Temporal Organization of Neurons Activity in Premotor Cortex Area During an Visually Guided Reach-to-Grasp Movements

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In this paper, the temporal organization of neurons in the premotor cortex area is investigated. The movement task which is studied in this paper is of reach-to-grasp type. Since the reach-to-grasp is a movement task, it is intuitive to investigate it in the premotor cortex area. We used electrophysiological signal provided by (1) to improve the understanding of the temporal organization of neurons in the premotor cortex area. Our results show a wide variety of patterns in this area similar to what have seen before (Churchland 2006 (2), 2007 (3)). Furthermore, the Fano factor decreased in this area after onset, which is similar to what has been seen in other parts of the brain (4). Moreover, Our results also illustrate the effect of the refractory period on inter-spike interval distribution and the type of point process that spikes are generated from. Overall, the study contributes to the improvement of understanding of temporal activity in the premotor cortex area with the help of analyzing the electrophysiological signal.

Macaque | Premotor Cortex| LFP | Reach-to-Grasp | Temporal Analysis

A crucial question regarding the neural control of movement has been whether or not there is a relationship between neural activity and movement parameters. This relationship between neural activity in motor cortex and movement is highly debated. Although many studies have examined the spatial tuning (e.g., for direction) of cortical responses, less attention has been paid to the temporal properties of individual neuron responses.

On one hand it is not clear if there is a straightforward relationship. Even for an area of the brain that generates movement, individual neuron responses may have no straightforward relationship with the movement parameters (Fetz 1992; Robinson 1992; Todorov 2000). On the other hand, a large body of work is focused on the simple relationship between the responses of motor cortex neurons and movement parameters such as speed and direction. In this view, neuron responses "code" different movement parameters, therefore implying that there is a straightforward relationship. Support comes from studies using a center outreaching task, during which cortical responses typically show cosine tuning for reach direction (Georgopoulos et al. 1982; Schwartz et al. 1988), perhaps implying that movement direction is coded (although see Mussa-Ivaldi 1988; Sanger 1994; Zhang and Sejnowski 1999).

In this paper, we aim to improve the understanding of the temporal response of different neurons to visually guided reach-to-grasp movements. We will first discuss the cumulative activity of neurons in response to different events, to find out the overall functionality of this region of the brain. Next, we focus on interspike interval (ISI) distribution to examine how well the Poisson process assumption fits the real-world data. And finally, we analyze the activity of the neurons individually to observe the variability of neurons functionally in this area.

Results

We represent the cumulative activity of neurons in response to different events using both raster plot and PSTH diagram. The time in which the monkey moves its hand is different in each trial because the monkey may have different reaction speed in each trial. Therefore, the SR-ON time is different in each trial. Hence, in Figure 1 which shows the general raster plot and general PSTH that we have extracted from the spike times data, the SR-ON line is evaluated by averaging the monkey's reaction time over all trials. General Rater plot is obtained by plotting time segments corresponding to each trial on top of each other and specifying occurrence times of each event as a vertical line on the plot. General PSTH is obtained by a simple averaging among PSTH vectors for each trial,

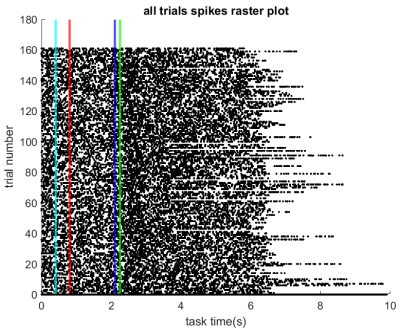
Note that we have done a trial-by-trial analysis on all of neurons, cumulatively; This means that there might be some interesting behavior in individual neurons which are masked by the "accumulation" that we have done (the fact that we thought of the whole electrode set as one giant neuron). This problem will be investigated later in the paper but for now, we are not empty-handed. By looking at the charts, one can observe that after specific events (GO-ON and SR-ON), the cumulative firing rate of neurons has increased; Both the density of black dots in Figure 1 (a), and the value of the PSTH plot in Figure 1 (b), have increased after the mentioned onsets.

This observation motivates us to investigate this matter more throughly. Figure 2 (a), shows the histograms of rate

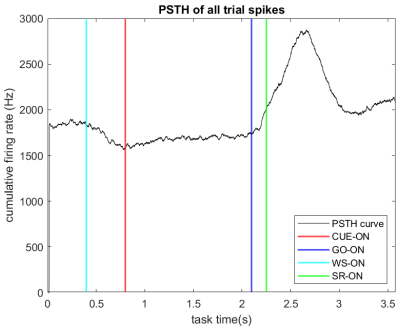
Significance Statement

Movement is an inseparable part of our lives. Scientists have been trying to understand how the movement is coded in the brain for a long time. In this paper, the temporal organization of neurons in the premotor cortex area is investigated. Firstly, we show a wide variety of patterns in this premotor cortex area. Next, we observe an increase in the regularity of spikes after the onset signal. Furthermore, we observe how the refractory period affects inter-spike interval distribution, and how considering this phenomenon changes the type of point process that spikes generate from.

Both authors contributed equally to this work.



(a) General Raster Plot



(b) General PSTH

Fig. 1. Cumulative Activity of Neurons. Each spike is marked using a black dot on the plot. $t = 0$ line corresponds to the TS-ON event. cyan, red, blue, and green line correspond to the time that WS-ON, CUE-ON, GO-ON, and SR-ON has happened respectively.

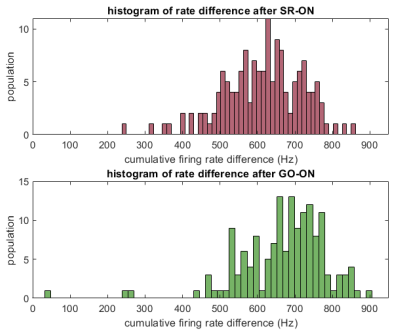
changes after GO onset and SR onset in all viable trials. After looking at this plot, one can guess that neurons are more sensitive to GO onset than the SR onset since the rate difference is more on average. We applied T-test to test this hypothesis. Figure 2 (b) shows the result of this test. The p-values obtained for SR onset and GO onset are 1.4e−87 and 5.0e−111 respectively. These p-values are very small, so one can confidently state that the firing rates change after the occurrence of either of those events.

Considering the nature of the events (both of which happen before the monkey moves its hand) and the fact that our data is recorded from the premotor cortex area, the results are similar to what we expected; The monkey has to react to the GO onset being displayed on the monitor by moving its hand and grabbing on the handle, actions all of which increase neuron activity in the premotor cortex area of the animal's brain.

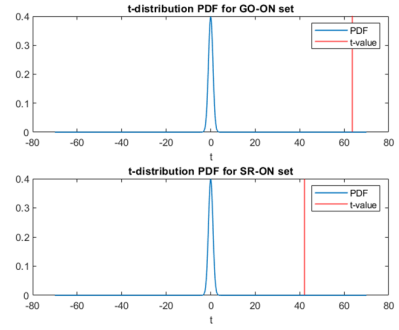
Moreover, figure 2 (c), which represents cumulative PSTH of all neurons time-locked to GO onset, indicates that neurons start to fire just after the GO onset. Ultimately, if we are to choose an event which has the most effect on neuron firing rate, we can choose the GO onset since the p-value associated to the firing rate difference after this event is smaller.

To further study the activity of recorded neurons, we follo two different approaches to analyze the spikes pattern based on possible tasks. First approach is to repeat the cumulative method but this time, we divide trials based on task type. Another way to analyze the spikes pattern based on task types is to look at the behavior of individual neurons and compare their PSTH curves during the execution of different task types.

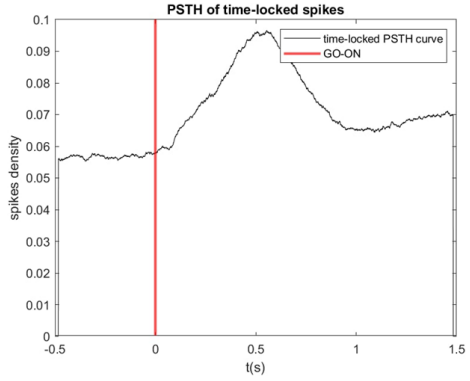
Figure 3 and Figure 4 illustrate the raster plots and PSTH



(a) Histograms of difference in firing rates after occurrence of GO onset and SR onset.



(b) Comparison between t-distribution and t-value for SR onset and GO onset



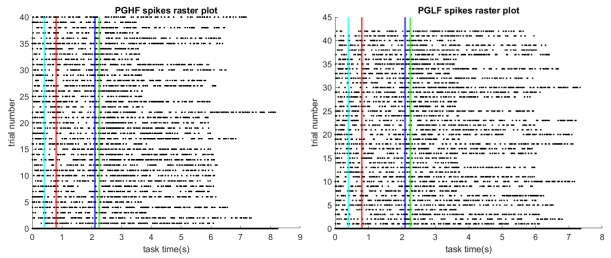
(c) PSTH time-locked to GO onset

Fig. 2. Sensitivity to Events. Different plots to compare the sensitivity of neurons to GO onset and SR onset.

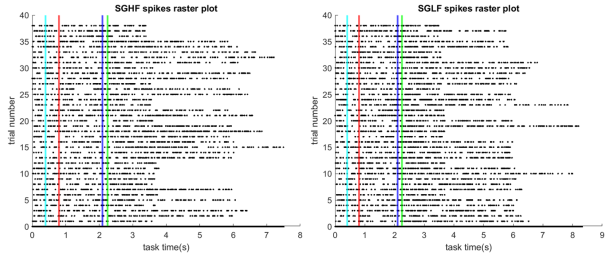
for each task type. As Figure 4 (e) indicates, comparing the PSTH diagrams associated to different task types, not much might be there to comprehend; Only that for PG tasks, the peak firing rate occurs with a rather slight delay and among the four grip types (SG or PG), the peak value is higher for low-force versions of the task.

We mentioned earlier that our method in analyzing the spikes cumulatively, masks the small, yet interesting behaviors appearing in individual neurons. And this is exactly what happened here and considerable behaviors were observed by analyzing individual neuron behavior, none of which were possible to observe in the cumulative analysis. Different neurons in this area, encode different events and actions in different ways, or they don't!

For instance, neuron no. 10, Figure 5 (a), seems to be more

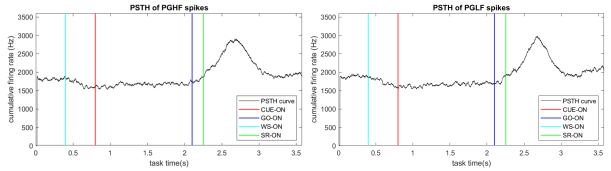


(a) Raster Plot of PGHF **(b)** Raster Plot of PGLF

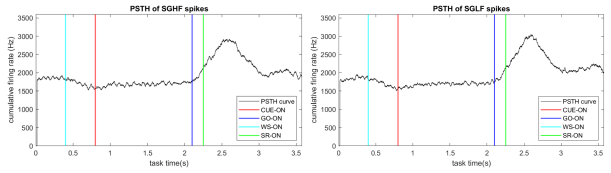


(c) Raster Plot of SGHF **(d)** Raster Plot of SGLF

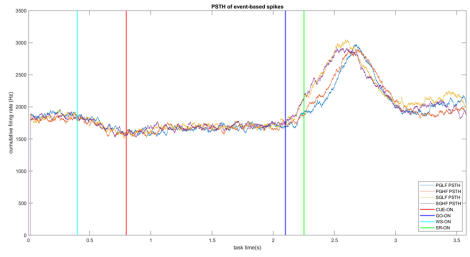
Fig. 3. Raster Plots for Different Tasks.



(a) PSTH of PGHF **(b)** PSTH of PGLF



(c) PSTH of SGHF **(d)** PSTH of SGLF



(e) Comparison of PSTH diagrams associated with different task types

Fig. 4. PSTH for Different Tasks.

active during high-force tasks, especially during the PGHF tasks and might be responsibe for encoding the force during task execution. Neuron no. 35, Figure 5 (b), seems to be much more active during PGLF tasks compared to other tasks. Neurons no. 43 and no. 76, Figure 5 (c) and (d), have more firing rate during SG tasks, meaning they probably take part in encoding the type of grip during task execution.

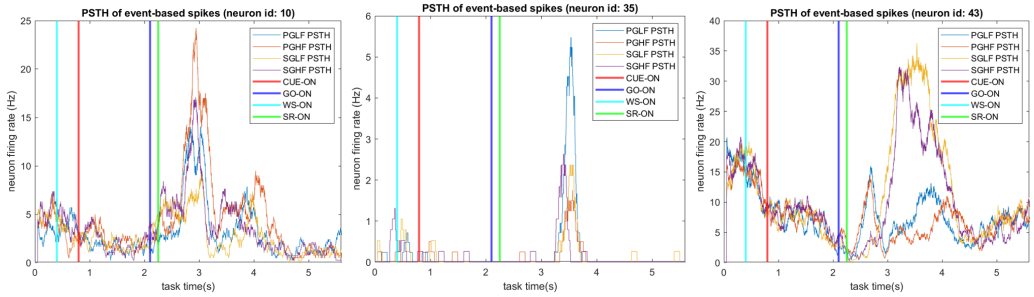
On the other hand, some neurons seem to behave indifferently to any type of tasks; Neurons no. 115 and no. 264, Figure 5 (e) and (g), are of this type. Another neuron of this type, is neuron no. 172, Figure 5 (f). What is more interesting about this neuron is that after the onsets that many other neurons experience an increase in firing rate, this one goes through a large decrease in firing rate. All of this illustrates how each individual neuron does a specific computation and emits a different signal compared to other neurons in the same area of the brain, and indicates that neurons in this area have a pretty complex behavior and can't be characterized by their functionality so easily.

As we mentioned, Figure 2 indicates that neurons are more sensitive to GO onset. Now we want to see if this signal has any significant effect on Fano factor. Figure 6 (b), shows histogram of Fano factor distribution before and after GO onset. After looking at this plot, one can guess that GO onset will affect Fano factor distribution and Fano factor will decreased after GO onset. We applied T-test to test this hypothesis. First we calculate the difference of these two vectors and then set up a null hypothesis: The fano factor does not change after the onset, or equally, the mean of the difference vector constructed is zero. The p-value for this test is 8.1.0e−5. This p-value is small enough so on can state that null hypothesis is rejected and that the Fano factor does change after the onset. This is caused by the increase in the average firing rate and decrease in the variance of firing rate because of GO onset occurrence.

In addition, we examine how well the Poisson process assumption fits the real-world data. We calculate the interspike interval (ISI) for each neuron from spikes data. Figure 7 (a) shows the histogram of ISI signal. At first glance, their empirical distribution is very similar to an exponential distribution. Figure 7 (b) shows the best exponential distribution that can be fit to this histogram, parameter of this distribution was calculated using nonlinear regression fitting. Therefore, one may assume spikes are generated from a Poisson point process. As Figure 7 (c) indicates, this observation is valid only if we are not too close to zero. And the histogram is more like a gamma distribution rather thanan exponential one and therefore it won't generate a poisson process at all. As Figure 7 (c) indicates, For a few milliseconds just after a spike, it's more difficult to evoke another spike. This is because of a property of neurons known as Refractory Period, which is the period of time during which neuron is incapable of evoking another spike. This Phenomenon is caused by the inactivation of the Na^+ channels that opened to depolarize the membrane and remain inactivated until the membrane hyperpolarizes.

Discussion

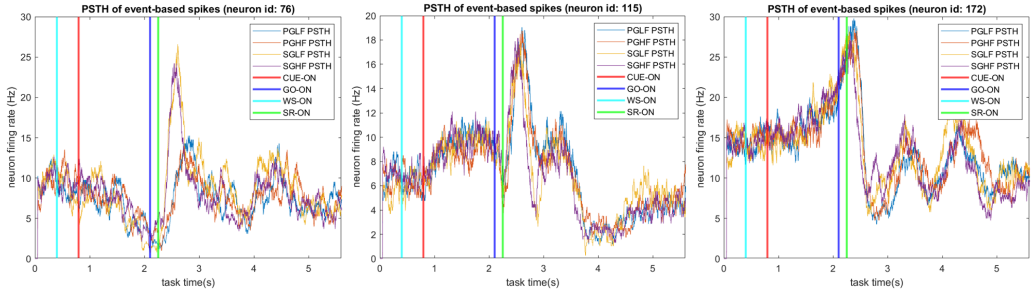
Our results are pretty much similar to what appears in Churchland and Shenoy's paper (3). In both cases, high versatility was observed among individual neurons in the same motor area. Both during a single task type and among all tasks, different neurons behaved in different ways, each "coding" a



(a) Comparison of PSTH diagrams for neuron no. 10

(b) Comparison of PSTH diagrams for neuron no. 35

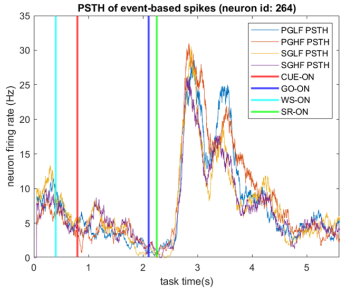
(c) Comparison of PSTH diagrams for neuron no. 43



(d) Comparison of PSTH diagrams for neuron no. 76

(e) Comparison of PSTH diagrams for neuron no. 115

(f) Comparison of PSTH diagrams for neuron no. 172



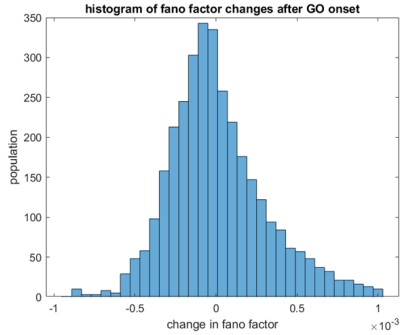
(g) Comparison of PSTH diagrams for neuron no. 264

Fig. 5. PSTH for Individual Neurons.

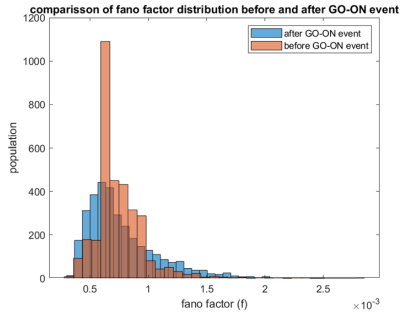
different aspect or parameter of movement. From neurons that may code every type of grasp task to neurons that behave completely indifferently, all lie within the same area of the brain. In the case of fano factor fluctuation, the reduction that was observed in our results is the same as what appears in (4). Although Falkner's work involved investigating a sensory area, the concept of fano factor change after onset remains the same; And although mean matching was performed in Falkner's paper to remove the effect of change in firing rate mean in calculation of fano factor so that only the variance parameter remains the main factor, we haven't included mean matching in our paper, yet the fano factor decreases after onset and by looking at other results, the same effect would probably have been observed in fano factor fluctuation. Furthermore, our results showed that spikes are not neccessarily generated from a humongous Poisson process. It's been observed that interspike interval (ISI) distribution does not exactly follow an exponential distribution when we are close to zero. This is mostly caused by the refractory period and inactivated NA^+ channels. We see that gamma distribution may fit better to the histogram of ISI's. further study is essential to examine this claim to find a reasonable explanation of this distribution to be a gamma distribution and may need to design some biochemical experiments to see whether we can explain this observation by some biochemical process. Another interesting means to improve this observation is to find out what the spike generation process will be if the intervals are drawn from a gamma distribution.

Materials and Methods

The dataset used for this paper was gathered by Brochier T. et al using chronically implanted 10-by-10 Utah electrode arrays in the premotor area of the brains of a macaque monkey "monkey N" during an instructed delayed reach-to-grasp task (1). During a trial, the monkey had to grasp the object using either a side grip (SG) or a precision grip (PG). The PG had to be performed by placing the tips of index and thumb in a groove on the upper and lower sides of a cubic object, respectively. For SG, the tip of the thumb and the lateral surface of the other fingers were placed on the right and left sides of the object. The monkey had to pull the object towards him/her against one of two possible loads requiring either a high or low pulling force (HF and LF, respectively). As a result,

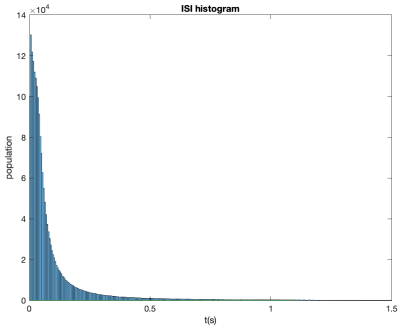


(a) Distribution of change in Fano factor after GO onset

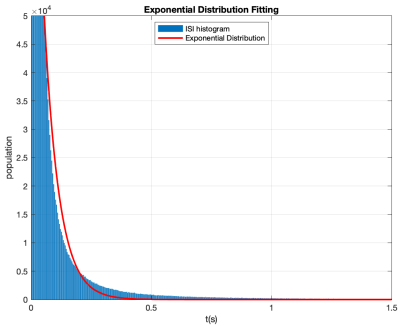


(b) Distribution of Fano factor before and after GO onset.

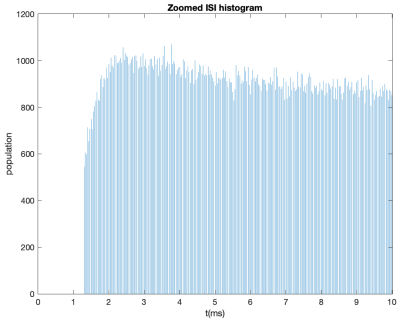
Fig. 6. GO onset Effects of Fano Factor.



(a) ISI Histogram.



(b) Exponential Distribution Fitted to ISI Histogram.



(c) ISI Histogram, Zoomed in.

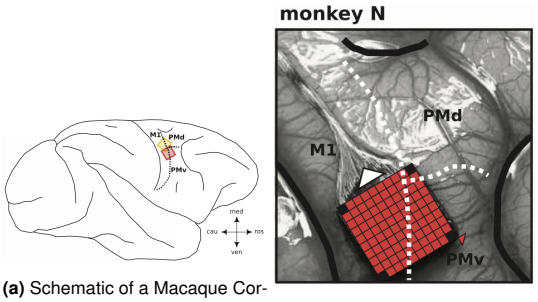
Fig. 7. GO onset Effects of Fano Factor.

from the possible combinations of grip types and object loads, the monkey had to perform in total four different trial types (SG-LF, SG-HF, PG-LF, PG-HF). In each trial, the grip and force instructions for the requested trial type were provided to the monkeys independently through two consecutive visual cues (CUE and GO) which were separated by a one second delay. Both cues were coded by the illumination of specific combinations of two LEDs of a five-LED cue panel positioned above the largest object. The providers performed also online spike waveform detection and classification controlled via the Central Suite software. The sorted spike times were stored in the data as well (which is the main data that we have used). The dataset also includes the times that each trial was executed in and each trial consists of several events: "TS-ON", WS-ON", "CUE-ON", "CUE-OFF", "GO-ON", "SR-ON", "RW-ON", "WS-OFF". Those events that were considered important and were used in the analysis provided in this paper are explained as follows: "TS-ON": The monkey has set its hand on the table and is ready for the trial to begin.
"CUE-ON": The CUE signal (used to identify whether the following task is of type PG or SG) is shown to the monkey.
"GO-ON": The GO signal (which is the last signal shown to the monkey before movement and is used to identify whether the following task is of type LF or HF) is shown to the monkey.
"SR-ON": The signal that comes from the table switch in which the monkey had rested its hand. When the monkey lifts its hand, the switch is released and a signal is received.
Figure 8 shows data set details.

Raster Plotting and PSTH calculation are two very common and helpful tools and methods used to analyze neuron behavior. Raster plot works by time-locking neuron spikes to a specified event and marking each spike observed in each trial with a dot; Therefore, one can easily understand that when the density of these dots in one area of the plot are higher than other areas, the neurons have higher firing rates during the event that happened around the mentioned area.

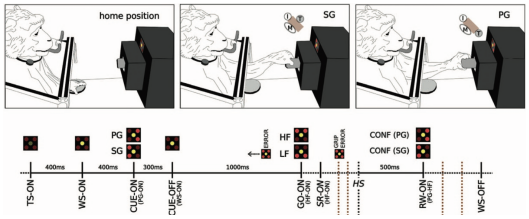
PSTH or Peristimulus time histogram is the histogram of the times at which neurons fire. This histogram is used to visualize the rate and timing of neuronal spike discharges in relation to an external stimulus or event. For PSTH calculation, we used the raster plots explained above, then convolved the vector associated with each trial with a rectangular window of size 1000 in samples (or $\frac{1}{30}$ in time) in order to calculate the firing rate of the neuron(s) during that specific trial.

To calculate and visualize the change in neurons' Fano factors after the selected event (the GO onset), we ran a loop on all neurons, in which we construct two vectors that one stored the spike data of the neuron from 0.1 seconds before the onset occurrence until onset occurrence and the other stored spikes data from onset occurrence up until 0.1 seconds after the onset occurrence. Then we calculate the PSTH of the neuron before and after the onset by convolving the two vectors with a rectangular window with length 1000 samples ($\frac{1}{30}s$). Then



(a) Schematic of a Macaque Cortex with Implant Location. The red area is for Monkey N.

(b) Exact location of the array for Monkey N.



(c) Experimental Apparatus and the Monkey Performing the Reach-to-Grasp Task.

Fig. 8. Dataset Details.

we choose responsive neurons by comparing the means of the two PSTH vectors and choosing neurons whose PSTH means increase after the onset (see Figure 6 (a)). Then we record the Fano factor of the two PSTH vectors by calculating $\frac{S^2}{\bar{X}}$, where $\bar{X}$ and S^2 are sample mean and sample variance of the PSTH vector we calculated before.

In this paper, we used T-test whenever we had a hypothesis to test. we used MATLAB's own ttest function. In this statistical test, the probability of the alternate hypothesis being true, given the empirical distribution of our data is calculated and a p-value is extracted; The smaller the p-value, the more the confidence of alternate hypothesis being true. In addition, a t-value is:

$$T = \frac{\bar{X} - \mu}{\frac{S}{\sqrt{N}}}, \text{where } \bar{X} = \frac{1}{N}\sum_{i=1}^{N} X_i, S^2 = \frac{1}{N-1}\sum_{i=1}^{N}\left(X_i - \bar{X}\right)^2 \quad [1]$$

are sample mean and sample variance of data. One can show that distribution of t-value is:

$$f(t) = \frac{\Gamma\left(\frac{\nu+1}{2}\right)}{\sqrt{\nu\pi}\Gamma\left(\frac{\nu}{2}\right)}\left(1 + \frac{t^2}{\nu}\right)^{-\left(\frac{\nu+1}{2}\right)}. \quad [2]$$

where $\nu = N - 1$ is the number of degrees of freedom and Γ is the gamma function.

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