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

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Abstract

Single units were recorded from the primary (MI) and supplementary motor area (SMA) of Rhesus monkeys performing one-arm (unimanual) and two-arm (bimanual) reaching tasks. During execution of the bimanual movements, the task related activity of half the neurons in each area (MI: 129/232, SMA: 107/206) differed from the activity during similar movements of one hand while the other was stationary. The bulk of this “bimanual related” activity could not be explained by any linear combination of activity during unimanual reaching, or by differences in kinematics or recorded EMG activity: single unit activity was relatively insensitive to the effects of movement variation compared to its sensitivity to bimanual effects. Further, 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. By rejecting these alternative explanations, we can conclude that activation of motor cortical areas during bimanual arm movements reflects unique cortical processing associated with bimanual movements and is not simply a reflection of the independent activations caused by separate movements of the two arms.
Introduction

Simultaneous movements of two limbs, bimanual movements\(^1\), present a special control problem for the central nervous system. Controlling two limbs simultaneously is often a significantly more complex task than sequential movements of several limbs: attention may be split during a bimanual task if each limb must approach a separate target; the combined forces generated by bimanual movements may require a unique postural set; synchronization of the limbs may also require control and attention. The greater demands of bimanual tasks have lead to the prediction that fundamental differences exist between bimanual and unimanual motor control (Kelso 1984; Tsutsui et al. 1998). If the motor cortex is to play an important role in bimanual movements, we should expect neural activity to reflect the greater complexity involved in these tasks compared to simpler, unimanual tasks.

It has been known for some time that the SMA is involved in bimanual motor control. Combined lesions of the SMA and surrounding area 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 (Penfield and Welch 1951; Laplane et al. 1977; Viallet et al. 1992; Bell et al. 1994) studies have also explored the role of SMA in bimanual tasks, although there are still questions regarding the extent of this involvement and whether the SMA is the only cortical motor area involved (Kazennikov et al. 1998; Wiesendanger and Wise 1992).

Tanji and his coworkers reported that, except for a tiny zone near the face area (Aizawa et al. 1990), MI does not specifically encode bimanual movements, but SMA and the premotor cortex do (Tanji et al. 1988; Tanji and Shima 1996). However, a clear difference between MI and SMA activity has not been demonstrated in tasks involving more proximal musculature, despite the expectation that this difference would be found (Tanji et al. 1988; Wiesendanger et al. 1996; Tanji and Shima 1996; Kermadi et al. 1998).

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\(^1\) "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").
1998; Donchin et al. 1998; Kazennikov et al. 1999). 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. 1999a) that the limited role of MI in distal bimanual tasks is a special case, and that MI involvement in bimanual arm movements generally rivals that of SMA. If correct, this would imply that MI provides a higher level of processing than simply the organization of muscle synergies (Phillips 1975). Other recent lines of evidence also appear to elevate the putative role of MI. Individual MI neurons can encode multiple parameters of movement (Kahlon and Lisberger 1999; Moran and Schwartz 1999; Fu et al. 1995). Populations of MI neurons reflect motor imagery (Georgopoulos et al. 1989; Porro et al. 1996) serial ordering (Carpenter et al. 1999), and perhaps stimulus-response associations (Zhang et al. 1997).

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 (Kazennikov 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 et al. 1988; Tanji and Shima 1996). 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, 4kg, and monkey G, 3.5kg) 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 towards the top of the screen of the display.

The time course of typical unimanual and bimanual task trials is schematized in Figure 1. A trial began when the monkey aligned both cursors on 0.8 cm diameter “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 diameter) could appear at a distance of 3 cm from the origin (Figure 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 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 Figure 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 (Figure 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 second 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 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 at least 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: 
\[\frac{\|\tilde{x}(t) - \tilde{x}(t + dt)\|}{dt},\]
where \(\tilde{x}(t)\) and \(\tilde{x}(t + dt)\) 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 8 different directions, making 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 below). Following a unimanual session, we examined the activity of the neurons that had been recorded and selected one primary direction for further study. We chose from a set of 4 possible directions (0°, 45°, 90° or 135°) 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, 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, electromyographic signals (EMG) were recorded differentially using pairs of 1 cm surface electrodes from 9 muscles; each muscle was recorded bilaterally. These muscles were the rhomboid, latissimus dorsi, teres major, pectoralis major, deltoïd, 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 RMS was computed with a frequency cutoff of 100 Hz (the RMS – root mean square – is a nonlinear filter that first rectifies and squares the signal and then smooths this squared signal to the cutoff frequency before it’s 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.

We used MRI (Biospec Bruker 4.7 Tesla animal system; fast-spin echo sequence; effective TE = 80ms and TR = 2.5 seconds, 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 (27×27mm) were surgically implanted above the right and left hemispheres and a head holder was attached to the occipital bone. The surgery was performed under isoflurane anaesthesia in aseptic conditions. The animals’ care and surgery procedures were in accordance with The NIH Guide for the Care and Use of Laboratory Animals (rev. 1996) 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 MΩ 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 (and occasionally three) isolated neurons to be recorded from most electrodes. 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 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.

At the end of each recording session, we tested unit receptive fields with passive manipulation of the limbs and tail, as well as tactile stimulation of the limbs, trunk, head and tail. Activity evoked by passive manipulation was evaluated by listening to the amplified signal passed directly into a loudspeaker. 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 µs cathodal pulses at 300 Hz with an intensity of 10-80 µA (BPG-2 and BSI-2, BAK Electronics, Germantown, MD). Typical train durations were 50 ms for MI and 100 ms for SMA. Except for initial mapping early in the experiment, currents were delivered at or near threshold levels at the end of each day’s recordings, and only at the recording sites. Passive manipulation was tested at these sites just before stimulation. When ICMS evoked movements, we documented the movements evoked and the stimulation intensity.

**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 at least 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 bin width 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) 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 (Ellaway 1977; Davey et al. 1986). 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 to 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, overlap 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 non-preferred 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 comparison of cells recorded during two direction sessions with cells recorded during eight direction sessions, we limited our current analysis of the eight direction sessions to two directions. 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 in order 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 direction
plus 180°. While this may have introduced some statistical differences in the number of cells that
showed significant responses in two direction and eight direction sessions, no such 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 below).

**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):

\[
\text{Laterality Index} = \frac{\text{contralateral EA} - \text{ipsilateral EA}}{\text{contralateral EA} + \text{ipsilateral EA}}
\]

(Eq. 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 to which unimanual activity the bimanual activity will be compared. Clearly, the bimanual activity should be compared to activity during one of the unimanual movements that compose it (although it could also be compared to some sort of combination of the activities during the two 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 Figure 6, the bimanual evoked activity in row B would be compared to 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 (Figures 6 and 7). 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:

\[ \text{"Bimanual Related" Effect} = \frac{\text{bimanual EA} - \text{unimanual EA}}{\text{bimanual EA} + \text{unimanual EA}} \]

where \( \text{bimanual EA} \) is the evoked activity during the bimanual movement, and \( \text{unimanual EA} \) is the evoked activity during the unimanual movement to which it is being compared. The bimanual evoked activity was compared to 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 lab) 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 are 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 $X^2$ 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 non-trivial linear
combination of unimanual NEAs. In order to test this possibility we used a linear model of the form

\[
\begin{align*}
B_{p,1} &= \alpha C_1 + \beta I_1 \\
B_{p,2} &= \alpha C_2 + \beta I_2 \\
B_{o,1} &= \alpha C_1 + \beta I_2 \\
B_{o,2} &= \alpha C_2 + \beta I_1
\end{align*}
\]

(Eq. 3)

where the $B$s represent NEA during bimanual movements, the $C$s represent NEA during unimanual
movements and the $I$s represent NEA during ipsilateral movements. We used a constrained linear fit to
generate $\alpha$ and $\beta$ and restricted $\alpha$ and $\beta$ to positive values (Matlab 5.3, Mathworks, \texttt{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. In order 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 ms to 450 ms after movement initiation, the movement
epoch) of each movement from the grand mean of all movements. 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 root mean square of individual EMG traces recorded during the EMG epoch (150ms before movement initiation to 350ms 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 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

\[
\text{Separation Strength} = \log_{10} \left( \frac{B_{\text{Different}} - U_{\text{Different}}}{B_{\text{Similar}} - U_{\text{Similar}}} \right)
\]

where \(U_{\text{Similar}}, U_{\text{Different}}, B_{\text{Similar}}\) and \(B_{\text{Different}}\) 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.
Histology

Monkeys were given an overdose of pentobarbital, and then perfused transcardially with 0.9% saline followed by 4% formaldehyde in 0.1M 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 \( \mu m \)). Alternate sections were stained with Cresyl Violet (0.1%). Surface penetration maps for both monkeys are shown in Figure 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.

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 average inter-arm interval (IAI) of less than 40 ms and reach the targets with comparable accuracy. On average, the right arm began movement before the left and finished movement after the left in both monkeys. Successful performance of the trial could be achieved with an IAI of up to 300 ms, and the actual performance of the monkey was more simultaneous than required. The IAIs are also much shorter than the reaction time and movement time. The average reaction time was \(~250\) ms and the average movement time was \(~600\) ms.

We performed Mann-Whitney tests to compare reaction time and movement time in unimanual and bimanual movements. For monkey F, no significant differences were found in either reaction time or movement time (p > 0.01 in all cases). However, in monkey G we found that unimanual movement times were slower than bimanual movement times (p < 0.01) and that the right hand’s reaction time was significantly faster in unimanual compared to bimanual movements (p < 0.01).
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 post-mortem. A total of 665 neurons were recorded from the two monkeys during 82 penetrations (328 electrode tracks) in SMA and MI (see Figure 3). Of these, 572 passed our criterion for waveform isolation, and out of these there were 438 for which isolation was maintained for at least 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.

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 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.

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 part A of the figure is strongly modulated during right handed (contralateral) movements (laterality index of 0.59, equation 1), while the neuron in part 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 table shows a mild contralateral preference in both MI and SMA. In both recording areas, ~1/3 of the neurons are activated only during contralateral movements while approximately ~1/5 of the neurons are activated only ipsilaterally. These findings are strengthened by Figure 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.

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 figures 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 (equation 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 Figure 14 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 (Figure 8). The figure allows a comparison of the activity of all the different muscles from which data was collected in one particular combination of unimanual and bimanual movements. The rightmost two columns show EMG activity of 9 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 end-point trajectories and velocity profiles also indicate similarity between bimanual and unimanual movements (see text below as well as Figures 10, 11, and 12).

**Extending earlier results**

To this point, the results described mirror those of our earlier report: both MI and SMA have significant proportions 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 Figure 7) at least as often as it is increased during bimanual movements (as in Figure 6). The figure also shows that the distribution of strengths is similar 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 Equation 1), in both MI and SMA, nearly all neurons show a reduction in activity during bimanual movements (results not illustrated).

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 normalized evoked activity (NEA) during bimanual movements against three null hypotheses: that bimanual NEA is equal to contralateral 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 (~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 (equation 3). While this model fit 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, in order 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.

Analysis of Behavioral Controls

As mentioned above, our preliminary analysis and visual inspection of movement trajectories, velocity profiles and EMG revealed that while all these measures were quite similar in all movements types they were not identical. The mean and standard deviations of the trajectories from one recording session are shown in Figure 10. Velocity profiles for the same recording session are shown in Figure 11, and examples of EMGs (recorded at the end of training) are shown in Figure 12. The largest “bimanual related” effect (0.067) for the movement trajectories shown in Figure 10 is in the comparison of unimanual left hand movements towards 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 Figure 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 and 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 13A and B show 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. 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 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 was collected in each condition. This permitted an analysis of the relation between the behavioral variables and the neural activity as illustrated in figure 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 figures 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 (B, “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 (equation 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 indexes 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, figure 14C shows an example of the separation analysis applied to the integrated EMG. The strength of the “bimanual related” effect for the neuron in A 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 figure 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 Figure 15A 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 shows 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 indexes for the trajectory deviations (Figure 15A, p > 0.1). It does reveal a difference for the distributions generated using the peak velocity (Figure 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 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 (Figure 15C). We used a lower level of significance for the “bimanual related” effect than in our other analyses (p < 0.01) in order 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” 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 upper 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**

**Summary of results**

The present work 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. Further, this report treats two key concerns raised by our earlier report (Donchin et al. 1999b): the degree to which kinematics and dynamics influence the major results, and degree to which the bimanual activity was simply a linear combination of unimanual activities.

In general, both kinematics and dynamics are poor predictors of neural activity specific to the differences 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 figure 13), and (2) that there is no correlation between the “bimanual related” effect and changes in kinematics or dynamics (also demonstrated by figure 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, the effects of movement variations might be obscured by averaging trials together. The second pair of analyses validates the use of mean values by checking to see if different subsets of movements contribute differently to the mean activation. The pair includes (1) looking at cortical activity when behavioral parameters are similar and comparing that to cortical activity when they are different in order 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 (Figure 14A). The results from this test indicate that the observed bimanual effect did not differ significantly between “typical” trials and trials with an extreme trajectory (Figure 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 (Figure 16). Equivalent analyses are carried out for velocity profiles and EMG activation (Figures 14-16). 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.

Given this battery of tests, it is very unlikely that trial-to-trial variations in the animal’s performance of the task can explain the strong differences in cortical activity observed during unimanual as compared to bimanual task performance. However, it is impossible to completely rule out the possibility. It is possible that a strongly non-linear relationship between movement variations and neural activity would evade detection in our analyses, or that muscular activation was different during neural recording than it was during the pre-recording period in which we collected EMG activity. Indeed, it is possible that the neurons we recorded, though located in the proximal arm area of MI, were actually responsive to activity of the postural musculature that was not reflected either in movements of the manipulanda or in obvious movements of the monkey’s body. A number of considerations suggest that this is not the case. First, the axial muscles we examined were not at all active. This point is weakened because we only examined a couple of axial muscles; however, it seems reasonable that extensive postural changes would involve almost the entire axial musculature and could not leave the rhomboids and latissimus dorsi completely inactive. A second consideration is that the cortical representation of the axial musculature is rather small while we recorded from a large area. It is unlikely that our recording would have been dominated by the relatively small postural representation.

The second concern not addressed by our early work is the possibility that differences in cortical activation during bimanual arm movements are simply the result of some linear combination of unimanual activities. In the present 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 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.

It would be very difficult to rule out all of the possible alternative explanations of the “bimanual related” effect. Indeed, it is likely that to some degree each of these hypotheses – variations in the subtle aspects of the movements, linear combinations of unimanual activity, and postural adjustment – explains some fraction of the changes in MI and SMA between unimanual and bimanual arm movements. However, it seems that each of these hypotheses on its own is relatively weak, and that one likely and simple explanation for our results is that there is, indeed, activation of some neurons in MI specific to bimanual movements.

**Comparison to prior studies**

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 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 (Kermadi et al. 1998; Kazennikov et al. 1999: 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 (Kazennikov et al. 1999, page 666; compare with Kermadi et al. 1998; Tanji et al. 1988; the methods section of this paper).

When we apply our definition to their published data by combining the units in 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 (Kermadi et al. 1998; Kazennikov et al. 1999) often produced such activity. One explanation, discussed in detail elsewhere (Donchin et al. 1998; Donchin et al. 1999a), 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 are predominantly bilateral, whereas distal movements are represented as more or less simple combinations of unimanual movements. The other explanation 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 requirement. This bilateral suppression would be almost entirely the same in both unimanual and bimanual button pressing, leading to two conditions in which the motor task facing the monkey was quite similar. If MI activity reflects those aspects of the task that challenge the motor system more than
SMA, we might expect MI activation to be similar in the bimanual and the unimanual conditions while SMA activation would be different. In our study, the major training hurdle was in teaching the animals to achieve simultaneous onset and offset of the arm movements in bimanual movement, and immobility of the one arm while the other moved in a unimanual movement. 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.” One 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 reward rate would not be expected to influence the strength of the bimanual effect.

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.
Acknowledgments:

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### Tables

**Table 1: Movement times, Reaction times, and Interarm intervals**

<table>
<thead>
<tr>
<th></th>
<th>Monkey F</th>
<th></th>
<th>Monkey G</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unimanual</td>
<td>Parallel</td>
<td>Opposite</td>
<td>Unimanual</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>289 (36.4)</td>
<td>280 (42.8)</td>
<td>268 (29.9)</td>
<td>277 (29.7)</td>
</tr>
<tr>
<td>Right</td>
<td>238 (14.4)</td>
<td>247 (18.6)</td>
<td>248 (13.4)</td>
<td>233 (16.6)</td>
</tr>
<tr>
<td><strong>MT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>576 (72.1)</td>
<td>550 (79.1)</td>
<td>546 (73.4)</td>
<td>622 (48.3)</td>
</tr>
<tr>
<td>Right</td>
<td>647 (54.8)</td>
<td>631 (49.7)</td>
<td>597 (53.6)</td>
<td>596 (58.7)</td>
</tr>
<tr>
<td><strong>IAI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>38 (46.0)</td>
<td>25 (21.5)</td>
<td></td>
<td>29 (28.3)</td>
</tr>
<tr>
<td>End</td>
<td>-42 (70.7)</td>
<td>-27 (48.3)</td>
<td></td>
<td>-14 (40.8)</td>
</tr>
</tbody>
</table>

Means (standard deviations) 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.
Table 2: Activation of cells in MI and SMA

<table>
<thead>
<tr>
<th>Area</th>
<th>Monkey</th>
<th>Total number of neurons</th>
<th>Cells with significant activation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>During any movement</td>
<td>During unimanual movements (but not bi)</td>
</tr>
<tr>
<td>MI</td>
<td>F</td>
<td>100</td>
<td>90 (90%)</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>132</td>
<td>97 (73%)</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>232</td>
<td>187 (81%)</td>
</tr>
<tr>
<td>SMA</td>
<td>F</td>
<td>83</td>
<td>75 (90%)</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>123</td>
<td>82 (67%)</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>206</td>
<td>157 (76%)</td>
</tr>
</tbody>
</table>

The table shows the numbers (percentages) of neurons with significant differences between baseline activity and activity during the *activation epoch*. The table compares 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).
Table 3: Lateralized Activation of cells in MI and SMA

<table>
<thead>
<tr>
<th>Area</th>
<th>Monkey</th>
<th>During any unimanual movement</th>
<th>During unimanual contra movements (but not ipsi)</th>
<th>During both contra and ipsi unimanual movements</th>
<th>During unimanual ipsi movements (but not contra)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>F</td>
<td>81</td>
<td>30 (37%)</td>
<td>39 (47%)</td>
<td>13 (16%)</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>68</td>
<td>12 (31%)</td>
<td>31 (46%)</td>
<td>16 (24%)</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>149</td>
<td>51 (34 %)</td>
<td>69 (46%)</td>
<td>29 (19%)</td>
</tr>
<tr>
<td>SMA</td>
<td>F</td>
<td>70</td>
<td>15 (21%)</td>
<td>40 (57%)</td>
<td>15 (21%)</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>65</td>
<td>21 (32%)</td>
<td>32 (49%)</td>
<td>12 (18%)</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>135</td>
<td>36 (27%)</td>
<td>72 (53%)</td>
<td>27 (20%)</td>
</tr>
</tbody>
</table>

The table shows the numbers (percentages) 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, activeated 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).
Table 4: Categorization of Cells According to the Linear Model

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

The numbers (percentages) 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.
**Figure Legends**

**Figure 1: Trial schematic**

This schematic shows the time course of typical successful unimanual and bimanual trials. In all trials, two 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 one or two targets. The 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.

**Figure 2: Different trial types**

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

**Figure 3: Penetration maps**

Penetration maps for both hemispheres of two monkeys. Each square represents a 4-electrode penetration in the arm area of SMA. Each circle represents a 4-electrode penetration in the proximal arm area of MI. On some penetrations, fewer than four electrodes recorded isolated neurons. Penetrations are marked at the coordinates of insertion into the cortex. SMA penetrations were angled at 30° to the sagittal plane and advanced until they reached the medial cortex.

**Figure 4: Unimanual responses of MI cell**

This figure illustrates activity during unimanual movements of two neurons recorded in left MI of monkey F. A) Neuron with strong contralateral preference (laterality index = 0.59, equation 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 PSTHs were smoothed using a filter with a cutoff frequency of 100 ms and the bin width is 2.5 ms; they are all to the same scale. Each dot display shows 74 trials.

Figure 5: Contralateral preference in MI and SMA
The two histograms show that only a small difference exists in the laterality index (Equation 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). The bin width is 0.1.

Figure 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 (Equation 2) for this neuron is 0.63. Each row contains PSTHs and raster displays depicting the cell activity during performance of one type of bimanual movement and the two unimanual movements that comprise it (unimanual left handed movements in the middle column and unimanual right handed movements in the right column). The 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 first arm) and sorted by reaction time. The 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. The bin width is 2.5 ms. Each dot display shows 200 trials.
Figure 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 (in fact, it seems that activity is even suppressed in row C). The strength of the “bimanual related” effect is -0.84. Format is the same as in Figure 6. Each dot display shows 130 trials.

Figure 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. In order to allow comparison between the muscles, activity is normalized for each muscle: each plot is scaled from the muscles baseline activation to 1.5 its maximum activation across all movements. 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 is from monkey G.

Figure 9: Strength of the “bimanual related” effect

Each subplot shows a histogram of the “bimanual related” effect (Equation 2) for cells recorded in one cortical area of one monkey. Negative values indicate larger evoked activity during unimanual movements while positive values indicate larger evoked activity during bimanual movements. The activity changes during bimanual movements are as strong in MI as they are in SMA. The dotted line separates neurons with a significant “bimanual related” effect (p < 0.001, below the line) from those without a significant “bimanual related” effect. The bin width is 0.2.

Figure 10: Comparison of movement trajectories in different trial types

Plot of the movement trajectories for unimanual and bimanual movements. The mean (shown by the trajectory) and standard deviation (shown by the lines perpendicular to the trajectory) of the movements are shown. Standard deviations bars are drawn every 50 ms. Data is from one day of recording in
monkey G. The 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.

**Figure 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 is from the same day of recording in monkey G as the movement trajectories shown in Figure 10. The “bimanual related” effect is strongest between unimanual movements of the right hand to 270° and bimanual opposite movements in the same direction. The strength of this effect is 0.187.

**Figure 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 is from monkey G.

**Figure 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. The 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 to the strength of the “bimanual related” effect in the EMG.

**Figure 14: Separation analysis**

The figure shows an example of the separation analysis applied to each of the behavioral parameters. For each of 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. The left column shows the PSTH for the neuron during one type of unimanual trial in red. The right column shows the PSTH for the neuron during one type of bimanual movement in blue. The middle column shows the 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.

**Figure 15: Distribution of the separation index**

The gray histograms show the distribution of separation indexes (Equation 4) resulting from applying the separation analysis to “bimanual related” neurons in both MI and SMA. The black line shows the distribution of separation indexes resulting from randomly dividing trials into two 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.
Figure 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 one 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 one of the three parameters of the movements. The Spearman’s $r$ for the correlation between “bimanual related” effect and separation index is given in the upper right of each plot. (A) deviation from mean movement path, (B) maximum velocity, and (C) integrated RMS of the EMG.
Figure 5

Number of neurons

Contralateral preference

MI

SMA
Figure 6

Donchin et al.
Single unit activity in bimanual movements

Bimanual | Left Ipsilateral | Right Contralateral
--- | --- | ---
A | 0 & 0 | 0 | 0
B | 180 & 180 | 180 | 180
C | 0 & 180 | 0 | 180
D | 180 & 0 | 180 | 0

Time (ms) from -700 to 950

fer 13feb 96, Cell 16, Left hemisphere, Direction 0
Files: 9-77, #Trials: xxx
Figure 7

Donchin et al.
Single unit activity in bimanual movements

Time (ms)

Bimanual

45 & 45

225 & 225

45 & 225

225 & 45

Left
Contralateral

45

225

45

225

Right
Ipsilateral

45

225

225

45

for 27mar 96, Cell 0, Right hemisphere, Direction 45
Files: 17-85, #Trials: xxx
Figure 9

Donchin et al.
Single unit activity in bimanual movements

Figure 9 shows the strength of 'bimanual related' effect for Monkey F and Monkey G. The histograms display the number of cells vs. the strength of the bimanual related effect for MI and SMA areas.
Donchin et al.
Single unit activity in bimanual movements
Figure 11

Left Hand Velocities

Right Hand Velocities

<table>
<thead>
<tr>
<th>Unimanual</th>
<th>Parallel</th>
<th>Opposite</th>
</tr>
</thead>
</table>

gal 28aug
Figure 12

Left Deltoid

Right Deltoid

Time (ms)

-250 750

Unimanual
Parallel
Opposite

gal lt: 18feb 1; rt: 18feb 2
Figure 13

A

**MI**

Effect in movement path

-0.05

---

**SMA**

Effect in movement path

0.03

B

Effect in velocity profile

0.11

---

Effect in neuron

0.02

---

Effect in neuron

C

Percentage of neurons/muscles

- MI (232)
- SMA (206)
- EMG (72)

---

Effect in neurons/muscles
Figure 14

A  
Unimanual Left  
Movement paths  
Bimanual Opposite

B  
Unimanual Right  
Velocities  
Bimanual Opposite

C  
Unimanual Left  
Anterior Deltoid  
Bimanual Parallel

---

Donchin et al.

Single unit activity in bimanual movements

Figure 14

for 4mar 16; 22–59; UniLt 45 BiOpp 45
for 7apr 24; 24–79; UniRt 45 BiOpp 225
gal 1-jun 6; 40(5)–48(51); EMG1; UniLt 315 BiDir 315
Figure 16

Strength of "bimanual related" effect