For each site we varied the current until an evoked movement was observed. The threshold, the current at which the movement was evoked 50% of the time, was determined by 2 observers. These threshold measurements were thus approximate, but allowed us to set the current to an appropriate level for quantitative testing. The average threshold measured in this fashion for sites in PZ was 21.5 μA (SD = 4.2 μA) with a range of 12–60 μA. In some cases, to confirm that stimulation of a site did not evoke any movement, the stimulating current was increased to 300 μA.

During stimulation, the monkey's behavior was monitored in 3 ways: by video at 30 frames/s; by an eye coil to measure eye position; and by EMG recordings from the right and left orbicularis muscles to measure the amount of the facial defensive movement.

Electromyographic recordings

During both air-puff trials and electrical stimulation trials, EMG activity was measured bilaterally in the orbicularis muscle. Fine insulated stainless-steel wires were threaded into a 22-gauge syringe needle and inserted into the muscle. The wires had an exposed tip of 1–2 mm. Three wires spaced about 5 mm apart were inserted in each muscle to provide input to a differential amplifier and its ground (single-neuron amplifier model 1800, A-M Systems, Sequim, WA). The amplifier filters were set with a low cutoff at 300 Hz and a high cutoff at 1,000 Hz.

During air-puff trials, the EMG signal was sampled every 2 ms. During electrical stimulation trials, however, a pulse of stimulation was applied to the brain every 5 ms, producing a periodic electrical artifact in the EMG signal. To avoid contamination by this artifact, the time of each stimulation pulse to the brain was measured and the EMG signal was sampled once within each 5-ms interpulse interval. We confirmed that with this method the resultant EMG signal did not contain any artifact from the electrical stimulation applied to the brain. Thus in stimulation trials, EMG was measured once every 5 ms or at 200 Hz, after which it was rectified. The magnitude of the EMG signal was normalized to the amount of activity measured in the intertrial interval, when the muscle was at a resting level. In the histograms shown in Fig. 2, the signal was integrated in 10-ms bins.

Location of PZ

PZ was identified on the basis of 3 main criteria.

1) *Response properties*. Neurons in PZ have tactile receptive fields on the head and upper body and visual receptive fields that are adjacent to the tactile receptive fields and that extend outward typically 5 to 30 cm from the body. These sensory response properties were confirmed in both monkeys.

2) *Properties of surrounding areas*. PZ is surrounded by distinctive cortical areas. The frontal eye fields, anterior to PZ, were identified in both monkeys by staircase saccades evoked by low threshold electrical stimulation (e.g., 20 μA). Motor cortex posterior to PZ was identified by the finger movements evoked by low threshold electrical stimulation (e.g., 10 μA). The cortex ventral to PZ was responsive during movements of the mouth, especially chewing. The cortex dorsal to PZ was responsive during reaching movements of the contralateral arm and hand.

3) *Cortical location*. During the experiment, the sulcal pattern was inferred by monitoring the pattern of cellular activity and silence as the electrode was advanced. In this way we were able to determine that PZ was located on the cortical surface just posterior to the arcuate sulcus. At the completion of the experiment, both monkeys were

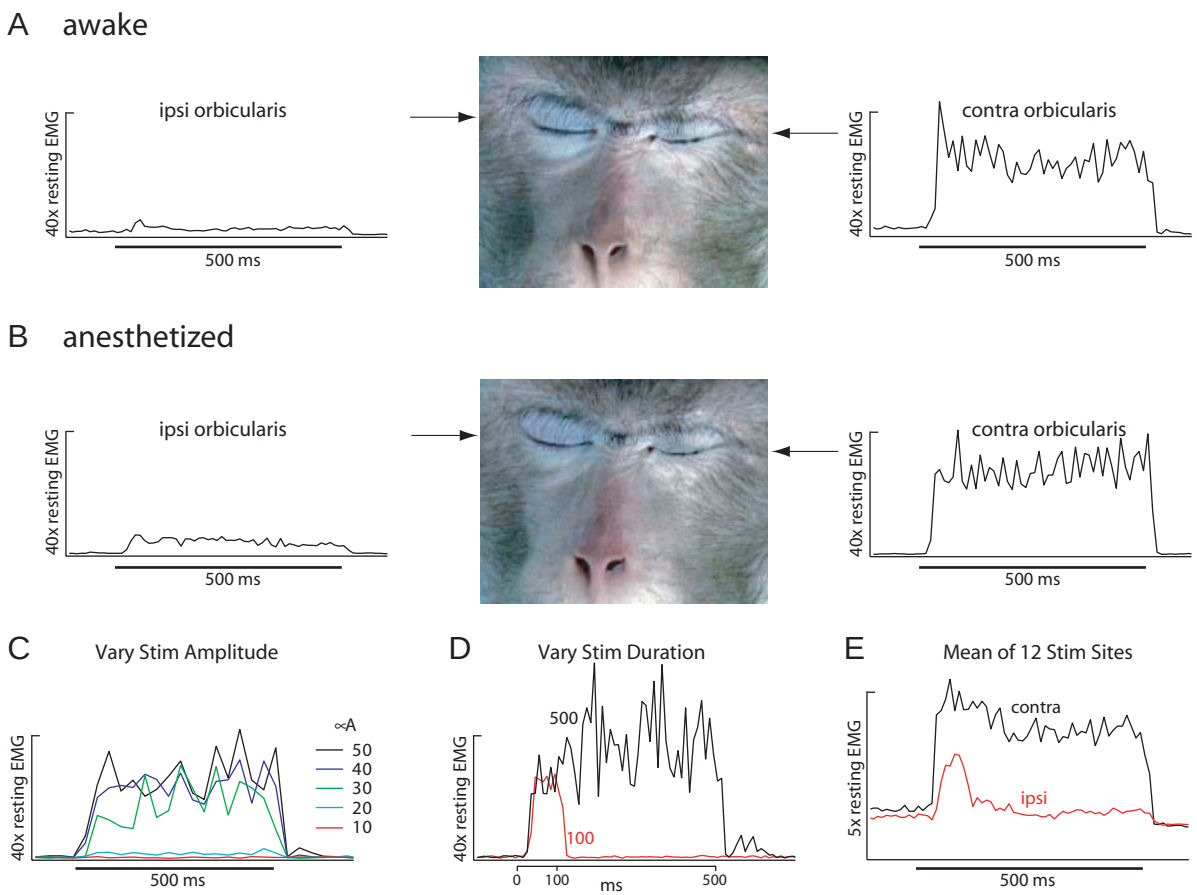


FIG. 2. Muscle activity evoked by stimulation of PZ in the right hemisphere. *A*: results from stimulating an example site with a tactile receptive field on the left (contralateral) side of the head and a visual receptive field near the tactile receptive field. Stimulation for 500 ms, 50 μA, and 200 Hz caused a blink and squint, shown in the video frame captured 300 ms after onset of stimulation train. Greater magnitude of the squint on the contralateral side of the face can be seen especially in the wrinkling of the skin on the upper part of the nose. Histograms show EMG activity from the orbicularis muscles surrounding the eyes. Each histogram is an average of 24 trials. EMG activity is normalized to the resting level of muscle activity measured in the intertrial interval. Horizontal line under each histogram shows the 500-ms stimulation period. *B*: results from same site as in *A*, but 10 min after administration of anesthetic. EMG activity is normalized to the resting level of activity in *A*, such that the magnitude of the effect in *B* can be directly compared with that in *A*. *C*: EMG activity from contralateral orbicularis obtained by stimulating the same example site with interleaved stimulation trains at current levels of 10, 20, 30, 40, and 50 μA. *D*: EMG activity from contralateral orbicularis obtained by stimulating the same example site with interleaved stimulation trains of 100- and 500-ms duration. *E*: mean EMG response in contralateral and ipsilateral orbicularis for 12 cortical sites tested with 500-ms stimulation trains in the awake monkey. Each site was tested with 24 stimulation trials.

euthanized and perfused with 4% paraformaldehyde. The head was put in a stereotaxic apparatus, the skull opened and the brain exposed. The arcuate and central sulci were photographed and measured stereotaxically. The location of the stimulation and recording sites were reconstructed to be just posterior to the bend in the arcuate sulcus, in the expected location of PZ.

RESULTS

Muscle activity evoked by stimulation of PZ

We first replicated our previous finding that electrical stimulation of sites in PZ evokes short-latency, defensive-like movements. Figure 2 shows the results of stimulation of a typical site in PZ. Neurons at this site had a tactile receptive field on the contralateral side of the face. They also responded to visual stimuli near the tactile receptive field, within about 20 cm of the face. Stimulation for 500 ms at 50 μA evoked a facial defensive movement. The video frame shown in Fig. 2*A* was captured 300 ms after the onset of the stimulation train and illustrates a bilateral squint that was more pronounced on the contralateral side. The histograms show the activity of the right and left orbicularis muscles, which surround the eyes and participate in blinking and squinting. Each histogram shows a mean of 24 trials. The evoked activity was larger on the contralateral side of the face. The latency of this evoked activity (the time at which the activity exceeded 2 SD above baseline) was 25 ms.

After testing this cortical site, we then injected the monkey with ketamine (10 mg/kg, intramuscularly). Because ketamine is fast-acting, within 10 min the monkey became fully unresponsive with little muscle tone and no reaction to stimuli such as an air puff to the face that would normally induce a defensive reaction. Figure 2*B* shows the results of stimulating the cortical site under these conditions of anesthesia. Again, the video frame shows a facial defensive movement and the EMG traces show activity in the left and right orbicularis muscle.

The evoked activity rose to a similar level as in the unanesthetized state. As expected, under anesthesia the baseline activity of the muscles was reduced.

We then varied the current amplitude, using 10, 20, 30, 40, and 50 μA on interleaved trials. Figure 2*C* shows the effect on the activity of the contralateral orbicularis muscle. No EMG response was obtained at 10 μA; little was obtained at 20 μA; and a robust response was obtained at 30, 40, and 50 μA.

We also varied the duration of the stimulation train, using 100- and 500-ms trains on interleaved trials. Figure 2*D* shows the effect of train duration on the EMG measured from the contralateral orbicularis muscle. The EMG response followed the time course of the stimulation train. The activity rose within a short latency after stimulation onset, remained at a high level during stimulation, and dropped within a short latency after stimulation offset. In the case of the 500-ms stimulation train, a second blink sometimes occurred just after the offset of the stimulation, as can be seen in the EMG activity.

Figure 2*E* shows the mean EMG response for 12 stimulation sites in PZ. All had a tactile and visual receptive field related to the contralateral side of the face. All were stimulated with 500-ms trains while the monkey was awake. The stimulation evoked an increase in activity that was greater in the contralateral muscle. The mean latency of the response was 31 ms (SD = 7 ms). After stimulation, both muscles returned to a low resting level. Note that the mean muscle activity was elevated before stimulation onset, compared with its resting level reached after stimulation. This initial elevation was greatest for the contralateral muscle. (The same initial elevation in EMG can also be seen in Fig. 2*A*.) We suggest that this elevation in activity before stimulation may have been the result of the monkey predicting the stimulation and slightly tensing the facial muscles in anticipation. This anticipatory elevation in muscle activity was not observed when the monkey was anesthetized, such as in Fig. 2*B*.

Centering eye movements

As described in the INTRODUCTION, one component of a facial defensive reaction is a distinctive centering of the eyes that is different from a saccadic eye movement (Cooke and Graziano 2003). Here we examine whether eye movements evoked by stimulation of PZ more closely resemble defense-related eye movements or saccadic eye movements.

Figure 3*A* shows the eye movements that were evoked in the present study by a puff of air directed at the monkey's face. Trials in which the eye was already in motion at the time of puff onset were eliminated. Thus in all trials shown, the eye was stationary at the start of air puff. The initial eye positions are skewed toward lower positions because the monkey tended to spontaneously fixate positions in the lower field. Each *green trace* shows the eye movement on one air-puff trial. For each trace, the black dot shows the eye position at the beginning of the air puff and the red dot shows the eye position 300 ms after air-puff onset. We selected 300 ms as the endpoint of the displayed data because the defense-related centering of the eye is typically complete by 300 ms (Cooke and Graziano 2003). The traces show a tendency of the eyes to center during the air puff. This centering can be seen especially clearly by comparing the large black oval (representing the *x* and *y* SD of eye position at the start of air puff) to the smaller red oval (the *x* and *y* SD of eye position 300 ms after air-puff onset).

The air nozzles were located in the lower visual fields about 45° below the horizontal meridian and 45° to the right and left of the vertical meridian. The pattern of results is not consistent with the eye saccading to these nozzle locations. As discussed in a later section, the centering eye movements are unlikely to represent saccades to any target because their velocity profile is different from that of a saccade (see Fig. 5).

Figure 3*B* shows the movement of the eyes during spontaneous saccades that occurred in the intertrial interval. No tendency toward centering is apparent. That is, the monkey did not show a natural tendency to saccade toward the center of gaze.

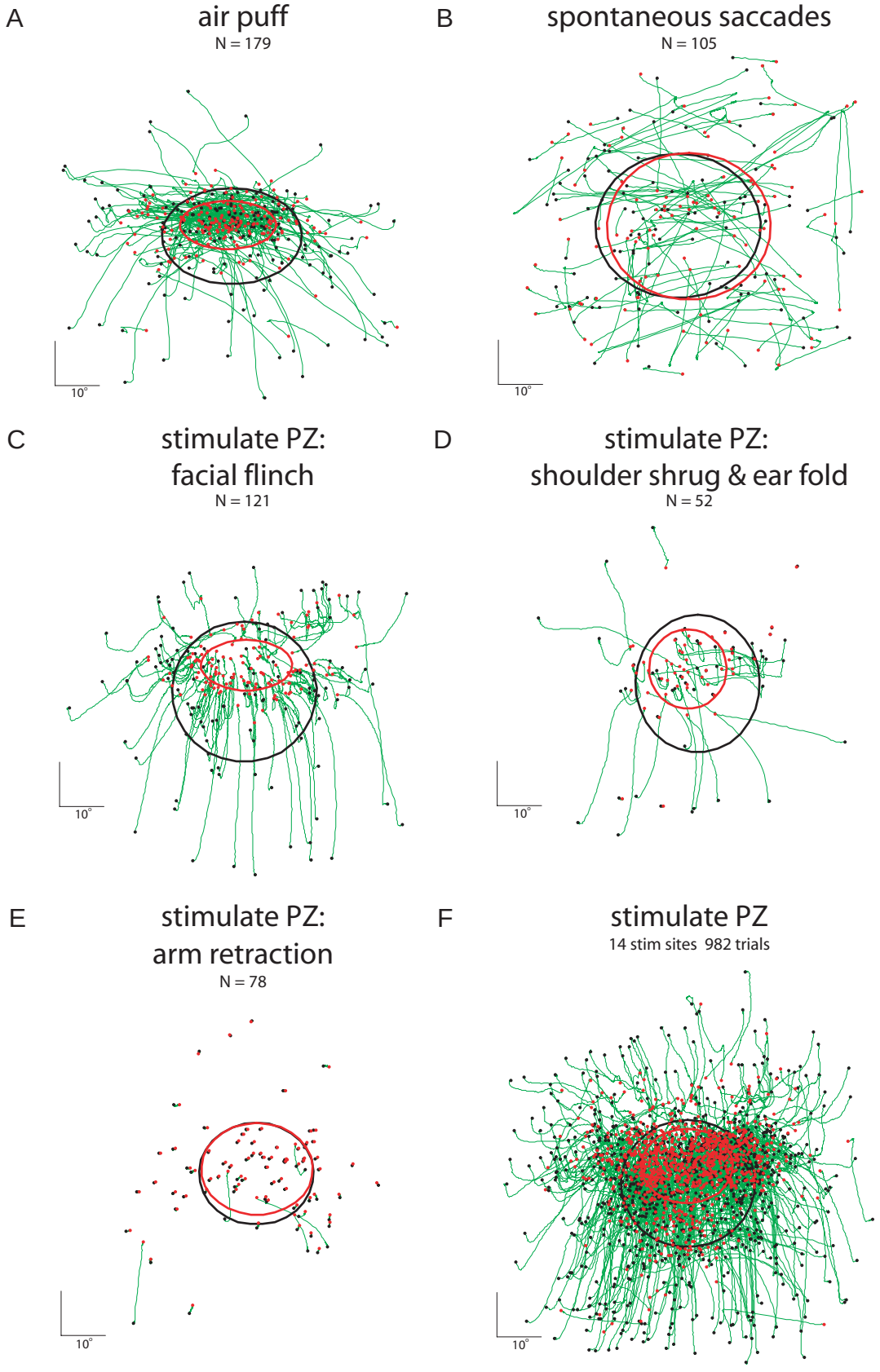
Figure 3*C* shows the eye movements evoked by stimulation of an example cortical site in PZ. Neurons at this site responded to tactile stimuli on the contralateral side of the face and to visual stimuli near the contralateral side of the face. Stimulation of this site evoked a squint, blink, lifting of the upper lip, and shoulder shrug. The traces show a centering of the eyes, similar to the centering shown in Fig. 3*A* that occurred during air puff.

Figure 3*D* shows the results from another example site in PZ. Neurons at this site had a tactile receptive field on the contralateral back of the head, including the ear, but not extending to the front of the face. The neurons also responded to visual stimuli presented in the contralateral periphery. Stimulation of this site evoked a shoulder shrug and a folding of the pinna backward against the head, both normal components of a defensive reaction. However, stimulation did not evoke any measurable movement on the front of the face. Squints and blinks were not observed, either on the video record or in the EMG recordings from the orbicularis muscle. Thus the defensive movements evoked by stimulation of this site were appropriate to the location of the sensory receptive fields. As shown in Fig. 3*D*, stimulation of this site still evoked a centering movement of the eyes. This result matches our previous finding that centering movements of the eyes can be evoked by air puff to the back of the head (Cooke and Graziano 2003). The result also indicates that the centering movements of the eyes were

FIG. 3. Comparison of air-puff evoked eye movements, spontaneous saccades, and stimulation-evoked eye movements. *A*: air-puff–evoked eye movements. Each *green trace* = 1 trial. Black dot at start of trace = eye position at puff onset; red dot = eye position 300 ms after puff onset. Black oval = *x* and *y* SD of eye position at puff onset; this oval is centered around mean eye position at puff onset. The center of the black oval is approximately the center of the monkey's gaze. Red oval = *x* and *y* SD of eye position 300 ms after puff onset; this oval is centered around mean eye position 300 ms after puff onset. *B*: similar plot but for spontaneous saccades that occurred during the intertrial interval. Each trace begins at time of saccade onset (black dot) and ends 300 ms later (red dot). *C*: results from an example site in PZ at which stimulation evoked a facial defensive movement. Each trace begins at stimulation onset (black dot) and ends 300 ms after stimulation onset (red dot). *D*: results from an example site in PZ at which stimulation evoked a shoulder shrug and a folding of the ear backward against the head. *E*: results from an example site in PZ at which stimulation evoked a retraction of the arm but no facial or head movement. *F*: group data for 14 sites in PZ at which stimulation evoked a defensive movement related to the head or face.

not a mechanical by-product of a blink or squint, in that no blink or squint occurred at this site.

Figure 3*E* shows the result for another example site in PZ. Neurons at this site had a tactile receptive field restricted to the contralateral hand and forearm. No sensory responses were found on or near the head. Stimulation evoked a withdrawal



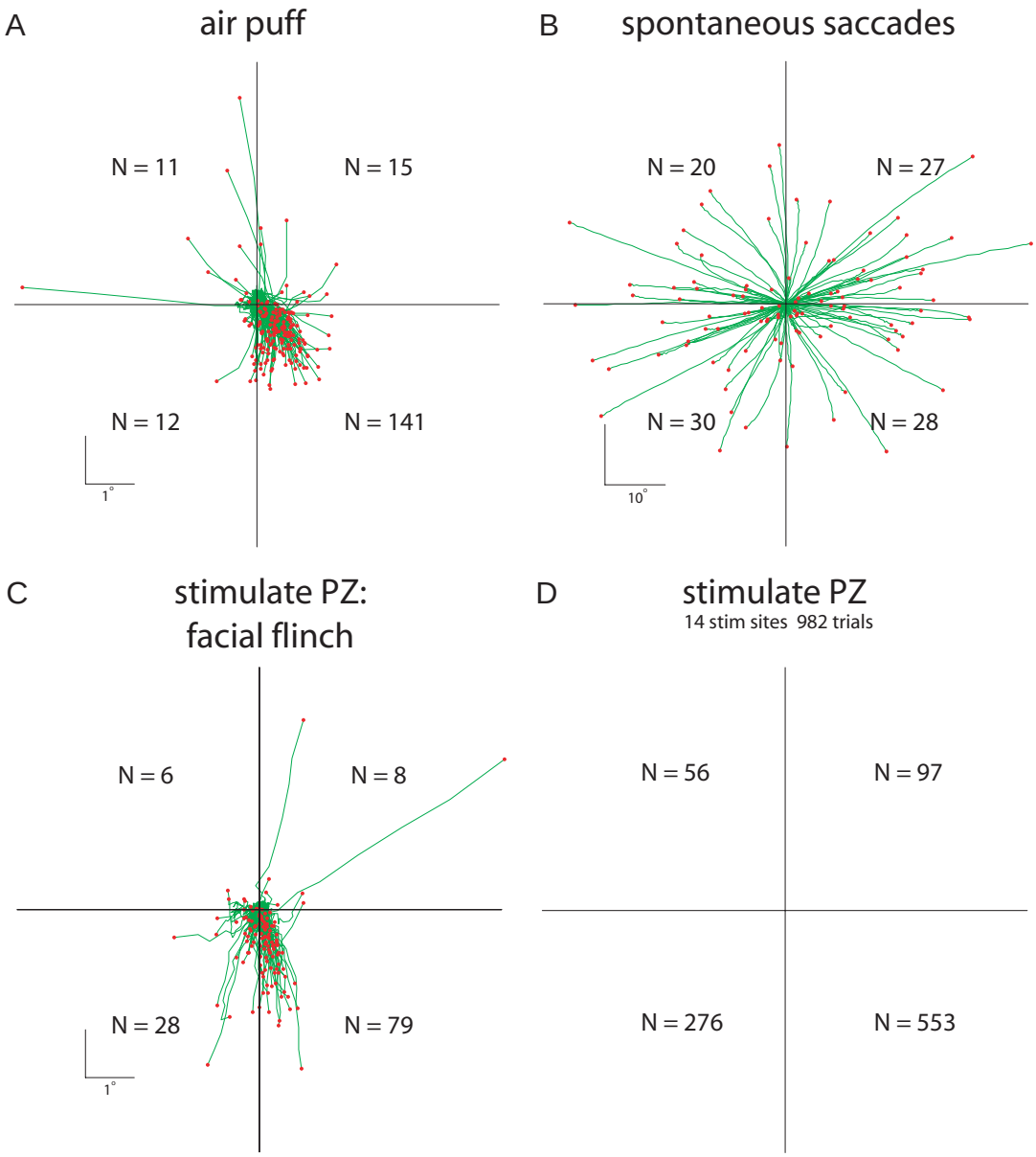


FIG. 4. Downward and nasal excursion at start of eye movement. *A*: results for air-puff–evoked eye movements. Same data as in Fig. 3*A* but showing a magnified view of the beginning of each eye movement. Each green line shows the *eye trace* on a single trial, starting at puff onset (plotted at center of graph) and ending 60 ms later (red dot). In each quadrant, N indicates the number of trials for which the eye moved into that quadrant. *B*: results for spontaneous saccades, showing no tendency toward downward and nasal movement. Each trace begins at saccade onset and ends 60 ms later. *C*: results for an example stimulation site, showing a tendency toward downward and nasal movement. Each trace begins at stimulation onset and ends 60 ms later. *D*: group results for 14 sites in PZ at which stimulation evoked a defensive movement related to the head or face.

movement of the arm but not any defensive movements related to the head, ear, face, or shoulder. As shown in the figure, stimulation of this site did not evoke a centering movement of the eyes. On most trials, no eye movement occurred.

Figure 3*F* shows the combined result for 14 cortical sites at which stimulation evoked some component of a head or face flinch. This group result shows a pronounced overall tendency for the eyes to center during the stimulation.

Downward and nasal component of eye movement

Defense-related movements of the eye often begin with a characteristic downward and nasal excursion of the eye that precedes the centering movement (Cooke and Graziano 2003). This downward and nasal movement can be seen in Fig. 3*A*, at the start of many of the *eye traces* shown. It is illustrated more clearly in Fig. 4*A*. Here, data from the same air-puff trials as in Fig. 3*A* are plotted such that the starting eye position for all trials is aligned on a single point. The plot shows the first 60 ms of eye data after puff onset. The green lines show individual trials and the red dots show the position of the eye 60 ms after puff onset. On most trials, the eye began movement in a downward and nasal direction. Figure 4*A* also shows the number of trials for which the initial eye movement was directed into the lower nasal, lower lateral, upper nasal, and upper

lateral quadrants. The distribution was significantly skewed toward the lower nasal quadrant ($\chi^2 = 104.3$, $P < 0.0001$).

Figure 4*B* shows that spontaneous saccades do not have the same tendency to begin in a downward and nasal direction ($\chi^2 = 1.2$, $P = 0.76$). Instead, their directions are relatively evenly distributed.

Figure 4*C* shows the results for stimulation of an example site in PZ. The site is the same as that illustrated in Fig. 3*C*. The traces in Fig. 4*C* show that the stimulation-evoked eye movements tended to begin in a downward and nasal direction ($\chi^2 = 50.83$, $P < 0.0001$).

Figure 4*D* shows the group results for 14 cortical sites at which stimulation evoked some component of a head or face flinch. The individual *eye traces* are not shown because the overlap of 982 trials obscures the plot. The number of trials that fell into each of the 4 quadrants is given in the figure. The evoked eye movements showed a significant tendency to begin in a downward and nasal direction ($\chi^2 = 303.9$; $P < 0.0001$). In this respect, stimulation-evoked eye movements were similar to air-puff–evoked eye movements, and both were different from saccades.

Speed of eye movement

Figure 5 shows the main sequence (peak speed vs. amplitude) for spontaneous saccades, puff-evoked eye movements, and stimulation-evoked eye movements. Spontaneous saccades followed a typical, roughly linear relationship between speed and amplitude. Puff-evoked and stimulation-evoked movements followed a similar pattern, but at a slower speed. Neither one followed the speed/amplitude relationship of normal saccades. Thus the eye movements evoked by stimulation of PZ resemble the distinctive pattern of defense-related eye movements, and do not resemble saccades.

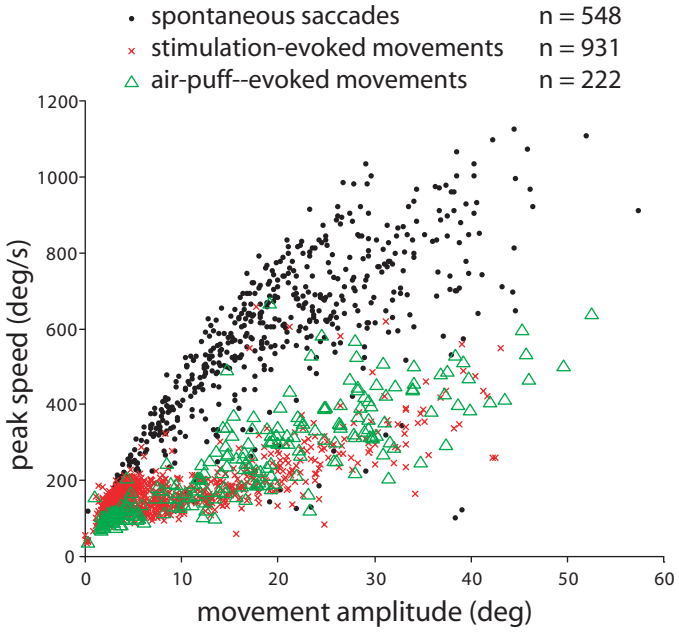


FIG. 5. Main sequence for spontaneous saccades, puff-evoked movements, and stimulation-evoked movements. *y*-axis: peak speed of movement; *x*-axis: amplitude of movement. Stimulation trials during which the eye did not move are not plotted on this graph because it was not possible in these cases to define the beginning point and endpoint of an eye movement. Thus the total number of stimulation trials represented in Fig. 5 is slightly less than the number represented in Figs. 3 and 4.

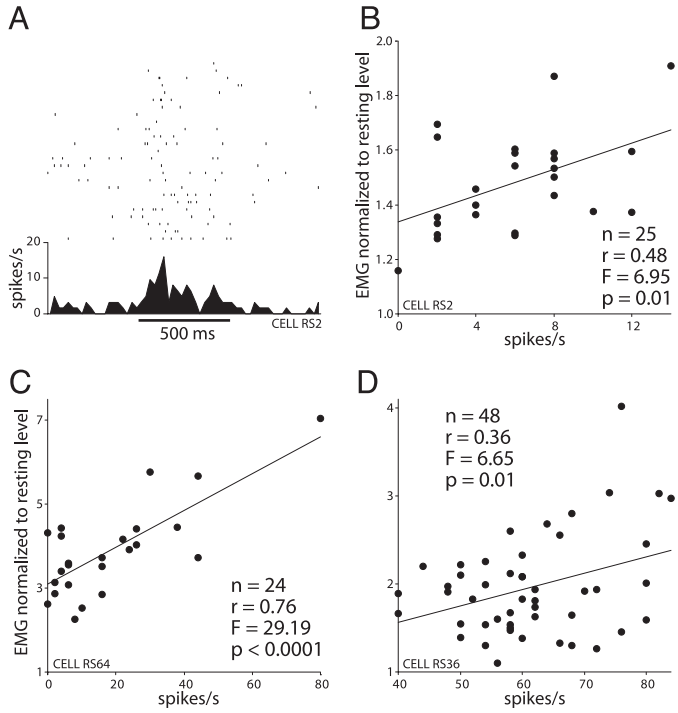


FIG. 6. Neuronal activity in PZ correlates with magnitude of defensive movement. *A*: rasters and histogram showing response of an example neuron in PZ to a puff of air directed at the contralateral cheek. This cell had a tactile receptive field on the contralateral cheek and a visual receptive field adjacent to the tactile receptive field (shown in Fig. 1*D*). *B*: data from same example cell as in *A*. *x*-axis: magnitude of the neuronal response during the 500-ms air puff; *y*-axis: magnitude of EMG activity from the contralateral orbicularis during the 500-ms air puff. Each point shows data from a single trial. Number of trials (N), the correlation coefficient (*r*), and the *F* and *P* values from a linear regression are also shown. *C* and *D*: two more example neurons showing a significant correlation between neuronal activity and magnitude of defensive movement.

Single neuron activity during air puff

To further test the relationship between neurons in PZ and defensive movement, we applied an air puff to the monkey's face while recording the activity of PZ neurons. Figure 6*A* shows the results for one example neuron. This neuron had a tactile receptive field on the contralateral side of the face and responded to visual stimuli presented near the tactile receptive field, within about 20 cm of the face (Fig. 1*D*). The rasters and histogram show the response of the neuron to air puff presented to the tactile receptive field on the contralateral cheek. Note that the response varied somewhat from trial to trial, as shown in the individual trial rasters. Are the trials with greater neuronal response associated with a larger defensive reaction?

To quantify the magnitude of the neuronal response on each trial, we used the spike rate during the 500-ms period of the air puff. To quantify the magnitude of the defensive reaction, we used the rectified EMG activity measured from the contralateral orbicularis muscle during the same 500-ms period of the air puff. Figure 6*B* shows the magnitude of the defensive reaction plotted against the magnitude of the neuronal response. Each point represents data from a single air-puff trial. For this neuron, 25 trials were tested. The 2 variables were

significantly correlated: a regression analysis showed a significant linear relationship ($r = 0.48$; $F = 6.95$; $P = 0.01$). Thus the trials in which the neuron was more active corresponded to the trials in which the monkey produced a larger defensive reaction.

Figure 6, *C* and *D* shows the results for 2 more example neurons. In each case, the activity of the neuron during air puff was significantly correlated with the monkey's defensive reaction to the air puff.

We studied 52 neurons in this fashion. Of these, 41 neurons gave an excitatory response to the air puff on the contralateral cheek (mean latency = 32 ms) and thus were included in the group analysis. Group data from these 41 neurons are shown in Fig. 7. Each line shows the correlation coefficient (r value) between neuronal activity and EMG activity, calculated within a time window of 100 ms, sliding in increments of 4 ms throughout the duration of the trial. Figure 7*A* shows the result for trials in which the air puff was delivered to the contralateral cheek. The solid line in Fig. 7*A* shows the correlation between neuronal activity and EMG activity in the contralateral orbicularis muscle. The correlation shows an increase just after the onset of the air puff, indicating that at this time during the trial the activity of the neurons was correlated with the activity of the contralateral muscle. The positive correlation 100 ms after the onset of the air puff was significant, based on a linear regression test ($F = 20.89$, $P < 0.0001$). Thus although the r value was relatively small, the significance level was high. The increase in correlation was transient; it was maintained for about 200 ms, even though the air puff itself had a duration of 500 ms.

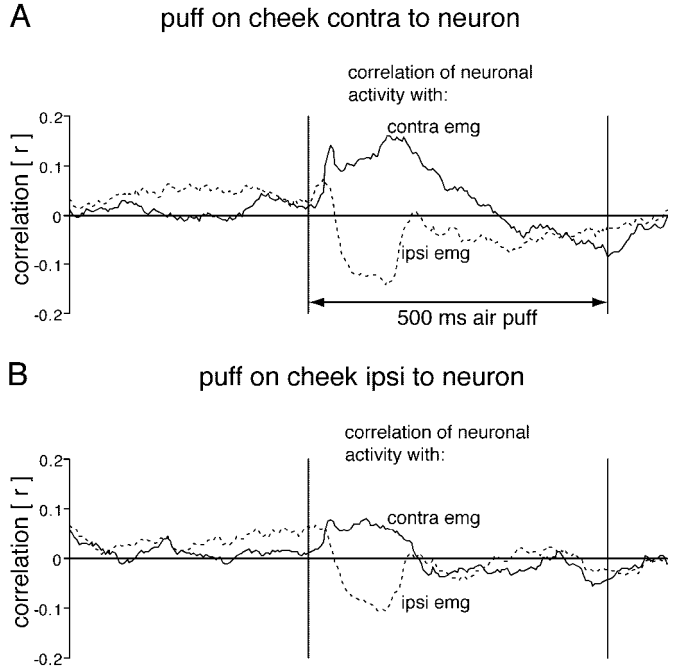


FIG. 7. Group data from 41 neurons showing that during a defensive reaction to an air puff, neuronal activity in PZ is positively correlated with the contralateral musculature and negatively correlated with the ipsilateral musculature. *A*: data from trials in which air puff was presented to contralateral cheek. Each line = correlation coefficient (r) calculated in a 100-ms sliding window at 4-ms intervals through the trial. Solid line = correlation between single neuron activity and EMG from contralateral orbicularis. Dotted line = correlation between single neuron activity and EMG from ipsilateral orbicularis. *B*: similar analysis of trials in which air puff was presented to ipsilateral cheek.

The dotted line in Fig. 7*A* shows the correlation between neuronal activity and EMG activity in the ipsilateral orbicularis muscle. The correlation shows a decrease just after the onset of the air puff, indicating that at this time during the trial the activity of the neurons was negatively correlated with the activity of the ipsilateral muscle. The negative correlation 100 ms after the onset of the air puff was significant, based on a linear regression test ($F = 23.06$, $P < 0.0001$). It is important to note that the dotted line and the solid line are based on data from the same trials. Each line represents the correlation with a different muscle. Thus after the onset of the air puff, the contralateral muscle became positively correlated with the activity of the neurons whereas, on the same trials, the ipsilateral muscle became negatively correlated with the activity of the neurons.

Figure 7*B* shows the results for those trials in which the air puff was delivered to the ipsilateral cheek. In these trials, the neuronal response to the tactile stimulus was typically weak or not present. However, a similar though smaller correlation result was obtained: just after puff onset, the neuronal activity became positively correlated with the contralateral muscle activity ($F = 9.79$, $P = 0.0018$, linear regression based on data 100 ms after onset of air puff) and negatively correlated with the ipsilateral muscle activity ($F = 13.85$ $P = 0.0002$, linear regression based on data 100 ms after onset of air puff).

In summary, the correlation between neuronal activity and behavior was specific in 2 ways. First, the neuronal activity became correlated with muscle activity during air puff, that is, during the defensive movement. Second, the neuronal activity was positively correlated with the contralateral muscle and negatively correlated with the ipsilateral muscle, regardless of the location of the stimulus. Thus the neuronal activity showed some motor specificity.

DISCUSSION

This study examined the relationship between PZ, a polysensory region in the precentral gyrus, and defensive movements. Neurons in the PZ are known to respond to objects near, approaching, or touching the face and upper body (Fogassi et al. 1996; Gentilucci et al. 1988; Graziano and Gandhi 2000; Graziano et al. 1997, 1999; Rizzolatti et al. 1981). Previous experiments showed that electrical stimulation of PZ evokes a set of movements that closely resemble the natural defensive reaction to a puff of air or a rapidly approaching object (Cooke and Graziano 2003; Graziano et al. 2002).

In the present study we extended these findings in the following ways.

1) We confirmed that stimulation of PZ evokes reliable, short-latency muscle activity in facial muscles involved in blinking and squinting. This activity is mainly contralateral to the stimulating electrode, is sustained through the stimulation period, and can be obtained even in anesthetized monkeys and at a range of stimulation intensities and durations.

2) We found that stimulation of PZ evokes centering eye movements. These eye movements closely resemble the distinctive eye movements that occur during a natural defensive reaction. The eye movements do not resemble saccades.

3) We found that the neuronal activity in PZ is positively

correlated with the monkey's defensive reaction on the contralateral side of the face, and negatively correlated with the monkey's defensive reaction on the ipsilateral side of the face. These findings add support to the hypothesis that at least one function of PZ is to coordinate spatially specific defensive reactions.

Other studies have reported blinking, squinting, and other defense-related movements on stimulation of a similar region of cortex just posterior to the bend in the arcuate sulcus (Dearworth and Gamlin 2002; Smith 1936). In one of the first systematic studies of the precentral gyrus, Ferrier (1873) noted an area posterior to the bend in the arcuate sulcus that, when stimulated, evoked a set of facial grimaces.

Startle versus spatially specific defensive reactions

In a previous study, we measured the EMG activity of the orbicularis muscle and other facial muscles during air puff to various locations on the face (Cooke and Graziano 2003). We found that the EMG response had 2 phases. The first phase was a short-latency (about 18 ms) transient spike that was bilaterally symmetric. This transient phase appeared to match the previously described startle response, a relatively nonspecific response that puts the body into an initial protective posture and that is thought to be subcortically mediated (e.g., Koch 1999; Landis and Hunt 1939; Strauss 1929; Yeomans et al. 2002). The second phase of the EMG response to air puff was a sustained activity that continued through the duration of the air puff and was asymmetric, that is, larger on the side of the face stimulated by the air puff. This second phase may reflect a more spatially specific, longer-latency set of defensive reactions that is commonly observed to follow startle (e.g., King and Cowey 1992; King et al. 1992; Landis and Hunt 1939; Schiff et al. 1962; Strauss 1929).

In the present study, we found that stimulation of area PZ evokes activity in the orbicularis muscle resulting in a blink and squint. This activity is not bilaterally symmetric: it is mainly contralateral. The mean latency is 31 ms. If this latency is added to the latency for PZ neurons to respond to a tactile stimulus, then the resultant estimate of the sensorimotor latency is 63 ms, much longer than the latency for a startle response (about 18 ms). In these respects, the muscle activity evoked in the present study by stimulation of PZ does not resemble a startle; rather, it resembles the secondary, longer latency, and more spatially specific defensive responses that tend to follow startle and that protect specific parts of the body from specific threats. The neurons in PZ also tend to respond in a sustained fashion to tactile and to visual stimuli, although often there is a greater response at the onset of the stimulus (Graziano et al. 1997).

One interpretation of these results is that the simple startle reflex and the more complex, secondary defensive movements that take into account stimulus location and trajectory may be mediated by separate mechanisms. Whereas the startle reflex is thought to be subcortically mediated (Koch 1999; Yeomans et al. 2002), the more spatially specific defensive movements may be mediated by cortical areas such as PZ. In this hypothesis, calculation of the location and speed of objects with respect to specific parts of the body surface may require cortical processing. Such a function is consistent with the properties of neurons in PZ. The neurons are sensitive to spatial location, speed, and direction of movement of tactile, visual, and auditory stimuli, with an emphasis on objects near specific parts of the body (Fogassi et al. 1996; Gentilucci et al. 1988; Graziano and Gandhi 2000; Graziano et al. 1997, 1999; Rizzolatti et al. 1981).

Motor output or reaction to sensory experience?

Did the stimulation of PZ directly activate a motor pathway or did it produce a sudden, unpleasant, sensory percept to which the monkey then reacted normally? Several observations may be relevant. First, we obtained apparently coordinated defensive movements on stimulating PZ in anesthetized monkeys. The magnitude of the reaction was similar, though not identical, in the anesthetized as in the awake state.

Second, in certain critical ways, the movements evoked by stimulation did not represent a normal defensive reaction. As described earlier, the electrically evoked movements lacked an initial, short-latency startle response. Instead, they were consistent with the activation of specific motor circuits responsible for only part of a defensive reaction in isolation of the startle reflex.

It is important to note, however, that the sensory-versus-motor question is inherently difficult to answer. Area PZ receives sensory input—its neurons respond with short latency to specific tactile, visual, and sometimes auditory stimuli (Fogassi et al. 1996; Gentilucci et al. 1988; Graziano and Gandhi 2000; Graziano et al. 1997, 1999; Rizzolatti et al. 1981). PZ also projects to motor structures, including other portions of motor cortex and the spinal cord (e.g., Dum and Strick 1991). Thus one view is that we stimulated part of a pathway that links certain sensory events with certain motor events. It is difficult to know what mental sensations the monkey experienced when this sensorimotor pathway was activated.

Centering eye movements

A threat to the head or face such as a puff of air or rapidly approaching object will evoke a centering movement of the eyes, in addition to other defensive movements (Bour et al. 2000; Cooke and Graziano 2003; Evinger et al. 1984; Ginsborg and Maurice 1959; Riggs et al. 1987). This centering movement is different from a saccade in that it is slower and begins with a characteristic downward and nasal excursion. This eye movement is thought to be a by-product of the protective retraction of the eye into the orbit, caused by the co-contraction of the extraocular muscles (Bour et al. 2002; Collewijn et al. 1985; Evinger et al. 1984). For example, in humans the eyeball retracts 1–2 mm during a blink (Bour et al. 2002; Evinger et al. 1984; Riggs et al. 1987). The centering of the eyes is most pronounced during a sustained defensive reaction, such as during a 0.5-s air puff to the face (Cooke and Graziano 2003). Briefer stimuli appear to cause only the initial, downward and nasal component of the eye movement, followed by a return to the original fixation position (Bergamin et al. 2002; Bour et al. 2000; Collewijn et al. 1985; Evinger et al. 1984; Riggs et al. 1987; Takagi et al. 1992).

Because these defense-related eye movements have such specific characteristics, they provide a useful test of the function of PZ. In the present study we found that stimulation of PZ caused eye movements similar to the defense-related eye

movements and different from saccades. The stimulation-evoked eye movements began with a downward and nasal excursion, then moved toward the center of gaze, and were on average slower than normal saccades. This finding supports the hypothesis that the set of movements evoked by stimulation of PZ represents a defensive reaction.

Centering movements of the eye on stimulation of the precentral gyrus were reported previously (Fujii et al. 1998). We suggest that the cortical area in this previous study may have overlapped PZ, and that the centering movements in that study may have been defense-related. However, it is also possible that other parts of the precentral gyrus are involved in eye movement and that the previous authors were studying a cortical area other than PZ. Goal-directed movements of the eye almost certainly have a variety of functions including those unrelated to defense. Saccades that converge toward a final position, and that are thought to be involved in acquiring a fixation target, can be evoked by stimulation of brain areas such as the dorsomedial frontal cortex (Tehovnik and Lee 1993).

Neuronal responses during defensive movements

Electrical stimulation is one of many useful techniques for studying cortical function. However, stimulation is unphysiological. Understanding the function of a brain area must also depend on studying neuronal activity during normal behavior. We therefore measured neuronal activity in PZ while the monkey reacted to a puff of air presented to the face.

We found that neuronal activity in PZ was correlated with the magnitude of the monkey's defensive reaction to the air puff. The monkey's reaction varied somewhat from trial to trial, and this variability in behavioral response matched the variability in the firing rate of PZ neurons. Furthermore, this relationship between neuronal activity and defensive behavior was obtained only for muscles on the contralateral side of the face—the side of the face that displays a defensive reaction when area PZ is electrically stimulated. Muscle activity on the ipsilateral side of the face, in contrast, was negatively correlated with the activity of PZ neurons. The same pattern of results was obtained whether the air-puff stimulus was presented to one or the other side of the face. Thus regardless of the position of the stimulus, the neurons were correlated with the contralateral musculature and anticorrelated with the ipsilateral musculature. This result cannot be explained by invoking trial-by-trial fluctuations in the salience of the stimulus, general attention, or arousal, all of which should affect both sides of the body equally. Instead, the result implies a specific relationship between the studied neurons and the output of certain muscles.

Comparison to area VIP

Multimodal responses almost identical to those found in PZ have been reported in the ventral intraparietal area (VIP) (Bremmer et al. 2002; Colby et al. 1993; Duhamel et al. 1998; Schaafsma and Duysens 1996). Neurons in VIP respond to tactile stimuli on the face and upper body, and to visual stimuli adjacent to the tactile receptive fields. More than half of the neurons in VIP prefer visual stimuli near the body surface, within about 25 cm, and many respond best to visual motion approaching the tactile receptive field. Electrical stimulation of VIP causes defensive movements similar to those evoked from PZ (Cooke et al. 2003; Thier and Andersen 1998), although the average threshold in VIP (89.6 μA) is larger than the average threshold in PZ (21.5 μA). Stimulation of VIP also appears to evoke centering movements of the eyes (Thier and Andersen 1998). VIP is monosynaptically connected to PZ (Lewis and Van Essen 2000; Luppino et al. 1999) and PZ projects to the spinal cord (Dum and Strick 1991). Thus one possibility is that VIP and PZ are part of a pathway that contributes to detecting nearby and approaching objects and organizing defensive movements.

One of the general principles of sensorimotor function appears to be that specific areas in the parietal lobe connect with corresponding areas in the frontal lobe, forming functionally specific pathways (Matelli and Luppino 2001). For example, the lateral intraparietal area and the frontal eye fields are interconnected and appear to be involved in the control of saccadic eye movements (e.g., Andersen et al. 1992; Bruce et al. 1985). The anterior intraparietal area and frontal area F5 are interconnected and appear to be involved in the control of prehension (Jeannerod et al. 1995). A related example is the control of language in humans by Wernicke's area in the temporal lobe and Broca's area in the frontal lobe (Damasio and Geschwind 1984). In all of these examples, the frontal area is focused relatively more on motor production, whereas the posterior area has a broader range of functions related to sensory representation, although the 2 sets of functions are partly intermixed. Areas VIP and PZ may provide another example of the same pattern, in this case involving the representation of nearby objects and the coordination of defensive movements. Experiments using reversible deactivation of areas VIP and PZ are currently in progress to further test this hypothesis.

Importance of defensive behavior

Hediger (1955) was one of the first to study what he called "the all-important escape tendency." In his view, "hunger and sexual appetite can be postponed; not so escape." Avoidance was also studied by Gibson (Gibson 1979; Schiff et al. 1962), who recognized the central ethological importance of the looming visual stimulus. Avoidance has even been studied sociologically. Dosey and Meisels (1969) recognized that human "personal space" was the result of a defensive mechanism that monitored potentially threatening objects near the body. Not just escape from enemies, but simple navigation around obstacles requires a spatial avoidance mechanism (Gibson 1979). Even during reaching, the arm moves in a manner to avoid obstacles (Vaughan et al. 2001). Given the prominence of defensive and avoidance behavior in everyday life, it is not surprising to find so much neural machinery related to it. Areas in the pigeon brain, locust brain, and fly brain have been implicated in the detection of looming visual stimuli and the control of avoidance (Rind 2002; Schuster et al. 2002; Sun and Frost 1998; Tammero and Dickinson 2002). Portions of the rat superior colliculus have been found to represent complex avoidance behaviors (Dean and Redgrave 1989). The startle reflex has been linked to several subcortical nuclei in the rat and cat (Koch 1999; Yeomans 2002). We suggest that certain regions in the primate cortex, including VIP and PZ, also

participate in the essential function of monitoring nearby objects and coordinating avoidance and defense.

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