Primary and supplementary cortex in bimanual movements: a study of cortical physiology

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By
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Abstract

The study of bimanual coordination is an area of intense recent research. This contrasts with a relative lack of interest in bimanual coordination – particularly in the area of cortical physiology – over the preceding years. This increased recent interest has been fueled in part by new theoretical approaches and recording techniques that place an emphasis on the role of neuronal interactions in the function of the nervous system and partly by an increasing emphasis on natural motion in the study of motor control. The central issues addressed by this research regard the nature of cortical involvement in coordinating bimanual movements, the relative role of different cortical areas, and the nature of the interhemispheric interaction underlying coordination.

This study of the neurophysiology of bimanual control focuses on the relative roles of primary motor cortex (MI) and supplementary motor cortex (SMA). MI is classically considered to play little role in bimanual coordination, while SMA has been thought to have a large role. We adapted the standard center-out reaching task used in many motor control and motor systems physiology experiments so that it was suitable for bimanual research. The subjects (rhesus monkeys) held one two-joint X-Y manipulandum with each hand. They first brought both hands to starting positions located roughly in front of each shoulder. Then the monkey was instructed to make either a unimanual or bimanual movement. Bimanual movement involved either parallel movements or anti-parallel movements of the hands, and both bimanual and unimanual movements could be in any of eight directions. During performance of this task, neuronal activity was recorded by four microelectrodes in each hemisphere in MI and SMA.

As expected, both in MI and SMA neurons showed activity during unimanual movements related to both contralateral and the ipsilateral movements. Also as expected, a slightly larger percentage of MI units responded contralaterally while more SMA units responded bilaterally. However, in contrast with our expectations, we found many units in both MI and SMA whose activity during bimanual movements was different than during unimanual movements. This surprising finding of "bimanual related" activity in units in MI proved resistant to explanation by differences in the kinematics or dynamics of the movements performed by the monkeys. It also turned out that, for many neurons, activation in bimanual movements could not be explained as a linear sum of activation during the unimanual movements. The percentage of MI neurons exhibiting such "bimanual related" activity was no lower than the percentage of SMA neurons, which is a strong indication for a role for MI in the coordination of bimanual movements.

To pursue the source of "bimanual related" components in single unit responses, we examined the relations between local field potentials (LFP) and single-unit activity. Like single neurons, activity in the LFP could be evoked in relation to movements of the contralateral and ipsilateral arms. However, in comparison with the single units, MI proved to be driven much more strongly by contralateral movements than SMA. Another difference between the LFP and single unit activations was that "bimanual related" activity in the single units could involve either an increase or a decrease in the spike rate, while LFP responses evoked on nearly all electrodes was greater during bimanual movements than during unimanual movements. This difference in the "bimanual
related” response may reflect a greater overall cortical activation during bimanual movements, which would mean an increased synaptic drive to the neurons in both motor areas. However, it remains to be explained why this increased synaptic drive would not produce an increase in the average firing rate. Another interesting difference between SMA and MI arising from analysis of the LFP is that there is a greater correlation between the responsiveness of neurons recorded in SMA and the size of the LFP evoked on the recording electrode than there is in MI. That is, SMA neurons seems to be more closely related to the LFP than MI neurons potentially indicating that a larger percentage of the drive to these neurons is local.

While it is premature to draw any far reaching conclusions from the research presented it here, there seems to be justification to say both that MI is involved in the control of bimanual coordination and that it may nevertheless be true that MI and SMA play different roles in the control of movement. In any case, this research will certainly force a re-examination of the role of MI in motor control and could prove a springboard for further research which explores the physiological basis and functional relevance of the “bimanual related” effect.
Cortical Representations of Bimanual Movements

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General Introduction

The relevance of bimanual coordination

In the last two years, three papers from different groups have been published on the nature of cortical activity in MI and SMA of primates during bimanual movements (Donchin et al., 1998; Kazennikov et al., 1999; Kermadi et al., 1998). This is striking given that only one work had addressed the subject previously, and that was more than 10 years ago (Tanji et al., 1988). This sudden surge in interest is also reflected in a large number of papers studying brain activity in humans during bimanual coordination (Andres et al., 1999; Goerres et al., 1998; Jancke et al., 1998; Sadato et al., 1997; Toyokura et al., 1999). Of course, many causes go into making a particular area popular – not the least of which is the popularity itself – but there are some good reasons why bimanual coordination has become interesting to many researchers recently.

One reason is an increasing interest in how it is that neurons communicate in order to accomplish tasks. The focus on neuronal communication has its roots in the growth of the field of theoretical neuroscience and its use of artificial neural networks as a research tool. Artificial neural networks enabled striking demonstrations of how different models of neuronal interactions can produce very different behavior in a neural system (Abeles, 1991; Shadlen and Newsome, 1998). However, another, possibly equally important influence promoting interest in neuronal communication is technological advancements: multiple electrode techniques permit explorations of the dynamics of neuronal interactions (Vaadia and Aertsen, 1992) and imaging technologies expose the interactions between small populations of neurons and larger areas of the brain (usually cortex) (Arieli et al., 1995).

In fact, it was earlier results in our laboratory (Vaadia et al., 1995) which originally led to the idea of studying cortical activity during bimanual movements. This study – in which multiple single units were recorded simultaneously in frontal cortex of monkeys performing a Go-NoGo task – showed that the interactions between neurons could be modulated on a fast time scale – tens of milliseconds – in relation to behavioral events. However, these results could not predict what functional relevance
these modulations in interaction strength might have. One of the priorities for the lab became finding a paradigm in which it might be possible to demonstrate functional relevance.

A theory proposing to explain the functional significance of neuronal interactions had been proposed some years earlier based on work in visual cortex (Gray et al., 1989; Singer and Gray, 1995). This theory proposed that neuronal firing rates reflect local properties of the stimulus while precise timing of spikes binds together different parts of the stimulus into a coherent whole. Evidence was presented using local field potentials and multi-unit activity in visual cortex of anesthetized cats, and so there was room for replicating the results in motor cortex of an awake, behaving monkey performing a task that depended on the binding together of information. It seemed fruitful to explore differences in neuronal activation during movements where one arm moved separately and movements where it was necessary to coordinate the motion of the arms and look for modulation of neuronal interaction.

Another reason for the interest in bimanual coordination is the growing realization among researchers of the complexity of the motor system and the difficulty involved when trying to separate out component parts of the system for study. This change in approach was partly fueled by the success of research into cortical activity during free arm movements in explaining a large percentage of the variation in the activity of most neurons in primary motor cortex (Georgopoulos et al., 1982; Schwartz et al., 1988). One of the interpretations applied to this research was that the planning in the motor system (motor planning is a function ascribed to motor cortex in this interpretation) is done in terms of the whole movement which needs to be performed, rather than a joint-by-joint or muscle-by-muscle planning which could conceivably be relatively insensitive to the entire movement. While the debate over the coordinate system in which motor cortex represents movements has yet to be resolved (Scott and Kalaska, 1995; Scott and Kalaska, 1997), there is an increasing respect for the sophistication of the motor control system and an interest in looking at multi-joint and multi-limb movements before assuming that they are well characterized as a linear combination of the component single-limb single-joint pieces.
Questions addressed by studying cortical physiology in a bimanual task

The nature of interhemispheric coordination

It is not necessary to fly to fancy ideas about the nature of motor control to find good reasons to study cortical physiology in a bimanual task. One obvious reason is the hope that this could shed light on the nature of interhemispheric coordination. The nature of interhemispheric coordination is currently a topic of active research, primarily by researchers using behavioral paradigms centered on visual processing. An oft-quoted result in the field is that, in many tasks, bilateral presentation of stimuli improve response time and accuracy when compared with situations in which the same stimuli are presented unilaterally (Dimond and Beaumont, 1972). This effect was called the bilateral advantage, and interpreted to imply that some level of cooperation between the hemispheres aids in accomplishing the required task. Later research found a correlation between the bilateral advantage and interhemispheric transfer time (as measured by latency of EEG waves) (Brown and Jeeves, 1993), suggesting that the hemispheric cooperation was facilitated by rapid information transfer between the hemispheres. However, another experiment by the same group (Larson and Brown, 1997) and experiments by other groups (Banich, 1998; Braun et al., 1997) suggested that the situation was more complex. The results showed a relationship between task difficulty and the extent of the bilateral advantage and a hemispheric asymmetry in the effect which seemed to generalize across tasks. In the information transfer model, the bilateral advantage should be reduced in more complex tasks (where more information needs to cross the callosum) and the hemispheric asymmetry should reflect the nature of the task (in some tasks the computations are performed largely in the left hemisphere while in others the computations are performed largely in the right hemisphere). This led to the suggestion that attentional mechanisms are involved. Larson and Brown suggest, specifically, that interhemispheric inhibition is involved in the process as well as interhemispheric cooperation.

Indeed, the idea that interhemispheric inhibition plays a role in hemispheric coordination has been proposed many times (as reviewed recently in Chiarello and Maxfield, 1996). In the motor cortex, this idea came from early observations of involuntary movement of one arm during movements of the
other in patients with lesions in the corpus callosum (Chan and Liu, 1999, is a study of the anatomical substrate of alien hand with a good review of the early literature). The idea received important recent support in experiments using transcranial magnetic stimulation (TMS). Using TMS, researchers have shown that electromyogram (EMG, a measure of muscle activity) response to cortical stimulation of contralateral motor cortex is inhibited by a conditioning stimulation of ipsilateral cortex (Ferbert et al., 1992). While there is evidence showing that this may be, in part, mediated through subcortical mechanisms (Gerloff et al., 1998), it apparently is also facilitated through an inhibitory effect of one hemisphere on the other. This conclusion comes from converging studies in patients lacking a corpus callosum (Meyer et al., 1995; Meyer et al., 1998) and in situations where it is possible to measure the ipsilateral cortical response more directly (Di Lazzaro et al., 1999).

In bimanual motor control, inhibitory processes and transfer of information may be occurring simultaneously. Early works (Preilowski, 1972; Preilowski, 1975) and more recent studies (Franz et al., 1996) show interhemispheric coupling which seems to involve transfer of motor information rather than interhemispheric inhibition. A recent review of the literature concurs with this view, suggesting that processes of information transfer, as are believed to occur in sensory processing, occur alongside processes of interhemispheric inhibition, primarily the inhibition of the motor commands of one hemisphere by the other (Geffen et al., 1994). The specifics of how the mechanisms of this communication operate remains open, and recording from the motor cortex in a bimanual task may well shed light on the question.

**The role of the supplementary motor area**

Before I began this research there was only one other study which had recorded the activity of single neurons in the motor cortex during bimanual movements (Tanji et al., 1988). That study primarily addressed the question of the role of the supplementary motor area (SMA) in bimanual control. It showed that SMA neural activity was modified idiosyncratically during bimanual movements while MI neural activity during bimanual movements was the same as during unimanual movements. This was not a surprising result. Brinkman had reported that unilateral SMA lesions prevented a monkey
from performing a learned bimanual task by causing a pathological tendency towards identical movements of the two arms (Brinkman, 1984). Bilateral lesion of SMA in the same monkeys mitigated the effects of the original lesions, and allowed performance of the task that was similar to that of the monkeys in their normal state. Tanji’s results were also consistent with findings regarding bimanual deficits following SMA lesion in humans. Various reports have shown a deficit in rapid alternating arm movements in humans following SMA lesion (Dick et al., 1986; Laplane et al., 1977; Penfield and Welch, 1951; Schell et al., 1986), a result which is particularly intriguing because similar deficits have been seen in Parkinsonian patients (Johnson et al., 1998) supporting the speculation that many of the effects of Parkinson’s disease are mediated through disruption of SMA function. More recently, imaging techniques have been used in humans to support the hypothesis of a role for SMA in bimanual control (Sadato et al., 1997; Stephan et al., 1999; Toyokura et al., 1999).

However, the role of the SMA in bimanual movements has also been challenged. Physiological studies of SMA activity have produced a bewildering array of candidate functions (Wiesendanger, 1993). Perhaps the most widespread understanding of the functional role of the SMA is in the production of what are called “self-generated” movements, proposed largely as a result of research on a movement-evoked EEG potential called the readiness potential (Kornhuber and Deecke, 1964). The readiness potential can be reliably evoked before self-initiated movements, and it seems likely that its source is the SMA (Deecke and Lang, 1996) which strongly suggests a role for the SMA in producing such movements. However, further support comes from single-unit studies (Mushiake et al., 1991; Romo and Schultz, 1987) and imaging studies (Deiber et al., 1991; Deiber et al., 1999).

It is not only the multiplicity of other candidate roles for the SMA which has caused the idea of a role for SMA in bimanual control to be challenged. Using both irreversible and reversible inactivation techniques, one group has reported absolutely no bimanual deficit following SMA lesion (Kazennikov et al., 1998; Kermadi et al., 1997). Preliminary results in our own laboratory confirm these findings (Gribova et al., 1998), and there are also reports of SMA lesions in humans that are not associated
with bimanual deficit. Thus, the role of the SMA in bimanual movements is far from resolved and the original Tanji results certainly bear re-examination.

**The role of the primary motor cortex**

While the role of the SMA in the control of movement is far from clear, this does not mean that the role of MI is better understood. While more studies have been done on MI, and different researchers have strongly held views on its place in the motor hierarchy, the debate over this issue is still raging. In principle, three possibilities are discussed. One is that activity of MI cells reflects dynamics of movement generation, meaning that MI cells will primarily be ‘muscle-like’ (Kakei et al., 1999) or ‘joint-like’ (Scott and Kalaska, 1997). Another is that activity of MI cells reflect the kinematics of movement generation, meaning that MI cells will primarily indicate intended direction or speed (Moran and Schwartz, 1999a). A final possibility is that MI neurons reflect higher-order aspects of task some of which may have nothing to do with the movements that the task requires (Carpenter et al., 1999). Some studies have addressed tried to resolve this issue by comparing the degree to which different task variables are related MI activity (Ashe and Georgopoulos, 1994; Taira et al., 1996), but the outcome has not been conclusive. The results of Tanji et al. (1988) that activity in MI during bimanual movements will be like during unimanual movements imply that either the first or second possibility is correct. However, if further research were to show that MI does respond differently during unimanual and bimanual movements that could have an important influence on the debate.

**The distinction between proximal and distal control**

One aspect of the earlier exploration of cortical activity during bimanual movements (Tanji et al., 1988) is that neural activity was recorded during exclusively distal movements. This is significant because converging evidence using different techniques has led to the hypothesis that there is a fundamental difference in control of proximal and distal movements of the upper limb (Brinkman and Kuypers, 1972; reviewed in Gazzaniga, 1998). The two MI are poorly connected through the corpus callosum for the hand and fingers and are well connected for the upper arm (Rouiller et al., 1994).
addition, studies of ipsilateral deficit following brain damage in humans confirm the result that control of the arms is more bilaterally organized than control of the fingers (Jakobson et al., 1994). While the study of motor control generally assumes that there is a single control strategy employed by our nervous system in the control of the different limbs and the different joints, it is possible that this is not the case. Exploring the difference between proximal and distal control in bimanual movements, it may be possible to uncover two different modes through which the cortex is involved in control of movements, and, thus, different strategies of motor control.

**Choosing a paradigm**

Research into cortical activity during bimanual movements touches on important issues in the study of cortical physiology and in the study of motor control. Touching on so many issues, I chose the simplest possible behavioral paradigm in order to avoid further complicating the situation. I borrowed the center-out reaching paradigm made popular by Georgopoulos (Georgopoulos et al., 1982) and generalized it to two hands simply by having each hand make its own center-out reaching movement. Coordination between the arms was necessary because the task required simultaneous movement initiation and simultaneous target acquisition. It was also possible to test different bimanual movements by having the hands either move in parallel or anti-parallel center-out movements. This paradigm involves primarily proximal movements which makes it different in an important way from the earlier work by Tanji (Tanji et al., 1988), although, like Tanji, I recorded activity of neurons in MI and in SMA hoping to corroborate the earlier results and provide a solid foundation for extending them. The intention was to select the task that with the greatest chance of providing information about all of the issues raised above.

A few other interesting questions, not necessarily central to the study of cortical physiology, can also be addressed with the data I collected. First, by choosing a behavioral task which extends the original Georgopoulos center-out task, I collect data which could potentially extend the population vector (PV) results which were based on that task (Georgopoulos et al., 1988). There has been no
consideration in the literature of how PVs could be used to describe bimanual movements — indeed, with the exception of the extension into movements with curvature (Moran and Schwartz, 1999b; Schwartz, 1992; Schwartz, 1994; Schwartz and Moran, 1999), there is little discussion of the generalization of the PV to descriptions of complex movements. Trying to use PVs for this purpose could be an important challenge to theories claiming functional relevance for what is fundamentally an inefficient data reduction technique (Sanger, 1996; Seung and Sompolinsky, 1993).

I also decided to record local field potentials (LFP) simultaneously with the activity of single units. LFP is simply the signal from the same electrodes used to record single units, but lowpass filtered below 100 or 200 Hz (where the signal used to isolate spike waveforms is bandpass in the approximate range of 300 to 10,000 Hz). Recording the LFP gives a way of measuring average synaptic activity in the vicinity of the electrodes, and the results can be used in conjunction with the single unit data to try to understand the input-output relationship of a small area of cortex.

Choosing one question

While the number of issues on which we touch is very large, it is, of course, necessary to focus on one scientific question if a piece of scientific research is to have any validity. In my research, the choice was made for me by my results. Despite my expectations, I discovered very different activity in primary motor cortex during bimanual movements (I call this a “bimanual related” effect). My data was so strikingly different from that which had been reported earlier (Tanji et al., 1988) that I was forced to focus my attention on discovering whether or not this result was simply some sort of artifact. Thus, two of the papers composing this doctorate are focused on the fact of this effect. The first of these (Donchin et al., 1998) presents the “bimanual related” effect to the scientific community for the first time and focuses on demonstrating the strength of the effect and the fact that it is widespread throughout neurons in both MI and SMA. The second paper (Donchin et al., 1999a) is more concerned with establishing the controls necessary to ensure that the “bimanual related” effect is not simply an artifact of differences in how the unimanual and bimanual movements are performed. This
paper has been submitted along with a companion paper (Donchin et al., 1999b) which presents the LFP recorded simultaneously with the single units. This paper makes the point that LFP is a very different signal than the single unit activity, and the paper shows that this signal can reveal aspects of cortical processing which are not seen in the single unit results. Finally, I include a review (Donchin et al., 1999c) which analyzes our results, relates them to results in bimanual control using other techniques, and discusses how they are being extended to address many of the issues discussed above.