Cognitive Neurophysiology of the Motor Cortex

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A major challenge of current neuroscience is to elucidate the brain mechanisms that underlie cognitive function. There is no doubt that cognitive processing in the brain engages large populations of cells. This article explores the logic of investigating these problems by combining psychological studies in human subjects and neurophysiological studies of neuronal populations in the motor cortex of behaving monkeys. The results obtained show that time-varying psychological processes can be visualized in the time-varying activity of neuronal populations. Moreover, the functional interactions between cells in the motor cortex are very similar to those observed in a massively interconnected artificial network performing the same computation.

The recording of the activity of single cells in the brain of behaving animals provides a tool for directly studying the functional properties of single cells, interactions between cells, and the dynamics of neuronal populations involved in a variety of cognitive processes, including attention, memory, perception, and motor intention. This method was introduced 36 years ago by Ricci, Doane, and Jasper (*1*) and was perfected and popularized later by Evarts (*2*). Evarts saw it as the only way to study voluntary movement, a function that by definition cannot be studied in anesthetized preparations. His and subsequent studies showed that changes in cell activity in the motor cortex precede the development of the motor output and relate quantitatively to its intensity (*3*) and spatial characteristics (*4–7*).

The main challenge with data obtained with this technique in studies of cognitive function is their interpretation. For example, a common finding is that cell activity changes in a certain brain area during a particular cognitive process. The crucial question is: how can we deduce the time-varying cognitive process from the single-cell recordings? How can purely temporal series of action potentials (spike trains) yield information about a cognitive process unfolding in time?

To solve this problem, one must realize that a cognitive process usually operates on a variable; for example, mental arithmetic operates on numbers. The process, then, is the operation, and the puzzle of how the brain performs multiplication is transformed to the problem of how numbers are being multiplied. The crucial idea is that if we can decipher the neural coding of numbers, then we have a good chance of deciphering the cognitive process of mental multiplication by observing neural activity during this process, recovering the numbers by decoding, and inferring how they are being operated upon in this particular process. The essence of the idea is that solving the problem of neural coding of a particular variable provides the means for potentially solving the problem of cognitive processing of that variable. These logical steps are shown in Table 1. The crucial step is step 2, namely that of neural coding. This is the step that connects cell activity with the variable of interest—that is, the step that provides the link between the neural dimension and the dimension of the variable. We illustrate below the successful application of this sequence of investigation to the study of cognitive processes involving motor operations in space. For that purpose, we chose the direction of reaching movement as the spatial variable of interest. We wanted to know how directional information is encoded in the motor cortex and how cognitive processes operating on direction (for example, memory or mental rotation) are reflected in motor cortical activity.

Table 1. Steps in deciphering brain mechanisms of cognitive processes.

1. Select a variable of interest.
2. Find the neural coding of the variable outside the cognitive process.
3. Select a cognitive process operating on the variable of interest.
4. Record brain activity during cognitive processing and infer how the variable is operated on.

The Problem of Coding: Single Cells and Neuronal Populations

The problem with the coding of the direction of movement in space is that direction is a closed (circular or spherical) variable and as such does not lend itself to simple monotonic coding by the intensity of cell activity. A possible simple solution to the problem would be to allocate cells that would be specifically activated only with movements in a particular direction—that is, for cells to be sharply tuned to the direction of movement. However, this is not the case. Instead, cells in the motor cortex (*4–7*) as well as in other structures (*8, 9*) are broadly tuned to the direction of movement. This means that the cell activity is highest for a movement in a particular direction (the cell's preferred direction) and decreases progressively with movements farther away from this direction. The changes in cell activity relate to the direction and not the target of the reaching movement (*10*). Quantitatively, the crucial variable on which cell activity depends is the angle formed between the direction of the movement and the cell's preferred direction: the intensity of cell activity can be approximated as a linear function of the cosine of this angle (*4–9*). The directional tuning equation is

$$D_i(\mathbf{M}_k) = b_i + a_i \cos \theta_{\mathbf{C}_i\mathbf{M}_k} \qquad (1)$$

where $D_i(\mathbf{M}_k)$ is the discharge rate of the i^{th} cell with movement in direction $\mathbf{M}_k$, b_i and a_i are regression coefficients, and $\theta_{\mathbf{C}_i\mathbf{M}_k}$ is the angle between the direction of movement $\mathbf{M}_k$ and the cell's preferred direction $\mathbf{C}_i$. An example is shown in Fig. 1. Some points concerning preferred directions are noteworthy. First, cells in a cortical column tend to have very similar preferred directions (*11*). Second, particular preferred directions are multiply represented in the motor cortex (*11*). And third, the preferred directions of single cells are not clustered in particular directions but range throughout the directional continuum (*4–9*) (Fig. 2). This indicates a distributed vectorial coding rather than coding of a coordinate frame (*12*); for example, if such a frame were Cartesian, the preferred directions would have clustered along the three cardinal directions.

The broad directional tuning indicates that a given cell participates in movements of various directions; from this result and from the fact that preferred directions range widely, it follows that a movement in a particular direction will involve the engagement of a

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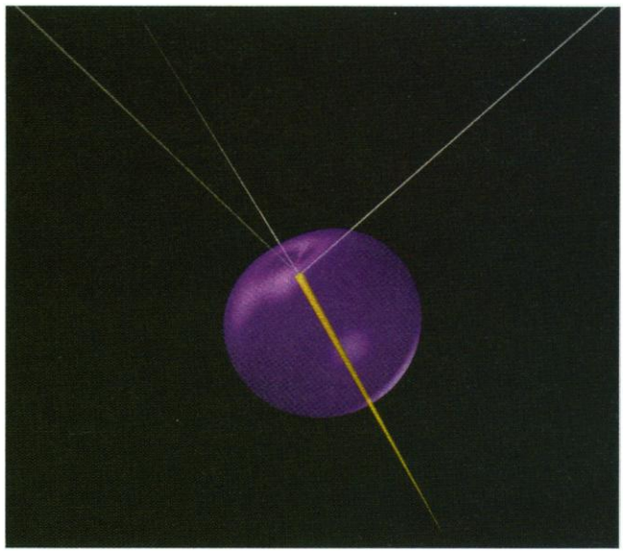

Fig. 1. Three-dimensional directional tuning. The axes (white) meet at the origin of the movement. For a particular movement, the discharge rate of the cell predicted by Eq. 1 is proportional to the length of a line pointing in the direction of the movement and drawn from the origin to the surface (purple)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

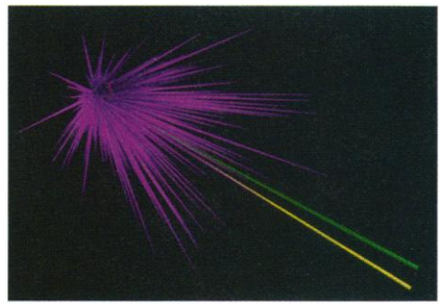

Fig. 3. The population vector (green) obtained from the set of cells with preferred directions shown in Fig. 2. The direction of movement is shown in yellow.

whole population of cells. How, then, is the direction of reaching encoded in an unambiguous fashion in a population of neurons, each of which is directionally broadly tuned? To answer this question, we hypothesized that the motor cortical command for the direction of reaching can be regarded as an ensemble of vectors (*13, 14*) in which each vector represents the contribution of a directionally tuned cell. A particular vector points in the cell's preferred direction and has a length proportional to the change in cell activity associated with a particular movement direction. For a given movement $\mathbf{M}_k$, the vector sum of these weighted cell vectors (the neuronal population vector **P**) can be regarded as the outcome of the ensemble operation

$$\mathbf{P}(\mathbf{M}_k) = \sum_i V_i(\mathbf{M}_k)\mathbf{C}_i \qquad (2)$$

where $\mathbf{C}_i$ is the preferred direction (*4*) of the i^{th} cell and $V_i(\mathbf{M}_k)$ is the activity of the i^{th} cell averaged over a period of time (for example, the reaction time). The population vector points at or near the direction of the movement (*12–16*) (Fig. 3). Three aspects of the population vector are noteworthy: its simplicity, its robustness, and its spatial characteristics. First, the calculation of the population vector is a simple procedure for it (i) assumes directional selectivity of single cells, which is apparent; (ii) weights vectorial contributions by single cells on the basis of the change in cell activity, which is reasonable; and (iii) is the outcome of the vectorial summation of these contributions, which is practically the simplest procedure to obtain a unique outcome. Second, the population vector is a robust measure, for it can still convey a good directional signal even with relatively few (100 to 150) cells (*15*). And third, the population vector is a spatial measure. The population analysis transforms aggregates of purely temporal spike trains into a spatiotemporal population vector.

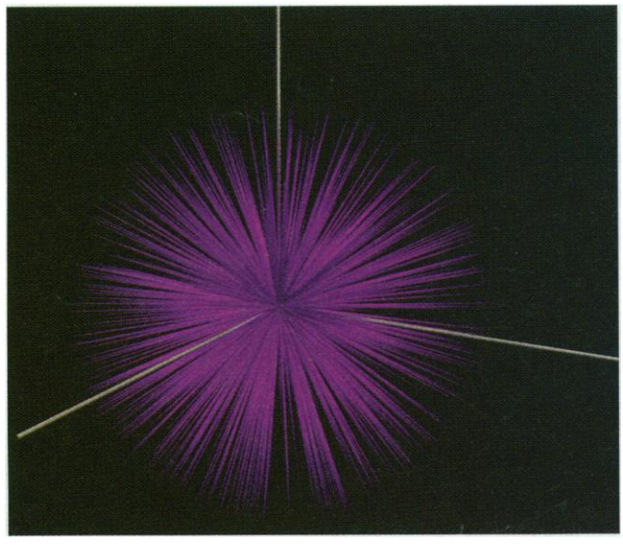

Fig. 2. Three-dimensional preferred directions (purple) of 634 motor cortical cells studied in three monkeys. The axes are in white.

The neuronal population performing the vectorial operation consists only of directionally tuned cells. Given that the preferred direction seems to be represented in cortical columns (*11*) and that the population operation involves cells with different preferred directions, it follows that this operation has to be intercolumnar. Moreover, the population vector is a good predictor of the direction of movement when it is calculated separately from subsets of cells recorded in the upper or lower cortical layers (*17*).

The neuronal population vector has proved to be a robust and accurate measure of the directional tendency of a neuronal ensemble under a variety of conditions, including movements from different origins (*9, 18*), continuous drawing movements (*19*), and isometric force pulses (*6*). Moreover, the analysis holds in other structures concerned with sensorimotor control (*8, 9*) or visual processing (*20*). Single cell activity is broadly tuned in other areas (*21*) and for other movements (*22*), although a population vector analysis has not been performed. Finally, a cosine directional tuning was observed in the elements of the hidden layer of a three-layer artificial network trained to perform the population vector operation (*23*).

Especially interesting is a recent generalization of the application of the population vector analysis to the coding of faces in the discharge of cells in the inferotemporal cortex of monkeys (*24*). In the studies of the motor cortex, the population vector and the vectorial contributions of single cells were in directions in physical space. The face coding study generalized the vector approach to an arbitrary space of multidimensional scaling of the similarity of face features. Thus, space need not be physical but can be any *n*-dimensional feature space. Even for motor function, this can be a powerful approach. For example, an interesting question is how the motor cortex controls finger movements during hand manipulation of objects that involve a large number of combinations of

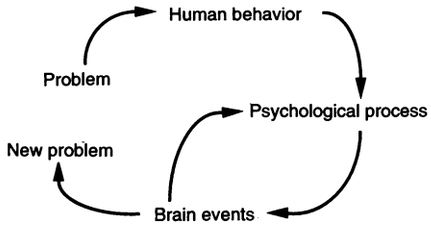

Fig. 4. Cognitive neuroscience loop.

finger movements. The hypothesis would be that (i) single cells code for combinations of manipulatory movements, (ii) a particular cell discharges most for a preferred combination, (iii) the intensity of cell activation follows a broad, possibly cosine, tuning with the various movement combinations when they are expressed in a continuum of similarity in a reduced "movement combination space," and (iv) when cell contributions are expressed as weighted vectors in the latter space, their vector sum (population vector) would provide an unequivocal signal for the coding of a particular manipulatory movement combination. Given a task that can provide the requisite variety of movement combinations, the hypothesis above can be tested rigorously.

The Population Vector as a Temporal Probe of Direction

The population vector can be used as a probe by which to monitor in time the changing directional tendency of the neuronal ensemble. One can obtain the time evolution of the population vector (Eq. 2) by calculating it at short successive intervals t (for example, every 10 or 20 ms) or continuously, during periods of interest:

$$\mathbf{P}(\mathbf{M}_k;t) = \sum_i V_i(\mathbf{M}_k;t)\mathbf{C}_i \qquad (3)$$

Thus, cortical mechanisms that underlie specific processes (for example, memorization) could be followed by observation of the time-varying population vector.

The feasibility of this approach was first documented when it was shown that the neuronal population vector predicts the direction of movement during the reaction time (*11, 14*). The visual reaction time is a period of approximately 300 ms that intervenes between the appearance of a visual target and the initiation of movement; during this period, the upcoming movement is being planned and its execution initiated. This is the simplest case of predicting the direction of the upcoming movement. In addition, the population vector predicts well the direction of movement during an instructed delay period (*25*). In these experiments, monkeys were trained to withhold the movement for a period of time after the onset of a visual cue signal and to move later in response to a "go" signal. During this instructed delay period, the population vector gave a reliable signal concerning the direction of the movement that was triggered later for execution. Finally, in an even more complex task, the population vector predicted well the direction of movement during a memorized delay period (*26*). In these experiments, the target of the movement was shown for only 300 ms. The monkeys were trained to withhold the movement for a subsequent period of time, during which the target was off, and then moved in the direction of the memorized target in response to a "go" signal. During this memorized delay period, the population vector pointed in the direction of the memorized movement.

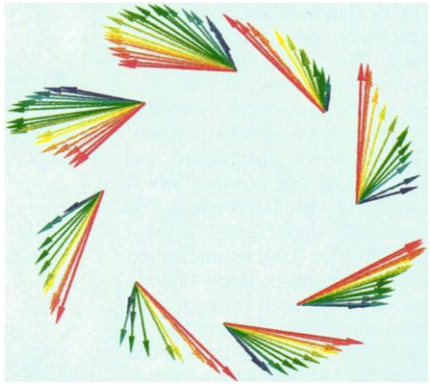

Fig. 5. Rotation of the neuronal population vector during the reaction time from the direction of the stimulus (blue) to the direction of the movement (red). Data from all eight stimulus directions used (*31*) are shown.

Neural Mechanisms of a Cognitive Process: Mental Rotation

The cognitive process we chose for study involved a transformation of an intended movement direction. Our general approach in studying the brain mechanisms of a cognitive function involves (i) defining the cognitive task, (ii) performing psychological experiments in human subjects, the results of which lead to hypotheses concerning the nature of the cognitive process, (iii) training monkeys to perform the same task and recording the activity of single cells in the brains of these animals during performance of the task, and (iv) connecting the neural results with those of the human studies and interpreting the psychological results on the basis of the neurophysiological ones. This cycle is illustrated in Fig. 4: the objective is to get as close as possible to relating neurophysiology and cognitive psychology. Below, we describe these steps as they were applied to a particular problem of a mental transformation of movement direction. Subjects were required to move a handle at an angle from a reference direction defined by a visual stimulus on a plane. Because the reference direction changed from trial to trial, the task required that in a given trial the direction of movement be specified according to this reference direction.

In human studies, subjects performed blocks of 20 trials in which the angle and its departure (counterclockwise or clockwise) were fixed, although the reference direction varied (*27*). Seven angles (5° to 140°) were used. The basic finding was that the reaction time increased in a linear fashion with the angle. The most parsimonious hypothesis to explain this result is that subjects arrive at the correct direction of movement by shifting their motor intention from the reference direction to the movement direction, traveling through the intermediate angular space. This idea is very similar to the mental rotation hypothesis advanced by Shepard and co-workers (*28*) to explain the monotonic increase of the reaction time with orientation angle about when a judgment has to be made about whether a visual image is normal or mirror-image. Interestingly, the mean rates of rotation (approximately 400° per second) and their range among subjects are very similar in both kinds of study. When the same human subjects performed both perceptual and motor rotation tasks, their processing rates were positively correlated (*29*), a result that indicates similar processing constraints for both tasks.

The results of neurophysiological studies (*30, 31*) provided direct evidence for the mental rotation hypothesis. Rhesus monkeys were trained to move the handle 90° and counterclockwise from a reference direction. The population vector rotated during the reaction time from the stimulus (reference) direction to the direction of the movement through the counterclockwise angle. This is illustrated in Fig. 5. The occurrence of a true rotation was further documented by showing that there was a transient increase during the middle of the reaction time in the recruitment of cells with preferred directions between the stimulus and movement directions (*31*). This neural rotation process, sweeping through the directionally tuned ensemble, provided for the first time a direct visualization of a dynamic cognitive process (*32*). The mean rotation rate and the range of rates observed for different reference directions (*31*) were very similar to those obtained in the human studies (*27, 29*).

The Motor Cortex as a Network: Real and Artificial

The population vector and its transformations are the results of operations within an

ensemble of cells. The cell activity is, in turn, the result of converging influences on the motor cortex of both external signals from other brain areas and of intrinsic interactions among the motor cortical cells. We investigated these local interactions by recording the impulse activity of several cells simultaneously by using seven independently movable microelectrodes (*33*). The data used here come from recordings of impulse activity during the reaction and movement time in the motor cortex of five monkeys during the performance of a reaching task (*4*). The seven electrodes were arranged in a linear array every 0.6 mm; cells were recorded at all interelectrode distances. A total of 1728 pairs were used in this analysis; in 1126 pairs, both cells in a pair were directionally tuned, whereas in the remaining 602 pairs none of the two cells in a pair were tuned. We wanted to know whether the prevalence of significant interactions differed significantly between the tuned and nontuned pairs and whether the strength of interaction was correlated with the similarity of preferred directions of cells in a pair. For that purpose, we estimated the strength of presumed interaction (synaptic weight) from the i^{th} to the j^{th} neuron in a pair using an analysis based on waiting time probability density function (*34*). An example is illustrated in Fig. 6.

There were two major findings of our analysis. First, significant interactions were 2.25 times more frequent in the directionally tuned (203 of 1126 cells or 18%) than in the nontuned (48 of 602 or 8%) group ($P < 10^{-5}$; chi-square test); significant interactions in the tuned cell group were observed for cells recorded at all interelectrode distances. Second, the mean synaptic strength (*34*) was negatively correlated with the angle (0° to 180°) between the preferred directions of the two neurons [correlation coefficient (r) = −0.815; $P < 0.004$] (Fig. 7A) throughout the range of connections from positive (excitation) to negative (inhibition). This is illustrated in the cover photograph.

The presence of interactions among cells in the motor cortex has been suggested on morphological grounds (*35*) and demonstrated by electrophysiological techniques (*36*). Our results demonstrate that the directional tuning of motor cortical cells is a significant factor governing the strength of interactions between cells. This finding is qualitatively similar to that observed in the visual cortex regarding the association of cells with similar orientation tuning (*37*).

The importance of directional tuning for the presence of cell interactions and the dependence of the strength of these interactions on the similarity of preferred directions provide a fertile ground on which to test hypotheses concerning the organization of artificial neural networks performing a population operation (*23, 38*). For that purpose we used a single layer, extensively interconnected nonsymmetric network that consisted of directionally tuned cells and performed the calculation of the neuronal population vector. We wanted to know whether the strength of interactions between its elements depended on the similarity of their preferred directions, as observed in the motor cortex. The fact that the neuronal population vector remains stable after an initial growth (*11, 15*) implies that during this steady-state period the activities V_i (Eq. 3) cease to change, so that $dV_i/dt = 0$ for all i. Activities V_i can be represented as $V_i = g(u_i)$, where u_i is the internal state of the i^{th} neuron (u, for example, might represent the membrane potential of the neuron averaged over a reasonable time interval) and g is an activation function having a saturation nonlinearity. Assuming that the internal state u is a linear function of inputs received by the neuron from the other neurons in the network, then at a stable state ($dV_i/dt = 0$) the equality

$$V_i(\mathbf{M}_k) = g[\sum_j w_{ij} V_j(\mathbf{M}_k)] \qquad (4)$$

is valid for all neurons (*39*) and, generally, for all directions **M**. The weights w_{ij} in Eq. 4 can be regarded as synaptic connection strengths. If activities V_i at a stable state are known for a given number of neurons and for an appropriate number of directions **M**, Eq. 4 can be used for determining the parameters w_{ij}.

Equation 4 shows that the stability of the population vector could be ensured by an appropriate set of synaptic connection strengths w_{ij}. To determine the general features of the sets of these strengths that would ensure stability, we searched for parameters w within different ranges of possible values $|w| < d$ (where d is a restriction parameter) and for different numbers of neurons N in a network. In routine calculations, the activation function g in Eq. 4 was specified as $g(u) = \tanh u$. A cosine tuning function was chosen for activities $V_i(\mathbf{M}_k)$ in accordance with experimental findings (*4*): $V_i(\mathbf{M}_k) = a_i \cos \theta_{ik}$ (Eq. 1), where a_i is a positive number and θ_{ik} is the angle between the preferred direction of the i^{th} cell ($\mathbf{C}_i$) and the direction of upcoming movement ($\mathbf{M}_k$). Directions $\mathbf{C}_i$ and $\mathbf{M}_k$ were randomly and uniformly distributed in space, and the values of a were randomly and uniformly distributed on the interval [0,1]. For each set of N randomly selected, cell-preferred directions and of K randomly selected movement directions, we obtained values of

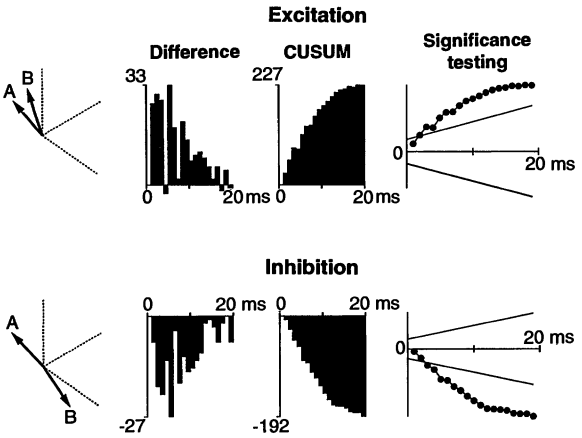

Fig. 6. Dependence of cell interactions on their preferred directions. Two cases illustrate the methods described in (*34*). Upper row, a case of cells with similar preferred directions (arrows). The "difference distribution" and the CUSUM are positive, which indicates an excitatory effect. The statistical significance of the CUSUM ($P < 0.04$) is established when it crosses the upper chance line. Lower row, a case of cells with very different preferred directions. The "difference distribution" and the CUSUM are negative, which indicates an inhibitory effect.

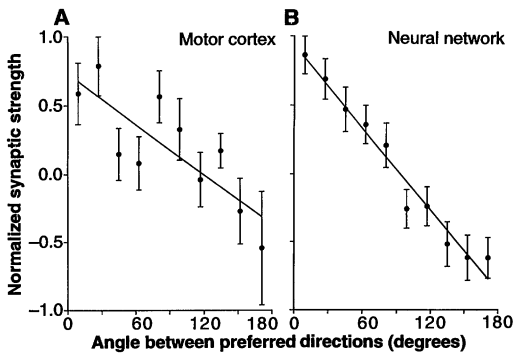

Fig. 7. The dependence of the mean value (± SEM) of synaptic strength on the angle between preferred directions of neurons involved in the connection. We calculated the mean value of synaptic strength by averaging over synaptic strengths between neurons, the preferred directions of which did not differ from each other by more than 18°. (**A**) Results from 203 pairs of directionally tuned neurons with significant interactions recorded simultaneously in the monkey motor cortex. The total number of values averaged for each of ten points plotted (from left to right) are 25, 33, 22, 24, 16, 21, 15, 15, 18, and 14. (**B**) Results of simulations for $N = 32$, $K = 32$, and $d = 0.2$. The total number of values averaged for each of ten points plotted (from left to right) are 134, 104, 104, 94, 94, 90, 96, 108, 100, and 100.

the w parameters that ensured the conditions described in Eq. 4 above by minimizing a cost function without assuming a symmetry of the matrix w_{ij} (*40*).

Figure 7B shows the result of the calculations for $d = 0.2$ and $N = 32$. The normalized mean value of synaptic connection strength w is plotted against the angle between the preferred directions of interconnected neurons: these parameters are negatively correlated ($r = -0.984$). Our calculations for different values of d and N confirmed that this correlation is always strong enough if possible values of synaptic connection strengths are restricted to $d \sim 1/N$ but practically disappears when the restriction becomes weak ($d \sim 1$) (*41*).

These simulation studies showed that weakly interconnected but correlated neurons can ensure the stability of the population vector. It is likely that converging external inputs initiate the changes in activity in the motor cortex and contribute to the ongoing activity of the population. However, such external contributions can be understood and evaluated properly only within the context of the dynamics of the cortical network itself. Our results show that the network can by itself support a stable process, which leads to the idea that external inputs may act as initiators or modifiers but need not be the exclusive determinants of this intrinsic process.

There are three points worth mentioning in comparing our data from the neural and artificial networks. First, the interactions between directionally tuned cells predicted by the network model were confirmed by the results of the neurophysiological studies. Second, the emphasis in our modeling on intrinsic cell interactions as means for sustaining cell activities within the network is warranted by the recent emphasis on intrinsic cortical interactions as means for amplifying and sustaining cortical excitation (*42*). And third, the prediction by our model that extensive but weak interactions are sufficient for the stability of a network operation provides a reasonable explanation of, and a possible function for, the extensive (*35*) but weak interactions observed between cortical cells (*43*).

Conclusion

Major progress has been made during the past decade toward determining the functional properties of single motor cortical cells with respect to behavior and the understanding of operations by neuronal populations. This knowledge, combined with an elucidation of the interactions among cells and rigorous network modeling, should lead to an understanding of how the cortex works and how cognitive operations are processed in specific brain areas. A limitation of the single cell recording technique is that it can be usually applied only to one restricted brain area at a time. Other techniques, including positron emission tomography, can provide a greater picture of areas of activation in the brain during performance of a task. A new major tool is the oxygen-based functional imaging of the brain with the use of nuclear magnetic resonance (*44*). This technique is noninvasive, sensitive, does not require averaging of data from more than one subject, possesses adequate resolution, and has already been successfully applied to imaging of the human motor cortex (*45*). This method provides information complementary to that obtained by single cell recordings and, together with the latter, can lead to major insights in brain function.

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39. Equation 4 is the usual condition for a desired state of the neuronal ensemble $V_i(\mathbf{M})$ to be an attractor of standard dynamical rules used in neural network theory [S. Amari, *IEEE Trans. Syst. Man Cybern.* **SMC-2**, 643 (1972); T. J. Sejnowski, *Biol. Cybern.* **22**, 203 (1976); S. Grossberg and M. Cohen, *IEEE Trans. Syst. Man Cybern.* **SMC-13**, 815 (1983); J. J. Hopfield, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 3088 (1984); A. Atiya and P. Baldi, *Int. J. Neural Syst.* **1**, 103 (1989)].
40. The cost function (F) was the following:

$$F(w) = (1/NK) \sum_{k}^{K} \sum_{i}^{N} |a_i \cos \theta_{ik} - g(\sum_{j} w_{ij} a_j \cos \theta_{jk})| \quad (5)$$

In routine calculations, the number of neurons N and the number of directions K were varied from 8 to 64. Initially, all w values were assigned randomly ($F \sim 0.5$) on the interval $|w| < d$, where d is the restriction parameter, and then the parameters w were adjusted to reduce the F function down to 10^{-5}. The latter procedure was carried out for $|w| < d$ by means of the simulated annealing algorithm [S. Kirkpatrick, C. D. Gelatt, Jr., M. P. Vecchi, *Science* **220**, 671 (1983)] with an annealing schedule fitted for the present problem. The cost function above was treated as "energy" of the system. Standard Monte Carlo procedures of changes in the w parameters were used to obtain the Boltzmann distribution over states (that is, sets of the w parameters) for a given "temperature." Generally, if the cooling of the system is slow enough (annealing procedure) the approach guarantees the achievement of the global minimum of the system at zero "temperature": this means that the resulting set of the w parameters provides the global minimum $F(w) = 0$ of the energy function (Eq. 5). We checked additionally that sets of the w parameters ensuring $F < 10^{-5}$ indeed yielded stable attractors when standard dynamical equations (*39*) were used to describe the temporal behavior of the neuronal ensemble. Moreover, we have checked the robustness of the results in respect to different series of random numbers used in the generation of a particular set of preferred directions and during the realization of the simulated annealing procedure (ten trials for each set of N and d values).
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