Different Neuronal Computations of Spatial Working Memory for Multiple Locations within versus across Visual Hemifields

Ayano Matsushima and Masaki Tanaka
Department of Physiology, Hokkaido University School of Medicine, Sapporo 060-8638, Japan

Spatial working memory is one of the most studied cognitive functions, serving as a model system to decipher computational principles of the brain. Although neuronal mechanisms for remembering a single location have been well elucidated, little is known about memory for multiple locations. Here, we examined the activities of prefrontal neurons during monkeys remembered positions of one or two visual cues. When the two cues were presented across the left and right visual fields, neurons exhibited a comparable response to the activity for the preferred cue presented alone. When the two cues were presented within the same hemifield, neurons exhibited an intermediate response between those to the individual cues. Subsequent computer simulations predicted a lower signal-to-noise ratio in the latter condition, which was further verified by behavioral experiments. Considering the separation of contralateral and ipsilateral visual processing, the lateral inhibition in local circuits might implicitly determine different neuronal computations and memory capacities for bilateral and unilateral displays.

Key words: memory capacity; prefrontal cortex; primate; single-unit recording; working memory
Materials and Methods

Animal preparation. Experiments were conducted on three Japanese macaques (*Macaca fuscata*, 6–7 kg female, Monkeys J, L, and O). All animal protocols were approved by the Animal Care and Use Committee of Hokkaido University and were in accord with the Guide for the Care and Use of Laboratory Animals. The animal preparation procedure was described previously in detail (Tanaka, 2005). Briefly, a pair of head holders was implanted on the skull using titanium screws and dental acrylic under general isoflurane anesthesia. A coil of stainless steel wire was implanted on the skull using titanium screws and dental acrylic described previously in detail (Matsushima and Tanaka, 2005). Use of Laboratory Animals. The animal preparation procedure was described previously in detail (Matsushima and Tanaka, 2005). Experiments were controlled in a darkened booth. Each trial began with the appearance of a fixation point (FP, 0.5° red square) at the center of the screen. Monkeys were required to maintain fixation for >300 ms to proceed with the trial. Correct performance was reinforced with a drop of liquid reward at the end of each trial.

During recording sessions, we presented two memory-guided saccade tasks. In the multiple memory-guided saccade (MMS) task (see Fig. 1A), two sample (200 ms) and three test stimuli were presented 12° eccentrically across a 2 s delay (1° white squares). One test stimulus was presented at the same location as either sample (matched stimulus), whereas the others were presented elsewhere (nonmatched stimuli). The location of the matched stimulus was chosen randomly from the two sample locations so that the animals had to remember both locations. Monkeys were required to keep their eyes within 5° of the central FP during the sample and delay periods, then to make a saccade to the matched stimulus in response to the FP offset and the simultaneous appearance of test stimuli (<400 ms). As a control, we also presented the single memory-guided saccade (SMS) task with only one sample (see Fig. 1B). When two samples were presented across the left and right visual fields (green), the activity was similar to that for the single sample presented in the RF (red, the same data as in A). When two samples were presented within the same visual field (green), the neuron exhibited an intermediate response to those for each stimulus presented alone (red and blue traces, the same data as in A and C).

Visual stimuli and behavioral paradigms. Experiments were controlled by a Windows-based real-time data acquisition system (TEMPO; Reflective Computing). Visual stimuli were presented on a 24-inch cathode-ray tube monitor (60 Hz) positioned 38 cm from the eyes and subtending 64 × 44° of visual angle. Experiments were performed in a darkened booth. Each trial began with the appearance of a fixation point (FP, 0.5° red square) at the center of the screen. Monkeys were required to maintain fixation for >300 ms to proceed with the trial. Correct performance was reinforced with a drop of liquid reward at the end of each trial.

During recording sessions, we presented two memory-guided saccade tasks. In the multiple memory-guided saccade (MMS) task (see Fig. 1A), two sample (200 ms) and three test stimuli were presented 12° eccentrically across a 2 s delay (1° white squares). One test stimulus was presented at the same location as either sample (matched stimulus), whereas the others were presented elsewhere (nonmatched stimuli). The location of the matched stimulus was chosen randomly from the two sample locations so that the animals had to remember both locations. Monkeys were required to keep their eyes within 5° of the central FP during the sample and delay periods, then to make a saccade to the matched stimulus in response to the FP offset and the simultaneous appearance of test stimuli (<400 ms). As a control, we also presented the single memory-guided saccade (SMS) task with only one sample stimulus (see Fig. 1B). In all recording sessions, the deviation of eye position from the FP was much less than the window size (mean ± SD, 0.51 ± 0.11°, 0.50 ± 0.14°, and 0.64 ± 0.14°, for Monkeys J, L, and O, respectively). Both sample and test stimuli appeared either at four oblique (45°, 135°, 225°, or 315° measured from rightward) or four cardinal (0°, 90°, 180°, or 270°) polar angles. Different tasks were presented pseudo-randomly within a block that usually consisted of the SMS trials in four oblique and/or four cardinal (90°—720°) polar angles.
Matsumura and Tanaka • Neuronal Correlates of Multiple Spatial Memories

J. Neurosci., April 16, 2014 • 34(16):5621–5626 • 5623

Results

We recorded from single neurons in the macaque PFC (Fig. 1D). In the MMS task (Fig. 1A), two sample and three test stimuli were presented across a 2 s delay. Monkeys maintained a central fixation throughout the cue and delay periods and then made a saccade to a test stimulus presented at the same location as either sample (matched stimulus). Because the matched stimulus was randomly assigned to one of the two sample locations, monkeys had to remember both locations during the delay. Two samples were always presented 90° apart from each other in the MMS trials examined in the current study. As a control, we also used the SMS task (Fig. 1B), in which only one sample was presented. All three monkeys performed very well in the SMS (mean ± SD of the rate of correct choice: 98 ± 2%, 98 ± 3%, and 98 ± 2%, for Monkeys J, L, and O, respectively) and MMS (90 ± 7%, 94 ± 6%, and 98 ± 2%, for Monkeys J, L, and O, respectively) tasks.

Consistent with previous studies (Funahashi et al., 1989; Matsumura and Tanaka, 2012), we found neurons exhibiting a sustained response to the visual cues. A representative neuron shown in Figure 2 exhibited an elevated activity throughout the delay period after a single sample presented in the upper-left receptive field (RF, Fig. 2A). When the cue was located 90° away from the RF, however, the delay-period activity disappeared (Fig. 2B, C). In the MMS trials with two samples presented across the left and right visual fields (Fig. 2D, Across condition), the same neuron exhibited strong activity (green trace), comparable with the response to a single cue presented in the RF (red trace, same data as in Fig. 2A). On the other hand, when the two cues were presented within the same hemifield (Fig. 2E, Within condition), the neuron exhibited an intermediate response between those to the preferred (red) and nonpreferred (blue) stimulus presented alone.

Neuronal responses in the two conditions were consistently different in the sampled population. In the Across condition, the population activity for the two cues in the MMS trials (Fig. 3A, green trace) was similar to that for the preferred cue presented
alone (Fig. 3A, red trace), but far stronger than that for the nonpreferred cue (Fig. 3A, blue trace). On the contrary, in the Within condition, the population activity was intermediate between the activities for the individual cues (Fig. 3B). The linear weight of population activities was significantly biased toward the preferred cue in the Across condition (0.75, 95% CI = [0.66 0.84], bootstrap repetition = 1000), but neither cue in the Within condition (0.40, 95% CI = [0.29 0.52]). To assess the separation of responses between the MMS and SMS trials in individual neurons, we computed ROC values for every 100 ms (20 ms step). The population average shows that the ROC values for the Across condition were closer to 0.5 when responses in the MMS trials were compared with those in the SMS trials for the preferred (Fig. 3C, red trace), rather than the nonpreferred sample (Fig. 3C, blue trace), indicating that the response to the two cues was closer to the response to the single cue presented at the preferred location. On the other hand, ROC values for the Within condition were equally separated from 0.5 when compared with either sample (Fig. 3D), indicating that the response to the two cues differed evenly from the response to the preferred or nonpreferred cue presented alone. When we computed the mean deviation of the ROC values from 0.5 in the last 1500 ms of the delay, we found a significant difference between those for the preferred and nonpreferred samples in the Across condition (paired t test, p < 0.001, Fig. 3E), but not in the Within condition (p > 0.1, Fig. 3F).

We also examined trial-by-trial response variability by computing the Fano factor during the delay but failed to find differences between the task configurations for the Across (two samples, 1.2 ± 0.5; single preferred, 1.1 ± 0.5; single nonpreferred, 1.2 ± 0.5, one-way ANOVA, n = 60, p > 0.5) and Within conditions (1.3 ± 0.5, 1.1 ± 0.5, 1.2 ± 0.4, p > 0.4). These results suggest that multiple locations might be represented by different firing rates of neurons depending on the relative stimulus locations. In the Across condition, neuronal activity is dominated by the preferred stimulus, almost in a winner-take-all manner. In the Within condition, neuronal activity is equally affected by individual stimuli, resulting in the average response.

Different neuronal modulations could not be attributed to other factors than the relative location across the visual fields. First, one might argue that monkeys attended to a specific sample in the Across condition. However, this is unlikely because monkeys performed equally well when the matched stimulus was presented at the preferred or nonpreferred location in the Across (preferred vs nonpreferred, 97.9 ± 4.8% vs 99.0 ± 3.1%, paired t test, p > 0.1) as well as in the Within condition (97.9 ± 5.8% vs 99.2 ± 2.7%, p > 0.1). Second, the nonpreferred stimulus might be presented inside the RF in the Within condition so that it competed with the preferred stimulus. However, as we fitted Gaussian tuning curves to delay-period activities in the SMS trials, the nonpreferred cues presented in both conditions were located 3.1 SD away from the RF center (mean ± SD, Across, 3.1 ± 1.8; Within, 3.1 ± 2.1, n = 60, paired t test, p > 0.7). Third, multiple locations might be remembered as a single entity encompassing the two samples in the Within condition. Incompatible with this, neurons tuned to the midpoint of the samples were suppressed when monkeys remembered the two locations simultaneously (Fig. 4). Furthermore, the rate of choosing the test stimuli when presented in between the two samples was much lower than the rate at the cued locations (see below, Fig. 5C–E). These results were analogous to those for multifocal attention; visual responses to a distractor flanked by attended objects were suppressed in the extrastriate visual area (Niebergall et al., 2011). Because the response variability was comparable between the MMS and SMS trials, the focus of working memory seemed to be divided, rather than fluctuating, between the two locations.

Based on the results of the neuronal recordings, we next attempted to simulate population activities during the delay in the MMS trials. In the Across condition where neurons responded in a “winner-take-all” manner (Fig. 5A, left), a neuron tuned to a specific location (black solid curve) would exhibit a comparable response to the activity for a single cue presented around its preferred location (blue dot at the level of intercept with vertical line indicating Sample 1). In the Within condition (Fig. 5A, right), however, the same neuron would exhibit an “Averaging” response of those to individual samples (red dot at the mean level of two intercepts). Repetition of similar computations for 16 spatially tuned neurons yielded a population coding with maximal activities at the two sample locations, both in the Across (blue) and Within conditions (Fig. 5A, red solid curves). This result indicates that cued locations are encoded by the most active neurons in the array, just like the previous computational model (Compte et al., 2000). However, the quality of the signal represented in the neuronal population appeared to differ between the two conditions, as further clarified by overlaying the normalized population activities (Fig. 5B); the activity contrast between the cued and the intermediate locations was reduced in the Within condition compared with the Across condition.

To see the corresponding behavioral outcomes, we conducted an additional experiment. In the behavioral test, one of the nonmatched stimuli was occasionally presented in between the two sample locations (Fig. 1C). As the choice probability was calculated for each test stimulus (Fig. 5C–E), we found that all monkeys made more errors in choosing the midpoint of two samples in the Within than in the Across condition (both-side z test, p <
0.05), consistent with the simulation results (Fig. 5B). Together, these results suggest that the interaction between neuronal representations of multiple locations might hinder the individuation of each spatial memory and ultimately could constrain behavioral performance.

Discussion
In the present study, we probed the neuronal correlates of working memory for multiple locations. When monkeys remembered two cues presented across the left and right visual fields, their neuronal activities were comparable with those for a single cue presented at the preferred location. When monkeys remembered two cues presented within the same hemifield, their neuronal activities were intermediate between the responses to individual cues. Our data might reflect an inherent, anatomical separation of contralateral and ipsilateral information processing along the visual pathways.

After the optic chiasm, visual inputs from the right visual field are transmitted to the left side of the brain, whereas those from the left visual field are transmitted to the right side. This laterality is especially evident in the early stages of cortical processing, in which RFs are confined to contralateral visual fields (Bullier, 2004). Reflecting the division into hemispheres, visual stimuli presented in opposite visual fields are more difficult to compare than those presented in the same hemifield (Banich and Belger, 1990; Sergent, 1990).

Even in the PFC, where neurons responding to contralateral and ipsilateral stimuli coexist (Rainer et al., 1998; Lennert and Martinez-Trujillo, 2013), inputs from different visual fields are known to reach distinct cortical columns (Goldman-Rakic and Schwartz, 1982). Related to this, behavioral performance is strongly influenced by the spatial arrangement of visual items even in tasks requiring higher order processing; humans can attend to (Alvarez and Cavanagh, 2005) or remember (Delvenne, 2005) more objects when presented bilaterally than unilaterally. As for the neural correlates, Buschman et al. (2011) recently showed that neuronal information about object identity is more reduced by the presence of other objects in the same compared with the opposite visual field. Our data might provide a reasonable explanation for these previous observations from the viewpoint of neuronal computation within local circuits. Signals from the same visual field are processed highly competitively and averaged through recurrent connections, whereas signals from opposite hemifields are processed almost independently and spared in distinct cortical columns.

Differences in neuronal computations were further verified by monkeys’ performance. Based on the observed firing modulations, we simulated the population activities during the delay in the Across and Within conditions. The simulation can be viewed as a specific form of the normalization model proposed by Reynolds and Heeger (2009), where individual neuronal activities are normalized by the total activity in each neuronal ensemble responsible for either visual hemifield. As suggested by a previous computational model (Compte et al., 2000), we found that the cued locations could be represented by the most active neurons in the population. Thus, in our task configuration, the matched stimulus would be simply read out by detecting a peak of activity when visual responses to test stimuli were added to the population activity. However, the generally noisy activities of neurons seemed to produce an accidental peak at uncued locations, causing errors. Corresponding to the relatively higher activity at the midpoint of the two sample locations, monkeys erroneously reported the midpoint as a cued location more often in the Within than in the Across condition. These results demonstrate that the interaction of multiple representations within each neuron determines the signal-to-noise ratio in the population activity and ultimately constrains the behavioral performance. Considering the columnar organization of contralateral and ipsilateral neurons in the PFC (Goldman-Rakic and Schwartz, 1982), the interactions might be mediated by interneurons constructing recurrent network with nearby functionally related pyramidal neurons (Gabbott and Bacon, 1996; Rao et al., 1999). Because there also exist long-range horizontal connections in the cortex (Stepanyants et al., 2009), signal processing in each cortical column might not be completely independent so that the magnitude of intracolumnar and intercolumnar interactions might be relatively, rather than absolutely, different. Nonetheless, our data suggest that the relative difference is sufficient to alter the neuro-
nal signals and behavioral performance in the Across and Within conditions. Because the balanced inhibition to excitation within local circuits is essential to prevent epileptic activity (Turrigiano, 2011), the working memory capacity limited by the recurrent inhibition might be computationally (Usher and Cohen, 1999) and evolutionarily (Hultsch, 1992) inevitable.

References