Mental Rotation of the Neuronal Population Vector

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A rhesus monkey was trained to move its arm in a direction that was perpendicular to and counterclockwise from the direction of a target light that changed in position from trial to trial. Solution of this problem was hypothesized to involve the creation and mental rotation of an imagined movement vector from the direction of the light to the direction of the movement. This hypothesis was tested directly by recording the activity of cells in the motor cortex during performance of the task and computing the neuronal population vector in successive time intervals during the reaction time. The population vector rotated gradually counterclockwise from the direction of the light to the direction of the movement at an average rate of 732° per second. These results provide direct, neural evidence for the mental rotation hypothesis and indicate that the neuronal population vector is a useful tool for "reading out" and identifying cognitive operations of neuronal ensembles.

A FUNDAMENTAL PROBLEM IN COGnitive neuroscience is the identification and elucidation of brain events underlying cognitive operations (1). The technique of recording the activity of single cells in the brain of behaving animals (2) provides a direct tool for that purpose. Indeed, a wealth of knowledge has accumulated during the past 15 years concerning the activity of cells in several brain areas during performance by monkeys of complex tasks. A major finding of these studies has been that the activity of single cells in specific areas of the cerebral cortex changes during performance of particular tasks; these changes are thought to reflect the participation of the area under study in the cognitive function involved in the task (3). However, a direct visualization of a cognitive operation in terms of neuronal activation in the brain is lacking.
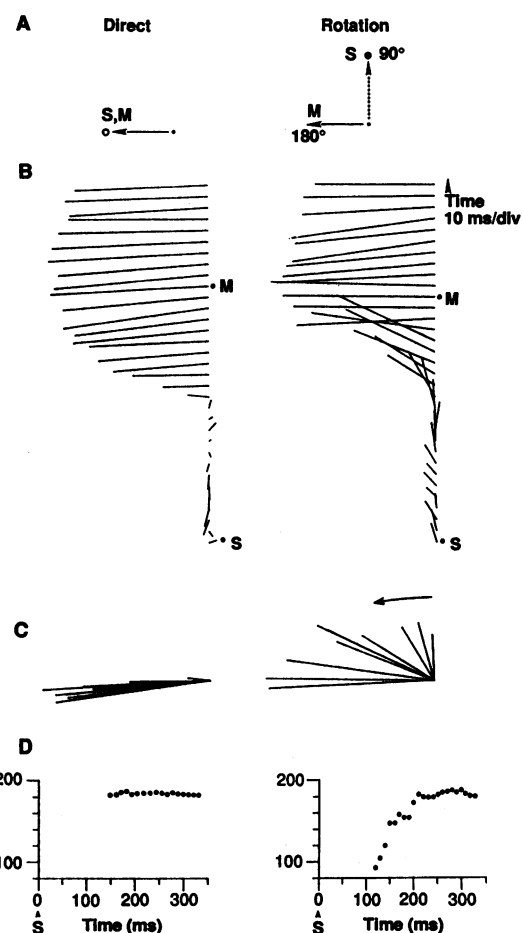
We chose as a test case for this problem the cognitive operation of mental rotation. Important work in experimental psychology during the past 20 years (4) has established the mental rotation paradigm as a standard in cognitive psychology and as a prime tool in investigating cognitive operations of the "analog" type. We adapted this procedure in a task that required movement of a handle in a direction that was at an angle with the

direction of a stimulus. Under these conditions the reaction time increased with the angle, which suggests that the subject may solve this problem by a mental rotation of an imagined movement vector from the direction of the stimulus to the direction of the actual movement (5). Now, the direction of an upcoming movement in space seems to be represented in the motor cortex as the neuronal population vector (6), which is a

weighted vector sum of contributions ("votes") of directionally tuned neurons: each neuron is assumed to vote in its own preferred direction with a strength that depends on how much the activity of the neuron changes for the movement under consideration. This vectorial analysis has proved useful in visualizing the directionality of the population in two- and threedimensional space during the reaction time (7) and during an instructed delay period (8).

Given the mental rotation hypothesis above and the neuronal population vector as a neural representation of the movement direction, a strong test is as follows: if a monkey performs in the above-mentioned task and the neuronal activity in the motor cortex is recorded during performance, would the population vector rotate in time, as the hypothesis for a mental rotation of an imagined movement vector would predict? Because the appropriate movement direction can be arrived at by either a counterclockwise or a clockwise rotation, which of these two rotations would be realized by the population vector? Of course, there is no reason that the population vector should rotate at all, and if it rotates, there is no a

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Fig. 1. Results from a direct (left) and rotation (right) movement. (**A**) Task. Unfilled and filled circles indicate dim and bright light, respectively. Interrupted and continuous lines with arrows indicate stimulus (S) and movement (M) direction, respectively. (**B**) Neuronal population vectors calculated every 10 ms from the onset of the stimulus (S) at positions shown in (A) until after the onset of the movement (M). When the population vector lengthens, for the direct case (left) it points in the direction of the movement, whereas for the rotation case it points initially in the direction of the stimulus and then rotates counterclockwise (from 12 o'clock to 9 o'clock) and points in the direction of the movement. (**C**) Ten successive population vectors from (B) are shown in a spatial plot, starting from the first population vector that increased significantly in length. Notice the counterclockwise rotation of the population vector (right panel). (**D**) Scatter plots of the direction of the population vector as a function of time, starting from the first population vector that increased significantly in length after stimulus onset (S). For the direct case (left panel) the direction of the population vector is in the direction of the movement (~180°); for the rotation case (right panel) the direction of the population vector rotates counterclockwise from the direction of the stimulus (~90°) to the direction of the movement (~180°).

priori reason that it should rotate in one or the other direction; for all we know, any of these alternatives is possible.

The activity of single cells in the motor cortex was recorded (9) while a rhesus monkey performed in the mental rotation task. In the beginning of a trial, a light appeared at the center of a plane in front of the animal, which moved its arm toward the light with a freely movable handle (10). After a variable period of time (0.75 to 2.25 s), the center light was turned off and turned on again, dim or bright, at one of eight positions on a circle of 2-cm radius (11). The monkey was trained to move the handle in the direction of the light when it came on dim (direct trials) or in a direction that was perpendicular (90°) to and counterclockwise from the direction of the light when it came on bright (rotation trials) (12). The movements of the animal were in the appropriate direction for both kinds of trials. The neuronal population vector was calculated every 10 ms starting from the onset of the peripheral light (that is, at the beginning of the

Fig. 2. Rotation of the population vector for a different set of rotation trials. The stimulus and movement directions are indicated by the interrupted and continuous lines at the top. The population vector in the two-dimensional space is shown for successive time frames beginning 90 ms after stimulus onset. Notice its rotation counterclockwise from the direction of the stimulus to the direction of the movement.

reaction time). The preferred direction of each cell ($n = 102$ cells) was determined from the cell activity in the trials in which the animal moved toward the light (direct trials). For the calculation of the population vector, peristimulus time histograms (10-ms binwidth) were computed for each cell and each of the 16 combinations (classes) used [eight positions and two conditions (direct or rotation), see (11) above] with counts of fractional interspike intervals as a measure of the intensity of cell discharge. A square root transformation was applied to these counts to stabilize the variance (13). For a given time bin, each cell made a vectorial contribution in the direction of the cell's preferred direction and of magnitude equal to the change in cell activity from that observed during 0.5 s preceding the onset of the peripheral stimulus (control rate, that is, while the monkey was holding the handle at the center of the plane). The population vector **P** for the jth class and k^{th} time bin is

$$\mathbf{P}_{j,k} = \sum_{i}^{102} w_{i,j,k} \mathbf{C}_i$$

where $\mathbf{C}_i$ is the preferred direction of the ith cell and $w_{i,j,k}$ is a weighting function $w_{i,j,k} = (d_{i,j,k}) - a_{i,j}$ where $d_{i,j,k}$ is the square root–transformed (13) discharge rate of the ith cell for the jth class and k^{th} time bin, and $a_{i,j}$ is the similarly transformed control rate of the ith cell for the jth class.

Figure 1 illustrates the results obtained when the movement direction was the same (toward 9 o'clock) but the stimulus was either at 9 o'clock (direct trials, left panel) or at 12 o'clock (rotation trials, right panel). In the direct trials the population vector pointed in the direction of the movement (which coincided with the direction of the stimulus) (Fig. 1, left). However, in the rotation trials the population vector rotated in time counterclockwise from the direction of the stimulus to the direction of the movement (Fig. 1, right). Another example is shown in Fig. 2 and illustrated in the cover photograph. The working space is outlined in blue. The time axis is the white line directed upwards. The population vector is shown in green, as it rotates during the reaction time from the stimulus direction (between 1 and 2 o'clock) to the movement direction (between 10 and 11 o'clock). The population vector was calculated with a 20-ms bin sliding every 2 ms. The red lines are projections of the population vector onto the working space.

The rotation of the population vector was a linear function of time with an average slope (for the eight positions of the light used) of $732 \pm 456°/s$ (mean $\pm$ SD). The population vector began to change in length 125 ± 28 ms (mean $\pm$ SD, $n = 8$) after the

stimulus onset. At this point its direction was close to the direction of the stimulus; the average angle between the direction of the population vector and that of the stimulus was 17° counterclockwise (the average absolute angle was 29°). The population vector stabilized in direction at 225 ± 50 ms after stimulus onset. At this point its direction was close to the direction of the movement; the average angle between the direction of the population vector and that of the movement was 0.5° clockwise (the average absolute angle was 8°). Finally, the movement began 260 ± 30 ms after stimulus onset, that is, 35 ms after the direction of the population vector became relatively stable; this difference was statistically significant ($P < 0.02$, paired t test).

These results support the hypothesis that the directional transformation required by the task was achieved by a counterclockwise rotation of an imagined movement vector. This process was reflected in the gradual change of activity of motor cortical cells, which led to the gradual rotation of the vectorial distribution of the neuronal ensemble and the population vector. The average slope of the rotation of the population vector (732°/s, see above) was comparable to but higher than that observed when human subjects performed a similar task (~400°/s) (5) and that observed in a task that involved mental rotation of two-dimensional images (~400°/s) (14). It is likely that all three experiments involved a process of mental rotation which, in the present case, was reflected in the motor cortical recordings of this study and identified by using the population vector analysis. Of course, other brain areas are probably involved in such complicated transformations; for example, recent experiments with measurements of regional cerebral blood flow (15) suggested that frontal and parietal areas seem to be involved in the mental rotation task of Shepard and Metzler (16), whereas frontal and central areas seem to be involved in a line orientation task (15); in both of these tasks there was a greater increase in blood flow in the right than in the left hemisphere.

The rotation of the neuronal population vector is of particular interest because there was no a priori reason for it to rotate at all. It is also interesting that the population vector rotated consistently in the counterclockwise direction: this suggests that the spatial-motor transformation imposed by the task was solved by a rotation through the shortest angular distance. Given that the mental rotation is time consuming, this solution was behaviorally meaningful, for it minimized both the time for the animal to get the reward and the computational effort which would have been longer if the rota-
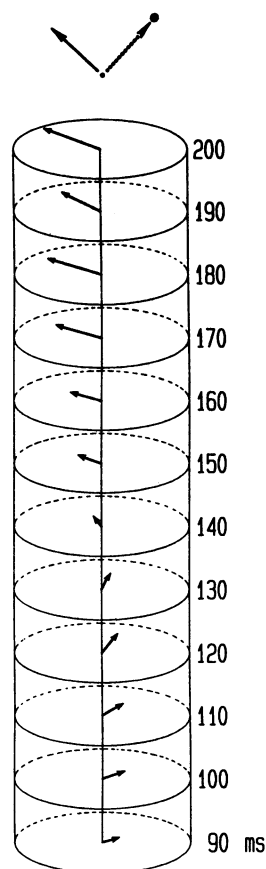
tion had been through 270° clockwise (17).

Finally, these results were obtained from one animal: because cognitive problems could be solved in different ways by different subjects, it is important that techniques for reading out brain operations be sensitive enough to be applied to single subjects. Indeed, the findings of our study indicate that the population vector is a sensitive tool by which an insight can be gained into the brain processes underlying cognitive operations in space.

REFERENCES AND NOTES

1. See, for example, V. B. Mountcastle, *Trends Neurosci.* 9, 505 (1986); M. A. Arbib and M. B. Hesse, *The Construction of Reality* (Cambridge Univ. Press, New York, 1986); J. Z. Young, *Philosophy and the Brain* (Oxford Univ. Press, New York, 1987).
2. R. N. Lemon, *Methods for Neuronal Recording in Conscious Animals* (Wiley, Chicester, 1984).
3. See, for example, *Handbook of Physiology*, Section 1, *The Nervous System, Higher Function of the Brain*, parts 1 and 2, V. B. Mountcastle, F. Plum, S. R. Geiger, Eds. (American Physiological Society, Bethesda, MD, 1987), vol. 5.
4. R. N. Shepard and J. Metzler, *Science* 171, 701 (1971); R. N. Shepard and L. A. Cooper, *Mental Images and Their Transformations* (MIT Press, Cambridge, MA, 1982).
5. A. P. Georgopoulos and J. T. Massey, *Exp. Brain Res.* 65, 361 (1987).
6. A. P. Georgopoulos, P. Caminiti, J. F. Kalaska, J. T. Massey, *ibid. Suppl.* 7, 327 (1983); A. P. Georgopoulos, A. B. Schwartz, R. E. Kettner, *Science* 233, 1416 (1986); *J. Neurosci.* 8, 2928 (1988).
7. A. P. Georgopoulos, J. F. Kalaska, M. D. Crutcher, R. Caminiti, J. T. Massey, in *Dynamic Aspects of Neocortical Function*, G. M. Edelman, W. E. Gall, W. M. Cowan, Eds. (Wiley, New York, 1984), pp. 501–524; A. P. Georgopoulos, A. B. Schwartz, R. E. Kettner, *J. Neurosci.* 8, 2928 (1988).
8. A. P. Georgopoulos, M. D. Crutcher, A. B. Schwartz, *Exp. Brain Res.*, in press.
9. The electrical signs of activity of individual cells in the arm area of the motor cortex contralateral to the performing arm were recorded extracellularly [A. P. Georgopoulos, J. F. Kalaska, R. Caminiti, J. T. Massey, *J. Neurosci.* 2, 1527 (1982)]. All surgical operations [A. P. Georgopoulos, J. F. Kalaska, R. Caminiti, J. T. Massey, *J. Neurosci.* 2, 1527 (1982)] for the preparation of the animal for electrophysiological recordings were performed under general pentobarbital anesthesia. Behavioral control and data collection and analysis were performed with a laboratory minicomputer.
10. The apparatus was as described in A. P. Georgopoulos and J. T. Massey [*Exp. Brain Res.* 65, 361 (1987)]. Briefly, it consisted of a 25 cm by 25 cm planar working surface made of frosted plexiglass onto which a He-Ne laser beam was back-projected with a system of mirrors and two galvanometers. The monkey (5 kg) sat comfortably on a primate chair and grasped a freely movable, articulated handle at its distal end, next to a 10-mm diameter transparent plexiglass circle within which the animal captured the center light.
11. The eight positions were equally spaced on the circle, that is, at angular intervals of 45°, and were the same throughout the experiment. The brightness condition (dim or bright) and the position of the light were mixed. The resulting 16 brightness-position combinations were randomized. Eight repetitions of these 16 combinations were presented in a randomized block design.
12. The term "counterclockwise" is simply descriptive; no counterclockwise or clockwise directions were indicated to the animal. The direction in which the animal was required to move can be described equivalently as either 90° counterclockwise or 270° clockwise. The animal received a liquid reward when

its movement exceeded 3 cm and stayed within ±25° of the direction required. The average direction of the actual movement trajectories was within ±5° of the direction required. Performance was over 70% correct trials.
13. The square root transformation was used as a variance-stabilizing transformation for counts [G. W. Snedecor and W. G. Cochran, *Statistical Methods* (Iowa State Univ. Press, Ames, Iowa, ed. 7, 1980), pp. 288–290.] Although the results obtained without this transformation were similar, the transformation is more appropriate because of the small size of the time bins (10 ms), and, therefore, the small number of counts.
14. L. A. Cooper and R. N. Shepard, in *Visual Information Processing*, W. G. Chase, Ed. (Academic Press, New York, 1973), pp. 75–176; L. A. Cooper,

Cognitive Psychol. 7, 20 (1975).
15. G. Deutsch, W. T. Bourbon, A. C. Papanicolaou, H. M. Eisenberg *Neuropsychologia* 26, 44 (1988).
16. R. N. Shepard and J. Metzler, *Science* 171, 701 (1971).
17. The same principles of minimization of the time-to-reward and of reduction of computation load, even at the expense of mechanical work, were observed in strategies developed by human subjects and monkeys in a different task [J. T. Massey, A. P. Schwartz, A. P. Georgopoulos, *Exp. Brain Res. Suppl.* 15, 242 (1986)].
18. We thank D. Brandt and N. Porter for help during some of the experiments. Supported by USPHS grants NS17413 and NS20868.

Technical Comments

Analysis of Ligand Binding Specificity of Receptor Chimeras

The elegant studies of Kobilka *et al.* (1) define the effects of exchange of individual transmembrane segments of α_2- and β_2-adrenergic receptors on the binding of the α_2-specific agonist p-aminoclonidine (PAC) and the β_2-specific agonist isoproterenol (ISO). Their results reveal a dominant role for transmembrane segment 7 in determining the specificity of binding of α_2-specific agonists versus that of β_2-specific agonists (1). Here I offer a quantitative analysis based on a calculation of the relative free energy of binding that further strengthens their conclusion.

The K_d value for a ligand defines its free energy of binding according to the relation $\Delta G = -RT\ln(1/K_d)$. Binding specificity of each receptor species for α_2-specific agonists versus that for β_2-specific agonists depends on the difference in the free energy of binding of the two ligands $\Delta(\Delta G) = RT\ln[K_d(PAC/K_d(ISO)]$. A plot of $\Delta(\Delta G)$ for binding of PAC versus that of ISO by each receptor chimera as a function of the number α_2 transmembrane segments in the chimera reveals progressive changes in the binding energy preference for these two ligands (Fig. 1). For the β_2-receptor and three chimeras having transmembrane segment 7 of the β_2-receptor (□), replacement of transmembrane segments 1 to 5 causes a reduction in the binding energy preference for ISO of approximately 0.8 kcal/mol for each segment replaced, as indicated by the linear relation of these points. Similarly, for the α_2-receptor and three chimeras having transmembrane segment 7 of the α_2-receptor (■), replacement of transmembrane segments 1 to 5 causes an increase in the binding energy preference for ISO of ap-

Fig. 1. Binding energy difference for α_2/β_2 receptor chimeras. The difference in Gibb's free energy of binding [$\Delta(\Delta G)$] of PAC and ISO was calculated from the agonist binding data of (1) with the use of the equation described in the text. $\Delta(\Delta G)$ values for the β_2-receptor and chimeras containing transmembrane segment 7 of the β_2-receptor are plotted versus the total number of α_2 transmembrane segments in the molecule (□). Similarly, $\Delta(\Delta G)$ values for the α_2-receptor and the chimeras containing transmembrane segment 7 of the α_2-receptor are also plotted versus the total number of α_2 transmembrane segments in the molecule (■). The individual α_2-receptor transmembrane segments in each molecule are indicated by the numerals with each data point. Note that substitution of transmembrane segment 7 displaces the linear relation by approximately 3.7 kcal/mol.