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Research Article

Local field potentials related to bimanual movements in the primary and supplementary motor cortices

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Abstract. We recorded local field potentials (LFP) in primary (MI) and supplementary (SMA) motor areas of rhesus monkey cortex in order to compare movement-evoked potentials (mEP) in bimanual and unimanual movements with single-unit activity recorded concurrently. The mEP was often different during bimanual and unimanual movements (a "bimanual-related" effect), but, unlike the single units, the size of the mEP in both MI and SMA was always greater during bimanual movements than during unimanual movements. This increase primarily reflected an increase in the late positive peak of the mEP, a result that may reflect greater overall cortical activation during bimanual movements. In addition, analysis of the mEP revealed differences between MI and SMA not seen in the single-unit activity. mEP in MI had greater contralateral preference than in SMA. Also, SMA mEP was more correlated to the single-unit activity than in MI. This greater correlation was also more apparent in the late peaks of the mEP than in the early peaks and may reflect a greater influence of recurrent activation in SMA than in MI. Our results further reinforce the idea that unimanual and bimanual movements are represented differently both in MI and in SMA and also show that a complex relationship between spikes of individual neurons and LFP may reflect the different input-output relations of different cortical areas.

Keywords. Motor cortex - Supplementary motor area - Frontal cortex - Movement physiology - Bimanual coordination - Single-unit recording - Evoked potentials - Rhesus monkey

Introduction

Single neurons in the proximal arm area of primary motor cortex (MI) and the arm area of supplementary motor cortex (SMA) behave differently during bimanual and unimanual movements (Donchin et al. *1998*;Donchin O, Gribova A, Steinberg O, Bergman H, Vaadia E, unpublished work). This paper analyzes local field potential (LFP) during bimanual movements. LFP is a signal that arises largely as a result of synaptic activity in the area of the recording electrode (Mitzdorf *1994*). The relationship between LFP and the activity of individual neurons remains unclear: there is evidence that they are highly correlated (Laas *1968*; Kenmochi and Eggermont *1997*), but other evidence shows that this correlation can vary over time (Murthy and Fetz *1996a*) or depend on context (Eggermont and Mossop *1998*), and that the response properties of the LFP and single units may differ (Mitzdorf et al. *1994*). In human motor cortex, studies have addressed the complex sequence of evoked EEG potentials preceding movement (Shibasaki *1975*; Lang et al. *1990*; Cui and Deecke *1999*). However, animal research on field potentials in motor cortex has focused on the relationship of synchronous oscillations to movement and to single-unit activity (Eckhorn and Obermueller *1993*; Sanes and Donoghue *1993*; Murthy and Fetz *1996b*; Donoghue et al. *1998*; Baker et al. *1999*). The character of the evoked potential in this area and its relationship to movement has not been fully explored.

The interpretation of the LFP has been hindered because its source is poorly understood. It is widely accepted that strong negative deflections reflect excitatory, spike-causing input to neurons in the neighborhood of the electrode (Arieli et al. *1995*). Current source density analyses of LFP can be used to determine the cortical layers in which synaptic currents are generated, and, in primary sensory cortices, such analyses have provided an interesting picture of the spatiotemporal events underlying sensory processing. These results allow interpretation of the LFP evoked by sensory stimulation (Mitzdorf *1985*, *1987*), but it is not clear whether such studies would have relevance for other cortical areas, particularly agranular cortex, or in animals which are actively performing a task. In this study, we present an analysis of the activity evoked in the LFP by movement, analyze the relationship of different components of the LFP signal to a motor task, and compare the activity in the LFP with activity in single units.

Methods

Behavioral paradigm and data acquisition

The task is identical to that described by Donchin et al. (*1998*; O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work). Two female rhesus monkeys (*Macaca mulatta*; monkey F, 4 kg, and monkey G, 3.5 kg) were trained to operate two separate low-weight, low-friction manipulanda. Each manipulandum was controlled with one arm and restricted to move in the horizontal plane; its motion controlled the motion of a corresponding cursor on a vertically oriented video screen placed in front of the monkey. The monkey was trained to use the manipulanda to perform unimanual movements (of either the right or the left arm) and bimanual movements (using both arms). During unimanual movements, the monkeys were required to keep the nonmoving arm still, and, during bimanual movements, the monkeys were required to begin and end movements of both arms simultaneously. All movements were made from central "origin" locations located in front of each of the monkeys shoulders and ended on circles of radius 3 cm around these origins.

Two recording chambers (27 × 27 mm) were surgically implanted above the left and right

hemispheres of the monkeys while they were under general anesthesia, in aseptic conditions. The animals' care and surgery procedures were in accordance with *The NIH Guide for the Care and Use of*

Laboratory Animals (revised 1996) and the Hebrew University regulations. Neural activity was recorded by eight glass-coated tungsten microelectrodes (impedence 0.2-0.8 MΩ at 1 kHz) from homologous sites in the two hemispheres (four electrodes in each hemisphere). Location of MI and SMA was determined using microstimulation and neural response during passive manipulation of the joints, as well as from the sulcal pattern seen during surgery. Interelectrode distance was approximately 500 μm at the dura. However, since the electrodes were individually driven, this distance only reflected the perpendicular dimension, and the interelectrode difference in depth varied from recording session to recording session.

The neural signal recorded on each electrode was amplified and filtered (MCP, Alpha-Omega, Nazareth, Israel) in two different ways to generate two different signals. One bandpass filter (300-8,000 Hz) was used to generate the signal from which we isolated the action potentials of individual neurons, and the analysis of that signal is reported by Donchin et al. (O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work). A second bandpass filter from 1 to 140 Hz was used to generate an LFP signal. This signal was sampled continuously at a rate of 400 Hz using in-house software built around data acquisition boards (DAP 3200e; Microstar Laboratories, Bellevue, Wash.) on a personal computer. Fifty-hertz noise caused by the A/C power supply was removed using a notch filter applied digitally after data collection (48- to 52-Hz, 4-pole Butterworth applied forward and backward to prevent phase shift). There were two different types of recording sessions: those involving two directions of movement and those involving eight directions of movement.

In order to allow pooling of the data, data analysis in this paper (O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work) is restricted to movements in two directions. That is, for each of the eight-directions sessions, we restricted our analysis to data from two directions. This was done by determining the mean preferred direction of single units recorded by that electrode and choosing the direction of movement which was closest to that averaged preferred direction as well as the direction 180° from that preferred direction. Analysis of data recorded from all eight directions is deferred to a later paper.

Data analysis

Some sites were excluded from analysis: those at which no single units were recorded, those where examination of the LFP during recording revealed recurring artifacts, and those where 50-Hz noise remained more than 1% of the power of the signal even after filtration. We examined the stability of the activity during both baseline and response periods. All further analysis was restricted to periods in which the electrode activity was stable.

LFP was averaged by aligning trials on the beginning of movement as described by Donchin et al. (O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work). We called the resulting mean the movement-evoked local field potential (mEP). Figure 1 demonstrates a few examples of individual LFP traces and the mean of 101 traces from which the examples were taken.

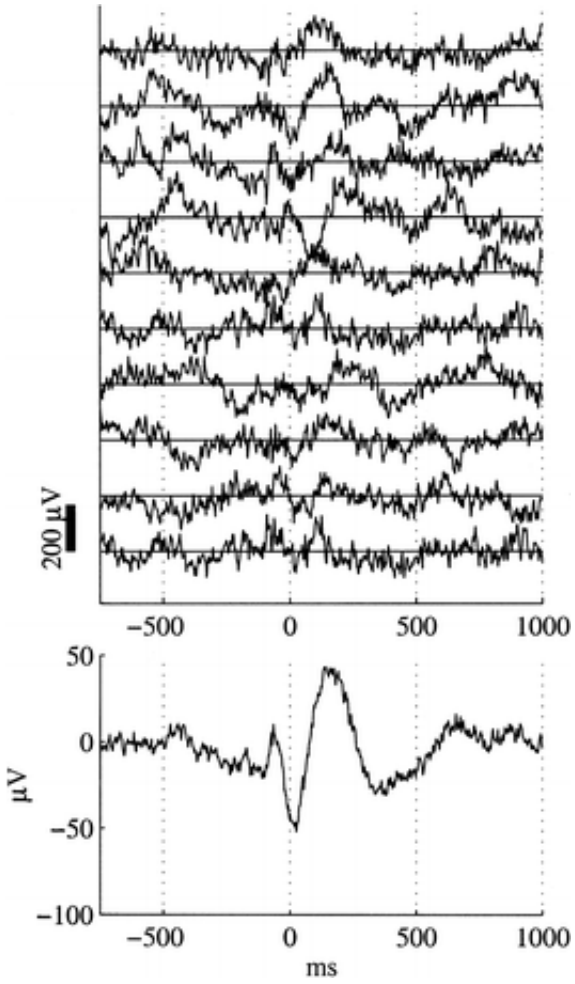

Fig. 1A,B. Local field potential (LFP) traces and averaged LFP. **A** Ten examples of individual LFP traces selected at random from one recording site in left primary motor cortex. These examples are taken from instances where the monkey was making unimanual right-handed movements toward 225°, and they are aligned at the beginning of movement (time zero). **B** The mean of all 101 LFP traces recorded during repetitions of the same movement

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The mEP had a characteristic shape (exemplified in Fig. 1) that we divided into four recurring peaks that were analyzed separately. The algorithm for dividing the mEP into peaks was as follows (see Fig. 1):

1. We found the minimum value in the range -250 ms to 250 ms around movement onset. From the first absolute zero crossing of the signal before this minima to the first zero crossing after this minima was area N1.

2. We then searched for a positive peak preceding N1, searching back up to 250 ms before the beginning of area N1. From the zero crossing before this maximum to the zero crossing after this maximum was area P1.

3. Similarly, area P2 enclosed the maximum in the range from the end of area N1 to 500 ms after the end of area N1.

4. Area N2 enclosed the minimum found between the end of area P2 and 500 ms after the end of area P2.

The algorithm depends on the fact that there is no DC offset in the LFP signal, so that zero volts is the overall mean of the LFP signal over time. This is indeed the case. Occasionally, any one of these peaks might not be significantly different from the noise; however, the algorithm did not treat such cases differently. For each of these areas we took the square root of the integral of the square (rms) of the mEP enclosed in that area as a measure of the strength of the peak (Eq. 1). We estimated the standard deviation of this value by projecting the signal in each trial onto the mean signal (in the window that defined the peak; Eq. 2) and then taking the standard deviation of these values (Eq. 3):

$$rms = \sqrt{\sum_{t=window\ start}^{window\ end} \overline{LFP}^2(t)} \quad (1)$$

$$projection_i = \sum_{t=window\ start}^{window\ end} \left(LFP_i(t) \cdot \overline{LFP}(t)\right) / rms \quad (2)$$

$$\sigma_{rms} = \sqrt{\frac{\sum_i \left(projection_i - \overline{projection_i}\right)^2}{N}} \quad (3)$$

(A bar over a value indicates the averaged quantity of that value across trials.) The overall rms was also calculated in a window extending from 250 ms before movement onset to 700 ms after movement onset, and the standard deviation of projections onto the mean was calculated as with the other areas. Significant differences between two mEPs were detected by *t*-tests, and the nominal threshold for significance was α <0.001. We also repeated the analyses using the maximum and minimum values of each area and of the whole signal but, since the results were the same as with the rms values, we do not present them here.

The contralateral preference of the mEP at a recording site was calculated using the formula:

$$Contralateral\ preference = \frac{contralateral\ mEP - ipsilateral\ mEP}{\sigma_{mEP}} \quad (4)$$

Out of the two unimanual contralateral movements performed during the recording of each LFP, we selected the one where the mEP was greatest. Similarly, out of the two unimanual ipsilateral movements, we selected the one which evoked the greater mEP. Thus, this is a comparison of the maximal mEP during a contralateral movement with the maximal mEP during an ipsilateral movement. σ_{mEP} is the standard deviation combined from the mEP in the two movements. The standard deviations were combined using the standard weighted average:
$\sigma_{12} = \sqrt{\left((N_1 - 1)\,\sigma_1^2 + (N_2 - 1)\,\sigma_2^2\right) / (N_1 + N_2 - 1)}$, where N_1 and N_2 are the number of trials over which each standard deviation is calculated. The strength of the "bimanual-related" effect

was generated using a very similar formula:

$$Effect\ Strength = \frac{bimanual\ mEP - unimanual\ mEP}{\sigma_{mEP}} \quad (5)$$

where σ_{mEP} is now calculated using the standard weighted average to combine the unimanual and bimanual standard deviations. This measure was calculated four times (once for each type of bimanual movement), and in each case the mEP was compared with the stronger of the two associated unimanual mEPs. The most significant of these differences, as determined by a *t*-test on the two responses, was taken to be the strength of the bimanual-related effect. Because four *t*-tests were performed in generating the final significance value, the actual significance is overestimated. One simple correction that can be used is to multiply the final significance achieved by the number of tests. While this is not an exact correction, it is generally conservative (that is, it underestimates the statistical significance). In our case, the probability was multiplied by 4 to account for the repeated tests. Selection of the maximally significant effect produced bimodal distributions of effect strength. As a result, nonparametric statistical tests were used when analyzing these distributions. We used the binomial test on the signs to test whether the bimanual-related effect was significantly skewed in the positive or negative direction and the Mann-Whitney *U*-test to compare the distributions. The bimanual-related effect is also presented when calculated separately for each bimanual movement type.

In addition, we calculated the degree of correlation between the mEP recorded by an electrode and the single units recorded by the same electrode. Correlations in this paper are calculated on the averaged activity correlated across recording sites and not, as is more common, on the trial-by-trial activation correlated within a given recording site. This reflects an interest in the task-related characteristics of the LFP and its relation to the task-related characteristics of single-unit activity. We address trial-by-trial correlations in a separate paper (S. Cardoso de Oliveira, O. Donchin, A. Gribova, H. Bergman, E. Vaadia, unpublished work).

For the purposes of calculating correlations, the single-unit firing rate was averaged over all trials from activation onset (as determined by a CUSUM algorithm; O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work) through 500 ms after activation onset. Baseline firing rate for a neuron was averaged from 300 ms before activation onset to 50 ms before activation onset. The measure of neural activation used in the correlations was:

$$neural\ activation = \frac{abs(activated\ firing\ rate - baseline\ firing\ rate)}{\sigma_{response}} \quad (6)$$

Similarly, for the LFP, the measure of response was:

$$LFP\ activation = \frac{rms_{peak}}{\sigma_{peak}} \quad (7)$$

where *peak* indicates one of N1, P1, N2, P2, or the overall rms as already described. For correlation of the activation of a neuron with the LFP, we chose either those movements for which the neuron was most responsive or those movements in which the mEP was greatest and performed the analysis on these two possibilities separately. For correlation of the contralateral preference or the

bimanual-related effect, we calculated the measures for the single-unit activity in the same manner as they were calculated for the mEP. The strength of these correlations was assessed using Spearman's *r*, a nonparametric measure of correlation, and the significance of this statistic was tested using the standard transformation to Student's *t*-distribution.

Results

Recording sites

The database included a total of 96 penetrations (usually paired simultaneous recordings at four recording sites in both the left and the right hemisphere), which included 347 recording sites. Of all the recording sites, 117 passed our criteria for continued analysis: 45 recording sites in MI (35 from monkey F and 10 from monkey G) and 72 recording sites in SMA (44 from monkey F and 28 from monkey G).

Shape of the mEP

mEPs were recorded in both MI and SMA in nearly every recording site with a characteristic shape. This characteristic shape can be demonstrated by averaging the mEPs recorded at all different recording sites (Fig. 2). The peaks we characterized in the Methods section can be clearly seen in the means from each recording area in both monkeys. Table 1 shows that peaks N1 and P2 were significant in 80% or more of the mEPs in both SMA and MI, and that peak P1 was less often significant than the others. Table 1 also shows a weak tendency for the mEP to include several (or all) peaks more often than expected by chance. This is an additional indication that the shape of the evoked mEP is preserved across different recording sites.

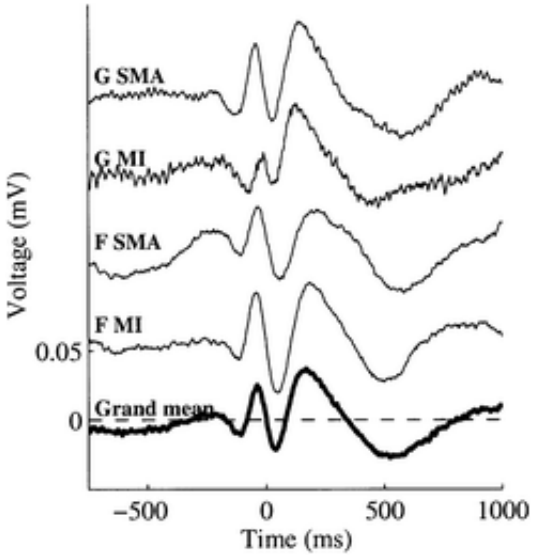

Fig. 2. Grand mean of LFP by monkey and area. The LFP averaged across recording sites in primary motor cortex (*MI*) and supplementary motor area (*SMA*) in each monkey, as well as the grand mean over all recording sites. Each trace has been offset by a fixed amount, but all are shown to the same scale; the means are similar

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Table 1. Percentages of significant peaks in movement-evoked local field potential (mEP). The numbers (and percentages) of mEPs in which each peak was significant, and the number of mEPs (and percentage of mEPs) in which two peaks were simultaneously significant. Where the simultaneous occurrence of peaks is shown, the first percentage is the actual value, and the second is the expected percentage under an assumption of independence [expected(peak1, peak2)=actual(peak1) × actual(peak2)/100]. Note that the actual percentage is always slightly greater than the second in the combinations of the individual peaks. The two percentages are equal in combinations of peaks with the overall rms because it was always significant

	P1		N1		P2		N2		Overall rms	
	n	%	n	%	n	%	n	%	n	%
MI	168/352	48	289/352	82	288/352	82	253/352	72	352/352	100
P1			153/352	43; 39	154/352	44; 39	129/352	37; 34	168/352	48; 48
N1					248/352	70; 67	223/352	63; 59	289/352	82; 82
P2							220/352	63; 59	288/352	82; 82
N2									253/352	72; 72
SMA	329/568	58	448/568	79	515/568	91	451/568	79	568/568	100
P1			268/568	47; 46	311/568	55; 53	270/568	48; 46	329/568	58; 58
N1					422/568	74; 72	376/568	66; 63	448/568	79; 79
P2							421/568	74; 72	515/568	91; 91
N2									451/568	79; 79

Evoked potentials during unimanual movements

Figure 3 shows the contralateral preference (Eq. 4) of recording sites in MI and SMA for the overall rms. A dotted line separates those recording sites for which a *t*-test indicated a significant difference in contralateral and ipsilateral activation of the peak (below the line) from those in which there was no significant difference (above the line). While for many of the recording sites there is not a significant difference between bimanual and unimanual activation, testing the distributions showed that the mean contralateral preference of the overall rms in MI was significantly greater than 0 at $P<0.001$. Figure 4 extends this analysis to the separate peaks in the mEP. The contralateral preference of peak P2 in MI was significantly greater than 0 at $P<0.001$. The mean of the contralateral preference of peaks P1 and N2 in MI was significantly greater than 0 at $P<0.01$. In contrast, in SMA, the means of the contralateral preference of peaks N1 and N2 were both less than zero ($P<0.01$ and $P<0.05$, respectively). Thus, MI shows a strong contralateral preference not shared by SMA, which shows a slight preference for the ipsilateral arm.

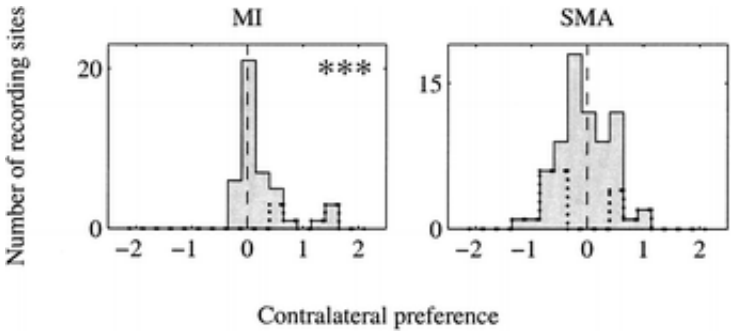

Fig. 3. Contralateral preference in the movement-evoked local field potential (mEP) during unimanual movements. Each histogram shows the contralateral preference of the overall rms of the mEP in either MI or SMA. The rms is taken during the movement in which activity was strongest for each type of movement (which is not necessarily the same direction). *Positive numbers* represent larger rms during movements of the contralateral arm. The histogram *below the dotted line* represents those recording sites in which a two-tailed *t*-test showed a significantly greater activation during either contralateral or ipsilateral movements. For all histograms, *asterisks* indicate significant deviation from zero toward the side on which the histogram appears (***$P<0.001$)

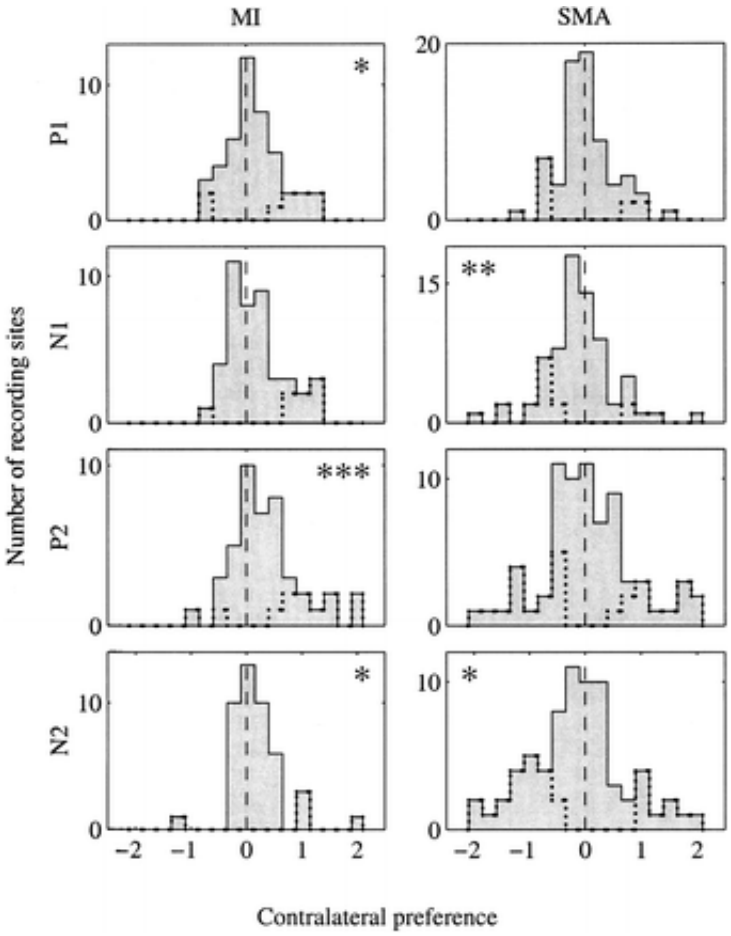

Fig. 4. Contralateral preference for different peaks. Each histogram shows the contralateral preference of the rms of one of the peaks in the mEP from either MI or SMA. Format is as in Fig. 3 (*P<0.05; **P<0.01; ***P<0.001)

Evoked potentials during bimanual movements

Figure 5 shows the mEP during unimanual and bimanual movements at a recording site where the difference between bimanual mEP and contralateral mEP is quite small. However, even in this example, the small effect (bimanual-related effect of 0.50; Eq. 5) is significant at P<0.001; this is because there is a significant difference between the bimanual activity in row 2 (bimanual parallel movement to 270°) and the unimanual activity. The value of the bimanual-related effect for each peak is as follows: P1, 0.27; N1, -0.24; P1, 0.82; N2, -0.68. Of these, peak P2 and peak N2 have significant bimanual-related effects at P<0.001. Figure 6 shows the LFP recorded at a different site in MI. Here the difference between the mEP during bimanual movements and unimanual movements is more striking. This is particularly evident in bimanual parallel movements to 315°, where the strength of the bimanual-related effect in the overall rms is 2.60 (broken down by peak: P1, -0.06; N1, 2.08; P2, 2.56; N2, -1.08. All peaks except P1 are significantly bimanual-related at P<0.001). A final example taken from SMA is shown in Fig. 7. Here, the strength of the bimanual-related effect for the overall rms is 1.33 as measured in bimanual parallel movements to 270° (P1, 0.35; N1, 0.90; P2, 1.49; N2, -1.17. All peaks except P1 are significant at P<0.001).

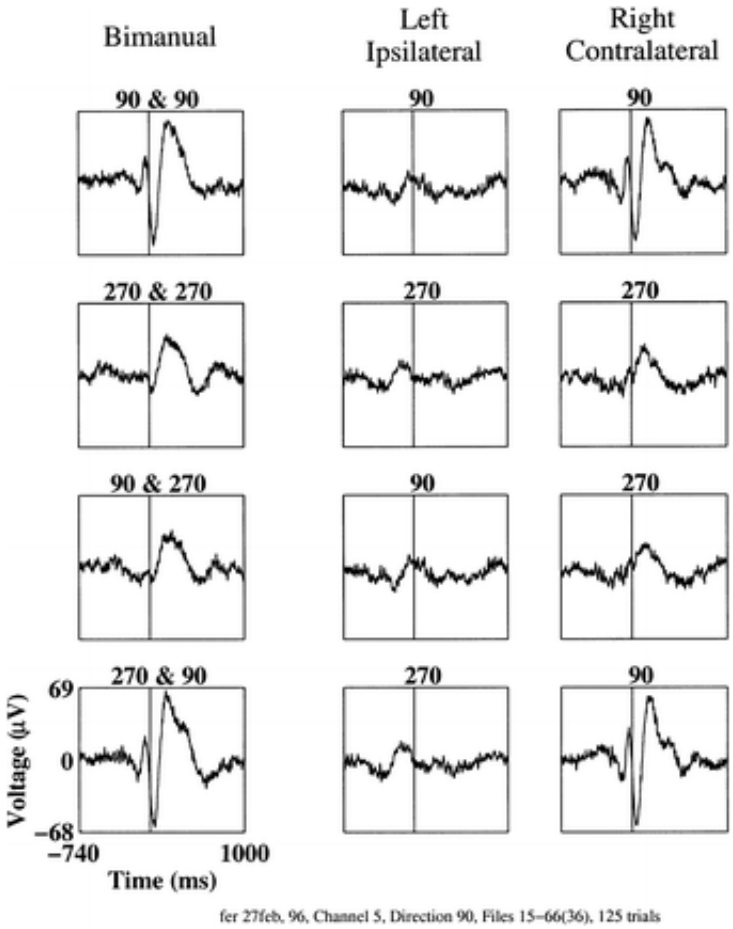

Fig. 5. Example of a recording site in MI with a small "bimanual-related" effect. Each *row* shows the mEP in one bimanual movement and the two unimanual movements that comprise it. All plots are at the same scale for both the *x*- and *y*-axes. *Numbers above each plot* indicate the direction of hand movement in degrees (with zero to the monkeys' right and positive degrees measured counterclockwise). Each trace is a mean over 125 trials

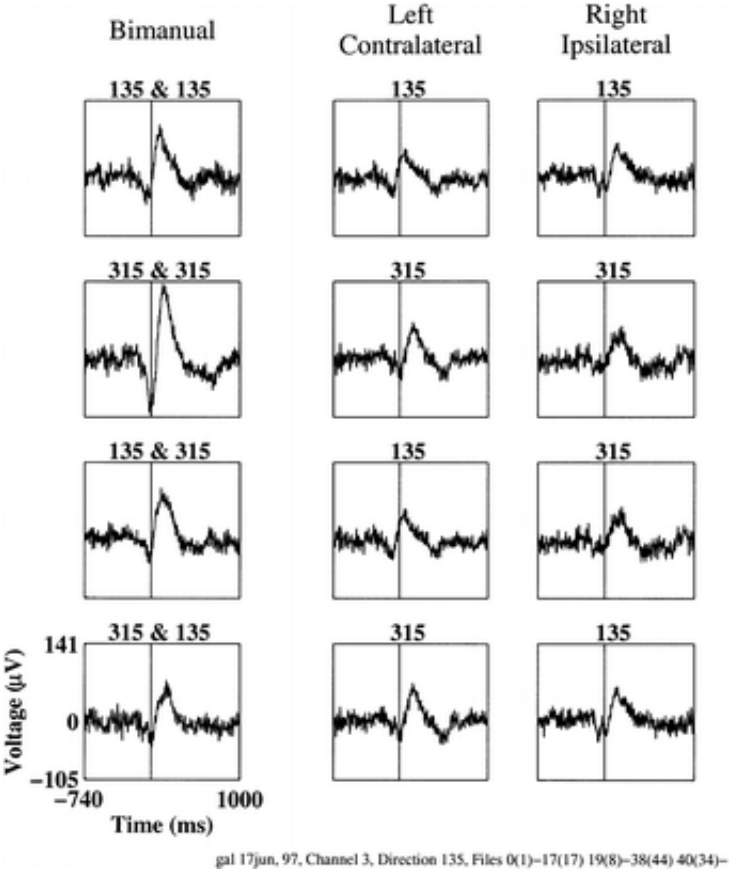

Fig. 6. Example of bimanual-related activity in MI. The format is as in Fig. 5. Each trace is a mean over 65 trials

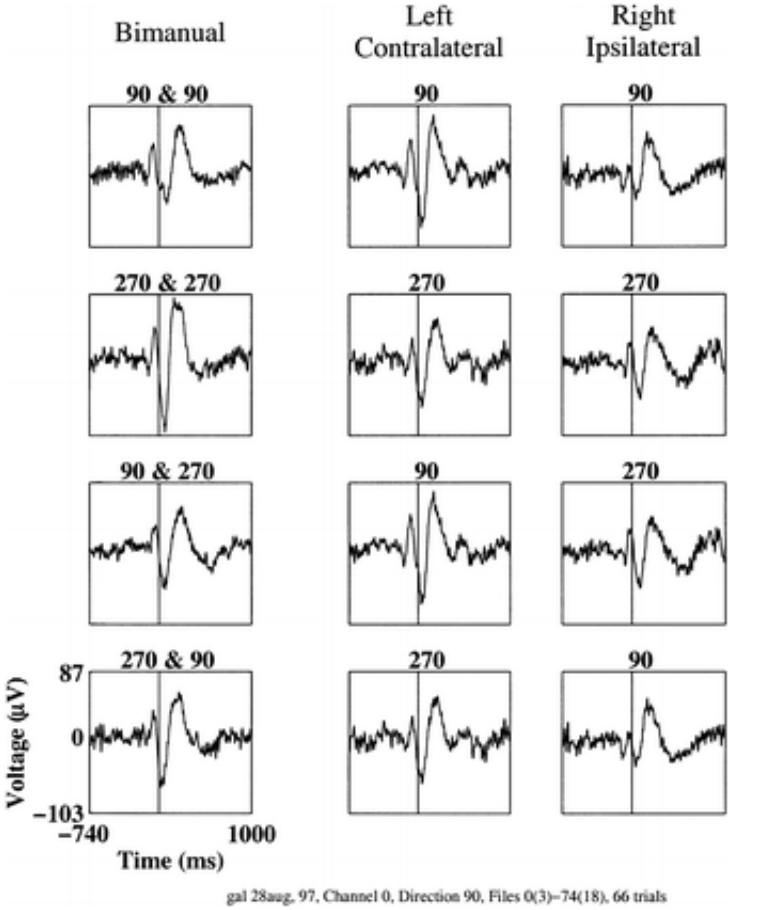

Fig. 7. Example of bimanual-related activity in SMA. The format is as in Fig. 5. Each trace is a mean over 66 trials

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Figure 8 demonstrates that positive bimanual-related effects in the overall rms characterize the population. The figure shows the bimanual-related effect for all recording sites in both MI and SMA for the full mEP. For both, the rms is greater during bimanual movements than during unimanual movements for nearly all recording sites. Figure 9 shows the bimanual-related effect in the different peaks. A binomial test on the signs shows that peak P1 in the SMA is significantly stronger during unimanual movements ($P<0.001$), and that peak P2 in both MI ($P<0.001$) and SMA ($P<0.01$) is significantly stronger during bimanual movements. Mann-Whitney tests comparing the distribution of the bimanual-related effect in MI and SMA showed significant differences ($P<0.01$) in peaks P1 and P2.

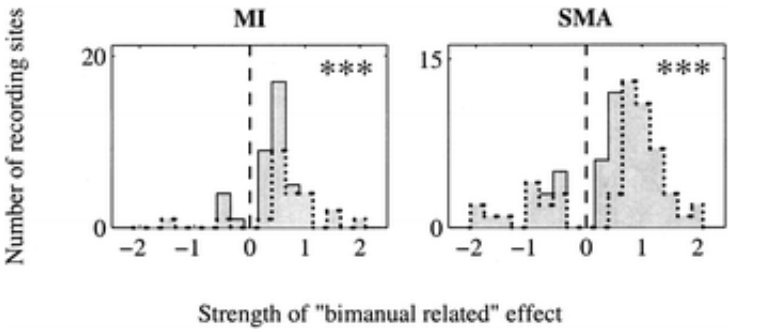

Fig. 8. Strength of bimanual-related effect in the mEP. The histograms show the strength of the bimanual-related effect in the overall rms of the mEP in MI and SMA. *Below the dotted line* are recording sites for which the bimanual-related effect was significant. (***P<0.001)

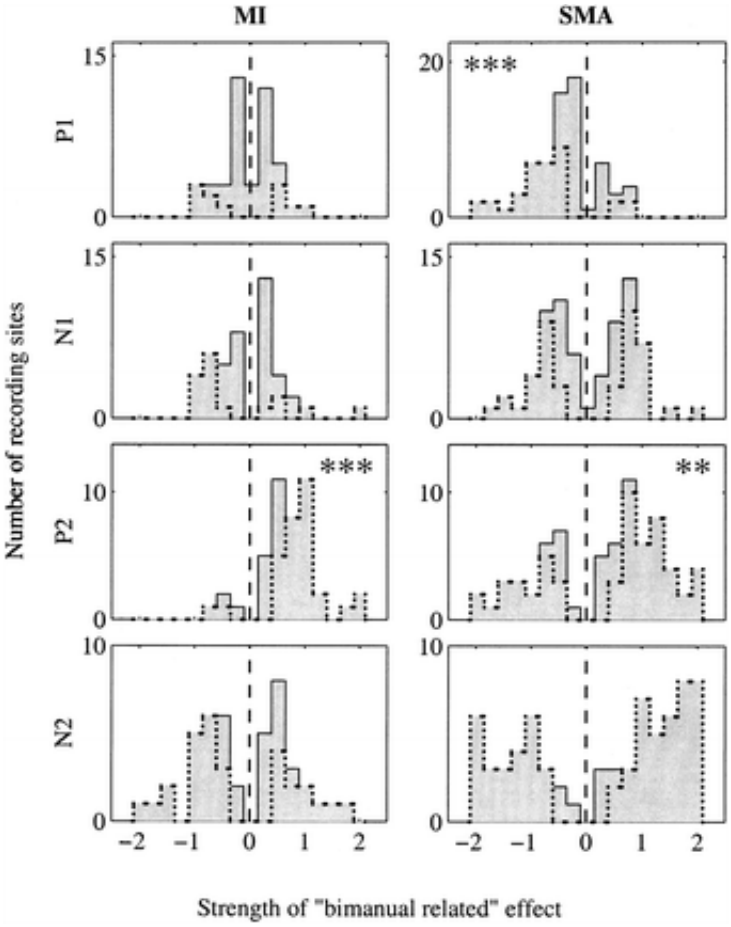

Fig. 9. Strength of signed bimanual-related effect in different peaks. Each histogram shows the strength of the bimanual-related effect for the rms of one of the peaks of the mEP. Format is as in Fig. 8. ***P*<0.01; ****P*<0.001

Figures 8 and 9 do not rule out the possibility that the overall rms of the mEP was larger during some bimanual movements but smaller during others. Figure 10 repeats the analysis of Fig. 8, but includes all four bimanual movements in the analysis rather than selecting the largest effect. The figure clearly indicates that most bimanual mEPs in both MI and SMA were larger than the associated unimanual mEPs (*P*<0.001). A comparison of the distributions failed to find any significant difference between them.

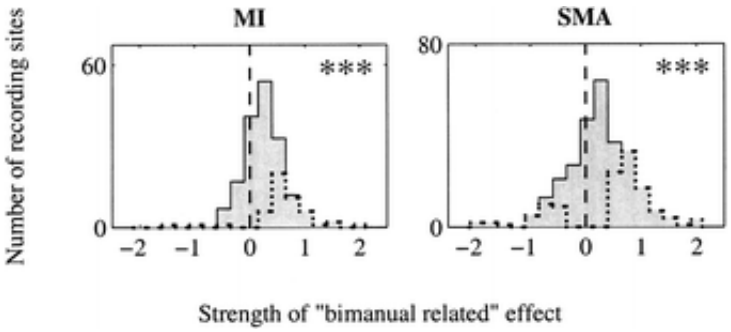

Fig. 10. Bimanual-related effect in all four bimanual movements. The bimanual-related effect has been calculated separately for each movement. Each recording site thus contributes four values to one histogram. The format is the same as Fig. 8. (***P<0.001)

In sum, for nearly all recording sites, bimanual mEPs are greater than unimanual mEPs, and this increase is caused by an increase in the positive components of the mEP, particularly P2. This result is different from the single-unit result (O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work), where the bimanual-related effect can be either an increase or a decrease in activity during bimanual movements.

Correlation of single-unit activity with LFP

In order to compare the functional relationship between the LFP and single-unit activity, we looked for correlations between the firing rate of single units (averaged over trials) and the mEP. We first explore general task-related correlation between the largest activity evoked in a single unit and the mEP recorded simultaneously or between the largest mEP at a recording site and the firing rate of cells recorded at the same site. Table 2 shows the outcome of this analysis: the correlation between the rms of the mEP (measured using Eq. 7) and the response of neurons recorded on the same electrode (measured using Eq. 6). The analysis was performed either by including that movement type for which the neuron responded most strongly (Max Cell w/LFP) or by including that movement type for which the mEP was strongest (Max LFP w/Cell), so that the correlation coefficients are always calculated with data from the same types of movements in the neural data and the mEP. mEP is significantly related to neuronal activity in SMA but not in MI. Further, the relationship is significant (P<0.001) when examining the firing rate in those movements where the LFP was strongest but less so (P<0.05) when examining the LFP in those movements where neuronal response was greatest.

Table 2. Correlation between maximal single-unit response and maximal mEP. The correlation of the response of single units recorded by an electrode with the size of the mEP recorded by the same electrode. In the *Max Cell* columns, the firing rate during movements in which the neuron was most responsive was paired with the mEP during that movement. In the *Max LFP* columns, the movement selected was that in which the LFP was maximal, and the neural activity was taken from that movement also

		MI		SMA	
		Max Cell w/LFP	Max LFP w/Cell	Max Cell w/LFP	Max LFP w/Cell
Peak	P1	0.09	-0.05	0.01	-0.17
	N1	0.14	0.04	0.29*	0.17
	P2	-0.02	0.02	0.24*	0.38**
	N2	-0.01	0.16	0.20	0.33**
Overall rms		-0.03	0.24*	0.30*	0.37**

Numbers shown are Spearman's *r*. *Significance at $P<0.05$; **significance at $P<0.001$

We next examined correlations in more specific aspects of mEP activity and single-unit activity. First, we asked whether contralateral preference in single units was similar to the contralateral preference of the mEP recorded at the same site. Figure 11 shows that, while in MI there is no such relationship between the contralateral preference in the mEP and in the single-unit activity, the results in SMA are less clear. For peaks P1 and N2, Spearman's *r* is weakly significant in SMA ($P<0.05$). In fact, all of the mEP peaks in SMA showed a (positive or negative) correlation of contralateral preference with the single units with $|r|>0.1$, while for MI all of the peaks had $|r|<0.1$.

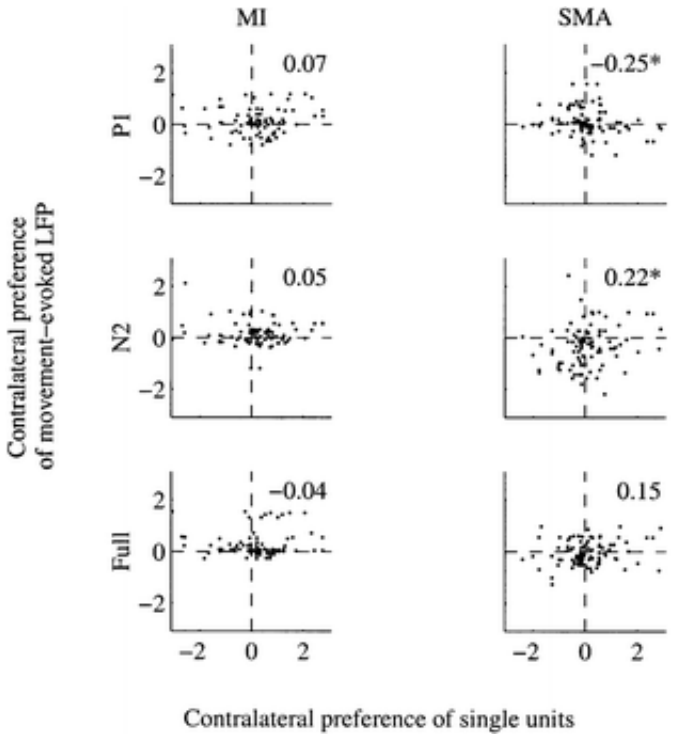

Fig. 11. Correlation of contralateral preference in LFP and single units. This figure demonstrates that contralateral preference in LFP and units in SMA are more strongly related than in MI. Only those peaks which were significant in SMA ($P<0.05$) and the overall rms are shown. Numbers in each plot are Spearman's r. (*$P<0.05$)

We also compared the strength of bimanual-related activation in the mEP and simultaneously recorded single units. Bimanual-related effects can be positive or negative (in single units they are often both, while in the mEP they are always positive) so we repeated the analysis both on the signed and on the absolute values of the effect. The analysis of the signed effect produced lower correlations (not shown) than the analysis of the absolute values (Fig. 12). The correlation of the bimanual-related effect in the N2 peak of the mEP with the bimanual-related effect of neurons recorded by the same electrode is highly significant in SMA and weakly significant in MI. The bimanual-related effect in the overall rms in SMA is also weakly correlated with the bimanual-related effect in the neurons. Here, as in the other correlation analyses, the late mEP in SMA is more strongly correlated with the single-unit activity than it is in MI.

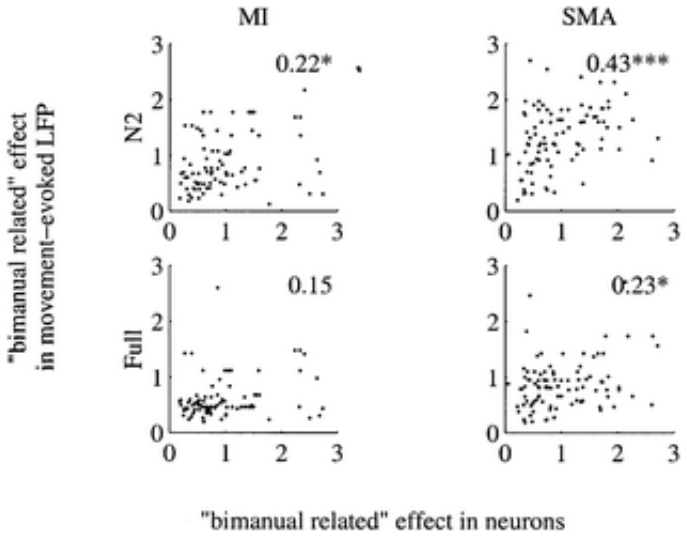

Fig. 12. Correlation of bimanual-related effect in single-unit activity and LFP. Format is similar to Fig. 11, but here the absolute value of the bimanual-related effect is compared rather than contralateral preference. Only those peaks with a significant correlation in either MI or SMA are shown. (*P<0.05)

Discussion

Bimanual-related effect always positive in the mEP

This paper analyzes the LFP, a mean of electrical fields from the vicinity of the electrode. We find that a bimanual-related effect exists in the LFP, as it does in the single-unit activity (Donchin et al. *1998*; O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work). The bimanual-related effect in the LFP is different from the effect in the single units. In the LFP, activity during bimanual movements (as measured by the overall rms of the mEP) is always greater than activity during unimanual movements; whereas, in the single units, the bimanual-related effect was as often a decrease in bimanual activation as it was an increase. The unidirectional nature of the bimanual-related effect in the LFP supports the hypothesis that the motor cortices represent bimanual movements differently from unimanual movement (Donchin et al. *1998*; O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work). Apparently, bimanual movements require neuronal control beyond simultaneous production of two unimanual control signals. However, while providing support to the hypothesis above, the result raises its own questions. Is there any physiological explanation for the increased LFP activation during bimanual movements? Is there any functional significance for the result?

There are four (not mutually exclusive) possibilities that offer an immediate explanation for the increased mEP during bimanual movements:

1. Neurons are more active in the area of the electrode.

2. Those neurons active in the area of the electrode are better aligned.

3. More neurons are active far from the electrode with efferent connection to the area of the electrode.

4. The synaptic activity in the area of the electrode is more synchronized.

The first possibility can be rejected because, as we have shown (O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work), the number of active single units and the mean firing rate do not increase in either MI and SMA during bimanual movements. The second possibility would be difficult to prove or disprove, and may warrant further investigation. Specifically, if pyramidal cells tend to show increased activity during bimanual movements, while interneurons tend to show decreased activity, then the greater anatomical alignment of pyramidal dendrites might lead to an overall positive effect on the mEP.

The fourth possibility is particularly intriguing in light of recent disagreements about the functional significance of neural synchronization. Work on synchronization of LFP oscillations has shown a relationship between synchronized oscillations in the LFP and synchrony in single-unit activity (Murthy and Fetz *1996b*), but research which specifically studied bimanual movements did not find increased LFP synchrony during these movements (Murthy and Fetz *1996a*). However, this negative finding is inconclusive because these studies analyzed periods of LFP synchrony rather than evoked potentials, and it is still possible that increased neuronal synchrony would correlate well with increases in mEP. Studies of unimanual movements suggest that synchronized activity is decreased during movements in the oscillatory components of the LFP (Sanes and Donoghue *1993*; Donoghue et al. *1998*) and that LFP oscillation is phase-locked to the single-unit activity (Baker et al. *1999*), results which suggest that there may be no functional role for synchrony during movements. However, it is feasible that, specifically during bimanual movements, synchrony does have such a functional role.

The second of the three possibilities listed above is not implausible. While for any particular neuron maximal bimanual activation may be less than maximal unimanual activation, it is still possible that the sum of bimanual activation across both hemispheres is more than the sum of unimanual activation. For instance, neurons in left cortex may be more active during movements of the right arm, while neurons in right cortex are more active during movements of the left arm, but during bimanual movements both sets of neurons are active (see Table 3). Since MI and SMA receive input from both contralateral and ipsilateral cortex, the amount of input each cortical area receives may be greater during bimanual movements than during unimanual movements. A group investigating the neuronal response as a function of stimulus size in visual cortex found a similar result: induced oscillations in LFP increase with increased stimulus size while single-unit discharge rates may increase or decrease (Bauer et al. *1995*). Further information regarding this hypothesis as well as the hypothesis that increased bimanual activation comes from neuronal synchrony might come from investigation of the trial-by-trial correlation of the LFP and single-unit signals within and between hemispheres (S. Cardoso de Oliveira, O. Donchin, A. Gribova, H. Bergman, E. Vaadia, unpublished work).

Table 3. Averaged activation of the two cortices. The slightly weaker (none of the differences are significant under a χ^2 analysis) activation of ipsilateral cortex during unimanual movements means

that, when summed across both cortices, total activation is slightly less during unimanual than during bimanual movements. This may explain the consistent increase in mEP during bimanual movements relative to unimanual movements. Numbers are firing rates (in spikes per second) averaged across all MI neurons analyzed in the companion paper and averaged across all movement types. Similar results were obtained in SMA, and when the analysis was restricted to particular bimanual movements and their component unimanual movements

	Unimanual left	Unimanual right	Bimanual
Left hemisphere	7.3	8.2	8.2
Right hemisphere	8.0	7.7	9.5
Total	15.1	15.8	17.8

Strong contralateral preference of the mEP in MI

We found that the contralateral preference of LFP from recording sites in MI was much greater than the contralateral preference of single units recorded in the same locations and in the same task. In the single-unit results, contralateral preference in MI was only slightly greater than the contralateral preference in SMA (O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work). In contrast, in the LFP, contralateral preference in MI was quite strong, while in SMA a bilateral activation with slight ipsilateral preference was found (Fig. 3). This difference between single-unit activity and the mEP was highlighted by a relative lack of correlation between the degree of contralateral preference of the mEP and the contralateral preference of the neurons recorded at that site (Fig. 11), particularly in MI.

The greater contralateral preference of the LFP in MI relative to the single units is consistent with findings in auditory cortex showing greater contralateral preference in LFP than in single-unit activity (Eggermont and Mossop *1998*). In our study, this increased contralateral preference is more evident in the late peaks of the LFP than in the early peaks (Fig. 4). In sensory cortices, the wider, late peaks in evoked responses have been seen to result from recurrent collaterals within a cortical area (Mitzdorf *1985*). This suggests that those neurons forming significant local connections may have greater contralateral preference than other neurons.

Magnitude of single-unit response correlated with mEP magnitude in SMA

The suggestion that the late peaks in the mEP reflect recurrent local activity following the movement-related activation of the neurons receives additional support from the correlation between the magnitude of neural response at a recording site and the magnitude of the late peaks in mEP at that site (Table 2). Why this correlation should be stronger in SMA than in MI is a question open to speculation, although one simple hypothesis is that a larger percentage of neurons have recurrent local collaterals in SMA. While the functional significance of anatomical differences between cortical areas is not well understood, it seems reasonable that the ratio of local to nonlocal input to an area might reflect how responsive the area is to events outside that area. Thus, an appealing hypothesis is that SMA, often thought to be involved in self-generated movements, would have a high proportion of recurrent local collaterals.

The relatively weak correlations between the neuronal response and mEP contrast with reports showing that single-unit activity can be quite tightly related to the LFP signal. Spike-triggered averaging has shown that spikes tend to occur preferentially during negative deflections of the LFP (Eckhorn and Obermueller *1993*). On the other hand, other work has shown that the relationship between LFP and single-unit activity can be quite complex (Mitzdorf *1994*; Murthy and Fetz *1996b*; Eggermont and Mossop *1998*). In our analysis, it was the late peaks (P2 and N2), and not the sharp negative deflection of peak N1, which were correlated with the neuronal activity. This probably reflects a difference in the correlation being measured. Usually, correlations are measured in the trial-by-trial variations in single-unit activity and LFP. This study focuses instead on correlations

between average evoked potentials. This correlation had the advantage here of addressing directly the results on mean evoked potentials reported in this paper and in our previous work (O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work). Trial-by-trial correlations will be addressed extensively elsewhere (S. Cardoso de Oliveira, O. Donchin, A. Gribova, H. Bergman, E. Vaadia, unpublished work).

Correlation of bimanual-related effect in neurons and mEP in SMA

A strong correlation was seen between the bimanual-related effect in the single-unit activity and the bimanual-related effect in peak N2 of the LFP, and a similar, but weaker, correlation was seen in the overall rms in SMA. As already discussed, the overall rms of the mEP was always greater during bimanual movements. To a large degree, the increase in overall rms during bimanual movements was the result of an increase in the rms of peak P2 (Fig. 9). The difference between the functional significance of peak P2 and peak N2 is difficult to guess, because no current source density analysis of the mEP in motor cortices exists in the literature. However, peak N2 seems to reflect the bimanual character of the neural activity more directly, while peak P2 may represent a different aspect of cortical processing of bimanual control.

Conclusions

Many questions remain regarding interpretation of the mEP, but it seems clear that understanding of cortical processing can be aided by examining this signal in addition to the single-unit activity and the oscillatory components of the LFP. Specifically, our results are consistent with an interpretation that understands early components of the LFP to reflect the input to a cortical area, and late components of the mEP to reflect recurrent synaptic activation. They show differences in the role of MI and SMA in controlling movement, and differences in the way that bimanual and unimanual movements are controlled. In this last sense, the results support the hypothesis (Donchin et al. *1998*; O. Donchin, A. Gribova, O. Steinberg, H. Bergman, E. Vaadia, unpublished work) which holds that bimanual movements have specific neuronal representations and are not generated by simple combination of two unimanual movements, and this fact is reflected in the activity of the cortical networks which produce the movements.

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References

Arieli A, Shoham D, Hildesheim R, Grinvald A (1995) Coherent spatiotemporal patterns of ongoing activity revealed by real-time optical imaging coupled with single-unit recording in the cat visual cortex. J Neurophysiol 73:2072-2093

Baker SN, Kilner JM, Pinches EM, Lemon RN (1999) The role of synchrony and oscillations in the motor output. Exp Brain Res 128:109-117

Bauer R, Brosch M, Eckhorn R (1995) Different rules of spatial summation from beyond the receptive field for spike rates and oscillation amplitudes in cat visual cortex. Brain Res 669:291-297

Cui RQ, Deecke L (1999) High resolution DC-EEG analysis of the Bereitschaftspotential and post movement onset potentials accompanying uni- or bilateral voluntary finger movements. Brain Topogr 11:233-249

Donchin O, Gribova A, Steinberg O, Bergman H, Vaadia E (1998) Primary motor cortex is involved in bimanual coordination. Nature 395:274-278

Donoghue JP, Sanes JN, Hatsopoulos NG, Gaal G (1998) Neural discharge and local field potential oscillations in primate motor cortex during voluntary movements. J Neurophysiol 79:159-173

Eckhorn R, Obermueller A (1993) Single neurons are differently involved in stimulus-specific oscillations in cat visual cortex. Exp Brain Res 95:177-182

Eggermont JJ, Mossop JE (1998) Azimuth coding in primary auditory cortex of the cat. I. Spike synchrony versus spike count representations. J Neurophysiol 80:2133-2150

Kenmochi M, Eggermont JJ (1997) Autonomous cortical rhythms affect temporal modulation transfer functions. Neuroreport 8:1589-1593

Laas Y (1968) A quantitative approach to the correlation of slow-wave and unit electrical activity in the cerebral cortex of the cat. Electroencephalogr Clin Neurophysiol 25:503-506

Lang W, Obrig H, Lindinger G, Cheyne D, Deecke L (1990) Supplementary motor area activation while tapping bimanually different rhythms in musicians. Exp Brain Res 79:504-514

Mitzdorf U (1985) Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. Physiol Rev 65:37-100

Mitzdorf U (1987) Properties of the evoked potential generators: current source-density analysis of visually evoked potentials in the cat cortex. Int J Neurosci 33:33-59

Mitzdorf U (1994) Properties of cortical generators of event-related potentials. Pharmacopsychiatry 27:49-51

Mitzdorf U, Li BH, Poppel E (1994) Mass-action view of single-cell responses to stimulation of the receptive field and/or beyond: exemplification with data from the rabbit primary visual cortex. Electroencephalogralogr Clin Neurophysiol 92:442-455

Murthy VN, Fetz EE (1996a) Oscillatory activity in sensorimotor cortex of awake monkeys: synchronization of local field potentials and relation to behavior. J Neurophysiol 76:3949-3967

Murthy VN, Fetz EE (1996b) Synchronization of neurons during local field potential oscillations in sensorimotor cortex of awake monkeys. J Neurophysiol 76:3968-3982

Sanes JN, Donoghue JP (1993) Oscillations in local field potentials of the primate motor cortex during voluntary movement. Proc Natl Acad Sci USA 90:4470-4474

Shibasaki H (1975) Movement-associated cortical potentials with unilateral and bilateral simultaneous hand movement. J Neurol 209:189-198