Population-Vector Analysis by Primate Prefrontal Neuron Activities

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Abstract. The population-vector analysis was applied to visualize neuronal processes of sensory-to-motor transformation in the prefrontal cortex while two monkeys performed two types of oculomotor delayed-response (ODR) tasks. In a standard ODR task, monkeys were required to make a quick eye movement to where the visual cue had been presented 3 s before, whereas in R-ODR task, monkeys were required to make an eye movement 90° clockwise to the direction that the visual cue had been presented. In both tasks, directions of population vectors calculated from cue- and response-period activity were almost the same as cue directions and saccade directions, respectively, indicating that population vectors of cue- and response-period activity represent information of visual inputs and motor outputs, respectively. To visualize neuronal processes of information transformation, population vectors were calculated every 250 ms during a whole trial. In ODR task, population vectors were directed the same direction as the cue direction during the delay period. However, in R-ODR task, population vector rotated gradually from the direction similar to the cue direction to the saccade direction during the delay period. These results indicate that visual-to-motor transformation occurs during the delay period and that this process can be visualized by the population-vector analysis.

Key words: directional selectivity, delay-period activity, information transformation, monkey, population vector, prefrontal cortex, single-neuron activity, spatial working memory

1. Introduction

Working memory is a mechanism for temporary active storage of necessary information as well as for processing stored information to perform such cognitive activities as thinking, reasoning, and decision making [1]. The prefrontal (PF) cortex has been known to participate in working memory [2, 12, 13]. Neurophysiological experiments have revealed that a tonic activation (‘delay-period activity’) is observed in many PF neurons during an imposed waiting period (the delay period) between the presentation of the visual cue and the motor performance [3, 7, 13, 14] and that this activity is a neuronal correlate of the mechanism for temporary storage of information [2, 8, 12, 13]. In addition, the experiments used pro- and anti-saccade tasks and conditional position discrimination tasks revealed that most (about 80%) of delay-period activity encodes information for sensory inputs (e.g.,

the location of the visual cue) whereas the remaining (20%) encodes information for motor outputs (e.g., the direction of the eye movement or the arm reaching movement) [6, 15, 17], suggesting that transformation from sensory information to motor outputs is performed in the PF cortex [2, 17]. However, it is not yet known how PF neurons perform such transformation. Since the neuronal mechanism for processing and manipulating temporary stored information is an important subject to understand working memory processes, a neuronal mechanism related to the transformation from sensory information to motor output could be an ideal model to examine processing and manipulating processes of stored information.

In the present experiment, we tried to visualize neuronal processes of transformation from sensory inputs to motor outputs in the PF cortex. We applied the population-vector analysis developed by Georgopoulos et al. [9, 11] for this purpose. The neuronal population vector has been shown to be a useful method for visualizing and identifying internal operations of cognitive tasks such as mental rotation processes [10, 16]. We calculated population vectors using single-neuron activities recorded from the PF cortex while monkeys performed two types of oculomotor delayed-response tasks (ODR and R-ODR tasks). In the ODR task, monkeys were required to make a quick eye movement to where the visual cue had been presented 3 s before, whereas in the R-ODR task, monkeys were required to make an eye movement 90° clockwise to the direction that the visual cue had been presented. In the R-ODR task, the transformation from visual input to motor output is necessary to perform correct eye movements. The present results indicate that transformation from visual inputs to motor outputs occurs during the delay period in the PF cortex and that this process can be visualized by the expression of population vectors.

2. Subjects and Behavioral Tasks

Two rhesus monkeys were used as subjects. All experiments were conducted according to the NIH (USA) Guideline for animal experiments, and were approved by the Animal Research Committee at Faculty of Integrated Human Studies, Kyoto University. During training and recording sessions, the monkey sat in a primate chair in a dark room and his head was fixed by a head restraining instrument. The monkey faced a 21-in. color monitor, on which a fixation point and visual cues were presented. Monkey's eye positions were monitored by a magnetic search coil technique. Two laboratory computers controlled monkey's behavior, presented visual stimuli on the monitor, recorded neuronal activities, and monitored eye movements.

Two types of oculomotor delayed-response (ODR) tasks were used in this experiment. In a *standard ODR task* (Figure 1A, left), the monkey was required to make a saccade to the location where the cue had been presented after the 3 s delay. After a 3 s intertrial interval (ITI), a fixation point (FP) (a white filled circle) was appeared at the center of the monitor. If the monkey looked at FP and maintained gazing at FP for 1 s (the fixation period), a visual cue (a white filled

Figure 1. A. Diagrams of temporal sequences of events during the ODR (left) and R-ODR (right) tasks. B. The shaded area in the figure indicates the cortical area where single-neuron activities were recorded. C. Eight locations of the visual cue used in the ODR task. The visual cue was a white filled circle. Four locations of the visual cue used in the R-ODR task were 0° , 90° , 180° , and 270° in this figure. The eccentricity was 17° .

circle) was presented for 0.5 s (the cue period) at one of the eight predetermined locations around FP (Figure 1C). The monkey was required to maintain fixation at FP throughout the 0.5 s cue period and subsequent 3 s delay period. At the end of the delay period, FP was extinguished. This was the Go signal for the monkey to make a saccade within 0.35 s (the response period) to the location where the visual cue had been presented. If the monkey performed a correct eye movement, he obtained a drop (about 0.2 ml) of water as reward.

In a *rotatory oculomotor delayed-response (R-ODR) task* (Figure 1A, right), the monkey was required to make a saccade 90° clockwise to the location where the visual cue had been presented. The temporal sequence of task events was the same between two tasks. The visual cue (a white filled circle) was presented for 0.5 s at one of the four predetermined locations around FP (a white + character). The monkey was required to maintain fixation at FP throughout the 0.5 s cue period and the 3 s delay period. At the end of the delay period, the monkey was required to make a saccade within 0.35 s 90° clockwise to the location where the visual cue had been presented. If the monkey performed a correct eye movement, he obtained a drop of water as reward. The eccentricity of the cue presentation was 17° in both tasks. The location of the visual cue was randomized over trials in both tasks.

3. Single-Neuron Activity in the PF Cortex

Single-neuron activity was recorded from the cortex within and surrounding the principal sulcus (Figure 1B) while the monkey performed both tasks. Raw neuron activity was recorded by glass-coated metal microelectrodes. We isolated single-neuron activity from amplified raw neuron activity using a window discriminator. Timings of single-neuron activity were input to the computer and stored together with task events in magnetic media. To examine characteristics of recorded single-neuron activity, we made raster displays and histograms triggered at several alignment points (e.g., the onset of the cue period, the end of the delay period) for each cue condition in both tasks.

Figure 2 is an example of a single-neuron activity recorded during two task conditions. In this example, tonic excitatory activity during the delay period (delay-period activity) is observed at the 270° and 315° cue conditions in the ODR task and at the 270° cue condition in the R-ODR task. Since this delay-period activity was observed during the delay period only during particular cue conditions, and since the monkey only looked at FP during the delay period in all cue conditions, delay-period activity has been considered a neuronal correlate of the temporary storage mechanism of information [2, 8, 12, 13]. By comparing directional preferences of delay-period activity between ODR and R-ODR tasks, we could know what information delay-period activity encodes. For example, the neuron shown in Figure 2 had delay-period activity encoding the locations of the visual cue, because this neuron exhibited delay-period activity at the 270° cue condition in both tasks, in spite of the difference of saccade directions between two task conditions (at the 270° cue condition, monkeys were required to make a saccade to the 270° direction in the ODR task, but to the 180° direction in the R-ODR task). A total of 304 single-neuron activities were recorded from the PF cortex. Among 56 showing delay-period activity, 86% encoded the location of the visual cue whereas 14% encoded the direction of saccade [17].

Forty-one neurons exhibited cue-period activity, which is a phasic excitatory response during the cue period. Cue-period activity is considered a visual response to the presentation of the visual cue [4], because all encoded the locations of the visual cue [17]. In addition, 53 neurons exhibited response-period activity. Response-period activity was classified into two groups; pre-saccadic activity ($n = 11$) and post-saccadic activity ($n = 42$). Pre-saccadic activity is a phasic excitatory activity that initiates 50–150 ms before the initiation of saccadic eye movement. On the other hand, post-saccadic activity is a phasic excitatory activity that initiates 100–200 ms after the termination of saccadic eye movement, but has directional selectivity. Among neurons having response-period activity, 33 encoded the directions of saccade whereas 20 encoded the locations of the visual cue [17]. Most of response-period activity encoding the directions of saccade was pre-saccadic [17], indicating that pre-saccadic activity could act as a trigger signal to initiate saccadic eye movements [2, 5, 17]. However, most of response-period activity encoding the

Figure 2. An example of directional delay-period activity of one prefrontal neuron recorded during two task conditions. In the ODR task, tonic excitatory activity was observed during the delay period at 270° and 315° cue conditions. In addition, a phasic excitatory response was observed during the response period at the 135° cue condition. In the R-ODR task, significant tonic excitatory activity was observed during the delay period and a phasic excitatory response was observed during the response period, both at the 270° cue condition. Since directions of eye movements were 90° clockwise to the directions of the visual cue in the R-ODR task, delay-period activity of this neuron encodes the location of the visual cue, whereas response-period activity encodes the direction of saccade. Circularly arranged 8 figures for ODR task and 4 figures for R-ODR indicate neuronal activity observed during corresponding cue conditions. C, D, and R represent the 0.5 s cue period, the 3 s delay period, and the response period, respectively.

location of the visual cue was post-saccadic, suggesting that post-saccadic activity could act as a control signal to modulate delay-period activity [2, 5, 17].

4. Population-Vector Analysis

Since the location of the visual cue was different from the direction of saccade in the R-ODR task, transformation from sensory information to motor outputs is

necessary to perform the R-ODR task correctly. The comparison of directional selectivity of task-related activity between ODR and R-ODR conditions revealed that most of delay-period activity encodes the locations of the visual cue whereas the remaining encode the direction of saccade [6, 15, 17]. These results suggest that transformation from sensory information to motor outputs is performed in the PF cortex [2, 17]. However, it is not known how PF neurons perform such transformation. In addition, a neuronal mechanism related to the transformation from sensory information to motor output could be an ideal model to examine processing and manipulating processes of stored information in working memory. Therefore, we performed the population-vector analysis to visualize neuronal processes of sensory-to-motor transformation.

The population-vector analysis was first introduced by Georgopoulos et al. [9, 11] to predict movement directions by the action of a population of motor cortical neurons. They calculated a cell vector based on each neuron's activity and a population vector, which is a weighted sum of all cell vectors. In this analysis, the magnitude of activity of individual neuron under a certain condition was described as a vector (cell vector) that corresponds to the weighted contribution along the axis of this neuron's preferred direction. The neuron's preferred direction is estimated from the tuning curve that is obtained by fitting mean discharge rates across all cue conditions on the cosine function. Similar to neurons in the motor cortex, most of task-related activity of PF neurons exhibited directional selectivity while monkeys performed the ODR task [3–5]. The characteristics of directional selectivity and the preferred direction for each task-related activity were estimated by constructing the tuning curve. In the present experiment, the tuning curve for each task-related activity was constructed by fitting neuronal activities on the cosine function. According to Georgopoulos's method [11], cell vectors were estimated from each PF neuron's task-related activity. For each cell vector, the direction of the vector corresponded to the preferred direction of task-related activity and the length of the vector corresponded to the magnitude of task-related activity at a corresponding cue condition.

After finishing the calculation of cell vectors, the population vector was calculated as a weighted sum of all cell vectors. The population vector (P) at a particular cue condition was calculated by the following equation

$$P = \sum W_i * C_i$$

where C_i is i th neuron's preferred direction and W_i is i th neuron's weighted function. W_i is estimated by the following equation

$$W_i = d_i - a_i$$

where d_i is a square root value of i th neuron's discharge rate at a particular cue condition and a_i is a square root value of the same neuron's baseline discharge rate. The baseline discharge rate was obtained as the mean discharge rate during the 1 s fixation period.

Figure 3. Cell vectors (thin black lines) and population vectors (thick dotted lines) calculated from cue-, delay-, and response-period activities during ODR performances. Although the ODR task has 8 cue conditions, the results based on 4 cue conditions are shown in this figure. Neuronal activities for calculating these vectors were based on the mean discharge rate during 300 ms (from 100 ms to 400 ms after the cue presentation) for cue-period activity, the mean discharge rate during the 3 s delay period for delay-period activity, and the mean discharge rate during 300 ms (from 200 ms to 500 ms after the Go signal).

5. Population-Vector Analysis of Task-Related Activity

A total of 195 single-neuron activities were recorded during both ODR and R-ODR tasks. Among them, 110 exhibited task-related activity in both tasks, and 36, 49, and 51 exhibited directional cue-, delay-, and response-period activity, respectively. Figure 3 is the results of the population analysis using these cue-, delay-, and response-period activities in the ODR task. Each figure includes cell vectors (thin lines) and population vectors (dotted thick lines) for 4 cue conditions.

Cell vectors and population vectors of cue-period activity (Figure 3, left) were constructed from single-neuron activity of 36 neurons that exhibited directional cue-period activity. The magnitude of cue-period activity used for calculating these vectors was the mean discharge rate during 300 ms (from 100 ms to 400 ms after the cue presentation) at each cue condition. As is seen in Figure 3, the population vector calculated from cue-period activity under each cue condition directed mostly toward the location of the visual cue. This result indicates that population vectors calculated from cue-period activity could predict the direction where the visual cue is presented. Since cue-period activity has been considered to represent visual responses to the presentation of the visual cue, this result also indicates that the spatial information of the visual cue is represented by the action of a population of PF neurons.

Cell vectors and population vectors of response-period activity (Figure 3, right) were constructed from single-neuron activity of 51 neurons that exhibited directional response-period activity. The magnitude of response-period activity used for calculating these vectors was the mean discharge rate during 300 ms (from 200 ms to 500 ms after the Go signal presentation) at each cue condition. The population vector calculated from response-period activity under each cue condition directed mostly toward the direction of saccadic eye movement. This result indicates that

population vectors calculated from response-period activity could predict the direction where the monkey makes saccades during the response period. Since most of response-period activity has been considered to represent information for saccade directions, this result also indicates that the direction of eye movement is represented by the action of a population of PF neurons. This result, together with the result obtained from the population-vector analysis of cue-period activity, indicates that population vectors well predict information representing by a population of PF neurons.

6. Population-Vector Analysis of Sensory-Motor Transformation

Similarly, cell vectors and population vectors of delay-period activity (Figure 3, middle) were constructed from single-neuron activity of 49 neurons that exhibited directional delay-period activity. The magnitude of activity used for calculating these vectors was the mean discharge rate during the 3 s delay period at each cue condition. Population vectors calculated from delay-period activity under each cue condition also directed mostly toward the location of the visual cue. Previous observations reveal that about 80% of delay-period activity encoded the location of the visual cue while the remaining 20% encoded the direction of the saccade [6, 15, 17], and that most of delay-period activity were maintained tonically during the delay period [3, 7]. In addition, the location of the visual cue and the direction of the saccade were the same for all cue conditions in the ODR task. Therefore, the direction of the population vector calculated from delay-period activity might direct toward the direction that corresponded to the location of the visual cue in the ODR task.

However, in the R-ODR task, the monkey was required to make a saccade 90° clockwise to the direction where the visual cue was presented. Therefore, the monkey needed to perform a transformation from the visual input to the motor output to perform correct saccades during the response period in the R-ODR task. In addition, as was seen in Figure 3, population vectors calculated from cue-period activity and response-period activity represent information of visual inputs and motor outputs, respectively. Therefore, transformation from visual information to motor output could occur during the delay period.

To visualize neuronal processes of transformation from visual inputs to motor outputs in a population of PF neurons, we divided one trial (a total of 4000 ms period from the beginning of the cue period until the end of the response period) into 16 250-ms-periods, and calculated population vectors using mean discharge rates during every 250-ms-period for 195 PF neurons. Figure 4A shows population vectors calculated by this method under the 270° cue condition of the ODR task. Directions of calculated population vectors were mainly directed toward the 270° direction and this directional selectivity was maintained during the delay period (Figure 4C). On the other hand, Figure 4B shows population vectors calculated every 250 ms under the 270° cue condition of the R-ODR task (the visual cue was

Figure 4. Population vectors calculated every 250 ms period from the beginning of the cue period and the end of the response period. A and C. Results obtained during the 270° cue condition of the ODR task. The direction of the visual cue and the direction of saccade were both 270° direction. B and D. Results obtained during the 270° cue condition of the R-ODR task. The direction of the visual cue was 270°, but the direction of saccade was 180°.

presented at the 270° position, but the direction of saccade was the 180° direction). In this task, directions of calculated population vectors were directed toward the 270° direction during the cue period and at the beginning of the delay period. However, directions of population vectors began to rotate at the middle of the delay period, continued to rotate slowly from the 270° direction to the 180° direction during the late half of the delay period, and finally directed mostly to the 180° direction at the response period when the monkey made saccades toward the 180° direction (Figure 4D). Since the PF cortex needed to generate the direction of saccade from the location of the visual cue by visual-to-motor transformation in the R-ODR task, the rotation of population vectors calculated from a population of activities of PF neurons indicates neuronal processes of visual-to-motor transformation occurred in the PF cortex.

The present results indicate that visual-to-motor transformation in the R-ODR task occurs during the delay period and that this process can be visualized by using neuronal population vectors calculated from a population of PF activities. The population-vector analysis not only visualizes internal neuronal processes themselves but also visualizes the time course of these processes. Similar analysis has previously been performed by Georgopoulos et al. (1989) [10]. They trained mon-

keys to move their arms in the direction either to a target light or counterclockwise to the direction of a target light, and collected single-neuron activities from the motor cortex. Then, they calculated neuronal population vectors every 10 ms from the onset of the target light under both conditions. As a result, they found that, when the monkey moved its arm in the direction counterclockwise to the direction of the target light, the population vector rotated gradually counterclockwise from the direction of the target light to the direction of the movement. These results indicate that the neuronal population vector is a useful method to demonstrate internal operations of cognitive processes by a population of neurons.

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