

Single-Unit Activity Related to Bimanual Arm Movements in the Primary and Supplementary Motor Cortices

O. DONCHIN,¹ A. GRIBOVA,¹ O. STEINBERG,¹ A. R. MITZ,² H. BERGMAN,¹ AND E. VAADIA¹

¹*Department of Physiology and the Center for Neural Computation, The Hebrew University, Hadassah Medical School, Jerusalem 91120, Israel; and* ²*Laboratory of Systems Neuroscience, National Institute of Mental Health, Bethesda, Maryland 20892*

Received 24 April 2001; accepted in final form 26 July 2002

Donchin, O. A. Gribova, O. Steinberg, A. R. Mitz, H. Bergman, and E. Vaadia. Single-unit activity related to bimanual arm movements in the primary and supplementary motor cortices. *J Neurophysiol* 88: 3498–3517, 2002; 10.1152/jn.00335.2001. Single units were recorded from the primary motor (MI) and supplementary motor (SMA) areas of Rhesus monkeys performing one-arm (unimanual) and two-arm (bimanual) proximal reaching tasks. During execution of the bimanual movements, the task related activity of about one-half the neurons in each area (MI: 129/232, SMA: 107/206) differed from the activity during similar displacements of one arm while the other was stationary. The bulk of this “bimanual-related” activity could not be explained by any linear combination of activities during unimanual reaching or by differences in kinematics or recorded EMG activity. The bimanual-related activity was relatively insensitive to trial-to-trial variations in muscular activity or arm kinematics. For example, trials where bimanual arm movements differed the most from their unimanual controls did not correspond to the ones where the largest bimanual neural effects were observed. Cortical localization established by using a mixture of surface landmarks, electromyographic recordings, microstimulation, and sensory testing suggests that the recorded neurons were not limited to areas specifically involved with postural muscles. By rejecting this range of alternative explanations, we conclude that neural activity in MI as well as SMA can reflect specialized cortical processing associated with bimanual movements.

INTRODUCTION

Simultaneous movements of two hands in space, bimanual movements,¹ present a special control problem for the CNS. Controlling two dissimilar hand trajectories simultaneously can be significantly more difficult than moving along the same trajectories sequentially. For example, a bimanual task may split attention if each hand, during reaching movements of the arm, must approach a separate target. A bimanual task may also require a unique postural set to manage the interaction forces generated by simultaneous movements of the two limbs. The particular demands of bimanual tasks have led to the prediction that fundamental differences exist between bimanual and unimanual motor control (Kelso 1984; Tsutsui et al. 1998). It is reasonable to hypothesize that the primary motor

cortex plays a role in controlling bimanual arm movements. If so, we should expect its neural activity to reflect the differences that characterize bimanual tasks.

It has been known for some time that the supplementary motor area (SMA) is especially involved in bimanual motor control. Combined lesions of the SMA and surrounding areas interfere with bimanual task performance (Brinkman 1984). A number of electrophysiological (Benecke et al. 1985; Deecke et al. 1987; Lang et al. 1990; Uhl et al. 1996), brain imaging (Sadato et al. 1997; Stephan et al. 1999; Toyokura et al. 1999), and clinical (Bell et al. 1994; Laplane et al. 1977; Penfield and Welch 1951; Viallet et al. 1992) studies have also explored the role of SMA in bimanual tasks. Yet, questions remain regarding how much SMA activity is specific to bimanual movements and whether SMA is the only cortical motor area with such neural specificity (Kazennikov et al. 1998; Wiesendanger and Wise 1992).

Tanji and his coworkers provided convincing evidence that, except for a tiny zone near the face area (Aizawa et al. 1990), primary motor area (MI) does not specifically encode bimanual finger movements, but SMA and the premotor cortex do (Tanji and Shima 1996; Tanji et al. 1988). This distinction between the two motor areas has not held up for tasks involving more proximal musculature, despite the expectation that this difference would be found (Donchin et al. 1998; Kazennikov et al. 1999; Kermadi et al. 1998; Tanji and Shima 1996; Tanji et al. 1988; Wiesendanger et al. 1996). Both Donchin et al. (1998) and Kermadi et al. (Kermadi et al. 1998) report equally strong bimanual effects in MI and SMA. We have speculated (Donchin et al. 1999) that the lack of bimanual-specific MI activity in the finger pressing task of Tanji reflects a special case, because MI has a well-established specialized role in the control of distal forelimb muscles (Andersen et al. 1975; Asanuma and Rosen 1972; Rouiller et al. 1994). If our speculation is correct, MI activity during most bimanual tasks reflects a higher level of processing than simply organizing muscle synergies (Phillips 1975). Recent studies also seem to point to a role for MI in other aspects of motor processing. MI neurons can encode multiple parameters of movement (Fu et al. 1995; Kahlon and Lisberger 1999; Moran and Schwartz 1999). Populations of MI neurons may reflect motor imagery

Address for reprint requests: O. Donchin, Dept. of Biomedical Engineering, Johns Hopkins University, 720 Rutland Ave., Traylor 416, Baltimore, MD 21205 (E-mail: opher@bme.jhu.edu).

¹ “Bimanual movements” in this sense refers to displacement of both hands in space, and is not intended to describe intrinsic movements of the hand (as in “manual dexterity”).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

(Georgopoulos et al. 1989; Porro et al. 1996) serial ordering (Carpenter et al. 1999), and perhaps stimulus-response associations (Zhang et al. 1997) and elements of transitive inference (Acuna et al. 2002).

If cortical activity differences between unimanual and bimanual arm movements reflect the different requirements involved in processing bimanual tasks, then the differences observed must be more elaborate than shifts in axial muscle activity or other simple variations in postural set. Tanji and his coworkers avoided this problem of changes in postural set by training monkeys to inhibit postural EMGs (Tanji et al. 1988). They reported that postural EMGs were not completely eliminated but were small and not time-locked to finger movements. Tanji et al. thus created a rather special motor control problem for the animal, one requiring months of training to inhibit “unwanted” motor outputs. Because it is impossible to achieve this level of control over proximal EMGs, the present study looks at whole arm movements and allows for natural postural adjustments by the subjects. The potential contribution of postural adjustment to bimanual effects is addressed with a more analytical approach.

While the majority of studies do report bimanual specific activity in frontal motor areas, one group did not find any substantial bimanual specificity in either MI or SMA (Kazenikov et al. 1999). These researchers have suggested that “subtle differences in the parameters of movement execution” explains the bimanual specific unit activity observed by others. This possibility has not been ruled out in any but the distal button pressing task of Tanji (Tanji and Shima 1996; Tanji et al. 1988). In the present paper, we rule out this possibility for a proximal task by analyzing the neural sensitivity to small differences in movements. Additionally, we rule out the possibility that differences in neural activity during bimanual arm movements are created by simple linear combinations of neural activities in unilateral movements.

METHODS

Behavioral paradigm

Two female rhesus monkeys (*Macaca mulatta*) (monkey F, 4 kg, and monkey G, 3.5 kg) were trained to operate two separate manipulanda, one with each arm. Each manipulandum was a low-weight, low-friction, two-joint mechanical arm, oriented in the horizontal plane. Movement of each manipulandum produced movement of a corresponding cursor on a vertically oriented 21" video screen located 50 cm in front of the monkey. The movement of each cursor was mapped to its corresponding manipulandum movement such that each millimeter of manipulandum movement yielded one millimeter of movement of the cursor on the video display. The angular origin, 0°, was to the monkey's right, and 90° was away from the monkey for the manipulandum movement and toward the top of the screen of the display.

The time course of typical unimanual and bimanual task trials is schematized in Fig. 1. A trial began when the monkey aligned both cursors on 0.8-cm-diam “origins” and held them still (as defined using velocity thresholds described in detail below) for 500 ms. The centers of the two origins were located 16 cm apart. For each arm, one of eight peripheral target circles (0.8 cm diam) could appear at a distance of 3 cm from the origin (Fig. 2). The small movement amplitude was chosen to minimize postural adjustments in accomplishment of the movements. Movements taking the cursor from the origin to the target were primarily elbow and shoulder movements, although the monkey was free to engage its wrists and fingers to accomplish the task. If only

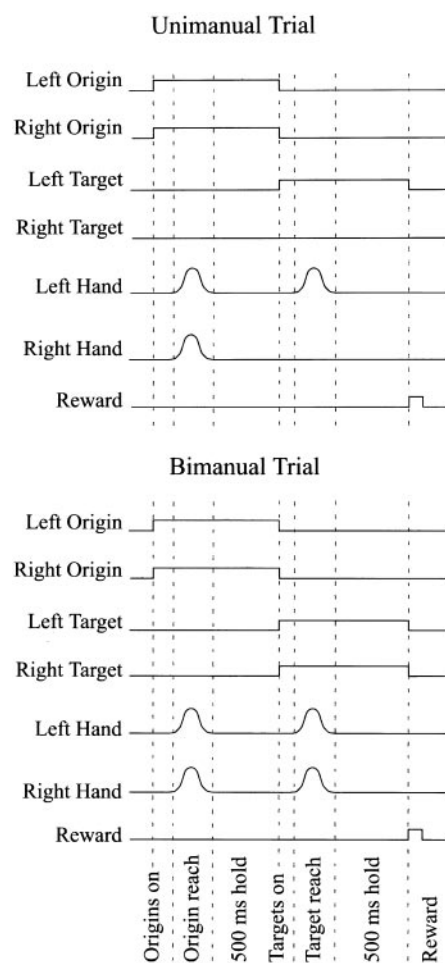


FIG. 1. Trial schematic. This schematic shows the time course of typical successful unimanual and bimanual trials. In all trials, 2 origins appear, and the monkey must acquire both of them. Following successful acquisition of the origins, the monkey held the cursor inside the origins for 500 ms, and this is followed by appearance of either 1 or 2 targets. Number of targets shown indicates whether the trial will be unimanual or bimanual. In unimanual trials, only the relevant arm is allowed to move. In bimanual trials, both arms must begin moving at the same time. In both unimanual and bimanual trials, the monkey must perform another 500-ms hold following target acquisition. Diagram is a schematic and neither the x nor y axis is drawn to any realistic scale. Rectangular traces represent the ON-OFF state of the described stimuli (left and right origin, left and right target, and reward). The y axis for left and right hand reflects velocity (m/s), and the portrayed velocity changes are intended to reflect the bell-shaped velocity profiles of typical reaching movements.

one target appeared—signaling a unimanual trial—the monkey moved the appropriate arm and brought the corresponding cursor into the target but did not move the other arm (again, according to the definition of movement initiation given below). Examples of the layout are shown in Fig. 2 (unimanual left and right). If two targets appeared—signaling a bimanual trial—the monkey moved both arms, such that the two cursors moved into the target circles on the screen. There were two classes of bimanual movements that were tested in the recording sessions: parallel and opposite (Fig. 2). Parallel bimanual movements were made to targets that were located in the same direction from their origins for each arm. For opposite bimanual movements, the direction from origin to target for one arm differed by 180° from the direction for the other arm. Every fourth successful trial was rewarded with liquid and followed by a 2-s pause to allow for fluid consumption.

The monkey's reaction time was not restricted per se, but targets had to be acquired within 1.2 s. For bimanual trials, the animal was

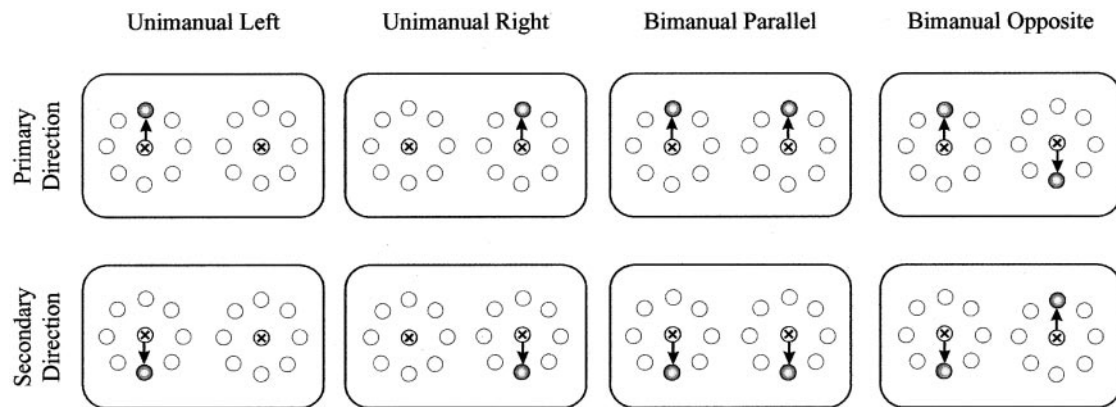


FIG. 2. Different trial types. Example of the 4 main types of trials (the empty circles are not visible to the monkey). The figure displays an example where 1 of the selected directions was 90° . The monkey performed these 4 types along with complementary 4 types of movements in the secondary direction (270°).

additionally required to begin movement of the arms within 300 ms of each other, and the targets had to be acquired within 300 ms of each other. Following acquisition of the targets, the monkey held both arms with no movement for ≥ 500 ms. In all cases where the monkey had to keep its arms still, as well as for the purposes of determining movement initiation, we defined movement using two velocity thresholds, checked at different intervals. Velocity was calculated from the position information: $\|\dot{\vec{x}}(t) - \dot{\vec{x}}(t + dt)\|/dt$, where $\dot{\vec{x}}(t)$ and $\dot{\vec{x}}(t + dt)$ are two measurements of position separated by time dt . The more restrictive velocity threshold (15 mm/s) was averaged over a greater time window (approximately 100 ms) and this detected slow drifts of the arms. The less restrictive threshold (30 mm/s) was averaged over a shorter time window (approximately 10 ms), allowing rapid detection of movement initiation.

There were three different kinds of recording sessions. In *unimanual sessions*, the monkey performed unimanual movements of both the left and right arms in eight different directions for a total of 16 different types of trials. *Unimanual sessions* were recorded only for brief periods at the beginning of the day's recording, as a prelude to a two-direction session (see *Data acquisition*). Following a *unimanual session*, we examined the activity of the neurons that had been recorded and selected one primary direction for further study. From a set of four possible directions (0° , 45° , 90° , or 135°), we chose the direction that seemed close to the average of the recorded cells' preferred directions. Trials in *two-direction sessions* included only movements in either the selected direction or in the direction opposed to it by 180° . Figure 2 shows all the different trial types in a *two-direction session*. In other sessions (*eight-direction sessions*), the monkey made unimanual, bimanual parallel, and bimanual opposite movements to all possible directions for a total of 32 different types of trials. In all sessions, trials were presented pseudo-randomly without any separation into blocks.

Data acquisition

During training in monkey G, electromyographic signals (EMG) were recorded differentially using pairs of 1-cm surface electrodes from nine muscles; each muscle was recorded bilaterally. These muscles were the rhomboid, latissimus dorsi, teres major, pectoralis major, deltoid, biceps brachii, triceps brachii, flexor carpi ulnaris, and extensor carpi ulnaris. Up to four muscles were recorded simultaneously. The EMG was amplified, filtered (140 Hz–4 kHz), and its root mean square (RMS) was computed with a frequency cutoff of 100 Hz (the RMS is a nonlinear filter that first rectifies and squares the signal and then smoothes this squared signal to the cutoff frequency before its square root is taken). EMG and manipulandum position were sampled by data acquisition boards (DAP-3200e, Microstar

Laboratories, Bellevue, WA) at 400 Hz and stored for off-line analysis. Both signals were smoothed off-line with a low-pass 4 pole Butterworth filter with a corner frequency of 10 Hz, using a zero-phase smoothing algorithm. EMGs were recorded in monkey F after the end of recording in that monkey. Unfortunately, recording ended in monkey F as a result of cortical insult that caused transient hemiparesis and EMGs were recorded only after the monkey recovered. While the EMG results for the two monkeys were similar, we could not exclude the possibility that EMGs in Monkey F do not accurately reflect the muscular activity during recording of neuronal activity. Thus only the results for monkey G are presented.

We used MRI (Biospec Bruker 4.7 Tesla animal system; fast-spin echo sequence; effective echo time [TE] = 80 ms and repetition time [TR] = 2.5 s, 13 coronal slices 2 mm wide) to help locate the stereotactic coordinates of the central and arcuate sulci. With the MRI pictures as a guide, two recording chambers (27×27 mm) were surgically implanted above the right and left hemispheres, and a head holder was attached to the occipital bone. The surgery was performed under isoflourane anesthesia in aseptic conditions. The animals' care and surgery procedures were in accordance with The National Institutes of Health Guide for the Care and Use of Laboratory Animals and all applicable Hebrew University regulations.

During recording sessions, the monkeys were seated in a primate chair placed in a dark room and the head was fixed. Single-unit activity was recorded by eight individually driven glass-coated tungsten microelectrodes (impedance 0.2–0.8 M Ω at 1 KHz) in the two hemispheres (4 electrodes in each hemisphere). Electrodes were introduced into the SMA at an angle of 30° to the sagittal plane. Neurons were selected for recording on the basis of the isolation quality of their spike waveforms and stability of their firing rates. Units with very low firing rates were not recorded, but no effort was made to select units for their "task-related" behavior. The electrode signals were amplified, filtered, and sorted (MCP and MSD, Alpha-Omega, Nazareth, Israel). The MSD performs spike sorting based on an eight-point template-matching algorithm that allows two isolated neurons to be recorded from most electrodes (from some electrodes it is possible to record 3 isolated neurons and occasionally only 1 neuron can be isolated). In addition, the MSD indicates every time that the signal crosses a user-determined threshold but does not match any of the templates currently being isolated. Spike arrival times, threshold crossings, and timing of behavioral events were recorded with a resolution of 24 kHz, but were down-sampled off-line to a resolution of 400 Hz. The waveforms of all detected spikes and all the waveforms surrounding all unclassified threshold crossings were also sampled at 24 kHz allowing off-line confirmation of spike sorting.

During selected neural recording sessions for monkey G, EMG was collected from two muscles bilaterally: right and left flexor carpi

ulnaris and right and left deltoid. We chose to record those muscles that seemed to us most different in unimanual and bimanual movements on the basis of the EMG results during training.

Following surgery in each animal, a number of penetration sessions were devoted to mapping the cortical area that had been exposed. During these penetrations, unit receptive fields were tested with passive manipulation of each individual limb separately and of the tail. While two researchers worked directly with the monkey to isolate the movement of individual joints, a third researcher evaluated neuronal response using the amplified signal from each electrode in turn passed directly into a loudspeaker. In addition to manipulation of the limb, we tested the neuronal response to superficial and deep somatic stimulation on the arms, legs, back, trunk, tail, stomach, face, and neck. Cases where somatic stimulation produced neuronal activity were noted. We also tested for visual and oculomotor responses by moving interesting stimuli within the monkey's field of view. Finally, we applied intracortical microstimulation (ICMS) with trains of 200- μ s cathodal pulses at 300 Hz with an intensity of 10–80 μ A (BPG-2 and BSI-2, BAK Electronics, Germantown, MD). Typical train durations were 50 ms for MI and 100 ms for SMA. Passive manipulation was tested at these sites just before stimulation. Movements were assessed following ICMS by two researchers in the recording room. They ascertained that the monkey was relaxed and completely still before stimulation. When ICMS evoked movements, current was reduced until it was possible to ascertain the smallest activation of a joint (or joints) possible at that site and the type of movement evoked. We documented the evoked movements and the stimulation intensity. Movements were classified as lower limb or tail movements if they caused movement of the lower limb or tail. Movements were classified as trunk movements if they caused a movement of the spine, contraction of musculature in the back, or translation of the shoulder. Movements were classified as upper limb proximal movements if they involved movement of the elbow or a rotation of the shoulder joint. Movements were classified as upper limb distal movements if they involved movement of the wrist or the fingers. In addition to these initial mapping sessions, additional corroboration of recording locations was acquired at the end of most recording sessions. After recording for the day was completed, passive manipulation and ICMS were tested at the recording site following the procedures outlined above. Little effort was made in these instances to optimize stimulation depth or to test the precise threshold of activation.

Histology

Monkeys were given an overdose of pentobarbital, and then perfused transcardially with 0.9% saline followed by 4% formaldehyde in 0.1 M phosphate buffer. After fixation, in one monkey, pins were inserted in defined locations to allow reconstruction of chamber coordinates. The brains were photographed. Blocks of tissue were sectioned coronally in a freeze-dry microtome (section width = 50 μ m). Alternate sections were stained with cresyl violet (0.1%). Surface penetration maps for both monkeys are shown in Fig. 3. Note that SMA penetrations are marked at the point of electrode insertion. Penetrations into the SMA were angled at 30° to the sagittal plane and advanced from the point of insertion until they reached the medial cortex. Generally, this meant that the electrodes were advanced through cortex into white matter and through that white matter before reaching SMA. The pattern: units—white matter—units was used as an indicator of recording location. Additionally, more lateral penetrations to the SMA involved crossing a greater extent of white matter and the consistency of this phenomenon was also used in assessing the locations of the recordings.

Ultimately the determination of the "proximal arm area" depended on a number of criteria included the MRI scans, the ICMS and passive response properties of the neurons, and the final histology. However, we limited it to almost completely exclude any penetrations where

ICMS or passive response properties implicated the fingers or any part of the body that are proximal to the shoulder or on the lower limb. There were three penetrations lying on the border of the proximal arm area where we could not completely exclude the possibility of a relationship to other parts of the body, although they showed strong activation associated with the proximal arm. These three penetrations contributed 11 neurons to the sample, of which 4 (36%) were bimanual-related. We included these 11 neurons in the analysis because the three penetrations met our criteria for the forelimb region; however, repeating the analysis without these neurons demonstrates that their inclusion does not substantially alter the statistical results.

Data analysis

All recorded units were assessed for stability of firing rate and responses before further analysis was performed. Units were selected for analysis if the stable period included ≥ 6 trials for each type of movement. No selection was made on the basis of responsiveness or task-related activity. (However, Table 2 shows that most recorded units—81% in MI and 76% in SMA—showed task-related activation). Standard raster displays and peri-stimulus time histograms (PSTH) were computed and examined. PSTHs were constructed with a binwidth of 2.5 ms and smoothed for display purposes with a digital low-pass 4-pole zero-phase Butterworth filter with a cutoff of 100 Hz. All PSTHs were aligned on movement onset, which was determined by an off-line algorithm (A. Arieli, unpublished data) and then confirmed manually. For purposes of alignment, the beginning of movement in bimanual trials was determined by the first arm to begin moving; for reaction times, the beginning of movement for each arm was calculated separately. End of movement was determined with the same algorithm used for determining movement onset. End time was determined separately for the right and left arms, and movement times for each arm were generated independently.

The onset of neural activity changes was determined for each PSTH using the CUSUM algorithm (Davey et al. 1986; Ellaway 1977). Onsets were limited to the time from target appearance to 400 ms after movement initiation. The trial-by-trial firing rate of the cell was averaged from activation onset until 500 ms after activation onset (termed the activation epoch). The firing rate during this epoch is termed the evoked activity. This was compared with a baseline firing rate taken from 350 ms before activation onset to 100 ms before activation onset (the baseline epoch). While this period could, in principle, include part of the reaction time, the algorithm guarantees that the neural activity is unchanged prior to response onset and therefore our results are insensitive to the precise timing of the baseline epoch. Generally, this was a period during which the monkey's arms were motionless at the origin position, and we averaged activity in this period for each neuron across the different types of movement. In cases with no response onset, as might occur for example in nonpreferred movement directions, we arbitrarily selected a default 500-ms period from 100 ms before movement initiation (the average activation onset across responsive units) to 400 ms after movement initiation.

To allow data from cells recorded during two-direction sessions to be combined with that of cells recorded during eight-direction sessions, we limited our current analysis of the eight-direction sessions to two directions. Combining the two-direction sessions data with eight-direction sessions is possible because each two-direction session includes a subset of the trial types performed in the eight-direction sessions. This was done using the following procedure. For eight-direction sessions, we used the firing rate in the activation epoch above to determine the primary direction to use for each cell. For each of the movement types—unimanual left, unimanual right, bimanual parallel, and bimanual opposite—we calculated the mean directional activity for the cell (Mardia 1972) and then combined these means to arrive at a single direction for each cell. This was taken to be the cell's primary direction, and its secondary direction was simply the primary

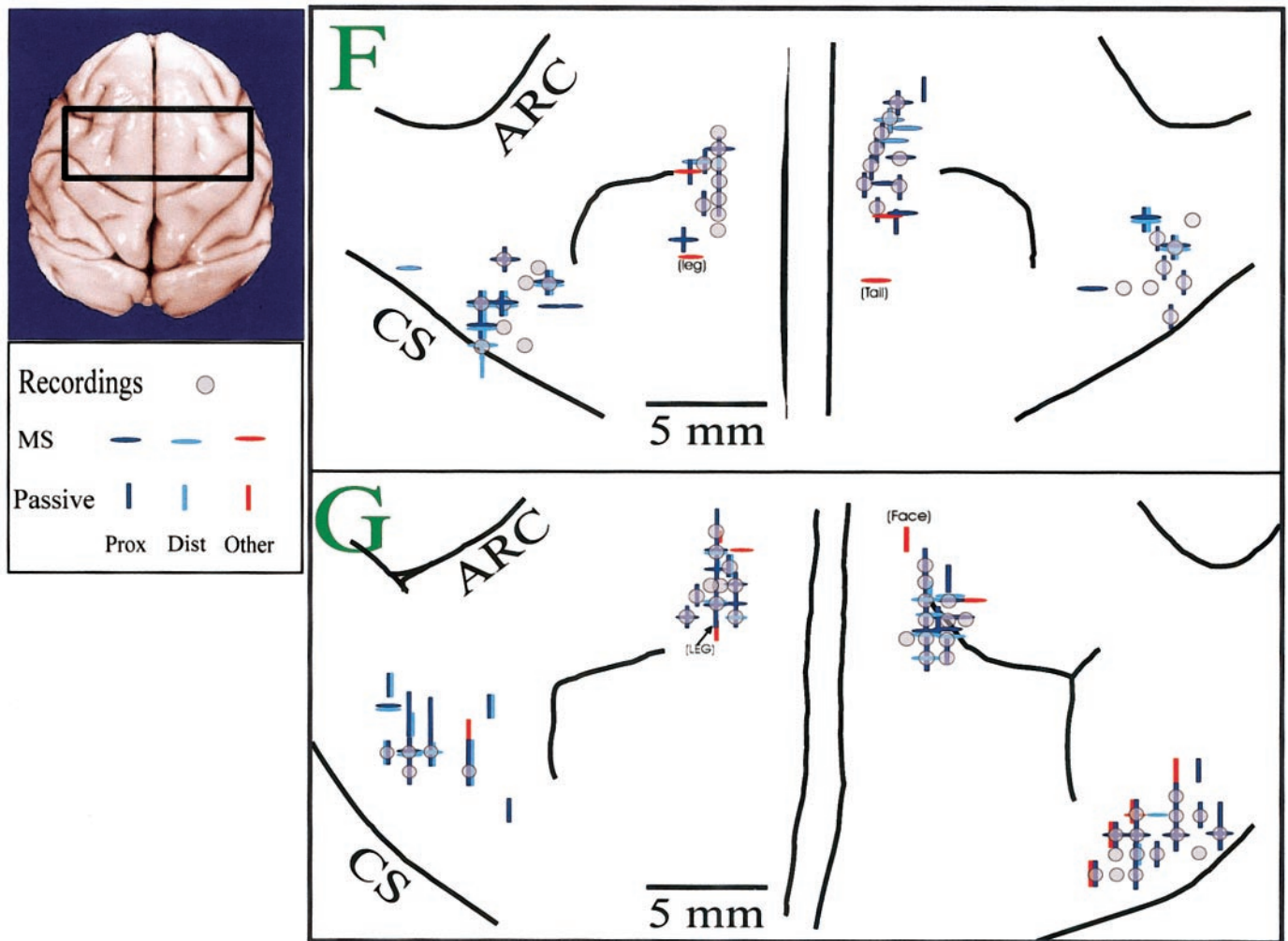


FIG. 3. Penetration maps. Penetration maps for both hemispheres of 2 monkeys. *Inset*: brain photograph indicating the location of the penetration map. As described in METHODS, proximal refers to shoulder- and elbow-related sites; distal refers to forearm-, wrist-, and finger-related sites. Sites in which microstimulation produced movements are marked with a colored horizontal bar. Sites in which touch or passive manipulation of the monkey's limbs produced clear neural activity are marked with a colored vertical bar. Sites where we found both microstimulation and passive manipulation effects are marked with a plus formed by the overlap of horizontal and vertical bars. Sites from which units were recorded during the task are marked with a gray dot. Each dot represents a 4-electrode penetration in either primary motor (MI) or supplementary motor (SMA) areas. On some penetrations, fewer than 4 electrodes recorded isolated neurons. Penetrations were inserted into the coordinates of insertion into the cortex. SMA penetrations were inserted into dorso-lateral cortex angled at 30° to the sagittal plane and advanced until they reached the medial cortex.

direction plus 180°. Although there may have been some difference in the power of the tests applied to the cells that showed significant responses in two-direction and eight-direction sessions, no such statistical difference was observed in the actual data. Similarly, the strength of the bimanual-related effect in two-direction and eight-directions sessions was comparable (note, however, that the statistical significance of the results was affected by differences in the number of trials per movement type, as discussed in the following text). In general, statistical tests of bimanual-related activity were performed on different types of trials using data from a single cell, so data from eight-direction sessions and two-direction sessions were only combined into a single statistical test when the population distributions are being tested.

Lateral preference

The Mann-Whitney rank statistic—calculated on the trial-by-trial firing rate during the activation epoch and the baseline epoch—was

used to evaluate statistical significance in all comparisons of neuronal activity. The statistical significance of the cells activation was evaluated by comparing the baseline epoch to the activation epoch; neurons were considered significantly activated if there was a statistically significant difference between baseline and evoked activity in at least one trial type. Contralateral preference of the neurons was determined by comparing the maximal evoked activity during unimanual contralateral movements to the maximal evoked activity during unimanual ipsilateral movements. The strength of the arm preference, termed the laterality index, was normalized by the summed evoked activity (EA)

$$\text{Laterality Index} = \frac{\text{contralateral EA} - \text{ipsilateral EA}}{\text{contralateral EA} + \text{ipsilateral EA}} \quad (1)$$

This index will be 1 for a neuron that responds only contralaterally, -1 for a neuron that responds only ipsilaterally, and 0 for a neuron with exactly the same response in ipsilateral and contralateral movements.

Bimanual-related activity

To compare evoked activity during bimanual movements to evoked activity during unimanual movements, it is necessary to choose which unimanual activity the bimanual activity will be compared with. Clearly, the bimanual activity should be compared with activity during one of the unimanual movements that compose it (although it could also be compared with some sort of combination of the activities during the 2 unimanual movements that compose it; this issue is addressed below). The question is, which of the two unimanual movements represents the appropriate comparison. One possibility is to always compare activity during bimanual movements to activity during a unimanual contralateral movement. However, this choice ignores the relatively large proportion of neurons with an ipsilateral preference in unimanual movements. We chose to compare the neural activity during bimanual movements to the neural activity in the unimanual movement that evoked a stronger response. In this way, we end up asking whether there is a difference between maximal activation in bimanual movements and maximal activation in unimanual movements. For example, in Fig. 7, the bimanual evoked activity in *B* would be compared with the ipsilateral evoked activity.

However, since there are four different bimanual movements performed by the monkey—two bimanual parallel movements and two bimanual opposite movements—this still leaves us with four different comparisons. These correspond to the four rows in each of our figures illustrating the activity of a neuron (Figs. 8 and 9). At this point we applied the logic that any difference between unimanual activation and bimanual activation represented an interesting effect from our point of view. Therefore we focused our attention on the comparison where the difference between unimanual and bimanual was largest.

Translating the logic of the preceding paragraphs into mathematical language, we performed four Mann-Whitney tests comparing the bimanual evoked activity to the unimanual evoked activity in each type of bimanual movement. The significance of the bimanual-related effect was taken to be the maximum significance over the four tests, and the criterion for significance (threshold at which *P* was deemed to be significant) was divided by 4 to correct for the compounded tests (a technique called the Bonferroni procedure).

The strength of the bimanual-related effect was quantified using a measure analogous to the laterality index

$$\text{Bimanual-Related Effect} = \frac{\text{bimanual EA} - \text{unimanual EA}}{\text{bimanual EA} + \text{unimanual EA}} \quad (2)$$

where bimanual EA is the evoked activity during the bimanual movement, and unimanual EA is the evoked activity during the unimanual movement to which it is being compared. The bimanual evoked activity was compared with the same unimanual evoked activity used in assessing statistical significance. Many other normalizations for the strength of the bimanual-related effect are possible. We examined several other measures of the effect (including subjective ranking by members of the laboratory) without uncovering any instability in the results. Note that the bimanual-related effect is not influenced by the baseline firing rate; it represents a direct comparison of the firing rates in the activation epochs of unimanual and bimanual movements.

Linear summation

One possible explanation for the existence of statistically significant bimanual-related effects is that evoked activity during bimanual movements may be a sum of the evoked activity during unimanual movements. While it is possible that absolute firing rates sum linearly, we thought that it was more likely that the evoked activity (the change from the baseline firing rate) in unimanual movements would be summed to give the evoked activity in bimanual movements. Therefore we normalized the evoked activity by subtracting the baseline activity [we call this the normalized evoked activity (NEA)].

First, we tested if NEA during bimanual movements is explained by

a simple linear summation of the unimanual movements that compose it. Here again, we require that the linear summation hold true for all four bimanual movements. Therefore the deviations from linearity in each type of bimanual movement were combined to produce a statistic that should distribute like χ^2 with 3 degrees of freedom (specifically, we calculated the sum of the squared differences between bimanual NEA and the sum of the unimanual NEAs divided by the combined variance of the bimanual and unimanual NEAs). We also tested for the possibility that NEA in bimanual movements is equal to NEA during contralateral movements and for the third possibility that it is equal to NEA during ipsilateral movements. If we could reject all three of these null hypotheses at $P < 0.05$, we determined that the bimanual activity of this neuron was not explained with the hypothesis of linear summation. Note that our failure to correct for the multiple statistical tests effectively increases the significance level since we are requiring that all three null hypotheses be rejected rather than requiring that only one of the three null hypotheses be rejected.

A more general possibility is that NEA during bimanual movements is some nontrivial linear combination of unimanual NEAs. To test this possibility we used a linear model of the form

$$\begin{aligned} B_{P,1} &= \alpha C_1 + \beta I_1 \\ B_{P,2} &= \alpha C_2 + \beta I_2 \\ B_{O,1} &= \alpha C_1 + \beta I_2 \\ B_{O,2} &= \alpha C_2 + \beta I_1 \end{aligned} \quad (3)$$

where the *Bs* represent NEA during bimanual movements, the *Cs* represent NEA during unimanual movements, and the *I*s represent NEA during ipsilateral movements. We used a constrained linear fit to generate α and β , and we restricted α and β to positive values (Matlab 5.3, Mathworks, *lsqnonneg* function). Goodness of fit was assessed using an *F* test.

Analysis of behavioral controls

We tested movement trajectories, velocity profiles, and the EMG for differences between bimanual and unimanual movements. To simplify quantitative analysis of these behavioral variables, we parameterized each variable with a single number for each movement. For the movement trajectories, we calculated the average deviation (from 50 to 450 ms after movement initiation, the movement epoch) of each movement from the grand mean of all movements in that direction. We call this the trajectory deviation. For the velocity, we calculated the peak velocity of each movement during the movement epoch, and call it the peak velocity. For the EMG, we calculated the integral of the RMS of individual EMG traces recorded during the EMG epoch (150 ms before movement initiation to 350 ms after movement initiation). This we called the integrated EMG.

Three different movements could involve a left arm movement to 45°. The left arm could move to 45° in a unimanual movement; it could move to 45° as part of a bimanual parallel movement in which the right arm also moved to 45°; and, it could move to 45° as part of a bimanual opposite movement in which the right arm moved to 225°. We examined plots of all three behavioral variables that allowed comparison of these three different movements. In addition, we applied an analysis similar to the one applied to the neural data, using the same measure of bimanual-related effect (Eq. 2). For the trajectories and velocity profiles, we also correlated the strength of this effect to the strength of the bimanual-related effect in the neurons, comparing the neuronal bimanual-related effect to a behavioral bimanual-related effect calculated on the same trials exactly.

Since much of the EMG was not recorded simultaneously with neuronal activity, it was not possible to correlate the bimanual-related effect of the integrated EMG with the neural effect as we did with the trajectory deviations and peak velocities. Instead, we analyzed the integrated EMG separately for each muscle and for each of the four primary directions (0°, 45°, 90°, and 135°). Like with the neuronal

TABLE 1. *Movement times, reaction times, and interarm intervals*

	Monkey F			Monkey G		
	Unimanual	Parallel	Opposite	Unimanual	Parallel	Opposite
RT						
Left	289 ± 36.4	280 ± 42.8	268 ± 29.9	277 ± 29.7	278 ± 30.2	262 ± 23.7
Right	238 ± 14.4	247 ± 18.6	248 ± 13.4	233 ± 16.6	255 ± 20.0	258 ± 19.4
MT						
Left	576 ± 72.1	550 ± 79.1	546 ± 73.4	622 ± 48.3	552 ± 47.1	535 ± 55.8
Right	647 ± 54.8	631 ± 49.7	597 ± 53.6	596 ± 58.7	595 ± 55.6	562 ± 69.4
IAI						
Start		38 ± 46.0	25 ± 21.5		29 ± 28.3	9 ± 17.0
End		-42 ± 70.7	-27 ± 48.3		-14 ± 40.8	-19 ± 38.7

Means ± SD over all recording sessions of the reaction time (RT), movement time (MT), and inter-arm interval (IAI) for both monkeys (all data in milliseconds). Reaction time and movement time are calculated separately for the left and right arm in bimanual trials. Interarm interval is calculated separately for start and end of movement and is positive when the right hand leads the left hand. Numbers in bold for the RT and MT of bimanual movements indicate values significantly different from the unimanual values (Mann-Whitney U , $P < 0.01$). Numbers in bold for IAIs indicate values significantly different from zero (sign test, $P < 0.01$).

data, we performed four paired comparisons (Mann-Whitney tests), of which we took the most significant. This process gave us a total of 18 muscles × 4 directions = 72 different data points. We compared this distribution of bimanual-related effects in the integrated EMG with the distribution of bimanual-related effects found in the evoked activity of neurons in MI and SMA.

Separation analysis

We also tested for a trial-by-trial relationship between the behavioral parameters and the neural activity. In this analysis, we used a behavioral parameter to divide the trials into two groups. One group contained trials that were matched as closely as possible for that parameter (the “similar” group), while the other group contained pairs of bimanual and unimanual trials that were as distant from each other as possible for that parameter (the “different” group). This sorting was further constrained so that the range in the similar group was smaller than the smallest difference between bimanual and unimanual trials in the different group.

We evaluated the differences in the neuronal evoked activity imposed by separation by comparing them with the differences between bimanual and unimanual evoked activity. To quantify this comparison we used the formula

$$\text{Separation Strength} = \log_{10} \frac{|Bi_{\text{Different}} - Uni_{\text{Different}}|}{|Bi_{\text{Similar}} - Uni_{\text{Similar}}|} \quad (4)$$

where Uni_{Similar} , $Uni_{\text{Different}}$, Bi_{Similar} , and $Bi_{\text{Different}}$ represent the evoked activity of the neuron in the different groups of trials. Thus we compare the differences in activity in trials where the behavior

is similar to the differences in trials where the behavior is different. The index should be close to 0 if the separation has no effect, meaning that the bimanual effect is not well explained by variations in the movement parameter. Using bootstrap techniques, we estimated the distribution of the index under the null hypothesis of no effect and used this estimate to generate stringent ($P = 0.001$) and permissive ($P = 0.15$) confidence limits for the index around 0. We considered the value to be significantly different from 0 if it lay outside the stringent confidence limits ($P < 0.001$) and relatively close to 0 if it lay within the permissive limits ($P > 0.15$). We also compared the distribution of separation indexes to a distribution of randomly generated separation indexes and tested the fit using the Kolmogorov-Smirnov test.

RESULTS

Task performance

The analysis of the movement initiation and offset in all recording sessions (Table 1) showed that in bimanual trials, the arms typically started to move together with an average inter-arm interval (IAI) of <40 ms and reached the targets with comparable accuracy. On average, the right arm began movement before the left and finished movement after the left in both monkeys, a trend that was significant in some cases (see Table 1). Successful performance of the trial could be achieved with an IAI of ≤300 ms, and the actual performance of the

TABLE 2. *Activation of cells in MI and SMA*

Area	Monkey	Total Number of Neurons	During any movement	Cells With Significant Activation		
				During unimanual movements (but not bi)	During both bimanual and unimanual	During bimanual movements (but not uni)
MI	F	100	90 (90)	8 (8)	73 (73)	9 (9)
	G	132	97 (73)	13 (10)	55 (42)	29 (22)
	Both	232	187 (81)	21 (9)	128 (55)	38 (16)
SMA	F	83	75 (90)	12 (14)	58 (70)	5 (6)
	G	123	82 (67)	19 (15)	46 (37)	17 (14)
	Both	206	157 (76)	31 (15)	104 (50)	22 (11)

Numbers in parentheses represent percent of neurons with significant differences between baseline activity and activity during the activation epoch and comparison of the number of neurons activated in any of the different movements with the number of neurons activated in at least one unimanual movement (and also, possibly, in bimanual movements). Significance of activation was determined with the Mann-Whitney ($P < 0.001$).

monkey was more simultaneous than required. The IAIs are also much shorter than the reaction time and movement time. The average reaction time was approximately 250 ms and the average movement time was approximately 600 ms.

We performed Mann-Whitney tests to compare reaction time and movement time in unimanual and bimanual movements. For monkey F, only the comparison of bimanual opposite movement times to those unimanual movement times showed a difference that was marginally significant ($P < 0.01$; note, however, that no correction has been made here for multiple comparisons). However, in monkey G, we found that unimanual movement times were usually slower than bimanual movement times ($P < 0.01$, except for bimanual parallel movements).

Neuronal population

In each session we made two simultaneous penetrations of four electrodes in each hemisphere, and recorded the activity of 8–16 isolated neurons. The proximal arm areas of SMA and MI were identified based on neuronal activity (during task performance, during somatosensory stimulation, and during passive limb movements), the effect of ICMS and the anatomy of the sulci and gyri determined by MRI and postmortem. A total of 665 neurons were recorded from the two monkeys during 82 penetrations (328 electrode tracks) in SMA and MI (see Fig. 3). Of these, 572 passed our criterion for waveform isolation, and of these, there were 438 for which isolation was maintained for ≥ 6 trials in each movement condition. Thus our analysis was performed on 438 cells, 232 from MI, and 206 from SMA. For all of our analyses, we tested the results on the right and left hemispheres of the monkeys separately. However, since no significant differences were found, data from both hemispheres of each monkey are presented together throughout the paper. Average activation onset for all units was -119 ± 183 (SD) ms, and no significant difference in activation time was found between MI and SMA units.

Table 2 shows the number of units whose activity varied significantly during performance of the task. As can be seen, activity of 81% (187/232) of neurons recorded in MI and 76% (157/206) of neurons recorded in SMA were significantly modulated during performance of the task, despite the fact that no selection was made on this basis during the recording sessions. Table 2 also demonstrates that about one-half of the neurons in both MI and SMA were significantly activated during both unimanual and bimanual movements. The number of units active only during unimanual movements is approximately equal to the number of units active only during bimanual movements. A χ^2 analysis applied to the combined data of the two monkeys shows a marginally significant difference between the areas ($P < 0.047$). The interpretation of this result is problematic, since the nominal significance level we have used for behavioral data are $P < 0.01$. Thus we are unable to conclude that the two areas have the same distribution of activation, but we are also unable to reject the hypothesis.

Neural activity during unimanual movements

Figure 4 shows the activity of two neurons recorded from left MI of monkey F during unimanual movements of both the right and the left arm. The neuron in Fig. 4A is strongly

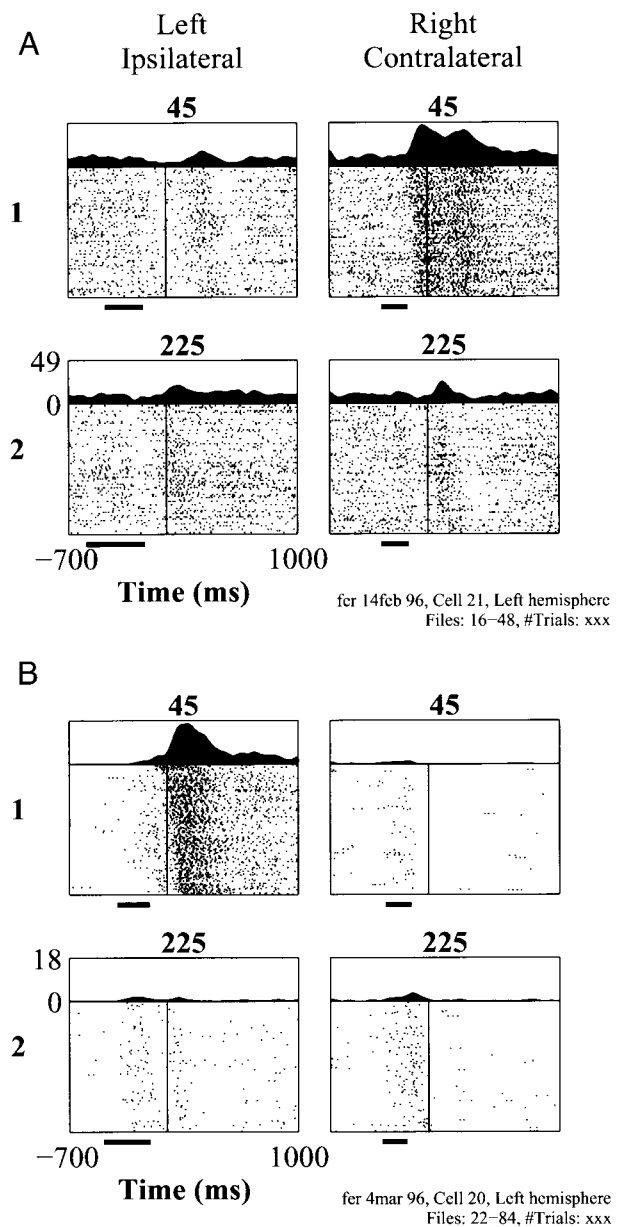


FIG. 4. Unimanual responses of MI cell. This figure illustrates activity during unimanual movements of 2 neurons recorded in left MI of monkey F. *A*: neuron with strong contralateral preference (laterality index = 0.59, Eq. 1). *B*: neuron with strong ipsilateral preference (laterality index = -0.77). Trials are aligned on beginning of movement and sorted by reaction time; the line below each plot indicates the range of target appearance times. The peristimulus time histograms (PSTHs) were smoothed using a filter with a cutoff frequency of 100 ms and a binwidth of 2.5 ms. The time axis for all PSTHs is the same; the rates for the PSTHs in *A* are all on the scale 0–49 as indicated, and the rates in *B* are on the scale 0–18. Each dot display shows 74 trials.

modulated during right-handed (contralateral) movements (laterality index of 0.59, Eq. 1), while the neuron *B* is strongly modulated during ipsilateral movements (laterality index of -0.77). Table 2 compares the number of neurons with significant evoked activity during unimanual movements to the number with such activity in both unimanual and bimanual movements, while Table 3 compares the number of significantly activated neurons during unimanual contralateral movements with the number during unimanual ipsilateral movements. The latter table shows a mild contralateral preference in

TABLE 3. *Lateralized activation of cells in MI and SMA*

Area	Monkey	Cells With Significant Activation			
		During any unimanual movement	During unimanual contra movements (but not ipsi)	During both contra and ipsi unimanual movements	During unimanual ipsi movements (but not contra)
MI	F	81	30 (37)	38 (47)	13 (16)
	G	68	12 (31)	31 (46)	16 (24)
	Both	149	51 (34)	69 (46)	29 (19)
SMA	F	70	15 (21)	40 (57)	15 (21)
	G	65	21 (32)	32 (49)	12 (18)
	Both	135	36 (27)	72 (53)	27 (20)

Numbers in parentheses represent percent of neurons with significant differences between baseline activity and activity during the activation epoch in unimanual trials. The table breaks down the neuronal activation during unimanual movements according to the side being activated creating three mutually exclusive categories: contralaterally but not ipsilaterally activated, activated both contralaterally and ipsilaterally, or ipsilaterally but not contralaterally activated. Neuronal activation during bimanual movements does not affect categorization on this table. Significance of activation was determined with the Mann-Whitney ($P < 0.001$).

both MI and SMA. In both recording areas, approximately one-third of the neurons are activated only during contralateral movements while approximately one-fifth of the neurons are activated only ipsilaterally. A χ^2 analysis of the data in this table (combined across the 2 monkeys) revealed no significant differences between MI and SMA. These findings are strengthened by Fig. 5, which shows the distribution of the laterality index in MI and SMA. The figure shows that a large proportion of the cells have no significant difference in maximal activation during contralateral and ipsilateral movements, and that many neurons in both MI and SMA are more strongly activated during ipsilateral movements. Nevertheless, there is a slight contralateral preference, and a tendency for neurons in MI to be more contralateral than neurons in SMA.

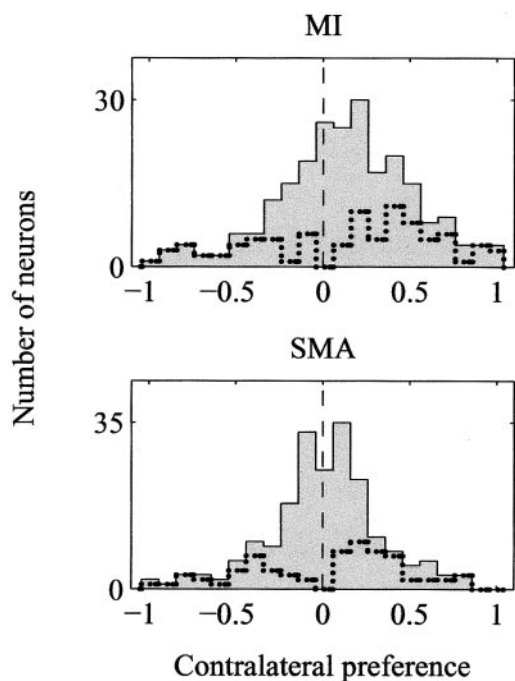


FIG. 5. Contralateral preference in MI and SMA. The 2 histograms show that only a small difference exists in the laterality index (Eq. 1) of neurons in MI and SMA, and that in both MI and SMA there are many cells that are more strongly activated during unimanual ipsilateral movements than during unimanual contralateral movements. For neurons below the dotted line, there is a significant difference between the maximal activation during contralateral and ipsilateral movements ($P < 0.001$). Binwidth is 0.1.

The number of neurons in monkey F with significant lateralization of activity is larger than in monkey G. This is because monkey F performed more trials in each type of movement than monkey G, improving the power of the statistical tests performed. In monkey F, most sessions were two-direction sessions, while in monkey G most sessions were eight-direction sessions. This led to a difference in the number of trials performed in each direction.

Neural activity during bimanual arm movements

The comparisons of the cells' activity in unimanual, bimanual parallel, and bimanual opposite trials revealed significant bimanual-related effects that are demonstrated in Figs. 6 and 7. Figure 6 shows activity of a left MI neuron during unimanual and bimanual movements. While there is slight modulation of activity during movements of the right (contralateral) arm, the neuron is strikingly active during one specific type of bimanual movement (bimanual parallel movements in which both arms move to 180° , i.e., to the left). The strength of the bimanual-related effect (Eq. 2) in this neuron is 0.63. Figure 7 shows a cell from the right SMA that shows evoked activity only in unimanual movements of the contralateral arm. This activity would normally be described as "classic motor-related" activity. Nevertheless, the cell has a strong bimanual-related effect. The clear, directionally selective, activity evoked during unimanual movements of the left (contralateral) arm disappears during all bimanual movements, and is replaced by a reduction in the firing rate of the neuron. The strength of the bimanual-related effect in this neuron is -0.84 . Dramatic examples of the bimanual-related effects, in MI as well as SMA, can also be found in Fig. 14 of this manuscript and in Donchin et al. 1998.

Muscular activity in unimanual and bimanual arm movements

The monkey performed short movements (3 cm) that did not require noticeable postural adjustment. Indeed, observation of the monkey during task performance (aided by video recordings) revealed no postural adjustments or other differences that distinguished movements during bimanual and unimanual trials, and examination of the EMG of the axial muscles (rhomboids and latissimus dorsi) showed very little activity during performance of the task (Fig. 8). The figure allows a compar-

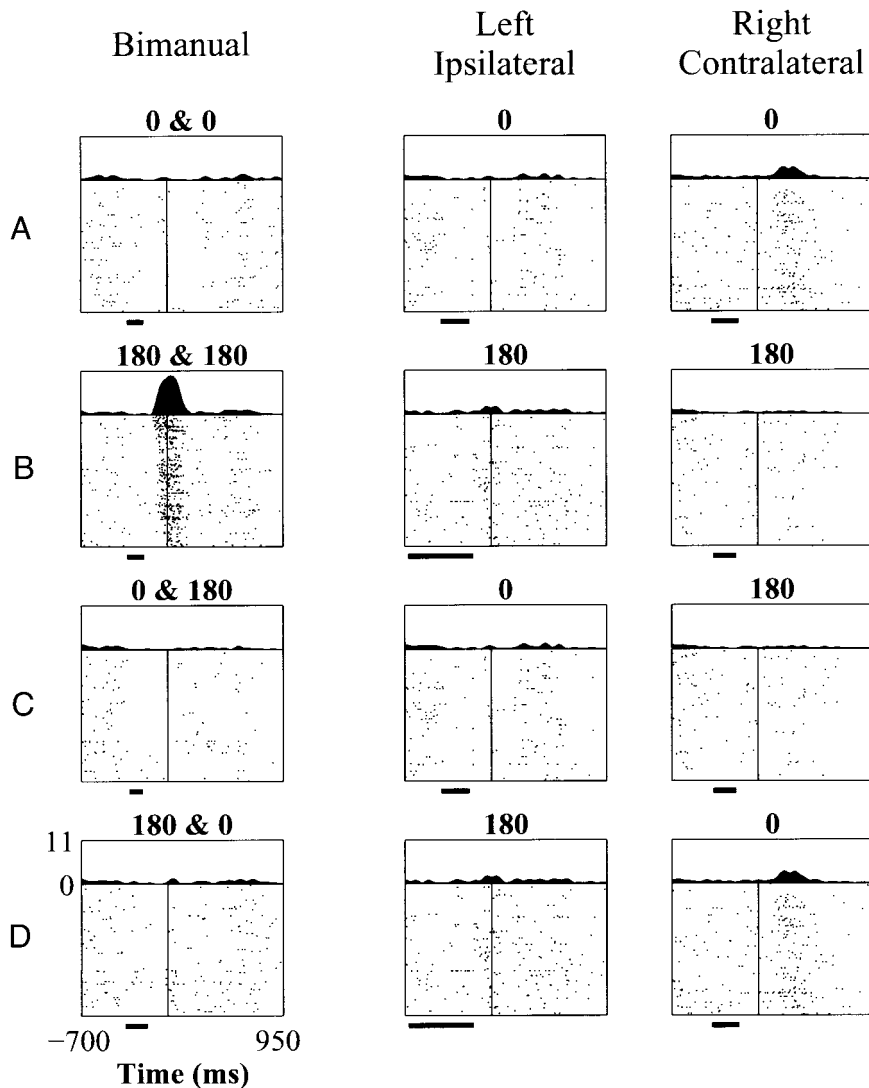


FIG. 6. bimanual-related activity in an MI cell. This figure demonstrates a bimanual-related effect in a neuron from left MI where activity during bimanual movements is different from activity during unimanual movements. The strength of the bimanual-related effect (Eq. 2) for this neuron is 0.63. Each row contains PSTHs and raster displays depicting the cell activity during performance of 1 type of bimanual movement and the 2 unimanual movements that comprise it (unimanual left-handed movements in the *middle column* and unimanual right-handed movements in the *right column*). Direction of movement of each arm is indicated above each plot: for bimanual trials, first the direction of the left arm and then the right; for unimanual trials, the direction of the arm that is moving. Trials are aligned on the beginning of the movement (of the 1st arm) and sorted by reaction time. Line beneath each dot display shows the range of target appearance times. PSTHs were smoothed using a filter with cutoff frequency of 100 ms, and the number of trials and PSTH scale are identical in all plots. Binwidth is 2.5 ms. Each dot display shows 200 trials.

for 13feb 96, Cell 16, Left hemisphere, Direction 0
Files: 9-77, #Trials: xxx

ison of the activity of all the different muscles from which data were collected in one particular combination of unimanual and bimanual movements. The rightmost two columns show EMG activity of nine muscles, recorded bilaterally from the left and right sides of the body, during a unimanual right movement to 45°. The middle two columns show activity of the same muscles during a unimanual left movement to the same direction and the leftmost two columns show the activity of those muscles when both hands are moving together in parallel to 45°. It is clear from this figure that there is very little contralateral EMG activation during unimanual movements. Similarly, it can be seen that the overall picture of EMG activation in the bimanual movement is similar (although not identical) to that in the two unimanual movements. Analysis of the arm endpoint trajectories and velocity profiles also indicate similarity between bimanual and unimanual movements (see *Extending earlier results* as well as Figs. 10–12).

Extending earlier results

To this point, the results described mirror those of our earlier report: both MI and SMA have significant propor-

tions of neurons with ipsilateral and contralateral preference and both areas have neurons with dramatic bimanual-related activity (Donchin et al. 1998). Now we extend these findings by more carefully quantifying the bimanual related activity and examining the hypothesis that subtle differences in the EMG of axial and arm muscles or changes in trajectories and velocity profiles suffice to explain the bimanual-related effect.

Distribution of bimanual related cells in MI and SMA

The percentage of cells that exhibited significant bimanual-related effects was high in both MI and SMA: 55% (129/232) in MI and 52% (107/206) in SMA. Figure 9 shows the strength of the bimanual-related effect in the population of analyzed cells. The histograms are separated into two by a dotted line that distinguishes cells found to be significantly “bimanually related” (below the line) from others. From the histograms, one can see that evoked activity is stronger in unimanual movements (as in Fig. 7) at least as often as it is increased during bimanual movements (as in Fig. 6). The figure also shows that the distribution of strengths is similar

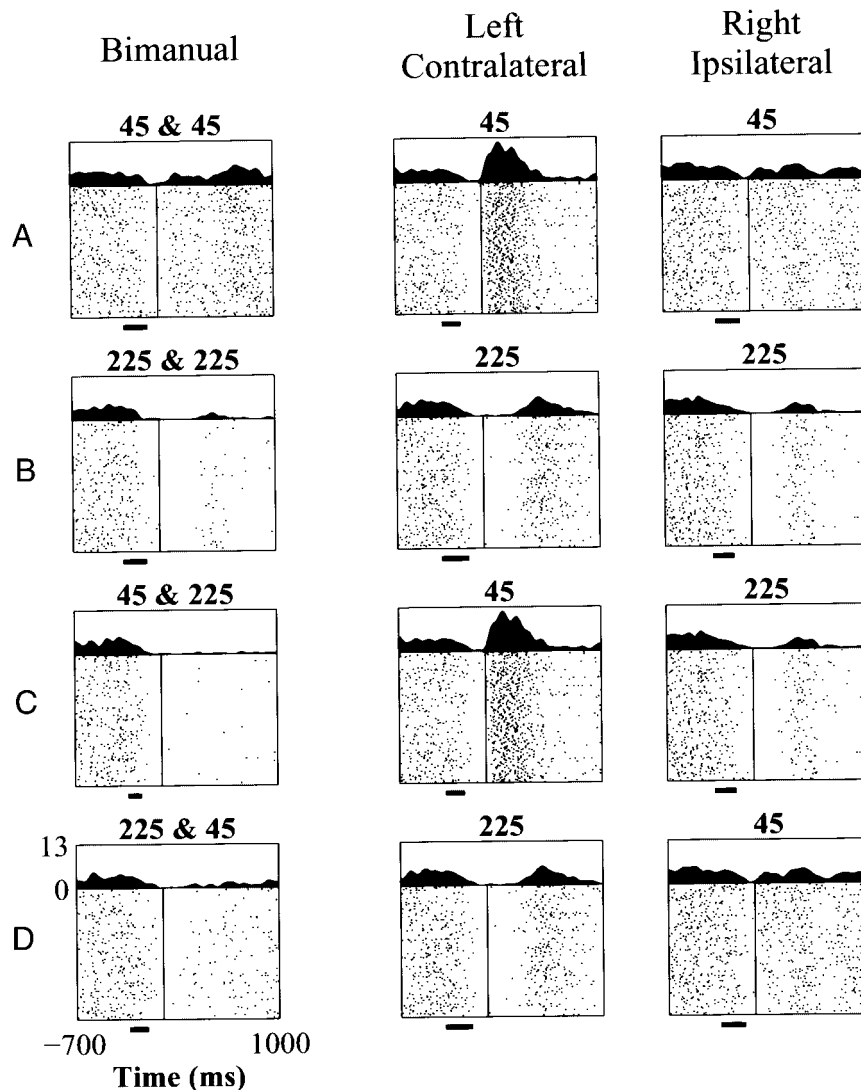


FIG. 7. Bimanual-related activity in an SMA cell. This cell from right SMA demonstrates a bimanual-related change in activity where evoked activity during unimanual contralateral movements is not evident during bimanual movements (perhaps activity is suppressed in row C). Strength of the bimanual-related effect is -0.84 . Format is the same as in Fig. 7. Each dot display shows 130 trials.

for 27mar 96, Cell 0, Right hemisphere, Direction 45
Files: 17-85, #Trials: xxx

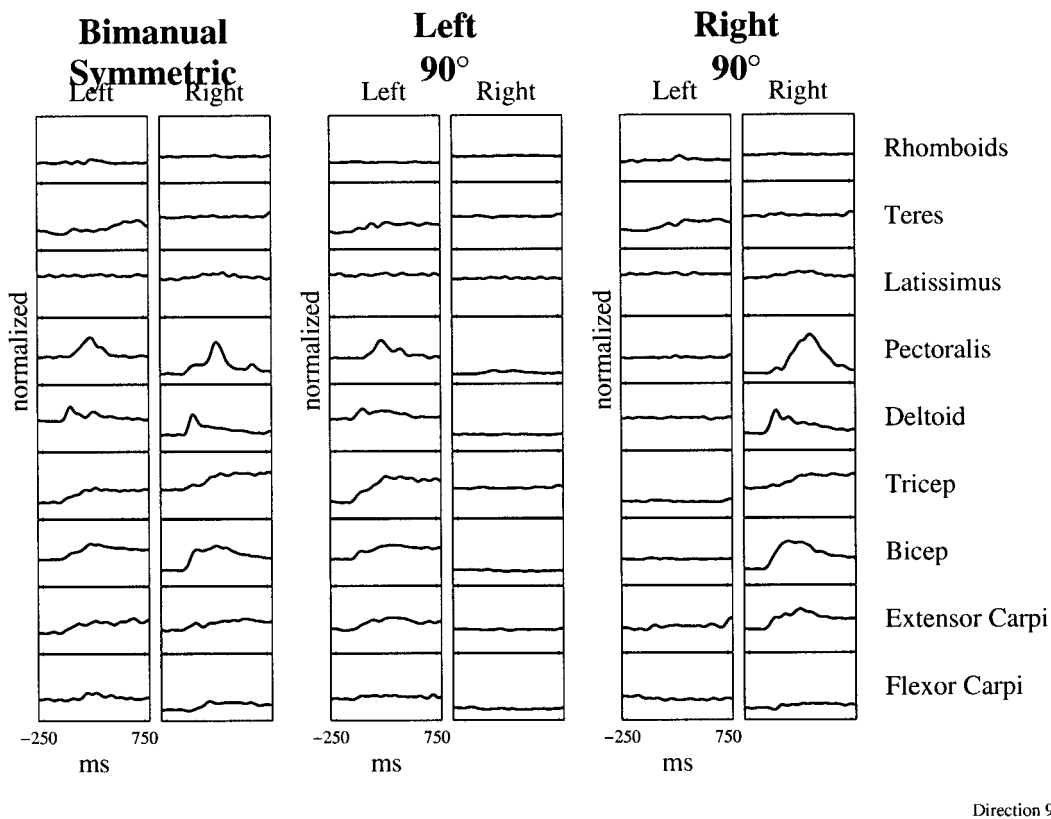
in MI and in SMA. This can be verified by a Kolmogorov-Smirnov statistic that shows no significant difference between the distributions ($P > 0.1$). Interestingly, there is an interaction between lateralization and the sign of the bimanual-related effect. For neurons with a contralateral preference, the bimanual-related effect is positive as often as it is negative. However, for neurons preferring the ipsilateral arm (negative values in Eq. 1), in both MI and SMA, nearly all neurons show a reduction in activity during bimanual movements (results not shown).

Again, a slightly smaller proportion of neurons from monkey G are significantly “bimanually related.” In this case, as with the contralateral preference, the smaller number of trials performed by monkey G in each movement type reduced the power of the statistical tests.

Linear combinations of unimanual activity

We tested the NEA during bimanual movements against three null hypotheses: that bimanual NEA is equal to con-

tralateral NEA, that it is equal to the ipsilateral NEA, or that it is equal to a sum of the two. Table 4 shows that for most of the bimanual-related neurons (approximately 80%), all of these hypotheses could be rejected at $P < 0.05$. In contrast, for neurons that were not bimanual-related, 60% of the neurons in MI and 72% of the neurons in SMA failed to reject one or more of the hypotheses at this level—namely, their responses might be explained by a linear combination of the unimanual responses. In an additional analysis, we fit the neuronal activity with a model that attempts to explain bimanual NEA using a general linear combination of unimanual NEAs (Eq. 3). While this model fits 26% of the bimanual-related neurons in MI and 19% of the bimanual-related neurons in SMA (Table 4), the parameters of the fit for different neurons were not clustered in any way. Note that, when the variance in neuronal activity was large, a neuron could fit several of the models tested. However, to be as strict as possible with our results, we did not perform any corrections for the repeated tests. In sum, the majority of the bimanual-related neurons did not admit any linear explanation of their bimanual activity.



Direction 90

FIG. 8. EMGs in unimanual and bimanual movements. This figure shows the activity of all the muscles from which EMG was collected during performance of unimanual and bimanual movements to 45° . Data is shown for unimanual movement and for bimanual *parallel* movements. To allow comparison between the muscles, activity is normalized for each muscle: each plot is scaled from 0 to 1.5 of its maximum activation on any single trial across all movements. Because of the noise inherent in the EMG, scaling by the maximum magnitude on a single trial allows for the possibility that the muscle would not appear active in any direction. This is the case, for instance, for the rhomboids that were not strongly activated in any movement. The lack of contralateral EMG activation during unimanual movements is apparent, as is the overall similarity of the EMG in bimanual and unimanual movements. Data are from monkey G.

Analysis of behavioral controls

As mentioned above, our preliminary analysis and visual inspection of movement trajectories, velocity profiles, and EMG, revealed that, while all of these measures were quite similar in all movement types, they were not identical. The mean and SDs of the trajectories from one recording session are shown in Fig. 10. Velocity profiles for the same recording session are shown in Fig. 11, and examples of EMGs (recorded at the end of training) are shown in Fig. 12. The largest bimanual-related effect (0.067) for the movement trajectories shown in Fig. 10 is in the comparison of unimanual left hand movements toward 45° with movements of the left hand during a bimanual opposite movement in the same direction. This difference is among the largest bimanual effects seen in the movements (in the 90th percentile). The largest bimanual-related effect in the velocity profiles of Fig. 11 is larger than the bimanual-related effects in the movement trajectories on this day. The bimanual-related effect for the difference between unimanual right hand movements to 270° and bimanual opposite movements in the same direction is 0.187. This difference is in the 80th percentile of bimanual-related differences in velocity. Figure 12 shows the activity of the left and right deltoid during performance of the task. These are two of the four muscles that were chosen for simultaneous recording with the neural activity on the basis of apparent differences in the

activity during unimanual and bimanual movements of our monkeys. The largest bimanual-related effect in these two muscles is -0.108 , which is obtained in the comparison between unimanual right handed movements to 135° and bimanual *parallel* movements in the same direction.

Figure 13 summarizes the relationship between the strength of the bimanual-related effect in neurons and the strength of the bimanual-related effect in the behavioral variables. Figure 13, A and B, shows scatter plots of the neuronal and kinematic effects. Figure 13C shows a histogram comparing the distribution of strengths of effect in evoked activity in MI and SMA to the distribution of the effect in integrated EMG for all the muscles we recorded. Since the muscles were recorded separately from the neurons, no scatterplot can be shown. We did, however, repeat the statistical analysis applied to the units to determine how much of the EMG activity showed a significant bimanual-related effect. Across all muscles from both sides in all four primary directions (a total of 72 data points), only 19 cases (26.4%) showed a significant bimanual effect. A binomial test shows that this number is significantly less than would be predicted by the fraction of neurons in MI that showed bimanual effects (55.6%). The bimanual-related effect is clearly stronger in the neurons than in any of the behavioral variables we analyzed. Moreover, where tested, there is no correlation between the strength of the bimanual-related effect

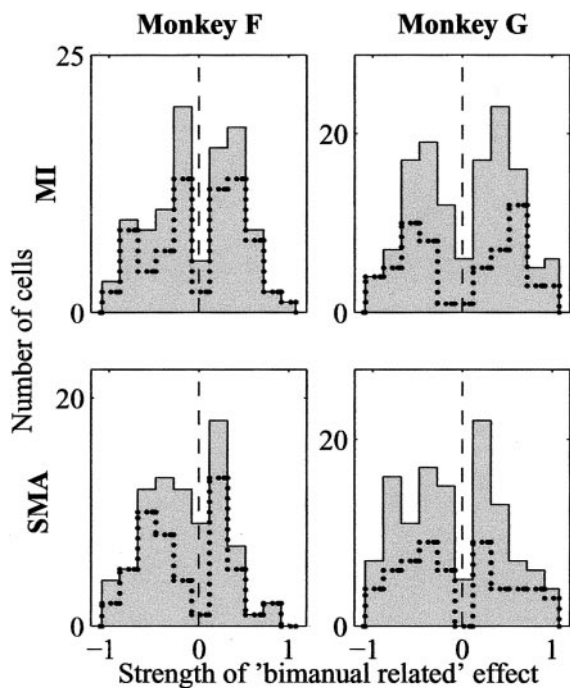


FIG. 9. Strength of the bimanual-related effect. Each subplot shows a histogram of the bimanual-related effect (Eq. 2) for cells recorded in 1 cortical area of 1 monkey. Negative values indicate larger evoked activity during unimanual movements while positive values indicate larger evoked activity during bimanual movements. Activity changes during bimanual movements are as strong in MI as they are in SMA. Dotted line separates neurons with a significant bimanual-related effect ($P < 0.001$, below the line) from those without a significant bimanual-related effect. Binwidth is 0.2 ms.

in a neuron and the strength of the effect in the behavioral variable.

Separation analysis

For many of the neurons, a large number of trials were collected in each condition. This permitted an analysis of the relation between the behavioral variables and the neural activity as illustrated in Fig. 14. The figure depicts the activity of bimanual-related units during performance of unimanual trials (*left column*, in red) and bimanual trials (*right column*, in blue). In each of the figure's three sections, the *top row* of plots shows the "similar" group (see METHODS) containing trials

where the difference in the behavioral parameter in bimanual and unimanual trials is small. The "different" group, shown in the *bottom row* of plots, contains trials where the difference in the behavioral parameter is large. Figure 14A demonstrates this analysis applied to the trajectory deviations. The bimanual-related neuron shown is more active during unimanual movements (bimanual-related effect of -0.76). The bimanual-related effect is preserved whether or not the trajectory deviations are similar or different. The separation index (Eq. 4) for the separation of the neuronal activity is -0.15 (not different from 0, $P > 0.15$), while the separation index for the movement trajectories is 4.88 (different from 0, $P < 0.001$).

Figure 14B applies the same analysis to the peak velocity for one "bimanual related" neuron. The neuron has a "bimanual related" effect of 0.22, and it is more active in bimanual movements than in unimanual movements. The separation index for the neural activity of the neuron is 0.3 (not different from 0, $P > 0.15$). The separation index for the velocity is 3.66 (different from 0, $P < 0.001$). For this example, as well, the bimanual-related effect is preserved despite the separation. Finally, Fig. 14C shows an example of the separation analysis applied to the integrated EMG. The strength of the bimanual-related effect for the neuron in Fig. 14C is 0.91. The separation index for the neuronal activity in this analysis is -0.11 (not different from 0, $P > 0.15$) while the separation index for the integrated EMG is 2.04 (different from 0, $P < 0.001$). As before, the bimanual-related effect is preserved.

Figure 15 shows that the examples in Fig. 14 are quite typical. The results of the separation analysis applied to trajectory deviation and peak velocity in all significantly bimanual-related cells is shown in Fig. 15, A and B. We compared the resulting distribution of separation indexes to a distribution of the analysis applied to the same neurons, but in which division into the "similar" and "different" groups was performed at random. The plots show the relationship between the actual distribution of separation indexes (gray histogram) and the random distribution (black line). A Kolmogorov-Smirnov test for the similarity of two distributions fails to find differences between the measured and random distributions of the separation index for the trajectory deviations (Fig. 15A, $P > 0.1$). It does reveal a difference for the distributions generated using the peak velocity (Fig. 15B, $P < 0.01$), indicating that for a few cells it may be possible to explain the bimanual-related effect as a reflection of differences in the kinematics of unimanual

TABLE 4. Categorization of cells according to the linear model

Area	Total	Ipsi Only	Contra Only	Sum	None	General Model
MI						
Not bimanual cells	103	41 (40)	47 (46)	30 (29)	41 (40)	19 (18)
Bimanual-related cells	129	5 (4)	13 (10)	2 (2)	110 (85)	33 (26)
All cells	232	46 (20)	60 (26)	32 (14)	151 (65)	52 (22)
SMA						
Not bimanual cells	99	47 (47)	56 (57)	37 (37)	28 (28)	29 (29)
Bimanual-related cells	107	8 (7)	12 (11)	4 (4)	87 (81)	20 (19)
All cells	206	55 (27)	68 (33)	41 (20)	115 (56)	49 (24)

The numbers in parentheses represent percent of cells for which one may not reject ($P > 0.05$) the hypothesis that particular summations explain their activation during bimanual movements. Three alternative null hypotheses were explored, and if all three could be rejected ($P < 0.05$) for a given neuron, it was counted in the "None" column. The percentages do not add up to 100% because the categories are not exclusive (except for the "None" column). The significance criterion for bimanual-related is $P < 0.001$. These hypotheses seem less appropriate for the bimanual-related neurons than for those that are not bimanual. A general linear model was also tested in which the bimanual activity could be any arbitrary linear combination of the ipsilateral and contralateral activity. In this model, also, most neurons did not fit the model, and there was no clustering of the parameters of the fit.

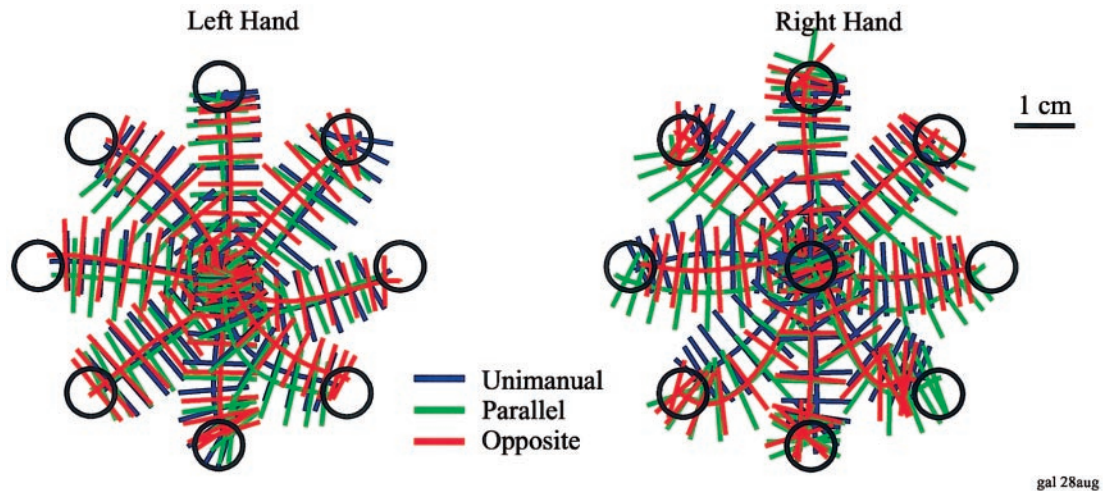


FIG. 10 Comparison of movement trajectories in different trial types. Plot of the movement trajectories for unimanual and bimanual movements. Mean (shown by the trajectory) and SD (shown by the lines perpendicular to the trajectory) of the movements are shown. SD bars are drawn every 50 ms. Data are from 1 day of recording in monkey G. Strength of the bimanual-related effect is strongest between unimanual movement of the left hand to 45° and bimanual *opposite* movements in the same direction. For this comparison, the bimanual-related effect is 0.067.

and bimanual movements. However, for the majority of neurons, the separation indexes measured are completely consistent with those generated by chance. In general, therefore these results are not consistent with an explanation of the bimanual-related effect purely on the basis of the differences either in the movement paths or in the velocities.

We also applied the analysis to 59 bimanual-related neurons recorded simultaneously with EMG (Fig. 15C). We used a lower level of significance for the bimanual-related effect than in our other analyses ($P < 0.01$) to increase the size of the sample analyzed for this purpose. The muscles recorded were the anterior deltoid and the flexor carpi ulnaris on both the left

and right side of the body. For each neuron, we performed a separation analysis separately with each of the four muscles recorded, but then discarded all but the most significant of these analyses (as determined by bootstrapping). This is because we were interested in finding the muscle to which the neuron was most strongly related. Figure 15C shows the distribution of the separation indexes we calculated (gray histogram) and the distribution generated by creating four separation indexes through random selection of trials and discarding all but the most significant (black line). There is no significant difference between these two distributions (Kolmogorov-Smirnov, $P > 0.1$). This analysis shows that the bimanual-related

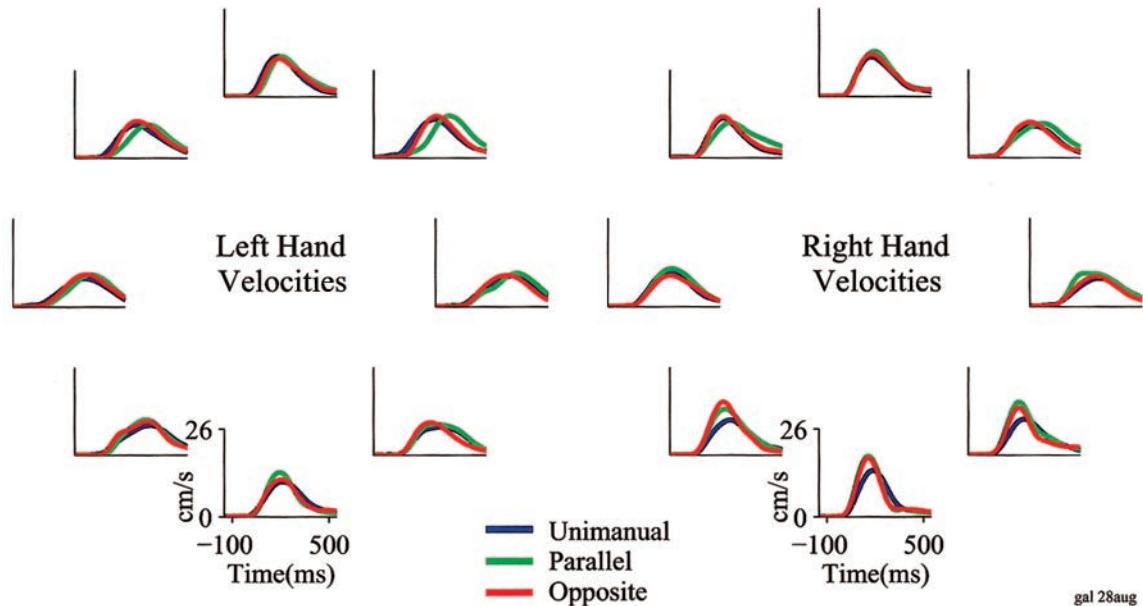


FIG. 11. Comparison of velocity profiles in different trial types. Plot of the velocity profiles for unimanual and bimanual movements. Velocity profiles shown are averages of repetitions aligned on beginning of movement. Data are from the same day of recording in monkey G as the movement trajectories shown in Fig. 10. The bimanual-related effect is strongest between unimanual movements of the right hand to 270° and bimanual *opposite* movements in the same direction. Strength of this effect is 0.187.

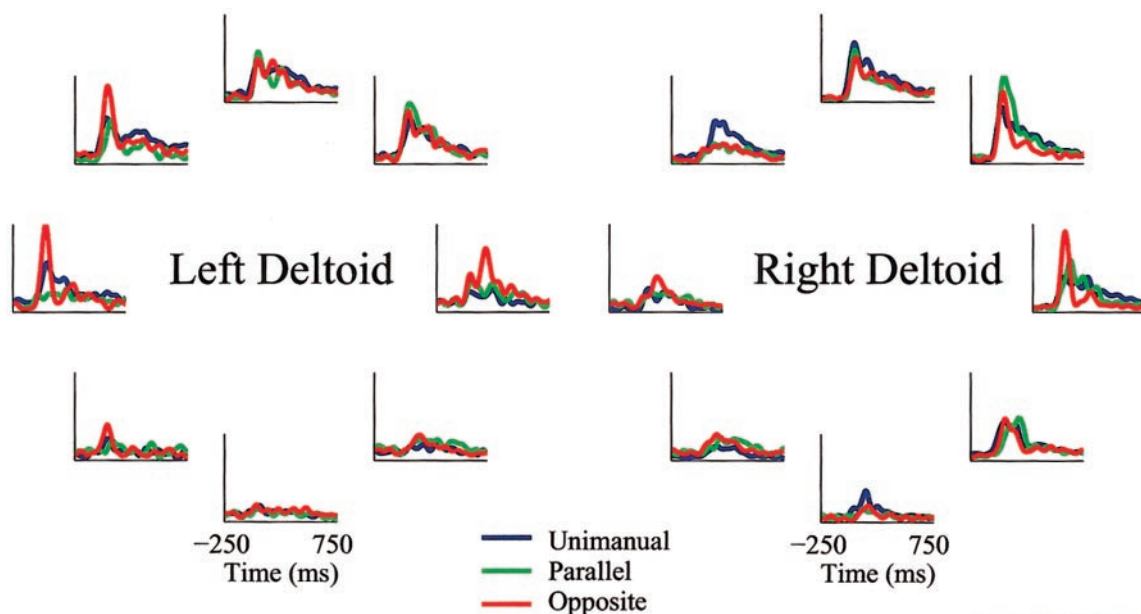


FIG. 12. Activity of left and right deltoid. This figure shows the activity of the left and right deltoid recorded during performance of all different movements. The largest bimanual-related effect for the left deltoid is 0.055 in the comparison between the unimanual movement and bimanual opposite movements to 0° . The largest bimanual-related effect for the right deltoid is -0.108 in the comparison between the unimanual movement and the bimanual symmetric movement to 135° . Data are from monkey G.

effect is not related to the activity in the muscles we recorded beyond chance levels.

Figure 16 shows the relationship between the results in the separation analysis and the bimanual-related effect for all three behavioral parameters. The lack of correlation between “bimanual relatedness” and the separation indexes is indicated by the r values shown in the *top right corner* of each plot. Thus the population of neurons in our study taken as a whole does not seem to show a strong relationship between variations in the kinematics and dynamics of the movements and variations in the neural activity associated with bimanual movements. The failure to find a relationship of this sort undermines the argument that the bimanual-related effect results solely from differences in the performance of bimanual and unimanual movements.

DISCUSSION

This study demonstrates substantial differences between the cortical activity associated with unimanual movements and that associated with bimanual arm movements. The differences seen between these two movement classes are as robust in MI as they are in the SMA. Some of the MI activity differences could be variations in the subtle aspects of the movements, both kinematic and dynamic. Other activity could be due to differences in postural adjustments or postural set between the two tasks. And, some of the observed bimanual activity might simply be linear combinations of unimanual activity. But, these various contributions do not account for the bulk of the observed unit activity differences between unimanual and bimanual arm movements.

In general, both kinematics and dynamics are poor predictors of changes in neural activity specific to the difference between unimanual and bimanual arm movements. Two pairs of analyses reinforce this view. In the first pair, we establish 1) that changes in unit activity are generally far greater between

the two task conditions than the similarly computed changes in kinematics or dynamics (summarized in Fig. 13) and 2) that there is no correlation between the bimanual-related effect and changes in kinematics or dynamics (also demonstrated by Fig. 13). This pair of analyses is strong evidence that the bimanual effects are not a result of differences in movement trajectories, velocity profiles, or details of EMG activation. However, averaging trials together might obscure the effects of movement variations. The second pair of analyses applies a trial-by-trial approach to validate the use of mean values by checking whether different subsets of movements contribute differently to the mean activation. This pair of analyses includes 1) looking at cortical activity when behavioral parameters are similar and comparing that to cortical activity when they are different to see if more extreme movements are associated with a greater “bimanual effect” and 2) looking for correlations between the degree of movement deviation from average and the strength of the bimanual effect. In the case of movement paths, we compare cortical activation during movements with a small trajectory deviation to cortical activation during movements with large trajectory deviations (Fig. 14A). The results of this comparison indicate that the observed bimanual effect did not differ significantly between “typical” trials and trials with an extreme trajectory (Fig. 14). The second pair of analyses is completed by showing that, in cases where the typical trials and the extreme trials are particularly distinct, the bimanual effect is no greater than in cases when extreme trials are more typical (Fig. 16). Equivalent analyses are carried out for velocity profiles and EMG activation (Figs. 15 and 16). In the analysis of the velocity profiles, a significant number of neurons was found whose bimanual-related effect could be, in part, explained by variations in velocity. However, for most neurons this was not the case. This battery of tests does not support the proposal by Kazennikov et al. (1999) that trial-to-trial variations in the

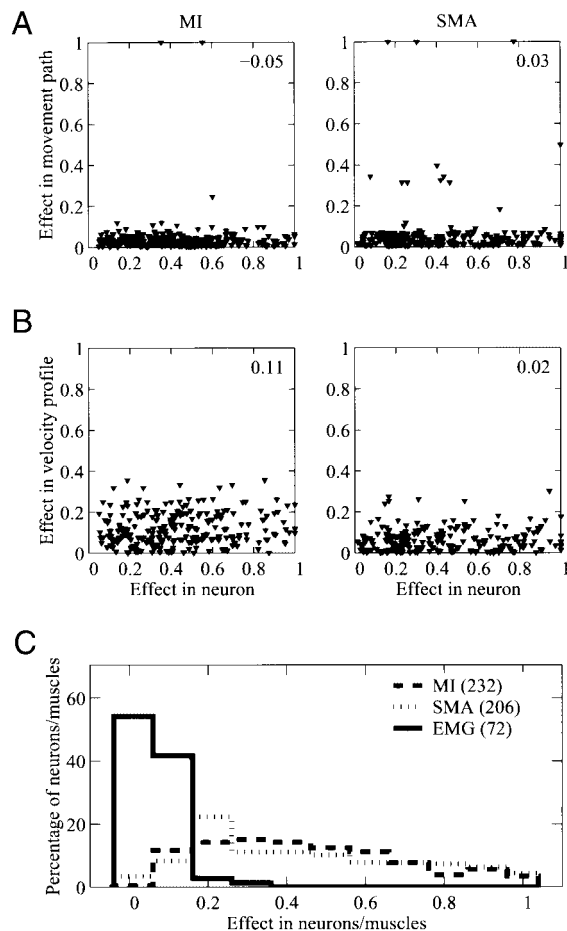


FIG. 13. Bimanual-related effect in neuronal activity, kinematics, and EMG. This figure compares the bimanual-related effect for each cell with the bimanual-related effect in the kinematics of the movements performed by the monkey and in the EMG. In the scatterplots (A and B), each point represents a single cell. The *x* axis is the bimanual-related effect for that cell; the *y* axis is the bimanual-related effect for the kinematics of the same bimanual and unimanual movement over which the neural effect was calculated. Numbers in the *top right corner* of each scatterplot give the Spearman's *r* for the data displayed in the plot. Comparison with the bimanual-related effect in the movement trajectories are shown (A), as well as comparison with the bimanual-related effect in the velocity profiles (B). In the histogram (C), the strength of the bimanual-related effect in the neurons in MI and SMA are compared with the strength of the bimanual-related effect in the EMG.

animal's performance might explain the strong differences in cortical activity observed during unimanual compared with bimanual tasks, unless one imagines a strongly nonlinear relationship between movement variations and neural activity that could evade detection in our analyses, or that the pattern of muscular activation during neural recordings differed from those during the earlier EMG collection phase.

It is impossible to completely discount contributions of axial and other relatively static postural muscles to the bimanual related effects as a result of postural adjustments that might occur when switching between unimanual and bimanual tasks. Indeed, it is true that a fraction of muscles showed a significant difference in activation between unimanual and bimanual movements. However, several lines of evidence argue against this possibility. The first line was just discussed. Bimanual effects are relatively insensitive to the small movement variations, and these are exactly the type of variations that typify

postural adjustments. Evidence from EMG recordings, as well as our own personal observations, show that the animals in this study did not make overt postural adjustments when asked to switch between the two experimental conditions. Our limited survey of EMG activity was carried out with surface recording electrodes (see METHODS) using electrodes that are more likely to oversample by including nearby muscles, rather than under-sample, e.g., record from only a limited region of the muscle. One of the striking aspects of the seated posture of the monkey and the mechanics of the arm manipulanda is that very little axial muscle effort is required to displace either hand. Thus it was not surprising that relatively little axial muscle activity was found during the survey. The axial muscles that were active showed little or no modulation with the task. The lack of modulation of axial activity contrasts sharply with the strong modulation of both the proximal arm muscles (Fig. 8) and the single units.

It is still likely that some axial muscles had EMG modulation correlated with the task and some MI modulation varied systematically between unimanual and bimanual tasks. This contribution to the overall recorded neuronal population would necessarily be small, however. The most pronounced feature of the MI topography is that postural muscles have a dramatically small motor representation (Craggs et al. 1976; Woolsey et al. 1952). Muscles with such a small motor representation would not dominate the results unless the recordings were selected for axial muscle activity, accidentally concentrated in one tiny region of MI, or altogether out of the arm area. Figure 3 shows that the recorded units in this study were far too widespread in MI to be dominated by such a small motor representation. Evidence of clear arm and shoulder related activity seen in our recordings, often localized to a single joint, as well as the microstimulation sites that produced frank single-joint arm movements confirmed that our recording sites in MI were in the well-established proximal arm and shoulder areas explored by other investigators (Georgopoulos et al. 1983; Kalaska and Crammond 1992). Subsequent (Steinberg et al. 2002) recordings from the same chamber of monkey G on the directional tuning of MI neurons during unimanual and bimanual movements showed tuning in most neurons in both unimanual and bimanual movements, further demonstrating that our sample was from the forelimb motor area.

We explored the possibility that differences in cortical activation during bimanual arm movements are simply the result of some linear combination of unimanual activities. In this study, we examine three simple models that might predict bimanual activity: left limb activity alone, right limb activity alone, and an equally weighted sum of left and right limb activities. We reject all three models for more than one-half of the units in both MI and SMA (Table 4). Even a more general version of the third model, one that allows independent weighting of the contributions from each limb, cannot explain the activity of most units. Moreover, units with a significant bimanual effect fit the linear model less often than others, further reducing the likelihood that the bimanual effect is explained by a linear model.

Given the clear difference in activity during unimanual and bimanual movements, and given that these differences are neither the result of variations in the movement parameters, nor simply the combination of individual limb-related activations, we are led to conclude that there are signals in MI and SMA

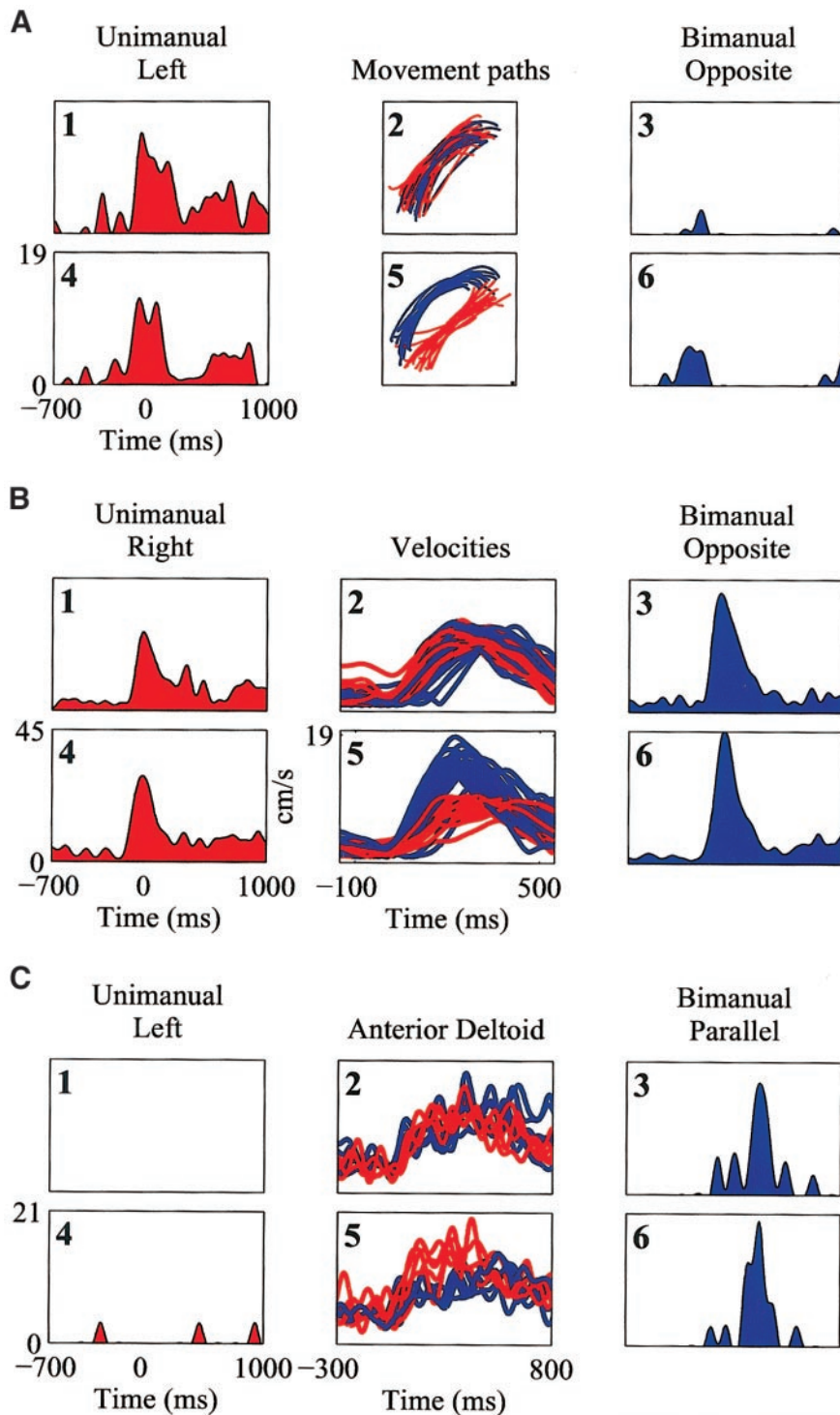


FIG. 14. Separation analysis. Figure shows an example of the separation analysis applied to each of the behavioral parameters. For *A*, *B*, and *C*, trials from the “similar group” are in the *top row*, and trials from the “different” group are in the *bottom row*. *Left column*: PSTH for the neuron during 1 type of unimanual trial (red). *Right column*: PSTH for the neuron during 1 type of bimanual movement (blue). *Middle column*: behavior, where trials in red are unimanual trials and trials in blue are bimanual trials. *A*: separation analysis of the trajectory deviation for a “bimanual-related” neuron from left MI. For this neuron, evoked activity is greater during unimanual movements. During movements of the right hand, activity of the neuron was at baseline. Number of trials for each histogram: 18. *B*: separation analysis of the peak velocity for a “bimanual-related” neuron from left SMA. This neuron is significantly less active during unimanual right-handed movements than during bimanual opposite movements. Number of trials for each histogram: 41. *C*: separation analysis applied to the integrated EMG for a “bimanual-related” neurons from right MI. For this neuron, evoked activity is greater during bimanual movements than it is during unimanual movements. The neuron is not activated during movements of the ipsilateral arm. Number of trials per histogram: 5.

that specifically reflect bimanual arm movements. Similar analyses were not possible in prior studies because movements were either too restricted to provide useful trajectory information (Tanji et al. 1988: button pressing task) or the movements were not continuously measured (Kazennikov et al. 1999; Kermadi et al. 1998: food retrieval task). The two more recent studies, both using very similar behavioral paradigms, draw contradictory conclusions. Kermadi et al. reported essentially

the same results as reported here: bimanual related units were common in MI (48%) and only slightly less so in SMA (44%). In contrast, Kazennikov et al. argued that their data did not support bimanual specificity in either MI or SMA, based on an unusually restrictive definition of bimanual specificity (Tanji et al. 1988; the methods section of this paper; compare with Kazennikov et al. 1999; Kermadi et al. 1998). When we apply our definition to their published data by combining the units in

fer 4mar 16; 22–59; UniLt 45 BiOpp 45
fer 7apr 24; 24–79; UniRt 45 BiOpp 225
gal 14jun 6; 40(5)–48(5); EMG1; UniLt 315 BiSym 315

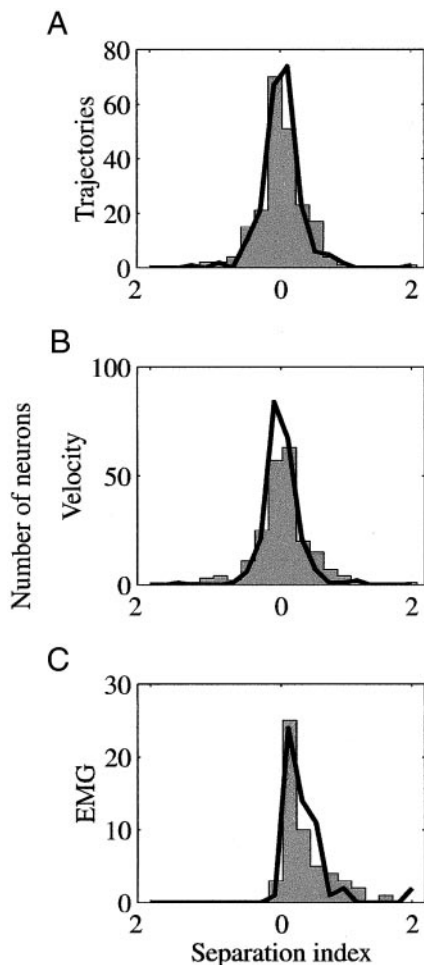


FIG. 15. Distribution of the separation index. Gray histograms show the distribution of separation indexes (Eq. 4) resulting from applying the separation analysis to bimanual-related neurons in both MI and SMA. Black line shows the distribution of separation indexes resulting from randomly dividing trials into 2 groups. *A*: distribution of separation indexes when separating by trajectory deviation. *B*: distribution of separation indexes when separating by peak velocity. *C*: distribution of separation indexes when separating by integrated EMG.

subclasses b, c, and e (Kazennikov et al. 1999, Table 1, under the assumption that “moderate” differences reported between bimanual and unimanual activation in subclass b and c are statistically significant), we find that 46% of units in MI and 48% of units in SMA have activity specific to bimanual arm movements. This interpretation is in agreement with Kermadi et al. as well as the present report.

The Tanji et al. (1988) study is unique in finding a substantial difference between MI and SMA in a bimanual task. In their study, the activity of units in MI and SMA was recorded during the performance of left handed, right handed, and bimanual finger presses. The monkeys were carefully trained, using EMG activity recorded during training and feedback from force transducers, to minimize undesired muscle activation. Undesired muscle activation included proximal muscle activity, activity in the contralateral muscles during unimanual movements, and differences in the activity of the ipsilateral muscles in bimanual and unimanual movements. Following this extensive training, most neurons in MI responded similarly during bimanual and contralateral unimanual movements. In

contrast, many units in SMA were activated during contralateral (unimanual) movements but not during bimanual movements or vice versa.

We offer two alternative explanations for the observation that the button-pressing task of Tanji et al. rarely produced MI activity specific to bimanual movements, while our planar tracking task and the food retrieval task (Kazennikov et al. 1999; Kermadi et al. 1998) often produced such activity. One explanation, discussed in detail elsewhere (Donchin et al. 1998, 1999), is that MI control of distal hand movements may be different from MI control of more proximal movements (including movements at the elbow). In this view, MI representation of proximal movements is predominantly bilateral, whereas distal movements are represented as more or less simple combinations of unimanual movements. The other ex-

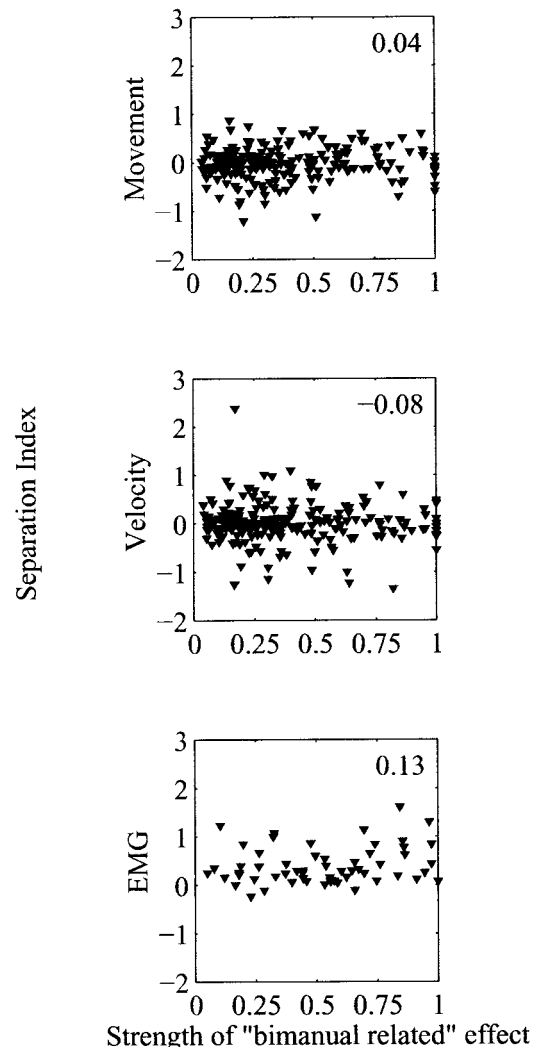


FIG. 16. Significance of bimanual-related effect vs. significance of separation. This figure shows the relationship between the strength of the bimanual-related effect in a neuron and the separation index when the neuronal activity is divided according to kinematic and dynamic parameters. Each wedge represents 1 neuron. The magnitude of the bimanual-related effect for that neuron is along the x axis. The y axis gives the separation index when separating according to 1 of the 3 parameters of the movements. The Spearman's r for the correlation between bimanual-related effect and separation index is given in the top right of each plot. *A*: deviation from mean movement path. *B*: maximum velocity. *C*: integrated root mean square (RMS) of the EMG.

planation suggests that different training requirements in the two tasks caused the difference in the results. The extensive training required for suppression of disallowed muscle activation in Tanji's study may indicate that bilateral suppression of muscle activity was a major task constraint. This constraint would be largely the same in both unimanual and bimanual button pressing. This could explain why MI activation was similar in both the bimanual and unimanual conditions. SMA, whose task representation may be more abstracted from muscular constraints, could still distinguish the task conditions. In our study, the major training hurdle was to achieve simultaneous onset and offset of the arm movements in bimanual movements and immobility of one arm in unimanual movements. These requirements called for a training period of several months and were clearly very different for bimanual and unimanual trials. We suggest that this type of extensive training shaped very different cortical activity patterns for the different conditions of the bimanual task, in contrast with the button pressing task.

Note that we differentiate "task requirements" from "variations in task performance." A prediction that follows from the second explanation above is that the differences required by the task are critical to the development of bimanual related cortical activity. Execution differences that have no substantial impact on the learning would not be expected to influence the strength of the bimanual effect. Nudo recently showed that dynamic changes in the MI motor map have a similar dependence on task requirements (Plautz et al. 2000).

It is still impossible to say whether the conjectural "learning-based" explanation of the bimanual effect is the correct explanation. The possibility that fundamental differences between proximal and distal motor control explains the dichotomy of results begs further investigation. Tasks that compare proximal and distal bimanual movements could be helpful in this regard, as would a study of the development of the bimanual effect through the course of the training procedure. However, one conclusion that emerges from the present work is that bimanual arm movements can be represented by cortical activity that is distinct from the representation used for unimanual movements. This finding challenges our understanding of the relationship of the motor control system, and our knowledge regarding the underlying basis for the representation of movements in the cortex.

We thank Y. Donchin for help with the surgical procedures and G. Goelman for help with the MRI. We also thank S. P. Wise and R. Paz for comments on earlier versions of the manuscript.

This research was supported by the Israel Science Foundation (including support to center excellence 8006/00), the United States-Israel Binational Science Foundation (BSF), and the German-Israeli Foundation for Scientific Research and Development (GIF). We thank the Clore Foundation for the fellowship that supported O. Donchin throughout this project.

REFERENCES

- ACUNA BD, WANG CK, SANES JN, AND DONOGHUE J. P. Transitive inference mechanisms and the involvement of prefrontal cortex. *Soc Neurosci Abstr* 24: 464.3, 2002.
- AIZAWA H, MUSHIAKE M, INASE M, AND TANJI J. An output zone of the monkey primary motor cortex specialized for bilateral hand movement. *Exp Brain Res* 82: 219–221, 1990.
- ANDERSEN P, HAGAN PJ, PHILLIPS CG, AND POWELL TP. Mapping by microstimulation of overlapping projections from area 4 to motor units of the baboon's hand. *Proc R Soc Lond B Biol Sci* 188: 31–36, 1975.
- ASANUMA H AND ROSEN I. Topographical organization of cortical efferent zones projecting to distal forelimb muscles in the monkey. *Exp Brain Res* 14: 243–256, 1972.
- BELL KR, TRAYLOR GH, ANDERSON ME, BERGER MS, AND OJEMANN GA. Features of targeted arm movement after unilateral excisions that included the supplementary motor area in humans. *Brain Res* 655: 202–212, 1994.
- BENECKE R, DICK JP, ROTHWELL JC, DAY BL, AND MARSDEN CD. Increase of the Bereitschaftspotential in simultaneous and sequential movements. *Neurosci Lett* 62: 347–352, 1985.
- BRINKMAN C. Supplementary motor area of the monkey's cerebral cortex: short- and long-term deficits after unilateral ablation and the effects of subsequent callosal section. *J Neurosci* 4: 918–929, 1984.
- CARPENTER AF, GEORGOPOULOS AP, AND PELLIZZER G. Motor cortical encoding of serial order in a context-recall task. *Science* 283: 1752–1757, 1999.
- CRAGGS MD, RUSHTON DN, AND CLAYTON DG. The stability of the electrical stimulation map of the motor cortex of the anesthetized baboon. *Brain* 99: 575–600, 1976.
- DAVEY NJ, ELLAWAY PH, AND STEIN RB. Statistical limits for detecting change in the cumulative sum derivative of the peristimulus time histogram. *J Neurosci Methods* 17: 153–166, 1986.
- DEECKE L, LANG W, HELLER HJ, HUFNAGL M, AND KORNHUBER HH. Bereitschaftspotential in patients with unilateral lesions of the supplementary motor area. *J Neurol Neurosurg Psychiatry* 50: 1430–1434, 1987.
- DONCHIN O, CARDOSO DE OLIVEIRA S, AND VAADIA E. Who tells one hand what the other is doing: the neurophysiology of bimanual movements. *Neuron* 23: 15–18, 1999.
- DONCHIN O, GRIBOVA A, STEINBERG O, BERGMAN H, AND VAADIA E. Primary motor cortex is involved in bimanual coordination. *Nature* 395: 274–278, 1998.
- ELLAWAY PH. An application of cumulative sum technique (cusums) to neurophysiology. *J Physiol (Lond)* 265: 1P–2P, 1977.
- FU QG, FLAMENT D, COLTZ JD, AND EBNER TJ. Temporal encoding of movement kinematics in the discharge of primate primary motor and premotor neurons. *J Neurophysiol* 73: 836–854, 1995.
- GEORGOPOULOS AP, KALASKA JF, CAMINITI R, AND MASSEY JT. Interruption of motor cortical discharge subserving aimed arm movements. *Exp Brain Res* 49: 327–340, 1983.
- GEORGOPOULOS AP, LURITO JT, PETRIDES M, SCHWARTZ AB, AND MASSEY JT. Mental rotation of the neuronal population vector. *Science* 243: 234–236, 1989.
- KAHN M AND LISBERGER SG. Vector averaging occurs downstream from learning in smooth pursuit eye movements of monkeys. *J Neurosci* 19: 9039–9053, 1999.
- KALASKA JF AND CRAMMOND DJ. Cerebral cortical mechanisms of reaching movements. *Science* 255: 1517–1523, 1992.
- KAZENNIKOV O, HYLAND B, CORBOZ M, BABALIAN A, ROUILLER EM, AND WIESENDANGER M. Neural activity of supplementary and primary motor areas in monkeys and its relation to bimanual and unimanual movement sequences. *Neuroscience* 89: 661–674, 1999.
- KAZENNIKOV O, HYLAND B, WICKI U, PERRIG S, ROUILLER EM, AND WIESENDANGER M. Effects of lesions in the mesial frontal cortex on bimanual co-ordination in monkeys. *Neuroscience* 85: 703–716, 1998.
- KELSO JAS. Phase transitions and critical behavior in human bimanual coordination. *Am J Physiol* 246: R1000–R1004, 1984.
- KERMADI I, LIU Y, TEMPINI A, CALCIATI E, AND ROUILLER EM. Neuronal activity in the primate supplementary motor area and the primary motor cortex in relation to spatio-temporal bimanual coordination. *Somatosens Motor Res* 15: 287–308, 1998.
- LANG W, OBRIG H, LINDINGER G, CHEYNE D, AND DEECKE L. Supplementary motor area activation while tapping bimanually different rhythms in musicians. *Exp Brain Res* 79: 504–514, 1990.
- LAPLANE D, TALAIRACH J, MEININGER V, BANCAUD J, AND ORGOGOZO JM. Clinical consequences of corticectomies involving the supplementary motor area in man. *J Neurol Sci* 34: 301–314, 1977.
- MARDIA KV. *Statistics of Directional Data*. New York: Academic Press, 1972.
- MORAN DW AND SCHWARTZ AB. Motor cortical representation of speed and direction during reaching. *J Neurophysiol* 82: 2676–2692, 1999.
- PENFIELD W AND WELCH K. The supplementary motor area of the cerebral cortex: a clinical and experimental study. *Arch Neurol Psychiatr* 66: 289–317, 1951.
- PHILLIPS CG. Laying the ghost of "muscles versus movements." *Can J Neurol Sci* 2: 209–218, 1975.

- PLAUTZ EJ, MILLIKEN GW, AND NUDO RJ. Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. *Neurobiol Learn Mem* 74: 27–55, 2000.
- PORRO CA, FRANCESCATO MP, CETTOLO V, DIAMOND ME, BARALDI P, ZUIANI C, BAZZOCCHI M, AND DI PRAMPERO PE. Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study. *J Neurosci* 16: 7688–7698, 1996.
- ROUILLER EM, BABALIAN A, KAZENNIKOV O, MORET V, YU XH, AND WIESENDANGER M. Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. *Exp Brain Res* 102: 227–243, 1994.
- SADATO N, YONEKURA Y, WAKI A, YAMADA H, AND ISHII Y. Role of the supplementary motor area and the right premotor cortex in the coordination of bimanual finger movements. *J Neurosci* 17: 9667–9674, 1997.
- STEINBERG O, DONCHIN O, GRIBOVA A, CARDOSO DE OLIVEIRA S, BERGMAN H, AND VAADIA E. Neuronal populations in primary motor cortex encode bimanual arm movements. *Eur J Neurosci* 15: 1371–1380, 2002.
- STEPHAN KM, BINKOFSKI F, HALSBAND U, DOHLE C, WUNDERLICH G, SCHNITZLER A, TASS P, POSSE S, HERZOG H, STURM V, ZILLES K, SEITZ RJ, AND FREUND HJ. The role of ventral medial wall motor areas in bimanual co-ordination. A combined lesion and activation study. *Brain* 122: 351–368, 1999.
- TANJI J, KAZUHIKO O, AND KAZUKO CS. Neuronal activity in cortical motor areas related to ipsilateral, contralateral, and bilateral digit movements of the monkey. *J Neurophysiol* 60: 325–343, 1988.
- TANJI J AND SHIMA K. Contrast of neuronal activity between the supplemental motor area and other cortical motor areas. *Adv Neurol* 70: 95–103, 1996.
- TOYOKURA M, MURO I, KOMIYA T, AND OBARA M. Relation of bimanual coordination to activation in the sensorimotor cortex and supplementary motor area: analysis using functional magnetic resonance imaging. *Brain Res Bull* 48: 211–217, 1999.
- TSUTSUI S, LEE TD, AND HODGES NJ. Contextual interference in learning new patterns of bimanual coordination. *J Motor Behav* 30: 151–157, 1998.
- UHL F, KORNUBER AW, WARTBERGER P, LINDINGER G, LANG W, AND DEECKE L. Supplementary motor area in spatial coordination of bilateral movements: a new aspect to 'the SMA debate'? *Electroencephalogr Clin Neurophysiol* 101: 469–477, 1996.
- VIALLET F, MASSION J, MASSARINO R, AND KHALIL R. Coordination between posture and movement in a bimanual load lifting task: putative role of a medial frontal region including the supplementary motor area. *Exp Brain Res* 88: 674–684, 1992.
- WIESENDANGER M, ROUILLER EM, KAZENNIKOV O, AND PERRIG S. Is the supplementary motor area a bilaterally organized system? *Adv Neurol* 70: 85–93, 1996.
- WIESENDANGER M AND WISE SP. Current issues concerning the functional organization of motor cortical areas in nonhuman primates. *Adv Neurol* 57: 117–133, 1992.
- WOOLSEY CN, SETTLAGE PH, MEYER DR, SENCER W, PINTO-HAMUY T, AND TRAVIS M. Patterns of localization in precentral and "supplementary" motor areas and their relation to the concept of a premotor area. *Res Publ Assoc Nerv Ment Dis* 30: 238–264, 1952.
- ZHANG J, RIEHLE A, REQUIN J, AND KORNBUM S. Dynamics of single neuron activity in monkey primary motor cortex related to sensorimotor transformation. *J Neurosci* 17: 2227–2246, 1997.