THE LATERAL INTRAPARIETAL AREA (LIP) plays a crucial role in signaling behaviorally relevant locations in the visual field to guide future actions during visuomotor transformation (Andersen and Cui 2009; Bisley and Goldberg 2010; Gold and Shadlen 2007; Gottlieb and Snyder 2010; Wardak et al. 2011). LIP neurons encode the location of a target among distractors during visual search by exhibiting elevated activation when the target is presented inside the neuron’s receptive field relative to when the distractor is presented inside the receptive field (Balan et al. 2008; Buschman and Miller 2007; Ipati et al. 2006; Nishida et al. 2013; Thomas and Paré 2007). They also exhibit persistent activation (delay-period activity) to represent the location where an extinguished target had been presented in memory-guided saccade (Chafee and Goldman-Rakic 1998; Gnadt and Andersen 1988; Nishida et al. 2014). Previous studies have investigated neuronal signaling of target location during visual discrimination separately from that occurring during maintenance of working memory (or the motor plan for a saccade; Barash et al. 1991a, 1991b). However, the two often appear to be inseparable sequential processes underlying goal-directed behaviors in real-life situations. Little is known about the way in which LIP processes these two types of target-location signaling under such a situation.

It has been theorized that the target-location signaling in visual discrimination and working memory (i.e., discrimination-related elevated activity and delay-period persistent activity) may share common neural circuits (Wang 2002; Wong and Wang 2006). Some LIP studies on neural mechanisms underlying visual discrimination exclusively examined neurons with persistent delay-period activity (e.g., Churchland et al. 2008; Huk and Shadlen 2005; Roitman and Shadlen 2002; Shadlen and Newsome 2001). However, a recent simulation study has suggested that although visual discrimination and persistent storage of information are supported by common neuronal mechanisms, these different functions are mediated by different local circuits (Standage and Paré 2011). Moreover, at the single-cell level, the temporal profile of LIP neuron responses shows considerable heterogeneity during delayed-response visual discrimination tasks, although the population average response across neurons exhibits continuous modulation contingent on the location of the response target (Meister et al. 2013; Premereur et al. 2011). Thus different LIP neurons appear to be engaged in target-location signaling in visual discrimination and working memory; however, the transition of target-location signaling by different neurons between the cognitive processes is not well understood.

To investigate this issue, we trained two monkeys to perform a delayed-response visual search task in which they were required to search for a color-singleton target among distractors during the stimulus period and remember the location where the target had been presented during a delay period until a saccadic response was required. This design allowed us to assess the transition of target-location signaling across visual discrimination and working memory within the same trial. We recorded single-unit activity in LIP as the monkeys performed the task and examined changes in the across-neuron pattern of response modulation contingent on target location in the different stages of the task.

METHODS

The general experimental procedure for single-unit recording from LIP in awake monkeys has been described in detail previously (Nishida et al. 2013, 2014; Tanaka et al. 2013). All animal care,
training, and experimental procedures were in accordance with the Guide for the Care and Use of Laboratory Animals of the National Research Council (1996) and were approved by the Animal Care and Use Committee of Kyoto University.

Subjects and Surgery

Experiments were performed on two female macaque monkeys (Macaca fascicularis; Y and S; 5.0 and 6.3 kg, respectively). A plastic head holder and recording chamber were secured to each monkey’s skull. The recording chambers (inner diameter, 22 mm) were placed at stereotaxic coordinates (P2 and L2.15 for monkey Y; P4.1 and L1.8, and P0 and L2.1 for monkey S) above the intraparietal sulcus (IPS) with the assistance of magnetic resonance imaging (MRI) performed before the surgery. An eye coil was surgically implanted beneath the conjunctiva of one eye (Judge et al. 1980).

Visual Stimuli and Behavioral Tasks

Visual stimuli were generated using a video signal generator (ViSaGe; Cambridge Research Systems, Rochester, UK) and presented on a video monitor with a 100-Hz refresh rate and 800 × 600 resolution (RDF223H; Mitsubishi, Tokyo, Japan). Stimuli were viewed binocularly from a distance of 42 cm in a dark room and subtended a visual angle of 51.5° × 40.0°. The color and luminance of the stimuli were measured using a ColorCAL colorimeter (Cambridge Research Systems).

Delayed-response visual search task. The task and stimulus conditions have been described previously (Nishida et al. 2013, 2014) and are depicted in Fig. 1A. Briefly, each trial began with sustained fixation (1,000 ms) within a ±1.5–2.5° window (fixation period). A six-element (circles 2.24° in diameter and 10 cd/m² luminance) search array consisting of one singleton element unique in color (target) and five additional identical elements (distractors) was then displayed on a gray background (1 cd/m²) for 500 (monkey Y) or 700 ms (monkey S) (stimulus period). After the array disappeared, a variable-delay fixation period was introduced (600–1,700 ms for monkey Y; 800–1,200 ms for monkey S) (delay period). When the fixation point was extinguished (the “go” signal), the monkeys were required to make a saccade toward the location at which the target had been presented (response period). If the monkeys made a single saccade landing inside a square window (±3.0° × 3.0°) centered on the target, another fixation point appeared at the target position. After 600 ms of fixation on this point, the monkey received a juice reward (successful trial). If the monkey made a saccade toward the location outside the target-centered window or could not keep the fixation within the window for 600 ms, the trial was immediately terminated with no reward (erroneous trial). Although the fixation break before the go signal also aborted the trial immediately, the trial was not included in either successful or erroneous trials. The target was randomly presented in the receptive field of the neuron under study or in the diametrically opposite location in the visual field with equal probability. Target and distractor color pairs were selected so that their colors were either orange and green, green and orange, yellowish orange and bluish green, or bluish green and yellowish orange.

This task design allowed us to assess the transition of target-location signaling across visual discrimination and working memory within the same trial. It should be noted that several studies of LIP have interpreted the delay-period modulation in neuronal response as the maintained motor plan for a saccade (Barash et al. 1991a, 1991b; Gnadt and Andersen 1988) in contrast to studies of the lateral prefrontal cortex which have posited that the delay-period modulation reflects maintained sensory representation of extinguished stimuli (Constantinidis and Wang 2004; Funahashi et al. 1989; Goldman-Rakic 1995; but see Lebedev et al. 2004). However, the difference of interpretations for the period modulation is not critical for our investigation, because “target-location signaling” as referred to in the present study simply means the spatial representation of a task-relevant location irrespective of whether the representation is predominantly associated with sensory or motor processing. Therefore, to avoid confusion, we use the term “working memory” throughout the article.

Reaction-time visual search task. The procedure for this task was identical to that for the delayed-response visual search task with the exception that no delay period was imposed. After fixation, an array
stimulus was displayed and the monkeys were required to make a saccade toward the target without an artificial delay. When the computer detected a saccadic eye movement, the visual stimuli and the fixation spot were immediately extinguished. The reaction-time visual search task contained trials with various stimulus configurations and target-absent (catch) trials in which all stimuli were identical distractors and the monkeys were required to hold the fixation throughout the trial (for details, see Nishida et al. 2013). However, only data from trials in which the array stimuli were the same as those used in the delayed-response visual search task were included in the analysis of the present study.

Memory-guided saccade task. This task was an isolated-stimulus version of the delayed-response visual search task and analogous to a conventional memory-guided saccade task (Hikosaka and Wurtz 1983). The procedure was the same as that for the delayed-response visual search task with the exception that an isolated stimulus, rather than a search array, was displayed. The data from this task were used to assess visually responsive, delay-period, and saccade-related activity (see below).

Trials for the three tasks were pseudorandomly interleaved on a trial-by-trial basis within a session. In addition, the memory-guided saccade task was conducted in a separate block at the beginning of individual recording sessions to identify the location of the receptive field for the neurons under study (see below). Behavioral performance during visual search varies with retinotopic eccentricity (e.g., Carssaro and Yeshurun 1998; Meinecke and Donk 2002; Wolfe et al. 1998); thus, for all tasks, the eccentricity of the visual stimuli was fixed at 8.5° in the periphery to minimize interneuron differences in task difficulty across recording sessions. The color or shape of the fixation spot identified the task type (yellow circle for the delayed-response visual search task; white square for the memory-guided saccade task; white circle for the reaction-time visual search task).

Data Collection

Eye position was monitored and recorded using the scleral search coil technique (Fuchs and Robinson 1966; eye position detector DSC-2001; Datel, Tokyo, Japan). Precise spikes were discriminated offline using a template-matching method. Eye-position signals were recorded at a sampling rate of 50 kHz but analyzed at 1-kHz resolution.

Single-cell activity was recorded using an epoxy-lute-insulated tungsten electrode (Frederick Haer, Brunswick, ME) with an impedance >2 MΩ measured at 1 kHz (model IMP-1; Bak Electronics, Germantown, MD). The electrode was advanced through guide tubes lowered to just above the dura mater surface using an oil hydraulic micromanipulator (MO-9TA-S; Narishige, Tokyo, Japan). Guide tubes were positioned using a set of plastic grids with holes spaced 1 mm apart and offset from each other by 0.5 mm. Extracellular activity was amplified using a microelectrode AC amplifier (model-1800; A-M Systems, Carlsborg, WA) and stored on a computer equipped with a multichannel analog-to-digital board at a sampling rate of 50 kHz (PCI-6143; National Instrument, Tokyo, Japan). Once isolated during a recording session, the location of the receptive field of all neurons was assessed using the memory-guided saccade task. An isolated stimulus was presented at one of six evenly spaced directions on an imaginary circle (eccentricity = 8.5°) because the target-location eccentricity was fixed at 8.5° during the visual search tasks. We manually adjusted these six directions so that one direction evoked the strongest activity. The direction evoking the strongest activity was identified as the location of the receptive field and used for the subsequent tasks and analyses. Note that the data obtained during the identification of the receptive field location were not used for the other analyses.

Recording site. Before initiation of the experiment, we determined the location of the IPS on the basis of its response properties; the medial bank of the IPS tends to exhibit activity related to somatosensory stimuli, whereas the lateral bank exhibits visual and saccade-related responses (Barash et al. 1991a; Maimon and Assad 2006; Mountcastle et al. 1975). We then recorded neurons in the lateral bank of the IPS from a region, regarded as LIP, in which neurons exhibit robust, spatially tuned responses during the delay period of a memory-guided saccade task (Barash et al. 1991a, 1991b; Colby et al. 1996; Gnadt and Andersen 1988; Shadlen and Newsome 2001). To ensure that our samples were in LIP rather than in area 7a, neurons recorded at a depth <3 mm from the surface of the dura mater were excluded from the analysis (Andersen et al. 1990; Gifford and Cohen 2004; Linden et al. 1999). The neurons under study were typically recorded at a depth >5 mm from the dura surface (88.1%). The majority of our neurons (52.4%) exhibited delay-period persistent activity (see also RESULTS), which is consistent with the percentage of LIP neurons reported in previous studies (e.g., Barash et al. 1991b; Falkner et al. 2010; Maimon and Assad 2006). Furthermore, we verified the recording positions on the basis of postoperative structural MRIs acquired for both monkeys on a 0.2-T open whole body scanner (Signa Profile; General Electric, Milwaukee, WI) as shown in our previous studies (see Fig. 2 in Nishida et al. 2013 and Fig. 2 in Nishida et al. 2014). To confirm the physiological properties of the recorded neurons and anatomic verification using MRI confirmed that our samples were recorded from the LIP.

Data Analysis

We recorded single-cell activity from a total of 92 LIP neurons in the 2 monkeys while they performed the delayed-response visual search task. Of those, the data sets of 84 and 74 neurons overlapped with those used for other purposes in our previous studies (Nishida et al. 2013 and Nishida et al. 2014, respectively). Unless otherwise indicated, only the data from successful trials were analyzed in the present study. All data analysis was performed using MATLAB (The MathWorks, Natick, MA).

Visually responsive, delay-period, and saccade-related activity. Data obtained from the memory-guided saccade task were used to analyze visually responsive, delay-period, and saccade-related activity. The location of the receptive field for individual neurons was determined in advance using the same task as described above. In this task, an isolated target stimulus was displayed at one of six evenly spaced directions on an imaginary circle. Of these, we tested the activity when the target was located inside the receptive field and the activity when the target was located diametrically opposite the receptive field. Neurons were classified as exhibiting visually responsive activity when activity occurring 50–150 ms after target presentation inside the receptive field was significantly greater than prestimulus activity occurring 200–400 ms before the target presentation. Neurons were classified as exhibiting delay-period activity when activity occurring 100–400 ms before the go signal was significantly different when the target appeared inside and opposite the receptive field. Neurons were classified as exhibiting saccade-related activity when activity occurring 0–100 ms before the initiation of the saccade toward the receptive field was significantly greater than that occurring 200–300 ms before the saccade initiation (t-test, P < 0.05).

Spike density functions. We constructed spike density functions with 1-kHz resolution by convolving spike trains with a combination of growth (1-ms time constant) and decay (20-ms time constant) exponential functions that resembled a postsynaptic potential (Thompson et al. 1996). Spike density functions for the reaction-time visual search task did not include spikes occurring after saccade initiation during each trial. Population average responses were calculated by averaging the responses across neurons.

Modulation index. Target-location signaling in the activity of LIP neurons was assessed by response modulations contingent on whether the target or the distractor appeared inside the receptive field. The strength of the response modulation for each cell was measured by calculating the modulation index (MI) as (Rg - Rp)/(Rg + Rp), where...
RESULTS

Behavioral Performance

We trained two monkeys to perform a delayed-response visual search task to investigate the transition of target-location signaling in the sequential processes of visual discrimination and working memory maintenance in LIP neurons. In this task, the monkeys were required to identify the location of a target among distractors in a search array and remember the location during a delay before making a saccadic response (Fig. 1A). The error rate during this task was 0.01 ± 0.02 (mean ± SD) for monkey Y and 0.04 ± 0.04 for monkey S. The mean saccadic latency during this task was 190 ± 12 ms for monkey Y and 163 ± 14 ms for monkey S. Unless otherwise indicated, only the data from successful trials were used in the following analyses.

Neuronal Database

We recorded the activity in a total of 92 well-isolated LIP neurons in two macaques performing the task. Of the 92 neurons, 84 (91.3%; 71 from monkey Y and 13 from monkey S) showed visually responsive activity during a conventional memory-guided saccade task and were included in the data analysis. Of those, 44 (52.4%) neurons also showed delay-period activity and 22 displayed saccade-related activity during the memory-guided saccade task. Data were collected from the 84 visually responsive neurons in 16–194 (53 ± 27, mean ± SD) trials in the delayed-response visual search task. Our samples involved no neuron in which the preferred location for visually responsive activity was mismatched with that for saccade-related activity.

Response Modulations in LIP Neuronal Activity During Delayed-Response Visual Search

We first examined the temporal profile of response modulations of LIP neuron population contingent on whether the target location was inside or opposite the neuron’s receptive field during the delayed-response visual search task. Population activity during this task is shown in Fig. 1B. The neuronal firing rate in response to the appearance of the target (target response; red trace) and the distractor (distractor response; cyan trace) in the receptive field was comparable in the first 100 ms following presentation of the stimulus. However, the target response was significantly greater than the distractor response by 96 ms after stimulus onset (paired t-test, \(P < 0.05\)). This significant difference persisted throughout the delay and response periods. The MI, the difference between the averaged target- and distractor-responses divided by their sum in a sliding window of 50 ms in 10-ms steps, was used to quantify the time course of the response modulation for each neuron. The average MI time course is shown in Fig. 1C. The MI gradually developed during 50–300 ms following presentation of the array. Although the MI decreased slightly 100–250 ms after stimulus offset, it remained significantly greater than zero during the delay and response periods (1-sample t-test, \(P < 0.0001\)). Thus the response modulation was consistently evident in the LIP population throughout the trial in the delayed-response visual search task. This finding is consistent with those of previous LIP studies using a delayed-response motion-discrimination paradigm (Kiani et al. 2008; Meister et al. 2013; Shadlen and Newsome 2001).

The response modulations for individual neurons were determined by calculating MIs during the stimulus (120–220 ms after stimulus onset; Fig. 2A), delay (100–400 ms before the
Change in the across-neuron pattern of MIIs was strong within the stimulus, delay, and presaccade periods; however, the correlations between the stimulus and the delay or the presaccade periods were weak. An important point is that the across-neuron pattern of MIIs appeared to change abruptly, rather than gradually, 150–200 ms after stimulus offset (left vertical and bottom horizontal dashed lines in Fig. 3A). The correlation matrix revealed two clear clusters with high correlation coefficients (bottom left and top right clusters in Fig. 3A). Thus LIP neurons change their target location-dependent response modulation in a stepwise manner within a brief interval around a specific time after the stimulus disappears.

To understand the precise time course of the change in the across-neuron pattern of MIIs, we performed a sequential correlation analysis in which Pearson’s correlation coefficients were calculated between MIIs in two successive, nonoverlapping windows of variable width (100, 200, and 300 ms) in 10-ms steps between 200 ms before stimulus offset and 500 ms after stimulus offset. The correlation value decreased sharply irrespective of window width, and the lowest correlation values were obtained 170–240 ms after stimulus offset (Fig. 3B; 170, 170, and 240 ms for 100-, 200-, and 300-ms window width, respectively). This analysis specifies the timing of an abrupt change in the response modulations and also confirms that the abrupt change in the across-neuron pattern of MIIs was not an artifact of the window width used in the calculation.

Changes in Response Modulation in Individual Neurons

To further investigate the across-neuron MI pattern, we examined the dynamics of the individual neurons underlying the abrupt change at the population level by determining the time point of substantial change in the MI ("change point") of...
each neuron by using a Weibull fit to the time sequence of MIs around stimulus offset. Goodness of fit was measured using $R^2$, and an $R^2$ value $>0.6$ was deemed to indicate a change in the neuron MI. Neurons were classified into three types (increase, decrease, and other; see METHODS). The time at which the best-fit Weibull function crossed the half-height of the maximum and minimum values was defined as the change point of the MI (green vertical lines in Fig. 4, A and B). Figure 4C shows the time course of individual neuron MIs during the task. About half of the neurons studied (38/84; 45%) exhibited a substantial change in their MI: 13 neurons were classified as the increase-type neurons (top rows; $R^2 = 0.61–0.94$, mean = 0.76), and 25 were decrease-type neurons (middle rows; $R^2 = 0.68–0.95$, mean = 0.82). Thus, at the single-neuron level, LIP neurons exhibited a strong heterogeneity in their temporal profiles of target location-dependent modulations. This finding is consistent with previous studies (Meister et al. 2013; Premereur et al. 2011).

Importantly, the MI change points (black dots in Fig. 4C) were narrowly distributed (histogram at top; 178 ± 19 ms, mean ± SE) and did not significantly differ between the increase- and decrease-type neurons (mean = 166 and 186 ms, respectively; 2-sample $t$-test, $P = 0.62$). Thus the change points occurred concurrently. The fact that the mean time of these change points (174 ms after stimulus offset) was similar to the timing at which the sequential correlation of MIs had the lowest value (170 ms; 100-ms window width in Fig. 3B) suggests that concurrent changes in the MI of a subset of LIP neurons produced the observed change in the across-neuron MI pattern.

We investigated this possibility by artificially adding random displacements to the actual MI time sequences of the 38 increase- and decrease-type neurons by using a bootstrap procedure (within a range of ±100 ms; 2,000 repetitions) and then calculating the sequential correlation of MIs in the same way as for the actual data (Fig. 3B). We hypothesized that if the concurrent MI changes in these neurons were important, the abrupt change in the across-neuron pattern of the MI would disappear. The results of the simulation confirmed our hypothesis: the sequential correlation did not decrease sharply when the MI time sequences for the increase- and decrease-type neurons were randomly displaced (orange trace in Fig. 4D); conversely, we observed a steep decrease in the sequential correlation when the MI sequences for the other-type neurons were randomly displaced (green trace). Comparison with the actual data (black trace) revealed that the sequential correlations in which the MI sequences for increase- and decrease-type neurons were displaced were significantly different from the actual data 170–180 ms after stimulus offset (horizontal bars; bootstrap test, $P < 0.05$), whereas those in which the MI sequence for other-type neurons were displaced were not significantly different. Thus concurrent changes in the MIs of the increase- and decrease-type neurons, but not the other-type neurons, were necessary for the observed sharp change in the across-neuron MI pattern.

Changes in LIP Neuronal Activity

To inspect what changes in the raw activity of LIP neurons produced the abrupt change in the across-neuron MI pattern, the temporal profile of target and distractor responses were examined separately. We performed a sequential correlation analysis of the normalized firing rate of either target or distractor response, using the same method described above (Fig. 3B), and found that there was no sharp decrease around 170 ms after stimulus offset in either case (Fig. 5A, vertical dashed line). Therefore, the abrupt change in the across-neuron MI pattern may not be explained simply by the abrupt change in across-neuron patterns of target or distractor responses.

To further investigate this issue, we constructed spike density functions separately for increase-, decrease-, and other-type neurons described above (Fig. 4C); the firing rates of the individual neurons were normalized and averaged across neu-
rons for the purpose of comparing the different types. The increase and decrease types of neurons showed different profiles of changes in their activity during the task (Fig. 5, B–D). For the increase-type neurons (Fig. 5B), the distractor response remained substantial before stimulus offset relative to other types (Fig. 5E; paired t-test, $P < 0.0001$, Bonferroni corrected), although information about the distractor positions was behaviorally irrelevant in this task. After stimulus offset, despite large decreases in both the target and distractor responses around 170 ms after stimulus offset (Fig. 5E; paired t-test, $P < 0.05$), the magnitude difference between the target and distractor responses was preserved. This would cause the increase in the MIs of the increase-type neurons. In contrast, for the decrease-type neurons (Fig. 5C), the distractor response decreased almost to baseline level before stimulus offset (Fig. 5F; 1-sample t-test, $P = 0.13$) and exhibited little change after stimulus offset (Fig. 5E; $P = 0.68$), whereas the target response largely decreased around 170 ms after stimulus offset (Fig. 5E; $P < 0.001$). These response modulations would cause the reduction of the MIs of the decrease-type neurons. The most striking difference in the response properties between the increase- and decrease-type neurons was the presence or absence of the distractor response at stimulus offset. This response-magnitude difference was not simply due to the stronger initial visual response for the increase-type neurons than for the decrease-type neurons, but rather was due to the difference in the decay rate of the visual response between the increase type and the other two types of neurons (Fig. 5G; $P < 0.05$, Bonferroni corrected). Taking these findings together, the increase in the MIs of the increase-type neurons is explained by...
the comparable magnitude reductions in the target and distractor responses, whereas the decrease in the MIs of the decrease-type neuron is explained by the reduction of only the target response.

These considerations posit that the different response properties across neuron types are not straightforwardly explained by their different profiles of MI changes, but rather may be linked with their different functional roles during delayed-response visual search (see DISCUSSION). Although the across-neuron pattern of the target or distractor responses themselves did not exhibit sharp changes around 170 ms after stimulus offset in either case (Fig. 5A), concurrent heterogeneous activity changes across different subsets of neurons (Fig. 5, B–D) would cause the observed abrupt change of the across-neuron MI pattern (Fig. 3).

It should be noted that the increase and decrease types did not depend on the presence or absence of saccade-related activity. The fraction of neurons showing saccade-related activity was not different across neuron types [increase type: 3/13 (23.1%); decrease type: 8/25 (32.0%); other type: 11/46 (23.9%); \( \chi^2 \) test, \( P = 0.73 \)].

Effect of the Visual Off-Response

Visual area neurons often display a phasic response to the disappearance of a visual stimulus in their receptive field (i.e., visual off-response). Thus it may be argued that the observed concurrent changes in MI were the result of LIP neuronal off-responses. To test this supposition, we assessed the appearance of an off-response for each of the 84 neurons. Only 3 neurons were found to exhibit off-responses when activity occurring 50–200 ms after stimulus offset was compared with the activity occurring 0–200 ms before stimulus offset (paired \( t \)-test, \( P < 0.05 \) for both target and distractor responses). Of
those, one neuron showed a substantial change in the MI after stimulus disappearance (increase-type neuron). Thus the rarity of off-responses in LIP neurons, which is consistent with previous reports (Ben Hamed and Duhamel 2002; Robinson et al. 1978), indicates that the concurrent changes in MIs cannot be explained by the effect of visual off-responses.

Effect of Small Eye Movements

Although the monkeys were required to fixate on a small spot located at the center of the display throughout the stimulus and delay periods, the fixation window criteria allowed small eye movements (i.e., microsaccades) within the window. Previous studies have found an association between such small movements and neuronal responses (Gur and Snodderly 2006; Hafed et al. 2009; Hafed and Krauzlis 2010; Martinez-Conde et al. 2004). This raises the possibility that the observed concurrent changes in the MI of LIP neurons were produced by small eye movements invoked by the disappearance of the stimulus array. To address this issue, we investigated whether the frequency of microsaccades changed around the time of stimulus offset. We counted the number of microsaccades using a 10-ms moving window in 1-ms steps between −200 and 500 ms from stimulus offset for each session (absolute eye velocity >20°/s, duration ≥10 ms) and averaged across the 84 sessions. The microsaccade rate revealed no substantial change after stimulus offset (1-way repeated-measures analysis of variance, \( P = 0.90 \)). Thus the effect of small eye movements cannot account for the concurrent changes in MI.

Relationship Between Target-Location Signaling in the Delayed-Response and Reaction-Time Visual Search

The population response of the 84 neurons exhibited continuous response modulation contingent on the target location until saccade initiation during the reaction-time visual search task (Fig. 6A), which is consistent with previous reports (Balan et al. 2008; Buschman and Miller 2007; Iapa et al. 2006; Nishida et al. 2013; Ogawa and Komatsu 2009; Thomas and Paré 2007). The reaction-time visual search task did not require a delay before the saccadic response, and as such, the across-neuron MI pattern may have been different from that of the delayed-response task. To examine this possibility, we first calculated the MIs in the 100-ms interval preceding saccade initiation in the reaction-time task (Fig. 6A, presaccade period; shaded area). Figure 6B shows that the MIs varied among neurons. The mean value was 0.19 (arrowhead), which was significantly greater than zero (1-sample \( t \)-test, \( P < 0.00001 \)). We then performed a correlation analysis between MIs in the presaccade period of the reaction-time task and MIs in the stimulus, delay, and presaccade periods of the delayed-response task. We found a significant correlation between MIs in the presaccade period of the reaction-time task and those in the stimulus period of the delayed-response task (Fig. 6C; Pearson’s correlation, \( r = 0.56, P < 0.00001 \)); however, the correlation with the delay and presaccade periods of the delayed-response task was not significant (Fig. 6, D and E; \( r = 0.06 \) and −0.01, \( P = 0.58 \) and 0.90, respectively). Thus the across-neuron MI pattern of the reaction-time task was analogous to that of the stimulus period of the delayed-response task, despite different task requirements between the two tasks.

DISCUSSION

The present study examines the degree of response modulations in individual LIP neurons contingent on the target location using MI and demonstrates that the across-neuron MI pattern of LIP neurons dynamically changed during the transition between the stimulus and delay periods in the delayed-response visual search task. The mean MI magnitude for the LIP population showed a moderate change during the task (Fig. 1). However, the across-neuron pattern of MIs varied between the stimulus and delay periods (Fig. 2) and exhibited an abrupt change ~170 ms after the stimulus disappeared (Fig. 3), which was the result of concurrent changes in the MIs of a subset of...
LIP neurons (Fig. 4). In addition, the concurrent MI changes were linked with heterogeneous patterns of activity changes across different subsets of neurons (Fig. 5). Of course, our population data were obtained during separate recording sessions conducted on different days; nonetheless, the observed concurrent changes in MI rather suggest that the phase-locked changes in the pattern of the response modulations are consistent across different days and populations. Our findings suggest that the target-location signaling by the across-neuron modulation pattern of LIP population discretely switches the modulation pattern after stimulus disappearance even when visual discrimination and working memory are continuously required for performing the task.

Relationship Between Target-Location Signaling in the Stimulus, Delay, and Presaccade Periods

Previous model studies have shown that neural circuits with excitatory reverberation that are primarily mediated by N-methyl-D-aspartate (NMDA) receptors encode target location in visual discrimination (Wang 2002; Wong and Wang 2006) and in spatial working memory (Camperi and Wang 1998; Compte et al. 2000; Renart et al. 2003). In addition, several neurophysiological investigations of the LIP neural mechanisms underlying visual discrimination have focused exclusively on neurons with delay-period persistent activity in a memory-guided saccade task (e.g., Churchland et al. 2008; Huk and Shadlen 2005; Roitman and Shadlen 2002; Shadlen and Newsome 2001). Thus a common neural substrate between visual discrimination and working memory has been tacitly assumed.

However, recent studies have suggested that excitatory reverberation mediated by NMDA receptors, which are essential for maintenance of working memory in vivo (Wang et al. 2013), is not necessarily effective for the neural computation in visual discrimination tasks (Shen et al. 2010; Standage and Paré 2011). Furthermore, the presence or absence of delay-period activity evokes little change in the response properties of LIP neurons during target discrimination in visual search (Ipata et al. 2006; Thomas and Paré 2007), and the strength of delay-period activity has little relationship with the magnitude of discrimination-related signals in the activity of LIP neurons during motion discrimination (Meister et al. 2013). Consistent with these findings, our results show that different subsets of LIP neurons were involved in discrimination-related and delay-period activities (Figs. 2, D and E, 3A, and 4C) even when visual discrimination and working memory were continuously required during a trial.

MIs in the presaccade period of the reaction-time task were not correlated with those in the presaccade period, but rather with those in the stimulus period, of the delayed-response task (Fig. 6, C and E) even though saccade preparation was similarly required in these two periods. One possible explanation for this result is that target-location signaling even for impeding saccades changes depending on the presence or absence of visual stimuli. This is consistent with a previous report that presaccadic LIP response during a motion discrimination task changes whether a saccadic target is present or absent in the neuron’s receptive field just before saccade initiation (Meister et al. 2013). In addition, reversible inactivation of LIP has no or little effect on the saccade generation itself in a visually guided saccade task (Li et al. 1999; Liu et al. 2010; Wardak et al. 2002) in contrast with that of other saccade-related areas such as the frontal eye fields (Dias and Segraves 1999; Wardak et al. 2006). Therefore, LIP neurons may not play a direct role in saccade generation, but rather convey perceptual or cognitive signals that are read out and used by downstream areas for guiding oculomotor behaviors (Mirpour and Bisley 2012).

According to this view, the increased response modulation we observed just before saccade initiation (Fig. 1C) may rather reflect intention (Andersen and Buneo 2002; Barash et al. 1991a, 1991b) or attention (Colby and Goldberg 1999; Gottlieb and Goldberg 1999).

Roles of Increase- and Decrease-Type Neurons

After entering the delay period, the MIs of a subset of neurons increased (increase-type neurons), whereas the MIs of another subset decreased (decrease-type neurons; Fig. 4C). The response properties of these two types of neurons were characterized especially by the differences in response profiles during the stimulus period (Fig. 5, B and C). The increase-type neurons showed slow decay of response to task-irrelevant distractors during the stimulus period (Fig. 5G), suggesting that these neurons have intrinsically long timescales of activation, which are advantageous for the maintenance of relevant sensory information even after a visual stimulus is distinguished (Nishida et al. 2014). The distractor response of the decrease-type neurons decayed fast and decreased almost to the baseline level even before stimulus offset (Fig. 5F), although the target response exhibited the substantial activity even in the same stimulus period, suggesting that these neurons receive signals for strong distractor suppression that is beneficial to shaping activity for visual selection (Falkner et al. 2010; Nishida et al. 2013). Therefore, consistent with MI changes, the differential response profiles of these two types of neurons might be linked with the heterogeneous functional roles for memory maintenance and visual discrimination.

Mechanisms Underlying the Abrupt Change in Target-Location Signaling

The concurrent MI changes of a subset of LIP neurons after stimulus disappearance were crucial for the abrupt change in across-neuron MI patterns (Fig. 4D). It is likely that cessation of visual signals as a result of stimulus disappearance triggered the concurrent changes. However, passive response attenuation due to the visual signal cessation is insufficient to explain the concurrent changes, because LIP responses have the large variability in decay time constant across neurons (Bisley and Goldberg 2006; Nishida et al. 2014). Therefore, an additional mechanism that characterizes population dynamics may contribute to aligning the timing of MI changes among neurons.

Previous studies have suggested that the discrete switch of across-neuron activity patterns reflects attractor dynamics for environmental representations in the rodent hippocampus (Colgin et al. 2010; Wills et al. 2005) or for olfactory representations in zebrafish (Mazor and Laurent 2005; Niessing and Friedrich 2010) when environmental or stimulus parameters are continuously varied. In addition, several theoretical studies have shown that attractor dynamics in the state space of neuronal population activity underlie neuronal behaviors involved in visual discrimination (Mante et al. 2013; Wong and...
Wang 2006; Wong et al. 2007) and working memory (Amit and Brunel 1997; Compte et al. 2000; Ganguli et al. 2008; Wang 1999). According to attractor models, different choices in visual discrimination are assumed to be represented by distinct attractor states, whereas persistent activation related to working memory is assumed to reflect a stable attractor state.

In the present study, target selection in the stimulus period would have pushed the activity of LIP neurons into a specific attractor state; however, cessation of external visual inputs as a result of stimulus disappearance would have globally altered the attractor landscape in the state space and induced the transition to another stable state. Such a state transition may produce the observed abrupt change in the across-neuron pattern of the response modulation at the transition from the stimulus to delay periods. The distinct attractor states in the stimulus and delay periods can operate target-location signaling by different neuronal circuits contained within an attractor network across these periods: one local network is more preferentially activated in one attractor state, whereas another local network is activated in another attractor state. In this meaning, we think that signals of the target location in the stimulus and delay periods are represented by different local networks rather than the same common network, although these local networks form an attractor network. This view is consistent with previous studies (Ganguli et al. 2008; Suzuki and Gottlieb 2012).

LIP neurons exhibit changes in activity associated with covert shifting of focused attention (Bisley and Goldberg 2003; Bracewell et al. 1996; Herrington and Assad 2009 2010). Herrington and Assad (2010) reported that it takes 160–230 ms for LIP neurons to alter their activity associated with an attentional shift between different objects following cue stimulus presentation. Thus the time at which the change in the across-neuron pattern of MIIs was most evident in our task (170 ms; Fig. 3B) may correspond to the time necessary for switching internal states of LIP neural circuits due to external events.

A limitation of the present study is that we used population data collected in separate recording sessions. This limitation makes it difficult to discuss the population dynamics underlying the abrupt changes in the across-neuron pattern of the response modulation. Nevertheless, our findings provide important clues to understand target-location signaling of neuronal activity in LIP. Further investigation using the techniques of computational modeling or simultaneous recording are needed to elucidate the underlying neuronal dynamics.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS
S.N. and T.T. conception of analytical design; T.T. and T.O. performed recording experiments; S.N. analyzed data; S.N. and T.O. interpreted results of experiments; S.N. prepared figures; S.N. drafted manuscript; S.N., T.T., and T.O. edited and revised manuscript; S.N., T.T., and T.O. approved final version of manuscript.

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