Motor Cortical Encoding of Serial Order in a Context-Recall Task
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The neural encoding of serial order was studied in the motor cortex of monkeys performing a context-recall memory scanning task. Up to five visual stimuli were presented successively on a circle (list presentation phase), and then one of them (test stimulus) changed color; the monkeys had to make a single motor response toward the stimulus that immediately followed the test stimulus in the list. Correct performance in this task depends on memorization of the serial order of the stimuli during their presentation. It was found that changes in neural activity during the list presentation phase reflected the serial order of the stimuli; the effect on cell activity of the serial order of stimuli during their presentation was at least as strong as the effect of motor direction on cell activity during the execution of the motor response. This establishes the serial order of stimuli in a motor task as an important determinant of motor cortical activity during stimulus presentation and in the absence of changes in peripheral motor events, in contrast to the commonly held view of the motor cortex as just an “upper motor neuron.”
ple, when looking up a telephone number and dialing the individual digits in the proper order. Neurophysiological studies have commonly used sequential reaching movement tasks in which a series of targets is presented to the subject, who must then execute a series of movements to the targets in the same order, under visual guidance or from memory (2). By contrast, in the context-recall task (3, 4), the subject makes a single motor response dictated by the serial order of a test stimulus in a memorized list of stimuli. This task provides the requisite conditions for investigating the neural mechanisms of processing the serial order of stimuli uncontaminated by a confounding translation of this order into a series of motor responses, that is, in the absence of signals related to the planning and execution of sequential movements.

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Fig. 1. (A) Schematic diagram of the context-recall task, illustrating a trial with a sequence of five stimuli. Time course of stimulus presentation and motor response (represented by EMG activity of anterior deltoid). After a 1000-ms control period where the monkey held the cursor in a center window, the stimuli appeared sequentially on the screen (S1 to S5). Therefore, each stimulus is defined jointly by its location and its serial position within the sequence. The periods between stimulus onsets (5) are referred to as epochs. Each epoch corresponds to a serial position. For example, epoch 1 represents the period from the onset of S1 in the downward position to the onset of S2 in the rightward position. At the end of the list presentation, the test stimulus consisted of a change in the color of one of the stimuli from yellow to blue. In this case, the third stimulus (S3) served as the test stimulus. The test stimulus serves as the go signal: The rule of the context-recall task is to move toward the stimulus that immediately followed the test stimulus in the sequence; therefore, in this example, the correct response is a movement to the fourth stimulus in the sequence (S4). This report deals with the list presentation phase of the task, namely, from S1 onset until test stimulus onset. The locations of the list stimuli in this example are illustrated below the EMG trace by small dots on a circle. RT, reaction time. (B) Schematic diagram of the trial depicted in (A), as it actually appears on the screen during the recall phase. The third stimulus (S3) has changed from yellow to blue, instructing the monkey to move the red cursor from the center window toward the fourth stimulus (S4). (C) Venn diagram of the proportions of cells showing (i) a statistically significant effect of Motor Direction (8) only during the motor response period (green MD section), (ii) a statistically significant effect of stimulus Serial Position, Location, or their interaction only during the list presentation phase (hot pink LP section), and (iii) statistically significant effects during both the motor response period and the list presentation phase (light pink MD + LP section). The areas of sections are proportional to the actual percentages (see text). (D) Bar graph illustrating the proportions of cells in which statistically significant effects were obtained for the main effect of Serial Position, Location, and Serial Position × Location interaction. (E) Cumulative frequency distributions of the level of statistical significance obtained for Motor Direction during the motor response time (green) and Serial Position (main effect only) during the list presentation phase (pink).
In a recent version of this task (4), several stimuli are presented successively on a screen, and then one of them changes color (the test stimulus); the subject is required to make a single motor response toward the stimulus that followed immediately the test stimulus in the list. In the present experiments, two monkeys were trained to perform the context-recall task shown in Fig. 1, A and B (5). They operated a semi-isometric joystick to control a force feedback cursor on a video screen. A trial began by turning on a white circle in the center of the screen, which the monkey captured with the force feedback cursor. After 1 s (the control period), three to five yellow stimuli were shown successively on a circle and stayed on (the list presentation phase); during both of these periods, the monkey had to keep the force feedback cursor within the white circle at the center of the screen (6). Then one of the stimuli (except the last) changed color from yellow to blue (the test stimulus), and this instructed the monkey to exert force to move the cursor from the center of the screen toward the stimulus that immediately followed the test stimulus during the list presentation phase. The reaction time was defined as the time from the onset of the test stimulus until the initiation of the motor response; the motor response period was defined as the time from the onset of the test stimulus until the threshold force was exceeded (5). In this task, each series of list stimuli was defined uniquely by the location of the stimuli on the screen and by their serial order in the series. We recorded the activity of 925 cells in the motor cortex during task performance (7).

As expected from the known role of the motor cortex in the initiation and control of movement, the activity of many cells during the motor response period was related to the direction of the response (8) (‘motor direction’ cells, 624/925 = 67.5%; green and light pink sections in Fig. 1C); a smaller proportion of cells (177/925 = 19.1%) showed relations only to motor direction (green section in Fig. 1C). Interestingly, a large proportion (447/624 = 71.6%) of these cells also changed activity during the list presentation phase in relation to stimulus parameters (serial position, location, or both), even though there was no overt motor response during that period (‘motor direction + list presentation’ cells, 447/925 = 48.3%; light pink section in Fig. 1C). In addition, 190/925 = 20.5% of cells showed such modulation of activity during the list presentation phase in the absence of a motor directional effect (‘list presentation’ cells, hot pink section in Fig. 1C); this brings the total number of cells engaged during the list presentation phase to 637/925 = 68.9% (hot pink and light pink sections in Fig. 1C). Finally, 111/925 (12%) of the cells did not show any significant effect.

Analyses of covariance (ANCOVA) tested the effects of the following factors that were varied during the list presentation phase: Serial Position (of a stimulus in the list) and Location (of the stimulus on the screen). The main effect of Serial Position was significant in 52.8 ± 10.67% of cells [mean ± SEM, N = 5 combinations of monkey and sequence size (5)] (Fig. 1D); the main effect of Location was significant in 7.8 ± 5.68% of cells, and the effect of the Serial Position × Location interaction was significant in 22.4 ± 6.41% of cells (9). To compare the Serial Position effect during the list presentation phase with a commonly assessed motor effect, such as the effect of Motor Direction on cell activity during the motor response period, we compared the level of statistical significance obtained for these two effects within the same sets of trials (8). The statistical significance of the Serial Position effect above was higher than that of the effect of Motor Direction during the motor response period [Fig. 1E; P < 0.0001, Kolmogorov-Smirnov test; N = 1012 and 978 cases for Motor Direction and Serial Position effects, respectively, out of a total of 1812 cases analyzed from the same trials (8)]

These results underscore the major impact...
of serial order of the stimuli on cell activity during the list presentation phase, and of the interaction of the serial order with stimulus location, which defines the direction of a potential motor response. These two findings, taken together, indicate that the changes in neuronal activity observed during the list presentation phase truly reflect aspects of the sequence itself. We tested this hypothesis by analyzing ensembles of simultaneously recorded neurons to evaluate how well the combined patterns of activity could classify items in the sequence (10), namely stimuli defined jointly by their serial position in the sequence and their location on the screen. Indeed, high rates of correct classification were obtained (11) (Fig. 2). The mean correct classification rate for each serial position in sequences of five stimuli was greater than 60% (Fig. 2A). The correct classification rate increased as a function of the number of cells in the ensemble (Fig. 2B), which suggests, in turn, that individual cells provide largely independent information about the items in the sequence. Together, these results demonstrate that during different epochs of presentation of the stimuli, the patterns of distributed activity in even small ensembles of motor cortical cells (12) are sufficiently distinct and robust to provide a basis for encoding the sequence.

Representative examples of single-cell activity during the list presentation phase are illustrated in Fig. 3. The histograms in Fig. 3, A and B, illustrate consistent changes in the activity of two cells in association with certain serial positions. The visual stimuli displayed during a specific serial position epoch differed for different sequences (Fig. 3, A and B). Other neurons were influenced by both the serial position of the stimuli in the sequence and their location on the screen (Fig. 3C). Changes in neural activity were not related to eye position (Fig. 4 and Fig. 5, left side) nor to the associated retinal location of the most recently presented stimulus (Fig. 5, right side). Concerning the latter point, it is conceivable that the serial position of this stimulus could be associated with a particular retinal location when it appeared on the screen, which then could account for the serial position-related activity. For example, it could be that the monkey fixated its eyes such that when the fifth stimulus appeared, it would always fall in the same retinotopic position. However, this was not the case. As shown in Fig. 5 (top right), the retinal location of the fifth stimulus for the cell illustrated in Fig. 3B was indeed distributed throughout the retinotopic space; that is, it was not confined to any unique location. Similarly, stimuli during the other four epochs were also distributed throughout the retinotopic space (Fig. 5, middle right). The broad distributions of stimuli on the retina shown in Fig. 5 (top right and middle right) allow the comparison of neural activity during the presentation of stimuli with different serial position but with the same, or closely similar, retinal locations. These stimuli are shown as the overlapping points in Fig. 5 (bottom right) and the corresponding neural activity levels shown in the bar graph in Fig. 5 (bottom right): The activity was much higher for the stimuli at serial position 5 than for those at serial positions 1 to 4, even though they were matched for retinal location. The same considerations apply for eye position (Fig. 5, left side). We conclude that the serial position of the stimuli is the important determinant for cell activity, and not their retinal location or eye position (13). This is not surprising because these recordings were from the arm area of the motor cortex (Fig. 3D).

Together, these results document a strong effect of serial order on cell activity: In 34.4% of the cells, Serial Position was the only significant factor (9), whereas in 52.8% of the cells it was a significant factor alone or together with other factors (Fig. 1D). In addition, the level of significance of this effect was even higher than that of Motor Direction (Fig. 1E). These findings establish serial order as an important factor for motor cortical cell activity. In contrast, stimulus Location, denoting the direction of a potential motor response, had a slight effect alone (9) but interacted frequently with Serial Position (Fig. 1D). This suggests that serial order had a strong, pure effect on cell activity, whereas stimulus location was engaged within the context of serial order.

These results can be interpreted with respect to three key aspects of the task performed: (i) Unlike other tasks (2), in the present task just a single, one-directional motor response was made in a trial, that is, no sequence of motor responses to each stimulus was performed; this
could explain why stimulus Location alone was not a frequent effect. (ii) The required single, correct response could be arrived at only by taking into account the serial order of the stimuli, which means that information about serial order was indispensable; this could explain why Serial Position was such a frequent and strong (relative to Motor Direction) effect. (iii) A crucial step in the task was the identification of the location of the stimulus that appeared immediately after the test stimulus during the list presentation, which means that stimulus Location was tied to Serial Position; this could explain why the Serial Position × Location interaction was a frequent effect. It is remarkable that all of these effects were documented in the motor cortex, an area traditionally regarded as composed exclusively of “upper motor neurons.” Our results add to a substantial body of evidence documenting the involvement of the motor cortex in other complex functions (14).

The neuronal responses described here were commonly phasic; that is, a change in neuronal activity, once evoked, was typically not maintained throughout the remainder of the list presentation phase (Fig. 3) (15). This suggests that the information about the sequence is processed in the motor cortex, which most likely participates as a component in a distributed network (2, 16) that collectively encodes, stores, and recalls the sequence. A prominent node in that network is the dorsolateral prefrontal cortex, which has been shown to play a key role in the capacity to act on the basis of serial order (17). Our results show that the motor cortex also participates in the processing of serial order information within the context of a motor task, that is, the serial order of stimuli on which the selection of a motor response must be based in the task used (18). This serial order information, once encoded and held in memory, is used after the presentation of the test stimulus to search the sequence, identify the serial position of the test stimulus in the sequence, and retrieve the stimulus associated with the next serial position, which specifies the required motor response. The unitary principle of this search was identified as an abrupt shift in the discharge of motor cortical neurons from that associated with the direction of a specific stimulus to that appropriate for the next one (4). The repeated application of this rapid-shift process from item to item would constitute memory scanning. Because the encoded sequence information can be accurately recovered from small ensembles of motor cortical neurons, this search could be monitored in time from the patterns of activity of these ensembles during the response time.

Fig. 5. Eye position, retinotopic location, and associated neural activity for the cell illustrated in Figs. 3B and 4. Upper panels (serial position 5): left, superimposed eye fixations (minimum of 100 ms duration) (N = 160 fixations); right, superimposed retinotopic positions of the fifth stimulus during these eye fixations; center, bar graph of mean (±SEM) neural activity during these fixations. Middle panels (serial positions 1 to 4): left, superimposed eye fixations (N = 420 fixations); right, superimposed retinotopic positions of the most recent stimulus (for each serial position) during these eye fixations; center, bar graph of mean (±SEM) neural activity during these fixations. Lower panels (superimposed records and neural activity for matched positions): left, eye positions for serial positions (SP) 1 to 4 (gray) and 5 (black); right, retinotopic positions for serial positions 1 to 4 (gray) and 5 (black); left bar graph, mean (±SEM) neural activity for the subset of eye positions that were similar (within 0.5°) between serial position 5 (black, N = 160) and serial positions 1 to 4 (gray, N = 116); right bar graph, mean (±SEM) neural activity for the subset of retinotopic positions that were similar (within 1.4°) between serial position 5 (black, N = 109) and serial positions 1 to 4 (gray, N = 73). Neural activity was consistently higher for serial position 5 than for serial positions 1 to 4. This difference was statistically highly significant when the overall rates were compared (bar graphs in upper versus middle panels) and when only the subsets of matched eye positions (bottom left) or retinotopic positions (bottom right) were compared (t test, P < 0.00000001 for each of the three comparisons above).

References and Notes
5. The monkeys were trained to exert a force pulse on a two-dimensional semi-isometric handle in eight different directions (at 45° intervals). The manipulandum was a vertical rigid metal rod, with a disc attached to the top, which was placed in front of the animal in the midsagittal plane and which the animal grasped with the hand pronted. A net force feedback cursor was displayed on a monitor in front of the monkey. This cursor was deflected constantly downward to simulate a bias force of 54g and reflected, at any given moment, the net force (the vector sum of this simulated force and the force exerted by the animal on the manipulandum). At the start of the trial, a white stimulus appeared in the center of the screen and the monkey had to place the force feedback cursor on the center stimulus by exerting a force of 54g in the upward direction and then keep it there within a 72g-radius circular window. After 1 s, three to five yellow stimuli were presented on a 270g-radius circle in different directions. During the presentation of the stimuli, the force feedback cursor had to stay within the central window. The response
6. The number of simultaneously recorded neurons ranged from 2 to 11 for monkey 1 and from 2 to 16 for monkey 2. A quadratic discriminant analysis was performed [P. A. F. C. Arbib, Encyclopedia of Neuroscience (New York, 1975)] because cells in a simultaneously recorded set commonly did not have a common covariance structure, hence a linear discriminant analysis was not appropriate. Percentages of correct classification were computed for each sequence within a list length and averaged across sequences.

11. The average percent of correct classification of serial position for a sequence of three stimuli was 69% (range 45 to 99%), for a sequence of four stimuli it was 64% (range 35 to 99.8%), and for a sequence of five stimuli it was 66% (range 32 to 94%). The chance levels of correct classification were 33.3%, 25%, and 20% for sequences of four, five, and six stimuli, respectively.

12. A power function was fitted to the data using least squares. The fitted function was: Percent correct classification = 20.9N^{0.567} (r^2 = 0.995), where N is the number of cells in the ensemble. Extrapolating the power function indicates that an ensemble of as few as 16 motor cortical neurons would correctly classify all the items in a sequence of five stimuli.

13. Careful qualitative inspection of the data, using plots such as in Figs. 3 to 5, indicated that changes in cell activity could not be correlated with eye movement, eye position, or stimulation of a specific part of the visual field. In addition, because the successively presented stimuli remained on the screen throughout the trial (Fig. 1A), there was a rich pattern of visual stimulation that differed from epoch to epoch and from sequence to sequence. Exhaustive quantitative analyses of these factors is beyond the scope of this report.

14. For reviews, see A. P. Georgopoulos, Annu. Rev. Neurosci. 14, 361 (1991); M. Taira, A. V. Lukashin, Science 260, 47 (1993). The changes in activity during the list presentation phase, such as those that were not related to concomitant motor events because no motor response occurred during this period (6). Instead, these changes in activity occurred while the monkeys were viewing a sequence of stimuli, whose order they had to transiently remember. It is possible that this activity may reflect intended, but not executed, limb movements. However, if this were the case, one would expect to detect the location of the currently presented stimulus, which would determine the direction of a hypothetical motor response. Instead, we found that cell activity was most related to serial position in the sequence rather than location.

15. A similarly phasic encoding response has been described for interhemispheric neurons during an object recognition memory task [A. F. Carpenter, G. Pellizzer, A. P. Georgopoulos, J. Neurosci. 13, 1460 (1993)].


18. This study was not designed to address issues of neural coding of serial order per se, as an abstract entity (that is, the first, second, second, third, etc., A-B-C-A-A-A-A-series of stimuli). Rather, we focused on a specific motor task whose correct performance depended on identifying the serial order of stimuli. The motor cortex (this report) as well as premotor and periretal areas [A. F. Carpenter, G. Pellizzer, A. P. Georgopoulos, Soc. Neurosci. Abstr. 24, 1426 (1998)] are involved in this task.

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