博士論文

Role of Medial Frontal Areas in Tactics-Based Action Selection

(戦略に基づいた行動選択における内側前頭３領野の役割)

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Research Summary

Goal directed behavior results in selection of appropriate action for relevant sensory cues. This selection of action involves sensorimotor transformations by processing the relevant sensory information, maintaining in short-term memory and then its use to convert these sensory signals to final action. For efficient and prompt selection of action animals utilize "behavioral tactics" to achieve the objective of the goal. Though many studies pointed out the role of lateral prefrontal areas in goal directed behavior but role of medial frontal areas in goal oriented behavior is not clear. Medial frontal areas having strong connections with the lateral prefrontal cortex are also connected with primary and secondary motor areas. It is not clear how medial frontal areas influence downstream motor areas for action selection. In my research I proposed the working model for medial prefrontal cortex, comparison within medial areas and their respective roles for tactics-based action selection. Single cell neuronal recording was performed for the medial areas of pmPFC (posterior medial prefrontal cortex) which is the posterior part of dorsomedial prefrontal cortex, pre-SMA (pre Supplementary motor area) and SMA (supplementary motor area). These areas correspond to Brodmann area 6 and area 8 in human brain anatomy.

We trained monkeys for tactics-based action selection tasks. Designing of these cognitive tasks included two tactics. One tactic is "towards the target" and the other one is "away from the target". We separately examined the neural correlates of the selection of tactics and action, by temporally dissociating these two processes. My study included two experiments. In the first experiment, monkeys were trained to memorize the cued tactics which they later used to transform the location of a visual stimulus into the direction of arm reaching. After presenting the tactics cue and variable length of delay, either the left or the right push button was back-

illuminated. The monkeys reached either to the illuminated or the non-illuminated button depending on the memorized tactics. In the second experiment in addition to behavioral task used in experiment 1, I added new variation of the task where monkeys were first given location of the visual stimuli and after variable delay tactics cue was given. Monkeys remembered the location and integrated it with tactics cue to perform appropriate action. Neuronal activity was analyzed by epoch based and moving time window analysis. To study the temporal variance for behavioral factors of tactics, action and cue position in each time window, linear regression analysis was performed and CPD (coefficient of partial determination) value was calculated for each behavioral factor. Neuronal population analysis was done for both versions of the task to reveal how each medial area encoded behavioral factors across time and context.

For Experiment 1, I analyzed the data recorded in **(Matsuzaka et al., 2016)** study, included pre-SMA in my analysis and compared 3 medial areas (pmPFC, pre-SMA and SMA) for encoding of the behavioral factors. These three areas were not compared before. For Experiment 2, I contributed in designing of cognitive tasks, trained monkeys, performed surgery to install the recording chamber, did single-cell neuronal recording and analyzed the data.

My results indicated the cardinal role of pmPFC in tactics-based action selection task. I found spatial selectivity in medial prefrontal cortex area pmPFC that was not reported before. pmPFC neurons showed selective activity for the location of the visual stimuli as well as the direction of the reaching movements. On the other hand, the activity of pre-SMA neurons encoded the tactics and action but lacked the spatial information. Neurons in the SMA mainly encoded the monkeys' action. My findings also demonstrated that in the two experiments (tactics cue first and position cue first) it is only pmPFC that shows task dependent activity after the cue signal. There are separate sets of neuronal populations in pmPFC that encode the behavioral factors (tactics, action, and cue position) in context dependent manner. I propose rostral-caudal

gradient with pmPFC on top (encoding and integrating all behavioral factors) followed by pre-SMA and SMA.

Medial frontal areas are involved in sensory-motor transformation based on tactics in a hierarchical manner. Medial frontal areas contribute to flexible integration of behavior factors in adaptive environments. Present study shed light on contribution of medial areas in goal directed behavior and understanding of how various behavioral factors are encoded and communicated across brain regions.

Introduction

The frontal lobe of primates' brain is most extensively developed among animal species. Frontal lobe syndrome is characterized by the inability to plan **(Shallice and Burgess,1991;Carlin et al., 2000)**, organize and execute actions to achieve the intention **(Reber et al., 2017)**. The past 70 years' of psychological, anatomical and physiological studies using human subjects and non-human primates as animal models have revealed that the frontal lobe consists of multiple sub-areas each of which plays distinct roles in the guidance of goal-directed behavior (**Figure. 1**). Human subjects and non-human primates have homologous areas in medial frontal cortex that share common functionalities to certain degrees. Human fMRI studies showed that SMA plays a key role in time processing (**Macar et al.,2006**) and preferentially activated for different time intervals **(Protopapa et al., 2019)**. Time related activities were also reported in monkeys' SMA **(Mita et al.,2009)**. Human fMRI study **(Cunnington et al.,2002)** reported that neuronal activity in pre-SMA started earlier in the case of self-initiated movements then externally triggered movement. Pre-movement activities were also reported in pre-SMA of the monkeys **(Halsband et al.,1994)**. Learning a new procedure requires attention initially and then the process becomes automatic (Declarative stage to Procedural Stage) and pre-SMA was activated in the transition **(Sakai et al., 1998)**. Also in monkeys pre-SMA play an important role in switching from automatic to controlled action **(Isoda et al.,2007)**. In the recent literature it has been shown that pmPFC area in monkeys was activated during social interaction **(Falcone et al.,2017)**. In humans it has been reported that dorsomedial prefrontal cortex was activated in social behavior predicting others' belief **(Jamali et al.,2021)**.

Lesions in medial frontal areas can cause multiple disorders both in monkeys and human. SMA lesions in monkeys caused deficit in bimanual movements **(Brinkman,1984)**.

Monkeys performed poorly when they had to perform arbitrary actions without external guidance following lesions in SMA **(Thaler et al.,1995)**. Bilateral removal of SMA in humans can cause "akinetic mutism" **(Heiferman et al.,2014)**. Ablation of pre-SMA caused deficit in learning new sequential movements **(Nakamura et al.,1999)**. Damage to SMC (SMA and pre-SMA) in humans may cause "alien hand syndrome" where the affected arm made unintentional movements **(Della et al.,1991)**. Damages in SMC caused failure to suppress the actions in response to the prompt (**Nachev et al.,2008)**. Lesions in SMC can cause contralateral motor neglect **(Krainik et al.,2000**).

In this thesis, I presented two studies about the role of the medial frontal cortex in the guidance of voluntary actions based on response tactics (i.e internal protocol to select actions). The prefrontal cortex is typically suggested as an area anatomically located anterior to the premotor cortex and supplementary motor area. PFC can be divided into 2 generalizable regions depending upon anatomical connections, the medial prefrontal cortex (mPFC) and lateral prefrontal cortex (lPFC) **(Dan D Jobson et al., 2021).** The posterior part of dorsomedial prefrontal cortex known as pmPFC **(Matsuzaka et al., 2012)** that corresponds to Brodmann's area 8b is connected to the higher order motor cortical areas of pre-SMA, rostral cingulate motor area and dorsal premotor areas **(Takada et al., 2004)**. The area caudal to pmPFC, seemingly at the interface between prefrontal and motor systems, is known as Supplementary motor complex (SMC) **(Picard and Strick,1996)** that consists of two functionally distinct regions, pre-SMA and SMA **(Matsuzaka et al.,1992)**. Pre-SMA has extensive prefrontal connectivity **(Nachev et al., 2007)** and receive dense afferent connection from the pmPFC that is unlike SMA which has direct connections to the spinal cord, somatotopically organized and no prefrontal connectivity **(Luppino et al.,1993)**. Three areas we explored are pmPFC, pre-SMA and SMA. These anatomical relationships in medial frontal cortex resemble that of the

dorsolateral prefrontal cortex to the lateral premotor area, but the role of the pmPFC in the guidance of voluntary action was little understood.

Matsuzaka's group examined the role of the pmPFC, pre-SMA and SMA in the selection of response tactics and action **(Matsuzaka et al., 2012)**. Higher mammals can flexibly alter the protocol for action selection across various behavioral contexts **(Stokes et al., 2013)**. Such an ability is the basis of adaptive behaviors for which the prefrontal cortex plays a cardinal role **(Koechlin et al., 2016)**. Neurons in the pmPFC exhibited prominent activity modulation in synchrony with the animals' reaching movements when the task required rapid selection of the tactics. Strikingly, when only one tactic was presented for prolonged period of time (>two weeks), rendering selection of tactics unnecessary, such neuronal activity disappeared even though the monkeys were still required to select the action (i. e. the direction of reaching), These results indicated that the pmPFC plays a critical role in the selection of response tactics, not the action per se. In contrast to the pmPFC, neurons in the pre-SMA and the SMA exhibited task-related activity modulation irrespective of whether the task necessitated the selection of tactics or not. The above results demonstrated that the selection of the tactics and action are implemented by different neural networks.

The subsequent study **(Matsuzaka et al., 2016)** indicated that the pmPFC had separate populations of neurons which participate in the encoding, retention and utilization of the tactics to transform the sensory information into action. On the other hand, neurons in the SMA mainly encoded the monkeys' action. However, the role of the pre-SMA in this tactics-guided sensorimotor transformation remained unanswered. The known anatomical and physiological properties of the pre-SMA indicated that it would play a distinct role from that of the pmPFC and the SMA.

Further, it has been little understood how the neural network, which consists of a finite number of neurons, can perform a virtually limitless number of behavioral and cognitive tasks. Do individual neurons switch their representation of task-relevant information across different tasks? Or, alternatively, do dedicated sets of neurons participate in encoding of task-relevant information for each context? And does the switching of neuronal representation differ across cortical areas?

To address these questions, we conducted two studies. In the first study, we compared the neuronal activity during a tactics guided sensorimotor transformation task among the three medial cortical areas (pmPFC, SMA and pre-SMA). In the second study, we analyzed the neuronal activity in the above three areas while monkeys were performing two variants of tactic-based sensorimotor transformation tasks.

Materials and Methods

Animals and Experimental setup

Research work discussed in this thesis included two neurophysiological experiments (named as Experiment1 and Experiment2 respectively). In both experiments we used Japanese Macaques (a male weighing 9. 5 kg and a female weighing 6.5 kg respectively in Experiment 1; 3 males weighing 10.0 kg, 7.5 kg and 6.0 kg respectively in Experiment 2). All monkeys were cared for according to the guidelines by the National BioResource Project Japan and Animal Care Center of Tohoku University. During these experiments monkeys were seated in the primate chair. Left arm was restrained to the primate chair and monkeys performed behavioral tasks with their right hand. While the monkey was sitting in the primate chair, it faced the panel equipped with Light Emitting Diodes (LEDs) and two push buttons. In resting state, the monkey's right hand is on the hold button. Push buttons were on the left and right side of the panel and were back equipped with full-color LEDs. The panel also had the central fixation equipped with full-color LED. Monkeys were trained to maintain fixation until reward is delivered (0. 5s after the correct button press). Each trial started when the monkey pressed the hold button for 1s. The design of the panel is shown in **(Figure.2).**

Experiment 1

We named the behavioral task in experiment 1 as **tactics-only task**. This task was initially designed and used in the study **(Matsuzaka et al., 2016)** and neuronal data was recorded during that time. Trial started when the monkey pressed the hold button for 1s. After 1s the central LED is turned on as either cyan or blue color. This visual cue instructed the monkey about the forthcoming tactics. If the color of visual cue was cyan it means that monkey had to reach the

illuminated target (pro-reach) after the delay period with the onset of Go-signal. If the color was blue, the monkey had to move away from the illuminated target (anti-reach). The visual color cue stayed on for 0. 5s and then turned off. It was then followed by the variable delay of 1-1.5s. After the delay period either the left or right push button was back-illuminated in white color. At the same time 1kHz tone from the speaker was turned on to serve as a Go signal and prompted the monkey to initiate its arm reach movement. Monkey received the liquid reward by selecting the correct target based on the selected tactics (illuminated for pro-reach and non-illuminated for anti-reach) within 1s. Both the spatial cue and 1KHz tone turned off when monkey pressed either (left or right) button or time period of 1s has elapsed. After the delivery of the reward, the next trial started. Two monkeys used in this experiment had correct performance rate as (**Monkey F:** Pro-reach 82% Anti-reach 85% , **Monkey H:** Pro-reach 94% Anti-reach 91.5%) respectively. Trial was termed as erroneous trial if monkey did not select the correct target based on the selected tactics or did not initiate the movement within 1s time frame. (**Figure.3)**

Experiment 2

In experiment 2, we designed two sub tasks named as **Tactics pre-cued** and **Position pre-cued** respectively. The correct performance of the monkey in two tasks was **(Monkey A:** Tactics pre-cued 83% , Position pre-cued 81% , **Monkey B:** Tactics pre-cued 76% ,Position pre-cued 71% **)** respectively. Tactics pre-cued was largely similar to tactics-only task except we added 2 more color cues (red and green) in addition to the previous cues (cyan and blue). Two color cues (cyan and green) corresponded to pro-reach (towards the target) and the other two (blue and red) to anti-reach (away from the target) condition. Addition of two more colors made the

task more challenging and to see if multiple color association with a single tactic had any effect on the behavior of the monkeys.

Second behavioral task was **Position pre-cued**. In tactics pre-cued, tactics information was followed by spatial information. Here we reversed the timing of presentation of tactics and spatial information. Trial started when the monkey pressed the hold button for 1s. After 1s either left and right button is back illuminated in white color for 0. 5s that served as spatial cue and then turned off. Monkey had to remember this spatial cue information to use it for future action selection After the variable delay period of 1-1. 5s central LED is turned on in either of 4 colors (cyan, green, blue or red). If the color of the cue was cyan or green it corresponded to the pro-reach tactic and monkey pressed the previously illuminated button and if the color cue was blue or red, it corresponded to the anti-reach tactic and monkey pressed the previously non- illuminated button. This tactic cue and 1KHz tone served as Go signal, both turned off when monkey pressed either (left or right) button or time period of 1s elapsed. After the delivery of the reward, the next trial started. **(Figure.4)**

Surgical Procedure

At the end of the training, monkeys underwent surgery to install head implants for immobilizing their head during neuronal recording. Under anesthesia induced by ketamine (10mg/kg) and atropine sulphate (0.05mg/kg) and then maintained by isoflurane, their skull was exposed. Screws were implanted in the skull that served as anchors. The skull was then covered by dental cement, on top of which head holding devices were installed.

After the recovery period of two weeks, we re-trained the animals. When they became used to head immobilization, the second surgery was performed to install the chamber to provide access to the cortical areas. The skull over the target area was opened and the chamber (outer dimension 30mm x 40mm) was installed to cover the medial prefrontal cortex. The location

and extent of the skull opening (anterior border to the ear=A37, posterior border to the ear=A5, width = -12 to +12 mm from the midline) was carved on the dental cement covering the target area.

Neuronal Activity Recording

We used conventional glass-coated elgiloy electrodes (impedance = 0. 9-1. 2 M ohms at 1kHz) that were driven into the cerebral cortex by hydraulic manipulator (MO-81, Narishige Inc). Spiking activity of the neurons was amplified and band pass filtered at 300-3. 3 kHz and sorted through the multi spike detector (Alpha-Omega) in experiment 1 and RASPUTIN software (Plexon Inc) in experiment 2. The behavioral task and data sampling was controlled by Visual TEMPO (Reflective Computing Inc) in experiment 1. In experiment 2, behavioral task was controlled by real time Linux-based software and data was collected by Plexon. For each cognitive task (experiment 1 and experiment 2) neuronal recording continued for 8-10 months respectively to collect sufficient data for analysis. During training and recording sessions monkeys roughly worked for 1-1.5 hours varying with motivation level of monkeys. Usually in a single recording session we recorded 10-15 neurons depending on monkeys' task performance and penetration site. It took 3 years for experiment 1 and 4 years for experiment 2 to complete that included the time period for training, surgical procedures, recording and analysis of neuronal activity. While advancing electrodes if we find any task related neuron, to make sure the same neuron is recorded across different conditions we present the same behavioral condition twice separated by other behavioral conditions. In experiment 1, pro-reach and anti-reach conditions were pseudo-randomly determined while in experiment 2 we switched tactics pre-cued and position pre-cued task after every 40 trials. If activity became

inconsistent or the waveform of the neuron changed, we stopped recording that neuron and its data was not used in the analysis.

To determine the border between three medial areas, pmPFC, pre-SMA and SMA sensory responses were examined. Intracortical microstimulation (cathodal current:10-80 uA ,pulse width: 300 us, interval :3 ms,12-80 pulses) was done to examine the evoked movements. Somatosensory and visual responses in each penetration site were examined by touching the monkeys' body, manipulating the joints, and moving objects in the monkeys' visual field. Some sensory responses waned over time while others were consistent. We considered consistent responses only. In this way we defined the three medial areas as pmPFC, pre-SMA and SMA (spanning A25 -A45 in Horseley Clarke's co-ordinate system). **(Figure.5)**

Neuronal Database

We recorded 229 pmPFC, 149 pre-SMA and 114 SMA neurons from medial frontal cortex. These neurons were recorded from 2 monkeys for experiment 1 (tactics-only task). The selection criteria for analysis of neuronal activity was a sufficient number of trials (at least 5 correct trials in all the possible combinations of tactics and action selection). For experiment 2 (tactics pre-cued and position pre-cued) we recorded 132 pmPFC, 142 pre-SMA and 166 SMA neurons from one monkey. The other two monkeys that were trained for the task, one died of health related issues before the neuronal recording and the other was not able to learn the complete task even after the extensive training. The criteria for selecting a neuron for analysis was at least 5 correct trials in all possible combinations of tactics and action in the tactics pre-cued and position pre-cued task. In analysis we only considered the correct trials. We excluded error trials and also those trials in which monkeys made the correct response after pressing the wrong target. We checked for the error trials in both experiments.

Statistical analysis

We examined the neuronal activity both at the single neuron and population level. We divided the temporal activity of the neuron as cue period, delay period and response period. Activity before the cue signal called as pre-cue was taken as the baseline activity. Cue period activity was 500 ms after the cue onset, delay period activity as 500ms before the onset of Go signal. Response period activity was after the Go signal. We divided the response period activity into three epochs of 300 ms each as neuronal activity in the response period can be time locked with the onset of Go signal, release of the hold button and pressing the target. These 3 epochs were 300 ms after the Go signal, 150 ms before and after the hold release and 300 ms before the target hit. We calculated average firing rate in these three epochs for the individual neurons and for particular neuron only selected that epoch that gave the highest firing rate and named it as response period activity.

We used custom built software for offline inspection and quantitative analysis of neuronal activity. We defined behavioral factors as tactics (either pro-reach or anti-reach), action (left or right reach) and cue position (left or right). To examine the temporal dynamics of neural representations of behavioral factors, we used moving time window analysis of neuronal activity. In this analysis we counted action potentials within a small time window (width 200ms) starting 1s before and continuing 1s after the cue onset and 1s before and after the Go signal. These windows were shifted in step size of 20ms. We calculated the instantaneous firing rate (IFR) in each time window. We analyzed the IFR's dependence on the behavioral factors with the following linear regression model.

$$IFR(t) = a1(t)*Tactics+a2(t)*Action+a3(t)*Cue\ position +b(t)+e(t)----------(1)$$

Where IFR(t) is instantaneous firing rate at that particular time t, Tactics was either pro or anti-reach, Action was left or right arm reach and Cue position was either left or right illuminated button. a1(t), a2(t) and a3(t) were regression coefficients b(t) as y-axis intercept and $\varepsilon(t)$ was the residual error at time (t).

We then quantified the neuronal selectivity for each behavioral factor as the coefficient of partial determination (CPD). The CPD was defined as the percentage of variance in the dependent variable that is ascribable to the variance of the particular factor (e.g tactics). Therefore, the selectivity of neural activity for factor *X* at time *t* was defined as:

$$CPD(X,t) = (SSE_{partial}(t) - SSE_{full}(t)) / SSE_{partial}(t) \quad \text{----------(2)}$$

Where $SSE_{partial}(t)$ was sum of squared errors when factor *X* was absent from the regression model (1) and $SSE_{full}(t)$ was the sum of squared errors when all the factors were present in the regression model (1). We calculated the CPD for the behavioral factors of (tactics, action and cue position) for experiment 1 and (tactics, action, cue position, cue color and trial type) for experiment 2. In computing CPD for behavioral factors we treated them as independent signals because there was no one to one correspondence between them. The CPD value for any factor was not equal to the sum of other CPD values.

In order to quantitatively compare the ensemble coding of behavioral factors among cortical areas we calculated the mean value of CPD for the particular factor *X* (e.g. tactics) at time *t* in 3 medial areas (pmPFC, pre-SMA and SMA) by averaging the CPD of individual neurons in that particular neuronal population.

$$CPD\ mean(X,t) = \sum_{i=1}^{n} \mathrm{CPD}i(\mathrm{X},\mathrm{t})/(\mathrm{n}) \text{ ----------(3)}$$

where n is the number of analyzed neurons in each area, and CPD*i*(X,t) is the *ith* neuron's CPD for factor X at time t. We then calculated the deviation of this mean CPD (3) from the pre-cue baseline period.

$$\Delta CPD\ mean(X,t) = CPD\ mean(X,t) - CPD_{base}(X) \text{ ----------(4)}$$

$$CPD_{base}(X) = \sum_{i=1}^{n} \sum_{j=1}^{T} CPDi(X,tj)/(n*T) \text{ ----------(5)}$$

where T is the number of time windows belonging to the pre-cue baseline period.

To examine if neuronal activity for the behavioral factors (tactics, action, cue position, trial type and cue color) in post cue, delay and response periods statistically differ from their baseline levels we performed the permutation test. Null hypothesis stated that CPD values in the baseline period and those in the particular time period t, belong to the same group. To create a null distribution we randomly swapped CPD values at time period t (CPD (X,t)) and those in baseline period. This generated a surrogate data set, one for CPD values in the baseline period and one for the time window in consideration. We then used this surrogate data set to compute the difference between *'CPD mean(X,t)* and *'CPD base (X)*, that is Δ*'CPD mean(X,t).* We repeated this process 10,000 times to obtain the distribution of Δ*'CPD mean(X,t).* The *CPD mean(X,t)* was considered significant if it exceeds the 99 % confidence interval of the distribution of Δ*'CPD mean(X,t).*

In experiment 2, to examine the effect of behavioral factors on firing rate, we performed multivariate analysis of variance ANOVA using tactics, cue position, action and cue color as factors for as linear regression model might not properly represent the relation between the IFR and a categorical factor that takes more than 2 values (i.e cue color).

Finally, we examined if trial type (tactics pre-cued or position pre-cued) had an influence on the firing rate. With trial type and action as factors and firing rate as dependent variable we performed multivariate analysis of variance (ANOVA). We used sum squared error of the ANOVA to compute *CPD (X,t)* in experiment 2 as in the analysis of experiment 1.

Results

In all the monkeys, we successfully identified three cortical areas: SMA, pre-SMA and pmPFC. In the SMA, located most caudally among three areas, neurons had topographically organized somatosensory receptive fields, with hindlimb located most caudally followed by back, shoulder, elbow, hand, digits and face in caudal to rostral order. SMA neurons were unresponsive to visual stimuli. Furthermore, ICMS in SMA evoked bodily movements with relatively low threshold (up to 66 uA x 44 pulses). The pre-SMA, located anteriorly to the face region of the SMA, was characterized by neurons responsive to visual but not to the somatic stimuli. ICMS in this region hardly evoked movements. Further rostrally, neurons were unresponsive to visual or somatic stimuli. ICMS had no evoked movements. Neurons only activated during task performance, this area was identified as pmPFC **(Fig2B, Fig5).** These properties were consistent with the previously reported anatomical and physiological properties of the SMA, the pre-SMA and the pmPFC **(Matsuzaka et al., 2012; Matsuzaka et al., 2016)**. Number of neurons recorded in all monkeys were different but recorded neuronal population showed similar pattern of selectivity for behavioral factors (tactics, action and cue position) and we did not find individual difference among subjects.

Individual neurons in Experiment 1

We examined how behavioral factors (tactics, action, cue position) were encoded in individual neurons across three areas (pmPFC, pre-SMA and SMA). For single neuron analysis we analyzed the neuronal activity in cue, delay and response period epochs by multiple regression analysis (see Materials and Methods). In tactics selective neurons, tactics-selective activity can appear during the cue, delay or the response periods while the action-selective activity appeared exclusively in the response period, for the selection of action was possible only after the Go

signal. Additionally, in the pmPFC, neurons exhibited activity selective for the location of the visuospatial cue.

(Figure. 6) illustrates a typical example of such a cue-location selective pmPFC neuron. This neuron showed selectivity for tactics in the delay and response period. For action and cue position this neuron showed selectivity in response period only as this information was only available to the monkey after the Go signal. This pmPFC neuron was tactics selective (firing for antireach), cue position selective (firing for left cue) and action selective (firing for right reach direction).

On the other hand, in the caudally adjacent pre-SMA, few neurons had cue-location selective activity. Instead, their activity was selective for either tactics or action. Such an example of pre-SMA neurons is shown in **(Figure.7)**. This neuron encoded tactics (selective for pro-reach) before the Go signal. The increased firing rate and CPD value for tactics just before the Go signal depicted this neuron retrieved the tactics information stored in the memory and with the Go signal when the information for cue position was also available, tactics activity peaked. This neuron did not show cue position selectivity and there was no significant difference in firing rate between the left or right cue presentation. This pre-SMA neuron showed action selectivity by higher firing rate only for left reaching direction. This neuron was tactics and action selective.

Finally, the SMA neurons mainly represented the monkeys' action **(Figure.8).** Spike and rasters histogram showed that this neuron showed action selectivity in the response period. For tactics under both pro-reach and anti-reach conditions there was no differential neuronal activity in all epochs. This neuron also showed no preference for cue position. This neuron fired selectivity when the monkey reached for the left direction but no increase in spiking was

observed for the right reach direction. CPD analysis also confirmed that in response period action selection was prominent. This neuron can be called as pure action selective.

Neuronal population in Experiment 1

Analysis of individual neurons revealed that the selectivity for the behavioral factors was variable across neurons even in the same area. Therefore, for inter-area comparison of neuronal representation of behavioral factors, we computed the averaged CPD for the pmPFC, pre-SMA and the SMA (**Figure .9)**. We sampled 153 neurons from pmPFC and on population level tactics selectivity became prominent after the cue onset. This activity continued through the delay and response period. Each pmPFC neuron encoded tactics in a small time epoch and there seemed to be a different population of neurons that were selective for tactics during the early and late delay period. At population level, even with the Go onset this tactics selectivity remained prominent and there was a second peak after the Go onset. After that tactics activity started to decline. As cue position was available to the monkey with the Go onset, we examined peak value for cue position selectivity with Go signal. It was one small peak where the monkey encoded the cue position. Action selectivity was significant after the Go signal. Cue position peaked first followed by action selection. There was integration of tactics information and cue position signal and final action was selected.

pre-SMA neuronal population tactics selectivity was of the same pattern as we observed in pmPFC but pre-SMA lacked cue position selectivity. With the cue onset tactics selectivity started to increase and remained persistently high through the delay period. Each neuron encoded tactics in a small time window. pmPFC activity continued through the response period while in the case of pre-SMA this activity seemed to decline with the Go signal. Cue position selectivity was not persistent in pre-SMA, with the Go signal. Action was well represented in

pre-SMA. Persistent action selectivity occurred in pre-SMA during the response period. Action information in pre-SMA seemed to be maintained in all the sub epochs of the response period (post Go, hold-release,target hit).

Our third recorded area SMA was mainly action selective and did not show any persistent tactics or cue position selectivity at population level. There were few neurons that showed selectivity for tactics in the early delay and response period but we didn't see any peak for tactics selectivity. Action selection was very clear in SMA. Action selectivity started after the Go signal and remained persistently high through the response period. In contrast to pre-SMA and pmPFC action selectivity declined later in SMA. At population level action information is maintained throughout the response period in SMA (post-Go, hold release and target hit).

Overall at population level we saw a dynamical shift of behavioral factors where pmPFC encoded and integrated tactics and cue position information to determine the final action. pre-SMA encoded tactics as pmPFC but the pattern of tactics encoding was different from pmPFC. SMA had strong and persistent action information throughout the response period.

Individual neurons in Experiment 2

Experiment 2 had two versions. Tactics pre-cued and Position pre-cued (see materials and method) both included the same behavioral factors (tactics, action and cue position) involved. We examined that if a neuron encoded the same behavioral factor across different versions of the task. For example, if a neuron is selective for tactics in Tactics pre-cued task will it also be selective for Tactics in position pre-cued task. We found that the majority of pmPFC neurons that were selective for particular behavioral factor in one task were not selective in the other task.

(Figure.10A) showed a representative pmPFC neuron. This neuron showed selectivity for behavioral factors in response period in position pre-cued trials but not in tactics pre-cued trials. When trials were sorted for two versions of the task based on tactics, action and cue position respectively, in the response period this neuron showed tactics selectivity (anti-reach), action (left reach), cue position (right cue) in position pre-cued trials. In tactics pre-cued trials there is some neuronal activity related to tactics and action but it is not prominent as in position pre-cued. Cue position selectivity was only represented in position pre-cued trials. This representative neuron provided insight how in pmPFC a single behavioral factor be encoded in one version of task but not the other. In my thesis we termed it as "trial type" or "task dependent" selectivity. **(Figure.10B**) represents CPD analysis for a single neuron across two versions of the task. This neuron was strongly encoding behavioral factors in position pre-cued trials.

(Figure.11) showed an another representative pmPFC neuron. This neuron showed high firing rate in both tactics and position pre-cued trials. CPD analysis showed that in the case of tactics pre-cued trials the neuronal activity was related to tactics and in the case of position pre-cued trials activity was related to cue position. This neuron exhibited the property of the pmPFC neurons that encode typical behavioral factor in one task but not the both. It also shows how flexibly the pmPFC neuron changed from being tactics encoder to spatial position encoder depending on the task demands.

(Figure.12) showed a representative pre-SMA neuron. In tactics pre-cued trials this neuron showed a high firing rate after the cue presentation. The CPD value for tactics was high and it peaked after the cue signal. In the case of the position pre cued trials there was no prominent representation of either tactics, action or cue position. pre-SMA encoded tactics selectivity in the similar fashion as in pmPFC where each neuron encoded tactics in small time epoch. This pre-SMA neuron is trial selective as it was activated only in tactics pre-cued condition.

In our previous studies we found that SMA was mainly involved in action selection. The results for experiment 2 were consistent with our previous results. (**Figure.13)** showed a pure action selective SMA neuron. This neuron showed increased spiking activity after the Go signal. As expected, action selectivity appears only in the response period when monkeys chose the appropriate action based on selected tactics. In both tactics pre-cued and position pre-cued trials, CPD value of action was high and we saw the spiking activity after the Go signal. There is no elevated CPD value for tactics and cue position in any time epoch and these results generalized the behavior of SMA that was involved in action selection and not trial type selective.

Neuronal population in Experiment 2

As in experiment 1, we computed mean CPDs of the tactics, action, cue position and cue color for comparison between the cortical areas because neurons in each area exhibited diverse representation of these behavioral factors. In all the medial areas and in both versions of the task the neuronal representation of action selectivity appeared during the response period as for the design of the behavioral tasks allowed the monkeys to select the action only after the Go signal. On the other hand, neural representation of cue position and tactics selectivity differed among the cortical areas.

Tactics pre-cued task in experiment 2 that was identical to experiment 1 except addition of 2 more colors as tactics cues, pmPFC neuronal population showed similar pattern of activity as in experiment 1. **(Figure.14)** shows pmPFC neuronal population in two versions of experiment 2. Tactics selectivity in pmPFC started during early delay period and was persistently high through late delay and response period. Cue position selectivity appeared after the Go signal when visuospatial cue was given to the monkey. We also examined if neuronal activity was modulated with any color (cyan, green, blue or red) of the tactics cue. We found no cue color related activity in pmPFC.

In **position pre-cued task,** the pmPFC neuronal population showed selectivity for tactics in response period as this information was provided with the Go signal. Cue position representation was significant in the early delay period with the spatial cue onset. Cue position selectivity remained significant throughout the delay period as the monkey retained this information for the future action selection. Action selectivity happened in the response period. Overall, pmPFC was encoding tactics in tactics pre-cued and cue position in position pre-cued in a persistent manner.

(Figure.15) illustrates pre-SMA neuronal population activity in experiment 2. pre-SMA encoded tactics in **tactics pre-cued task**. Tactics activity became significant for a short time interval after the cue onset then remained persistently low throughout the delay period and it became significant during the response period again. We observed little cue position selectivity in the response period. Cue position became significant for a short time interval but we didn't have any peak as in the case of pmPFC. Action selection was prominent in the response period. Pre-SMA did not encode tactics and cue position in **position pre-cued task** and their CPD values remained within the chance level. Action selectivity was prominent after Go signal but in contrast with pmPFC that had sustained activity for action in position pre cued task, pre-SMA activity declined earlier. There was no neuronal activity related to cue color in pre-SMA.

SMA was mainly involved in action selection. **(Figure.16)** shows SMA neuronal population activity in experiment 2. In tactics pre-cued task SMA did not encode tactics in the delay period. There was little tactics related activity in SMA in response period but this activity was not persistent as in pmPFC and pre-SMA. Persistent cue position selectivity was also absent. Action presentation was quite notable and maintained throughout the response period in the epochs of post-Go, hold release and target hit. In **position pre-cued** task SMA did not encode tactics and cue position in the delay and response period. Unlike pmPFC and pre-SMA action

selection in position pre-cued task had more ramp-like behavior. Activity started to increase in the early response period and peaked in the late response period. There was no cue color selectivity in SMA.

Trial Type selectivity in Medial Frontal Areas

We examined the influence of trial type (tactics pre-cued or position pre-cued) selectivity in the medial frontal cortex for experiment 2. In both versions of the task in experiment 2, trial type and action selection were temporally similar as in both action happened in response period and once trial type is decided with cue onset it remained similar throughout the trial.

(Figure .17) showed medial frontal areas neuronal populations for the behavioral factors of trial type and action selection. pmPFC activity started to ramp up even before the cue onset as if the monkey was expecting which trial type would appear. On cue onset the monkey got information that if the trial type was tactics pre-cued or position pre-cued. Trial type activity remained within chance level before the cue signal and became significant only after the cue onset in pmPFC. During the early delay period a small peak appeared then this activity tended to decrease. In the late delay period trial type activity ramped up again as if monkey was reinforcing its belief about the trial type. All along the response period trial type activity remained high. It seemed pmPFC was activated for trial type with cue onset when the initial cue signal was decisive on which type of the trial would appear. With the Go signal monkey had to implement his action plan based on tactics or position information. For action selection there was a peak in response period as expected.

For pre-SMA the trial type selectivity was not above chance level during cue and delay period. This activity remained insignificant until the start of the response period when the monkey started performing action based on tactics. Few milliseconds after the Go signal, the trial type

selectivity becomes significant and then remains high during the response period. SMA showed peak in trial type activity only in the response period. SMA showed more similarity to pre-SMA in action selection.

Overall our results suggested that only pmPFC encoded the trial type information after cue signal and during delay period.

Same or Different Neuronal Population

We examined how the medial frontal neurons behaved across two different sub tasks (tactics pre-cued and position pre-cued) in experiment 2. Although the timing of presentation of tactics cue and spatial cue was different, the behavioral factors (cue position, tactics and action) were the same across two tasks. We analyzed neuronal activity in the response period only where behavioral factors were similar across two versions of the task. We found the majority of pmPFC neurons encoded particular behavioral factor in one version of the task but not the other. All of the pmPFC neurons encoded cue position in one version of the task only. 70 percent of pmPFC neurons encoded tactics in one version task but not the other. 75 percent of pmPFC neurons encoded action in one version of the task only. These results suggested separate neuronal populations exist in pmPFC that encode behavioral factors in each of the sub tasks. (**Figure .18)** showed Venn diagrams for the number of pmPFC, pre-SMA and SMA neurons that showed selectivity for tactics, action or cue position in the response period for two versions of the task in experiment 2. The number of cue position selective neurons were abundant in pmPFC as compared to pre-SMA and SMA. SMA was mainly action selective. These results were consistent with our previous publication.

Error Trials

We checked the error trials in both experiments. As monkeys were proficient in the task and in single neuron number of error trials in comparison to the correct trials were very few we were not able to make an elaborative statistical analysis. However, we found a good example that showed how neuronal activity changed in error trials. (**Figure .19)** shows the neuronal activity in error trials for a pre-SMA neuron where monkey mistakenly perceived the cued tactics. In correct trials this neuron showed selectivity for pro-reach condition but in the error trials the same neuron showed increased firing for the anti-reach condition.

Discussion

Our results showed that in our recorded medial frontal areas (SMA, pre-SMA and pmPFC) only the pmPFC encoded cue position selectivity. We found that tactics were encoded by both pmPFC and pre-SMA. In pmPFC individual neurons encoded tactics in different time epochs, and maintained the tactics information as a whole throughout the delay period. SMA mainly participated in action selection. In experiment 2, we found that only pmPFC encoded information about the trial type (either tactics pre-cued or position pre-cued) during the delay period. As monkeys were performing two similar tasks with different context in experiment 2, we found that pmPFC neurons encoded particular behavioral factors (tactics, action or cue position) in one task but not the both.

Main Questions

We were interested in tactics-based action selection and role of medial frontal areas in encoding these behavioral factors. Our target areas were post medial prefrontal cortex (pmPFC), pre-Supplementary motor area (pre-SMA) and Supplementary motor area (SMA). In this study we discussed three behavioral tasks in total. In **experiment 1** (Tactics-only task) the tactics cue and action selection were separated by the delay period while in **experiment 2** we further had two versions. The first subtask (tactics pre-cued) was quite similar to the tactics-only task but here we added two more colors for tactics cue (one for pro-reach and one for anti-reach) and tactics information preceded the position signal similar to experiment 1. The addition of two more colors provided the more compelling evidence that this neuronal selectivity in these medial areas are not because of the color of cues but because of the tactics selection. In experiment 2, two colors (cyan and green) cued the pro-reach tactic and two colors (blue and red) cued the anti-reach tactics. We did not find any color selectivity in single neuron or

population level in all 3 medial areas. In second subtask (position pre-cued) we reversed the order of presentation of the tactics-cue and position cue. For details see (Materials and Methods). Our main questions were how a single neuron in the medial frontal cortex encoded the behavioral factors of tactics, action and cue position. We also wanted to explore if there were any differences or similarity in neuronal population activity of pmPFC, pre-SMA and SMA. We wanted to examine that if we reverse the presentation of tactics and position cues do neurons encode the same behavioral factors across two versions of the same task. It is also important to know how neuronal activity changes through different phases of training. I only recorded the neuronal activity when monkeys fully learnt the task and became proficient (over-trained). As monkeys were trained on the cognitive task step by step, we hypothesize in the initial phase of the training when monkey was selecting target based on simple Stimulus-Response association neural activity would have appeared in both SMA and pre-SMA. Learning new sequential movements activated the pre-SMA **(Hikosaka et al.,1996)**. Pre-SMA also has role in forming the visuo-motor associations **(Sakai et al.,1999)**. SMA has an important role in the performance of the motor tasks **(Tanji,1994)**.

When monkey learned "one tactic" either pro-reach (towards) or anti-reach (away) neuronal activity related to tactics would have become more prominent in pre-SMA. In the next phase when monkey learnt "two tactics" and pro-reach and anti-reach condition were mixed neuronal activity in pmPFC became prominent. In over-trained monkeys tactics activity appeared both in pmPFC and pre-SMA.

pmPFC Cardinal Role

In our results pmPFC played the pivotal role in encoding the behavioral factors. For a correct action selection integrating tactics and spatial information was necessary and pmPFC was

responsible for this integration. One study (**Ferrucci et al., 2022)** suggested the more flexible coding of pmPFC neurons in comparison with other premotor areas. Adjacent premotor area pre-SMA has an intermediate role that encodes tactics and action but not cue position. SMA was action selective only. In this way we found a hierarchical gradient of functionality from rostral to caudal axis with pmPFC at the top of the hierarchy followed by pre-SMA and SMA. In pmPFC there was a separate set of neuronal populations that encoded particular behavioral factors across two versions of the task. Although in both versions (tactics-pre-cued and position pre-cued) the behavioral factors were the same i.e tactics, action and cue position but most of the pmPFC neurons encoded behavioral factors in one condition but not the other. One study (**Luk and Wallis.,2009)** proposed role of medial prefrontal cortex in encoding information related to the task and separate neuronal populations encoding the response and outcome. We found the trial type selectivity was specific to pmPFC. This trial type selectivity started during the post-cue and continued through delay and response periods.

Tactics Selectivity or Alternative Hypotheses

pmPFC was activated and encoded behavioral factors when monkeys performed pro-reach (towards the target) and anti-reach trials (away from target) intermixed but not when monkeys performed only pro-reach or anti-reach trials. When pro-reach and anti-reach trials were mixed, monkeys had to respond promptly by selecting the required tactic (towards or away). This selection of tactic was not required while performing pro-reach only or anti-reach only trials in which monkeys always either move towards or away from the illuminated button. An alternative hypothesis could be that there is no tactics selectivity and monkeys select the target based on color cues and the stimulus position but this hypothesis is unlikely because as monkey became proficient in the task the reaction times between pro-reach and anti-reach conditions became negligible **(Awan et al.,2020; Matsuzaka et al.,2012)** and they attained the behavioral

condition where they utilize tactics to promptly select the action. The tactics selectivity in the pmPFC area appeared only in the case when pro-reach and anti-reach trials were mixed. If monkeys were choosing action based on color and stimulus position, there should be no disappearance of activity in pmPFC in the case of pro-reach or anti-reach only condition. Finally, previous studies never reported the neuronal activity in pmPFC for color conditional motor tasks. One study **(Matsuzaka et al.,2012)** showed that when selection of tactic was made the reaction times were few milliseconds longer than when no selection of the tactic was made. Another question arises how this tactics selectivity is different from "Interference Resolution". In interference resolution there is response conflict and two potentially relevant sensory information are available (e-g Simon conflict task). In interference resolution activity for the relevant stimulus is enhanced and for the irrelevant stimulus is suppressed. In my study in each trial, the relevant tactics cue was specified there was no conflict between pro-reach and anti-reach in the single trial. In previous study neuronal activity was also recorded from anterior cingulate cortex but didn't find any tactics related activity **(Matsuzaka et al.,2012)**. Interference resolution results activity in cingulate cortex, an area responsible for conflict monitoring and in interference resolution there is decrease in performance in the case of incongruent trials but in my study performance was comparable between pro-reach and anti-reach trials. In this way tactics selectivity hypothesis is different from interference resolution. In addition to tactics selectivity these areas were also involved in action selection. In previous studies both tactics and action selection occurred during the response period and the question remained that if tactics selection is independent of action selection. Later studies **(Matsuzaka et al.,2016)** introduced the delay period and tactics cue presentation was temporally separated from action selection and showed that tactics selectivity occurred independently from action selection.

Dynamic and Flexible Coding

Our results indicated more dynamic and flexible coding in pmPFC. Our cognitive task included three main behavioral factors including tactics, action and cue position. Individual neurons in pmPFC and also at population level encoded tactics during the epochs of delay period and response. Action was encoded after the onset of the Go signal. Mixed selectivity is an important feature of PFC. These high dimensional neuronal representations encode all task-relevant information and their combinations. From a computational perspective mixed selectivity is central to complex behavior and cognition **(Rigotti et al., 2013)**. Single neuron encoding the behavioral factors of tactics, action and cue position or their combinations provided the computational advantage over single neurons encoding single behavioral factor. We proposed that neurons in medial frontal areas encoded behavioral factors in mixed fashion. Medial frontal neurons also showed property of sensorimotor transformation. An individual neuron encoded behavioral factors of tactics (tactics pre-cued task) or cue position (position pre-cued task) in the delay period and action selection in the response period playing a role in transformation from the information representing tactics or spatial position to the information representing action selection. Various studies have proposed the role of the prefrontal cortex in sensorimotor transformation. One study **(Takeda et al., 2002)** suggested the role of the prefrontal cortex in the transformation of information from sensation to the motion signal. Another study **(Amemori et al., 2006)** proposed that neurons in the frontal cortex change their pattern of activity depending on the behavioral rule to guide action.

Difference between medial areas

Another important question arises: what is the difference between these adjacent areas of pmPFC, pre-SMA and SMA? The present studies found that neuronal populations in three

medial frontal cortical areas were involved in different processes of sensorimotor transformation when using multiple tactics. The present study indicated that the pmPFC encoded relevant sensory information (i. e., cue location) in addition to tactics and action and that this information was absent in the pre-SMA and the SMA. We also found trial dependent selectivity in pmPFC during the delay period which was not represented in pre-SMA and SMA. Anatomical studies have indicated that the primate PFC receives afferent projections from higher-order sensory association cortices in which peripheral sensory information is integrated to reconstruct internal representations of the behavioral context **(Rao et al., 1997; Fuster, 2000, 2015; Wallis and Miller, 2003).** Additionally, the PFC is one component of a supervisory attentional system **(Norman and Shallice, 1986)** that contributes to the evaluation and the selection of information relevant to the guidance of purposeful behaviors **(Stuss, 2011).** Consistent with these previous findings, the present results showed that neuronal representations of tactics, action, and cue position were present in the pmPFC. Efferent projections from the PFC are directed to cortical motor areas, particularly rostral motor areas such as the pre-SMA, rostral premotor areas, and rostral cingulate motor area **(Tanji and Hoshi, 2008).** In contrast, caudal motor areas, including the SMA, receive few, if any, projections from the PFC, which instead heavily project to the primary motor cortex and the spinal cord **(Luppino et al., 1993; Dum and Strick, 1996).** Thus, the presence of tactic-related representations in the pre-SMA and the predominance of action representation in the SMA likely reflected their distinct afferent and efferent projection systems.

A notable difference between the pmPFC and the pre-SMA observed was the presence of cue position representations in the pmPFC and their absence in the pre-SMA. Previous studies have shown that neurons in the pre-SMA exhibit spatially tuned activities during arm reaching movements done either in prescribed orders **(Nakamura et al., 1998; Akkal et al., 2002)** or to a chosen target **(Hoshi and Tanji, 2004).** Furthermore, anatomical studies found that the pre-

SMA receives an abundance of afferents from the PFC **(Luppino et al., 1990, 1993)**, a region where neurons exhibit spatially tuned visual responses **(Goldman-Rakic, 1995)**. The present finding that pre-SMA neurons have little visuospatial information representation seems to contradict these past studies.

This discrepancy would be ascribable to the requirement for the selection of tactics and the involvement of the pmPFC in our study. In previous studies, the protocols to select appropriate actions were invariant even though the task called for the selection and the execution of actions on trial-by-trial basis. Under such condition, the pmPFC would not participate in the regulation of voluntary behavior **(Matsuzaka et al., 2012)**. The involvement of the pmPFC in tactic-based sensorimotor transformation in the present study may have relieved the pre-SMA of the need to process the spatial information provided by the visual cue. The anatomical relationships between the parietal association cortex and the frontal cortex would be relevant to this interpretation. Although the pre-SMA receives dense projections from the PFC, direct projections from the parietal association cortex to the pre-SMA are sparse **(Luppino et al., 1993)**. This finding suggests that spatial information sent to the pre-SMA is gated by the PFC. In support of this interpretation would be the view that the pre-SMA function is dynamically controlled by the PFC **(Picazio et al., 2014)**. It is also noteworthy that the hypoactivity in the PFC of schizophrenic patients is accompanied by increased compensatory activity in the pre-SMA, which suggests that normal functioning in the PFC represses downstream motor areas in healthy brains **(Cieslik et al., 2015)**.

Similarity between medial areas

In addition to the difference between the pmPFC and the pre-SMA, the present study also demonstrated a striking similarity between these areas. We found tactics information not only

in pmPFC but also in pre-SMA. One interpretation of our findings is that pre-SMA might be involved in encoding and maintaining tactics but not in utilizing tactics, and pmPFC plays a supervisory role over pre-SMA. pmPFC might be involved in the "dynamic monitoring" of tactics. If multiple tactics are involved in behavior, pmPFC would play a supervisory role and integrate all relevant sensory information, including cue position. Pre-SMA would then be "unburdened" from integration of tactics and cue position **(Koechlin and Summerfield, 2007)**. Pre-SMA still plays an important role in implementing action by following determination of action in pmPFC. Finally, SMA is recruited in the execution of action with pre-SMA. The finding that some SMA neurons represented tactics by their activity is consistent with our previous report **(Matsuzaka et al., 2012)**, but such neurons were not prevalent. Consequently, at the population level, SMA failed to retain tactics information until the response like in pmPFC and pre-SMA. Once action execution starts, pmPFC would cease to supervise and control is shifted to lower motor areas. In our previous study, we found that the dynamic alterations of action selectivity in SMA depend on the demand for tactics **(Matsuzaka et al., 2013)**. Following this line of interpretation, pre-SMA shows dynamic alterations of visual cue selectivity depending on the demand for tactics. Based on current and previous findings, we call this process "dynamic supervisory control" by a hierarchically ordered shift of control from the rostral to the caudal medial frontal areas **(Norman and Shallice, 1986)**.

Medial Prefrontal Social Context

The medial prefrontal cortex of primates has been recently implicated for decision making and the evaluation of the outcome of one's and other individual's action under social context **(Yoshida et al., 2011, 2012; Noritake et al., 2018)**. A quantitative comparison of the neurons in the pmPFC, the pre-SMA, and the SMA revealed that only the pmPFC contained a special group of neurons whose activity was predictive of the other agent's intention **(Falcone et al.,**

2017). Regulation of voluntary behavior while interacting with other individuals requires flexible switching of protocol for action determination. The present studies would shed light on a significant contribution of this area during social interactions when the tactics of behavior change dynamically.

Context Dependent Selectivity

We also found the trial type or context dependent selectivity in pmPFC in the delay period. Lateral Prefrontal cortex has long been thought for its role in context dependent, flexible control system and associate response-outcome **(Tsujimoto and Sawaguchi.,2004)**. Prefrontal cortex is important for processing cognitive context which gives information about the task situation. **(Watanabe and Sakagami.,2007)**. One Study **(Assad et al., 2000)** reported that when monkeys were trained to alternate between different tasks many neurons in the prefrontal cortex were task dependent. Medial prefrontal cortex studies for context dependency are scarce but our study pointed out the role of medial prefrontal cortex (pmPFC) in trial type selectivity. Another study **(Ramawat et al., 2022)** reported that PFC encodes more abstract variables like task difficulty while PMd manages task variables related to motor preparation. A plausible explanation of this activity in pmPFC but not in the adjacent areas of pre-SMA and SMA as pmPFC being the part of PFC and has connections with DLPFC and no connections with PMd while SMA and pre-SMA have direct connections with PMd.

Conceptual Model

We developed the conceptual model where we proposed the working mechanism of medial frontal areas **(Figure .20)**. The dorsolateral prefrontal cortex has connections with the parietal association cortex and Inferotemporal- area (IT) area in the temporal cortex. Parietal area is

known for coding spatial position **(Chafee et al., 2007)** and the Inferotemporal area for encoding the color information **(Koida et al., 2007)**. According to our model these task relevant information was then processed by DLPFC and contextual information about the task sent to pmPFC and pre-SMA. pmPFC then integrated task relevant sensory information, made selection of tactic and calculated the final action. We found trial dependent or context dependent selectivity in pmPFC and there exists well established criteria that this activity being present in dLPFC. We found that in addition to dLPFC this context dependent selectivity was also present in pmPFC but we still don't know the origin of this activity. pre-SMA had an intermediate role. It encoded tactics and final action communicated by pmPFC. pre-SMA then influenced SMA to take final action which further activates lower motor areas for the movement execution. We proposed two-way communication between lateral and medial prefrontal cortex where lateral provided all the contextual information and medial informed lateral about the chosen tactics to further guide the behavior.

Limitation of studies and future direction

In all our task designs we dealt with two tactics, towards and away from the target. A future study design that include more than two tactics, it would be interesting to know how the medial prefrontal cortex will behave. We mainly recorded from 3 areas pmPFC, pre-SMA and SMA, these areas are most important in the study but by recording from dorsolateral prefrontal cortex that has direct connections to pmPFC and pre-SMA will shed light that if dorsolateral prefrontal cortex encode tactics or not. We have a wealth of knowledge that this area encodes abstract rules but we have no information about tactics encoding in this area. In some sessions we recorded simultaneously from two areas as we were able to control a maximum of two electrodes, multiple channel recording using electrode arrays from medial, lateral and premotor

areas will help to find where neuronal activity for tactics selection, spatial position and action selection originate.

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Figure .1

Medial frontal Areas in Human and Monkeys' brain

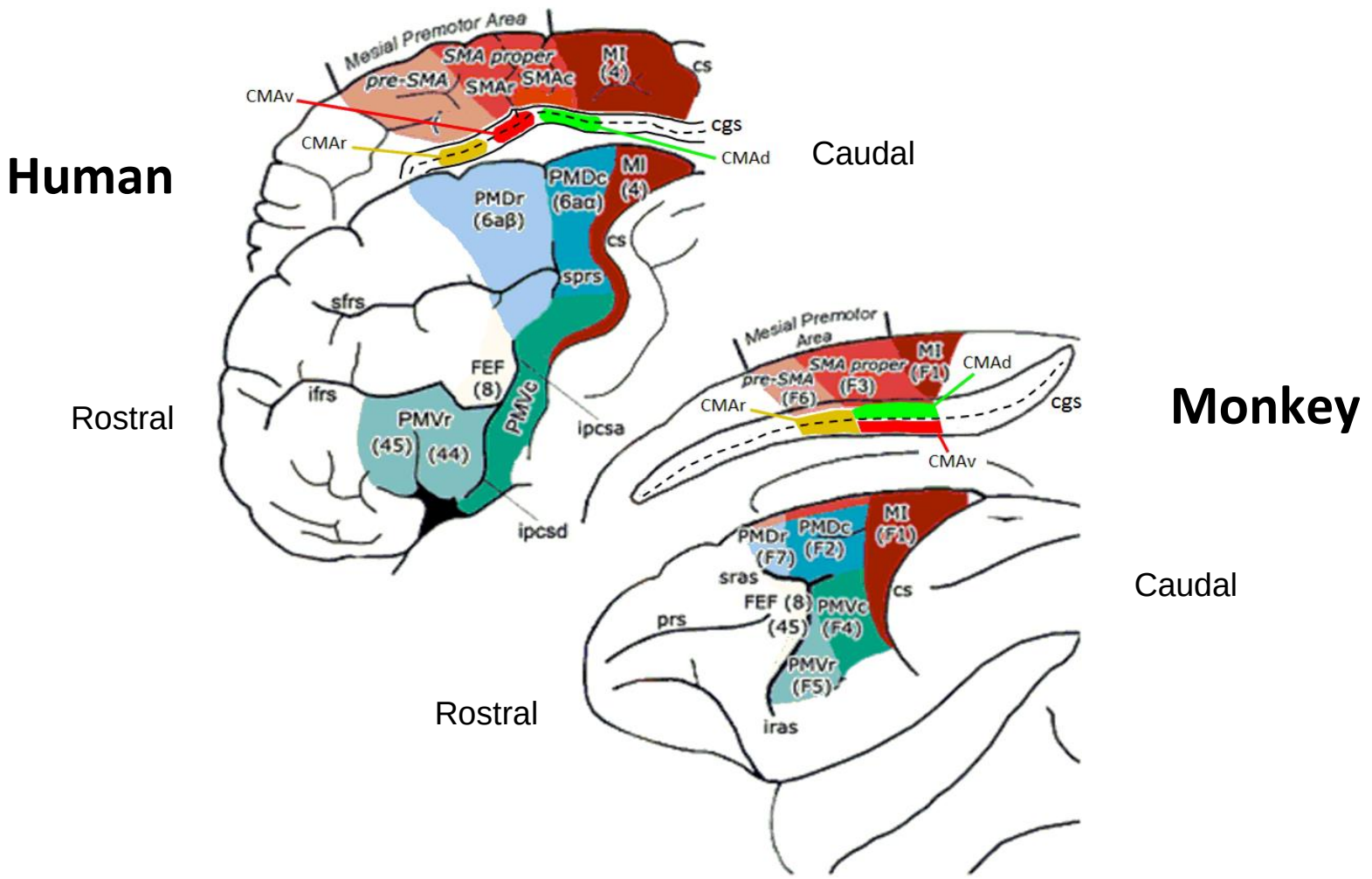


Figure 1. Cortical motor areas in human (upper left) and macaque (lower right) frontal lobe **MI**: primary motor cortex; **SMA**: supplementary motor area; **pre-SMA**: presupplementary motor area; **PMDr, PMDc**: rostral and caudal part of the dorsal premotor area; **PMVr**, **PMVc**: rostral and caudal part of the ventral premotor area; **CMAr, CMAd, CMAv**: rostral, dorsal and ventral cingulate motor area; **FEF**: frontal eye field; **cs**: central sulcus; **cgs**: cingulate sulcus. Symbols in parenthesis are the histologically defined cortical areas either by Brodmann's (numbers) or Rizzolatti's nomenclature (F1 - F6). (Brain Science Dictionary. DOI：10. 14931/bsd. 973).

Figure .2

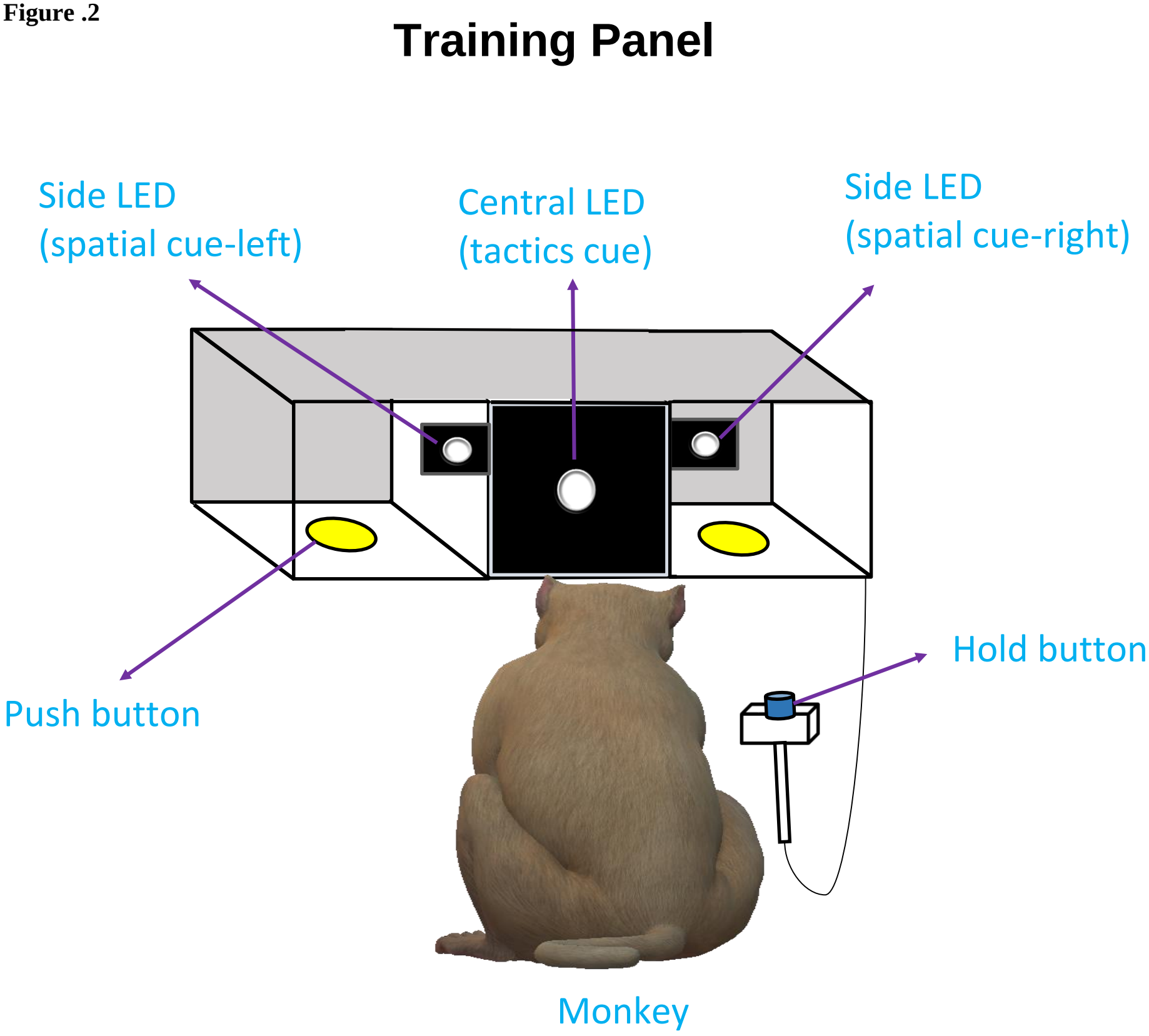
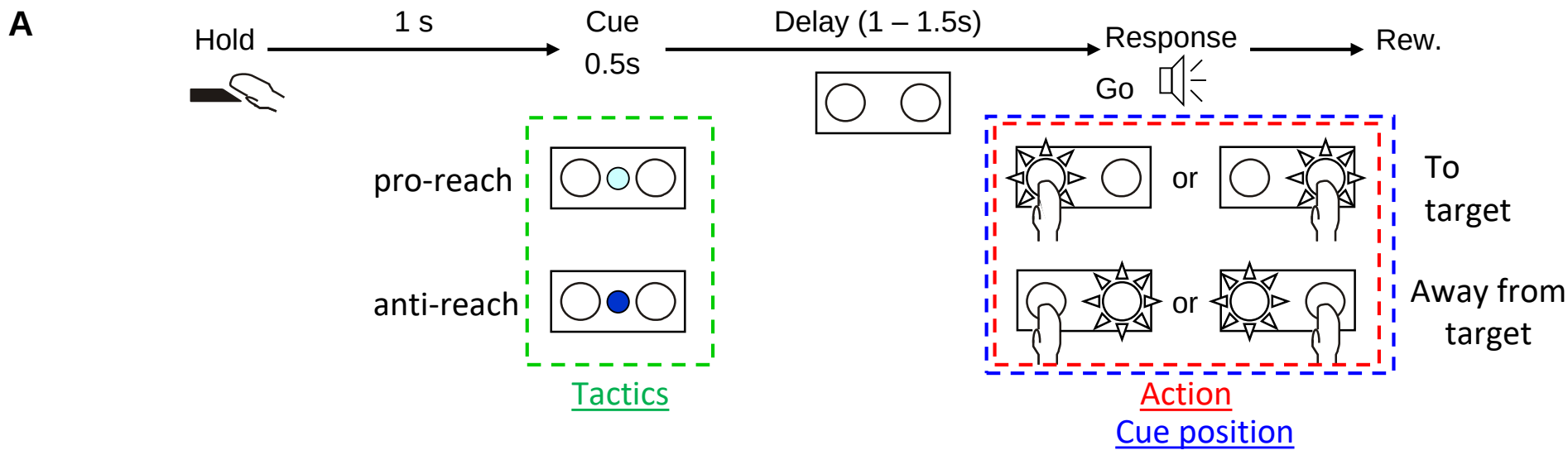


Figure 2. shows panel used for training of monkeys on tactics-based action selection tasks. It is equipped with a hold button (blue color) and two push buttons (yellow color). The panel was equipped with central LED where tactics cue was presented. Push button were also equipped with full color LED where spatial cue was given shown in the figure as Side LED (left and right side). For details see (materials and methods)

Figure .3

Experiment 1



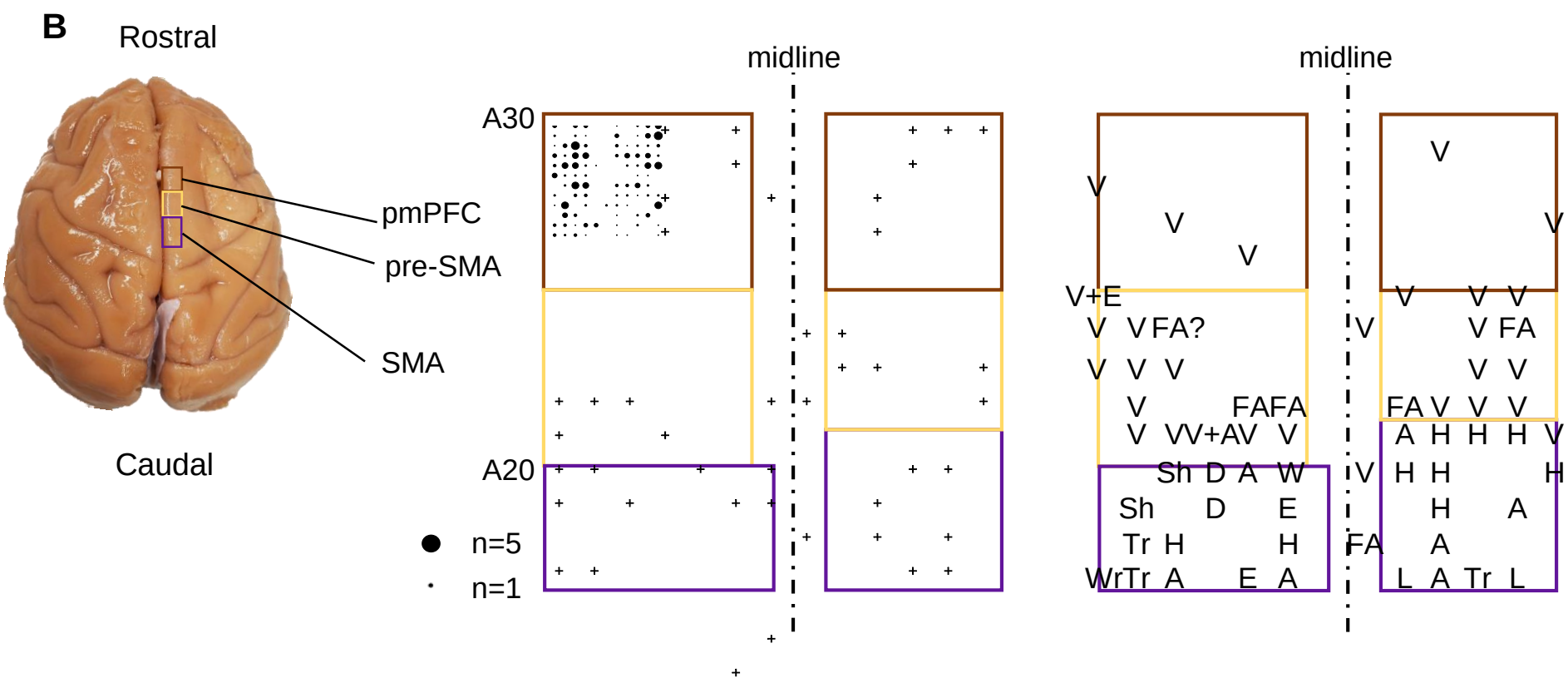


Figure 3. **Task design 1** and map of the three cortical areas. **(A)** Behavioral task. A trial started when the monkey pressed the hold button for 1s, and the center color cue was turned on for 500 ms. The color cue instructed which tactics would be necessary for the subsequent reaching movement (cyan for pro-reach and blue for anti-reach). The cue was followed by random delay varying from 1 to 1.5 s. At the end of the delay, either the left or the right push button was back-illuminated by a white light-emitting diode, and the go signal (1 kHz beep tone) was simultaneously turned on, prompting the monkey's response. The monkeys received a liquid reward for reaching toward (pro-reach) or away from (anti-reach) the appropriate illuminated button. **(B)** Left: illustration of the locations of the three cortical areas (posterior medial prefrontal cortex, presupplementary motor area, and supplementary motor area). Middle: distribution of one monkey's task-related neurons. The size of the filled circles represents the numbers recorded in individual penetrations, and the cross signs represent the penetrations where no task-related neurons were recorded. Right: sensory response maps. A, arm; D, digits; E, elbow; FA, face; H, hand; L, leg; Sh, shoulder; Tr, trunk; Wr, wrist; and V, visual.

Figure.4

Experiment 2

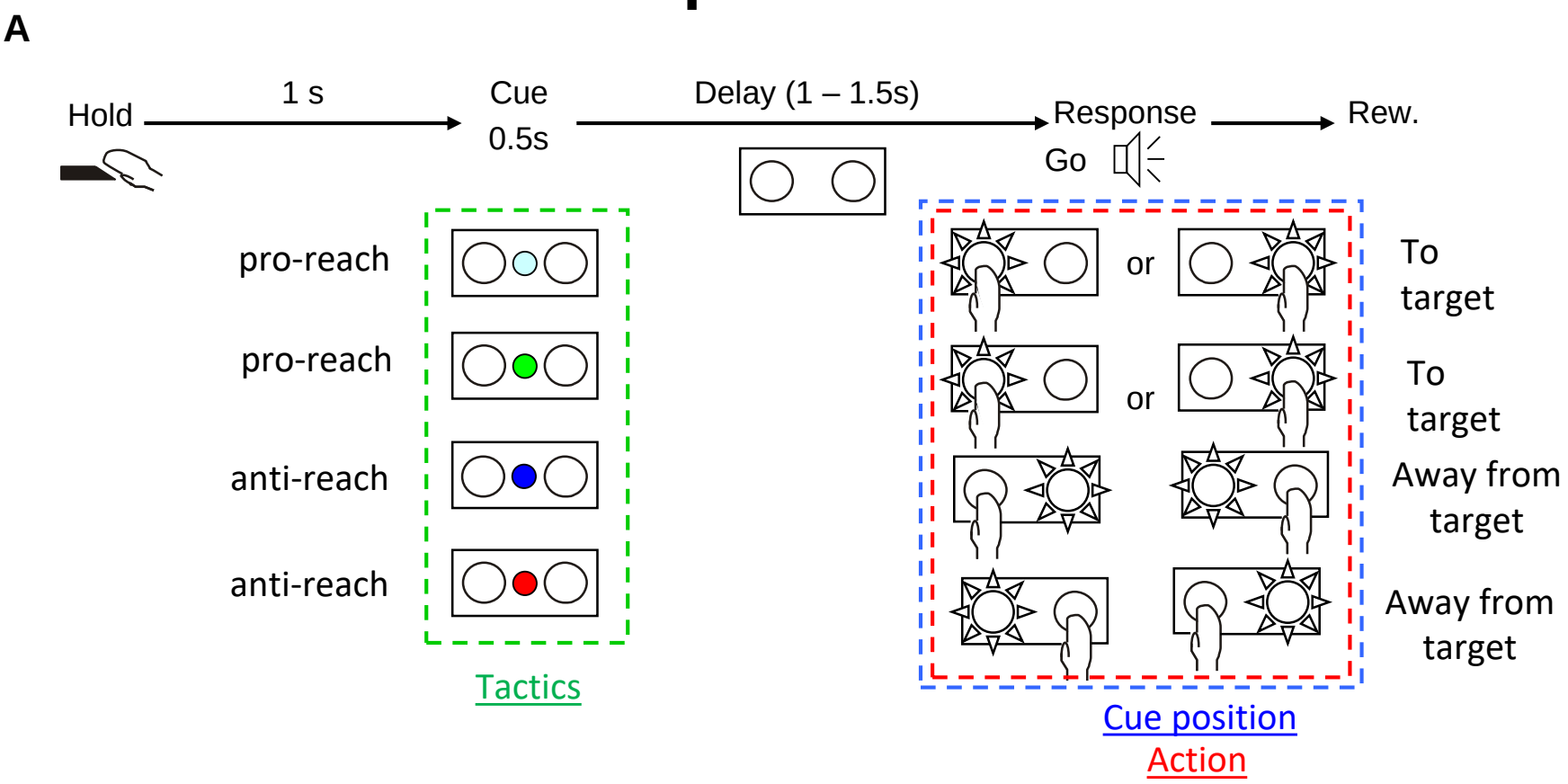


Figure.4. **(A) Tactics Pre-cued**. A trial started when the monkey pressed the hold button for 1s, and the center color cue was turned on for 500 ms. The color cue instructed tactics (cyan and green for pro-reach, blue and red for anti-reach). The cue was followed by random delay varying from 1 to 1.5 s. At the end of the delay, either the left or the right push button was back-illuminated by a white light-emitting diode, and the go signal (1 kHz beep tone) was simultaneously turned on, prompting the monkey's response. **(B) Position Pre-cued.** After pressing hold button for 1s monkeys are given cue position signal when either left or right button is illuminated. Cue position signal is then turned off, after 1 to 1.5 s the central LED is turned on with either of 4 colors (green and cyan for pro-reach and blue and red for anti reach) and go signal turned on simultaneously. Monkey select the appropriate action based on the remembered spatial position and the given tactics. For pro reach (cyan and green) monkey pressed the previously illuminated button ,for anti reach (blue and red) monkey press previously the non-illuminated button.

Figure .5

Cortical Areas in Experiment 2

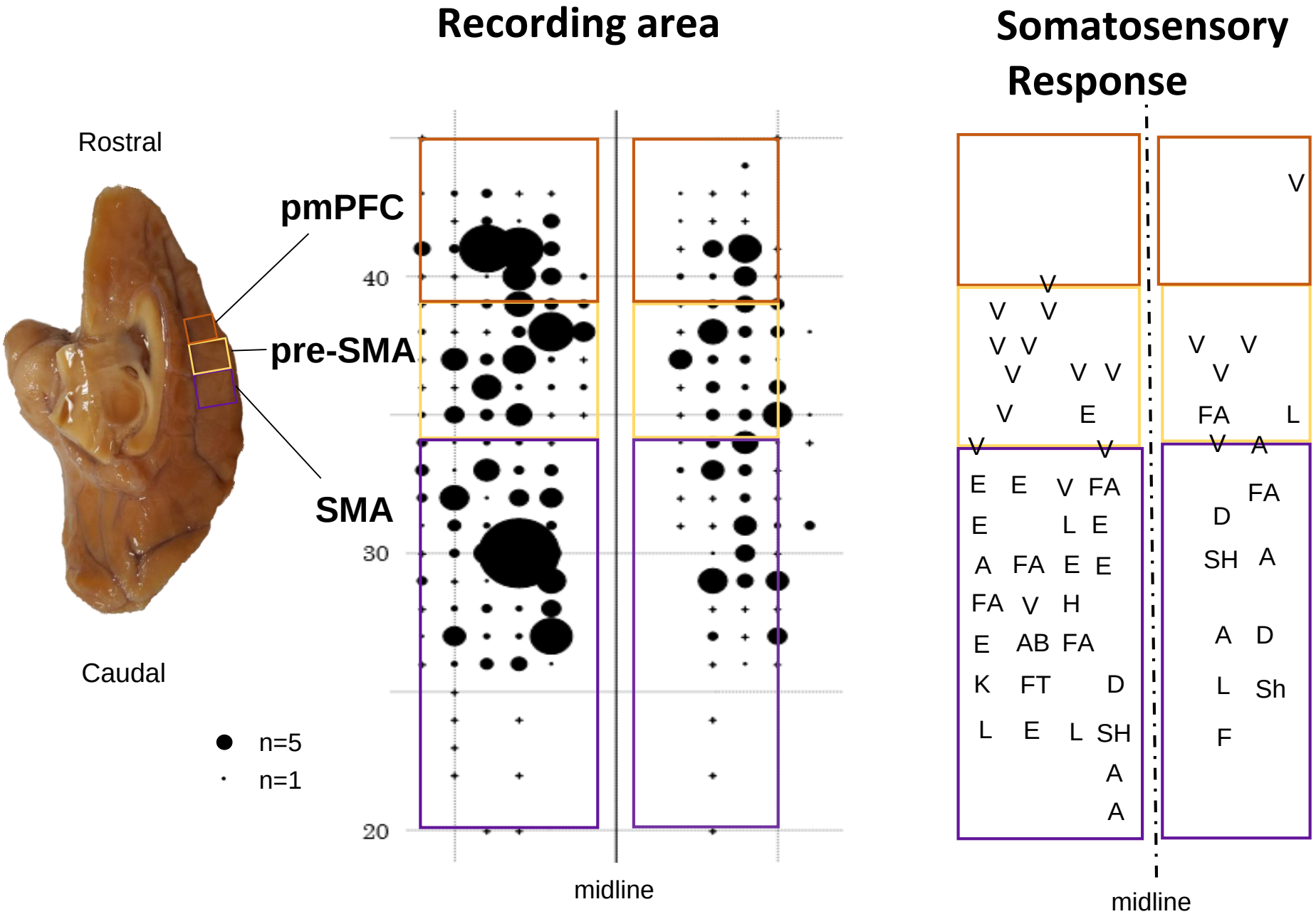


Figure 5. **Left**. Locations of the three cortical areas (posterior medial prefrontal cortex, presupplementary motor area, and supplementary motor area) shown as the medial view of monkeys' right hemisphere **Middle.** distribution of task-related neurons in one monkey. The size of the filled circles represents the numbers recorded in individual penetrations, and the cross signs represent the penetrations where no task-related neurons were recorded. **Right.** sensory response maps. A, arm; D, digits; E, elbow; FA, face; FT, foot; H, hand; K, knee; F, Flank, L, leg; SH, shoulder; and V, visual.

Figure .6

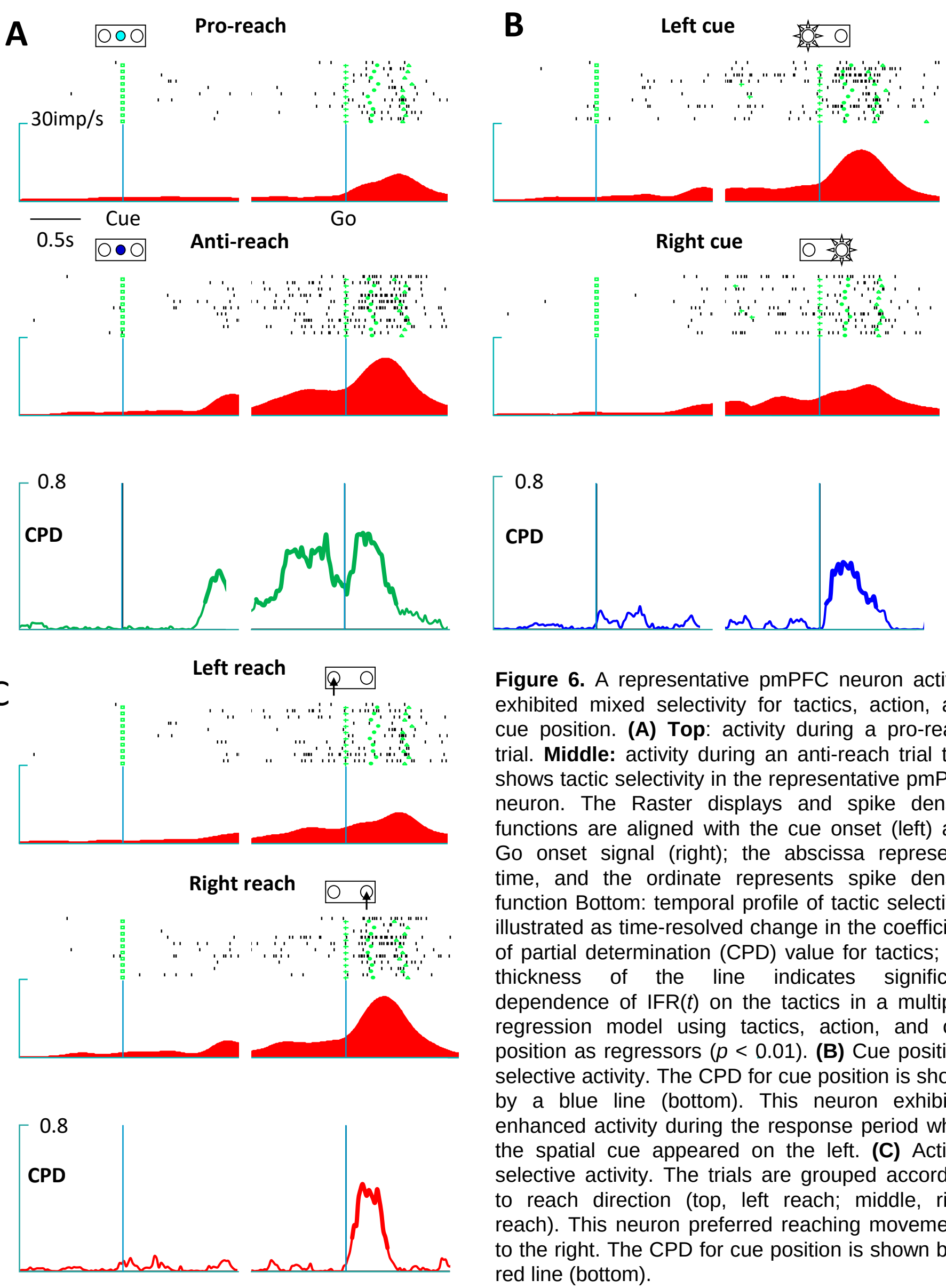


Figure 6. A representative pmPFC neuron activity exhibited mixed selectivity for tactics, action, and cue position. **(A) Top**: activity during a pro-reach trial. **Middle:** activity during an anti-reach trial that shows tactic selectivity in the representative pmPFC neuron. The Raster displays and spike density functions are aligned with the cue onset (left) and Go onset signal (right); the abscissa represents time, and the ordinate represents spike density function Bottom: temporal profile of tactic selectivity illustrated as time-resolved change in the coefficient of partial determination (CPD) value for tactics; the thickness of the line indicates significant dependence of IFR(t) on the tactics in a multiple-regression model using tactics, action, and cue position as regressors ($p < 0.01$). **(B)** Cue position-selective activity. The CPD for cue position is shown by a blue line (bottom). This neuron exhibited enhanced activity during the response period when the spatial cue appeared on the left. **(C)** Action-selective activity. The trials are grouped according to reach direction (top, left reach; middle, right reach). This neuron preferred reaching movements to the right. The CPD for cue position is shown by a red line (bottom).

Figure .7

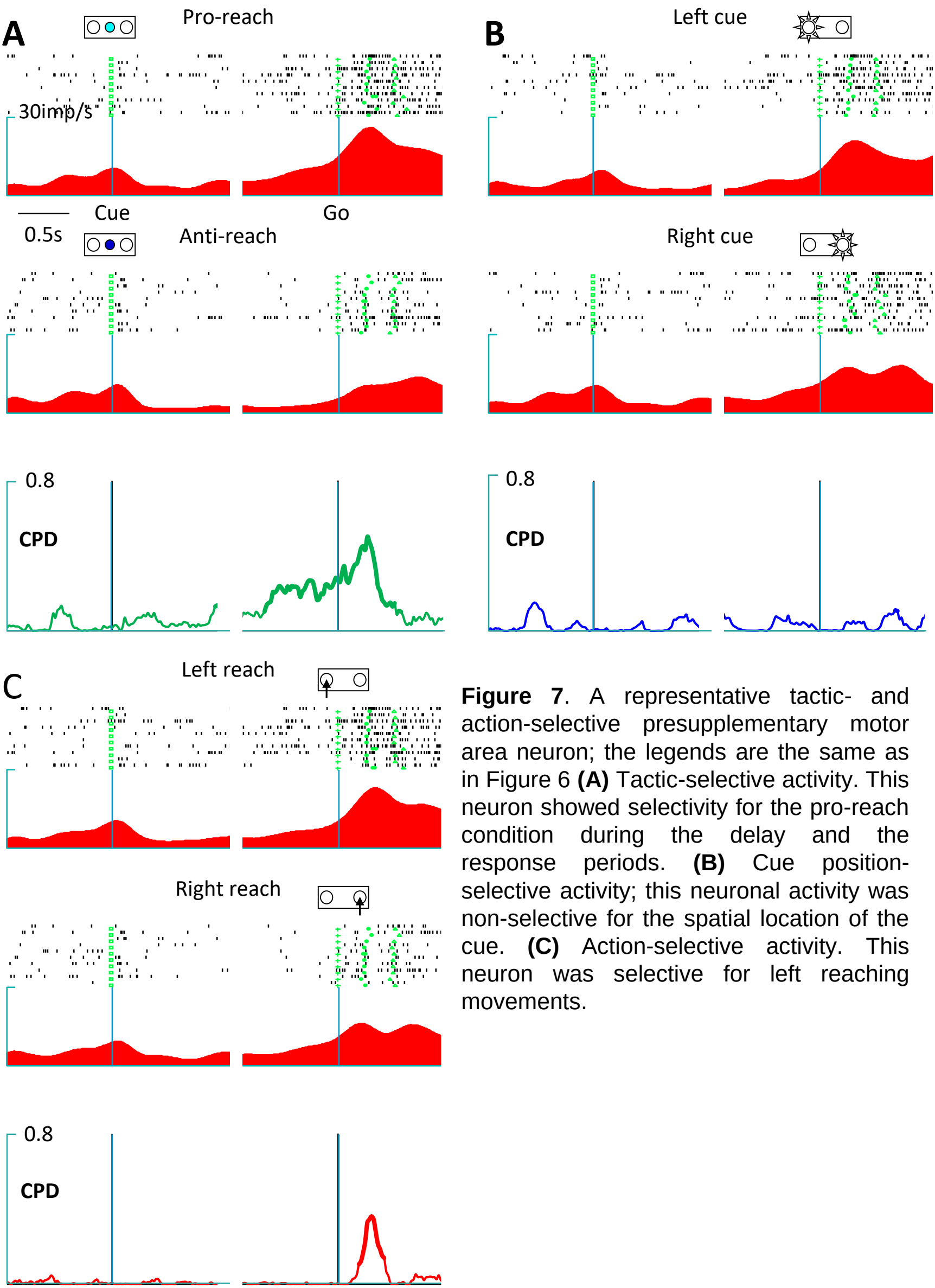


Figure 7. A representative tactic- and action-selective presupplementary motor area neuron; the legends are the same as in Figure 6 **(A)** Tactic-selective activity. This neuron showed selectivity for the pro-reach condition during the delay and the response periods. **(B)** Cue position-selective activity; this neuronal activity was non-selective for the spatial location of the cue. **(C)** Action-selective activity. This neuron was selective for left reaching movements.

Figure .8

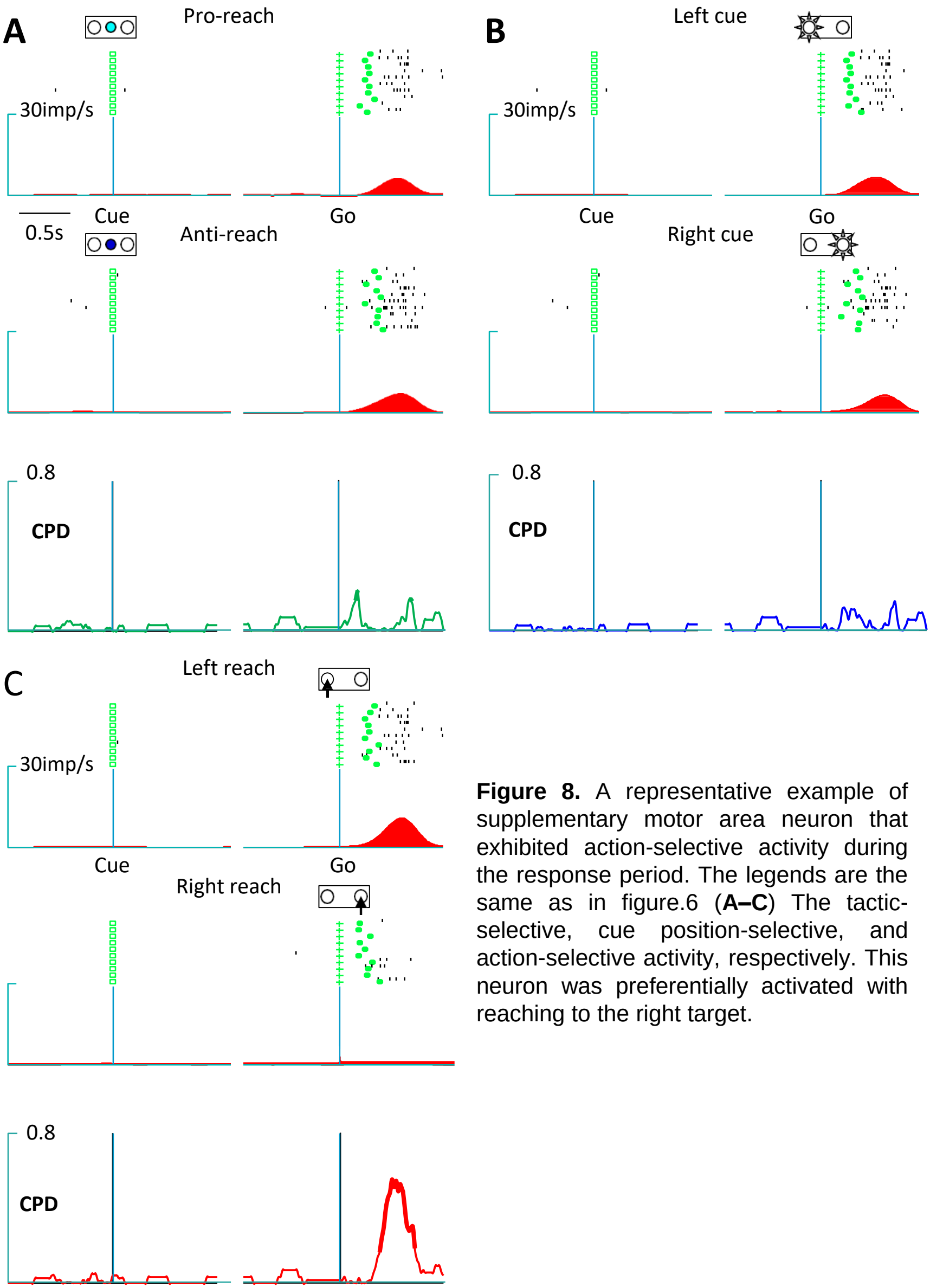


Figure 8. A representative example of supplementary motor area neuron that exhibited action-selective activity during the response period. The legends are the same as in figure.6 (**A–C**) The tactic-selective, cue position-selective, and action-selective activity, respectively. This neuron was preferentially activated with reaching to the right target.

Figure .9

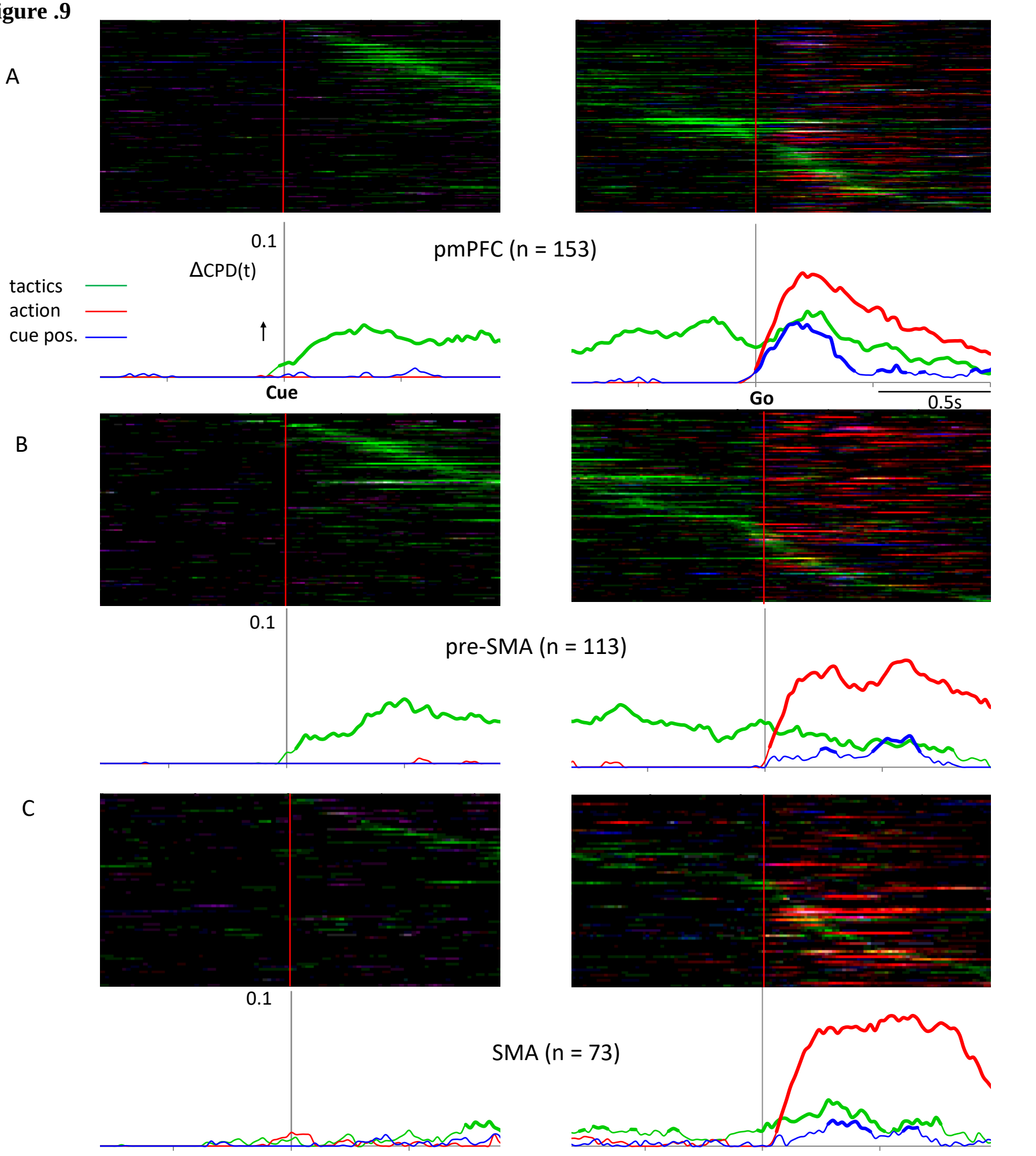


Figure 9. Temporal variance of neuronal selectivity for tactics, action, and cue position calculated from the instantaneous firing rate of neurons (A) pmPFC neuronal population (n = 153), the individual neuron's (CPD) values are illustrated as color-coded matrix. Each horizontal line represents a single neuron's activity aligned with the onset of the tactics cue (left) and the go signal (right). The neurons are sorted by the timing of the peak CPD value for tactics. The CPDs of tactics, action, and cue positions are coded in green, red, and blue. The line graphs illustrate the mean CPD value averaged across the population. The ordinate is the dCPD (increase of the mean CPD from the baseline period). The thickness of the lines represents a significant increase from the baseline period (permutation test, $p < 0.01$). (B) Neuronal population from presupplementary motor area (n = 113) showing selectivity for tactics and action during the delay and the response periods; cue position selectivity was not prominent. (C) Supplementary motor area (SMA) neuronal population (n = 73) showing action selectivity during the response period.

Figure 10. A

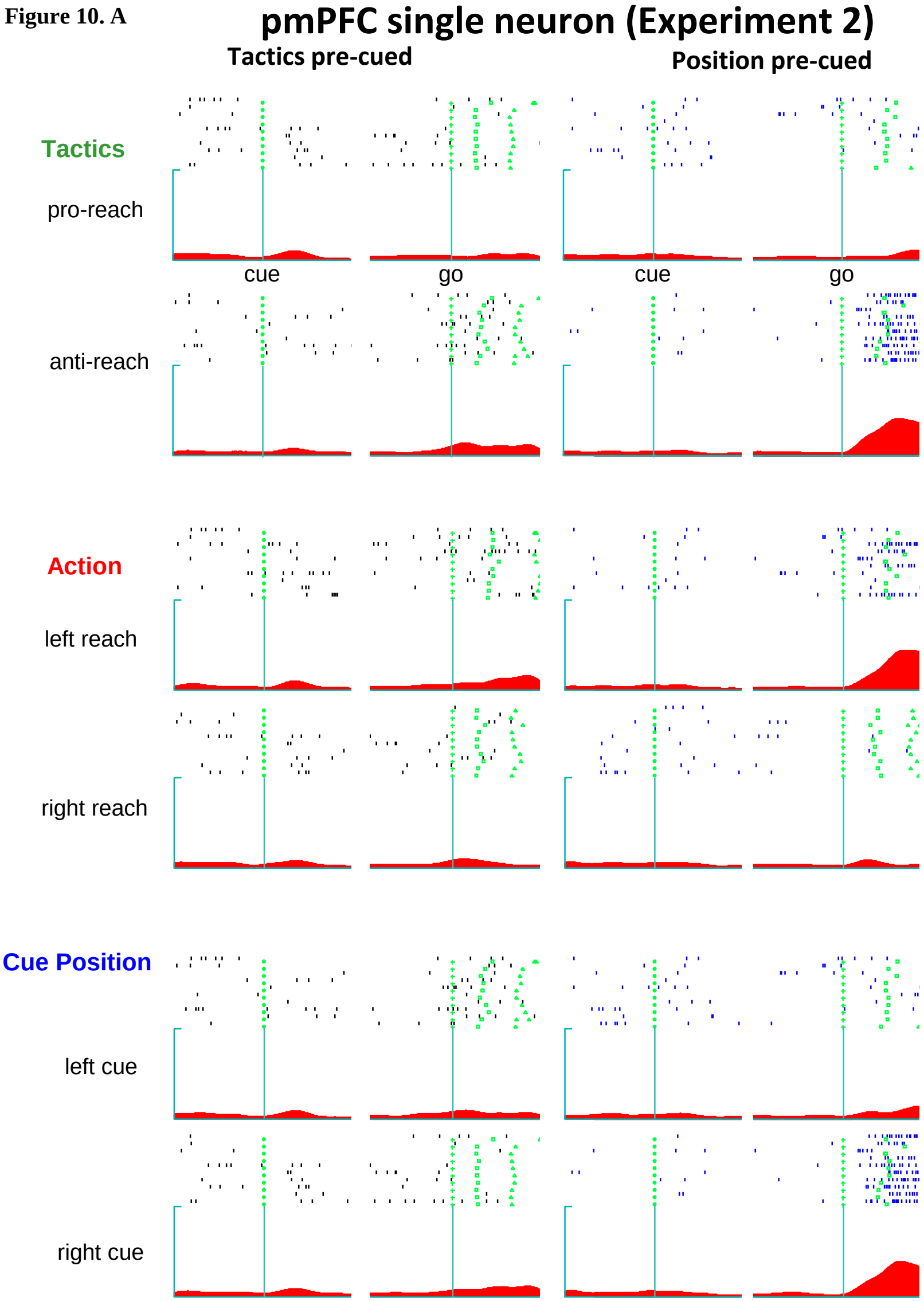
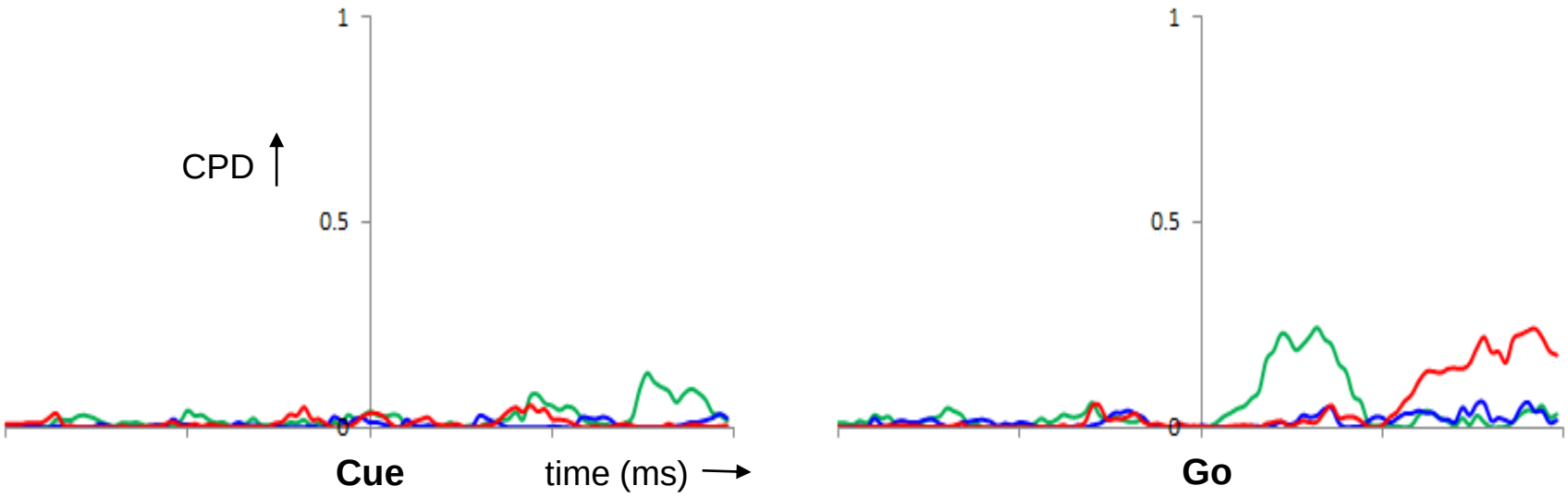


Figure 10 A. Raster and Spike density function shown for the pmPFC neuron. Left column showed trials sorted by tactics ,action and cue position for tactics pre-cued and right column for position precued respectively. In response period (after go signal) this neuron shows high firing rate for tactics, action and cue position in position pre-cued trials only

Figure 10.B

pmPFC single neuron (Experiment 2)

Tactics Pre-cued



Position Pre-cued

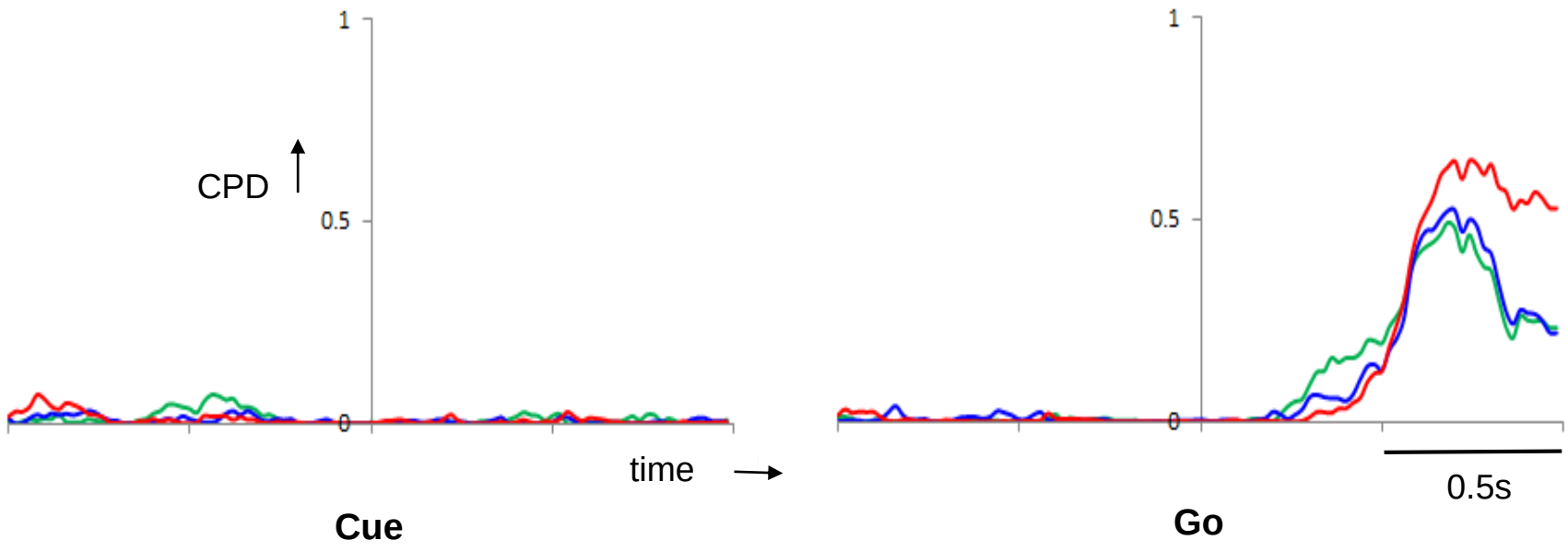


Figure 10 B. CPD analysis for **tactics**(green color), **action** (red color), **cue position** (blue color) selectivity for pmPFC neuron shown in figure 10A. (**Top**). Tactics precued trials. Left graph show CPD graph aligned with cue onset and right one aligned with the Go onset.**(Bottom)** Position pre-cued trials, data alignment is same as in tactics pre-cued. This neuron showed elevated CPD values for tactics, action and cue position in response period for position precued trials only.

Figure .11

pmPFC single neuron (Experiment 2)

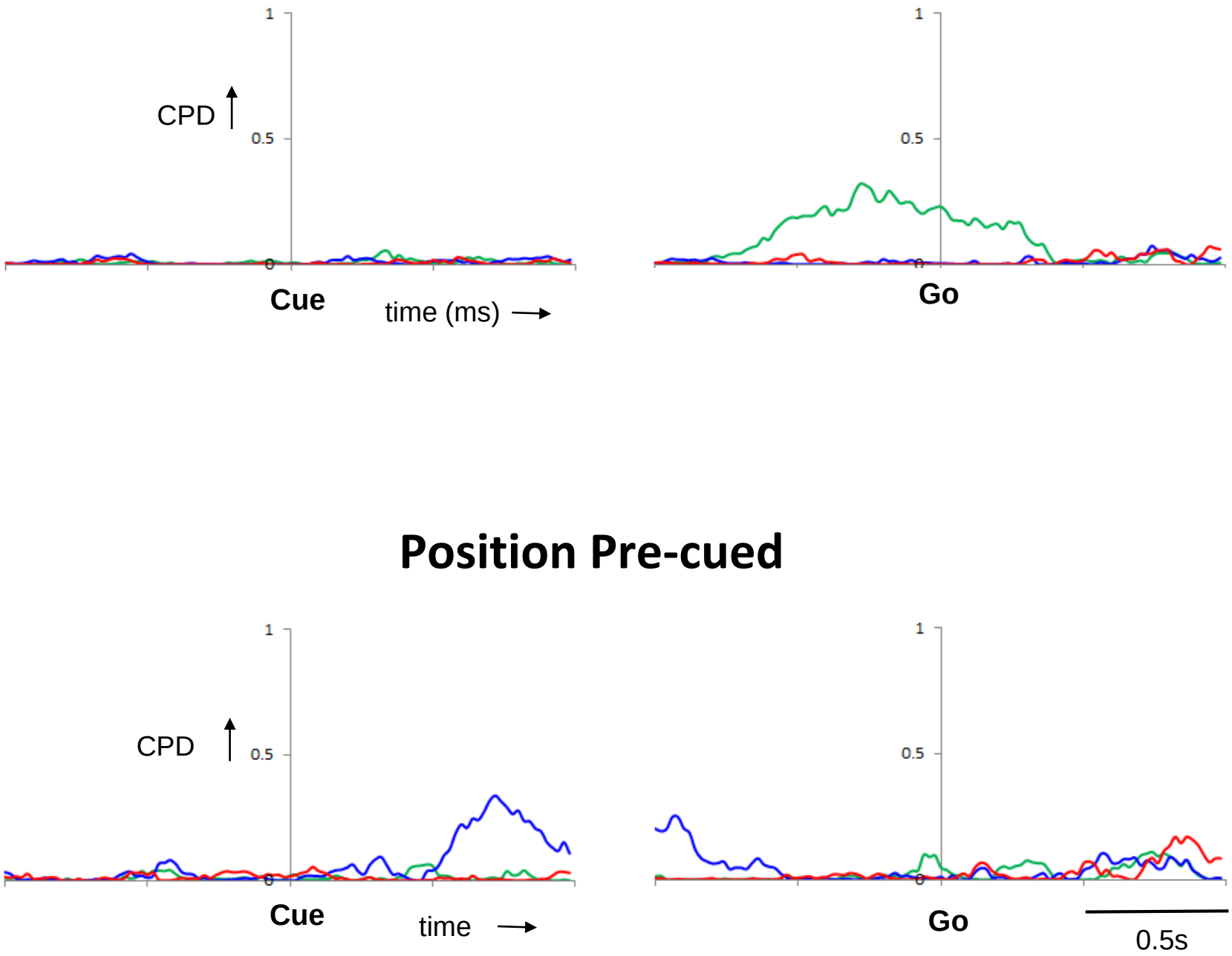


Figure 11.pmPFC neuron selective for tactics and cue position **(A) (Top) .**Tactics precued trials. CPD values for tactics precued task shown as **tactics** (green color), **action**(red color) and **cue position** (blue color). **(B) Bottom.** Position precued trials. This neuron showed cue position encoding during the delay period. CPD analysis show elevation of tactics selectivity in tactics while cue position in position pre-cued trials.

Figure .12

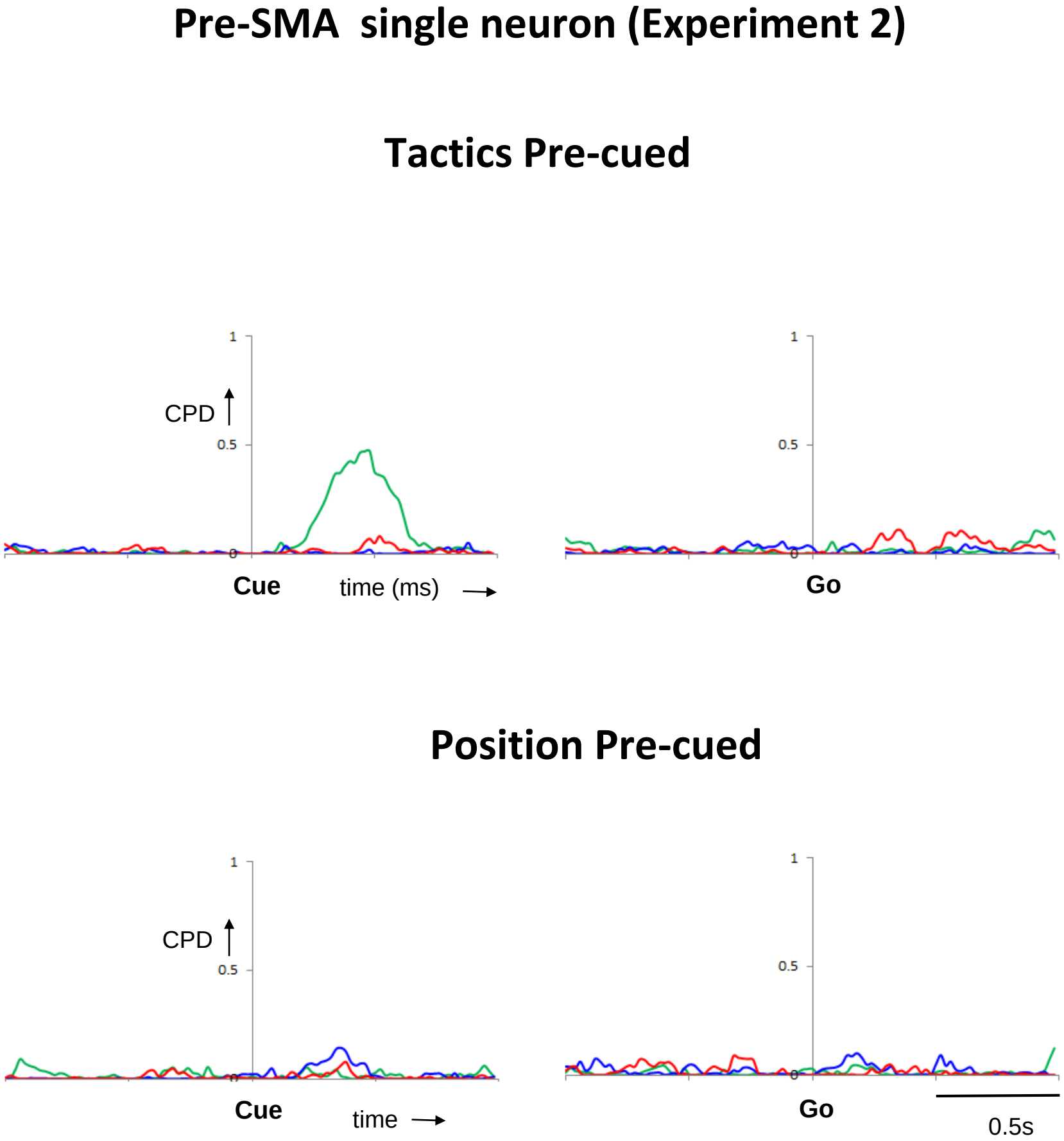


Figure 12.preSMA neuron selective for tactics in tactics pre-cued task **(A) (Top)**.Tactics precued trials. CPD values for tactics precued task shown as **tactics** (green color), **action**(red color) and **cue position** (blue color). **(B)** (**Bottom)**. Position precued trials. CPD analysis show significant elevation of tactics selectivity in tactics pre-cued task and no major selectivity in position pre-cued trials.

Figure .13

SMA single neuron (Experiment 2)

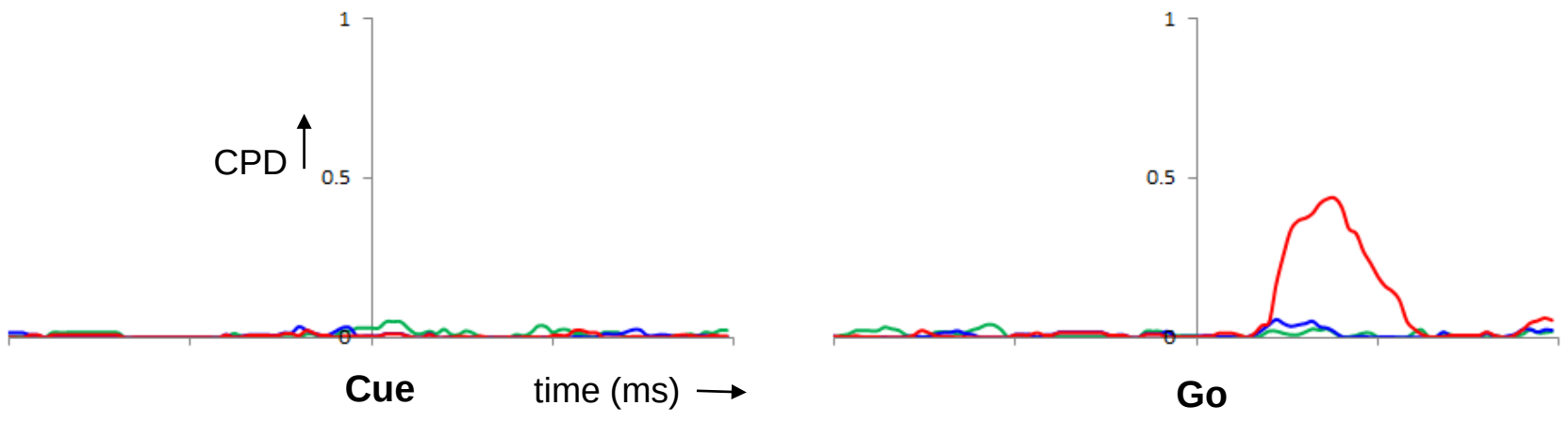


Figure 13. SMA neuron selective for action selection **(A) (Top).** Tactics pre-cued trials. CPD values for tactics pre-cued task shown as **tactics** (green color), **action**(red color) and **cue position** (blue color). **(B) (Bottom).** Position precued trials. CPD analysis show elevation of action selectivity in both tasks after the Go signal.

Figure .14

pmPFC Population Analysis

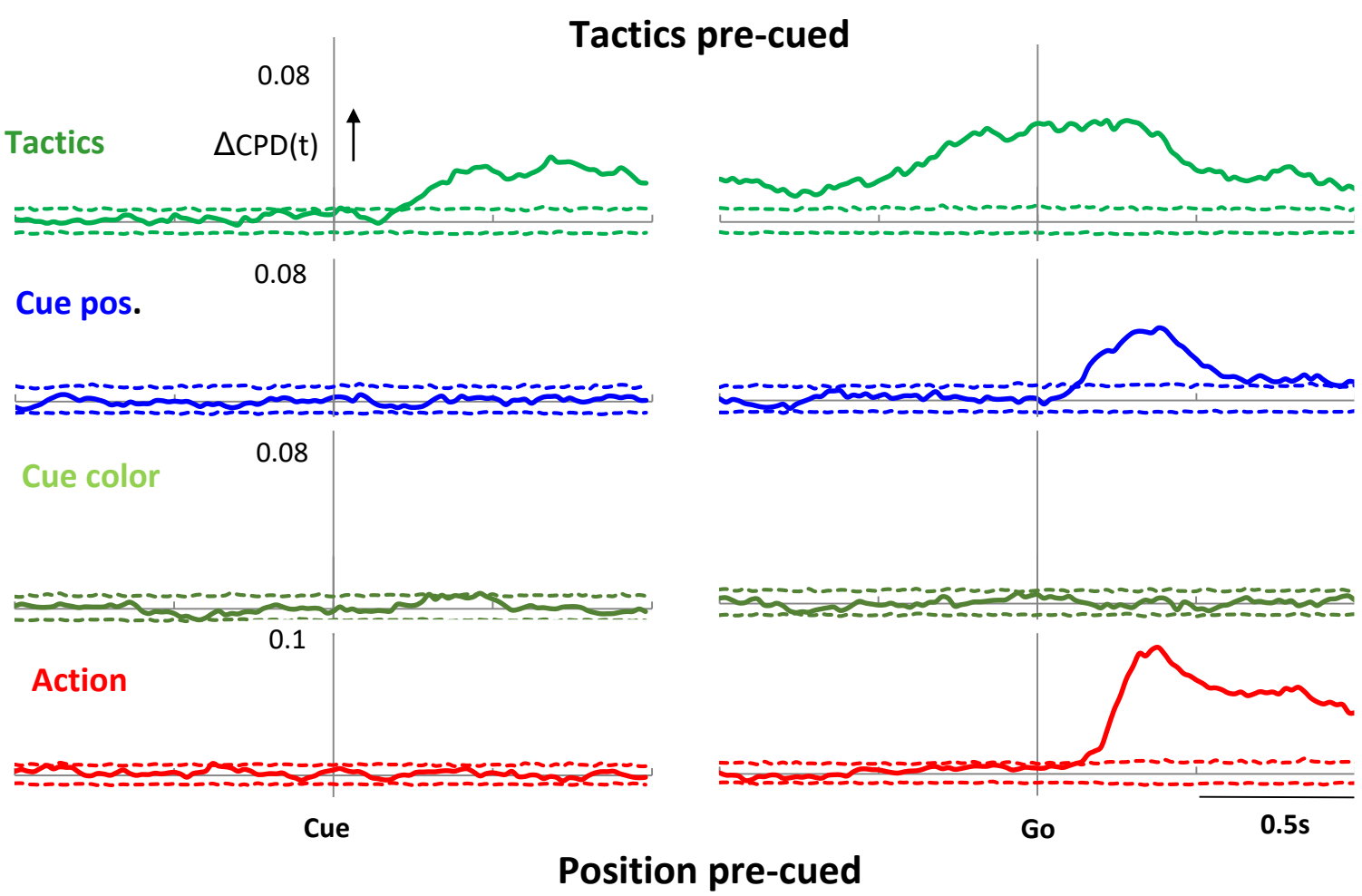


Figure 14. Temporal variance of neuronal selectivity for tactics, cue position, cue color and action calculated from the instantaneous firing rate of neurons of pmPFC for two tasks **(A) Tactics Pre-cued Task.** pmPFC neuronal population (n = 132).The CPDs of tactics, cue position ,cue color and action are coded in green, blue, light green and red respectively. The line graphs illustrate the mean CPD value averaged across the population. The ordinate is the dCPD (increase of the mean CPD from the baseline period). Two dotted lines for each respective graph show 99 percent confidence interval of pre-cue baseline activity **(B) Position Pre-cued Task.** Legends same as in **(A).**CPD values for cue position show significant modulation after the onset of cue onset (shown in blue color).

Figure .15

Pre-SMA Population Analysis

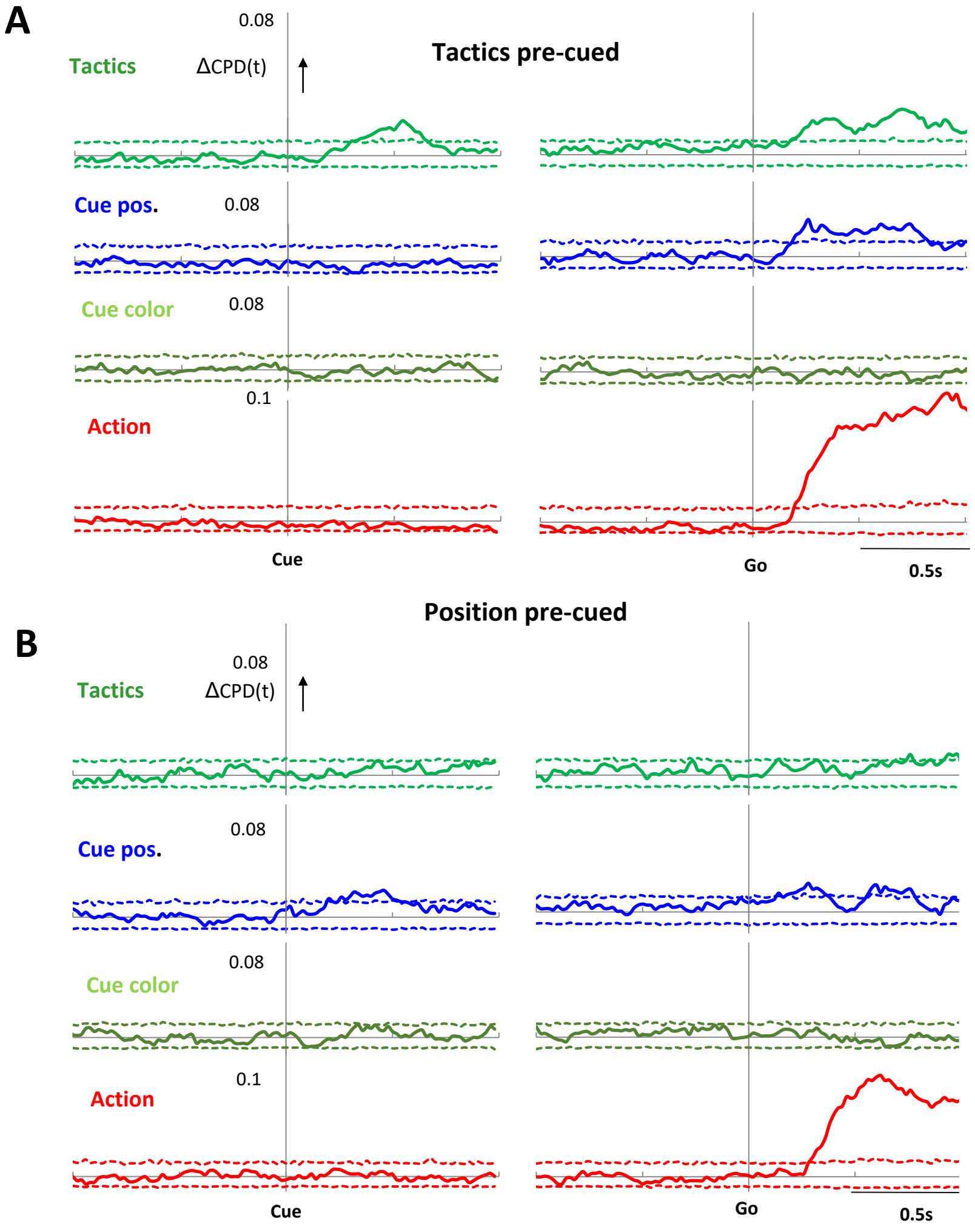


Figure 15. Temporal variance of neuronal selectivity for tactics, cue position, cue color and action calculated from the instantaneous firing rate of neurons **(A) Tactics Precued Task.** pre-SMA neuronal population (n = 142) The CPDs of tactics, cue position ,cue color and action are coded in green, blue, light green and red respectively. The line graphs illustrate the mean CPD value averaged across the population. The ordinate is the dCPD (increase of the mean CPD from the baseline period). Two dotted lines for each respective graph show 99 percent confidence interval of pre-cue baseline activity **(B) Position Precued Task**

Figure .16

SMA Population Analysis

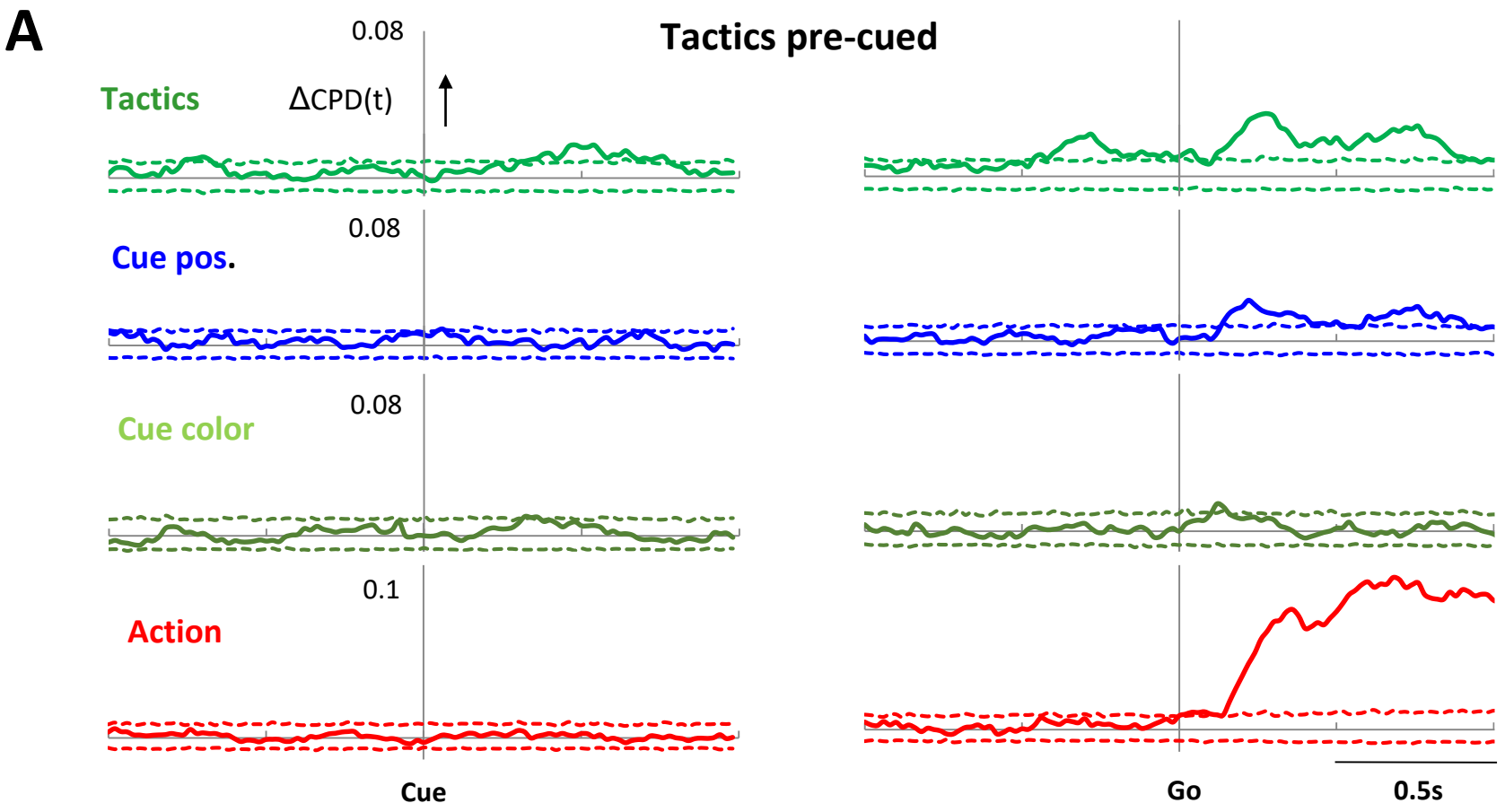


Figure 16. Temporal variance of neuronal selectivity for tactics, cue position, cue color and action calculated from the instantaneous firing rate of neurons **(A) Tactics pre-cued Task** SMA neuronal population (n = 166). The CPDs of tactics, Cue position ,cue color and action are coded in green, blue, light green and red respectively. The line graphs illustrate the mean CPD value averaged across the population. The ordinate is the dCPD (increase of the mean CPD from the baseline period). Two dotted lines for each respective graph show 99 percent confidence interval of pre-cue baseline activity **(B) Position pre-cued Task**.

Figure .17

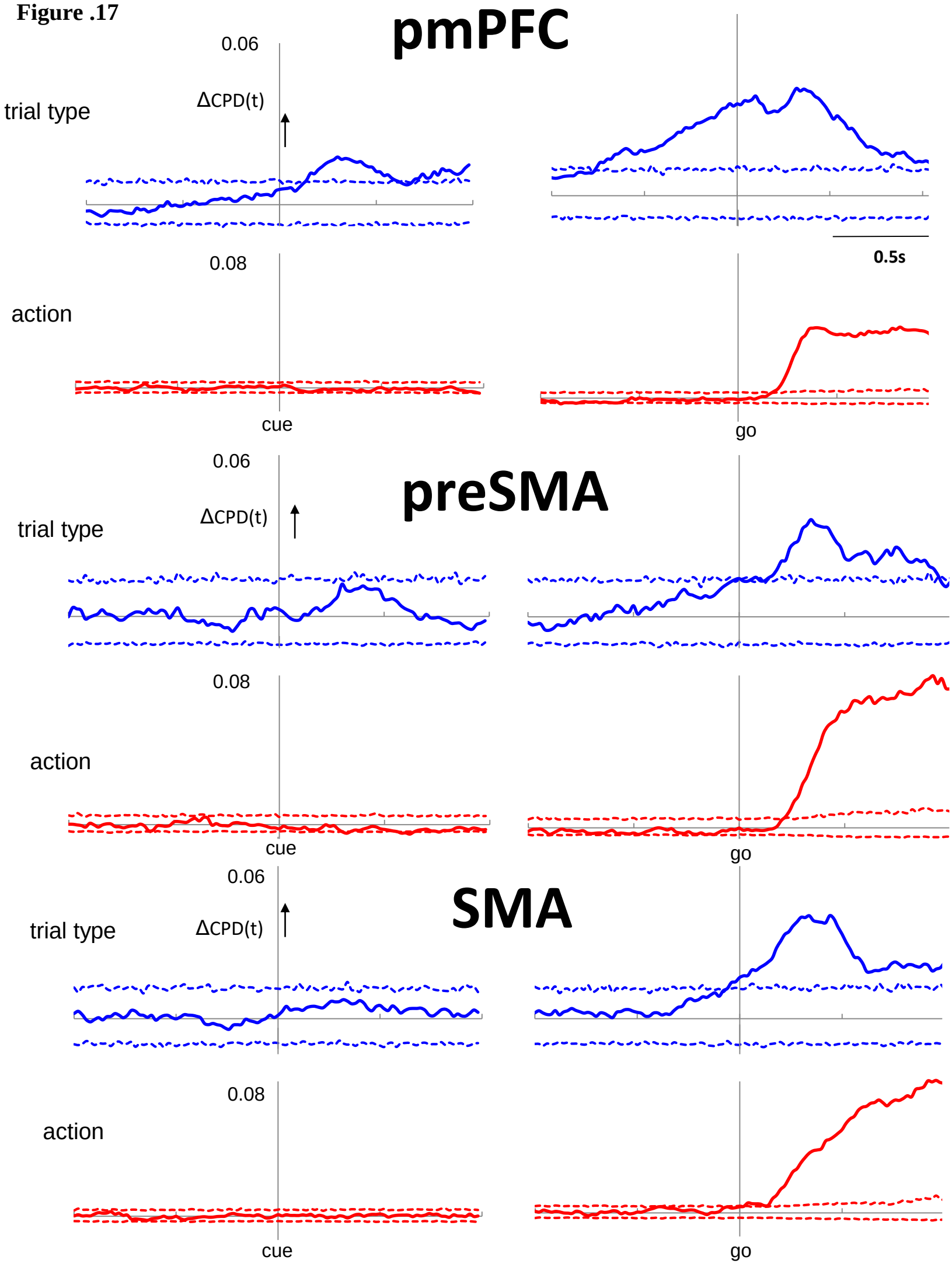


Figure 17. Three medial areas pmPFC, preSMA and SMA were analyzed for trial type (tactics pre-cued or position pre-cued) ,action (left or right movement) by multivariate ANOVA. pmPFC (n=132) show significant increase in trial type selectivity (shown in blue color) after cue onset and delay period which is not visible in preSMA (n=142) and SMA (n=160). The two dotted lines show 99 percent confidence interval for the pre-cue baseline period.

Figure .18

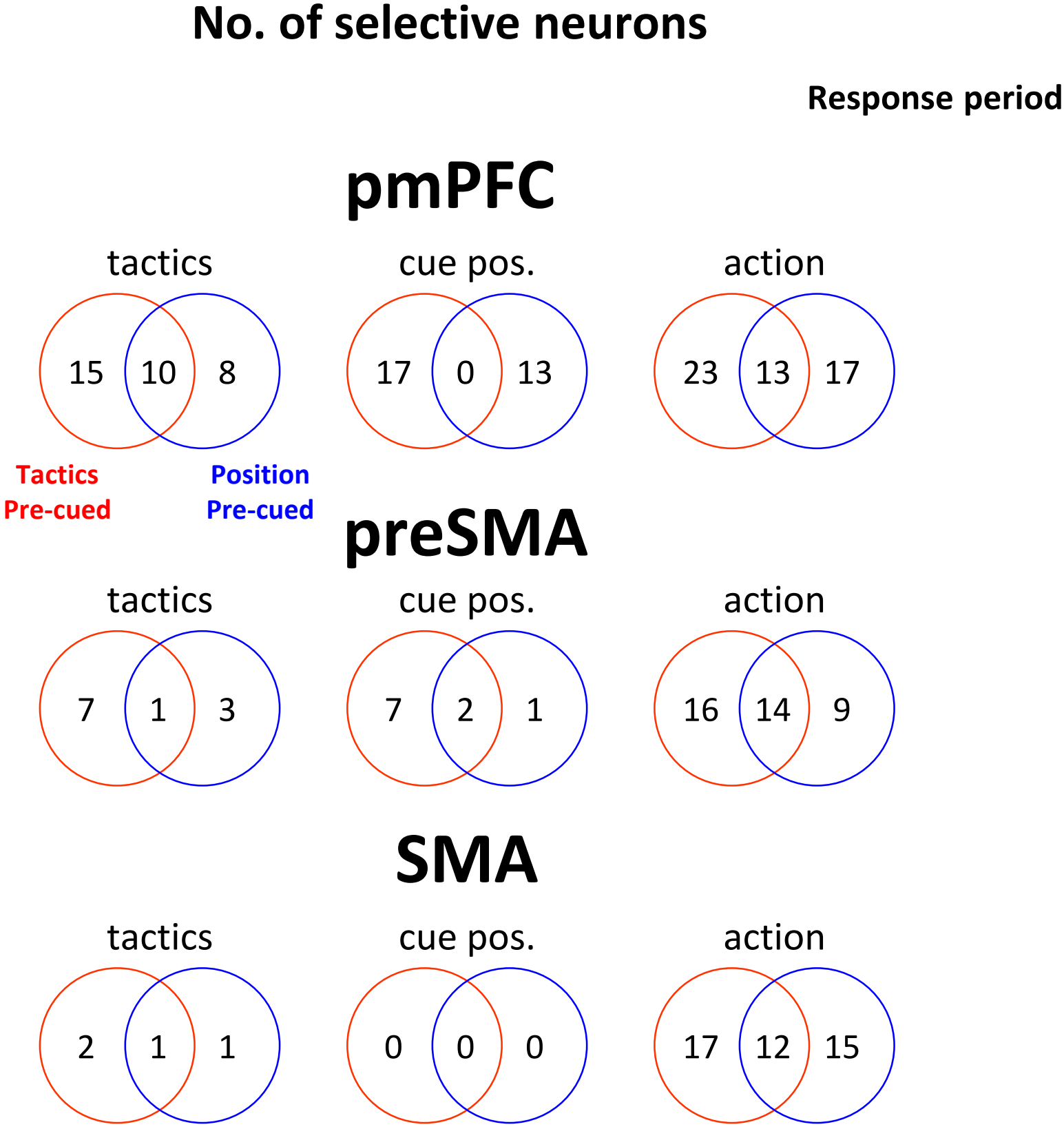


Figure 18. Number of Neurons shows significant modulation for tactics (left column) ,cuepos (middle column) and action (right column) in the response period for three areas **pmPFC** (top,n=132), **pre-SMA** (middle,n=142) and **SMA** (bottom,n=166).The red circle show the tactics pre-cued task and the blue circle for the position pre-cued task.

Figure .19

Error Trials

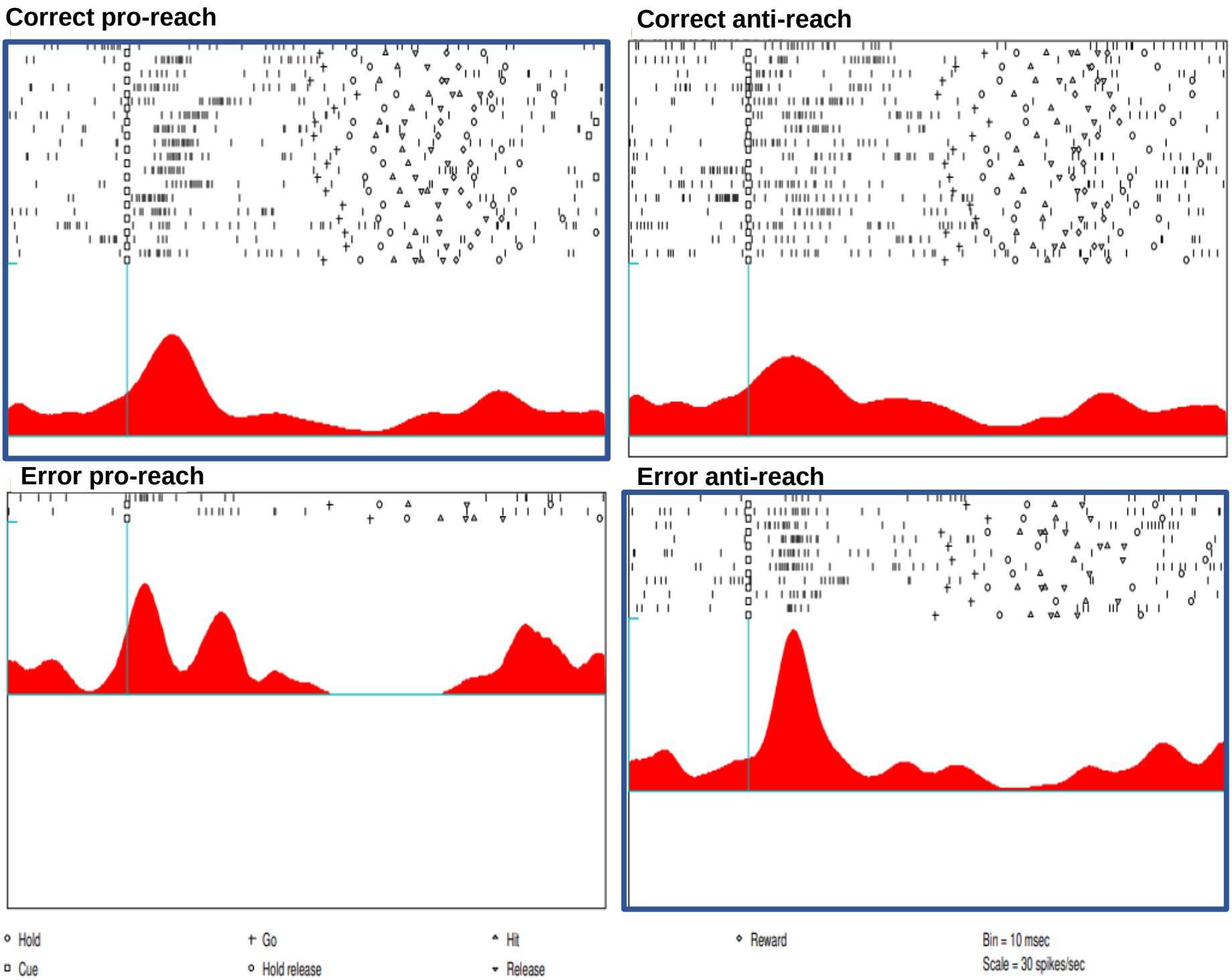


Figure 19. Example of a pre-SMA neuron for correct and error trials . The first row represents correctly performed trials for pro-reach and anti-reach condition. Second row represents the trials where monkey made an error for pro-reach and anti-reach condition respectively. In correct trials this neuron show high firing rate in pro-reach condition but the same neuron showing high firing rate for anti-reach condition in the error trials. Monkey mistakenly perceived the cued tactics in error trials. Two blue boxes show the resemblance of firing rate across two conditions respectively.

Figure .20

Conceptual model

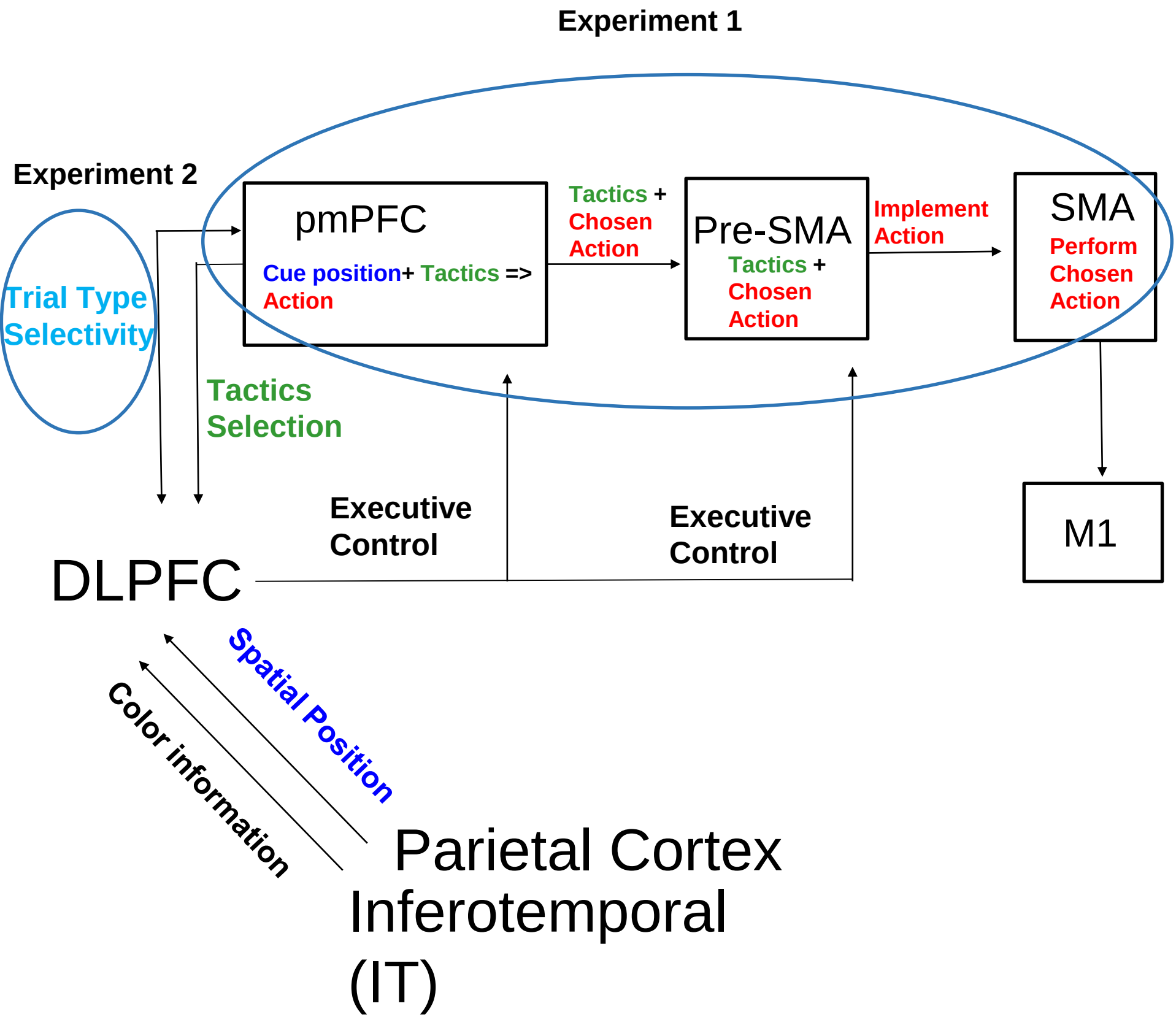


Figure 20. Hypothetical conceptual model for tactics-based action selection in medial prefrontal. pmPFC area receives information about the task context, spatial and color information through DLPFC. DLPFC being higher in hierarchy exert executive control on medial areas. pmPFC integrates the behavioral factors and determine the final action. pmPFC being connected to pre-SMA sends the tactics information and chosen action to pre-SMA. Final action is then communicated to SMA through pre-SMA.SMA connects to primary motor cortex area (M1) and modulate it for motor execution.