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**Neurophysiology of brain area related to movement and motor control**

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3. Sensory cortical areas
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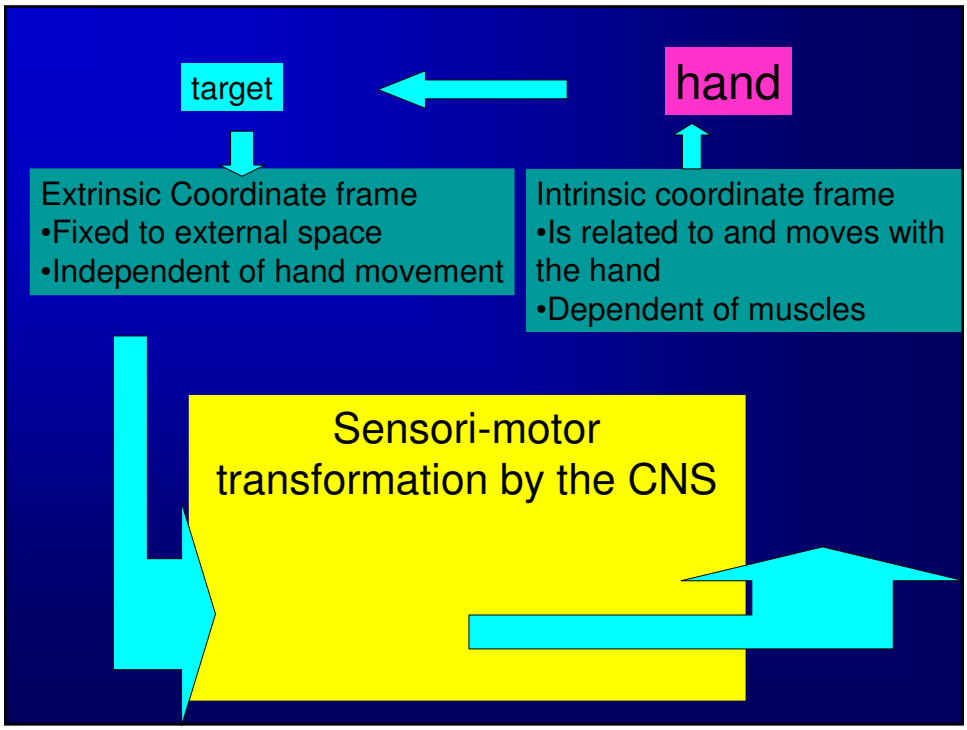
5. Synthesis of motor output organization
6. Toward parcellation, specialization and complexity
7. Pre-motor area definition, identification
8. Basal-ganglia organization direct & indirect pathways
9. Sensory motor transformation



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14. Cortical plastcity

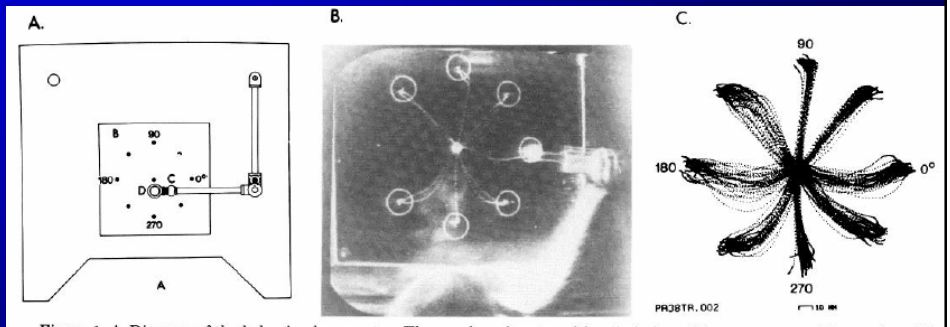
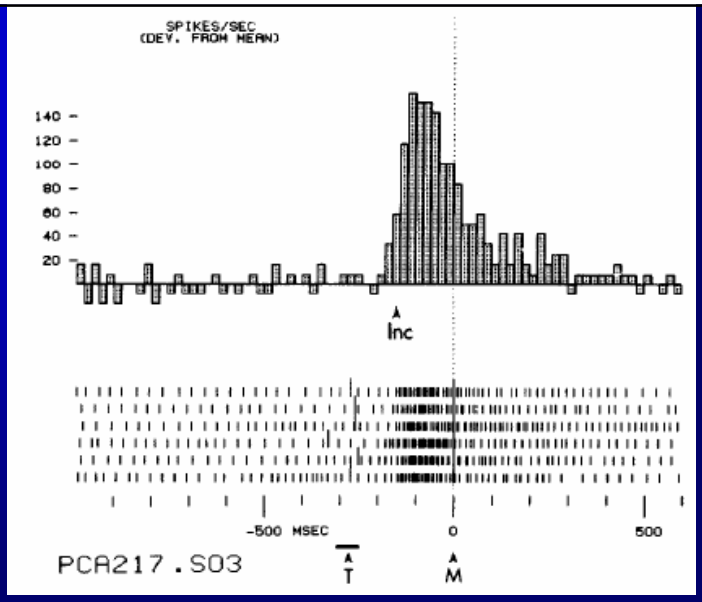



*Figure 1.* *A*, Diagram of the behavioral apparatus. The monkey sits at *position A*, facing a 25-cm square working surface (*B*) on which there are nine light-emitting diodes (LEDs). One LED is at the center of the working surface and eight are on a circle with an 8-cm radius; they are numbered from 0 to 315° counterclockwise. The monkey grasps an articulated manipulandum at its end (*C*) and moves it across the *x-y* surface of the plane to capture within a clear plastic circle (*D*) whichever LED is illuminated. The plane is tilted 15° from the horizontal toward the animal. *B*, Overhead view of a monkey performing the task displayed on a television monitor. The monkey has moved the manipulandum from the center to the target LED (in this case, the movement direction is 0°) to complete a trial. The trajectories of movement for this trial and for a few previous trials are superimposed on the television image as *light lines*. The *small circles* are the 25-mm-diameter target windows around each target LED. The starting (*center*) window had a diameter of 15 mm. *C*, Trajectories of 30 movements to each target made by a well trained monkey. Each *dot* is the position of the center of the target-capturing circle on the end of the manipulandum taken at 10-msec intervals.

(Georgopoulos et al 1982, JN)




Exemple of the determination of the timing of the first change in neuronal activity. Impulse activity was recorded from a single neuron during 6 movements toward the same target and is displayed as a raster (bottom) and as a perievent histogram (top). All trials and the histogram are oriented to the onset of movement . (Georgopoulos et al 1982, JN)

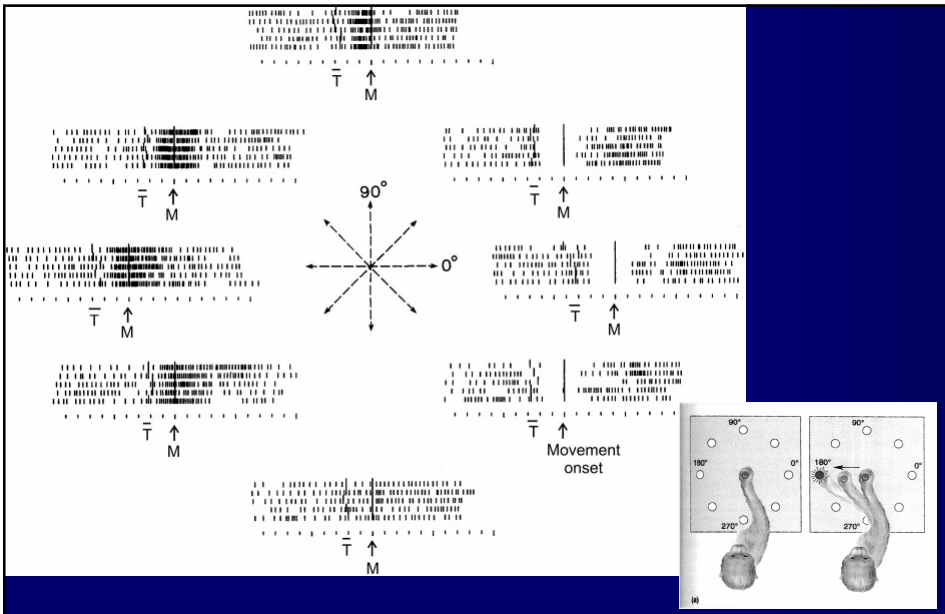
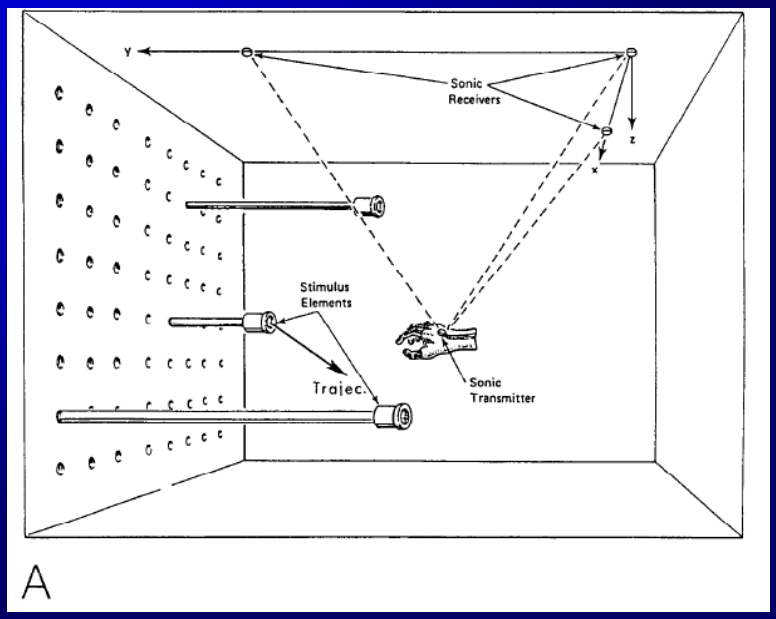



Fig. 1. Raster activity of a single cell recorded in the motor cortex of a monkey during movements on a plane in different directions, indicated by the arrows at the center. T, range of target onset. Rasters are aligned to M, movement onset. Notice the short-latency, abrupt decrease of activity for movement direction at 2 o'clock Georgopoulos et al 1982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Sonic
Receivers
z
x
Stimulus
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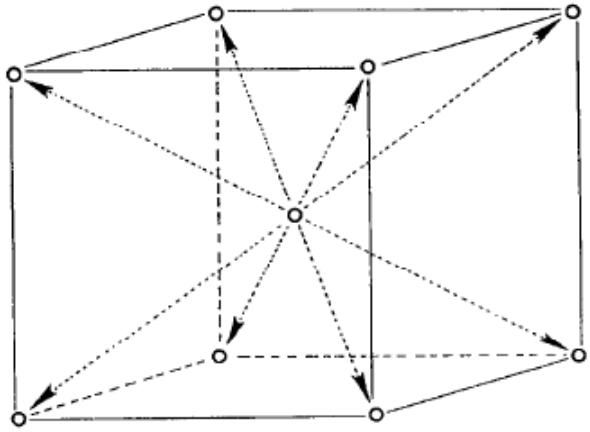
Trajec.
Sonic
Transmitter

A



B

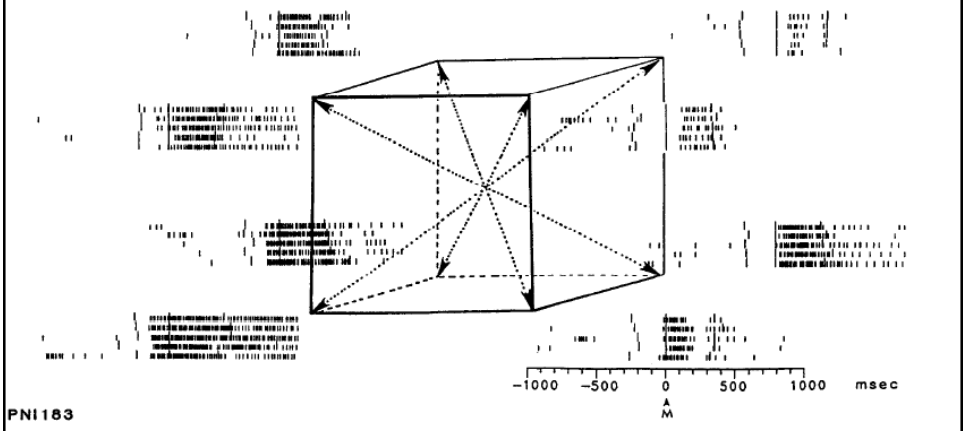



*Figure 7.* Impulse activity (*short bars*) of a directionally tuned cell with movements in different directions (*arrows*). Rasters of 5 repeated trials for every movement direction are aligned with the onset of movement (*M*). *Longer bars* preceding and following the movement onset indicate the onset of the target and the end of the movement, respectively.

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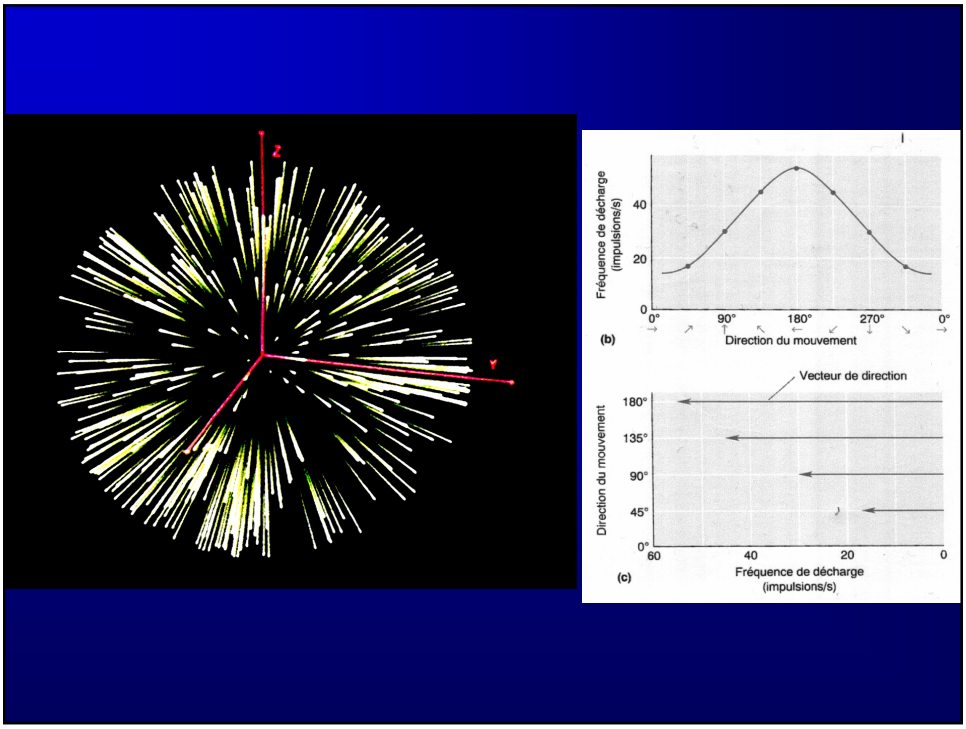


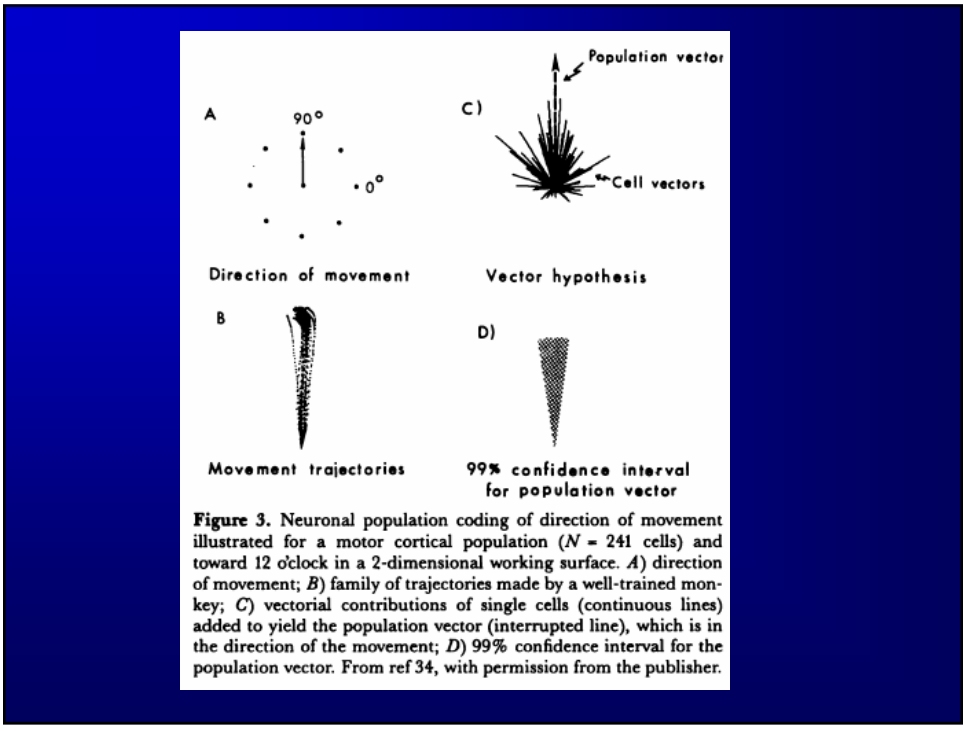
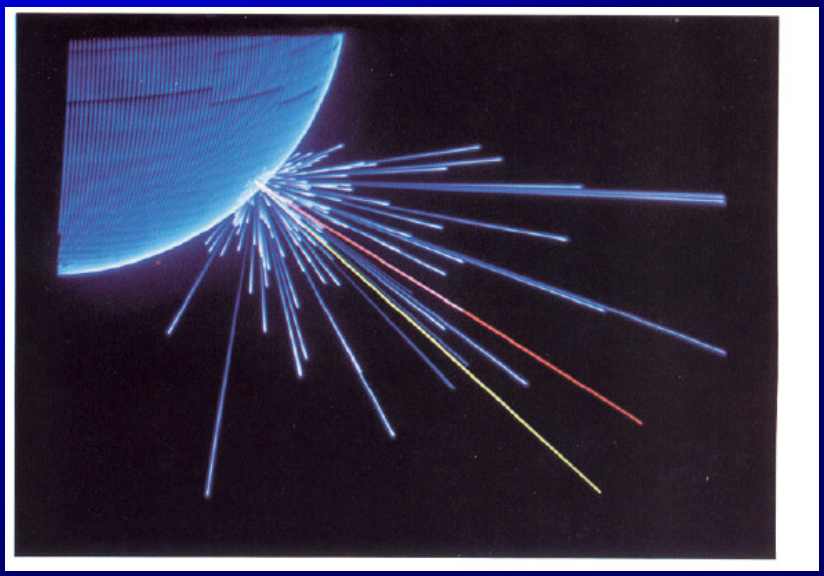
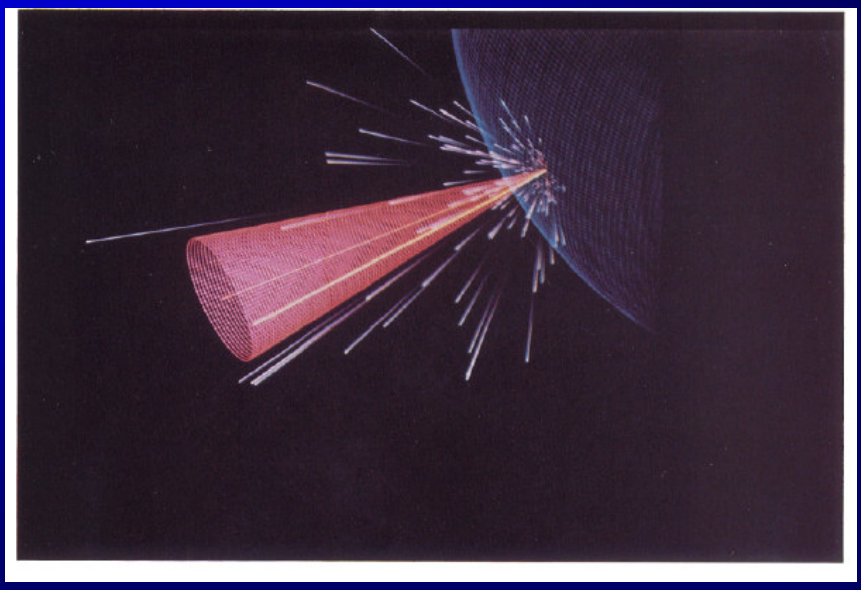



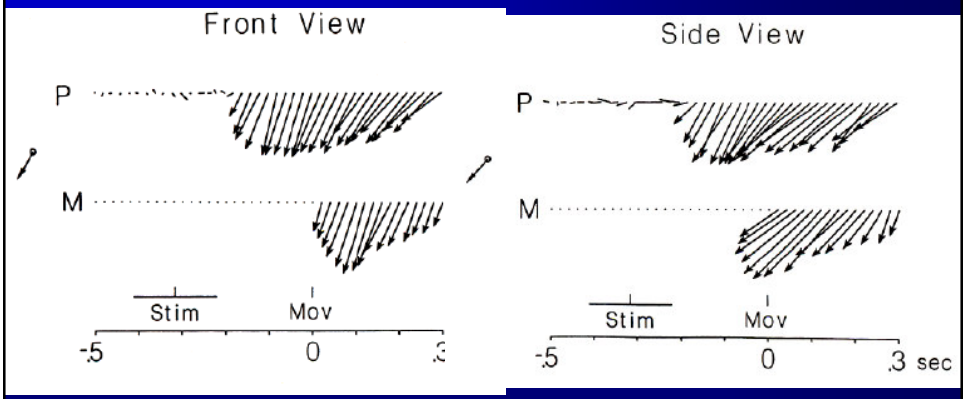

**Figure 3.** Neuronal population coding of direction of movement illustrated for a motor cortical population ($N$ = 241 cells) and toward 12 o'clock in a 2-dimensional working surface. *A*) direction of movement; *B*) family of trajectories made by a well-trained monkey; *C*) vectorial contributions of single cells (continuous lines) added to yield the population vector (interrupted line), which is in the direction of the movement; *D*) 99% confidence interval for the population vector. From ref 34, with permission from the publisher.



An example of population coding of movement direction. The blue lines represent the vectorial contributions of individual cells in the population (N = 475). The movement direction is in yellow and the direction of the population vector in red.



A 95% directional variability cone around the population vector (red). The population is the same as in Figure 1, but the movement direction (yellow) is different




Evolution of the population vector in time. Front and side views of time series of population (P) and movement (M) vectors are shown. Population and movement vectors are normalized relative to their respective maximum. Movement vectors are averages from one animal. STZM, onset of target light; MOV, onset of movement

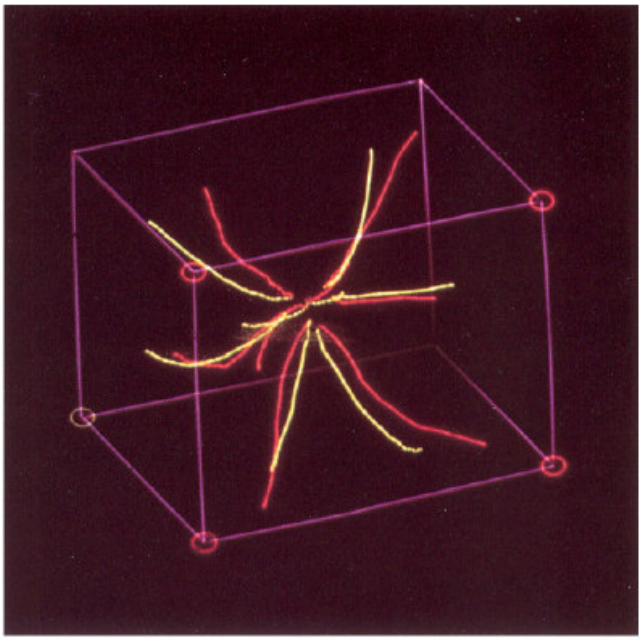


*Figure 5.* Normalized actual (*yellow*) and "neural" (*orange*) trajectories. See text for details.

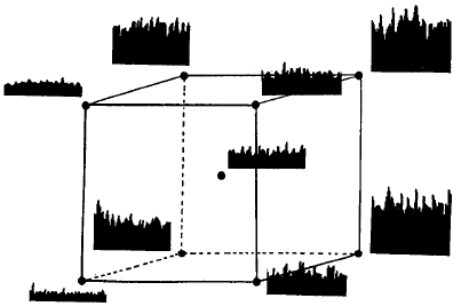


*Figure 2.* EMG activity of acromiodeltoid muscle during holding of the hand at positions indicated. Each histogram is an average of 8 trials and is 0.5 sec long.

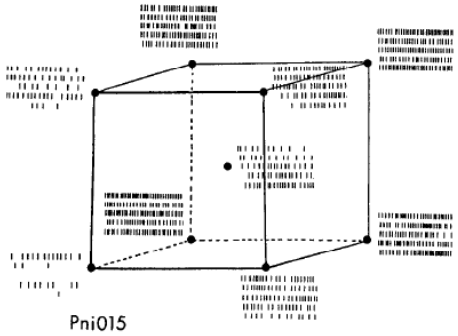



*Figure 3.* Impulse activity (5 trials) of a cell during holding of the hand at positions indicated. Each trace is 0.6 sec long.

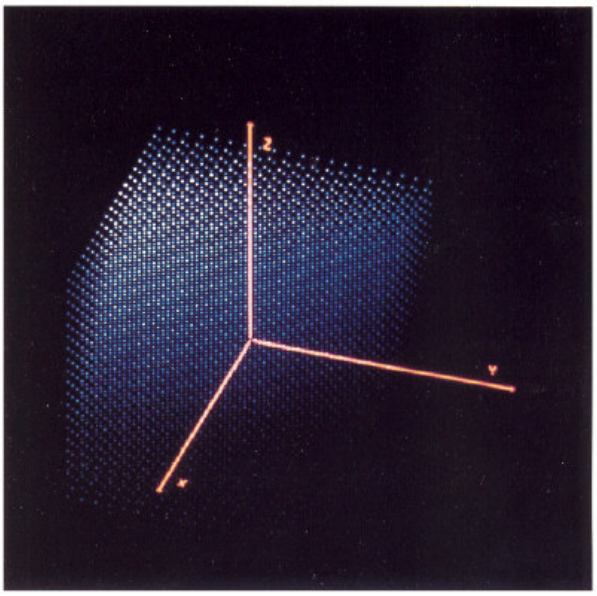



*Figure 5.* The 3-D positional gradient from another cell illustrated as a 3-D plot. Each dot represents a position within the workspace. The intensity of a dot is proportional to the intensity of cell discharge predicted by the positional gradient function.

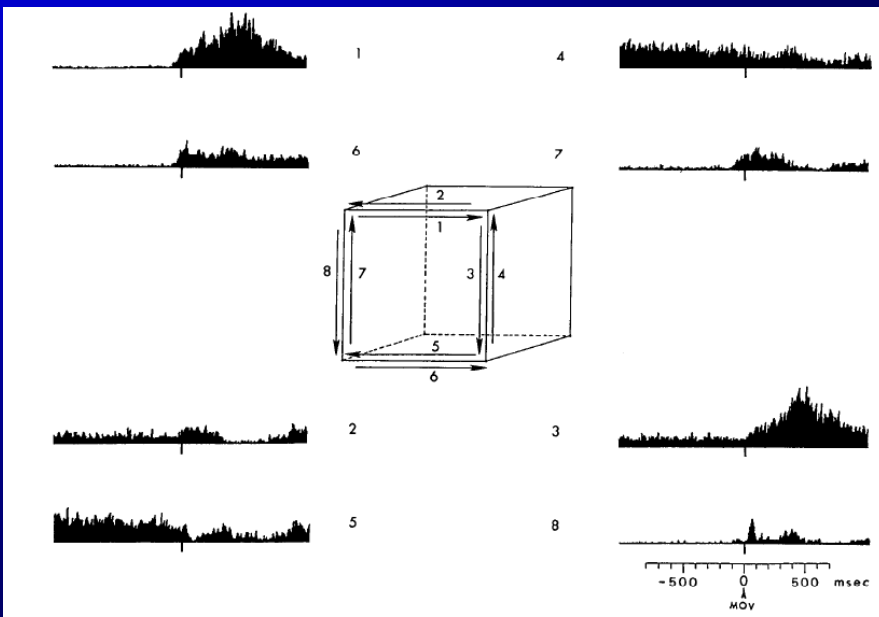



*Figure 9.* EMG activity of acromiodeltoid muscle in the parallel task. Each histogram is an average of 8 trials and is aligned to the onset of movement (*MOV*). *Arrows* indicate the direction of movement. Plots have been arranged in pairs corresponding to parallel movements, as identified by the numbers.

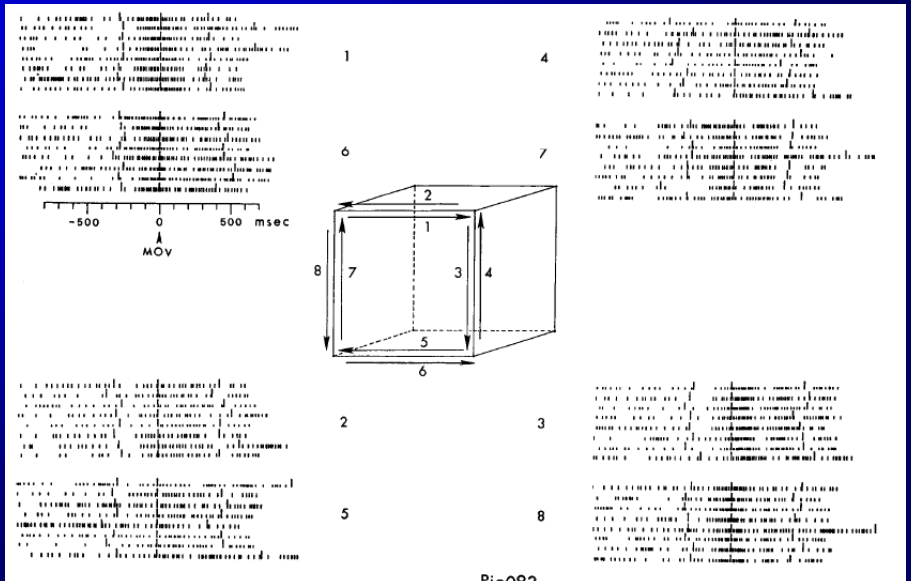



*Figure 10.* Impulse activity of a cell in the parallel task. Five repetitions are shown aligned to the onset of movement (*MOV*). *Longer vertical bars* preceding the movement onset indicate the time of target onset. Same arrangement as in Figure 9.

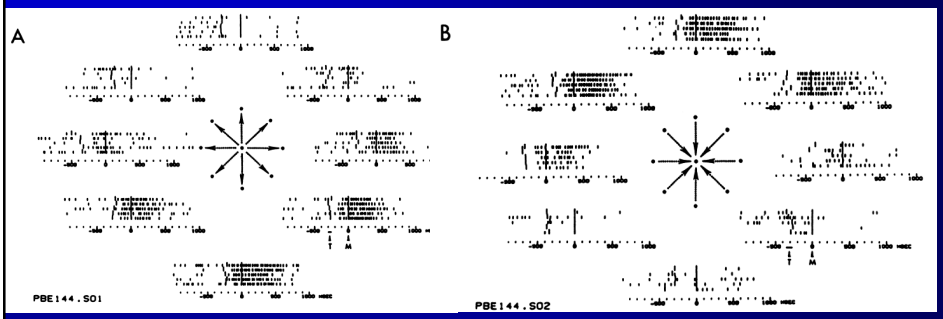



**Figure 2.** Cell discharge varies with the direction of movement, not its endpoint. *A*) Impulse activity of a motor cortical cell during five equal-amplitude movements made from the center of a planar working surface to eight peripheral targets; *B*) impulse activity of the same cell during movements made from identical peripheral targets toward the same endpoint at the center, as indicated by center diagram. Notice that the discharge varies with the direction of movement (as in *A*) although all movements terminated at the same endpoint. T, onset of target; M, onset of movement. From ref 34, with permission from the publisher.

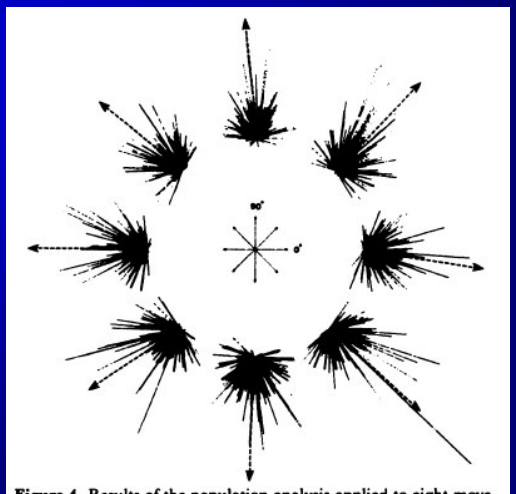


**Figure 4.** Results of the population analysis applied to eight movement directions studied in 2-dimensional space. Each cluster represents the same population (conventions as in Fig. 3*C*); the direction of movement is shown in the diagram at the center. The population vector (arrow) points in the direction of (or near to the direction of) the movement. From ref 36, with permission from the publisher.

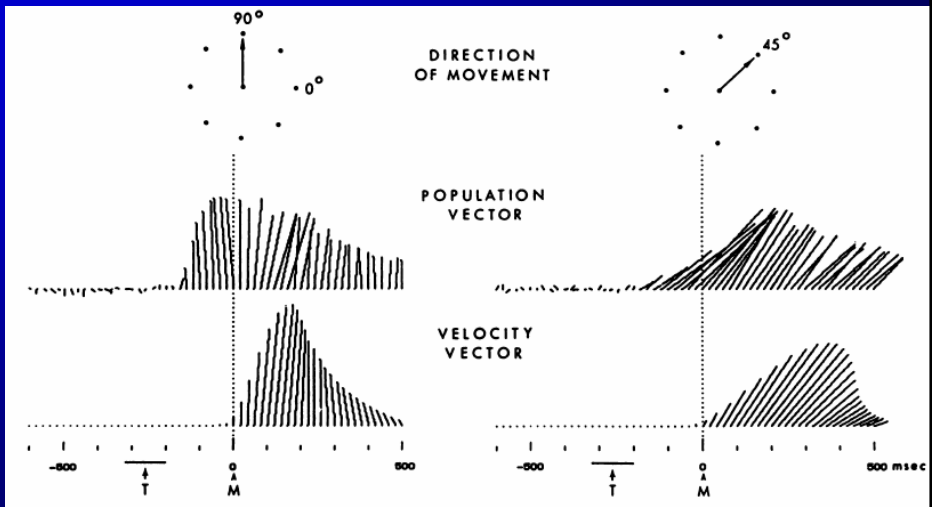



**Figure 5.** The population vector points in the direction of movement well before the movement begins. The results for two directions of movement in the 2-dimensional task are illustrated (top); the population vector was calculated every 20 ms (middle); the average instantaneous (20 ms/bin) velocity of the movement is also shown (bottom). Before the target onset (T), the population vector is very short and its direction varies from moment to moment. Well before the onset of movement (M), it increases in length and its direction points to the direction of the upcoming movement. This finding suggests that even the earliest inputs to the motor cortex are relevant to the direction of the upcoming movement. From Georgopoulos 34; reproduced with permission from the publisher.

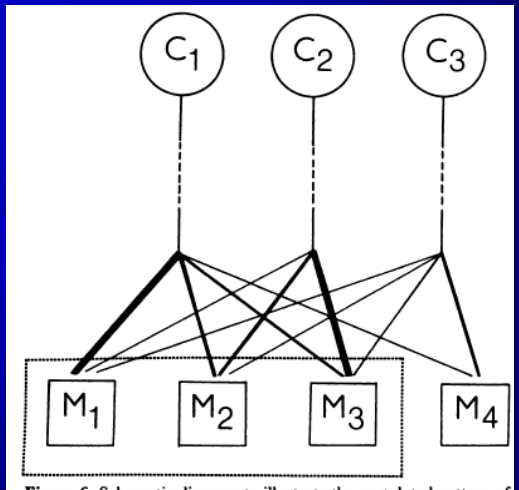



**Figure 6.** Schematic diagram to illustrate the postulated pattern of weighted divergent and convergent influences exerted on motoneuronal pools ($M_1$, $M_2$, $M_3$, $M_4$, . . .) by single motor cortical cells ($C_1$, $C_2$, $C_3$, . . .). The dashed lines indicate intercalated neurons (e.g., C3-C4 propriospinal neurons). The line thickness indicates the weighted influence. Motor cortical cell $C_2$ influences a weighted combination of motoneuronal pools ($M_1$, $M_2$, $M_3$) enclosed within the interrupted parallelogram.

## CONCLUDING REMARKS

The findings previously summarized refer to the relations between the discharge of motor cortical cells and the direction of arm movements in space. The reaching movement involves changes in the angles of the shoulder and elbow joints; these changes in joint angles are effected by changes in the torques applied at those joints, which are in turn produced by changes in the activity of muscles acting on the upper arm and the forearm. Theoretically, a signal from a motor structure, such as the motor cortex, could relate to any of various aspects: trajectory of movement in space, joint angles, joint torques, or muscle activity. However, free-reaching movements in space are quite stereotyped, and it is possible (even probable) that variables that could appear to be independently controlled may not be allowed to vary independently, thus losing their individual degrees of freedom; for example, shoulder and elbow angles covary (19–21) during reaching independently of movement speed (20). Dissociation of motor variables could provide information concerning their own control by a motor structure, but such studies may not reveal the role of that structure in the control of these variables, which are coupled together in a natural movement.

We suggest that the reaching movement may be specified as a whole by supraspinal structures and that it may be initiated by hard-wired spinal circuits. These circuits seem to be complex and sophisticated, yet appropriately developed for this function. It is possible that the matching of motor cortical output to spinal motor mechanisms that underlie reaching is a product of evolution and of the long period of trial and error when infants learn to reach accurately in space (see ref. 43 for a review). FJ

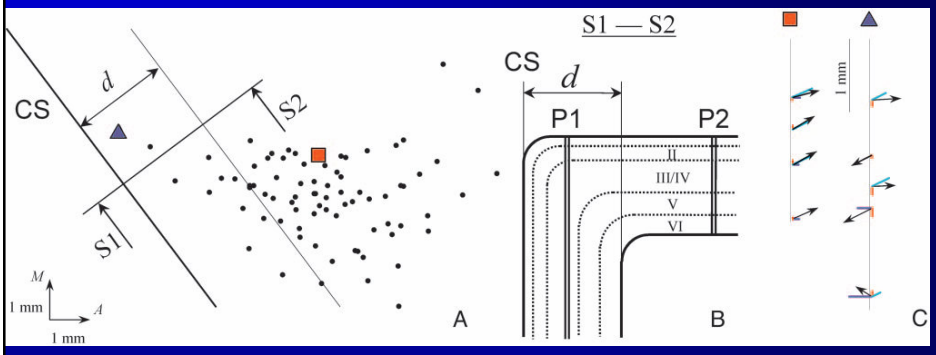
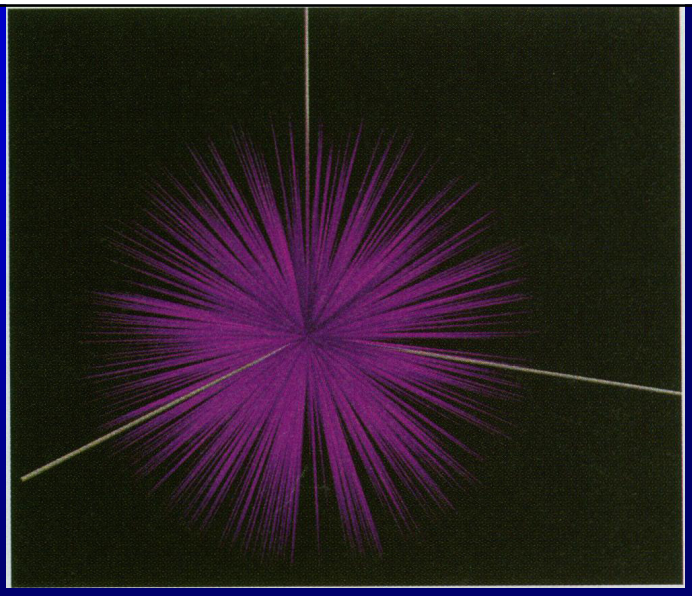


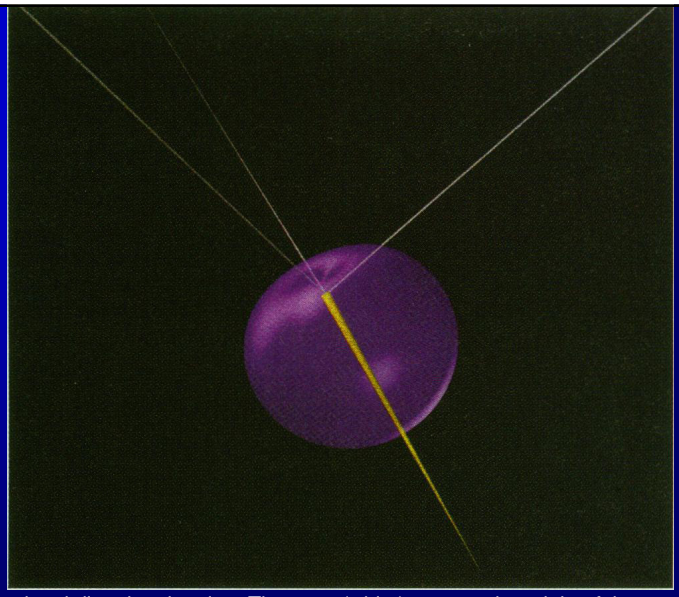

**Fig. 1.** (*A*) Surface view showing the location of entry points with respect to the CS of 79 penetrations used in the present study. For graphical purposes, data from four hemispheres are transformed and plotted on an outline of a right hemisphere (see figure 6 in ref. 17). The transformation is invariant with respect to the distance between a particular entry point and the CS. The continuous line parallel to, and at a distance *d* from, the CS represents a borderline that demarcates the cortical surface into two regions (see text). The imaginary sections S1–S2 orthogonal to the CS is shown in *B*. A, anterior; M, medial. (*B*) Section view of the cortical depth in a plane orthogonal to the CS (S1–S2, in *A*). Dotted curves schematically represent the cortical laminae. Double lines illustrate the orientations of two imaginary penetrations P1 and P2 made nearby and farther away from the CS, respectively. The bisecting borderline is shown here in a similar fashion as in *A*. II–VI cortical layers. (*C*) Examples of two penetrations analogous to P1 and P2. The entry points of the penetrations are color-shape coded in *A* and *C*. The PDs of directionally tuned cells isolated along the penetrations are shown as arrows, with the corresponding direction cosines in color. It can be seen that PDs were very similar along the penetration resembling P2 (red square), whereas they differed appreciably in the penetration resembling P1 (blue triangle). The average angle between PDs of all cell pairs was 19° for the former and 96° for the latter penetration.

(Amirikian and Georgopoulos, 2003 PNAS)

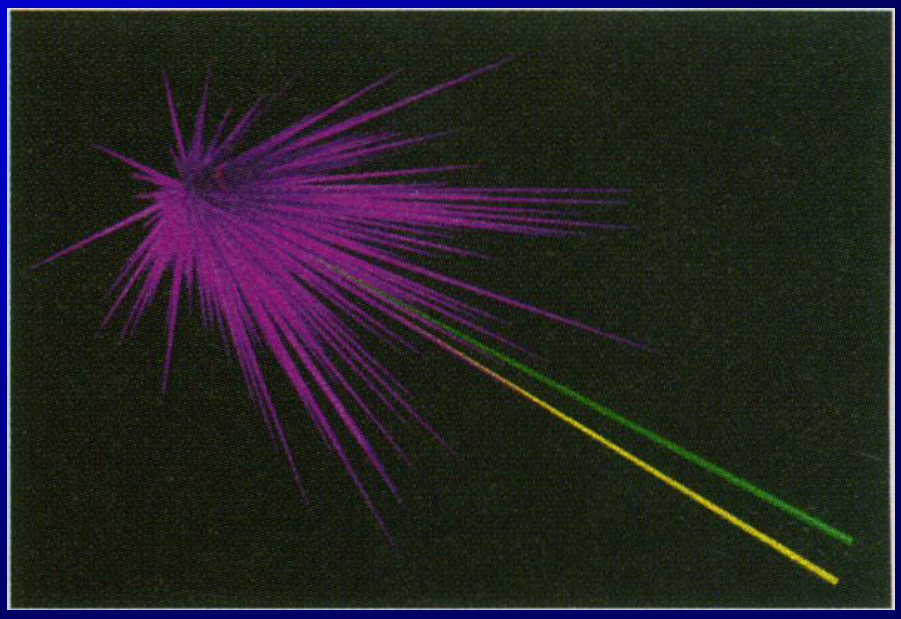


Three-dimensional preferred directions (purple) of 634 motor cortical cells studied in three monkeys. The axes are in white.

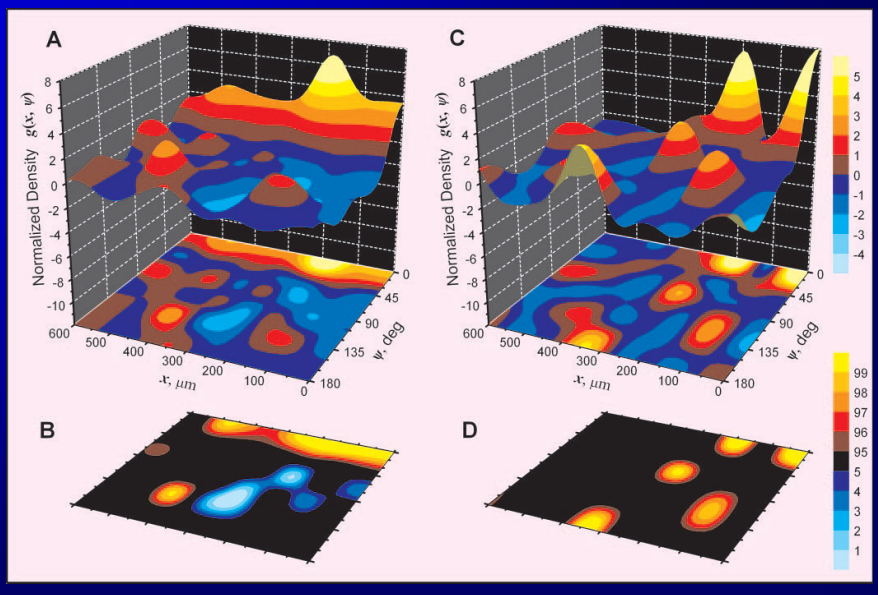
(Georgopoulos et al., 1993 Science)



Three-dimensional directional tuning. The axes (white) meet at the origin of the movement. For a particular movement, the discharge rate of the cell predicted by Eq. 1 is proportional to the length of a line pointing in the direction of the movement and drawn from the origin to the surface (purple) of the tuning volume. The cell's preferred direction is indicated by the yellow cone.



The population vector (green) obtained from the set of cells with preferred directions shown in Fig. 2. The direction of movement is shown in yellow.




Images representing functional neuron density fields computed for two mutually orthogonal dimensions (Amirikian and Georgopoulos, 2003 PNAS)

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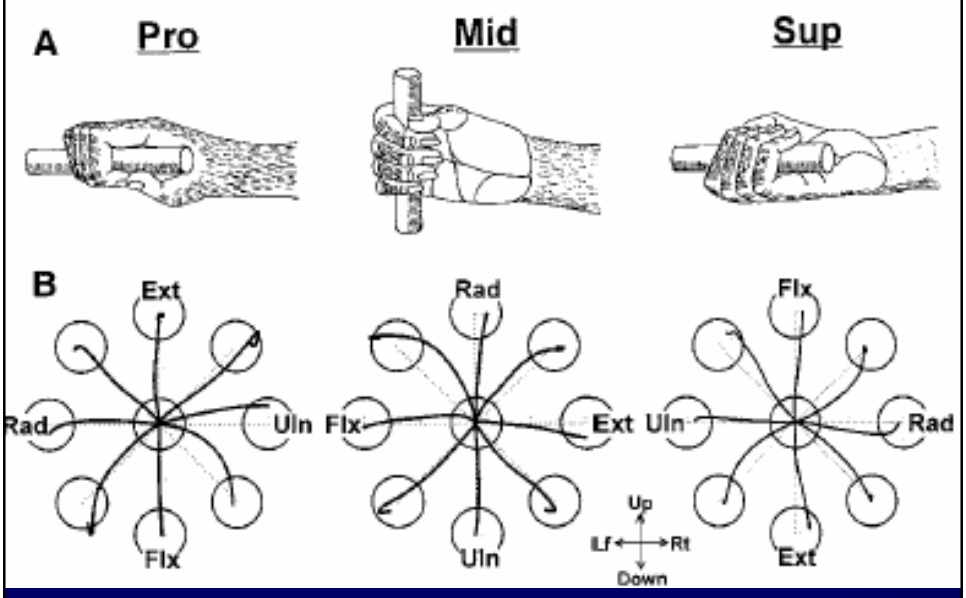



Kakei, Hoffman, Strick
*Science, 1999*

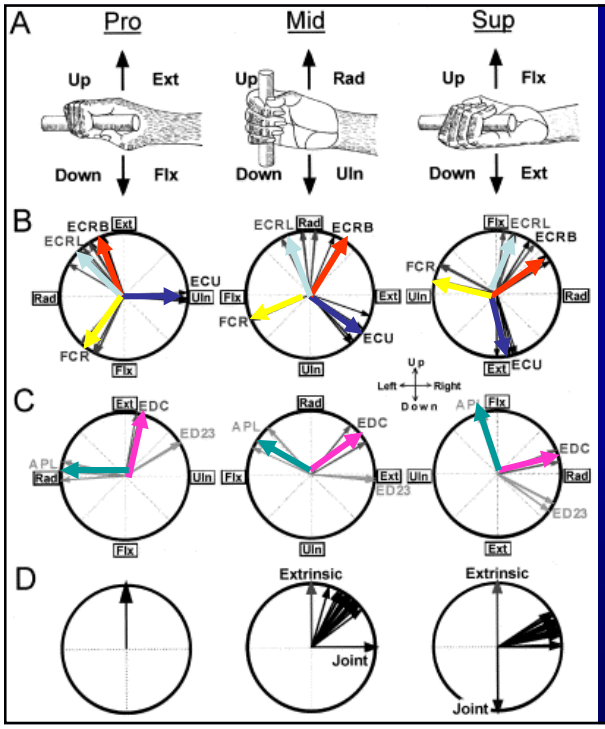
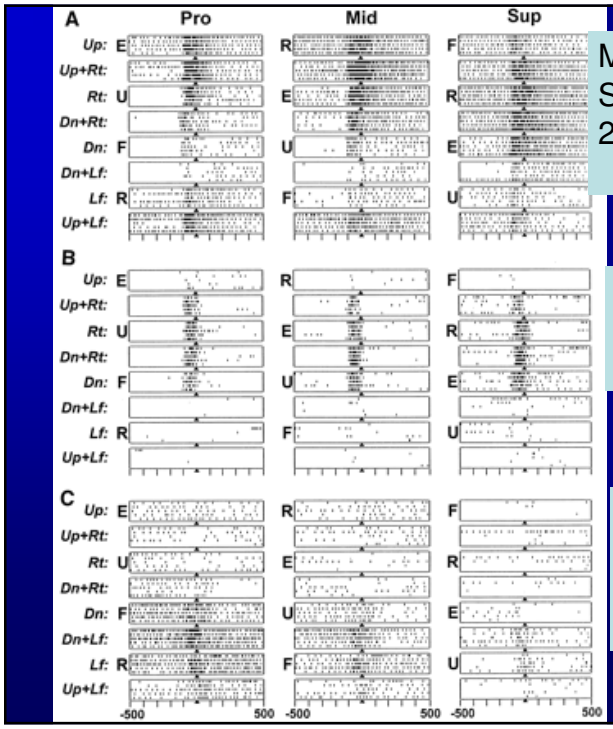



Fig. 1. Experimental design: dissociation of extrinsic, joint and muscle coordinate frames with changes in forearm posture. (A) the monkey right hand gripping the handle of the manipulandum in 3 forearm postures. Pro, pronated; Sup, supinated, Mid, midway between pronation and supination. Ext, extension; Flx, flexion; Rad, radial deviation; Uln, ulnar deviation. Up and Down indicate direction of movements in space. (B, C) PDs of the seven task-related muscles ((B) 4 wrist muscles and (C) 3 finger muscles, respectively) when the limb was in the 3 forearm postures . APL, abductor pollicis longus; ECRB, extensor carpi radialis brevis; ECRL, extensor carpi radialis longus; ECU, extensor carpi ulnaris; ED23, extensor digitorum 2,3; EDC, extensor digitorum communis; FCR, flexor carpi radialis. (D) Normalized shifts of PDs of the task-related muscles in the three forearm postures. Left circle, the single vector represents the PDs of the task-related muscles in the Pro position, which were normalized to the Up direction. Middle circle, the unlabeled vectors represent the relative shifts of the PDs of the task-related muscles with forearm rotation from Pro to Mid. Right circle, the unlabeled vectors represent the relative shifts of the PDs of the task-related muscles with forearm rotation from Pro to Sup. The vectors labeled 'Extrinsic' represent the PDs of ideal vectors fixed to an extrinsic coordinate frame. The vectors labeled 'Joint' represent the PDs of ideal vectors fixed to the wrist joint. Note that the unlabeled vectors are clearly separated from the Extrinsic and Joint vectors.




Muscle-like neuron in M1
Shift de 79° Pro-Sup
28 out 88

Extrinsic-like neuron
in M1
44 out 88

Extrinsic-like neuron
In M1 influenced by joint
Posture
16 out 88

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*Science*, 1999

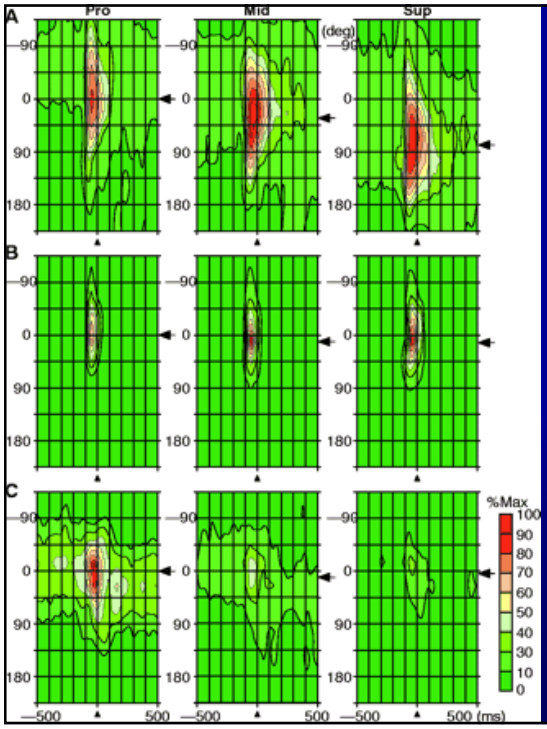


**Fig. 3.** Spatiotemporal maps of activity of the same M1 neurons illustrated in Fig. 2. Neurons (**A**), (**B**), and (**C**) in this figure correspond to neurons A, B, and C in Fig. 2. To construct these maps, we calculated averaged spike numbers in a 50-ms time window, sliding the time window by 25 ms, from2500 to 1500 ms relative to the movement onset. The calculation was performed for each movement direction in each wrist posture. Then, contour plots of the spatiotemporal distribution of the neuron activity were generated with Surfer (Golden Software, Golden, Colorado). The maximum activity for any of the three wrist postures in the 50-ms analysis window was normalized to 100% (A: 155; B: 98; C: 124 spikes persecond). PDs in the Pro position were set to 0¡ in order to demonstrate the amount of the shift. PDs of neuron activity (*18*) for each posture are indicated by arrows.

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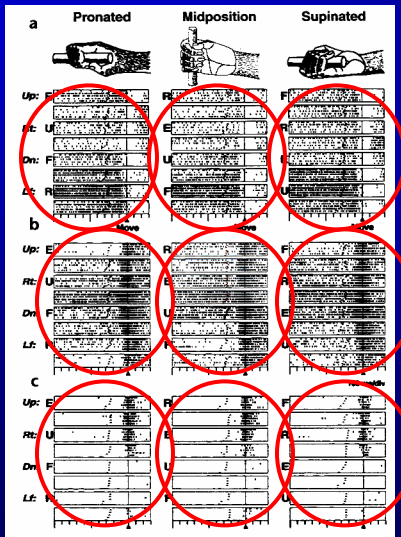
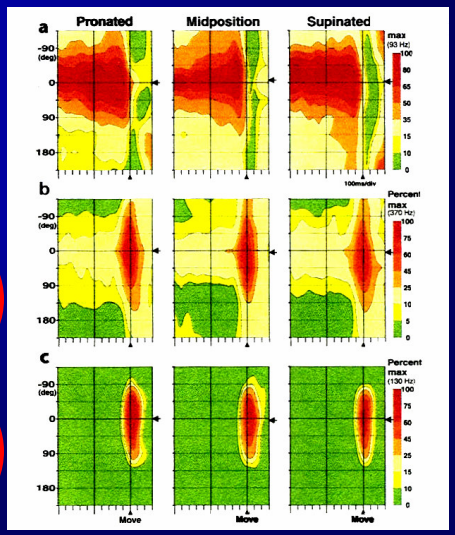
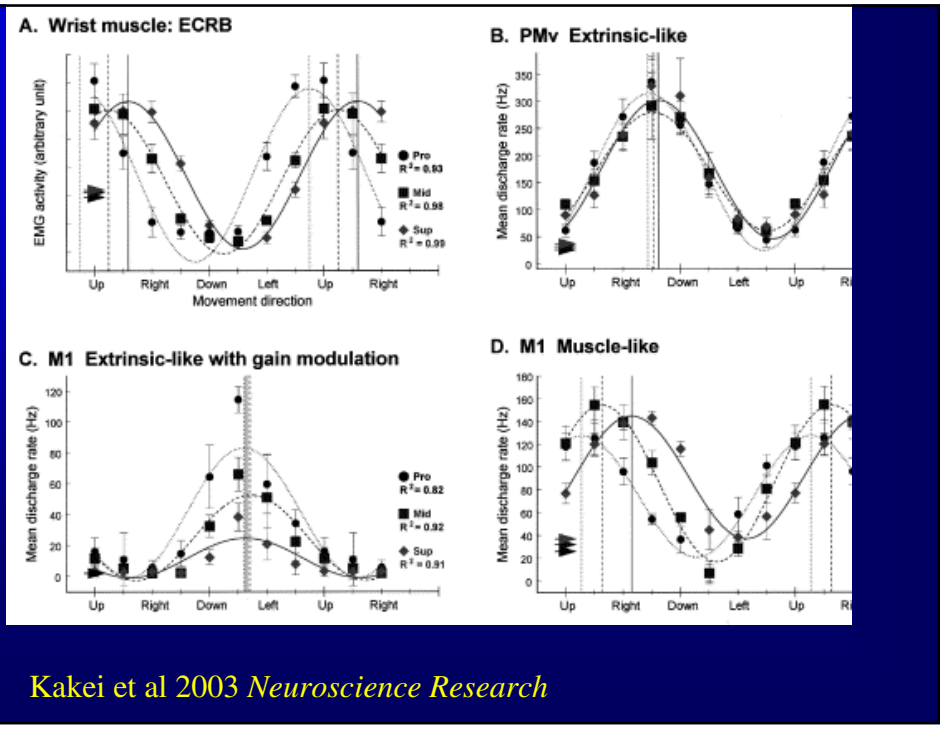
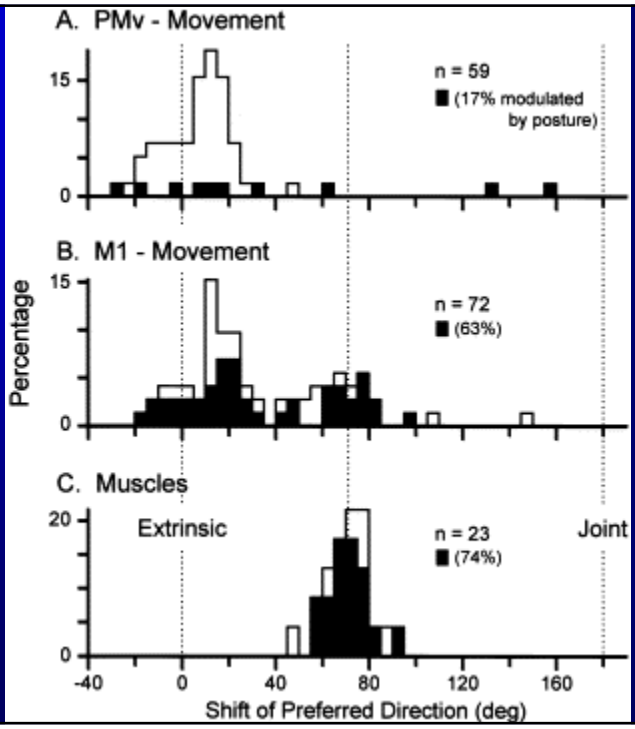
# Pre-motor cortex function

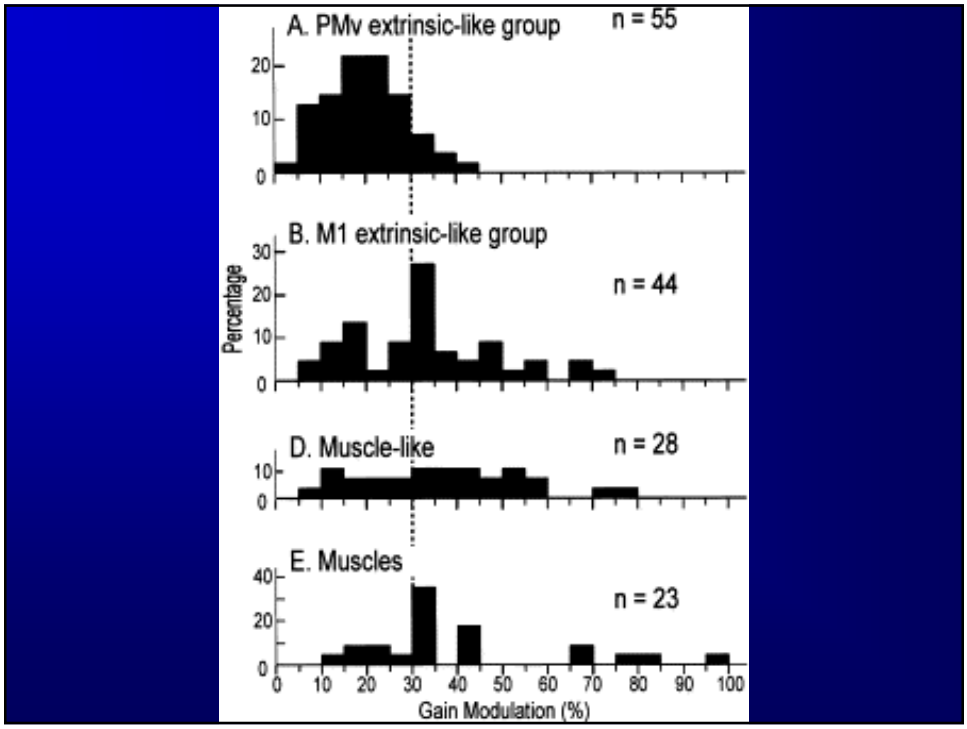


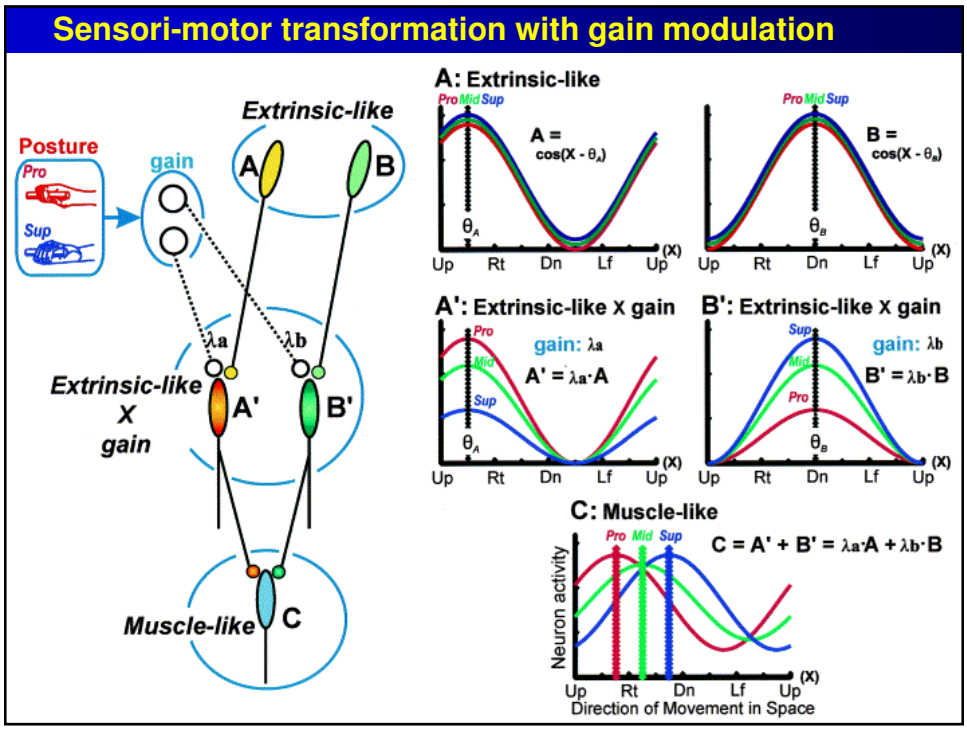






Kakei et al 2003 *Neuroscience Research*




A. PMv extrinsic-like group
n = 55
B. M1 extrinsic-like group
n = 44
D. Muscle-like
n = 28
E. Muscles
n = 23
Percentage
Gain Modulation (%)


Sensori-motor transformation with gain modulation
Posture
Pro
Sup
gain
Extrinsic-like
A
B
λa
λb
Extrinsic-like
X
gain
A'
B'
Muscle-like
C
A: Extrinsic-like
A' : Extrinsic-like X gain
B' : Extrinsic-like X gain
C: Muscle-like
C = A' + B' = λa·A + λb·B
Neuron activity
Direction of Movement in Space

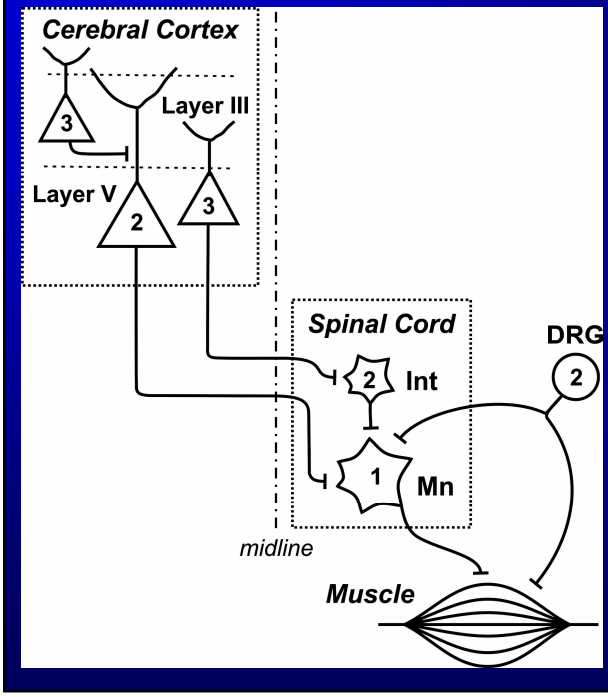



Fig. 1. Retrograde transneuronal transport of rabies virus from single muscles. When rabies virus is injected into a single digit muscle, it is transported in the retrograde direction to infect the motoneurons (i.e., first-order neurons) that innervate the muscle. Then virus is transported transneuronally in the retrograde direction to label all those second-order neurons that synapse on the infected motoneurons. These include dorsal root ganglion cells that supply group Ia muscle spindle afferents, spinal cord interneurons, and cortical neurons in layer V (CM cells). At longer survival times, virus can undergo another stage of retrograde transneuronal transport and label all those third-order neurons that synapse on the infected second-order neurons. For example, virus can move from second-order neurons in layer V to third-order neurons in layer III. Similarly, virus can move from second-order inter-neurons in the spinal cord to third-order cortical neurons in layer V. DRG, dorsal root ganglion cell; Int, interneuron; Mn, motoneuron; 1, first-order neuron; 2, second-order neuron; 3, third-order neuron.

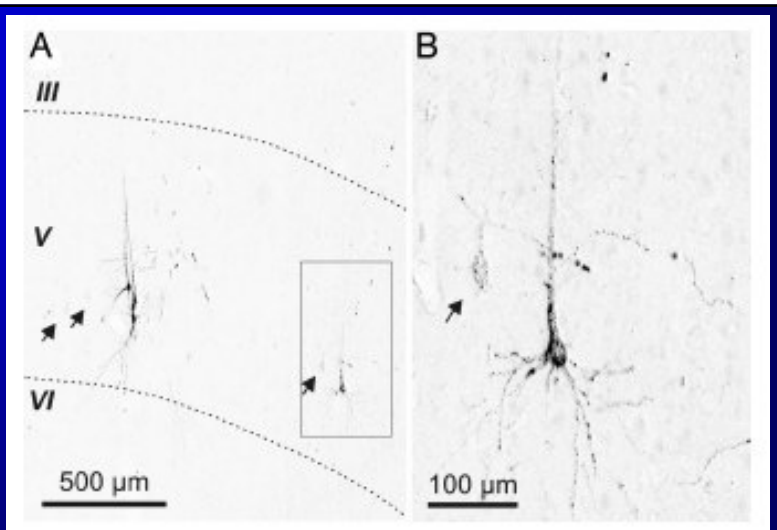



Fig. 2. CM cells infected with rabies. (*A*) CM cells in layer V labeled by retrograde transneuronal transport of rabies from an injection of virus into ADP. Dotted lines indicate the borders between cortical layers. (*B*) CM cells of different size in layer V taken from the box in *A*. Arrows indicate the location of lightly labeled neurons.

**How are the neurons that directly influence the motoneurons of a muscle distributed in the primary motor cortex (M1)? To answer this classical question we used retrograde transneuronal transport of rabies virus from single muscles of macaques. This enabled us to define cortico-motoneuronal (CM) cells that make monosynaptic connections with the motoneurons of the injected muscle. We examined the distribution of CM cells that project to motoneurons of three thumb and finger muscles. We found that the CM cells for these digit muscles are restricted to the caudal portion of M1, which is buried in the central sulcus. Within this region of M1, CM cells for one muscle display a remarkably widespread distribution and fill the entire mediolateral extent of the arm area. In fact, CM cells for digit muscles are found in regions of M1 that are known to contain the shoulder representation. The cortical territories occupied by CM cells for different muscles overlap extensively. Thus, we found no evidence for a focal representation of single muscles in M1. Instead, the overlap and intermingling among the different populations of CM cells may be the neural substrate to create a wide variety of muscle synergies.Wefound two additional surprising results. First, 15–16% of the CM cells originate from area 3a, a region of primary somatosensory cortex. Second, the size range of CM cells includes both ''fast'' and ''slow'' pyramidal tract neurons. These observations are likely to lead to dramatic changes in views about the function of the CM system (Rathelot & Strick, PNAS, 2006)**

## Objectives
## Neurophysiology of brain area related to movement and motor control

1. Ascending pathways (sensory input)
2. Sensory input treatment, and thalamo-cortical & cortico-thalamic filter
3. Sensory cortical areas
4. Descending pathways (motor output) &motor unit definition
5. Synthesis of motor output organization
6. Toward parcellation, specialization and complexity
7. Pre-motor area definition, identification
8. Basal-ganglia organization direct & indirect pathways
9. Sensory motor transformation
10. Preferential direction of M1 neurons extrinsic-like code
11. Neuronal population coding
12. Emergence of muscle-like neurons in M1
13. Global movement induced by electrical stimulation of the cortex
14. Cortical plastcity

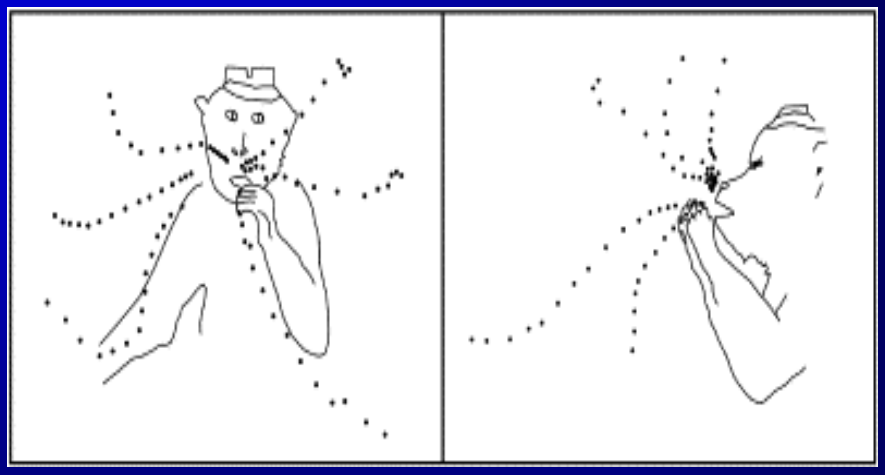


Figure 1. An Example of a Complex Posture Evoked from Monkey 1 by Microstimulation of Precentral Cortex When this site was stimulated the left hand closed into a grip posture, turned to the face, moved toward the mouth, and the mouth opened. Stimulation was for 500 ms at 100  A and 200 Hz. Drawings were traced from video footage acquired at 30 frames per second. The 11 dotted lines show the frame-by-frame position of the hand for 11 different stimulation trials. Each dot shows the part of the video image of the hand that was farthest from the elbow. The start point of each trajectory was distant from the mouth; the end point was at or near the mouth.

Graziano et al EBR, 2004

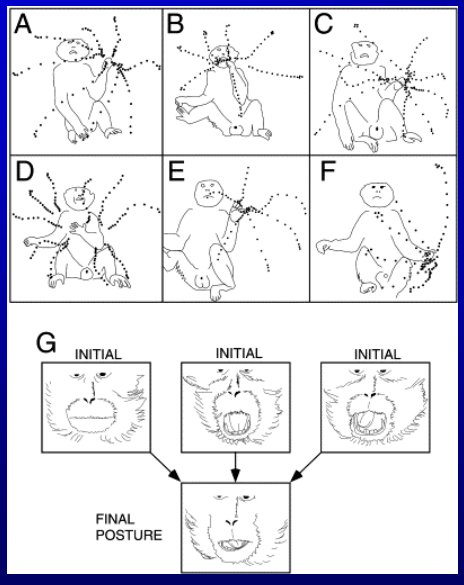



Figure 2. Examples of Postures Evoked by Microstimulation of Precentral Cortex(A–F) Six examples of postures of the left arm evoked from monkey 2. Stimulation on the right side of the brain caused movements mainly of the left side of the body Postures of the right limbs shown in these traced video frames are incidental and not dependant on the stimulation. Final postures that involved the left hand near the edge of the workspace, such as in (F), could not be tested from all directions, but still showed convergence from the range of initial positions tested.(G) A posture of the mouth and tongue evoked from monkey 1. When this site was stimulated, the mouth opened partly and the tongue pointed toward the left canine (final posture). Three initial postures of the mouth and tongue are shown. For the evoked movements shown in (A), (D), and (E), stimulation was at 50  A; (B), (C), and (G), 100  A; (F), 75  A. For all sites, stimulation trains were presented for 500 ms at 200 Hz.

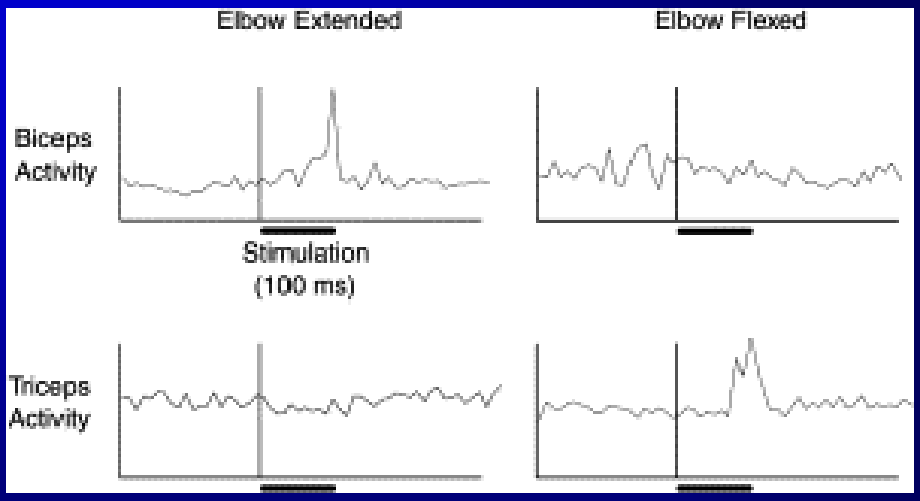



Figure 3. Electromyographic (EMG) Activity from Muscles of the Upper Arm during Stimulation of One Site in Primary Motor Cortex Stimulation at this site for 500 ms at 100 A evoked a final posture of the arm and hand including a partial flexion of the elbow. When the elbow was fully extended, stimulation caused it to flex to its final posture. When the elbow was fully flexed, stimulation caused it to extend to the final posture.

Graziano et al, 2004, JNP

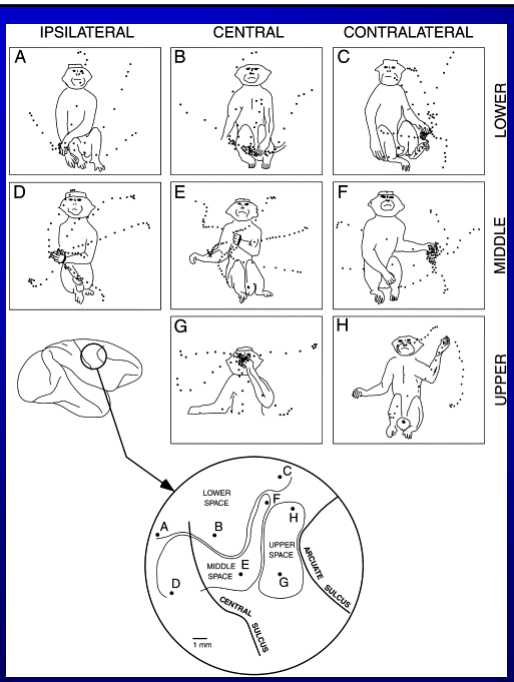



Figure 5. Eight Example Postures Illustrating the Topographic Map Found in Precentral Cortex of Monkey 1A similar map (not shown) was obtained in monkey 2. The circle on the brain shows the area that could be reached with the electrode. The magnified view at the bottom shows the locations of the stimulation sites. The area to the left of the lip of the central sulcus represents the anterior bank of the sulcus. Stimulation on the right side of the brain caused movements mainly of the left side of the body. Postures of the right arm shown in these traced video frames are incidental and not dependant on the stimulation. For the evoked movements shown in (A) and (G), stimulation was at 50 A. In (B)–(F) and (H), stimulation was at 100 A. For all sites, stimulation trains were presented for 500 ms at 200 Hz.

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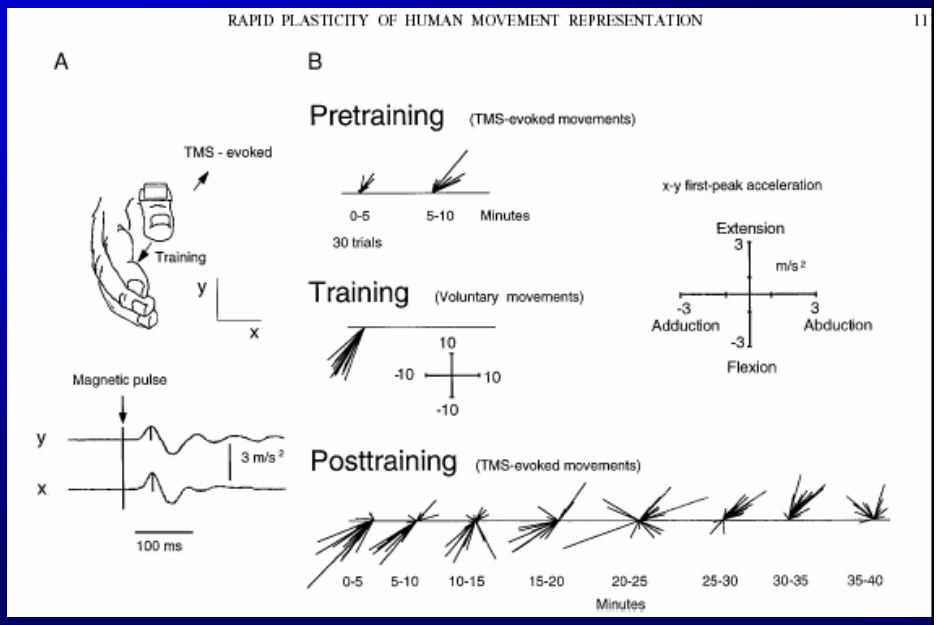


Classen et al ,1998, *JNP*

# conclusions

From these results, it appears likely that the motor cortex undergoes continuous plastic modifications. Frequently repeated movements reinforce particular network connectional patterns, but those patterns weaken if the movements have not been recently executed. This principle may underlie the beneficial effect of preperformance practice ( e.g., in athletics or musical performance). It also may be a requirement for purposeful skill acquisition in intact humans and in the rehabilitation of persons with brain damage

The main mechanisms that have been suggested for mediating reorganization in the cerebral cortex involve the unmasking of existing, but latent, horizontal connections (for a review, see Sanes and Donoghue 2000)

Modulation of synaptic efficacy such as long-term potentiation (LTP) (Hess and Donoghue 1994; Hess and others 1996) or long-term depression (LTD) (Hess and Donoghue 1996). Such modification of synaptic efficacy was recently demonstrated in the horizontal connections in the motor cortex of rats that underwent training of a skilled motor task (Rioult-Pedotti and others 1998).

Concept that the motor cortex contains multiple overlapping motor representations (Donoghue and others 1992; Schieber and Hibbard 1993; Sanes and others 1995) functionally connected through an extensive horizontal network (Huntley and Jones 1991).

Although connections are abundant within somatic representations, they are sparse between them (Huntley and Jones 1991). By changing the strength of horizontal connections between motor neurons, functionally different neuronal assemblies can form, thereby providing a substrate to construct dynamic motor output zones.

# Pharmacological modulations

- Lorazepan (LZ): $GABA_A$ enhancement, blocks induction of LTP
- Dextromethorphan (DM): blocks NMDA receptors involved in LTP induction
- Lamotrigine (LTG): gating of NA+ and Ca++ without affecting LTP induction