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Neural correlates of memory retrieval in the prefrontal cortex

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Abstract

Working memory includes short-term representations of information that were recently experienced or retrieved from long-term representations of sensory stimuli. Evidence is presented here that working memory activates the same dorsolateral prefrontal cortex neurons that: (a) maintained recently perceived visual stimuli; and (b) retrieved visual stimuli from long-term memory (LTM). Single neuron activity was recorded in the dorsolateral prefrontal cortex while trained monkeys discriminated between two orientated lines shown sequentially, separated by a fixed interstimulus interval. This visual task required the monkey to compare the orientation of the second line with the memory trace of the first and to decide the relative orientation of the second. When the behavioural task required the monkey to maintain in working memory a first stimulus that continually changed from trial to trial, the discharge in these cells was related to the parameters – the orientation – of the memorized item. Then, what the monkey had to recall from memory was manipulated by switching to another task in which the first stimulus was not shown, and had to be retrieved from LTM. The discharge rates of the same neurons also varied depending on the parameters of the memorized stimuli, and their response was progressively delayed as the monkey performed the task. These results suggest that working memory activates dorsolateral prefrontal cortex neurons that maintain parametrical visual information in short-term and LTM, and that the contents of working memory cannot be limited to what has recently happened in the sensory environment.

Introduction

Goal-directed behaviour depends on two sources of information to working memory: transient representations of information recently experienced and transient representations of information retrieved from long-term memory (LTM; Baddeley, 1986; Miyake & Shah, 1999; Nyberg *et al*., 2000). There is evidence from anatomical, human neuroimaging and non-human primate studies that the working memory processes depend on a network, in which the prefrontal cortex (PFC) and the posterior regions (parietal and temporal lobes) play an important role (Jones & Powell, 1970; Pandya & Yeterian, 1985; Owen *et al*., 1996; Fuster, 1997b; Miyashita, 2004). The PFC is involved in working memory components such as executive control – i.e. encoding and retrieval – and, together with the posterior regions it is also involved in active maintenance of information (Fuster & Alexander, 1971; Niki, 1974; Funahashi *et al*., 1989; Goldman-Rakic *et al*., 1990; Romo *et al*., 1999; Miller & Cohen, 2001; Braver & Bongiolatti, 2002). Combined behavioural tasks, such as discrimination or delayed matching to sample memory tasks, together with electrophysiological recordings in the dorsolateral PFC (PFCdl) of non-human primates have shown categorical and parametrical representations of recently experienced stimuli in working memory (Hernandez *et al*., 1997; Romo *et al*., 1999; Kim & Shadlen, 1999; Freedman *et al*., 2001). The role of PFCdl in retrieval and maintenance of stimuli from LTM has received less attention, however. The medial temporal lobes and inferior temporal cortex are the storehouse of visual LTM, and retrieval by feedback signals from PFC is necessary to keep information updated (Mishkin, 1982; Eacott & Gaffan, 1992; Fuster, 1997a; Hasegawa *et al*., 1998; Tomita *et al*., 1999; Smith & Jonides, 1999; Kostopoulos & Petrides, 2003). There is evidence from functional neuroimaging techniques and from the effects of localized damage in humans of the involvement of the PFCdl in LTM retrieval (Tulving *et al*., 1996; Cohen *et al*., 1997; Nyberg *et al*., 2000; Cabeza & Nyberg, 2000; Cadoret *et al*., 2001; Braver *et al*., 2001; Petrides *et al*., 2002; Dobbins *et al*., 2002; Kikyo *et al*., 2002; Buckner, 2003; Ptak & Schnider, 2004). We therefore reasoned that appropriate behavioural tasks would reveal the PFCdl involvement in temporary holding of information from recently experienced stimuli and from stimuli retrieved from LTM.

The activity of single PFCdl neurons was recorded while the monkeys performed in two tasks (Vazquez *et al*., 2000). In the first task ('continuous discrimination task'), the monkey perceived the first stimulus (the orientation of a bar), stored a trace of it in memory, perceived the second stimulus (the orientation of another bar), compared the second with the trace of the first, and chose a motor act based on this comparison to communicate the result of the discrimination. The same cells were also studied in a variant of the above task ('fixed discrimination with implicit reference'), in which the first stimulus remained the same throughout several trials in a

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block and was not shown. To solve this variant of the task, subjects have to retrieve from LTM a trace of the first stimulus to compare it with the second stimulus. We show here that working memory activates PFCdl neurons that encode information: (a) of what happened in the visual environment a few hundreds of milliseconds before; and (b) of LTM.

Materials and methods

General

Experiments were carried out on two male monkeys (*Macaca mulatta*, 3–5 kg). Animals (BMV3 and BMV4) were handled according to the standards of the European Union (86/609/EU) and Spain (RD 223/88). The experimental procedures were approved by the Bioethics Commission of the University of Santiago de Compostela (Spain). The experimental set-up, description of the stimuli and behavioural tasks were described elsewhere (Vazquez *et al*., 2000). The monkeys looked binocularly at a monitor screen placed at 114 cm from their eyes (1 cm subtended 0.5° to the eye), in an isolated, sound-proof room. Monkeys had their head fixed during the task, and their right arm operated a lever. A panel with three buttons was in front of the monkey within hand reach. In the discrimination tasks, monkeys used right and left buttons to signal the orientation of the visual stimuli to the right and to the left, respectively. Monkeys used the third button in the eye fixation task (to calibrate the set up) to signal the tilt of the fixation bar. Eye movements were recorded with the magnetic eye search coil technique (C-N-C Engineering, Seattle, WA, USA) (Robinson, 1963), sampled at 740 Hz and acquired with SciWorks (DataWave Technologies, http://www.dwavetech.com).

Visual stimuli were created in a 90 MHz Pentium PC using a 40 MB Matrox MGA Millennium II PCI graphic card driven by MGL Libraries from SciTech and presented in a NOKIA multigraph 445X monitor, with 75 Hz vertical refresh rate, and 1280 × 1024 pixel resolution. CORTEX (http://www.cortex.salk.edu/) was used for task control and to generate visual stimuli.

The stimuli were stationary bright lines, subtending 3° lengths. Three different reference orientations were used: 85°, 90° and 95° (all angles with respect to the horizontal). Different test lines, eight per reference stimulus, were presented clockwise and counter-clockwise to the reference line in steps of 3°. To avoid the use of end points of the line as a cue, the line was pseudo-randomly displaced in both horizontal directions. This forces subjects to rely only on the orientation of the line to complete the task.

Surgery

A head holder was implanted on the monkeys' skulls to fix the head during the experiments. A three-turn monocular scleral eye coil was implanted to measure gaze direction (Judge *et al*., 1980). The recording chamber was fixed to the skull, above the PFCdl following stereotaxic coordinates and magnetic resonance imaging. The chamber, 20 mm in diameter, was used as a pedestal for a hydraulic microdrive. All surgery procedures were carried out under general anaesthesia and aseptic conditions. The animals were first anaesthetized with ketamine (10 mg/kg i.m.). This was followed by pentobarbital sodium (15 mg/kg i.v.) for induction and maintained with a continuous i.v. infusion of pentobarbital sodium (3.5 mg/kg/h) and fentanyl (5.25 μg/kg/h) in saline, at 10 mL/h. Animals were intubated and artificially ventilated with a mixture of oxygen and air. Expiratory CO_2, electrocardiogram trace and temperature were monitored continuously during surgery. Antibiotics and analgesics were administered after surgery.

Discrimination tasks

Continuous variable discrimination task (CD)

Two monkeys were trained to discriminate up to their psychophysical thresholds in the two visual discrimination tasks sketched in Fig. 1. The stimuli, orientated lines, were presented in the centre of the monitor screen, and eye movements were restricted to a 5° × 5°

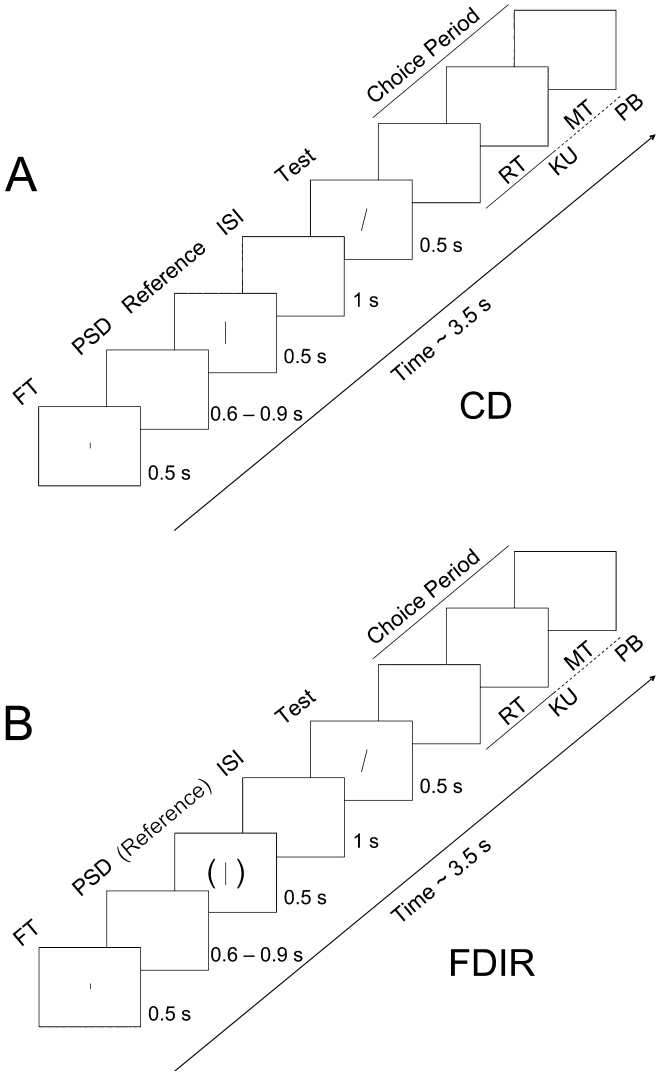

FIG. 1. Visual discrimination tasks. (A) Sequence of events during the discrimination trials in the continuous discrimination (CD) task. The monkey initiated the trial by pressing a lever key with his free hand and a fixation target (FT) comes on in the centre of the monitor screen and disappears. Eye fixation must be maintained during the trial, otherwise it is aborted. Then two stimuli, each of 500 ms duration, appeared in sequence with an interstimulus interval (ISI) of 1 s. After the second stimulus disappeared, the monkey released his hand from the key (key up, KU) and pressed one of two buttons (PB) to indicate whether the orientation of the second stimulus was clockwise or counter-clockwise to the first. (B) In the fixed discrimination with implicit reference (FDIR) task, the reference stimulus, which was implicit for that particular block of trials (between brackets), was not shown and only the test stimulus changed from trial to trial. MT, movement time; PSD, prestimulus delay; RT, reaction time.

window. During the trial, eye movements larger than 2.5° aborted the task. The orientation discrimination task was a modified two-alternative forced choice. A masking white noise signalled the beginning of the trial, and when the monkey pressed the key with his free hand the fixation target appeared in the middle of the screen (FT, Fig. 1A). If fixation was maintained, the FT disappeared for the rest of the trial, and after a variable prestimulus delay (PSD, 600–900 ms) two stimuli (reference and test), each of 500 ms duration, were presented in sequence, with a fixed interstimulus interval (ISI, 1 s). At the end of the second stimulus, the subject released the key in a 1200-ms time window, and pressed one of the two buttons, indicating whether the orientation of the second stimulus was clockwise or counter-clockwise to the first. Trials lasted about 3.5 s, separated by a variable intertrial interval (1.5–3 s). Monkeys were rewarded with a drop of liquid for correct discriminations. A modulation of the masking noise signalled the errors. Monkeys' weights were measured daily to control hydration, and once a week the animals had access to water *ad libitum*. The level of training was assessed by the psychometric functions. Once trained, the monkeys performed about 1000 trials per day.

Subjects received three reference stimuli (85°, 90°, 95°) presented pseudo-randomly and followed by the corresponding test stimuli. A reference stimulus of 85° was followed by a test stimulus ranging from 73° to 97° in 3° steps. A reference stimulus of 90° was followed by a test stimulus ranging from 78° to 102° in steps of 3°. A reference stimulus of 95° was followed by a test stimulus ranging from 83° to 107° in 3° steps. In this task, the first and second stimuli varied continuously from trial to trial. During the CD task (Fig. 1A) animals paid attention to the orientation of the first line (reference), stored some trace of it during the delay between the two stimuli (ISI, 1 s), paid attention to the orientation of the second stimulus, and compared the stored trace to the orientation of the second stimulus (test). Monkeys had to decide whether the orientation of the second stimulus was to the right or the left of the reference, and to communicate their decision by pressing one of two buttons with their hand. Subjects can only solve the CD task by paying attention to both stimuli in each trial. In fact, when in the CD task the first stimulus was not shown, humans and monkeys were not able to solve the task (Hernandez *et al*., 1997; Vazquez *et al*., 2000); this suggests that maintenance of the first stimulus in working memory is crucial to solve the task.

Fixed discrimination task (FD)

Once the monkeys performed well in the CD task they were trained to discriminate between the orientation of the second stimulus and the first stimulus in the FD task. This task was used only in the training sessions. In the FD task the first stimulus changed at the beginning of each block of trials and was the same for the entire block. The sequence of the trial and the orientation of the lines was the same as in the CD task, except that the first stimulus did not change from trial to trial. The orientation of the reference stimulus (85°, 90° or 95°) was kept fixed in blocks of 80 trials, where only the test stimuli changed. In the FD task the first and second stimulus were shown sequentially, each for 500 ms, separated by a fixed ISI (1 s). We used three different blocks (about 80 trials/block), each corresponding to the three different reference stimuli. A reference stimulus of 85° was followed by a test stimulus ranging from 73° to 97° in 3° steps in a randomized fashion. A reference stimulus of 90° was followed by a test stimulus ranging from 78° to 102° in steps of 3° for 80 trials. A reference stimulus of 95° was followed by a test stimulus ranging from 83° to 107° in 3° steps for 80 trials.

Fixed discrimination with implicit reference task (FDIR)

Once the monkeys performed well in the FD task they were tested in the same task but with the reference line removed so only the test stimulus was presented in each trial, which randomly changed from trial to trial; this was the FDIR task (Fig. 1B). The sequence of the trial and the orientation of the lines were the same as in the FD task, except that the reference stimulus was not shown. The implicit reference changed at the beginning of each block of trials and was valid for the entire block. The monkeys performed three randomly presented blocks of about 80 trials, each corresponding to the three reference stimuli that were not shown. During the FDIR task, (Fig. 1B) monkeys: fixated the FT, maintained fixation during the PSD, during the time corresponding to the unshown reference stimulus and during the ISI; then they perceived the orientation of the second stimulus, and were rewarded for correctly categorizing the test stimulus as to the right or the left of the unshown reference stimulus. They had no explicit indication of what reference stimulus marked the division between the two categories, and had to discover this by trial and error. They generally performed well almost from the beginning, after which they made precise categorizations. To solve the FDIR task, subjects needed a reference of the first stimulus to categorize the orientation of the second. Due to the extensive training in the above tasks, the monkeys had stored and consolidated the trace of the reference stimuli in LTM and this enabled them to retrieve the trace from long-term store, compare the orientation of the second stimulus with the trace of the reference, and decide whether the orientation of the second stimulus is clockwise or counter-clockwise to the reference (Vazquez *et al*., 2000).

In the tasks, subjects classified the test stimulus as 'to the right' or 'to the left' of the reference stimulus. Subjects made four possible decisions that we classified as hits, errors, false alarms and correct rejections (Macmillan & Creelman, 1991). Because we assumed that our task is symmetrical (task optimal criterion is 0), we classified decisions as correct (hits and correct rejections) or incorrect (miss and false alarms). The criteria used by the subjects do not have to be symmetrical. Reaction time (RT) was measured from the termination time of the test stimulus until when the lever key was released (Spoehr & Lehmkuhle, 1982). Movement time was measured from the time of the key release until when the target switch was pressed.

Recording sessions and sites

Extracellular single unit activity was recorded with tungsten microelectrodes (Frederick-Haer, http://www.fh-co.com; epoxylite insulation, 1.5–3 MΩ) in the lateral bank of the *sulcus principalis* and adjacent surface in the PFC, in the four hemispheres of the two monkeys (Fig. 2C). Microelectrodes were advanced through the intact *dura mater* to the cortex. Signals were amplified, filtered and viewed on an oscilloscope screen. Raw extracellular unit activity together with records of the eye position were displayed and stored in a computer for off-line analysis (DataWave Technologies, http://www.dwavetech.com/). To assure the same spikes were maintained through each recording session, oscilloscope pictures of the action potentials were taken at the beginning and end of each behavioural block of trials.

In each daily recording session, the monkeys began by working in the eye fixation task (about 50 trials) to calibrate the eye coil system. The extracellular single unit activity was recorded while the monkeys worked in the CD and FDIR tasks, and the task order presentation changed from day to day.

The animals were killed with an i.v. overdose of pentobarbital sodium. Four pins were inserted in the brain at the borders of the

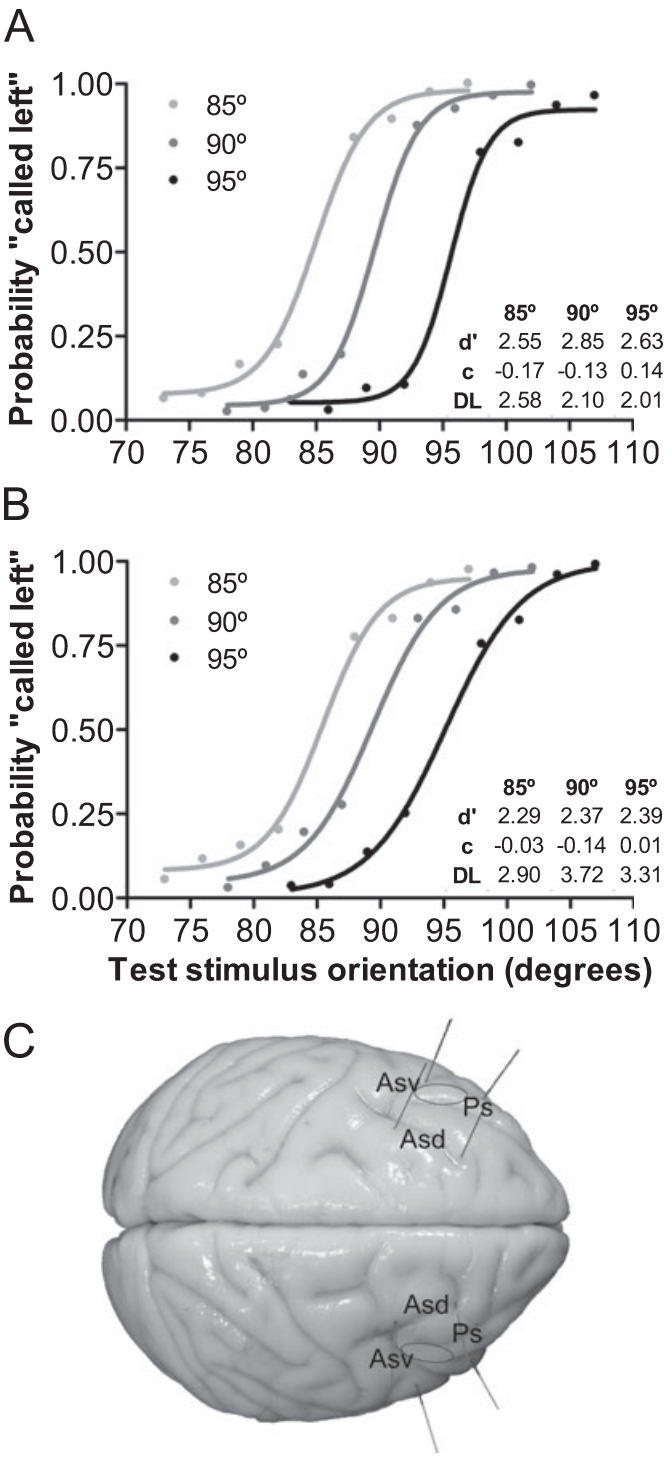

FIG. 2. Psychometric functions obtained in (A), the CD, and in (B), the FDIR tasks (monkey BMV3) while recording the activity of the example neuron shown in Fig. 3. Insets show the difference limen (DL), sensitivities (d') and criterion (c) used by the monkey. (C) View of the BMV3 monkey's brain with the recording areas (circle). Asd, sulcus arcuatus dorsalis; Asv, sulcus arcuatus ventralis; Ps, sulcus principalis.

craniotomies parallel to the microelectrode penetrations. The head was perfused through the heart with saline followed by 10% formaldehyde. Each microelectrode penetration was marked on the surface map of the brain area delimited by the four pins. The brain was removed and kept in 10% formaldehyde. After cryoprotection in 30% sucrose solution, 100-μm frozen sections of the region of interest were Nissl stained. No electrolytic lesions were made during recording sessions; therefore we did not have detailed references of the trajectory of the microelectrode penetrations. However, the marks left by the inserted pins, the surface map of the penetrations, together with the readings of the microdriver counter taken during the recording sessions, allowed us to reconstruct the area where recording took place (Fig. 2C).

Data analysis

To determine the effect of the reference stimuli on the neuronal firing rate we carried out random-effects ANOVA for each neuron and task (CD and FDIR). The dependent variable was the firing rate, and the factors were the reference stimuli orientations (85°, 90°, 95°) and the time periods, categorized as 1, 2, 3, 4, 5, 6 and 7 of 250 ms each (Fig. 3), and the RT. The random-effects ANOVA was also used to assess the effect of the following; the angle of the line (−12, −9, −6, −3, 3, 6, 9, 12) and the task (CD, FDIR) on the reaction time. Box–Cox transformation was performed to obtain approximate normality distribution and homogeneity of variances of the dependent variable across the different groups defined by the factors. In this analysis, *post hoc* contrasts were carried out to perform pair-wise comparisons between orientations and also between time intervals, where appropriate. The mean firing rate across trials for each task was modelled as a function of time by using a Poisson generalized additive model (Poisson-GAM) (Hastie & Tibshirani, 1990). For the model estimation, the local scoring algorithm was used. The temporal evolution of the firing rate was smoothed by using local linear (Gaussian) kernel smoothers (Kauermann & Opsomer, 2003), and the automatic selection of the smoothing windows (bandwidths) was determined by cross-validation. To ascertain whether the reference stimuli affected the temporal course of single or population neural firing rate, the 'reference-by-time' interaction term was introduced in the Poisson-GAM. At instant t, being $\lambda\ (r,\ t)$, the temporal firing rate for the r^{th} reference stimuli ($r = 1,\ 2,\ 3$), the Poisson-GAM model takes the form: $\lambda\ (r,\ t)$

$$\log\left(\lambda(r,t)\right) = \alpha + f(t) + g_r(r,t)\, for r = 1,2,3. \qquad (1)$$

In this expression, α is a fixed parameter; f a time function; and g the reference-by-time interaction term given by $g_{85°}$ (85°, t), $g_{90°}$ (90°, t) and $g_{95°}$ (95°, t) for the reference stimulus 85°, 90° and 95°, respectively (Fig. 3E and F).

Model (1) is a flexible and general application model that has several advantages, among them the following. (a) Discretizations of the data down to bins of 1 ms is allowed in order not to lose information. (b) The 'event-by-time' term that was introduced in the logistic GAM to assess the temporal effects of task behavioural events on neural firing rate. In this way, the resulting GAM produced different firing profiles for each level of the selected event. To further quantify time periods in which discharges were different between the events' levels, the temporal discrimination index (DI), a measurement analogue to the temporal odds ratio or to receiver operating characteristic curve (ROC) index (Britten *et al.*, 1992), was computed (c) It allows the automatic selection of the optimal smoothing windows. (d) The significant reduction of the computational burden implements binning-type acceleration techniques once the samples were large enough.

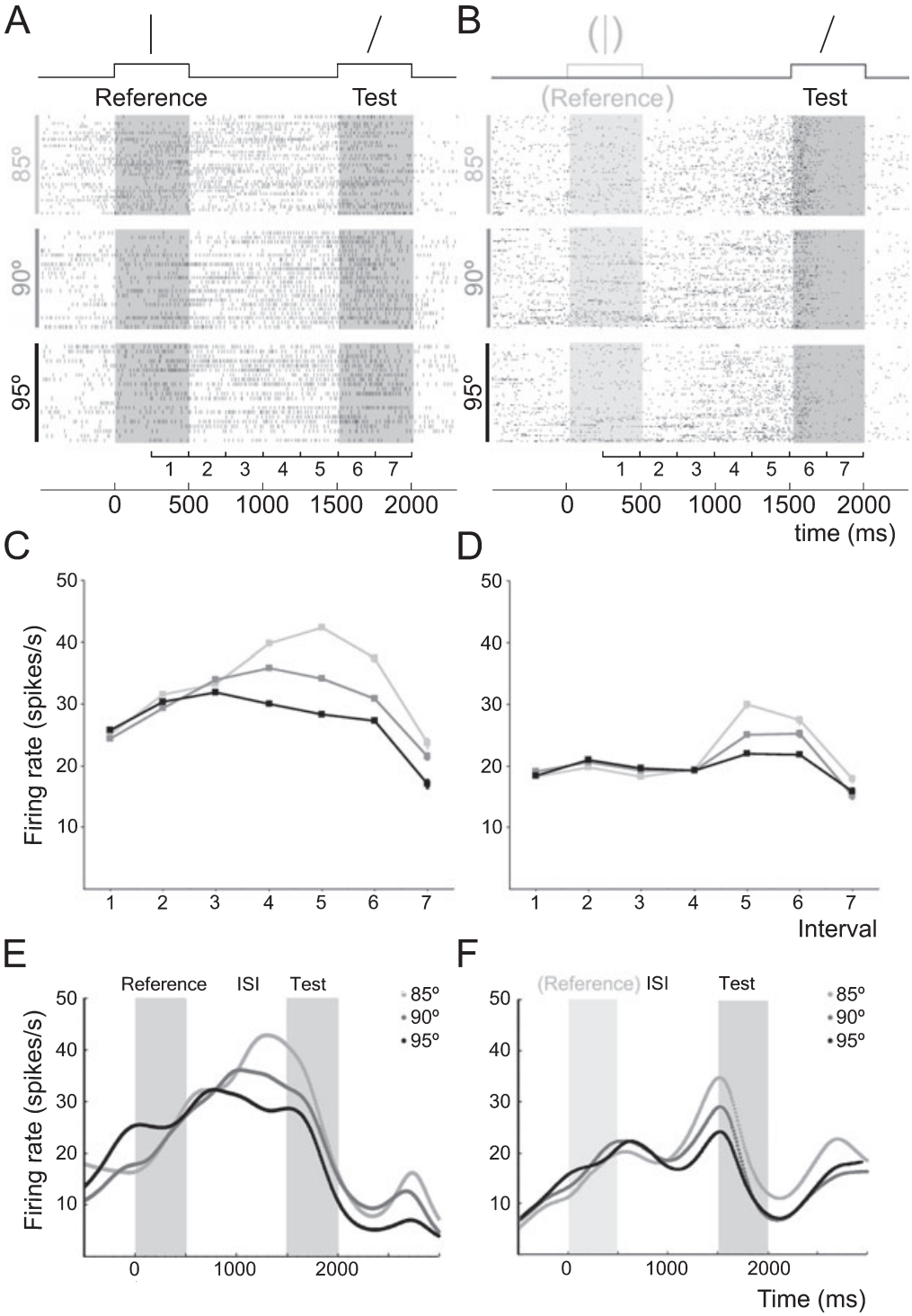

FIG. 3. Responses during the delay period. Above (A) sequence of events during the CD and (B) FDIR tasks (ISI, interstimulus-interval) in monkey BMV3. Below are the rasters for correct discriminations: each row of dots represents a trial and each dot an action potential. Rasters in each block are in order of presentation, from bottom to top. (A) Trials in the CD task were presented in random order, but have been sorted here into blocks of equal reference stimulus (indicated to the left: 85°, 90°, 95°). (B) In the FDIR task, we used three different blocks of trials, also presented in random order, each corresponding to one reference stimulus, which is not shown. Grey boxes indicate reference and test stimuli presentation of 500 ms each. The 90° bar between brackets in (B) indicates that the implicit reference was not shown. (C and D) Firing rates averaged over different 250-s intervals of the trials are indicated below the rasters with numbers 1–7 (see Materials and methods). (E and F) Temporal evolution of the firing rates. (C and D) At each time interval, bars indicate the 95% CIs for mean firing rate. Grey scale for each reference stimuli (A and B) indicates corresponding curves in (C–F).

In our study, model (1) gave a firing profile of any behavioural event. To quantify the time periods in which the discharge was different for each reference stimulus (i.e. when the cell firing rate discriminated between reference stimuli), we computed the degree of discrimination for each pair of reference stimuli expressed as a percent change in firing rate (Fig. 7). In accordance with model (1),

TABLE 1. Mean latencies over each group of trials of the significant increase in the firing rate (from the end of the first stimulus to the beginning of the second)

	Continuous discrimination task (CD)			Fixed discrimination task with implicit reference (FDIR)		
Trial group	Latency (ms)	95% CI LL	95% CI UL	Latency (ms)	95% CI LL	95% CI UL
1	186	−172	621	98	−142	807
2	46	−280	337	186	23	733
3	167	−72	555	324	153	816
4	42	−94	263	448	376	555
5	169	−151	549	587	485	649
6	11	−224	182	623	602	741
7	192	−170	549	636	582	803
8	155	−117	366	705	667	754

Group of trials sorted by presentation order from the first to the eighth (see Materials and methods). Data from the neuron of Fig. 3. CI, confidence interval. LL, lower limit; UL, upper limit.

at instant t we define $DI_{r_1}^{r_2}(t)$for a given pair of reference stimuli, r_1 and r_2, as

$$DI_{r_1}^{r_2}(t) = \frac{\lambda(r_2,t) - \lambda(r_1,t)}{\lambda(r_1,t)} \times 100\% \qquad (2)$$

When $DI_{r_1}^{r_2}(t)$ was different from zero there was discrimination between the stimuli pair.

Another advantage of using model (1) is that the derivatives of the mean firing rate may be easily calculated. We had computed the first and second derivatives of the smoothed mean firing rate function (Yang *et al*., 2003) to obtain three important aspects of neural activity: (1) the time at which the firing rate was maximal (i.e. the time at which the first derivative equals zero) (Fig. 5); (2) the magnitude of the maximal rate; and (3) the latency of the significant increased in the firing rate (determined by computing the time during the ISI at which the second derivative of the response to each reference stimulus equals zero) (Table 1). Inferential issues of Poisson-GAM were solved through the bootstrap methodology (Efron & Tibshirani, 1993; Rodríguez-Campos *et al*., 1998). Specifically, we constructed 95% bootstrap confidence intervals (CI) for the DIs, the time at which firing attained its maximum rate, the peak firing rate and for the latencies. The above methodology was also used to analyse groups of eight trials (Figs 4 and 5). To determine the number of neurons carrying a significant signal about the reference stimulus in the ISI period, we used the DI as statistical criterion (Fig. 6). Explicitly, we calculated the time period with a significant DI, i.e. the time period in which the 95% bootstrap CI for the true DI does not contain the value zero. Finally, the non-parametric Wilcoxon test was used to ascertain whether the latencies over the entire population depend on the task.

Psychometric functions of the monkeys' discriminations between different orientations were obtained (Fig. 2A and B). We plotted the percentage of the test stimuli identified as orientated to the left of the reference stimuli against the orientation of the test stimulus. Data were fitted to a logistic Boltzmann equation:

$$p_b(a) = \frac{A_1 - A_2}{1 + e^{-\left(\frac{a-a_0}{a_1}\right)}} + A_2$$

where $p_b\,(a)$ is the percent of trials called 'at the left of'; A_1 and A_2 are the maximum and minimum values of $p_b\,(a)$, respectively; a_0 is the orientation for which $p_b\,(a) = (A_1 - A_2/2)$; a_1 represents the width of the function. All regressions fitted the data significantly, with a χ^2 of $P < 0.05$. Difference limen (DL), or threshold, was calculated as the value of the minimum angle that elicited 75% of correct responses.

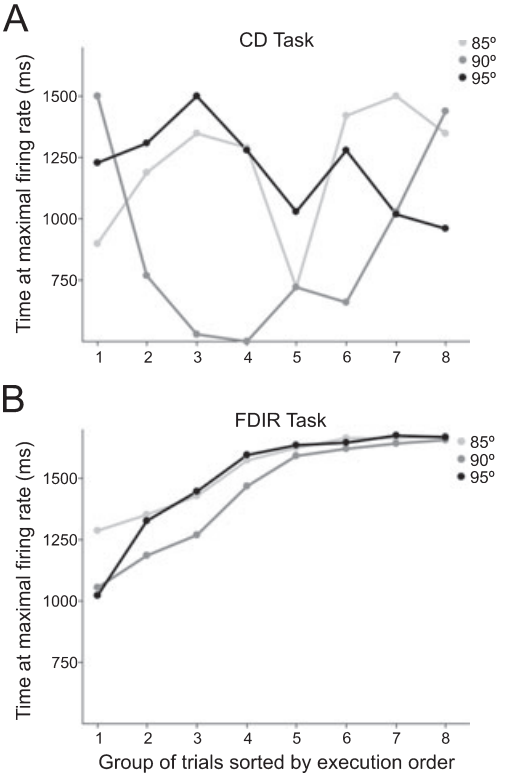

FIG. 4. Temporal evolution of the neuron maximal discharge during the 1-s delay period. Time at which the firing rate is maximal across groups of correct trials, sorted from first to eighth, and sorted for 85°, 90° and 95° reference stimuli (see Materials and methods). (A) Continuous discrimination (CD); (B) fixed discrimination with implicit reference tasks (FDIR). Data from the neuron of Fig. 3. Grey scale for each reference stimulus indicates corresponding curves in (A and B).

Signal detection theory analysis was applied to obtain sensitivities (d') and criterion (c) used by the monkeys (Green & Swets, 1966; Macmillan & Creelman, 1991). d' measures the distance, in standard deviation units, between the means of the signal and the noise distributions. This distance was determined by using the hit and false alarm rates, $d' = z(H) - z(F)$, where $z(H)$ and $z(F)$ are the inverse of the normal distribution functions for hits (correct counter-clockwise responses) and false alarms (incorrect counter-clockwise responses), respectively. The bias measure for signal detection theory, called c (for criterion) is defined as $c = -0.5[z(H) + z(F)]$. Negative and positive values of c signify a bias towards responding counter-clockwise and clockwise, respectively.

Results

The psychometric functions showed in Fig. 2A and B correspond to the monkey's performance (BMV3) in the CD and FDIR tasks, respectively, during the recording of the activity of the example neuron showed in Fig. 3. Signal detection theory analysis was applied (see Materials and methods), obtaining sensitivities (d') and criterion (c) used by the monkeys (insets Fig. 2A and B). The positive value of c suggested a slight bias to assign the test stimuli clockwise from the

FIG. 5. Time, from the beginning of the presentation of the first stimuli until the end of the presentation of the second, at which the firing rate is maximal across groups of correct trials, sorted from first to eighth (see Materials and methods). Data from the whole neuron population with significant activity during the delay period ($N = 49$). Black line: fixed discrimination with implicit reference task (FDIR); grey line: continuous discrimination task (CD). Dotted lines; upper and lower limits of the 95% of the bootstrap CIs.

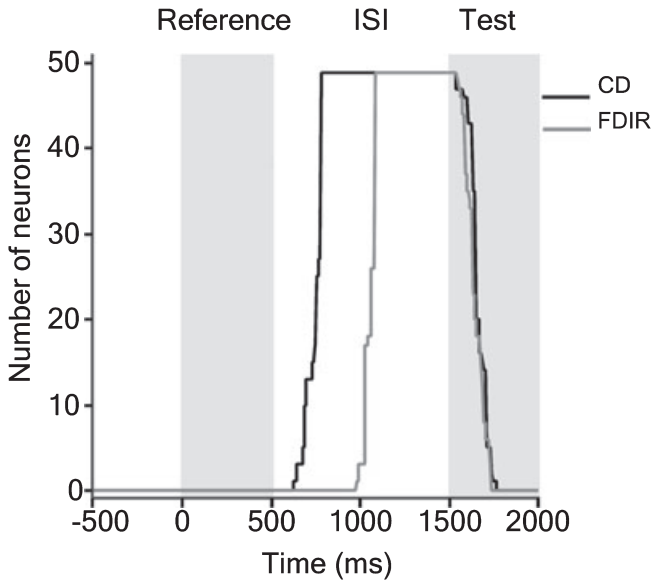

FIG. 6. Neural response dynamics. Total number of recorded neurons carrying a significant signal of the reference stimulus during the 1-s interstimulus interval (ISI) (see Materials and methods). The significant signal for the continuous discrimination (CD) (black line) trails the fixed discrimination with implicit reference (FDIR) task (grey line) by 322 ms (CI 95%; 312.59, 331.75).

reference stimulus of 95° in the CD task (Fig. 2A). In the FDIR task, the negative values of c suggested a slight bias to assign the test stimuli counter-clockwise from the reference stimulus of 85° and 95° (Fig. 2B). Monkey performance in the FDIR task was unaffected by the absence of the reference stimuli (Fig. 2B, data in the inset). DL and d' obtained in the CD and FDIR tasks showed that thresholds and sensitivities changed very little from one task to another: the DL decreased and d' increased in the CD task, evidence that the performance in the CD task was slightly better than in the FDIR task. DLs suggested that the monkey performed the task close to his psychophysical thresholds.

RT was taken from the end of the presentation of the test stimulus to the release of the key-lever. Mean ± SD RT was 191 ± 1.2 ms in the CD task, and 202 ± 2.4 ms in the FDIR task. In both tasks, RTs were faster for correct decisions than they were for incorrect decisions: CD 185 ± 1.6 ms and 224 ± 9.4 ms; FDIR 189 ± 2.0 ms and 226 ± 3.6 ms, respectively. In the two tasks, RTs of both monkeys were slower when the test lines were closer to the reference line than when the test lines were further from the reference line ($F = 10.594$, $P = 0.003$) (see Materials and methods).

While the monkeys worked on the tasks, the extracellular unit activity was recorded in the lateral bank of the sulcus principalis and inferior convexity of the PFC in the four hemispheres (Fig. 2C). Every well-isolated spike was tested in six blocks each of about 80 trials. In total, 396 neurons were recorded. Sixty neurons were not driven during the execution of the task. Three hundred and thirty-six neurons were driven during the execution of the task; 133 (40%) during the ISI, and 203 (60%) during the presentation of the second stimulus. The population of neurons that discharged during the ISI was different from the neuron population driven during the presentations of the second stimulus. This paper only deals with the population that modulates the activity during the ISI ($N = 133$; 40%). In our database there were no neurons that modulated their activity during the presentation of the reference stimulus. Every neuron driven during the ISI in the CD task was also driven in the FDIR task. However, the whole protocol (i.e. the same neuron tested in the two tasks) could be completed in only 49 neurons. Therefore, 84 neurons were partially tested. These 84 neurons were not incorporated in the database because their response could not be compared between the two tasks. The neurons fully tested in only one of the two tasks were also analysed, and in the task tested (either the CD or FDIR) these neurons displayed a parametrical increase in activity during the ISI.

For the whole population ($N = 133$), some neurons discharged more after stimulation with some reference orientations and less for the others; 85°, 90°, 95° ($N = 35/133$, 26.31%); 95°, 90°, 85° ($N = 28/133$, 21.05%); 90°, 85°, 95° ($N = 23/133$, 17.29%); 90°, 95°, 85° ($N = 16/133$, 12.03%); 85°, 95°, 90° ($N = 20/133$, 15.03%); 95°, 85°, 90° ($N = 11/133$, 8.27%). For the neurons that could be tested in the whole protocol ($N = 49$), the parametrical representation of the reference orientations during the ISI was the same in the two tasks (CD and FDIR): 85°, 90°, 95° ($N = 11/49$, 22.44%); 95°, 90°, 85° ($N = 10/49$, 20.40%); 90°, 85°, 95° ($N = 8/49$, 16.36%); 90°, 95°, 85° ($N = 7/49$, 14.28%); 85°, 95°, 90° ($N = 7/49$, 14.28%); 95°, 85°, 90° ($N = 6/49$, 12.24%).

The activity of the example neuron shown in Fig. 3 was obtained while the monkey worked in the two tasks. In the CD task the discharge rate increased during the delay period (ISI), and also varied depending on the reference stimulus shown (85°, 90° or 95°) (Fig. 3A). We compared the average firing rate during different intervals; the last 250 ms of the presentation of the first stimulus, the four 250-ms intervals of the ISI, and the first and second halves of the presentation of the second stimulus. The cell showed significantly higher activity during the delay period ($F = 503.881$, $P < 0.000$), and this activity was significantly different for each reference stimulus ($F = 228.504$, $P < 0.000$), i.e. there was a parametrical representation of the reference stimulus in the firing rate (Fig. 3C and E).

The same cell was tested during the monkey's performance in the FDIR task. The discharge rate varied during the ISI in each block of trials according to the reference stimulus that was not shown (Fig. 3B, D and F). To assess this, a comparison of the average firing rate during

the same intervals was performed as with the CD task (Fig. 3B and D). The results showed that there was significantly higher activity during the delay ($F = 232.739$, $P < 0.000$) for each reference stimuli ($F = 77.417$, $P < 0.000$) (see Materials and methods) in the same way as in the CD task, i.e. there was a parametrical representation of the not-shown reference stimuli in the firing rate (Fig. 3B and F).

The trials in each block of Fig. 3A and B are aligned in presentation order, from bottom to top. The inspection of the three blocks of rasters obtained in the CD task showed an increase of the firing rate after the presentation of the reference stimuli. When the monkey performed the FDIR task, the increase of the firing rate during the ISI began earlier in the first trials than in the later ones until it was stabilized (Fig. 3B). To assess this, for each block of trials (85°, 90° and 95°), the trials were sorted into eight groups by the order of execution, and from the beginning of the ISI (500 ms) to the second stimuli (1500 ms) we computed the following: (a) the time at which the firing rate was maximal; and (b) the latency with which the firing rate significantly increased (see Materials and methods). For the CD task the time at which the firing rate was maximal varied across the eight groups of trials during the delay period (Fig. 4A), and the mean latency of the significant increase of the neural activity during this period varied across the eight groups of trials between 11 ms and 192 ms (Table 1). When the monkey performed the FDIR task the increase of the firing rate during the delay period began earlier in the first trials than in the later ones, until it had stabilized (Fig. 4B). Accordingly, the mean latency of the neuron response increased from 98 ms for the first group of trials to 705 ms for the last group of trials (Table 1). This dynamic was also seen in the whole population ($N = 49$); Fig. 5 showed the time (ms), from the beginning of the presentation of the first stimuli, at which the firing rate was maximal for the eight groups of correct trials and for the two tasks (see Materials and methods). In the CD task the time at maximal firing rate varied across trials. However, in the FDIR task the time at maximal firing rate was attained earlier in the first three blocks of trials than in the later four. In the CD task, the mean RT varied between 274 ± 122 ms (SD) in the first group of trials to 220 ± 27 ms (SD) in the last one. In the FDIR task the mean RTs were slower than in the CD task. The mean RT decreased from 290 ± 135 ms (SD) in the first group to 231 ± 83 ms (SD) in the eighth group (Table 2).

The neural responses during the delay period were not static (Fig. 3), and with a fixed ISI the monkey can anticipate the timing of the second stimulus. For the whole population ($N = 49$, 14%), the times during the ISI when its firing rate encoded a significant signal about the first stimulus orientation were determined (see Materials and methods). In the CD task most neurons carried a signal about the reference stimuli orientation for almost the whole second of the delay period (median, 690 ms) (Fig. 6). However, in the FDIR task the same population shifted their activity and carried a signal about the reference stimulus orientation during the last 1012 ms of the delay period (Fig. 6). In both tasks the signal about the reference stimulus orientation decreased at the same time, i.e. at the beginning of the second stimulus.

TABLE 2. Mean reaction time in the CD and FDIR tasks for each group of trials sorted by presentation order, from the first to the eighth

	Reaction time	
Trial group	Continuous discrimination task (CD)	Fixed discrimination task with implicit reference (FDIR)
1	274 ± 122	290 ± 135
2	230 ± 82	273 ± 127
3	208 ± 51	268 ± 90
4	234 ± 53	264 ± 133
5	198 ± 56	256 ± 119
6	205 ± 63	251 ± 135
7	190 ± 37	248 ± 119
8	220 ± 27	231 ± 83

Data are presented as mean ± SD and are from the neuron of Fig. 3.

In these tasks, the monkey cannot decide on his motor response before the second stimulus was shown. Furthermore, the probability of the monkey deciding that the orientation of the second stimulus is to the right or the left of the first one is about 50%. To assess whether the activity of these cells was related to decisions about choices, i.e. to push the left or the right button, we computed the mean firing rate in response to the eight test stimuli of each reference stimulus, and also for decisions taken to the right and the left. We analysed the whole time period from the end of the first stimulus to the reward in 250-ms intervals (see Materials and methods). The results of these analyses showed that there were no significant differences in the mean firing rate for decisions taken to the left or the right, for either the DC ($F = 0.21$, $P = 0.884$) or the FDIR ($F = 1.815$, $P = 0.178$) tasks.

The rasters of Fig. 3, collected during trials of correct discriminations, were sorted in order of presentation from bottom to top. The inspection of the rasters revealed that a higher level of sustained activity occurred during the 1-s delay period in the CD task (Fig. 3A). In the FDIR task, however, the beginning of the sustained activity occurred earlier on in the delay period in the first trials than in the later ones (Fig. 3B). This was assessed by sorting the trials into eight groups by the order of execution, and then computing, for each group, the time at which the firing rate was maximal and the latency with which the firing rate significantly increased (sees Materials and methods). The results shown in Fig. 4 revealed that the dynamics of the firing rate during the ISI period were different for the CD and FDIR tasks. Furthermore, the dynamics of the firing rate during the delay period in the FDIR task were different in the first three groups of trials as opposed to the last five. The first three groups of trials and the last five of each block were analysed independently for hits and errors for the whole population ($N = 49$; Fig. 7) (see Materials and methods). For the correct responses in the CD task there was no difference between the first three groups of trials (grey trace) and the last five groups (black trace) (Fig. 7A). The errors in the CD task were associated with a firing rate decrease during the delay for all groups of trials, and changes in the discharge dynamics were also seen (Fig. 7B).

For the FDIR task the dynamics of the neural activity for the correct trials changed according to the group of trials they were associated with (Fig. 7C, grey and black traces, and see also Fig. 4B). When a hit occurred in the first three groups of trials the increase in the firing rate occurred during the whole delay period (Fig. 7C, grey trace); when a hit occurred during the last five groups of correct trials, the neuron activity increased in the second half of the delay period (Fig. 7C, black trace). Errors in the FDIR task clearly reversed this pattern (Fig. 7D): when an error occurred in the first three groups of trials there was a decrease of activity during the first part of the delay period followed by an increase in the firing rate (Fig. 7D, grey trace). Conversely, when an error occurred in the last five groups of trials, the increased firing rate started before the delay period (Fig. 7D, black trace).

Discussion

The major observation in this study is that working memory activates the same PFCdl neurons that maintain parametrical visual information recently perceived and visual information of LTM.

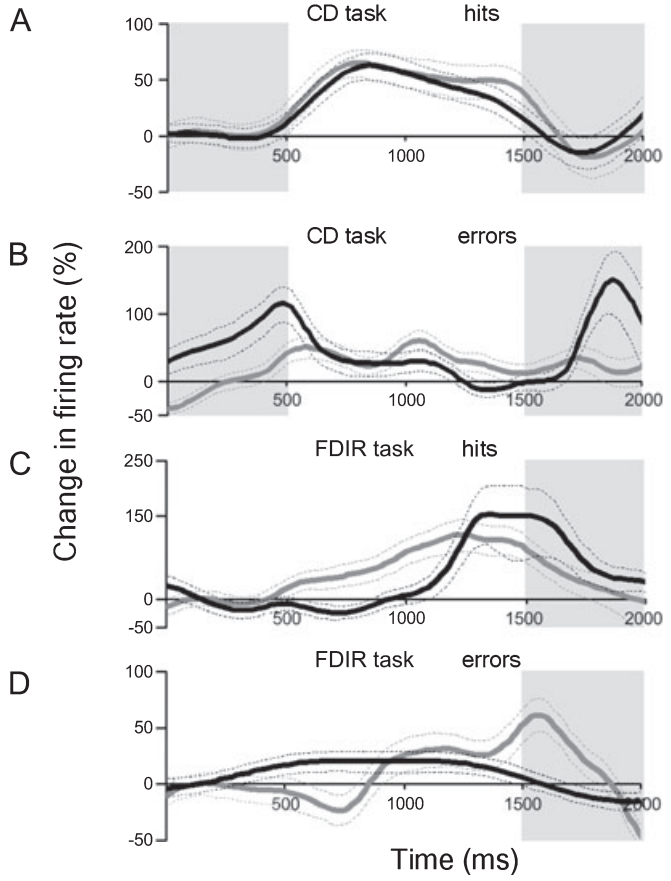

FIG. 7. Population change in firing rate for hits and errors. Continuous discrimination (CD, A and B) and fixed discrimination with implicit reference (FDIR) tasks (C and D). Discrimination index averaged over the first three groups of the trials (grey curve), and the last five (black curve) for hits (A and C) and errors (B and D). Grey boxes indicate reference and test stimuli presentation. Dotted curves: 95% bootstrap CIs.

Neural correlates of working memory were found in the PFC using different tasks (e.g. Fuster & Alexander, 1971; Fuster, 1989; Funahashi *et al*., 1989; Miller *et al*., 1996; Rainer *et al*., 1998; D'Esposito *et al*., 2000; Freedman *et al*., 2001). The two sources of information for working memory (Miyake & Shah, 1999), representations of information recently experienced or retrieved from LTM, can be studied in the CD and FDIR tasks, respectively (Hernandez *et al*., 1997; Romo *et al*., 1999; Vazquez *et al*., 2000). For the PFC to play a role in working memory, the information from both sources has to be represented in the activity of its neurons. For the monkey to solve the CD task requires perceiving a stimulus, storing it in working memory, comparing the stored trace with the current stimulus, deciding on the orientation of the second stimulus to the first, and communicating the results to the motor apparatus. Using a vibrotactile CD task, Romo *et al*. (1999) found a parametric representation of the first stimulus in PFCdl. Our CD task, which is equivalent to the vibrotactile task of Romo *et al*. (1999) has also revealed a parametric representation of the visual stimuli during the delay period in the activity of PFCdl neurons, confirming their results for another sensory modality. In our FDIR task, parametrical information is also represented in the activity of the same neuron during the delay period. In the FDIR task the implicit reference, which was a part of LTM, has to be updated to become working memory. The most parsimonious explanation is that for the monkey to solve the FDIR task requires it to recover the parameters of the stimuli from LTM, maintain the trace of it in working memory, compare the trace with the current stimulus, decide on the orientation of the second stimulus to the first, and to communicate the results to the motor apparatus. In what follows we will discuss successively: the representation of sensory modalities in PFC neurons; the preparation of movement, attention or maintenance of information in the neuron activity; the PFC participation in retrieving contents of working memory; and the interpretation of the present results in the light of models of PFC.

In the PFC, excitatory responses to sensory stimuli do not always occur, as happens in our sample ($N = 396$). In delayed-matching to sample or category (DMS; DMC) tasks, excitatory responses at the time of the cue or at the time of the choice stimulus may or may not be present (e.g. Funahashi *et al*., 1993; Fuster, 1995; Rainer *et al*., 1998; Hoshi *et al*., 2000; Miyashita & Hayashi, 2000; Freedman *et al*., 2001; Tanji & Hoshi, 2001; Xiang & Brown, 2004; Sakurai *et al*., 2004). In tasks that require discrimination between two stimuli, less than 20% of neurons respond in a sensory way to the first stimulus (e.g. Romo *et al*., 1999). Failure to pay attention to the first stimulus could be the cause of the lack of neural response, but there are several facts that preclude it from being so; to solve the CD task monkeys have to pay attention to the first and second stimuli otherwise they can not solve it (Hernandez *et al*., 1997; Vazquez *et al*., 2000); parametrical representation of the first stimulus is present during the delay period in both tasks; and, in a different neuron population, a trace of the first stimuli is present during the comparison period (Acuña *et al*., 2005). This result agrees with those of Romo *et al*., in the PFCdl (Romo & Salinas, 2003) and in other cortical areas (Romo *et al*., 2002, 2004; Hernandez *et al*., 2002) neuron populations reflect the parameters of the information of the first stimulus during the response to the second.

Temporal integration of behaviour, a function of the PFC, involves working memory and prospective attention, expectancy or preparation for anticipated events, and therefore they might not be easy to separate (Fuster, 1997a). Consequently, higher sustained neuron activity during the delay period between stimuli could be due to mnemonic activity or to expectancy of actions, stimuli or reward (Quintana & Fuster, 1992; Watanabe, 1996; Asaad *et al*., 1998; Romo *et al*., 1999; Rainer *et al*., 1999; Fuster, 2001). The timing discharge of the neurons reported here is like that in other PFC anticipatory neurons during delayed response tasks (Kojima & Goldman, 1982; Funahashi *et al*., 1989; Hoshi *et al*., 1998). The monkeys' intention of preparation to move their hand, regardless of the direction of movement, could be a potential source of modulation of the neural activity (Niki & Watanabe, 1979; Kutas & Donchin, 1980; Fuster *et al*., 1982; Fuster, 2001). However, studies designed to dissociate sensory from motor signals during the delay period of activity in the PFCdl support the idea that the delay period of activity reflects the memory of sensory cues more than represents motor preparation (di-Pellegrino & Wise, 1993; Funahashi *et al*., 1993; Wise *et al*., 1996). In a vibrotactile task similar to this, it was found that PFCdl neurons attuned to the parameters of the first stimulus do not encode the impending motor act (Romo *et al*., 1999). In the CD and FDIR tasks, the decision about the orientation of the second stimulus to the first can only be taken at some time during the presentation of the second stimulus. In both tasks, the motor response is initiated after the second stimulus disappears. These tasks require the monkey to perform a binary response: to the left or the right. The increase in firing during the delay is parametrically attuned to the three reference stimuli, but it is not attuned to the two impending responses. Furthermore, there is evidence of attention modulation in PFC during the delay period (Rainer *et al*., 1998; Everling *et al*., 2002; Lebedev *et al*., 2004). If the motor preparation or attention modulates the neuron discharge, such a modulation will be

above the parametrical modulation provoked by the trace of the three reference stimuli. The data presented here suggest that: (a) there is a parametrical modulation of the discharge during the ISI depending on the three reference stimuli; (b) during the ISI neurons do not discriminate between the monkey's choices (left or right).

To solve the FDIR task, the first stimulus, either vibratory or visual, has to be recovered from LTM (Hernandez *et al*., 1997; Vazquez *et al*., 2000). We show here that the same neurons that represent a parametric memory trace of stimuli recently perceived also represent parametric memory traces of the visual stimuli recovered from LTM. There are two main differences in the dynamics of the neural activity between the two conditions. In the CD task, the neural discharge increases from the beginning of the delay period (Figs 3C and 4A), while in the FDIR task the beginning of the discharge starts later (Figs 3D and 4B). Memories depend on a cortical network, which includes medial-temporal, parietal and prefrontal areas (Fuster, 1997a). There is evidence that once memories are consolidated, the PFC plays the integrative role between cortical areas via reciprocal connections (Hasegawa *et al*., 1998; Tomita *et al*., 1999; Miyashita & Hayashi, 2000; Miyashita, 2004; Frankland & Bontempi, 2005). Consistent with the above, pharmacological inactivation of PFC disrupts recall of LTM (Frankland & Bontempi, 2005; Pasternak & Greenlee, 2005).

The data presented here suggest a commonality of neural substrate for LTM and working memory. In a FDIR trial the monkey could use at least two chronological layers of past memory: the rules of the basic task and the implicit reference for that particular block of trials. There is ample evidence of PFC participation in retrieving, updating and checking the contents of working memory (e.g. Smith & Jonides, 1999; Kostopoulos & Petrides, 2003). Patients with PFC damage have impaired recall of information (Wheeler *et al*., 1995; Buckner, 2003), and neuroimaging studies reveal PFC activation during memory retrieval (Incisa della & Milner, 1993; Tulving *et al*., 1994). Furthermore, in neuroimaging studies, PFC shows strong activation during tasks involving working memory as well as long-term retrieval (Duncan & Owen, 2000). The process of recovery depends on reciprocal connections and physiological interactions between PFC, infero-temporal (IT) and parietal cortices (Naya *et al*., 1996; Fuster, 1997a; Hasegawa *et al*., 1998; Tomita *et al*., 1999; Smith & Jonides, 1999; Chafee & Goldman-Rakic, 2000; Simons & Spiers, 2003; Kostopoulos & Petrides, 2003). The comparison of cell activity in PFC and IT cells in monkeys performing a DMS suggests that PFC plays a primary role in working memory and may be a source of feedback input to the IT cortex (Miller *et al*., 1996). Visual associative LTMs are stored in the IT cortex (Mishkin, 1982; Naya *et al*., 1996; Hasegawa *et al*., 1998), and the retrieval of this information is under executive control of the PFC (Hasegawa *et al*., 1998). Evidence of top-down signals from PFC comes from cell activity recorded in the IT in the absence of bottom-up signals (Tomita *et al*., 1999). Moreover, in a long-term recognition memory task, PFC activity starts after that in IT and might be related to retrieval processes (Xiang & Brown, 2004). Our results suggest that, as the monkey progresses in the execution of the FDIR task, the stepwise delay in PFCdl neurons' higher sustained activity can be ascribed to the PFC control over memory retrieval of the implicit reference stimulus necessary to solve the task (Incisa della & Milner, 1993; Hasegawa *et al*., 1998; Miyashita & Hayashi, 2000; Simons & Spiers, 2003; Miyashita, 2004; Frankland & Bontempi, 2005; Pasternak & Greenlee, 2005).

Our results give support to the view that the two sources of visual sensory information are important to working memory; the same PFCdl neurons are used for temporally maintaining the information that is obtained from the outer world as well as from the LTM (Miyake & Shah, 1999), and can be interpreted in the light of current models of PFC function (Fuster, 1997a; Miller & Cohen, 2001; Wood & Grafman, 2003). One model proposed that the main function of PFC is the temporal organization of behaviour, such as working memory. Working memory is mediated by PFC activity and also by interactions between PFC and posterior cortices (Fuster, 1997a), emphasizing the PFC role in top-down (executive) control on posterior cortical regions, the store-house of visual LTM (Fuster, 1995; Miller, 2000; Miyashita & Hayashi, 2000; Cadoret *et al*., 2001). Our results suggest that the PFCdl is engaged in both processes, i.e. to maintain in working memory a parametrical representation of information that has recently been experienced and retrieved from LTM. These findings emphasize executive control mechanisms of PFC (Miyake & Shah, 1999).

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Abbreviations

CD, continuous discrimination; CI, confidence intervals; DI, discrimination index; DL, difference limen; DMC, delay-matching to category; DMS, delay-matching to sample; FD, fixed discrimination; FDIR, fixed discrimination with implicit reference; FT, fixation target; GAM, generalized additive model; ISI, interstimulus interval; IT, infero-temporal cortex; LTM, long-term memory; PFC, prefrontal cortex; PFCdl, dorsolateral prefrontal cortex; PSD, prestimulus delay; RT, reaction time; ROC, receiver operating characteristic curve.

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