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Discharge Synchrony during the Transition of Behavioral Goal Representations Encoded by Discharge Rates of Prefrontal Neurons

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To investigate the temporal relationship between synchrony in the discharge of neuron pairs and modulation of the discharge rate, we recorded the neuronal activity of the lateral prefrontal cortex of monkeys performing a behavioral task that required them to plan an immediate goal of action to attain a final goal. Information about the final goal was retrieved via visual instruction signals, whereas information about the immediate goal was generated internally. The synchrony of neuron pair discharges was analyzed separately from changes in the firing rate of individual neurons during a preparatory period. We focused on neuron pairs that exhibited a representation of the final goal followed by a representation of the immediate goal at a later stage. We found that changes in synchrony and discharge rates appeared to be complementary at different phases of the behavioral task. Synchrony was maximized during a specific phase in the preparatory period corresponding to a transitional stage when the neuronal activity representing the final goal was replaced with that representing the immediate goal. We hypothesize that the transient increase in discharge synchrony is an indication of a process that facilitates dynamic changes in the prefrontal neural circuits in order to undergo profound state changes.

Keywords: behavioral goal, monkey, prefrontal cortex, synchrony, temporal coding

Introduction

Neuronal coding mechanisms, generated by correlating the activity of neurons, have been assessed on both experimental (Abeles et al. 1993; Shadlen and Newsome 1994; Singer and Gray 1995; Softky 1995) and theoretical grounds (von der Malsburg 1981; Shimizu et al. 1985; Aertsen et al. 1989; Abeles 1991; Diesmann et al. 1999). Although most studies that analyzed the activity of single neurons in the central nervous system examined firing rates, information may also be encoded in the timing of individual neuronal spikes, especially in the synchronous discharge of small assemblies of neurons. Although experimental evidence for precise temporal relationships among spiking activities of multiple neurons exists primarily for cortical sensory areas (Eckhorn et al. 1988; Gray et al. 1989; Ahissar et al. 1992; Nicolelis et al. 1995; deCharms and Merzenich 1996), synchrony modulation has also been reported in the motor cortex (Aertsen et al. 1991; Vaadia et al. 1995; Riehle et al. 1997; Baker et al. 2001), supplementary motor area (Lee 2003, 2004), and prefrontal cortex (Funahashi and Inoue 2000; Constantinidis et al. 2001, 2002). These previous reports suggested that spike synchrony might be modulated independently of mean firing rate and may be linked to changes in expectation, attention, response latency, and rivalry (for review, see Salinas and Sejnowski 2001); its relevance to object recognition is still a matter of debate (Gray 1999; Shadlen and Movshon 1999; Singer 1999).

The lateral prefrontal cortex (lPFC) appears to receive information from a large number of cortical and subcortical areas and then to transform it for use in behavioral planning (Fuster 1997; Romo et al. 1999; Miller 2000; Miller and Cohen 2001; Tanji and Hoshi 2001). Much research has focused on persistent changes in neuronal activity (Fuster and Alexander 1971; Goldman-Rakic 1987; Wang 2001; Brody, Hernandez, et al. 2003), which has been interpreted as representing working memory or an enduring process of executive behavioral control. Recent theoretical models equated such persistent activity with an "attractor" state of elements constituting a neural circuit (Compte et al. 2000; Brody, Romo, and Kepecs 2003; Major and Tank 2004). In such models, a steady state is maintained with properties inherent to neuronal circuits (Wang 2001), until intervening external stimuli lead to the state change. Neurons belonging to neural circuits in such a steady state are thought to hold information for subsequent use. On the other hand, the nature and content of information represented by steady-state neuronal activity is altered. This dynamic transition between different representations of information has been demonstrated experimentally (Rainer et al. 1999; Takeda and Funahashi 2002; Mushiake et al. 2006), leading to the question of how neural circuits achieve the state transition. Theoretical studies have suggested that a state transition could be induced by the operation of external inputs having synchronous properties (Salinas and Sejnowski 2000; Aoyagi and Aoki 2004; Fujii and Tsuda 2004; Aoki and Aoyagi 2007), including transient synchrony in the network (Gutkin et al. 2001).

In a previous study, we provided experimental evidence for the existence of behaviorally meaningful transitions in lPFC representations: information indicating a final behavioral goal was transformed into information specifying an immediate goal as the first step toward obtaining the final goal (Saito et al. 2005). This finding was based on a rate-coding analysis of neuronal activity. To address how the pattern of correlations among lPFC neurons would vary during this transformation of information, we analyzed the synchrony of neuronal activity separately from changes in the firing rates of individual neurons. We found enhanced synchrony during the transition period between the representations of the final and immediate

goals. This suggests the role of synchronization in processes that induce representational transitions of neural circuits from one steady state to another, each with a specific content of information. A preliminary account of this study has appeared elsewhere (Sakamoto et al. 2002).

Materials and Methods

Animals and Apparatus

Experiments were performed on 2 monkeys (*Macaca fuscata*, 6.8 and 7.5 kg), cared for in accordance with the Guiding Principles for the Care and Use of Laboratory Animals of the National Institutes of Health and the Guidelines for Animal Care and Use of our institution. Each animal, seated in a primate chair with its head restrained, was oriented toward a computer monitor displaying a maze. The monkey could operate manipulanda with either forearm to move a cursor on the maze, and its eye movements were monitored using an infrared eye camera (R21-C-AC; RMS, Hirosaki, Japan) with a 250-Hz sampling rate.

Behavioral Task

The behavioral task (path-planning task) was identical to that was used in Saito et al. (2005). The monkeys were trained to perform a path-planning task that required step-by-step cursor movements, controlled with the manipulanda, to reach a goal in a checkerboard-like maze (Fig. 1). Supination and pronation of each forearm were assigned to 4 cursor directions. A trial commenced when the animal held the manipulanda in a neutral position. After 1 s (Initial Hold), a green cursor appeared at the center of the maze (Start Display), and 1 s later, a red square was displayed for 1 s, indicating the position of a final goal within the maze (Final Goal Display). Then, after a delay of 1 s (Delay 1), 1 of 4 possible paths from the starting position to the goal was removed or blocked. This was followed by another 1-s delay (Delay 2) during which the cursor had to be kept at the starting position. Thereafter, the color of the cursor was changed from green to yellow, serving as a go signal to initiate the first-step movement (First GO). The animal was required to move the cursor within 1 s to the first position (immediate goal) and to keep it there until the cursor became yellow again, 1 s later. Then the animal had to move the cursor stepwise to reach the goal; that is, it had to stop at each intersection of the checkerboard-like maze. When the cursor reached the final goal, the animal was rewarded with fruit juice. The monkeys were free to select any path available, but they usually selected the 1 or 2 paths that took the minimum number of steps (3) to complete the task. To dissociate arm and cursor movements, the arm–cursor assignments were altered in 3 different combinations, on completion of a block of 48 trials (Fig. 1). This study focused on neuronal activity during the Final Goal Display and the Delay 1 and Delay 2 periods (the preparatory period) during which neuronal activity represents the final goal position, followed by the immediate goal.

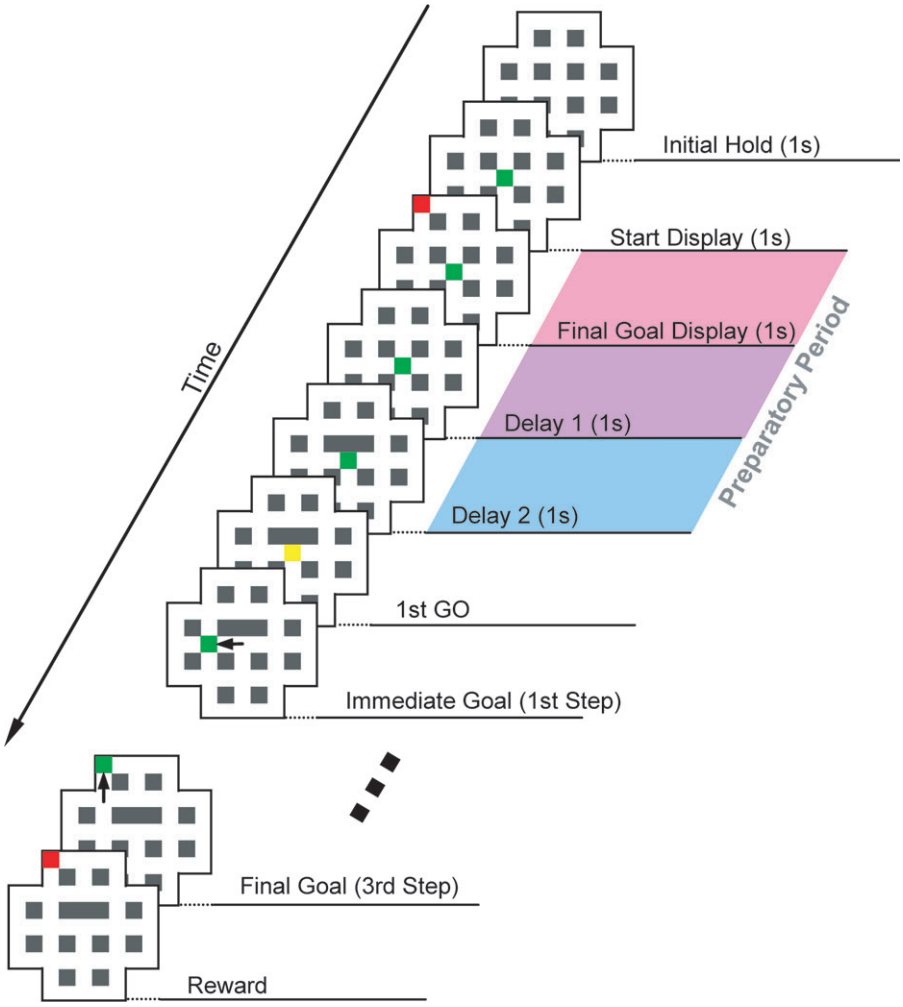

Figure 1. Temporal sequence of events in the behavioral task. The behavioral sequence is depicted from the top right to the bottom left. Each panel represents a maze displayed on a monitor, with green squares denoting current cursor positions and red squares indicating the positions of the final goal. Yellow squares represent movement initiation (GO) signals. Black arrows delineate cursor movements. Light red, purple, and blue bands to the right of the panels indicate the task periods defined as Final Goal Display, Delay 1, and Delay 2, respectively, constituting the preparatory period.

Surgery and Neuronal Recording

After the behavioral training, an acrylic recording chamber was attached to each monkey's skull under aseptic conditions. During surgery, the animals were anesthetized with ketamine hydrochloride (10 mg/kg intramuscularly) and pentobarbital sodium (30 mg/kg intramuscularly). Following surgery, cortical sulci were identified using a magnetic resonance imaging scanner (OPART 3D-System; Toshiba, Tokyo, Japan). Prior to recording neuronal activity in the lPFC, the frontal eye field (FEF) was defined using intracortical microstimulation. Neuronal activity was recorded rostral to the FEF, including the banks of the principal sulcus and the adjacent cortical convexity.

Single-neuron activity was recorded using up to 4 glass-insulated Elgiloy microelectrodes (1–2.5 MΩ at 333 Hz) aligned linearly by an electrode-positioning system (Alpha-Omega, Nazareth, Israel). Individual spikes were isolated using a template-based discriminator (multi-spike detector; Alpha-Omega), and only well-isolated spikes that were stable over the entire recording session were included in the analysis. There was not a consistent relationship between eye movement/position and neuronal activity during the periods analyzed (Saito et al. 2005). For detailed descriptions of the experimental procedures, see Mushiake et al. (2001) and Saito et al. (2005).

Analysis of Goal Representations by Neuronal Firing Rate

We examined whether the firing rate of each neuron represented selectivity for either the final or immediate goal during the preparatory period of 3 s (i.e., during Final Goal Display, Delay 1, and Delay 2). For this purpose, we performed multiple linear regression analysis (Saito et al. 2005) for the position of the final goal displayed during the Final Goal Display period (Final Goal [FG]) and for the position of the cursor at the first step (Immediate Goal [IG]), using the following formula:

$$\text{Firing rate} = \beta_0 + \beta_1(\text{Final Goal}) + \beta_2(\text{Immediate Goal}),$$

where β_0 is the intercept and β_1 and β_2 are the coefficients. The firing rate was calculated as spike counts within 100-ms time frames. The regressors indicated in parentheses were entered into the analysis as dummy variables. The categorical factors for the final goal were the 4 positions instructed during the Final Goal Display period; those for the immediate goal were the 4 positions available for the first movement of the cursor. In the analysis, n categories require n–1 dummy variables; therefore, we used 3 different dummy variables each for the FG and IG (Draper and Smith 1998). Accordingly, each of the 2 regression coefficients refers to a vector containing 3 dummy variables. Then, we obtained t values for each regression coefficient by dividing them by the standard error of the mean. To test the effects of FG and IG on neuronal activity, we set the significance level at $P < 0.05$ for each goal, with Bonferroni's correction for multiple comparisons, using commercial software (MATLAB 6.5; MathWorks, Natick, MA). In order to examine the time course of the t values at the population level, we normalized the t values of the regression coefficients by dividing them by the t value at the significance level. After that, we combined the elements of each of the 2 vectors of the regression coefficients by calculating the size of the vectors, to obtain variables defined as the Final Goal selectivity (FGS) and Immediate Goal selectivity (IGS). Figure 3*B* shows an example for FGS and IGS. For the purpose of display, it was smoothed by using a sliding average in 500 ms. In addition to the analysis of goal selectivity based on linear regression analysis described so far, we also performed a correlation analysis to calculate correlation coefficients. See Supplementary Data for the results of analysis using the correlation coefficients. Our previous study revealed that the firing rate of prefrontal neurons does not reflect motor variables such as left/right pronation and left/right supination (Saito et al. 2005).

To complete the goal representation analysis, the transition time from final to immediate goal representation (F–I transition) was individually determined for each neuron, based on the selectivity time plot described above. The F–I transition was defined as follows. First, the F–I index was defined as a function of time during trial t with the formula:

$$\text{FI index}(t) = [\text{IGS}(t) - \text{FGS}(t)]/[\text{IGS}(t) + \text{FGS}(t)],$$

Each was calculated by normalizing the regression coefficients as described above. Based on the time course of the F–I index obtained from the smoothed goal selectivity, we determined the times when the F–I index was at its maximum (t_{max}) and minimum (t_{min}). Then, we performed a regression analysis over the time period between t_{max} and t_{min}, using a linear model with the formula:

$$\text{FI index}(t) = \beta_0 + \beta_1 t,$$

where t is the time of a trial, β_0 is the intercept, and β_1 is the coefficient. For this regression analysis, the F–I index(t) was calculated from the unsmoothed goal selectivity for final and immediate goals. When the index was significantly correlated with t ($P < 0.05$), and β_1 was positive, the time when $\beta_0 + \beta_1 t$ crossed zero was defined as the F–I transition time, and the neuron showing the F–I transition was defined as the F–I transition neuron. When a neuronal pair included at least one F–I transition neuron, the pair was regarded as a pair with F–I transition. If both neurons in the pair belonged to F–I transition neuron, the F–I transition time of a neuron pair was determined by calculating their means. If otherwise, the F–I transition time of an F–I transition neuron was used to represent the pair (see Fig. 5*A*).

To examine the time course of goal selectivity at the "population" level, we plotted the time-varying goal selectivity for either the final or the immediate goal, starting from the onset of the initial hold period (1000 ms before the onset of the Final Goal Display) to the end of Delay 2. For that purpose, we averaged the magnitudes of goal selectivity calculated for individual neurons based on neuronal activity during a successive 100 ms (as described above). To display the time course of the population-level goal selectivity, we calculated the mean and standard deviation (SD) of the selectivity at the onset of the hold period (500 ms) as a reference value, subtracted the mean value from each of the time-varying goal selectivity, and then divided the selectivity by the SD before plotting (Fig. 4*A*).

Analysis of Neuronal Synchrony

We analyzed synchrony of neuron pairs simultaneously recorded during a period spanning the behavioral period of more than 2 arm–cursor assignment blocks (96 trials). We used the time-resolved cross-correlation method (Pauluis and Baker 2000; Baker et al. 2001) to assess the changes in synchrony of neuron pairs independently of changes in the firing rate of individual neurons during a behavioral task (Brody 1998, 1999), using the instantaneous firing rate (IFR) estimate of Pauluis and Baker (2000) to correct for firing rate modulation.

Spike trains were analyzed for 3 s before the appearance of the First GO signal (i.e., from Start Display to Delay 2, with a resolution of 1 ms), and then the raw time-resolved cross-correlation (RTCC) was plotted (Fig. 2*A*). The RTCC represents the spike timing of one neuron (response spike) within a time window (±200 ms) when the other neuron fires (trigger spike) during the task period. In Figure 2*A*, the horizontal coordinate of each dot represents the time of the trigger spike, taking the time of the appearance of the Final Goal Display as zero. The ordinate represents the delay between the response and trigger spikes. Each dot in the RTCC was smoothed using a 2-dimensional Gaussian kernel (with SDs of 100 ms in the horizontal and 2 ms in the vertical dimensions) and divided by the trial number to obtain the smoothed time-resolved cross-correlation (STCC; Fig. 2*B*).

Following the method of Pauluis and Baker, we calculated the IFR (Pauluis and Baker 2000; Baker et al. 2001) and then produced an instantaneous firing rate predictor (IFRP) by cross-correlating the IFR of the neuron pairs. The IFRP was smoothed as described above to construct an instantaneous firing rate predictor–based cross-correlogram (IBCC; Fig. 2*C*). The IBCC was subtracted from the STCC at each data point (Fig. 2*D*), and this value was summed over the task period to create the standard cross-correlation histogram (CCH). The CCH was used to select significantly synchronous pairs according to the following criteria: the number of spikes that contributed to the cross-correlation estimate was more than 2000 spikes, the CCH had a positive peak of more than 4.41 SD above baseline ($P < 0.00001$), and the significant peak was within ±25 ms of the center of the CCH (Constantinidis et al. 2001; Harris et al. 2003).

To examine the synchrony of significantly correlated pairs of spikes over time, we first calculated the raw synchrony (RS) by averaging synchrony magnitudes in the STCC, taken from the half-width area around the peak in the CCH. The mean half-width of the CCH peaks was 9.3 ± 10.6 ms ($n = 45$). Then, to plot the time course of the RS, we

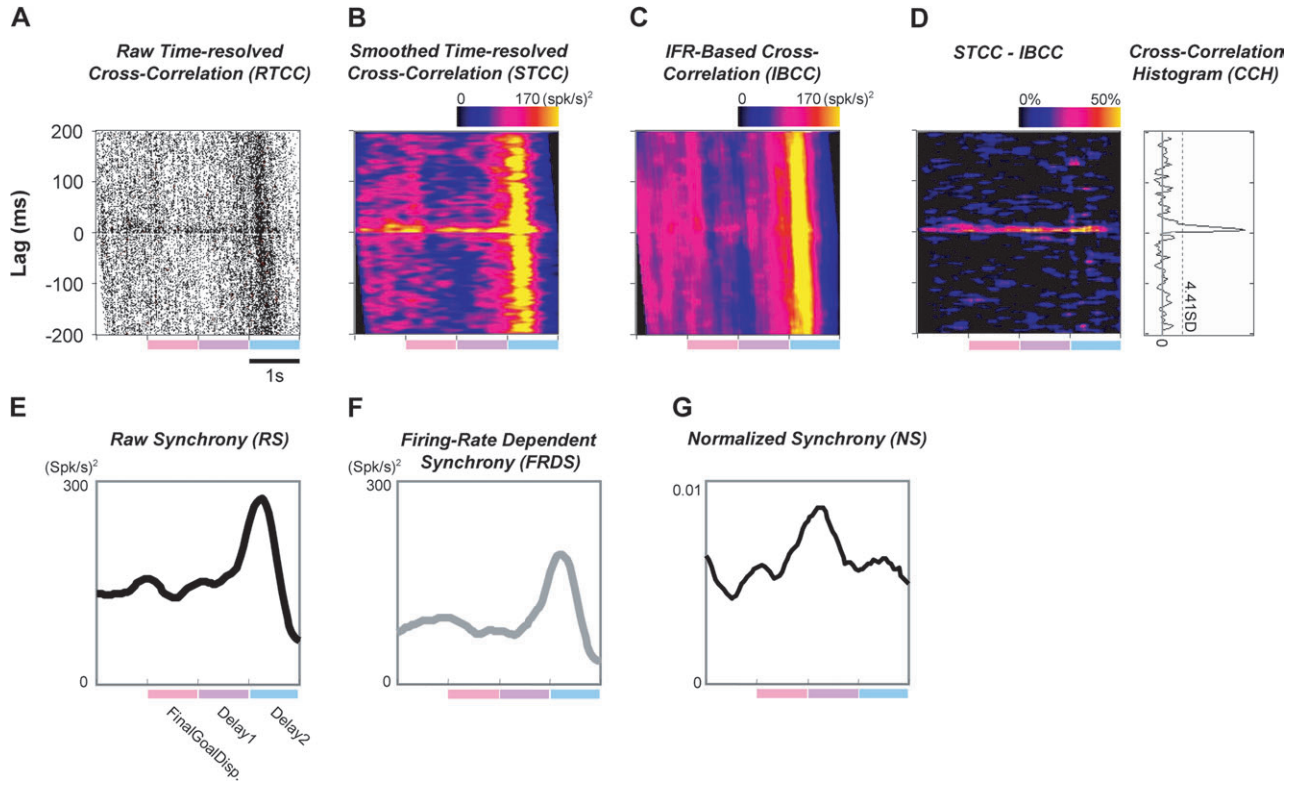

Figure 2. Time-resolved cross-correlation analysis of synchrony in the firing of a neuron pair. (*A*) RTCC for a neuron pair, where each dot represents a single spike. The abscissa represents time during task performance, with light red, purple, and blue bands indicating the task periods defined as Final Goal Display, Delay 1, and Delay 2, respectively. The ordinate represents the time lag between response and trigger spikes. (*B*) STCC, obtained by smoothing the RTCC in (*A*) using a Gaussian kernel. (*C*) Cross-correlation based on the IFR, termed IBCC. (*D*) Genuine cross-correlation, calculated as STCC − IBCC (left panel), and the standard CCH (right panel). (*E*) RS, calculated by averaging the magnitudes of synchrony in the STCC. (*F*) FRDS, obtained from the IBCC in the same manner as for the RS. (*G*) NS, calculated by subtracting FRDS from RS.

calculated the running average of the RS using a sliding time window of 500 ms for the 3 s of the task period preceding the First GO signal (as plotted in Fig. 2*E*). Similarly, we calculated the firing rate–dependent synchrony (FRDS) as a reference or a predictor for synchrony estimated from the firing rate (Fig. 2*F*).

To visualize the time course of genuine synchronization that was unaffected by changes in firing rate, we calculated the difference between RS and FRDS (divided by the SD of the latter for normalization) and plotted the values as the normalized synchrony (NS; Fig. 2*G*).

Results

Neuronal Database

We examined the synchrony of discharges in 425 pairs of neurons that satisfied the following criteria, which were regarded as necessary for the purpose of the present study (Table 1). Each neuron in the pair was recorded simultaneously during the performance of more than 96 trials of the present motor task, had sufficient firing rates that yielded more than 2000 spikes in the RTCC, and exhibited task relevance, namely significant changes in activity during the preparatory period, based on the Wilcoxon signed-ranks test ($P < 0.05$) that compared the activities during the preparatory and control periods of 500 ms in the initial hold period. Among the 425 pairs, 45 exhibited significant synchrony. The selection of these pairs was based on the CCH (see Materials and Methods) with a statistically significant peak (at an SD of 4.41). The mean half-width of the CCH peaks was 9.3 ± 10.6 ms. Aside from these 45 neuron pairs, we found modest synchrony for 197 neuron pairs (at an SD of >2.0). The data for these pairs are described in the Supplementary Section.

Table 1
Classification of neuronal pairs

	Pairs with F–I transition			Pairs without F–I transition	
	Cell pairs	Number of cells	Number of cells with F–I transition	Cell pairs	Number of cells
Synchrony (4.41 SD in CCH)	21	42	28 (67%)	24	47
Modest synchrony (2 SD in CCH)	84	134	74 (55%)	113	177
Total	219	290	133 (46%)	206	262

Neuronal Activity Exhibiting a Transition in Behavioral Goal Representations

A total of 133 neurons exhibited initial selectivity for the final goal and subsequent selectivity for the immediate goal during the preparatory period. An example of lPFC neurons that exhibited an F–I transition is shown in Figure 3*A*. In the early phase of the preparatory period, the firing rate increased selectively when the final goal was located at the bottom right of the computer screen. In the late phase of the preparatory period, the firing rate was highest when the animals had planned on the immediate goal being located to the right of the

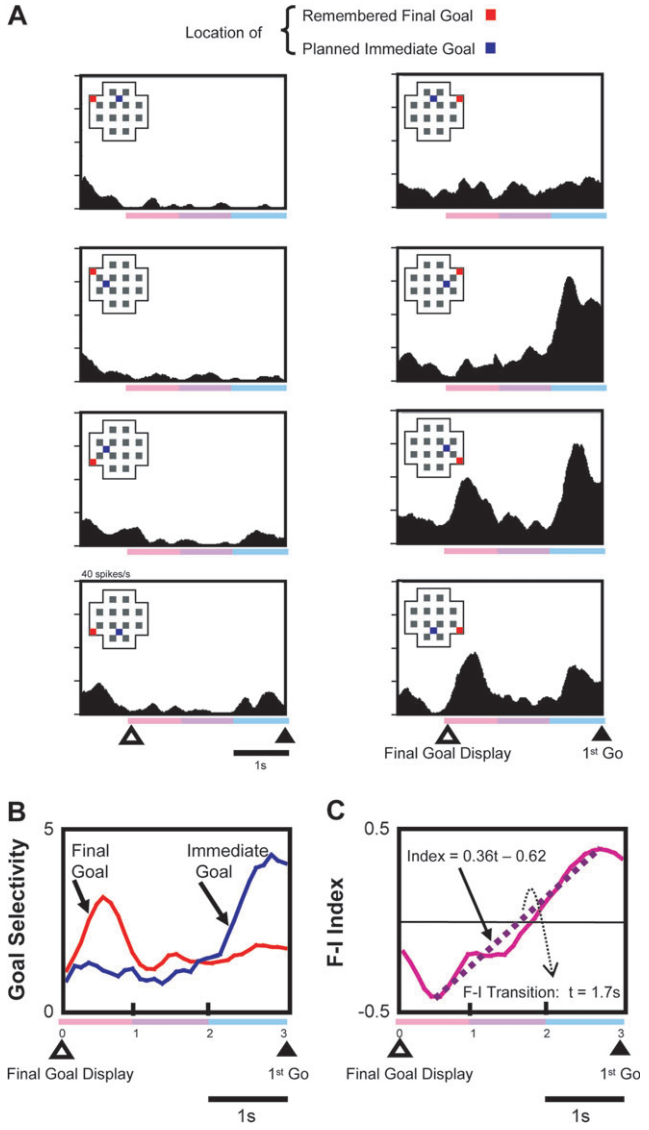

Figure 3. Discharge properties of an lPFC neuron that represented the final goal position followed by the immediate goal position during the preparatory period. (*A*) Spike-density histograms of neuronal activity under task conditions, showing each combination of final and immediate goals. A red square indicates the location of the final goal remembered during the preparatory period; a blue square indicates the planned immediate goal. In the early phase of the preparatory period, this neuron was selectively active when the final goal was located at the bottom right of the maze; in the late phase, selectivity was most prominent when the immediate goal was at the right of the starting position. (*B*) The time course of modulation of the FGS and IGS during the preparatory period. The regression coefficient is normalized and plotted for the FG (red) and IG (blue), calculated for consecutive time frames of 100 ms. (*C*) The F–I index, calculated for consecutive 100-ms time frames, was initially negative but became positive during the late phase. The time course of the F–I index was linearly approximated by a regression analysis (dashed line). The F–I transition was defined as the zero-cross point of the linear approximation (see Materials and Methods).

start position. To visualize the time course of representations of this cell for the final and immediate goals, we plotted the goal selectivity (FGS and IGS) determined by the regression analysis for consecutive 100-ms time frames, as described above (Fig. 3*B*). The results show how the final goal representation was developed, was reduced, and then was replaced with the immediate goal representation. To determine the transition time between the 2, we plotted the F–I index (Fig. 3*C*). Using the zero-cross time of the linear regression equation (see Materials and Methods), the transition time was determined to be 1.7 s from the start of the Final Goal Display, approximately corresponding to the transition between Delay 1 and Delay 2.

Temporal Relationship between Goal Representations and Neuronal Synchrony (population analysis)

To assess how the synchrony of neuronal spikes developed during the preparatory period and the temporal relationship between the goal representations and synchrony, we obtained 21 neuron pairs that satisfied the criteria for significant synchrony (see Materials and Methods) and exhibited the final–immediate goal representation transition with a definable F–I transition time. These 42 neurons included 28 F–I transition neurons (Table 1).

Figure 4*A* plots the average FGS (red line) and IGS (blue line) over time, calculated for F–I transition neurons with highly significant synchrony (see Materials and Methods). The time course of synchrony (NS) of each neuron pair, normalized to its maximum value during the preparatory period and averaged across the 21 neuron pairs, is superimposed on the graph (black line). Synchrony developed markedly toward the end of Delay 1 and peaked at the transition between Delay 1 and Delay 2. The presence of the peak was tested statistically, using a bootstrapping method. The peak was higher than the significance level estimated from 10 000 quasi-population NSs (generated by shuffling the values of the NS of each pair taken at random data points) ($P < 0.05$). These population data clearly show that peak synchrony coincided with the F–I transition time.

We performed a separate statistical analysis based on unitary event analysis (Grammont and Riehle 2003) to evaluate the time course of the spike synchrony. For this analysis, we examined the time course of the difference between RS and FRDS and assessed statistical significance using a Poisson distribution with the mean set to the FRDS value as the cumulative probability P of observing a RS larger or smaller than expected by chance. Each time the RS exceeded a significance level of 5%, the occurrence was considered a significant unitary event. Then, we examined how the unitary event was distributed in time during the preparatory period, by constructing binary vectors for consecutive time frames of 100 ms for each pair. We assigned "1" to individual time frames if the unitary event was significant ($P < 0.05$) and "0" if the event was not significant. Then, pooling these binary vectors, we plotted the probability of significant synchronization as a function of time. The results showed a peak around the end of Delay 1 (Fig. 4*B*), approximately coinciding with the NS peak shown in Figure 4*A*. The area around this peak was significant ($P < 0.05$ as tested by a bootstrapping method). Thus, the unitary event analysis supported the finding that synchrony was maximized during the transition between final and immediate goal representations.

Temporal Relationship between Synchrony Enhancement and the F–I Transition of Neuron Pairs

To examine whether the peak of synchrony of paired neurons correlated in time with the F–I transition of each individual neuron, we constructed a scatterplot diagram (Fig. 5*A*). A regression analysis revealed that the time of appearance of the

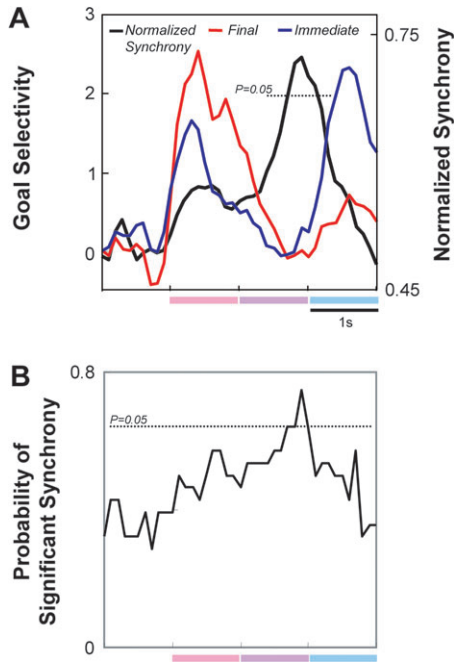

Figure 4. Temporal relationship between synchrony and goal selectivity of neuronal activity analyzed for neuron pairs with F–I transition neurons. (*A*) Selectivity for final (red line) and immediate (blue line) goals calculated for the population of neurons with F–I transitions (see Materials and Methods). NS of each neuron pair was calculated by taking the peak value as 1, and values were then averaged over the preparatory period (black line). (*B*) The time course of the probability of synchrony among neuron pairs, based on unitary event analysis (Grammont and Riehle 2003). For each neuron pair, the statistical significance of the RS value at each time frame was assessed using a Poisson distribution estimated from the FRDS. The probability of significant synchrony in consecutive time frames of 100 ms is plotted. The dotted lines signify the level of statistical significance (at $P = 0.05$ by a bootstrapping test).

F–I transition was significantly correlated with the appearance of the NS peak ($r = 0.53$, $P < 0.05$).

To visualize the temporal development of the final and immediate goal representations of the population in direct relation to the peak in synchrony for all analyzed neuron pairs, we recalculated the magnitudes of the goal selectivity of individual neurons at specific time epochs in the preparatory period, that is, at 100-ms time bins preceding or following the time of occurrence of the synchrony peak (over a range of 3 s) during the preparatory period. Thereafter, we plotted the mean values of the selectivity for the 2 goal representations, taking the time of peak synchrony as zero (Fig. 5*B*). The significance of the increases in the final goal representation, which appeared before the synchrony peak, and the immediate goal representation, which appeared after the peak, was evaluated with a bootstrapping test (Lurito et al. 1991). The increases in FGS and IGS were both significant ($P < 0.01$).

Subsequently, we examined whether the enhancement of synchrony developed in advance of the F–I transition in individual pairs. For this analysis, the onset of the significant synchrony (calculated as the time when the NS significantly exceeded the control level before forming a peak) is plotted against the F–I transition time (Fig. 5*C*). We found that a great majority of data points are located above the diagonal line ($P < 0.001$, binomial test), indicating that the synchrony generally started to occur before the occurrence of the F–I transition.

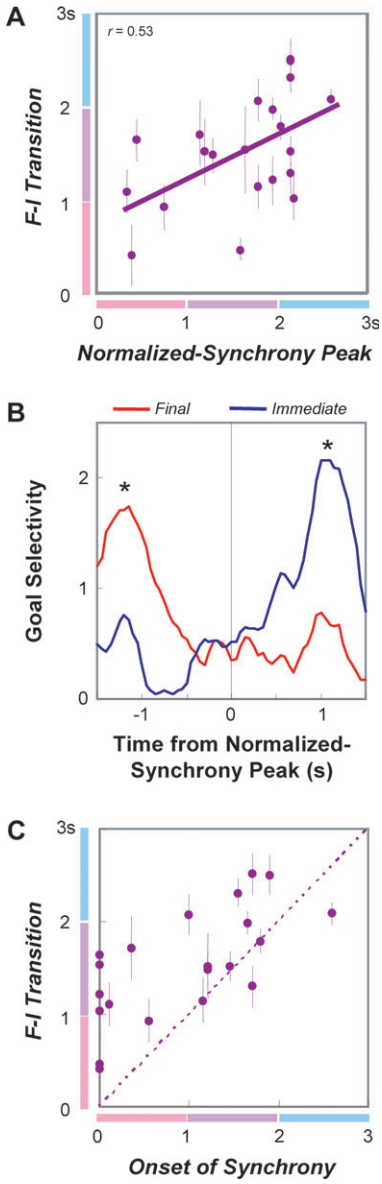

Figure 5. Temporal relationship between the synchrony peak and the transition of goal representations for individual neurons. (*A*) The peak in NS is plotted against the F–I transition time (purple dot) and its standard error (bars). The straight line represents the linear regression fit to the correlation between the 2 variables ($r = 0.53$, $P < 0.05$). (*B*) A peri-event time histogram of selectivity for final and immediate goals aligned to the peak in NS. The selectivity for final (red line) and immediate goals (blue line) of each neuron, calculated for 100-ms time frames, were aligned to the NS peak and averaged across neurons. A bootstrapping test was used to assess whether the peak amplitudes of FGS and IGS for synchronous pairs were significant, based on statistical estimation of the temporal profile of goal selectivity using 10 000 randomly selected pairs. The asterisks signify a statistical significance of $P < 0.01$. (*C*) The F–I transition time is plotted against the onset of significant synchrony. A great majority of data points are above the diagonal dotted line ($P < 0.001$, binomial test), indicating that the significant synchrony begins before the F–I transition. The mean values for F–I transition time, synchrony peak, and the onset of significant synchrony were 1540 ± 590 ms, 1620 ± 670 ms, and 1400 ± 650 ms, respectively.

Analysis of Synchrony for Neuron Pairs without an F–I Transition

We did not detect an F–I transition for 206 neuron pairs (Table 1). A majority of the neurons in these pairs exhibited continuous goal selectivity throughout the Final Goal Display and Delays 1 and 2. Only a few exhibited other types of goal

selectivity. Therefore, we examined the time course of the synchrony of neuron pairs (n = 204) with neurons exhibiting FGS throughout the delay periods.

Among the 204 neuron pairs examined, 24 exhibited significant synchrony (peaks > 4.41 SD in CCH) during the preparatory period (Table 1). The time course of the synchrony during the preparatory period for these pairs is plotted in Figure 6*A* (black line), along with the time courses of FGS (red) and IGS (blue). The selectivity for the final goal developed during the goal display period and remained at a high level throughout the delay periods, continuously higher than the selectivity for the immediate goal. The level of synchrony was elevated throughout the preparatory period, without any significant peaks at the end of Delay 1. The absence of significant synchrony peaks was also confirmed by the unitary event analysis (Fig. 6*B*).

Independence of Discharge Synchrony and Neuronal Firing Rate

In principle, the normalization technique using SD, adopting the method of Pauluis and Baker (2000), would ensure the independence of NS and the firing rate. To further confirm this independence, we examined the correlation between NS and mean firing rate for pairs that exhibited significant synchrony (n = 45). Six data points were obtained from each neuron pair in 500-ms intervals during the 3-s period. Figure 7 shows the scatterplot of NS against mean firing rate. The correlation coefficient of <0.09 indicates no correlation between NS and firing rate (P = 0.15). This is in contrast to a significant correlation (r = 0.51) between the FRDS, a measure we used for the FRDS, and the mean firing rate (P < 0.001).

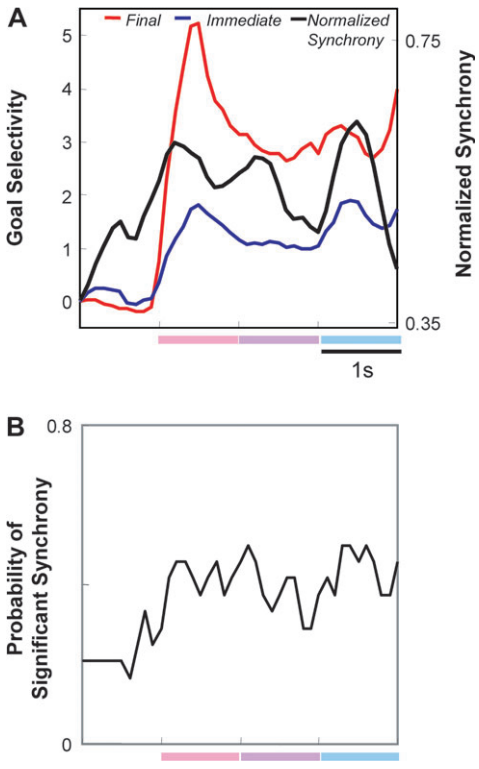

Figure 6. Analysis of synchrony for neuron pairs without F–I transition. (*A*) Temporal relationship between synchrony and goal selectivity of neuronal activity calculated for the population of neuron pairs that exhibited significant synchrony and included neurons that represented the final goal continuously during the delay periods. The format of the display is the same as in Figure 4*A*. (*B*) The time course of the probability of significant synchrony calculated on the basis of unitary event analysis, similarly plotted as in Figure 4*B*.

Discussion

We investigated the temporal relationship between neuronal activity representing behavioral goals, as coded by firing rates, and discharge synchrony of neuron pairs. To do so, we assessed synchrony separately from variations in the firing rate of individual neurons by using a time-resolved cross-correlation method (Pauluis and Baker 2000; Baker et al. 2001) because changes in correlated activity may be confounded by simultaneous variations in average firing rate. Our main findings indicated that synchrony varied in time during a specific phase of the behavioral task, with a peak corresponding to the transition period between the final and immediate goal representations.

There is growing interest in the functional relevance of temporally correlated neuronal activity independent of individual firing rates (for reviews, see Salinas and Sejnowski 2001; Averbeck and Lee 2004). In the primary visual cortex of cats, robust changes in synchrony were observed from one perceptual condition to another, imposed by interocular rivalry (Fries et al. 1997). That is, when neurons were driven by the eye providing the percept, synchrony was much stronger in the rivalrous condition than in the monocular condition. Neurons in the secondary somatosensory cortex exhibited modulation of synchrony when attention was directed to the fingertips (Steinmetz et al. 2000). Neurons in the visual association area (V4) also showed enhanced synchrony at a gamma-frequency range when activated by an attended stimulus (Fries, Reynolds, et al. 2001). This synchrony modulation might enhance the processing of information at the cortical level because the latencies of synchronized neurons in the primary visual cortex responding to a visual stimulus tended to shift in unison (Fries, Neuenschwander, et al. 2001). In that report, when the local field potentials of 2 electrodes both had a strong gamma

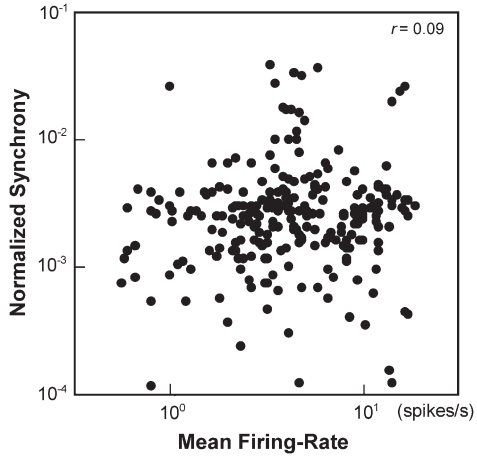

Figure 7. Relationship between the NS and the mean firing rate of the 2 neurons included in individual neuron pairs during the 3-s preparatory period, analyzed for the neuron pairs showing significant synchrony (n = 45). Six data points were obtained for each neuron pair at 500-ms intervals during the 3-s time period. NS was not significantly correlated with the mean firing rate of the pair (r = 0.09), confirming independence between the 2 measures.

component, the latency covariation between 2 neurons from the same pair of electrodes was high.

The behavioral relevance of synchrony modulation has also been studied in the frontal cortex. In the primary motor cortex, synchrony is associated with self-paced grasping movements or visually guided reaching tasks (Murthy and Fetz 1992, 1996). Synchronous activity of neurons in the primary motor cortex (MI) may be stronger during a period of steady holding than during motor movements (Baker et al. 2001) and may provide information about movement direction and reaction time (Hatsopoulos et al. 1998; Grammont and Riehle 2003). In the supplementary motor area, synchronous oscillations in the activity of neuron pairs may anticipate visual signals that indicate movement targets (Lee 2003) or the location of rewarded targets (Lee 2004). Previous studies on the lPFC reported that the incidence and strength of firing synchrony were highest among cells sharing similar spatial tuning and temporal profiles of activation across task epochs (Funahashi and Inoue 2000; Constantinidis et al. 2001). In those 2 reports, however, the time course of synchrony modulation during multiple phases of behavioral tasks and its relationship to the modulation of firing rates were not the primary focus.

The main aim of our study was to investigate the task phase-dependent development of synchrony among neurons that exhibited transitions in behavioral goal representations with changes in firing rate. We found that for neuron pairs, including this particular category of neurons, neuronal synchrony during the preparatory period developed with a peak at a specific task phase corresponding to a transition between Delay 1 and Delay 2. During Delay 1, information about the final goal obtained during the Final Goal Display had to be maintained. During Delay 2, the subjects had to determine the first step to take toward the immediate goal and had to plan a motion to achieve that behavioral goal. It is important to note that information about the final goal was provided via an external visual signal (on the monitor), whereas information about the immediate goal was generated internally. Both categories of information were represented by unique firing rates of individual neurons. F–I transition seemed to occur slightly before the end of Delay 1 period. It is probably because the monkeys planned or prepared their preferred path from the information about final goal before the information about immediate goal was provided. As shown in Figure 4, neuronal synchrony developed gradually as the neuronal activity representing the final goal decreased, and neuronal synchrony reached its peak during the transition of representation from final to immediate goals. The peak in synchrony was prominent among neuron pairs with a high degree of synchrony (>4.41 SD in the cross-correlation analysis). When synchrony was modest (>2 SD), the enhancement of synchrony during the transition was less obvious, although significant (Supplementary Fig. 2). These findings suggest that neuron pair synchrony may be distinct enough to reveal the task period–specific enhancement of synchrony over the effects of occlusion by noise. It was confirmed by analyzing individual neurons that the synchrony peak was temporally correlated with the F–I transition (Fig. 5). Therefore, it appears that neuronal synchrony reflects changes in the correlation structure among a population of neurons during a period when externally provided information must be transformed in the neural circuit into information that specifies a behavioral goal. Riehle et al. (1997) also reported changes in neuronal synchrony as a function of internal state, without accompanying variations in mean firing rate, in monkeys. In that study, neurons in the MI showed increased synchrony around the time the monkeys expected a GO signal, even when it was not displayed. We also found that in neuron pairs that included neurons representing the final goal continuously for the delay periods, the level of synchrony was also high throughout the delay periods. This finding supports the view that lPFC neurons are involved in the maintenance of information for short periods of time and that the coding specificity of individual neurons extends to the local circuits to which they belong, which could be observed as synchronous firing among neurons representing common specific properties (Constantinidis et al. 2001).

Although the neural coding mechanisms involved in the modulation of firing rates and temporal correlations have often been considered separately, the 2 coding mechanisms may work in a complementary manner (Abeles 1991; Tsodyks and Markram 1997, 2000; Masuda and Aihara 2002). Moreover, a cortical neural network may be involved in population-level firing rate coding or synchronous coding, depending on the types of feedback coupling and shared connectivity (Masuda and Aihara 2004). Alternatively, the spatiotemporal correlation of inputs (Fujii et al. 1996), membrane leak rate, inhomogeneity in constituent neurons (Masuda and Aihara 2003), or balance between excitatory and inhibitory inputs (Salinas and Sejnowski 2000) may affect which coding dominates. Physiological studies have supported this view by showing synchronization among neurons in the middle temporal or superior middle temporal areas (de Oliveira et al. 1997) or in the MI (Riehle et al. 1997) during stimulus expectation. Interestingly, in both of those studies, synchronization was low or not observed when visuomotion stimulus or visual GO signals did appear, despite the apparent modulation of the neuronal firing rate. Our findings of complementary modulation of the firing rate and synchrony extend previous findings by showing behavioral phase-selective complementary modulation in the lPFC. Based on these results and recent theoretical studies (Aoyagi and Aoki 2004; Aoki and Aoyagi 2007), we propose that the enhancement of synchrony may be an indication that, with synchronous inputs serving as a facilitative drive, the neuronal network in the lPFC undergoes a state transition resulting in a switch between the states of the neuronal network. This synchrony-induced switching of states would lead to differences in the way information is processed and, therefore, could alter what is represented in the network. It is possible that the enhancement of synchrony observed in our study prompted the alteration of representations in the prefrontal network from the final goal to the immediate goal, with the former being informed by an external signal and the latter being generated internally. Thus, it may be argued that neuronal synchrony could regulate the flow of information in the cortical circuit not only by changing the gain (Salinas and Sejnowski 2000) but also by switching the network states. Previous studies have reported that the nature of information represented by firing rate coding of cortical neurons could exhibit abrupt and profound alterations at a certain behavioral stage (Zipser et al. 1996; Sugase et al. 1999; Hegdé and Van Essen 2004; Romo et al. 2004; Machens et al. 2005). It would be interesting to study whether these abrupt transitions of representations are also facilitated with transient alterations of synchrony.

Supplementary Material

Supplementary Data and Supplementary Figure 2 are available at http://www.cercor.oxfordjournals.org/.

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