



Comparison of neural activity related to working memory in primate dorsolateral prefrontal and posterior parietal cortex

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Neurons in a distributed network of cortical and subcortical areas continue to discharge after the presentation and disappearance of stimuli, providing a neural correlate for working memory. While it is thought that the prefrontal cortex plays a central role in this network, the relative contributions of other brain areas are not as well understood. In order to compare the contributions of the dorsolateral prefrontal and posterior parietal cortex, we recorded neurophysiological activity in monkeys trained to perform two different visuo-spatial working memory tasks: a Match/Nonmatch task, and a Spatial Delayed-Match-to-Sample Task. Neurons in both areas exhibited discharges in the delay periods of the tasks that could be classified in two forms. Sustained discharges persisted after the presentation of a stimulus in the receptive field with a constant or declining rate. Anticipatory responses increased in rate during the delay period, often appearing after presentation of a stimulus out of the receptive field. Despite similarities, we uncovered distinct differences between patterns of delay period in each brain area. Only in the prefrontal cortex sustained responses related to the original stimulus survived presentation of a second stimulus, in the context of the Match/Nonmatch task. Our results provide insights on the nature of processing in two areas active during working memory, and on the unique role of the prefrontal cortex in memory maintenance.

Keywords: monkey, neurophysiology, vision, principal sulcus, intraparietal sulcus, persistent activity, spatial memory

INTRODUCTION

Working memory refers to the ability to maintain and manipulate information in memory over a time interval of seconds (Baddeley, 1992). Neurophysiological recordings in animal models have provided a neural correlate of working memory in the form of neuronal discharges that are elicited by physical stimuli but which persist even after the stimuli are no longer present (Fuster and Alexander, 1971; Funahashi et al., 1989). Although first described in the prefrontal cortex, persistent discharges have now been reported in most areas of the association cortex and several subcortical areas (Constantinidis and Procyk, 2004; Pasternak and Greenlee, 2005). Nonetheless, the magnitude and time course of persistent discharges differs between cortical areas, suggesting that different areas play distinct roles in the maintenance of working memory.

Early studies comparing patterns of neuronal activity in the prefrontal cortex and inferior temporal cortex revealed unique properties of the prefrontal cortex. In animals tested with a Delayed Match-to-Sample-Task, activity of prefrontal neurons activated by the sample stimulus continued to persist and survived the presentation of nonmatch stimuli that the monkeys had to ignore in order to perform the task (Miller et al., 1996). In contrast, inferior temporal neurons were activated by each stimulus appearing in sequence. Therefore their activity could only represent the most recent stimulus, whether it was the sample that needed to be remembered or a nonmatch stimulus that was to be ignored (Miller et al., 1993). Two other studies examining responses of neurons during spatial working memory reached equivalent conclusions for the prefrontal and

posterior parietal cortex: Activity of Prefrontal neurons appeared to survive distracting stimulation (di Pellegrino and Wise, 1993) whereas, activity of posterior parietal neurons only tracked the most recent stimulus (Constantinidis and Steinmetz, 1996). Based on these results, it was concluded that prefrontal cortex was unique in its ability to maintain information in memory in the face of distraction. However, these studies relied on quite different behavioral tasks and it is not known to what extent the choice of task affected the pattern of responses. The only direct comparison of prefrontal and posterior parietal neurons in the same animals performing the same task relied on an oculomotor delayed response task, which did not involve a distractor, and revealed little difference between prefrontal and parietal areas in terms of delay period activity (Chafee and Goldman-Rakic, 1998).

In the last few years, some studies have challenged the idea of an absolute dichotomy between the properties of the prefrontal cortex and its cortical afferents. Neurons in inferior temporal cortex were shown to represent a stimulus retrieved from long-term memory even when distracting stimuli intervened (Takeda et al., 2005). Another recent study in the inferior temporal cortex suggested that a few inferior temporal neurons continue to represent the sample even after the presentation of a nonmatch stimulus (Woloszyn and Sheinberg, 2009). These results suggest that the properties of prefrontal cortex may be quantitatively rather than qualitatively different (Sigala, 2009). In order to determine whether this was the case for spatial working memory as well, we tested neuronal responses from the prefrontal and posterior parietal cortex of the same animals recorded during the working memory intervals of

spatial memory tasks. Our study addresses how patterns of activity relating to spatial working memory differ between cortical areas and in the context of different tasks.

MATERIALS AND METHODS

Four male, rhesus monkeys (*Macaca mulatta*) weighing 5–12 kg were used in these experiments. All animal experiments were performed in compliance with the guidelines set forth by the National Institutes of Health as reviewed and approved by the Wake Forest University Animal Care and Use Committee.

ANATOMICAL LOCALIZATION

Neural recordings were performed in two cortical regions, the dorsolateral prefrontal cortex and posterior parietal cortex (**Figure 1**). Prefrontal recordings targeted areas 46 and 8 including the caudal part of both banks of the Principal Sulcus, the area between the Principal and the Arcuate sulci, and part of the superior convexity of the lateral prefrontal cortex. Posterior parietal recordings were conducted in area 7a, an area directly interconnected with the prefrontal areas targeted in this study (Cavada and Goldman-Rakic, 1989). During experimental sessions, the depths of the cortex encountered by electrodes provided a coarse map of anatomical location. Upon completion of the experiments, the anatomical location of electrode penetration was superimposed onto an image of the cortical surface obtained through MR imaging.

BEHAVIORAL TASKS

Setup

The monkeys sat in a primate chair with their head fixed under dim illumination and viewed a computer monitor positioned 60 or 68 cm away. Eye movements were monitored during the experiments; the monkeys were trained to keep their gaze on a white fixation target, 0.2° in size. While maintaining fixation, visual stimuli were presented on the screen. Eye position was monitored using an infrared eye position tracking system (model RK-716; ISCAN, Burlington, MA, USA). Eye position was sampled at 240 Hz, digitized, and recorded. Breaks in fixation exceeding a 2° window terminated the trial. Correct completion of a trial resulted in a liquid reward. In-house software (Meyer and Constantinidis, 2005) controlled the visual stimulus presentation, online monitoring of eye position, and synchronization of stimuli with neurophysiological data. The system was implemented in MATLAB (Mathworks, Natick, MA, USA), using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). Two behavioral tasks that required working memory were used, a Match/Nonmatch task and a Delayed Match to Sample Task.

Match/Nonmatch task

Two of the monkeys were tested in the Match/Nonmatch task. The task required animals to remember the spatial location of a stimulus flashed briefly on the screen, to observe a second stimulus, and to indicate whether the two stimuli appeared at the same or different locations (**Figure 2A**). Trials began with the appearance of the fixation point on which the animals needed to fixate throughout the trial. This was followed by presentation of the cue, which consisted of a 2° white square that could appear at one of nine locations on a 3×3 grid of 10° spacing between adjacent stimuli. The

position of the cue varied randomly from trial to trial so that the monkey could not predict its location. The cue was presented for 0.5 s, and was followed by a delay period of 1.5 s, during which only the fixation point was visible on the screen. Then a second stimulus was presented for 0.5 s, either at the same location as the cue, constituting a match, or at the diametric location, constituting a nonmatch. This was followed by a second delay period of 1.5 s. At the end of this interval, the fixation point disappeared and two Choice Targets appeared, consisting of a green and a blue square. The Choice Targets appeared at locations orthogonal to the Cue and Nonmatch and the location of the blue and green target randomly varied from trial to trial. If the second stimulus matched the location of the cue, the animals were trained to make an eye movement to the green target and maintain fixation for 0.5 s; if the second stimulus was a nonmatch, then the animals were required to saccade to the blue target in order to receive a reward. Typically 10 repetitions of each cue-stimulus (match or nonmatch) combination were collected during the neurophysiological recordings.

Delayed match-to-sample task

Another two monkeys were tested with the Delayed Match-to-Sample Task. This task required the monkeys to remember the location of an initial stimulus, ignore stimuli appearing at other locations, and release a lever when a stimulus appeared at the location of the first stimulus (**Figure 2B**). The trial started with the animals pulling a behavioral lever and foveating the fixation point. Then the cue stimulus was displayed at one of nine locations, arranged along a 3×3 grid of 10° separation between adjacent stimuli. For a few sessions, grid sizes of 15° were used. Stimuli consisted of green or red squares of 1.5° size. The color of the stimulus was the same for each neuron studied and had no significance for this experiment. The cue presentation lasted for 0.5 s and was followed by a delay period of 1.0 s. A pseudorandom sequence of 0–2 nonmatch stimuli followed, each lasting 0.5 s and being separated by delay periods of 0.5 s. The sequence was completed by a match stimulus appearing at the same location as the cue. The monkeys were trained to wait for the full presentation of the match stimulus (lasting 0.5 s) and to release the lever within 0.5 s after that in order to receive a reward. Release of the lever at any other time during the trial constituted an error and immediately aborted the trial.

The two animals used in this experiment were additionally trained in variants of the Delayed-Match-to-Sample task, in which the fixation point moved during the trial and the animals were required to match the location of the cue in either screen-centered or retinal coordinates (Rawley and Constantinidis, 2010). Only data from blocks of trials of the basic task (**Figure 2B**) were analyzed for the current study.

SURGERY AND NEUROPHYSIOLOGY

After the animals were trained to perform the tasks, they were prepared for neurophysiological recordings. A 20-mm diameter craniotomy was performed over the prefrontal and parietal cortex, and two recording cylinders were implanted. The location of recording cylinders was assessed with anatomical MRI imaging. Neurophysiological recordings were performed with either single or multiple microelectrodes. We used glass-coated, tungsten electrodes of 250- μm diameter, with an impedance of 1 M Ω at 1 kHz

(Alpha-Omega Engineering, Nazareth, Israel) and epoxy-coated tungsten electrodes with a diameter of 125 μm and an impedance of 4 $\text{M}\Omega$ at 1 KHz (FHC Bowdoin, ME, USA). Arrays of up to 8-microelectrodes spaced 0.2–1.5 mm apart were advanced into the cortex through the dura with a microdrive system (EPS drive, Alpha-Omega Engineering, Nazareth, Israel). The electrical signal from each electrode was amplified, band-pass filtered between 500 and 8 kHz, and recorded with a modular data acquisition system (APM system, FHC, Bowdoin, ME). Waveforms that exceeded a user-defined threshold were sampled at 25- μs resolution, digitized and stored for off-line analysis.

DATA ANALYSIS

Action-potential waveforms recorded from microelectrodes were sorted into separate units using an automated cluster analysis method based on the KlustaKwik algorithm (Harris et al., 2000). The method relied on principal component analysis of the waveforms and was implemented in MATLAB. Firing rate of units was then determined for each of the task epochs.

We focused our analysis on neurons that responded to the visual stimuli, evidenced by significantly elevated firing rate in the 0.5-s interval of a stimulus presentation, compared to the 0.5 or 1-s interval of fixation (paired *t*-test; $p < 0.05$). The spatial tuning of visually responsive neurons was assessed by comparing the discharge rates during the presentation of single stimuli at the nine grid locations. Neurons with significantly different responses to the nine stimulus locations (ANOVA; $p < 0.05$) were included in further analysis. We tested whether a neuron exhibited persistent activity in the delay period following a stimulus by comparing its discharge rate during the delay period with its rate during the baseline, fixation period. Neurons were deemed to be exhibiting persistent responses if they displayed significantly different responses between fixation and delay period as judged by a paired *t*-test, ($p < 0.05$).

Population responses were evaluated by averaging discharges from multiple neurons and constructing population Peri-Stimulus Time Histograms. To compare responses recorded from the two brain areas and from the different tasks, we first averaged the raw firing rates from each population and then we normalized this averaged firing rate by the average firing rate recorded during the fixation period that preceded the cue presentation.

We distinguished between the patterns of delay period activity depending on whether the firing rate increased during the stimulus presentation period or not, comparing the firing rate at the beginning and end of the delay period at the location that elicited the best delay-period response. Neurons whose firing rate after the offset of the cue remained at the same levels or declined by the end of the delay period were classified as “sustained”. Neurons whose firing rate increased during these time points were classified as “anticipatory”.

RESULTS

DATABASE

Neuronal activity was recorded from area 7a of the posterior parietal cortex and areas 8 and 46 of the dorsolateral prefrontal cortex of four monkeys (Figure 1). Anatomical localization of penetrations was aided by MRI imaging performed after implantation of the recording cylinders. For each of the two tasks used, we

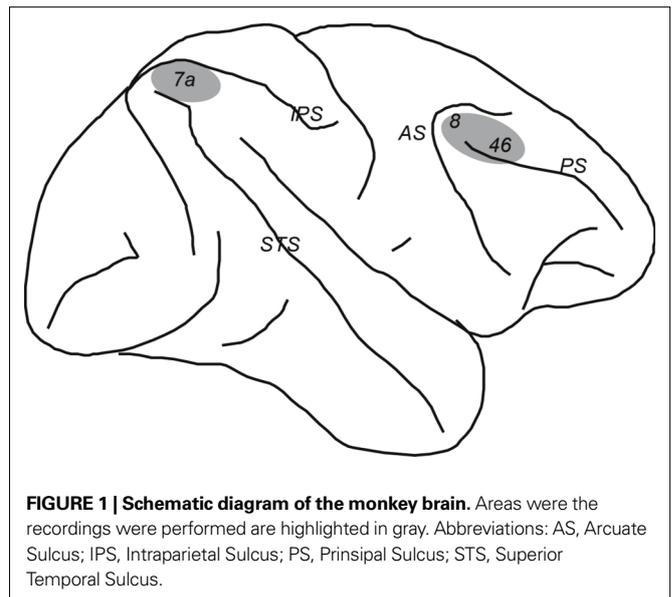


FIGURE 1 | Schematic diagram of the monkey brain. Areas where the recordings were performed are highlighted in gray. Abbreviations: AS, Arcuate Sulcus; IPS, Intraparietal Sulcus; PS, Principal Sulcus; STS, Superior Temporal Sulcus.

selected a sample of neurons that a) responded to visual stimuli, b) displayed significant selectivity for the spatial location of the stimuli (ANOVA, $p < 0.05$), allowing us to identify locations in and out of their receptive fields, and c) exhibited significantly elevated discharges in the delay period after the offset of the cue stimulus compared to the baseline period (paired *t*-test, $p < 0.05$). We used these neurons to examine how responses varied following a second stimulus presentation in or out of the receptive field (although the activity recorded in the second delay period was not a selection criterion).

Two monkeys were tested with the Match/Nonmatch task (Figure 2A). We recorded from 149 neurons in the dorsolateral prefrontal cortex that responded to visual stimuli (*t*-test, $p < 0.05$) and exhibited selectivity for the spatial location of the cue (ANOVA, $p < 0.05$). Of those neurons, 83 exhibited significantly elevated activity during the first delay period after the cue presentation (*t*-test, $p < 0.05$) and were tested at locations inside and out of the receptive fields. We also recorded from 60 visually responsive and spatially selective neurons in the posterior parietal cortex of the same animals. Of those, 38 exhibited delay period activity and were tested at locations inside and out of the receptive fields. These 83 and 38 neurons respectively make up the sample under study from the Match/Nonmatch task.

Two different monkeys were tested with the spatial version of the Delayed Match-to-Sample task (Figure 2B). In this experiment, we recorded from 148 visually responsive and spatially selective neurons in the dorsolateral prefrontal cortex. Of those, 48 neurons exhibited delay period activity and were tested at locations inside and out of the receptive fields. Finally, we recorded from 119 visually responsive and spatially selective neurons in the posterior parietal cortex, 36 of which also exhibited delay period activity and were tested at locations inside and out of the receptive fields. Analysis was performed on this sample of 48 and 36 neurons from the Delayed Match-to-Sample task. The total number of neurons included in our sample, broken down by task, monkey, brain area and response type (explained in the next section) are shown in Table 1.

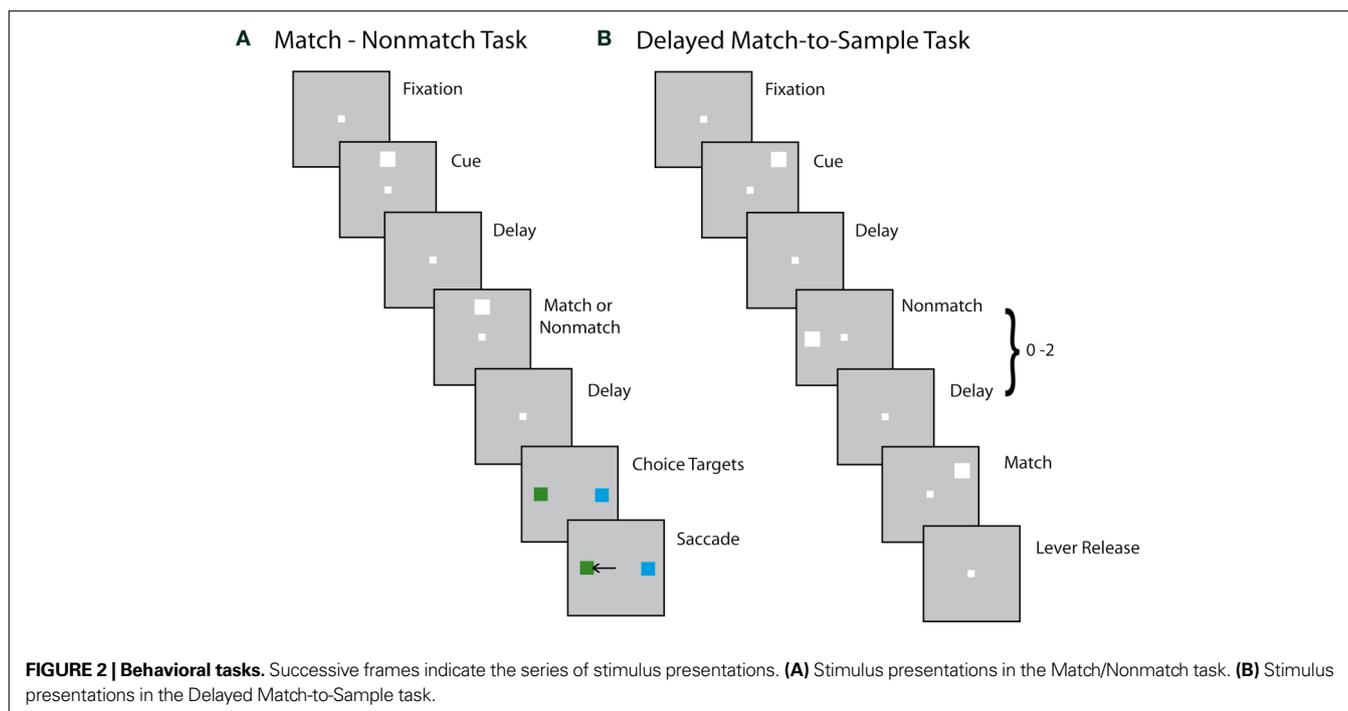


Table 1 | Number of neurons recorded in each area and monkey.

Task	Monkey	Area	Sustained	Anticipatory
Match-Nonmatch	EL	PFC	42	23
		PPC	19	19
	AD	PFC	16	2
		PPC	0	0
	Total	PFC	58	25
	PPC	19	19	
Delayed match to sample	CA	PFC	1	0
		PPC	2	0
	DA	PFC	37	10
		PPC	15	19
	Total	PFC	38	10
	PPC	17	19	

TYPES OF DELAY PERIOD ACTIVITY

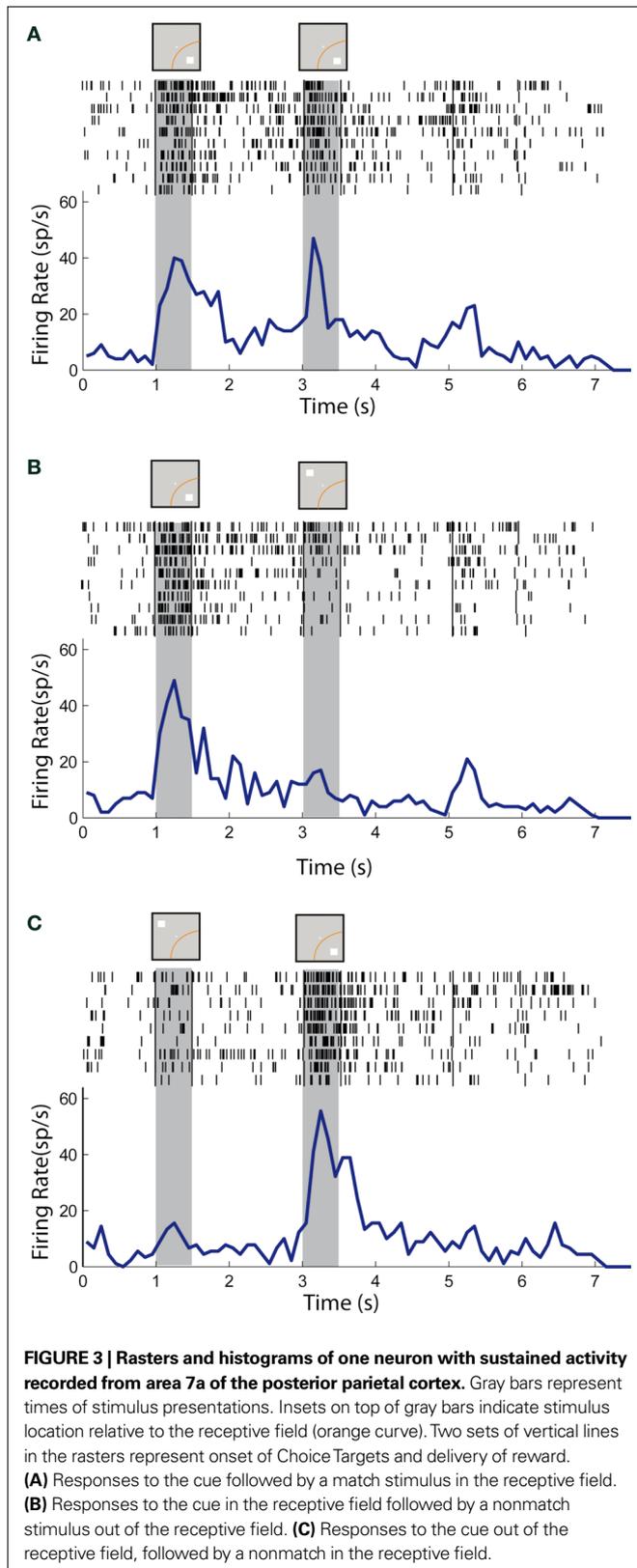
By examining the time course of delay period activity, we found that neurons exhibited one of two different types of responses, as it has also been described in previous studies (Quintana and Fuster, 1992; Constantinidis and Steinmetz, 1996). One class of neurons exhibited persistent responses with a fairly constant or slightly declining rate, which appeared to extend a response to the cue presentation; we refer to these as sustained responses (Figure 3). Across the two tasks, 96 prefrontal neurons and 36 parietal neurons were classified as exhibiting sustained activity. Another class of neurons started to discharge after the offset of the cue, with a rate that accelerated during the delay period; we refer to these as anticipatory responses (Figure 4). The strongest delay-period anticipatory responses were often observed in the delay period following a cue presentation out of the receptive field (Figure 4C). A total of 35 prefrontal and 38 parietal neurons were classified as anticipatory.

DELAY PERIOD ACTIVITY IN THE MATCH/NONMATCH TASK

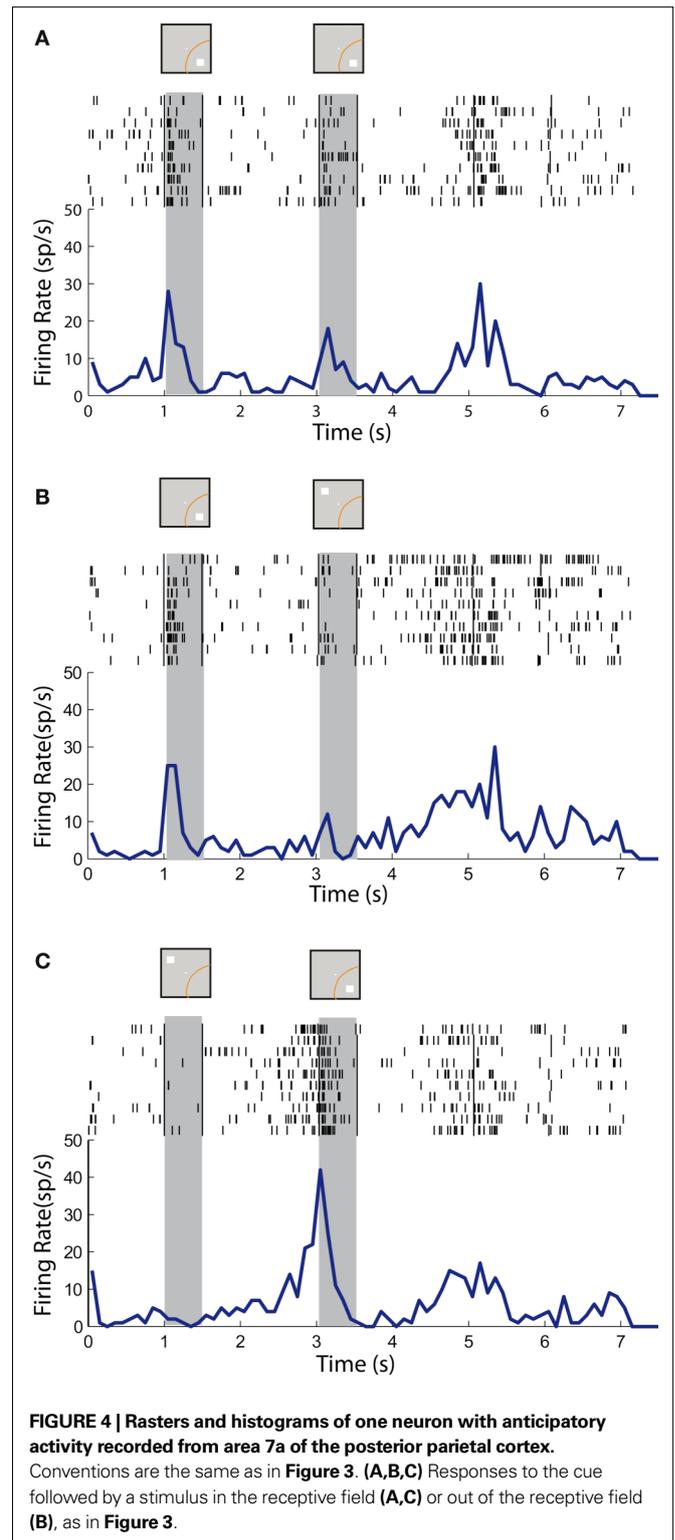
We first examined the responses of prefrontal and parietal neurons in the Match/Nonmatch Task. In this task, the animals were required to remember the location of the cue stimulus and to decide if the second stimulus appeared in the same or different location (Figure 2A). We sought to determine if activity in the delay periods differed after the presentation of a stimulus in and out of the receptive field. Examples of neurons with sustained activity recorded from the posterior parietal and dorsolateral prefrontal cortex are shown in Figures 3 and 5, respectively. In agreement with previous studies, we found that posterior parietal neurons that exhibited sustained responses after a cue presentation in the receptive field, typically ceased to respond after presentation of a subsequent non-match stimulus out of the receptive field (Figure 3B). In contrast, neurons in the prefrontal cortex during execution of the same task continued to discharge even after a transient decrease in activity caused by the nonmatch stimulus (Figure 5B).

These patterns of activity were evident on the population response as well. The population of both prefrontal and parietal neurons responded robustly with sustained activity above the baseline in both delay periods in trials of cue and match stimuli appearing in the receptive field (Figure 6A). More importantly, in trials where the cue appeared in the receptive field but was followed by a stimulus out of the receptive field, prefrontal neurons continued to discharge in a robust manner in the second delay period whereas the activity of parietal neurons returned to baseline (Figure 6B), which constituted a significant difference between the two areas (*t*-test, *p* < 0.05).

We further examined the phenomenon on a neuron-by-neuron basis, by plotting the firing rate we observed in two conditions. Each data point in Figure 7 represents the firing rate of a single neuron during the delay period following presentation of a nonmatch stimulus out of the receptive field (as in Figure 6B) as a function of the firing rate observed in the delay period after presentation

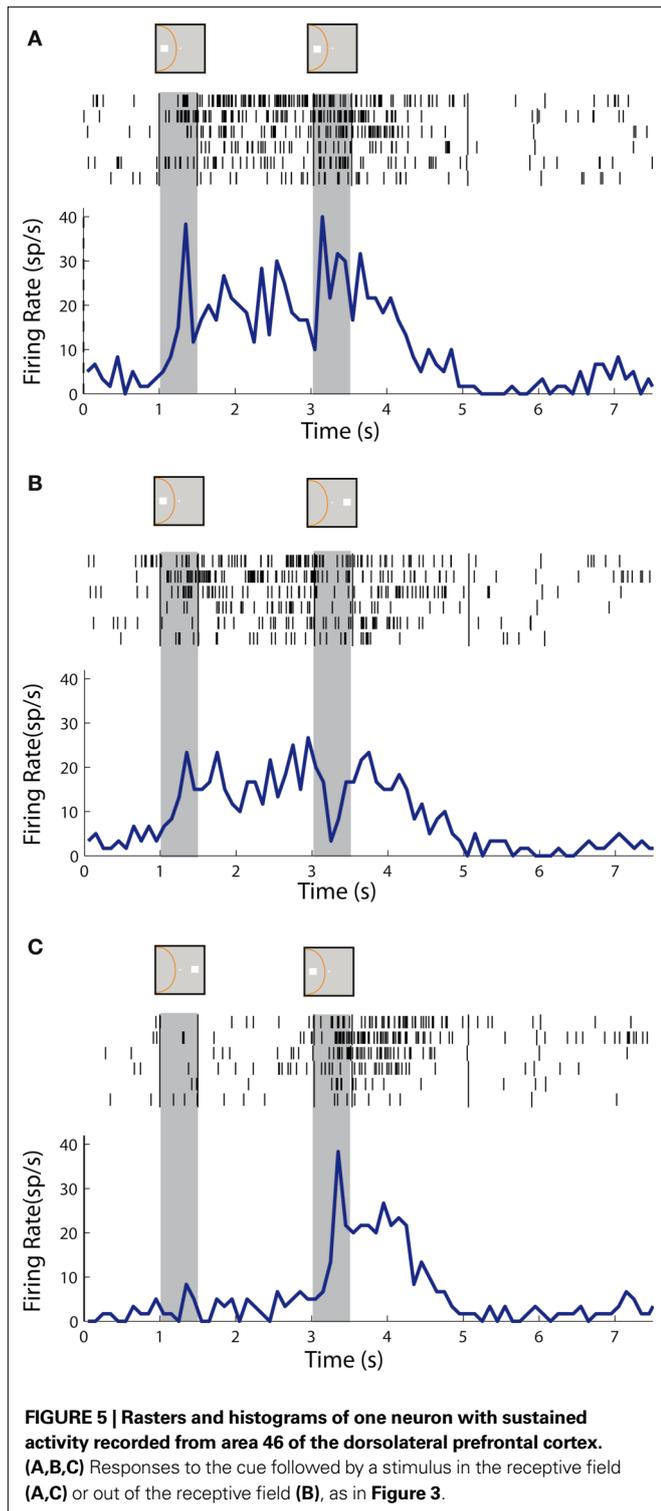


of a match stimulus in the receptive field (as in **Figure 6A**). A regression analysis indicated that for prefrontal neurons these responses were essentially equal (regression slope = 1.03, practically coinciding with the diagonal). Parietal neurons responded

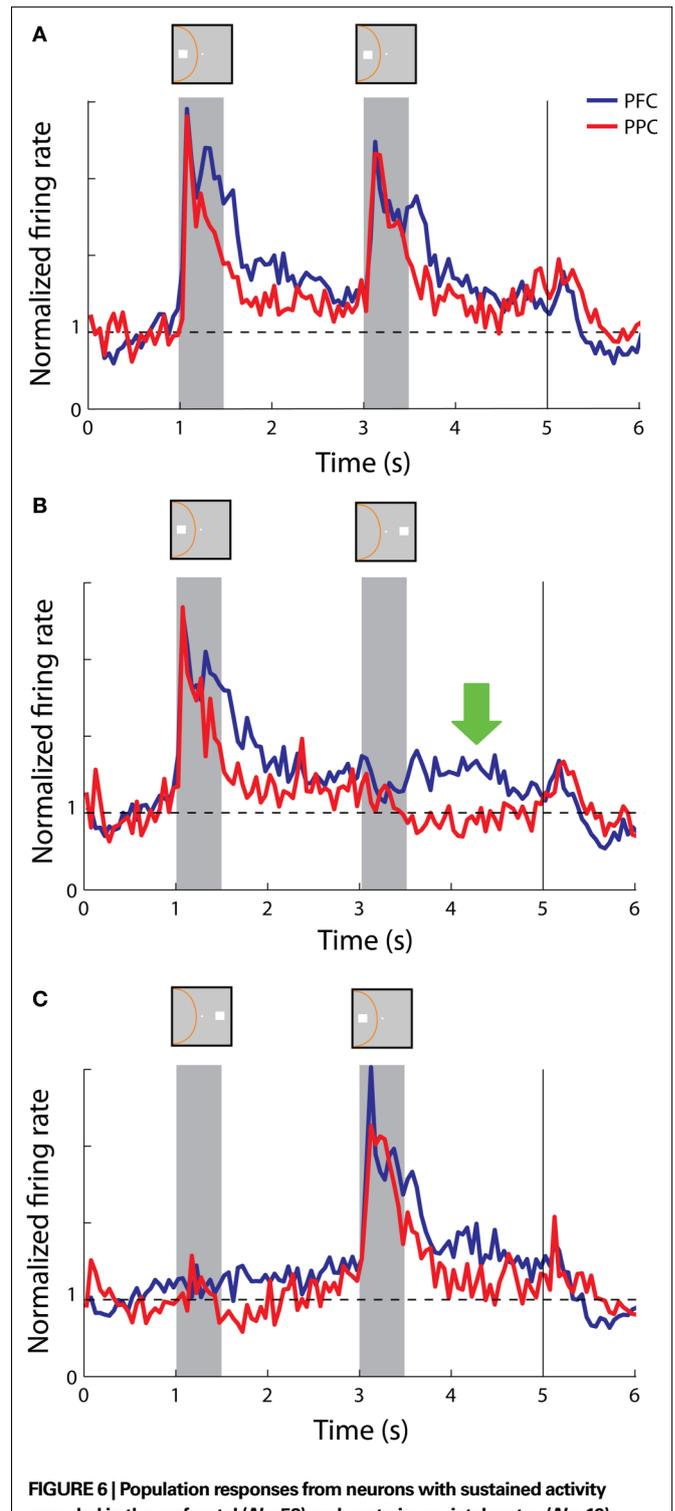


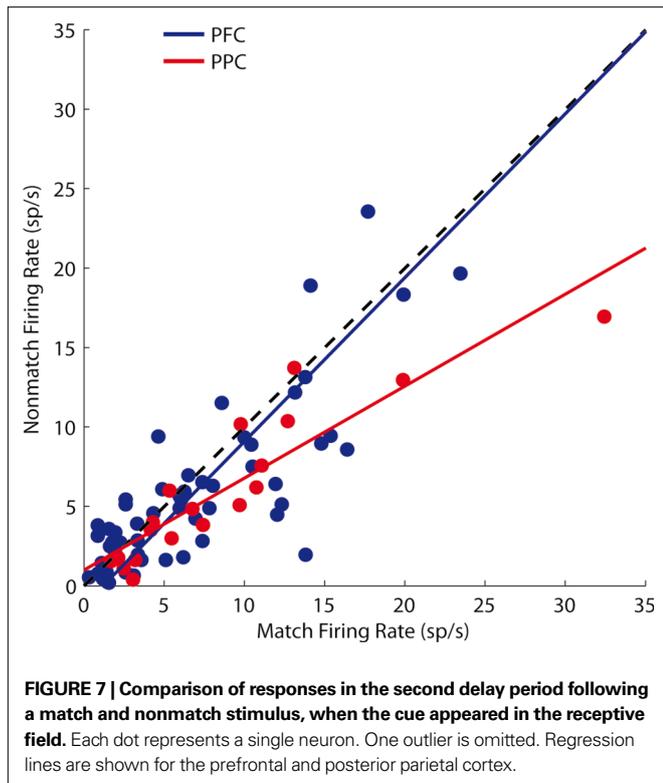
with consistently lower firing rates after nonmatch stimuli appeared out of the receptive field (regression slope = 0.58). The slopes of the two regression lines were significantly different from each other (*F*-test, *p* < 0.05).

On the other hand, we saw examples of both parietal neurons and prefrontal neurons that continued to display sustained discharges after the appearance of the second stimulus in the



receptive field, when the initial cue appeared out of the receptive field (Figures 3C and 5C, respectively). This was also evident in the population responses from the two areas (Figure 6C). We should point out that the nonmatch stimulus was behaviorally relevant in this task; the animals were required to consider both stimuli and make a decision on whether they matched each other or not. Our



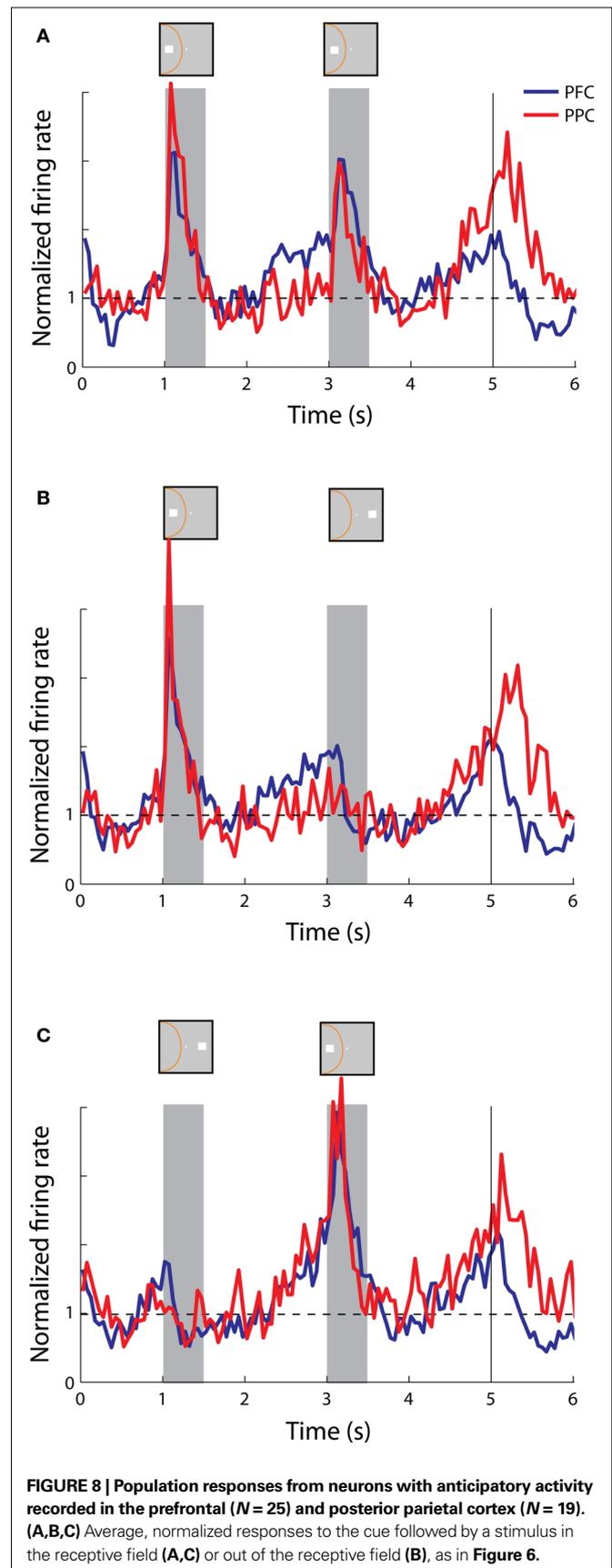


findings show that both prefrontal and parietal neurons continued to represent a previous stimulus that appeared in their receptive field, even though the cue appeared outside.

Anticipatory activity averaged across the population of neurons was generally not informative about the location of the cue or preceding stimulus, in or out of the receptive field. Individual neurons exhibited a wide range of response envelopes but we observed stronger anticipatory activity in the first delay period when it followed a cue presentation out of the receptive field (Figure 8C) than a cue in the receptive field (Figures 8A,B). We also observed robust anticipatory activity in the second delay period in both the prefrontal and posterior parietal cortex whether the second stimulus was a match in the receptive field, a nonmatch out of the receptive field, or a nonmatch in the receptive field (Figure 8). Although weaker, anticipatory activity was also evident even before the appearance of the cue (Figure 8, time interval 0-1 s).

DELAY PERIOD ACTIVITY IN THE DELAYED MATCH-TO-SAMPLE TASK

We repeated our analysis of delay period activity in the Delayed Match-to-Sample task. In this task, the animals were required to remember the location of the cue, to ignore a random number of nonmatch stimulus presentations, and to release a lever when a match stimulus appeared at the same location as the cue (Figure 2B). We again distinguished between sustained and anticipatory responses. As was the case for the Match/Nonmatch task, the strongest anticipatory responses were not aligned with the presentation of the cue in the receptive field (data not shown). We therefore focused on sustained responses and we sought to determine if responses during the delay period differed depending on whether the cue and nonmatch stimuli appeared in or out of the receptive field.



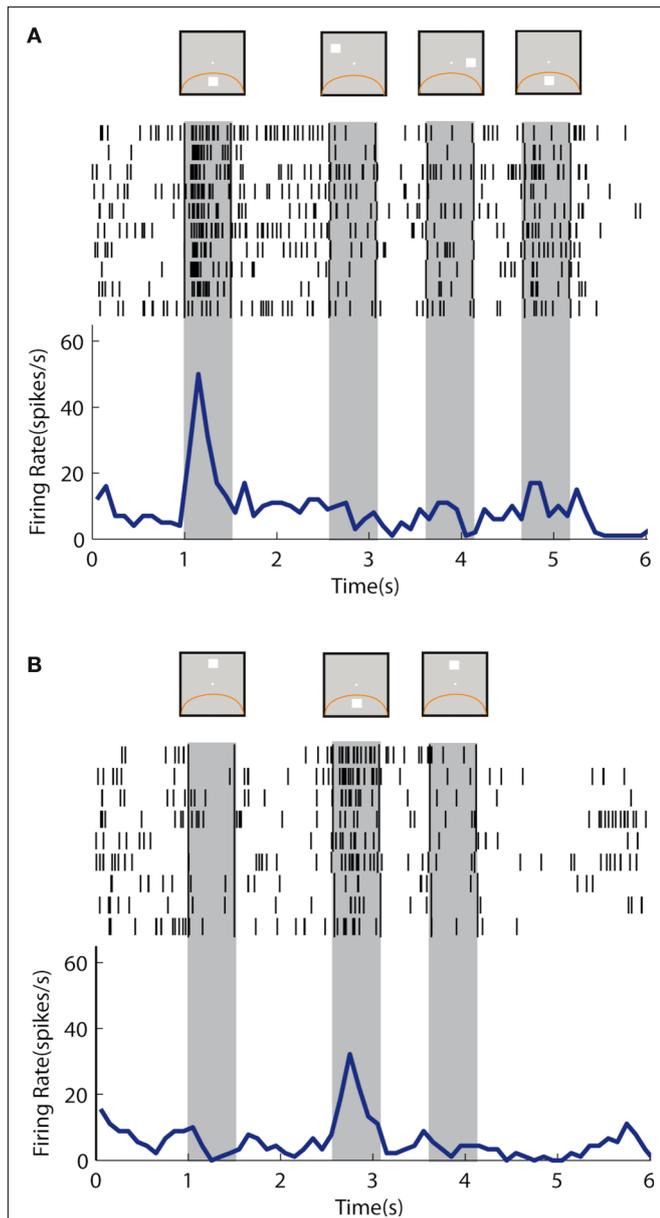


FIGURE 9 | Rasters and histograms of one neuron with sustained activity recorded from area 7a of the posterior parietal cortex, tested with the delayed match-to-sample task. Data are shown from the Match/Nonmatch task. **(A)** Responses to a cue presentation in the receptive field followed by nonmatch presentations out of the receptive field. **(B)** Responses to a cue presentation out of the receptive field followed by a nonmatch stimulus in the receptive field.

An example neuron with sustained activity recorded from the posterior parietal cortex is shown in **Figure 9**. The neuron responded with sustained activity after presentation of the cue in the receptive field, which was diminished after presentation of a nonmatch stimulus out of the receptive field (**Figure 9A**). The same neuron was activated by a nonmatch stimulus that appeared in the receptive field though that was not followed by appreciable delay period activity (**Figure 9B**). A neuron recorded from the prefrontal cortex is shown in **Figure 10**.

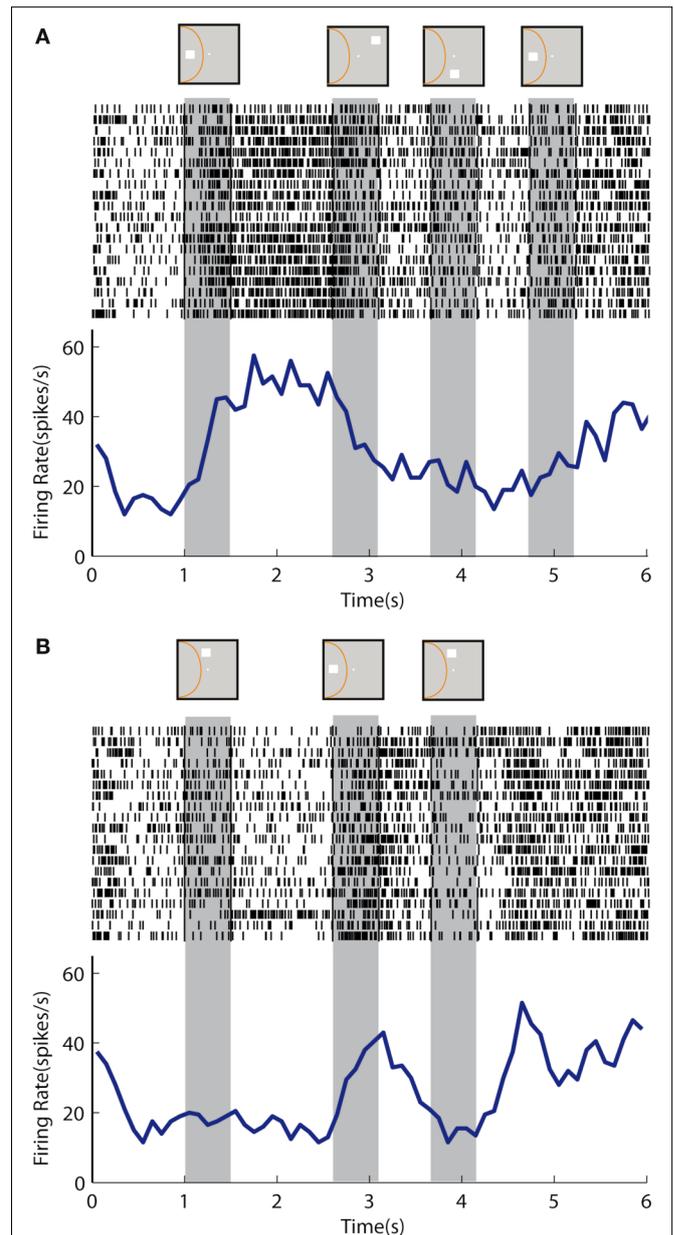
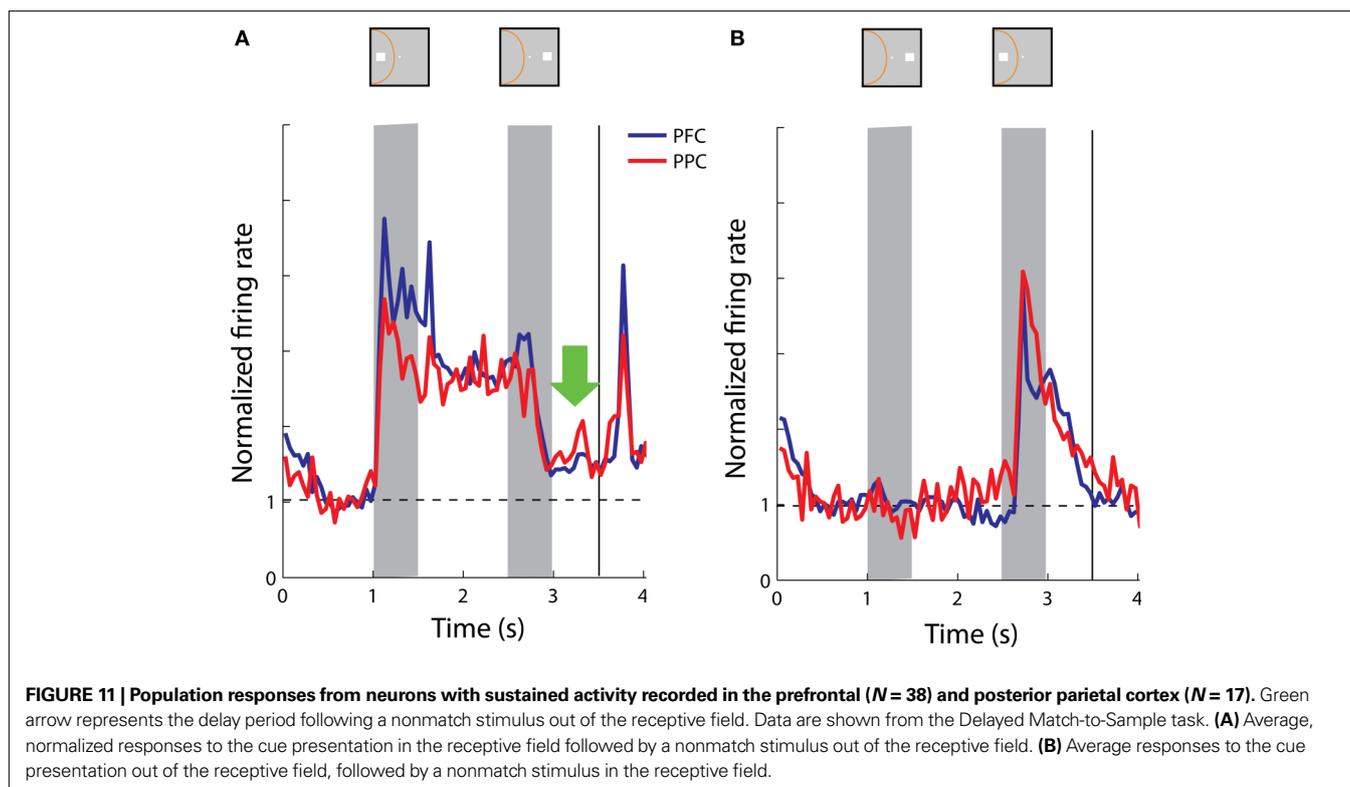


FIGURE 10 | Rasters and histograms of one neuron with sustained activity recorded from area 46 of the dorsolateral prefrontal cortex, tested with the delayed match-to-sample task. **(A)** Responses to the cue presentation in the receptive field followed by nonmatch presentations out of the receptive field. **(B)** Responses to the cue presentation out of the receptive field followed by a nonmatch presentation in the receptive field.

The neuron exhibited sustained responses after the cue presentation in the receptive field, which declined after presentation of nonmatch stimuli out of the receptive fields (**Figure 10A**). This neuron also responded to a nonmatch stimulus in the receptive field and continued to discharge in the delay period, until a match stimulus out of the receptive field was presented (**Figure 10B**). Activity after presentation of the last stimulus is associated with the lever movement, release of fixation control and reward delivery.



We again constructed population histograms of delay period activity and investigated whether sustained activity following a cue presentation in the receptive field was interrupted by a stimulus out of the receptive field and vice versa. Note that the match stimulus terminates the trial (the monkey releases the lever) and for this reason the period after the match stimulus is not informative and is not shown in **Figure 11**, unlike **Figure 6**. When we compared sustained responses in the delay period following a nonmatch stimulus out of the receptive field across the populations of parietal and prefrontal neurons, we found no significant differences (t -test, $p > 0.2$) between average response rates in the two areas (**Figure 11A**). The same was true for activity following a nonmatch stimulus in the receptive field, when the cue appeared out of the receptive field; both prefrontal and posterior parietal neurons continued to be active in the second delay period (**Figure 11B**).

DISCUSSION

OVERVIEW OF THE FINDINGS

Our study revealed differences between the patterns of delay period activity among prefrontal and parietal neurons in a spatial working memory task. These became clear when we distinguished between sustained and anticipatory responses. Distinct patterns of responses were observed in the populations of neurons with sustained responses which exhibited differences in the prefrontal vs. the parietal cortex (**Figure 6**). Anticipatory responses with similar time courses were observed in the two areas (**Figure 8**). Our main finding was that dorsolateral prefrontal activity representing the spatial location of a cue survives the presentation of a nonmatch stimulus out of the receptive field in the context of a Match/Nonmatch task (**Figure 6B**).

At the same time, we found considerable similarities between the regions. Both prefrontal and parietal neurons continued to be active after the presentation of a nonmatch stimulus in the Match/Nonmatch task (**Figures 3C and 5C**). We also found responses of prefrontal and parietal neurons to be quite similar in the context of the Delayed Match-to-Sample task. Although we observed individual examples of prefrontal neurons that were able to resist the appearance of multiple nonmatch stimuli and continue to discharge in response to an initial cue stimulus (**Figure 10B**), overall the populations of prefrontal and parietal neurons exhibited delay period activity that was diminished but not extinguished after a nonmatch stimulus out of the receptive field (**Figure 10A**). Similarly, both prefrontal and parietal neurons continue to represent a nonmatch stimulus in the receptive field in the delay period following it, although the monkeys were required only to remember the location of the cue in this task (**Figure 10B**).

TYPES OF RESPONSES

Analysis of our data set identified two general types of neuronal activity in the delay period, in agreement with previous studies (Quintana and Fuster, 1992; Constantinidis and Steinmetz, 1996). Sustained activity was characterized by persistent discharges that extended beyond the initial response to a stimulus into the delay period and could encode the location of the preceding stimulus. This is the type of activity commonly thought to provide a neural correlate of working memory for the preceding stimulus (Goldman-Rakic, 1995).

Anticipatory activity tended to appear after presentation of a stimulus at any spatial location, most often outside the neuron's receptive field. This type of activity is commonly observed in

neurophysiological recordings in the prefrontal cortex (Rainer and Miller, 2002; Brody et al., 2003) however its properties are not as straightforward. Previous studies have shown that anticipatory activity after a stimulus presentation is not simply related to expectation about the appearance of a subsequent stimulus, but it is in fact tuned depending on the location of the preceding stimulus (Constantinidis and Steinmetz, 1996). This was the case even when the location of the subsequent stimulus was randomized, making it impossible for the monkey to truly anticipate its location. In sum, anticipatory activity can be informative about the location of the preceding stimulus, however it displays a tuning that differs from the tuning observed during the stimulus presentation. Recent computational studies have shown that firing rates of individual prefrontal neurons exhibit a wide variety of time courses, with memory-related activity components accounting only for a small percentage of the total variance (Machens et al., 2010). In our experiments, prefrontal and posterior parietal neurons exhibited very similar patterns of anticipatory activity that could not distinguish the two areas.

In recent years, mechanisms of memory maintenance in the absence of increased firing rate in the delay period activity have also been described (Sugase-Miyamoto et al., 2008). Modeling studies have demonstrated that synaptic changes in the absence of increased firing rate can account for such phenomena (Mongillo et al., 2008).

PREVIOUS COMPARISONS OF PARIETAL-PREFRONTAL ACTIVITY

An earlier study directly comparing prefrontal and parietal activity in the oculomotor delayed response (ODR) task observed remarkable similarities between neurons in the two regions (Chafee and Goldman-Rakic, 1998). The ODR task involves presentation of a single stimulus, followed by a delay period, and the animals are required to execute an eye movement towards the location of the remembered cue. Data from other experimental paradigms that involved presentation of multiple stimuli only one of which the animals were required to remember suggest differences between regions (di Pellegrino and Wise, 1993; Constantinidis and Steinmetz, 1996). It should be clear however that comparison between results from those studies is not straightforward since the corresponding studies involved different task and behavioral paradigms, conducted in different laboratories. Our current results provide the first direct distinction of prefrontal and parietal responses in the same animals, while performing the same task (Figure 6).

TASK EFFECTS

The two behavioral tasks that we used in this study place different demands on memory. The Match/Nonmatch task requires the animals to remember the initial stimulus (cue) and to compare it with a second stimulus presentation (match or nonmatch). At the end of the second stimulus presentation, the animals no longer need to remember either stimulus and simply have to decide on whether the two stimuli matched each other or not. Nonetheless, we observed responses in the second delay period that continued to represent either the initial or second stimulus. A similar representation of a previously presented stimulus has been described for tactile stimuli (Romo et al., 1999, 2002). In the task used by Romo et al., monkeys were presented with two vibratory stimuli in sequence separated by delay periods. At the end of the trial, the animals were required to decide if the second frequency was lower

or higher than the first. As in our task, activity of some prefrontal neurons continued to represent stimulus attributes in the second delay period. We have recently observed responses in the prefrontal cortex that continue to track a visual stimulus, even in the complete absence of a memory requirement, in animals only trained to fixate (Meyer et al., 2007). A similar effect, albeit using a much shorter delay period, was also observed in the posterior parietal cortex (Joelving et al., 2007). These results suggest that prefrontal and parietal neurons continue to track properties of physical stimuli even when they are not required to do so by a behavioral task.

The choice of task was critical in revealing differences between the two areas. As was the case with the use of the Oculomotor Delayed Response task (Chafee and Goldman-Rakic, 1998), we observed no significant differences in the averaged prefrontal and parietal responses in the context of the Delayed Match To Sample Task. This finding indicates that computational power related to the maintenance of spatial information is considerably distributed between the prefrontal and posterior parietal cortex and differences between the two areas are task dependent.

IMPLICATIONS FOR FUNCTIONAL SPECIALIZATION

The posterior parietal and dorsolateral prefrontal cortices are strongly interconnected (Cavada and Goldman-Rakic, 1989) and share many functional properties. Our current results indicate that the prefrontal cortex has unique properties in its ability to preserve information in working memory even after the presentation of additional stimuli, at least in the context of some behavioral tasks. What intrinsic properties of the prefrontal cortex give rise to this unique ability is largely an open question although many candidates have been identified. Computational models have demonstrated that dopamine can serve to stabilize working memory (Durstewitz et al., 2000). This is thought to occur through an increase of NMDA conductance (Yang and Seamans, 1996; Seamans et al., 2001; Chen et al., 2004), which can facilitate persistent activity by its slow time constant, leaving the postsynaptic neuron in a depolarized state for a longer time interval (Wang, 2001). The prefrontal cortex, unlike the posterior parietal cortex, receives a significant dopaminergic innervation from the ventral tegmental area, which could account for the physiological differences. NMDA receptor density itself may be a factor in the ability of cortical neurons to resist interference (Compte et al., 2000) and evidence suggests that prefrontal neurons may be characterized by unique patterns of NMDA activation (Wang et al., 2008). Other differences in the intrinsic circuits of the prefrontal and parietal cortex in terms of dendritic tree size and numbers of synapses may also be contributing factors; prefrontal pyramidal neurons exhibit the most extensive dendritic trees and highest number of spines of any cortical neurons (Elston, 2000, 2003). Finally, the relative composition of interneuron types may be different for the prefrontal cortex (Wang et al., 2004). It appears likely that a combination of factors endows the prefrontal cortex with unique properties, such as those we observed in our neurophysiological recordings.

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