THE NEW COGNITIVE NEUROSCIENCES

Second Edition

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A BRADFORD BOOK
THE MIT PRESS
CAMBRIDGE, MASSACHUSETTS
LONDON, ENGLAND

37 Neural Mechanisms of Motor Cognitive Processes: Functional MRI and Neurophysiological Studies

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ABSTRACT The neural mechanisms of cognitive processes cannot be elucidated using a single method; instead, useful insight can be gained by employing various approaches. In this chapter, the author attempts a discussion in this direction, namely the investigation of the mechanisms underlying some motor cognitive processes using behavioral, neurophysiological, and functional neuroimaging methods.

At the extremes, pure motor or cognitive processes are separate, for example, in the cases of the stretch reflex or mental calculation. However, they commonly are associated to varying degrees, for example, when you play chess. In fact, chess playing can be regarded as a motor-cognitive task par excellence because it consists essentially of actual and imagined movements of the chess pieces and the hand. During the past several years, we have developed two tasks at the interface of motor and cognitive processing and used them to investigate the neural mechanisms underlying their performance. Specifically, both tasks require the making of hand movements at a different direction from a stimulus direction but based on different rules. In both tasks, human subjects and monkeys moved a two-dimensional (2-D) handle and responded to visual stimuli appearing on a display. In the first task, the movement had to be at a constant angle from the stimulus direction (Georgopoulos and Massey, 1987), whereas in the second task, the movement had to be selected based on the serial order of stimuli in a sequence (Georgopoulos and Lurito, 1991). The mechanisms involved in these two tasks were investigated using classical chronometric, experimental psychological methods (Georgopoulos and Massey, 1987; Georgopoulos and Lurito, 1991), functional magnetic resonance imaging (fMRI) of the brains of human subjects (Tagaris et al., 1998), and recording of the activity of single cells in the brain of behaving monkeys (Georgopoulos et al., 1989; Lurito, Georgakopoulos, and Georgopoulos, 1991; Pellizzer, Sargent, and Georgopoulos, 1995). Each of these investigations provided unique, crucial insights into the processes involved that were complementary with each other. However, each of these sets of studies gives only a partial view of the whole, and it is only after all the results are looked at together that one can get a more adequate glimpse of the whole problem. Following is a summary of the essential findings from these individual studies, with an attempt at the end to sketch the whole as I see it emerge from these partial views.

Behavior

In the mental rotation task, the subject had to move a handle at an angle (clock- or counterclockwise [CCW]) from a stimulus direction. Thus, the direction of the movement was spatially connected to the direction of the stimulus and was at a constant angular relation to it. Experiments in human subjects (Georgopoulos and Massey, 1987) showed that the response time (RT) increased as a linear function of the instructed angle. This finding suggested that the psychological process in this task involves a mental rotation of the motor intention from the direction of the stimulus to the direction of the movement. This is similar to the mental rotation of visual images proposed by Shepard and colleagues (see Shepard and Cooper, 1982) in a different setting.

In the context-recall memory-scanning task, the subject had to move the handle in a direction specified by a serial order rule with respect to the onset of a particular stimulus in a sequence. Two to seven stimuli were presented successively on a circle (list stimuli), and then one of them (except the last one) was shown again (test stimulus); the subject was required to move in the direction of the stimulus that followed the test stimulus in the list sequence. In this case, the RT was a linear function of the number of list stimuli (Georgopoulos and Lurito,

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1991). This finding suggested a memory scanning operation analogous to the one suggested by Sternberg (1969) for a visual recognition task.

Thus, these two tasks required that movements be made away from a stimulus direction but based on different rules, namely a spatial transformation or a temporal order rule. The monotonic increase of the RT with key task variables suggested two different psychological processes as the cardinal features of these tasks, namely mental rotation in the former and memory scanning in the latter task. The next step was to find out which brain areas are involved in these processes and how information is being processed at the neuronal level. For the former objective, we used fMRI; for the latter, we employed single-cell recordings in behaving monkeys.

Functional magnetic resonance imaging of mental rotation and memory scanning

GENERAL CONSIDERATIONS Functional brain imaging provides a means by which the patterns of activation of various brain areas in a task can be determined. The main advantage of these techniques is that they can provide functional activation images of the whole brain, but they lack functional specificity at the cellular level because the "activation" reflects changes in blood flow or metabolic signals that only indirectly relate to neuronal activity. Therefore, the data obtained from such studies are interpretable only in the context of other information (e.g., from neuropsychological or neurophysiological studies) concerning the role of specific areas in particular tasks. These considerations are exemplified in the results of our studies, discussed in a subsequent section.

THE TASKS USED: COGNITIVE OPERATIONS AND THEIR OPERANDA Cognitive processes do not happen in vacuo; essentially, they are operations carried out on operanda. For example, mental arithmetic operates on mental representations of numbers. A major objective of our studies has been to design experimental paradigms in which cognitive operations of interest and their operanda are chosen so as to provide distinct task dimensions. These task dimensions provide, in turn, an abstract space that serves as a guidepost for interpreting the results of functional imaging studies, an explanation of which follows.

We used four cognitive tasks in these experiments (Tagaris et al., 1998). They were combinations of two cognitive processes (mental rotation and memory scanning) operating on two kinds of operanda (visual images and intended arm movement direction). Thus, four operation–operandum combinations were generated, as illustrated in figure 37.1. We wanted to identify the brain activation patterns for each one of the four tasks and, hopefully, relate them in some abstract way to the tasks themselves. The crucial question is: Can we recover the dimensions of the tasks (i.e., operation and operandum) from the brain activation patterns?

Typical trials of the four cognitive tasks used are illustrated in the first column of figure 37.2 (see also color plate 22), and trials of matched "control" tasks are illustrated in the second column. In the visual mental rotation task (figure 37.2A), the letter G was shown rotated from −160° to +160° from the upright at 20° intervals, in a random order in different trials. Normal and mirror images of the letter were presented for each angle above. Subjects responded by pressing the left or the right of two buttons to indicate whether the letter was in normal or mirror image orientation, respectively. In the control task (figure 37.2), the same letter was shown in normal and upright positions, and the subjects responded simply by pressing a button without having to make any judgment. In the movement mental rotation task (figure 37.2B), an instruction angle was shown for 900 ms and was followed by a stimulus in 1 of 12 positions on a circle, every 30°; 12 stimuli were shown for each of five instruction angles (30° to 150° CCW, every 30°) in a randomized block design. Subjects responded by moving a joystick-controlled cursor in a direction away from the stimulus at the instructed angle. In the control task, a zero angle was instructed, and subjects responded by moving the joystick in the direction of the stimulus shown. In the context-recognition visual memory-scanning task (figure 37.2C), a sequence (list) of two to seven visual stimuli was shown in a random order on a circle, and then two consecutive (test) stimuli were shown again in the same or reverse sequence; subjects responded by pressing the left or the right of two buttons to indicate whether the two test stimuli were presented

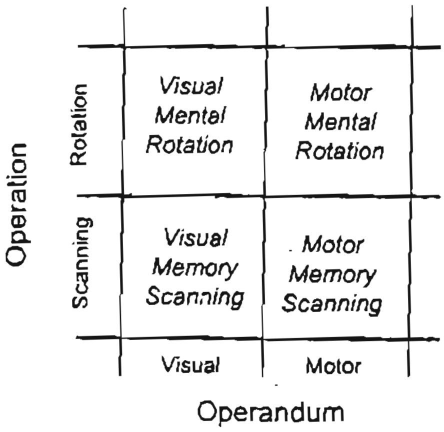

FIGURE 37.1 Experimental task design.

in the original or reverse sequence, respectively. In the control task, two to seven stimuli were shown but only one as a test stimulus, and the subjects responded by pressing a button without having to make any judgment. Finally, in the context-recall movement memory-scanning task (figure 37.2D), a sequence of two to seven stimuli was shown in a random order on a circle, and then one (test) stimulus (except the last) was shown again; subjects responded by moving a joystick-controlled cursor in the direction of the stimulus that was presented next to the test stimulus in the sequence. In the control task, the same display was shown, and the subjects responded by moving the joystick in the direction of the test stimulus. For both memory-scanning tasks, eight circular positions were used, every 45°. Each visual stimulus was shown for 600 ms and then went off while the next stimulus came on; the delay from the end of the presentation of the last stimulus to the onset of the first test stimulus was 900 ms.

Each of these four cognitive tasks was performed during the "task period," which was preceded and followed by a "control period," during which the corresponding control tasks were performed. The sequence of presentation of these four tasks was randomized. Key presses and directed movements were recorded using a nonmagnetic keypad and joystick, respectively. Directed movements were considered correct when they were within +30° from the required direction. The response time was measured with a precision of 1 ms. Eye movements were recorded during performance in the magnet by electro-oculography using Ag/AgCl electrodes and graphite wires. In general, eye movements were infrequent during data acquisition.

THE ISSUE OF CONTROL TASKS As expected, the RT increased as a linear function of the angle of rotation in the two mental rotation tasks or of the number of list stimuli in the two memory-scanning tasks used (data not shown). This suggests that the hypothesized operations were indeed employed in these tasks. The crucial item in interpreting the following results concerns the tasks performed during the control period because the judgment on whether a brain area was involved or not in these tasks rested on a statistical comparison between the fMRI signal during the task period and that during the control period. As explained previously, the control tasks differed for each of the four cases because our objective was to factor out the visuomotor events between the control and task periods, and thus isolate the particular cognitive condition under study, that is, the particular combination of a cognitive operation (i.e., mental rotation or memory scanning) and its operandum (i.e., visual image or intended arm movement direction) (figure 37.1). This design is crucial because if the control tasks were not matched for the corresponding cognitive ones with respect to simple visuomotor events (e.g., if, during the control period, the subjects simply rested with eyes closed), then the comparison between task and control periods would have reflected differences in simple sensorimotor processing in addition to the aforementioned cognitive aspects. Therefore, for the interpretation of the following results, the brain activation patterns observed refer to the cognitive aspects of the tasks employed.

BRAIN ACTIVATION PATTERNS Functional activation maps were derived from fMRI images acquired at high magnetic field (4 Tesla; see Tagaris et al., 1998, for the technical details of data acquisition and initial statistical processing). Overall, a conservative combination of criteria was used to identify highly consistent activation. The assignment of activated pixels to specific areas was based on anatomic landmarks in 2-D images and in three-dimensional (3-D) reconstructions of brain volumes (VoxelView/Ultra 2.5, Vital Images Inc., Fairfield, IA) as well as on Talairach coordinates (Talairach and Tournoux, 1988). Thirty brain areas were used for these analyses. The percentages of subjects (N = 10 subjects, 5 women and 5 men) in whom a specific area was activated in a given task are shown as shades of gray in figure 37.3; the columns represent brain areas, and the rows represent the four cognitive tasks used. Thus, a whole column shows the varying consistency of involvement of a given area in the four tasks, whereas a whole row shows the varying involvement of the various areas in a given task. This representation can be interpreted as a probability map that depicts the probability that a particular area will be activated during performance of a given task; alternatively, this representation can be interpreted as a consistency map, which shows the consistency by which a particular brain area will be activated in a given task. This is a quantitative way of analyzing binary functional activation maps, that is, brain maps in which an area of interest is considered either activated or not. Usually, such maps are treated descriptively, and little if any use is made of the information pertaining to the consistency of activation of a given area across subjects. In contrast, we used precisely this information in our analyses because it is the primary datum at the level of the population of subjects imaged.

MULTIDIMENSIONAL SCALING: GENERAL CONSIDERATIONS Multidimensional scaling (MDS) is a multivariate analysis technique by which a representation in a high-dimensional space is reduced to a representation in a low-dimensional space while trying to keep the relative

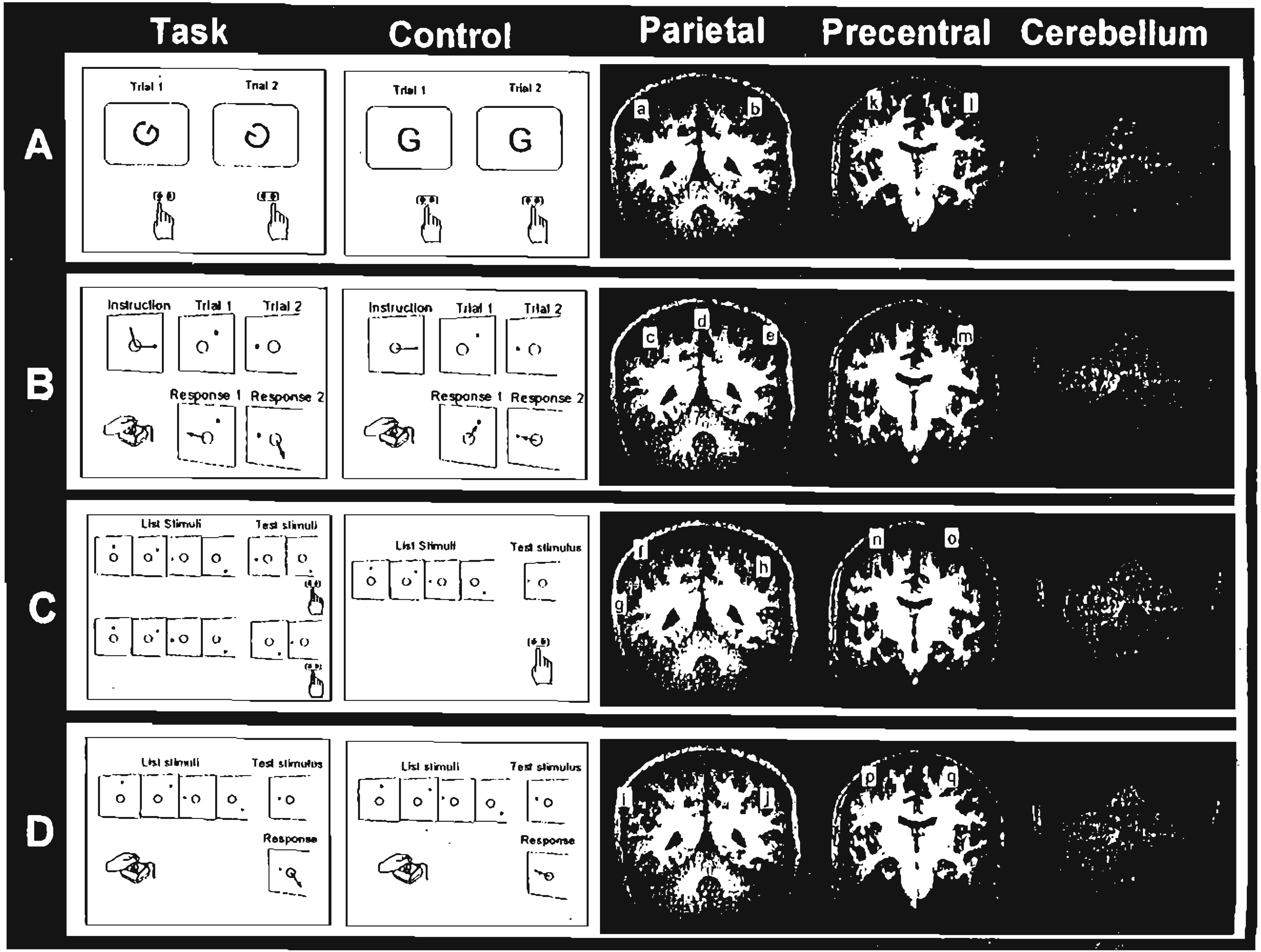
Task
Control
Parietal
Precentral
Cerebellum
A
B
C
D
Trial 1
Trial 2
G
Instruction
Response 1
Response 2
List Stimuli
Test stimuli
Test stimulus
List stimuli
Response
a
b
c
d
e
f
g
h
i
j
k
l
m
n
o
p
q

FIGURE 37.2 Schematic drawings of the tasks used and functional activation maps from one subject. (A) Visual mental rotation; (B) motor mental rotation; (C) visual memory scanning; (D) motor memory scanning. *Task:* experimental tasks. *Control:* control tasks. The control tasks were designed so that the visual display and the motor responses were very similar with those of the corresponding experimental tasks. Therefore, the functional activation maps reflect the combination of task dimensions and not sensorimotor events. *Activation:* Functional activation maps illustrate typical examples from one subject. Areas a, b, c, f, h, and j correspond to the intraparietal sulcus. Area e corresponds to the right superior parietal lobule. Areas g and h correspond to the left inferior parietal lobule. Areas k through q correspond to the precentral gyrus. Talairach coordinates for the center of activation shown (in mm on mediolateral, anterior-posterior, and inferior-superior axis) are as follows: a:33/-40/ 44; b: 30/-38/ 46; c: 32/-40/ 43; d: 1/-35/-45; e: 32/-39/ 52; f: 32/-40/ 45; g: 46/-43/ 28; h: 31/-39/45; i: 45/-43/ 30; j: 34/-38/ 36; k: 17/-19/ 59; l: 257-20/-55; m: 23/-16/ 64; n: 22/-15/ 61; o: 24/-16/ 58; p: 18/-20/ 60; q: 12/-21/67.

distances between corresponding points in the two spaces as similar as possible (Shepard, 1980). The data entered in this analysis consist of dissimilarities (e.g., Euclidean distances) between pairs of measurements, commonly arranged in a symmetric "dissimilarity" matrix. The main outcome of MDS is a plot of the variable of interest (e.g., stimuli or tasks) in what is called derived configuration space. The dimensions of this space are usually two, as one strives to reduce the number of original dimensions as much as possible, but the choice of the number of the reduced dimensions is somewhat arbitrary. Therefore, it is especially useful if this choice is guided by considerations other than those of parsimony. Such considerations existed in the present application, for which the configuration space was that of the four cognitive tasks; because, by design, we had two dimensions in the task domain (one for the cognitive operation and another for the operanda, see figure 37.1), a choice of two dimensions was dictated for the configuration space. This also provided a substantial reduction in dimensionality of the original space, from a 30-dimensional brain area space to the 2-D task configuration MDS space.

The MDS analysis can be performed on a single dissimilarity matrix. However, if several such matrices are available for a given problem, each individual matrix can be weighted separately in the analysis, resulting in what is called weighted MDS (WMDS), or individual scaling (INDSCAL) procedure, which we used. In the present application, we had data concerning the functional activation of each one of 30 brain areas for the four tasks used; therefore, we constructed 30 4 × 4 dissimilarity matrices and used the INDSCAL procedure of the SPSS statistical package (version 7, SPSS, Inc., Chicago, IL, 1996) for a weighted MDS. There are two additional advantages of the WMDS. One is that the position of the points in the derived configuration space is fixed, which makes the dimensions potentially interpretable. And the other is that it yields an additional plot showing what is called derived subject weights. In this plot, the points plotted correspond to the individual "subjects" (in the present case, these are the brain areas), and the axes are exactly the same as those in the task configuration space. Although it looks like a scatter plot, this is a vector plot: all vectors originate from the origin of the axes and end on the plotted points; therefore,

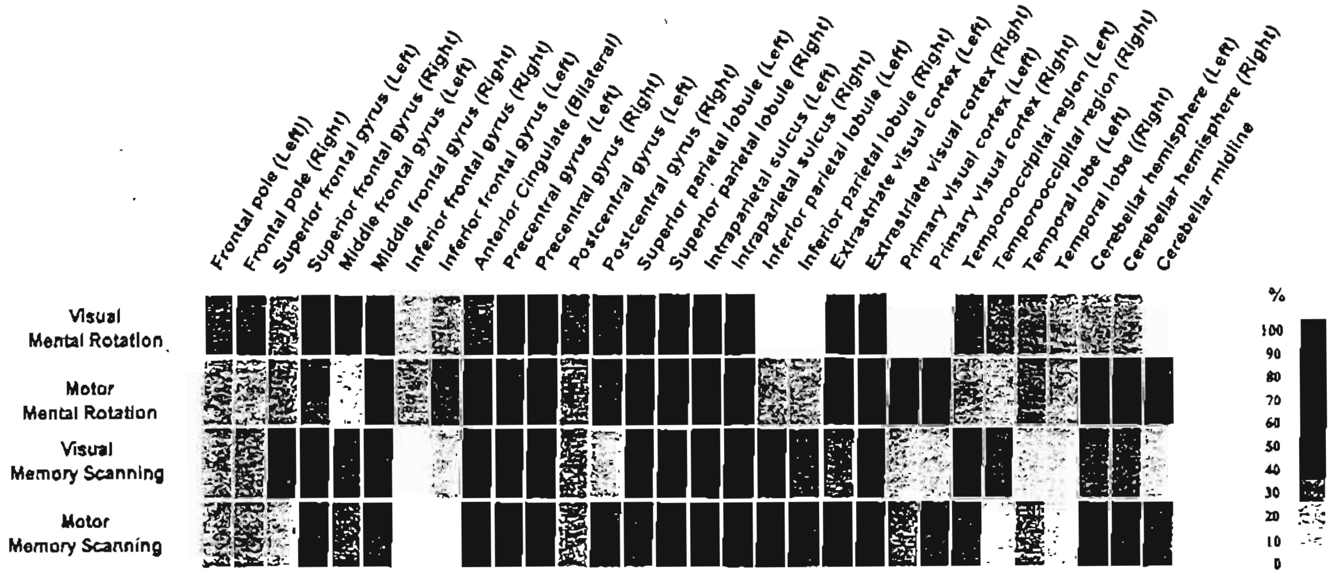

FIGURE 37.3 Schematic diagram showing the percentage of subjects who showed activation of the areas indicated (*N* = 10 subjects). (Reprinted from Tagaris et al., 1998, Copyright 1998, page 110, with permission from Elsevier Science.)

there are as many vectors as points plotted. For the interpretation of this plot, the task configuration space-plot is derived by weighting individual dissimilarity matrices, and, therefore, it represents an overall "average" configuration, which may or may not be optimal for a particular "subject." The vectors in the derived subject weight plot concern these aspects, which are reflected in the length of the vector and its angular orientation. Specifically, in our application, the length of a vector (from 0 to 1) indicates how "good" the derived task configuration space is for a particular brain area: the longer the vector, the closer this configuration "suits" this brain area. Conversely, the orientation of the vector indicates the relative importance of the two dimensions for this area, as reflected in the ratio of the projections of the vector on the two axes (i.e., the slope of the line). This means that if the dimensions are interpretable, then a statement can be made about the relative participation of a brain area in the aspect(s) reflected in these dimensions.

MULTIDIMENSIONAL SCALING: RESULTS The task configuration space derived using INDSCAL and a ratio level of measurement is shown in figure 37.4. Twenty-nine areas contributed to this analysis. (One area was dropped because it yielded a dissimilarity matrix of all zeros. This area was the right middle frontal gyrus, which was activated in exactly the same number of subjects in all four tasks [figure 37.3] and, therefore, could not provide information differentiating these tasks.) It can be seen that the four points corresponding to the four cognitive tasks used fell in each of the four quadrants such that the two dimensions could be identified as relating to the operation (ordinate) or the operandum (abscissa). In fact, these were the two task dimensions by design, as illustrated in figure 37.1. These results mean that the MDS analysis recaptured the cognitive-psychological dimensions of the tasks from the brain activation patterns. Figure 37.5 recapitulates this correspondence by showing the formal similarity between the planned task dimensions (left panel) and the derived task dimensions (right panel). This is a remarkable finding and a tribute to the power of MDS as a tool by which to analyze complex neuroimaging patterns of activation.

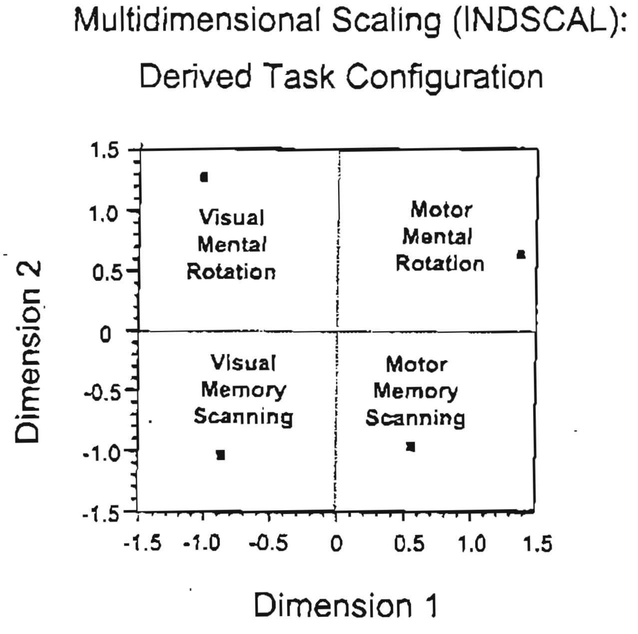

FIGURE 37.4 Task configuration space derived by multidimensional scaling (MDS), individual scaling (INDSCAL) model (see text for details).

Figure 37.6 plots the derived area weights. It seems that the vectors plotted fall into three groups, as follows. The first group is closer to the abscissa, the second is around the main diagonal, and the third is closer to the ordinate. Our interpretation of this plot is along the lines discussed previously; namely, that the areas in the first group are involved with the dimension of the abscissa (i.e., operandum), those of the third group with the dimension of the ordinate (i.e., operation), whereas those in the middle are involved with both dimensions. The second point concerns the goodness of fit of the derived task configuration space for particular brain areas. As aforementioned, this is indicated by the length of the vector: the longer the vector, the better the goodness of fit. (Other measures also can be used, such as Kruskal's stress formulae or R^2.) Interestingly, in figure 37.6, the vectors closest to the axes were longer than those in the middle, with lengths close to the maximum possible value of one. This suggests that in the context of the tasks used, brain areas are rather specialized in processing information concerning the cognitive operation or its operandum, rather than dealing with both of them. Finally, this plot provides interesting information regarding the possible involvement of particular areas in these functions. Thus, the areas with a good fit (e.g., long vectors) that presumably are concerned with the operandum dimension (group nearest to the abscissa) included occipital (primary visual and extrastriate cortex bilaterally), cerebellar areas (cerebellar hemispheres bilaterally and cerebellar midline), and the left middle frontal gyrus. The areas presumably concerned with the operation dimension (group nearest the ordinate) included parietal areas (inferior parietal lobule bilaterally, right superior parietal lobule), the right temporal cortex, and the anterior cingulate gyrus (this area was not split in left and right). All other areas had shorter vectors or belonged to the group in the middle.

Thus, the MDS analysis provided a novel way by which neurobehavioral relations were explored. It re-

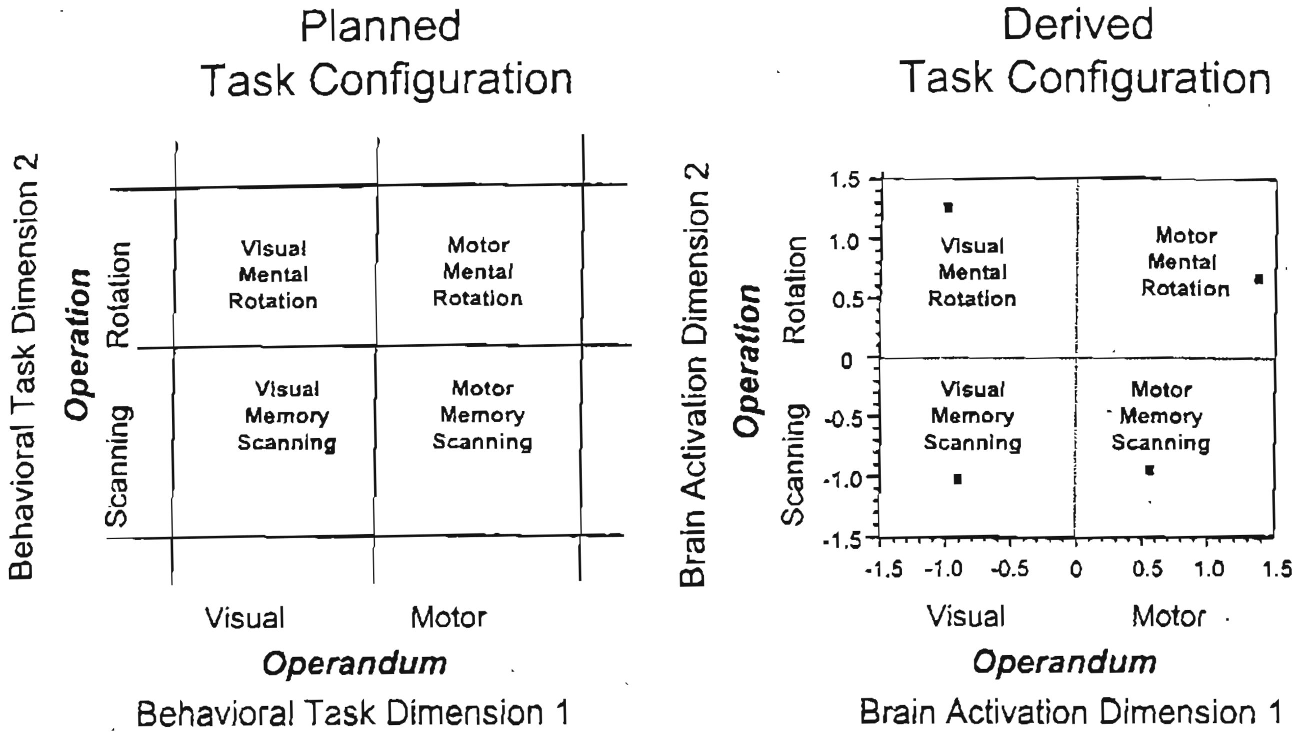

FIGURE 37.5 Interpretation of the results of the multidimensional scaling analysis illustrated in figure 37.4. Left: Experimental task design, as depicted in figure 37.1. Right: Same plot as that of figure 37.4, but here the axes are interpreted to indicate the task dimensions, as on the left panel.

covered the task dimensions from the brain activation patterns and identified areas specifically associated with those dimensions. By necessity, the grain of exploring brain function based on any kind of analysis is constrained by the grain of separating brain areas. In the present analyses, this grain was more coarse for some areas (e.g., extrastriate cortex and cerebellum) than for others (such as the parietal areas). A finer parcellation of anatomic areas can be achieved by several means, such as using finer anatomic landmarks or additional tasks known to activate certain areas. In any case, this is an open-ended problem, and, most probably, it always will be desirable to strive for even finer parcellations. However, as more and more areas are distinguished, correlations in their patterns of activation also are likely to increase, which essentially will limit the usefulness of this approach. Of course, a crucial objective is to determine the level of the coarseness of the grain necessary and sufficient for a given study, and it is likely for this to differ from study to study. Therefore, this remains an active field of investigation. However, the present study captured a bird's eye view of the specific problem, and, given the encouraging results obtained, it seems that the parcellation of brain areas used might have not been very far from the appropriate one for this study.

Single cell neurophysiology of mental rotation and memory scanning

GENERAL CONSIDERATIONS As aforementioned, the signal measured by functional neuroimaging methods is related only indirectly to the electrophysiological activity. Crucial validation studies have shown a correspondence between the expected activation of a brain area (e.g., visual cortex, motor cortex) based on prior neurophysiological evidence and the one actually observed using neuroimaging (e.g., see Ogawa et al., 1992; Kim et al., 1993). However, the situation becomes fairly complicated when more complex tasks are considered because a change in a neuroimaging signal (e.g., blood flow in PET or BOLD activation in fMRI) is not uniquely associated with neurophysiological events, such as excitation or inhibition. The detailed cellular mechanisms can be investigated only by using suitable methods, and one of the finest ones is the recording of single cell activity in behaving animals. The impulse activity is recorded by microelectrodes, and several such electrodes can be employed to record simultaneously the activity of many cells (Eichenbaum and Davis, 1998). The spike trains thus collected then are analyzed with respect to behavioral events, and the relations between these two kinds of data are analyzed. Therefore, the major advantage of this

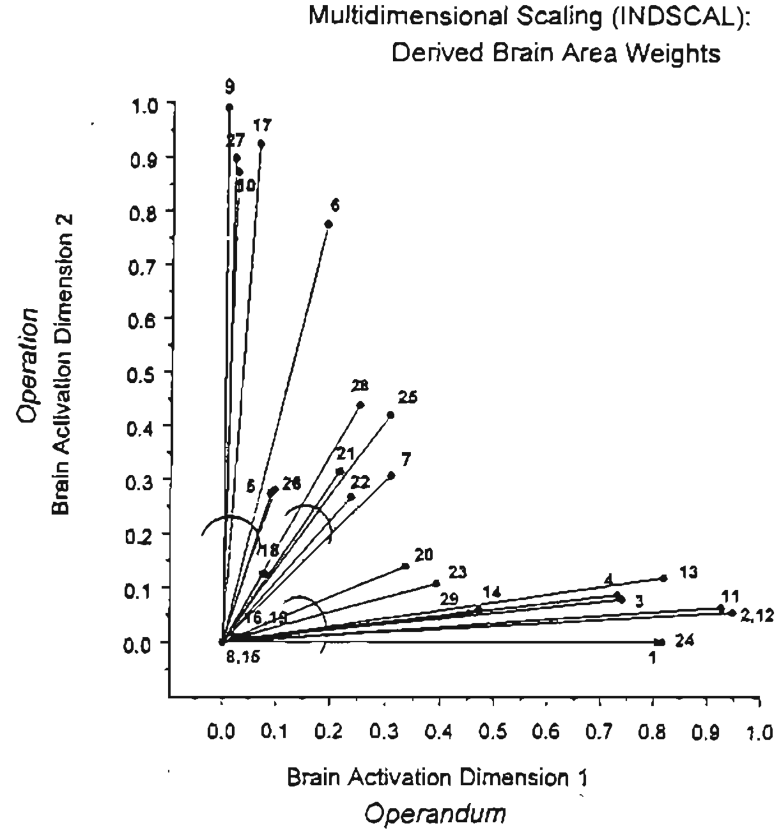

FIGURE 37.6 Brain area weight plot derived by individual scaling (INDSCAL) model. The numbers in the plot correspond to the following areas: *1*, left primary visual cortex; *2*, right primary visual cortex; *3*, left extrastriate visual cortex; *4*, right extrastriate visual cortex; *5*, left superior parietal lobule; *6*, right superior parietal lobule; *7*, left intraparietal sulcus; *8*, right intraparietal sulcus; *9*, left inferior parietal lobule; *10*, right inferior parietal lobule; *11*, left cerebellar hemisphere; *12*, right cerebellar hemisphere; *13*, cerebellar midline; *14*, left temporooccipital region; *15*, right temporooccipital region; *16*, left temporal lobe; *17*, right temporal lobe; *18*, left postcentral gyrus; *19*, right postcentral gyrus; *20*, left precentral gyrus; *21*, right precentral gyrus; *22*, left superior frontal gyrus; *23*, right superior frontal gyrus; *24*, left middle frontal gyrus; *25*, left inferior frontal gyrus; *26*, right inferior frontal gyrus; *27*, bilateral anterior cingulate; *28*, left frontal pole; *29*, right frontal pole.

method is its fine grain and the detail by which it can probe cellular mechanism, but its drawback is that it can only explore a very limited part of the brain (usually of the order of millimeters), especially as compared with neuroimaging methods that can scan the whole brain in a matter of seconds. It is obvious that each of the two methods can provide important, albeit partial, information about the brain mechanisms of behavior. In our studies, we have been using both of these methods to obtain this kind of complementary information. The results of our analyses of fMRI data during mental rotation and memory scanning were described in the preceding section; in what follows, we discuss the results of neurophysiological studies in monkeys trained to perform the aforementioned movement mental rotation and movement memory-scanning tasks. However, we summarize first the neural coding of movement direction by motor cortical cells.

NEURAL CODING OF MOVEMENT DIRECTION The activity of single cells in the motor cortex is tuned directionally—that is, cell activity is highest for a given direction ("preferred direction") of movement and decreases gradually with directions farther and farther away from the preferred one (Georgopoulos et al., 1982; Amirikian and Georgopoulos, 1998). Typically, the frequency of cell discharge varies as a linear function of the direction cosines of the movement vector (relative to its origin), or, equivalently, of the cosine of the angle formed between the direction of a particular movement and the cell's preferred direction (i.e., the direction of movement for which cell activity would be highest). Preferred directions differ for different cells and are distributed uniformly in 3-D space (Schwartz, Kettner, and Georgopoulos, 1988). Finally, the preferred direction is very similar for movements of different amplitudes (Fu, Suarez, and Ebner, 1993).

Single cells provide only the building elements of the neural construct underlying movement generation and control: this construct invariably involves populations of neurons. The use of neuronal populations in this context differs from common statistical measures of populations, such as averages, variances, and frequency distributions of functional cell properties. Instead, the hypothesis is that a single neuron carries only partial information about a movement parameter that therefore is represented uniquely in the whole neuronal ensemble. This analysis was applied to the coding of the direction of movement, as follows. The broad directional tuning indicates that a given cell participates in movements of many directions; from this result, and from the fact that preferred directions range widely, it follows that a movement in a particular direction engages a whole population of cells. A unique code for the direction of movement was proposed (Georgopoulos et al., 1983; Georgopoulos, Schwartz, and Kettner, 1986; Georgopoulos, Kettner, and Schwartz, 1988) that regarded this population as an ensemble of vectors. Each vector represents the contribution of a directionally tuned cell; it points in the cell's preferred direction and is weighted (i.e., has length) according to the change in cell activity associated with a particular movement direction. The weighted vector sum of these neuronal contributions was called the "neuronal population vector." The population vector points in the direction of reaching (Georgopoulos et al., 1983; Georgopoulos, Schwartz, and Kettner, 1986; Georgopoulos, Kettner, and Schwartz, 1988; Kalaska, Caminiti, and Georgopoulos, 1983; Kalaska et al., 1989; Fortier, Kalaska, and Smith, 1989; Caminiti et al., 1991). Although preferred directions tend to change in the horizontal plane as the origin of the movement changes, the population vector remains an unbiased predictor of the direction of the movement (Caminiti et al., 1991). Three aspects of the population vector analysis are remarkable: its simplicity, its robustness, and its spatial outcome. With respect to simplicity, the ongoing calculation of the population vector is a simple procedure, for it (1) assumes the directional selectivity of single cells, which is apparent, (2) involves weighting of vectorial contributions by single cells on the basis of the change in cell activity, which is reasonable, and (3) relies on the vectorial summation of these contributions, which is practically the simplest procedure to obtain a unique outcome. With respect to robustness, the population vector is a robust measure, for it still can convey a good directional signal even with only 100 cells (Georgopoulos, Kettner, and Schwartz, 1988). Finally, the population vector is a directional measure, isomorphic direction in space. Indeed, the population analysis transforms aggregates of purely temporal spike trains into a spatiotemporal signal.

These properties of the population vector suggest that it may be robust in the temporal domain as well. Indeed, when it was calculated as a time-varying signal every 20 ms, it provided an accurate prediction during the response time regarding the upcoming movement trajectory (Georgopoulos et al., 1984; Georgopoulos, Kettner, and Schwartz, 1988). This finding demonstrated the feasibility of using the population vector as a measure of the directional tendency of a neuronal ensemble and gave the impetus to new studies in which delays were imposed such that the movement was initiated after a period of time following a cue stimulus and in response to a "go" signal. The first of these studies (Georgopoulos, Crutcher, and Schwartz, 1989) involved an instructed delay period: The cue stimulus came on and stayed on while the monkey waited immobile for the occurrence of the go stimulus, which triggered the movement. Under those conditions, the population vector pointed during the delay in the direction of the cue, which was the same as that of the upcoming movement. Therefore, using this analysis, the directional information in the neuronal ensemble could be identified during the waiting period. The second study (Smyrnis et al., 1992) went a step further and included a memorized delay period: The cue stimulus came on but stayed on for only 300 ms, after which it was turned off. There ensued a memorized delay period during which the monkey waited immobile for the occurrence of the go signal but during which there was no target stimulus on display. The monkey was required to move, at the presentation of the go signal, in the direction of the (now absent) cue. Therefore, this cue direction had to be kept in memory during the delay period. Indeed, the population vector pointed in the direction of the memorized cue direction during the delay period. The results of these delay studies demonstrated the usefulness and power of the population vector analysis by which to monitor in time cognitive operations. In the two subsequent experiments discussed next, the tasks used required transformations of the intended direction of movement, one based on a spatial rule (mental rotation task) and another based on a temporal order rule (context-recall memory scanning task). These two tasks were very similar to the movement mental rotation and memory-scanning tasks used in the fMRI studies, as discussed previously. Therefore, they provide two interesting cases in which to compare the results and their implications for the neural mechanisms involved.

Neurophysiology of motor mental rotation The knowledge gained from single-cell and population analyses with respect to the neural coding of the direction of movement was applied to interpret changes in neuronal activity when a transformation was imposed on the upcoming movement, namely that it points in a direction at and angle from a reference direction indicated by a stimulus on the plane. In these experiments (Georgopoulos et al., 1989; Lurito, Georgakopoulos, and Georgopoulos, 1991), rhesus monkeys were trained to move a handle 90° CCW from a reference direction ("transformation" task); these trials were intermixed with others in which the animals moved in the direction of the target ("direct" task). The cell activity in the arm area of the motor cortex (contralateral to the performing arm) were recorded extracellularly. The neural activity was analyzed at the single-cell and neuronal population levels. We found the following. The changes in the activity of single cells in the direct task were related to the direction of movement, as described previously (Georgopoulos et al., 1982). The cell activity also changed in the transformation task, but there were no cells that changed activity exclusively in this task. Therefore, at the level of the motor cortex, the required transformation did not seem to involve a separate neuronal ensemble. The patterns of single-cell activity in the transformation task frequently differed from those observed in the direct task when the stimulus or the movement was the same. More specifically, cells could not be classified consistently as "movement"- or "stimulus"-related because frequently the activity of a particular cell would seem "movement-related" for a particular stimulus-movement combination, "stimulus-related" for another combination, or unrelated to either movement or stimulus for still another combination. Thus, no obvious insight could be gained from such an analysis of single-cell activity. However, an analysis of the activity of the neuronal population using the time evolution of the neuronal population vector revealed an orderly rotation of the neuronal population vector from the direction of the stimulus toward the direction of the movement through the 90° CCW angle (figure 37.7) (Georgopoulos et al., 1989; Lurito, Georgalopoulos, and Georgopoulos, 1991). There are several points of interest in this analysis that were surprising. First, there was no a priori reason to expect that the population vector would point to any other direction than the direction of the movement, on the simple hypothesis that the motor cortex is involved only in the production of movement. Our interpretation of the population vector as the directional motor intention suggests that in the transformation task, the motor intention is not restricted to the movement direction but occupies intermediate directions during the reaction time. Second, there was no a priori reason to expect that the population vector would shift in an orderly fashion in the CCW direction, for no explicit instruction was given to the animals to that effect. The results obtained suggest that the directional motor intention spanned the smallest angle. This could, presumably, minimize the time and computational load involved in the transformation required.

The hypothesis was tested that this apparent rotation of the population vector could be the result of activation of two subsets of cells, one with preferred directions at or near the stimulus direction and another with preferred directions around the direction of movement: if cells of the former type were recruited at the beginning of the reaction time, followed by those of the second type, then the vector sum of the two could provide the rotating population vector. However, such a preferential activation of "stimulus direction"-centered and "movement direction"-centered cells was not observed. Conversely, a true rotation of the population vector could be reflected in the engagement of cells with intermediate preferred directions during the middle of the reaction time. Indeed, such a transient increase in the recruitment of cells with intermediate (i.e., between the stimulus and movement) preferred directions during the middle of the reaction time was observed. This supports the idea of a true rotation of the population signal. Finally, a rotation of the population vector through several angles, including 180°, has been described in a different context (Wise, di Pellegrino, and Boussaoud, 1996).

Neurophysiology of motor memory scanning This task required that a movement be made in a direction away from a stimulus direction based on a temporal, serial order rule (Pellizzer, Sargent, and Georgopoulos, 1995). This is a very different rule from the spatial one applied to the task described in the preceding section. Two monkeys were trained to perform a task that was very similar to the movement memory-scanning task described in the fMRI section. Briefly, two to five list stimuli were presented on a circle every 0.65 s at pseudorandom locations; when one of them (except the last) changed color (test stimulus), the monkeys made a motor response toward the next light in the sequence. Obviously, unlike the mental rotation task, in this task, the direction of the motor response bears no consistent relation to the direction of the test stimulus. Instead, this task seems to involve a memory-scanning process, in which list directions are searched until the test one is identified and the next one in the sequence selected. This kind of process was suggested by the results of early experiments in the visual domain (Sternberg, 1969) and by those of later experiments in the motor

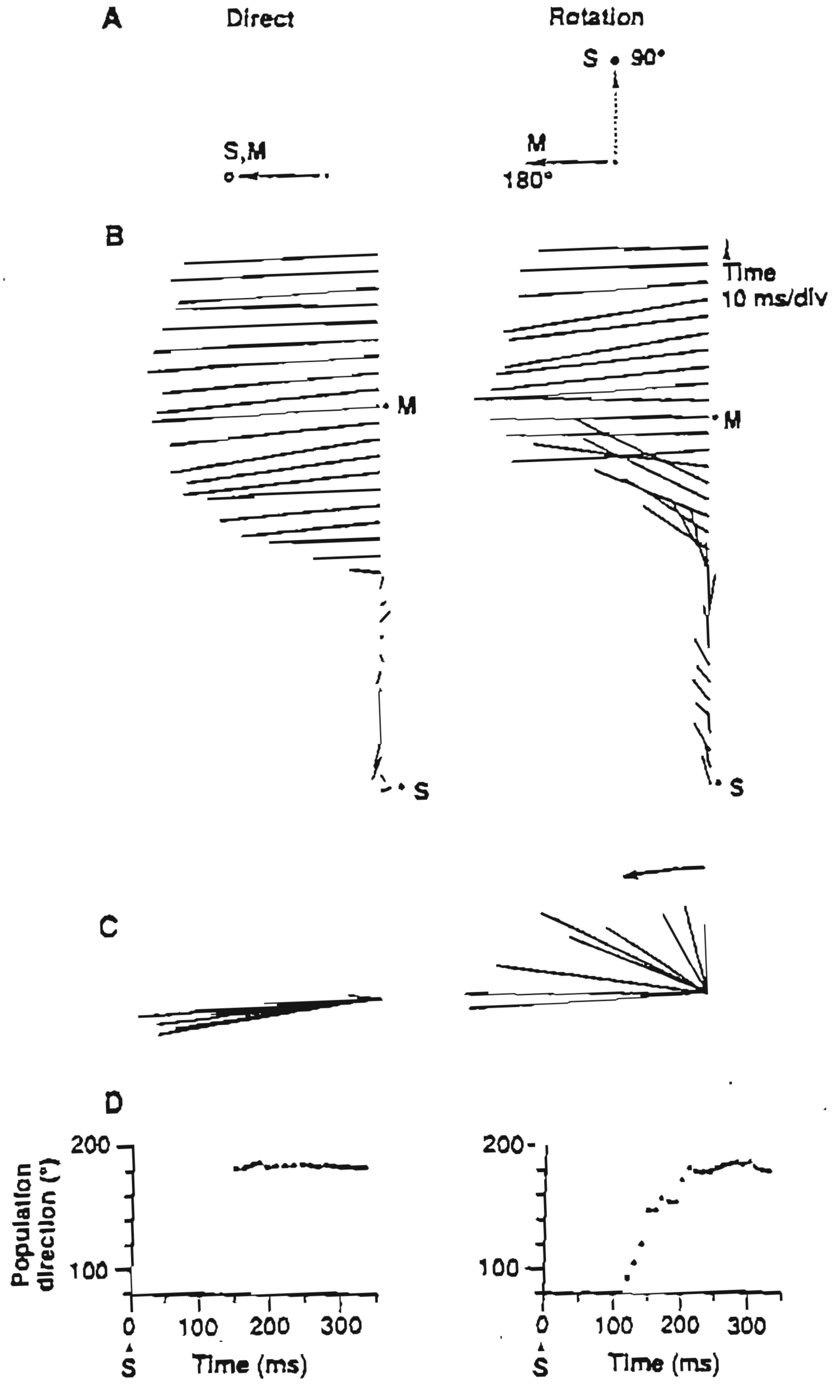

FIGURE 37.7 Results from a "direct" (left) and "rotation" (right) movement. (A) Task. Unfilled and filled circles indicate dim and bright light, respectively. Interrupted and continuous lines with arrows indicate stimulus (*S*) and movement (*M*) direction, respectively. (B) Neuronal population vectors 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). (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 following stimulus onset (*S*). For the direct case (left), the direction of the population vector is in the direction of the movement (~180°); for the rotation case (right), the direction of the population vector rotates counterclockwise from the direction of the stimulus (~90°) to the direction of the movement (~180°). (From Georgopoulos et al., 1989. Reproduced with permission of the publisher. Copyright AAAS, 1989.)

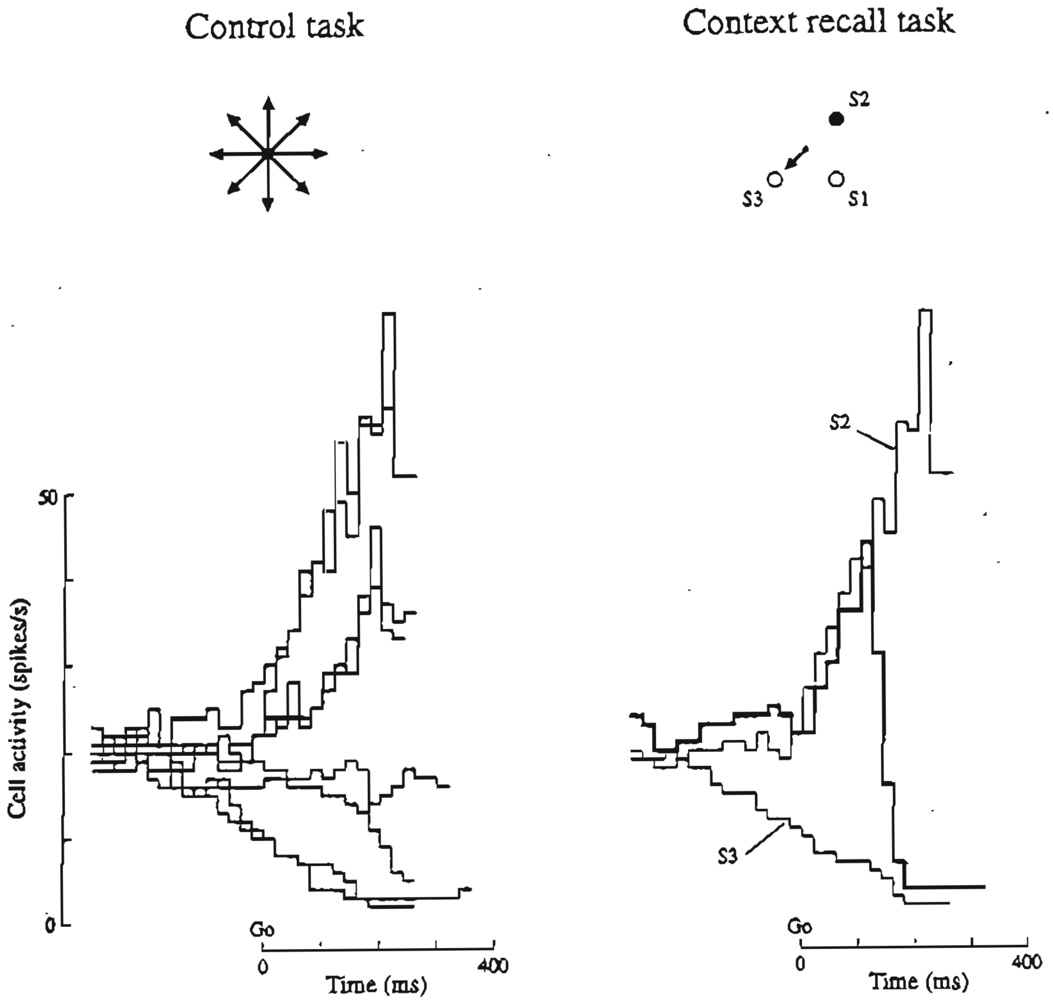

FIGURE 37.8 Peristimulus histograms of activity of a motor cortical cell are shown for eight directions in the control task (left), and one case of the context-recall task (right). In the left panel, histograms of cell activity are color coded for motor responses in different directions in the control task. In the right panel, two of these histograms are reproduced as thinner lines together with the histogram (black) of cell activity in the condition of the context-recall task illustrated on the top. After the go signal, cell activity (black) initially increased in the same way as in the control case (thin red line) for the direction toward the test stimulus (*S2*) and then changed abruptly and decreased to the level corresponding to the control activity for the direction of the motor response (toward *S3*). (From Pellizzer, Sargent, and Georgopoulos, 1995.)

field (Georgopoulos and Lurito, 1991); namely, that the response time increases as a linear function of the number of list stimuli. Indeed, this relation also was present in the monkey performance (Carpenter, Pellizzer, and Georgopoulos, 1996). The question, then, is what are the neural mechanisms of this memory scanning process? The results of neurophysiological studies in the motor cortex (Pellizzer, Sargent, and Georgopoulos, 1995) showed that the basic element of these mechanisms involves an abrupt (~40 ms) switching between the directions being searched. This was evident both at the single-cell and population levels. Specifically, single cells showed an abrupt change in activity from the pattern associated with the direction of test stimulus to that associated with the direction of the motor response; an example is shown in figure 37.8 (see also color plate 23). At the ensemble level, the neuronal population vector switch abruptly from test to the motor direction. The difference between the neural mechanisms of this task and that of mental rotation was exemplified further by analyzing the activity of cells with preferred directions intermediate between the stimulus and the movement. As discussed in the preceding section, these cells were recruited selectively during the response time in the mental rotation task. In contrast, they were not engaged in the memory-scanning task. This is shown in figure 37.9. Therefore, the mental rotation and memory-scanning tasks involve fundamentally different kinds of

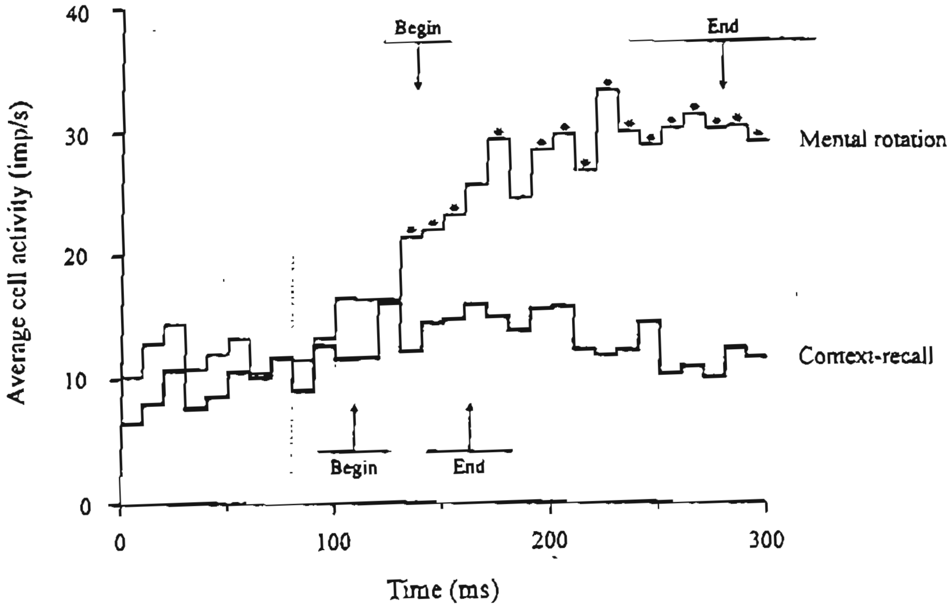

FIGURE 37.9 Peristimulus time histograms (10 ms binwidth) of the activity of cells with preferred direction at the intermediate direction (±10°) between the stimulus and movement directions in the mental rotation task (*2,3*), and between the test stimulus (*S2*) and motor response (*S3*) in the context-recall task (*19*). Histograms start at the onset of the go signal (time zero). In the mental rotation task, the activity of such cells (thin line) increased by more than threefold and was statistically significant (indicated by *), whereas in the context-recall task, cell activity remained almost constant (thick line) and was not statistically significant compared with cell activity during the first 80 ms (dotted line; *baseline period*) (*20*). The arrows indicate the average time (±SD) at which the population vector began to change direction (*Begin*) and when it attained the direction of the motor response (*End*). (From Pelizzer, Sargent, and Georgopoulos, 1995.)

mechanisms (slow rotation vs. abrupt switching) both of which were identified, remarkably, within the same (proximal arm) area of the motor cortex.

Conclusions

Our studies of the motor mental rotation and memory-scanning tasks using both fMRI and single-cell recordings provide a useful ground for trying to define the boundaries of the gain in knowledge provided by these methods. The neurophysiological studies showed clearly that the motor cortex is involved in both of these tasks, and this also was documented by the fMRI studies. Therefore, there is an excellent correspondence between the two methods regarding this point. Because of the kind of fMRI signal, this is as far as the fMRI studies can go: they cannot provide information concerning the nature of the cellular information processing mechanisms involved. These can be glimpsed at from the results of the neurophysiological studies. These results demonstrate clearly that the neural mechanisms both at the single cell and at the population levels are very different in the two cases. Of course, no neuroimaging study could have distinguished between these two different mechanisms. This consideration brings forward an important point, namely that the "activation" of an area needs to be considered cautiously, within the context of other information gained from studies using different methods. Conversely, no single-cell recording study could have produced the "bird's eye" view provided by the fMRI study and the insight provided by the MDS analysis, in regard to both the task dimensions and the differential involvement of brain areas with information processing along these dimensions. Neurophysiological studies are appropriate for examining in depth the cellular mechanisms but not the overall activation patterns. Therefore, the two methods are complementary and together can provide a more integrated view of the neural mechanisms of behavior.

ACKNOWLEDGMENTS This study was supported by United States Public Health Service grants NS17413, NS32919, and RR088079, the United States Department of Veterans Affairs, and the American Legion Chair in Brain Sciences.

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