Noise Correlation is Modulated by Reward Expectation in the Primary Motor Cortex Bilaterally During Manual and Observational Tasks in Primates

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Keywords

Motor Cortex, Reward, Reinforcement Learning, Temporal Difference, Reward Prediction, Reward Prediction Error.

Abstract

Reward modulation is represented in the motor cortex and could be used to implement more accurate decoding models to improve brain computer interfaces (BCIs) (Zhao et al. 2018). Analyzing trial-to-trial noise correlations between neural units in the presence of rewarding and non-rewarding stimuli adds to our understanding of cortical network dynamics and provides a clearer picture of the neural encoding involved in reward. We utilized Pearson's correlation coefficient to measure shared variability between simultaneously recorded units and found significantly higher noise correlation during non-rewarding trials as compared to rewarding trials. This pattern is evident in data from 2 non-human primates (NHPs) during center out reaching tasks, both manual and action observation versions. We conducted mean matched correlational analysis in order to decouple known interactions between event triggered firing rate changes and

crosscorrelation. Isolated reward discriminatory units demonstrated similar correlational changes to units unresponsive to reward firing rate modulation, indicating correlational changes within the network can serve as another information channel to be exploited by BCIs that track the underlying cortical state, such as reward expectation, or attentional modulation. Reward expectation and attention in return can be utilized with reinforcement learning towards autonomous BCI updating.

Introduction

The neural representation of reward has been traced to deep brain structures including the substantia nigra pars compacta and ventral tegmental area (Schultz, Dayan, and Montague 1997). Reward associated signals have also been shown to occur in multiple cortical areas including the orbitofrontal and sensorimotor cortices (Tremblay and Schultz 1999; Ramkumar et al. 2016; Ramakrishnan et al. 2017; Zhao et al. 2018; An, Yadav, Badri Ahmadi, et al. 2018; McNiel, Choi, et al. 2016a; Marsh et al. 2015). Previous studies have linked cortical responses to dopaminergic pathways, which can explain cortical responses on multiple time scales (Kunori, Kajiwara, and Takashima 2014) and indicates the complex interactions that exist between deep structure reward signaling and M1 units. For example, dopamine has proven necessary for learning in M1 (Molina-Luna et al. 2009) and has a significant effect on long term potentiation (LTP) in the motor cortex, for review see (Francis and Song 2011).

Studies of the motor cortex reveal a complex dynamical system (Churchland et al. 2012). In addition to kinematic, directional, and force tuning information, M1 neurons encode value and demonstrate reward modulation (Marsh et al. 2015; An et al. 2019; An, Yadav, Ahmadi, et al. 2018; Ramkumar et al. 2016; Ramakrishnan et al. 2017; Zhao et al. 2018). Neural responses to reward expectation have also been recorded in M1 and associated regions (Platt and Glimcher 1999; Zhao et al. 2018; Musallam et al. 2004; Tanaka et al. 2004; Campos et al. 2005; Shuler and Bear 2006; Louie, Grattan, and Glimcher 2011; Toda et al. 2012; Marsh et al. 2015;

Tarigoppula et al. 2018b). Models indicate that signals encoding value and reward expectation in M1 play a significant role in the reinforcement learning process (Tarigoppula et al. 2018b; Dura-Bernal et al. 2015). This information is encoded during active movement, as well as during action observation and motor planning which further implies an interconnection between reward, learning, and expectation (Tkach, Reimer, and Hatsopoulos 2007; Dushanova and Donoghue 2010; Marsh et al. 2015).

Many of the single and multi-unit activity studies of reward modulation in M1 have utilized firing rate, with some exceptions (An, Yadav, Hessburg, et al. 2018; An, Yadav, Badri Ahmadi, et al. 2018; Marsh et al. 2015). However, the correlation between individual units can also provide insight into how populations of neurons change with behavior. There is notable variability in individual unit responses to a repeated stimuli (Tolhurst, Movshon, and Dean 1983), and this variation is often shared between neurons (Shadlen and Newsome 1998). Research has shown that the correlation between trial-to-trial fluctuations has a significant impact on coding efficiency, specifically in relation to attention, learning, and behavior (Zohary, Shadlen, and Newsome 1994; Abbott and Dayan 1999; Nirenberg and Latham 2003; Averbeck and Lee 2006; Cohen and Newsome 2008).

Changes in correlation occur even in the absence of changes in firing rate, suggesting that correlation dynamics are a critical part of the neural code (Vaadia et al. 1995). Correlation reveals neural population interactions that contribute to our understanding of network architecture. Analysis of changes in correlation in different contexts indicates increased correlation between similarly tuned ensembles and local circuits, affecting learning-related plasticity (Komiyama et al. 2010). In addition, correlation has also proven useful in understanding potential connectivity across regions and populations (Reid and Alonso 1995).

In studying the correlation of M1 units in the presence of rewarding and non-rewarding stimuli, there are several factors to consider. Previous work has demonstrated correlation changes related to spatial attention, learning, and internal state. These factors are likely to coexist

in a reward task experimental paradigm with conditioned visual cues and may also be driving factors in the results. However, these fluctuations in cortical state may occur on distinct and significantly slower timescales (Muller, Teder-Salejarvi, and Hillyard 1998) and may be separable. Second, correlation can be significantly affected by the strength of the stimulus response (Ecker et al. 2010), which was shown to contribute to 33% of the across-study variance reported in V1 (Cohen and Kohn 2011). Lastly, the composition of the population plays a role in the relationship between correlations and coding efficiency, which means that the results obtained may be interpreted differently depending on the ensemble of units with predictable variations across subpopulations. For example, while increasing correlation has proven detrimental in homogenous populations and similarly tuned neurons, it may increase information carrying capacity in heterogeneous populations and differently tuned units (Chelaru and Dragoi 2008; Abbott and Dayan 1999).

The goals of this study were to 1) determine the extent and direction of changes in correlation in response to rewarding and non-rewarding stimuli on M1 neural activity and 2) interpret the role of correlation in improved neural encoding of rewarding vs. non-rewarding moments, for example we found that M1 tuning curve amplitudes are larger during rewarding trials as compared to non-rewarding (see Fig.4 in (Zhao et al. 2018)). Given the capacity for reward modulation observed in previous studies within the sensorimotor cortices (Marsh et al. 2015; McNiel, Bataineh, et al. 2016; McNiel, Choi, et al. 2016b; Hessburg, Zhao, and Francis 2019; An et al. 2019; An, Yadav, Ahmadi, et al. 2018; Ramkumar et al. 2016; Ramakrishnan et al. 2017; Zhao et al. 2018), and the association of decreased correlation with increased encoding accuracy, we predicted that the mean response of the M1 population would show noise correlation decreases during rewarding trials, and that this decrease would include not only reward modulated units, but the M1 network at large. We recently showed evidence in line with this prediction in the interaction between neural spike trains and the underlying local field potential

(LFP) in M1 (An et al. 2019), however we did not report on interactions between single and multi-units, such as changes in the correlational structure between pairs of units as we do here.

Methods

The data used in this study was collected and processed as described in Marsh et al., 2015.

Surgery

Two bonnet macaques (*Macaca radiata*) were implanted in the primary motor cortex with a 96-channel microelectrode array (10 × 10 array separated by ~400 μm, 1.5 mm electrode length, 400 kOhm impedance, ICS-96 connectors, Blackrock Microsystems) using techniques detailed in previous work (Chhatbar et al., 2010). All surgical procedures were conducted in compliance with guidelines set forth by the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were further approved by the State University of New York Downstate Institutional Animal Care and Use Committee.

Non-human primates (NHPs) were implanted with a headpost (Crist Instrument) three to six months before the electrode implantation. Implantation was performed after animals were trained to complete the manual task (see below) with a success rate of 90%.

Data Collection

After 2-3 weeks of recovery, single-unit and multi-unit activity were recorded using multichannel acquisition processor systems (Plexon). The signals were amplified, bandpass filtered from 170 Hz to 8 kHz, and sampled at 40 kHz before the waveforms were sorted using principal component methods (Marsh et al. 2015). There was no segregation between single and multi-units. For NHP A, data is taken from the contralateral M1 and from the ipsilateral M1 for NHP Z.

For NHP A manual task, there were 4 same-day recording sessions included in this analysis with 80, 80, 80 and 112 units detected after sorting from sessions 1, 2, 3 and 4 respectively. For the observation task, there were 3 same-day recording sessions included with

91 units recorded in each. Number of trials N = 190 R and 61 NR for manual NHP A, 469 R and NR for OT1 NHP A. For Monkey Z manual task, there were 3 different-day recording sessions used for this analysis with 38, 36, and 32 units detected after sorting. For the observation task, there were also 3 different-day recording sessions included with 42, 45, and 40 units recorded in each. Number of trials 326 R and 159 NR for manual NHP Z, 519 R and 258 NR OT1 NHP Z.

Experimental Task

The non-human primates (NHP) performed two tasks, manual and observation, that were used for analysis. First, the animals were trained to perform a center-out reaching task using their right arm inside a KINARM exoskeleton (BKIN Technologies). For the manual task, a right hand movement was made from a center target to a peripheral target (0.8 cm radius) located 5 cm to the right (Figure 1)(An, Yadav, Badri Ahmadi, et al. 2018). A cursor provided visual feedback of the hand position. The NHP initiated the trial by holding on the center target for 325 ms, which was then followed by a color cue period (100-300 ms) where the colored peripheral target appeared and the color of center target changed indicating if the trial would be rewarding or non-rewarding. After a required hold period of 325-400 ms, a GO cue indicated the NHP could move to the peripheral target where it had to hold for 325 ms (Figure 1A). At that time the animal would receive a liquid reward (R) or no reward (NR), depending on the trial type. If the NHP failed to correctly finish a trial, the same trial type would be repeated. For the manual task, the trial types were randomized otherwise. For the observation task, the trials were presented in a sequenced pattern alternating between R and NR trial types for NHP A. For NHP Z the observational data was biased with a 2 to 1 ratio in favor of R trials.

For the observational task (OT), the NHP observed the hand feedback cursor automatically move at a constant speed from the center to the peripheral target (Figure 1B). The KINARM was locked into place and the left arm restrained to prevent reaching movements. Eye-tracking was used to ensure that the NHP was looking at the computer projection in the horizontal plane on a semi-transparent mirror where the tasks were displayed during the OT trials.

From each trial, there are four periods of time included in this analysis: pre cue (500 ms), post cue (800 ms), pre reward (500 ms), and post reward (500 ms).

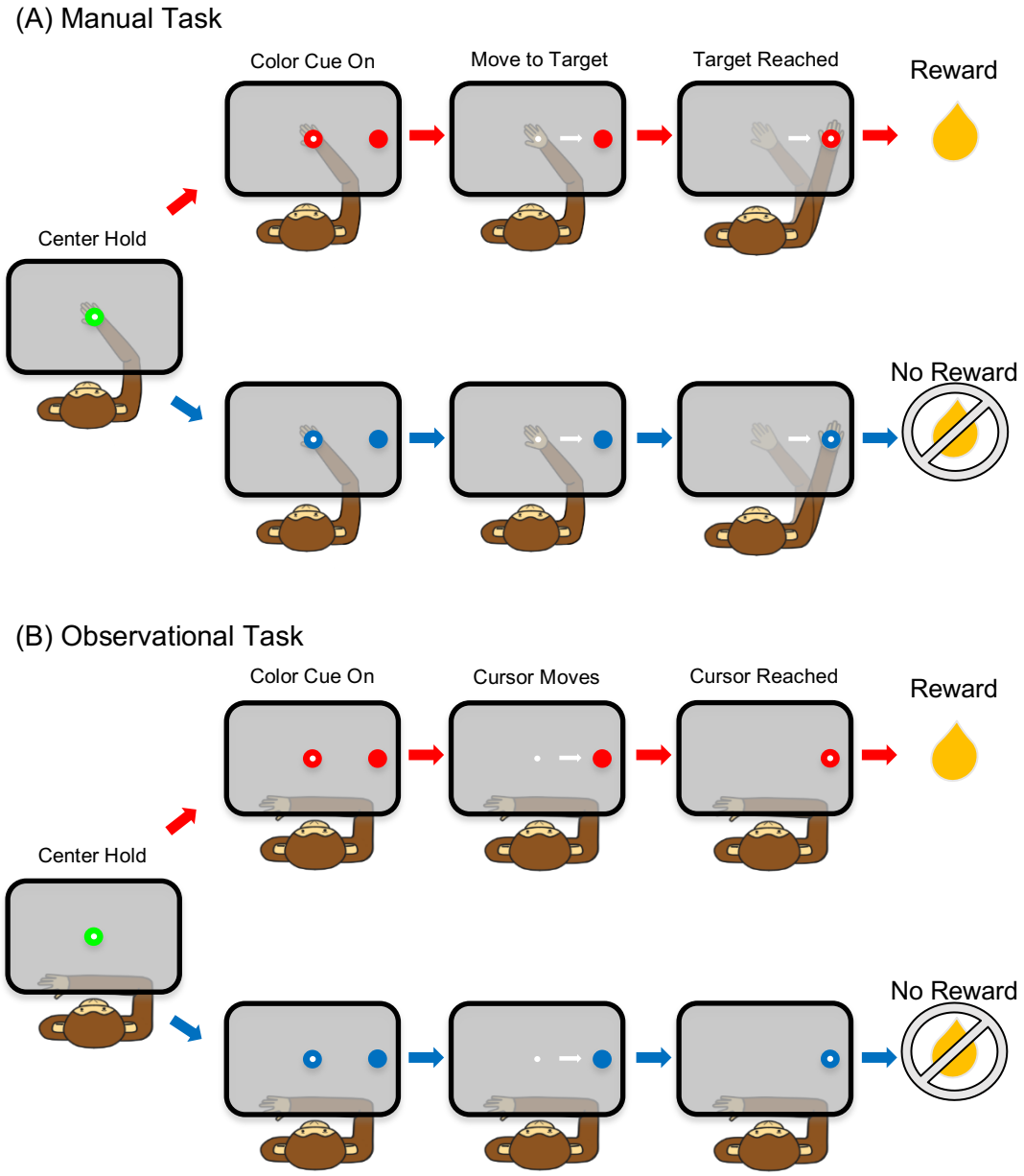

Figure 1. Schematic of the (A) manual task and (B) observational task.

Data Analysis

Firing Rate

To determine differences between rewarding and non-rewarding trials, firing rates were calculated using overlapping bins of 100 ms moving in increments of 5 ms. For each unit, n, the firing rate, $V_n^k(b)$, of each bin, b, of each trial, k, is determined by

$$V_n^k(b) = \frac{c_n^k(b)}{T}, \qquad (1)$$

where $c_n^k(b)$ is the number of spike counts per bin and T is the length of the bin in ms. For each unit, the firing rate is normalized across the entire session using min max normalization,

$$Vnormalized_n^k(b) = \frac{V_n^k(b) - \min(V)}{\min(V) - \max(V)}\ . \qquad (2)$$

The normalized firing rate, $Vnormalized_n^k(b)$, is distributed between 0 and 1.

Noise Correlation

Noise correlation refers to the trial-to-trial variations that are shared between pairs of units (Cohen and Kohn 2011). Noise correlation is equivalent to the Pearson correlation of the trial-by-trial firing rate variation of two units about their respective binwise means (Bair, Zohary, and Newsome 2001; Kohn and Smith 2005). The trial-by-trial firing rate variation was calculated for each unit, n, by

$$Vnoise_n^k(b) = Vnormalized_n^k(b) - \frac{\sum_{k=1}^{K} Vnormalized_n^k(b)}{K}, \qquad (3)$$

where K was the total number of trials. The Pearson coefficient of $Vnoise$ was found by

$$r_{noise}(n_1, n_2) = \frac{\mathrm{cov}(Vnoise_1, Vnoise_2)}{\sqrt{\mathrm{var}\,(Vnoise_1)\ \mathrm{var}\,(Vnoise_2)}}, \qquad (4)$$

and was calculated using the Matlab function “corr”. Correlation was calculated separately for each trial period and all trials of the same trial type were concatenated to find a single coefficient per unit pair. Only significant coefficients (p-value < 0.05) were selected for inclusion.

Evoked Response

The effect of firing rate on the noise correlation was quantified by analyzing the relationship between the unit pairwise evoked response and the crosscorrelation coefficient during the evoked response period of all unit pairs. The evoked response, $V_{ER}(n_1, n_2)$, was defined as the difference between the firing rate minimum during the "baseline" (pre cue) period and peak/maximum response firing rate during the (post cue) time period. It was calculated for each unit pair using the following set of equations:

$$V_{max}^{k}(n_1) = \max\,(n_1^k\,), \tag{5a}$$

$$V_{min}^{k}(n_1) = \min\,(n_1^k\,), \tag{5b}$$

$$V_{baseline}(n_1, n_2) = \sqrt{\frac{\sum_{k=1}^{K} V_{min}^{k}(n_1)}{K} * \frac{\sum_{k=1}^{K} V_{min}^{k}(n_2)}{K}}, \tag{5c}$$

$$V_{peak}(n_1, n_2) = \sqrt{\frac{\sum_{k=1}^{K} V_{max}^{k}(n_1)}{K} * \frac{\sum_{k=1}^{K} V_{max}^{k}(n_2)}{K}}, \text{ and} \tag{5d}$$

$$V_{ER}(n_1, n_2) = V_{peak}(n_1, n_2) - V_{baseline}(n_1, n_2)\,, \tag{5e}$$

where $V_{max}^{k}(n_1)$ is determined from the post cue period and $V_{min}^{k}(n_1)$ is determined from the pre cue period. The evoked response and correlation coefficient during the post cue period was found for each unit pair. Unit pairs from all sessions were combined for analysis.

Percent of Population

To better understand how correlation is affected by rewarding stimuli and contributes to reward modulation for individual unit pairs, significant differences in noise correlation between trial types were determined for each pair. To achieve this goal, noise correlation was calculated by trial by modifying the noise correlation equation (Equation 4) to

$$r_{noise}\left(n_1^k, n_2^k\right) = \frac{\mathrm{cov}\left(Vnoise_1^k, Vnoise_2^k\right)}{\sqrt{\mathrm{var}\,\left(Vnoise_1^k\right)\ \mathrm{var}\,\left(Vnoise_2^k\right)}}\,, \tag{6}$$

which provides a correlation coefficient for each trial, k, for each unit pair that had previously shown significant noise correlation as determined by Equation 4 (p-value < 0.05).

Identifying Reward Modulating Subpopulations

Selecting reward discriminatory units was achieved using the Pearson correlation between reward value and unit firing rate, where reward was assigned a value of 1 and non-reward is assigned a value of 0. We arbitrarily used the top 20% of units with the highest correlation coefficients, showing strong positive correlation with reward, were classified as “High Positive” units. The bottom 20% of units with the lowest correlation coefficients, showing strong negative correlation with reward, were classified as “High Negative” units. Lastly, the bottom 20% of units with the lowest absolute value correlation coefficients, showing the weakest correlation with coefficients close to zero, are classified as “Non-responsive” units. These subpopulations were determined for each time period separately, which means they may consist of different units during each period.

Mean-Matching Method

Reducing the effects of firing rate will increase the likelihood that observed changes in noise correlation are attributable directly to differences in modulation of stimulus response rather than a by-product of the rate changes already recorded. Mean-matching allows for a comparison of noise correlations under different states by equalizing the firing rate of the population between the different conditions. To mean-match correlation coefficients between rewarding and non-rewarding trials, the common distribution of geometric mean firing rates between the two trial types is determined. The common distribution is used to randomly select unit pairs such that two (rewarding and non-rewarding) subsets of unit pairs are created with identical distributions of firing rates. Mean-matching was performed with a bin width between 0.01 and 0.05 depending on the minimum firing rate in each period.

First, a histogram of the geometric mean firing rates was created for rewarding and non-rewarding trials with bins that are evenly spaced. For each bin, the lowest shared value was selected. For example, let’s say there were 56 unit pairs with a geometric mean firing rate between 0 and 0.015 for rewarding trials, and 16 unit pairs with a geometric mean firing rate between 0

and 0.015 for non-rewarding trials. Therefore, the common distribution would be 16 unit pairs with a firing rate between 0 and 0.015.

Next, a correlation distribution is created using a randomly selected subset of unit pairs based on the common distribution such that the rewarding and non-rewarding trials now share the same distribution of geometric mean firing rates. For example, for the rewarding trials there will be 16 unit pairs randomly selected from the 56 unit pairs with a firing rate between 0 and 0.015. Using this method for each bin of the common distribution, a subset of unit pairs is found for the rewarding trials and the correlation coefficients of these unit pairs is used to create the correlation distribution. The process is repeated 1000 times for both the rewarding and non-rewarding trials.

Finally, the correlation distribution is reduced to the mean-match correlation distribution. Because the correlation distribution is the cumulative result of 1000 random selections, using the correlation distribution to directly determine significant differences between trial types will result in a much greater significance than the number of real values can produce. The mean-match correlation has an identical distribution of correlation coefficients, but with the same total number of unit pairs as the original common distribution. For example, the first bin of the rewarding correlation distribution contains 1201 values and is reduced through a 1 time random selection to 120 unit pairs in the mean-match distribution. After mean-matching, both rewarding and non-rewarding trials share the same distribution of firing rates. This means that any significant differences between the distributions of correlation coefficients cannot be attributed to differences in firing rate. It is important to consider the unmodified correlation as firing rate and noise correlation are not independently occurring events and their interaction may be an equally important carrier of information. However, generating the mean-matched noise correlation coefficients confirms the presence of noise correlation changes in response to reward value.

The distribution of correlation coefficients after mean-matching remains higher for non-rewarding trials in the post cue period (Wilcoxon rank sum $p < 0.05$), and there was no longer any significant

differences between firing rates for all periods. The distribution of correlation coefficients is similar before and after mean-matching, however, there are two differences that can be seen in the Monkey A data. After mean-matching, non-rewarding trials are no longer significantly greater in the post reward period for the manual task, and rewarding trials have significantly higher coefficients for the observation task. The post cue period was the only period which showed consistently higher non-rewarding correlation during both tasks for both NHPs. For mean-matching the unit pair populations were combined over all sessions, bin widths of 0.04, 0.02, 0.045, and 0.04 were used for Monkey A manual, Monkey A OT1, Monkey Z manual, and Monkey Z OT1, respectively.

Results

In figure 2 we have plotted the average min-max normalized firing rate by trial type, rewarding or non-rewarding, across all units for all sessions. Changes in the normalized firing rate averaged across the whole population showed a peak firing rate during the 800 ms post cue period for NHP A manual task, NHP A observation task, and NHP Z manual task. During the observation task, NHP Z has a peak firing rate during the pre-reward period. These results align with previous work showing increased firing rate in response to a preferred stimulus and a higher overall rate for rewarding stimuli, which is strongest following cue onset (Marsh et al. 2015; Tarigoppula et al. 2018a). This trend can be observed in both the manual and observation tasks, indicating that reward modulation occurs in the motor cortex while performing a reaching movement and during passive observation as expected (Marsh et al. 2015). In addition, there are differences between the manual and observation tasks consistent with previous research (Tarigoppula et al. 2018a). The pre-cue period in NHP A and Z observation task (Figure 2B and 2D) showed significant differences in firing rate between the trial types not present in the manual task. This separability can be attributed to the predictable nature of the sequencing in the OT task for NHP A, which had a repeating sequence of R trials followed by NR trials, in comparison to the

randomized trial sequence in the manual tasks, and for NHP Z OT presumably due to the bias in the R trials at 2 to 1 over NR trials. As subject A learned the sequence of R-NR the differences in firing rate can be seen before the cue onset. For more on this tracking of the sequence structure see (Tarigoppula et al. 2018a).

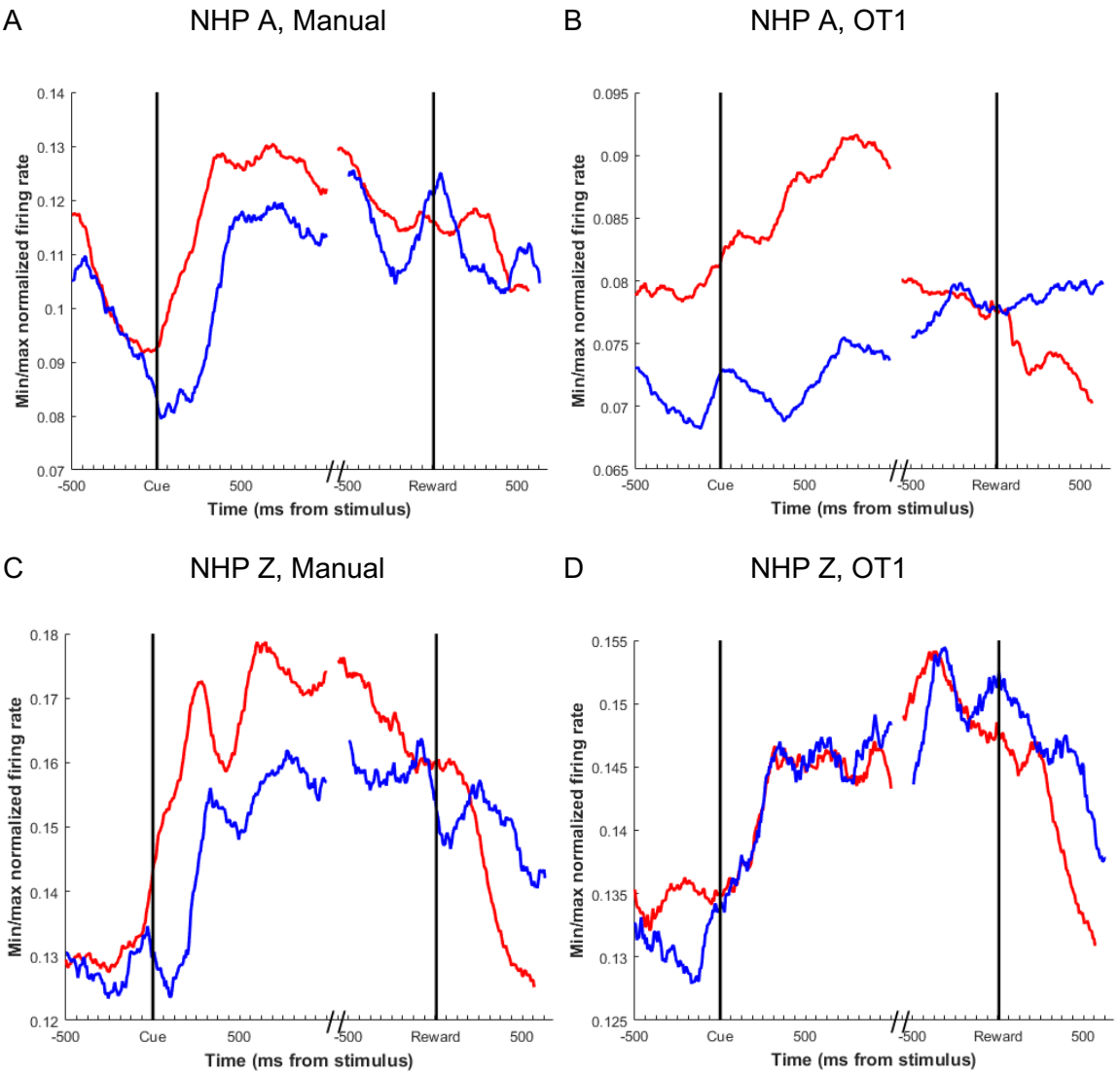

Figure 2. Normalized firing rate for rewarding (red) and non-rewarding (blue) trials averaged across all units and sessions, N = 3 for each plot except for plot A with 4 session.

While the combined activity of all recorded units shows separability between rewarding and non-rewarding trials, there is evidence that this separability can be attributed to select units (Marsh et al. 2015). Analysis of these data sets revealed a subpopulation with increased firing

rate during rewarding trials and another with increased firing rate during non-rewarding trials. Figure 3 illustrates the percentage of units in each time period that modulate for reward. In each graph, red indicates a higher firing rate for reward, blue indicates a higher firing rate for non-reward, and grey indicates no significant difference between the two trial types (Wilcoxon rank sum, $p < 0.05$). For both NHPs, most of the units modulate for reward when firing rate is compared in each time period. There are a larger percentage of units with significantly higher firing rates for rewarding trials in the pre-cue and post-cue periods (Figure 3). During the pre-reward and post-reward periods of the OT task, both NHP A and NHP Z show a greater percentage of units with increased firing rate in non-rewarding trials.

The differences in firing rate between rewarding and non-rewarding trials confirms that reward modulation occurs in the motor cortex during center-out reaching tasks (Marsh et al. 2015). This metric alone, however, does not provide a complete perspective on the dynamics of these populations. Further analyzing the interactions between these units is critical to understanding the more broadly the cortical state.

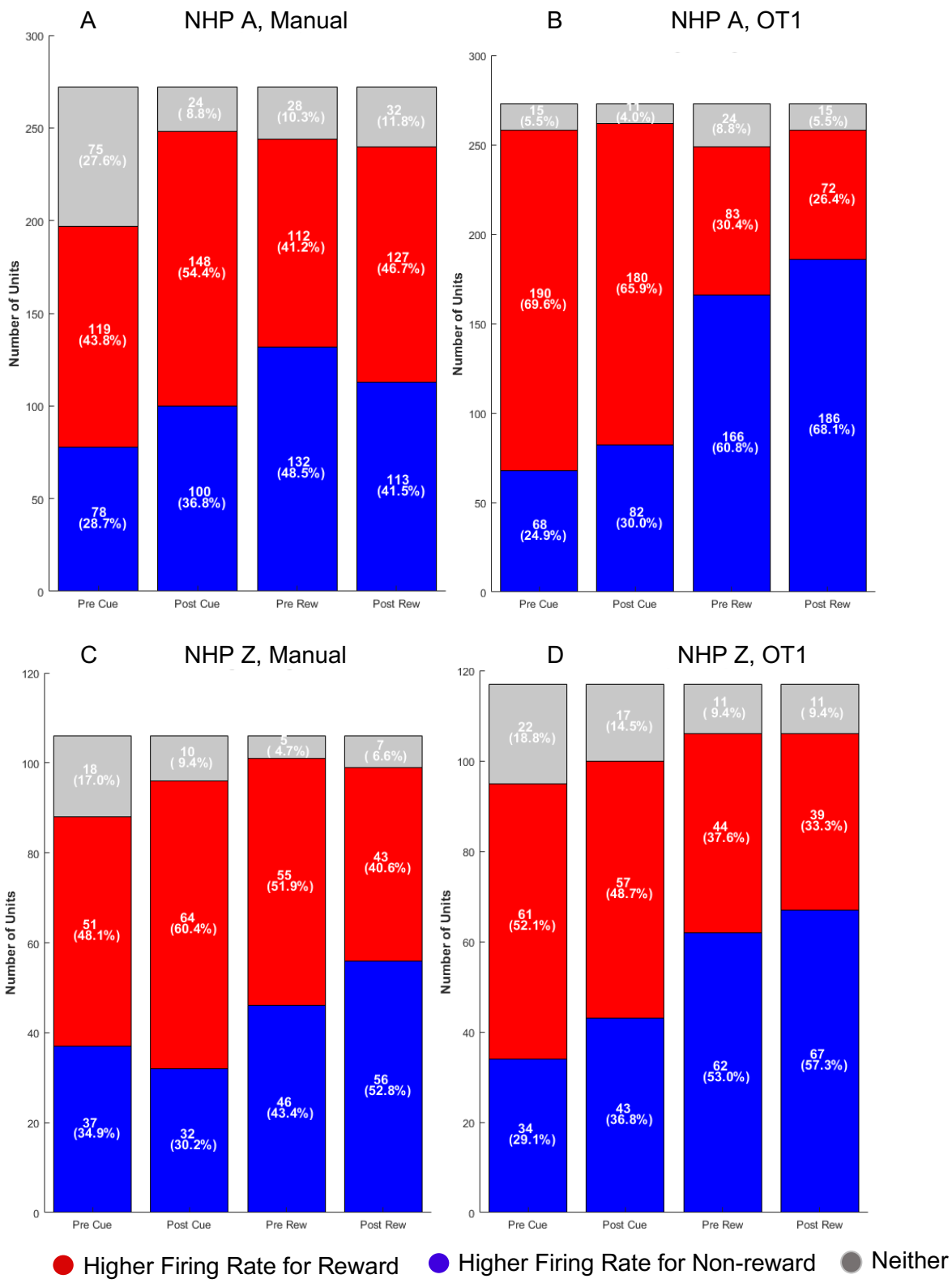

Figure 3. Percentage of units with significantly higher firing rates for rewarding (red) and non-rewarding (blue) trials in each time period.

Noise Correlation

The observed correlation includes both positive and negative coefficients which results in a mean noise correlation close to zero, similar to the range given by Ecker et al., of 0.01 to 0.03 (Ecker et al. 2010). Figure 4 displays the mean-matched correlation coefficients. The mean-matched correlation is the mean correlation of a subset of unit pairs selected such that the rewarding and non-rewarding trials share the same unit pair geometric mean firing rate (see methods). This process serves to reduce the effect of firing rate on noise correlation and is necessary to prove that noise correlation differences cannot be explained solely by the changes in significant differences in firing rate observed between the rewarding and non-rewarding trials (Figure 3). The results show higher correlation coefficients for non-rewarding trials, with some variation across time periods, task, and subject. During the manual and observation tasks, both subjects showed significantly higher correlation for non-rewarding trials during the post cue period, which holds true for the non-mean-matched data as well (data not shown).

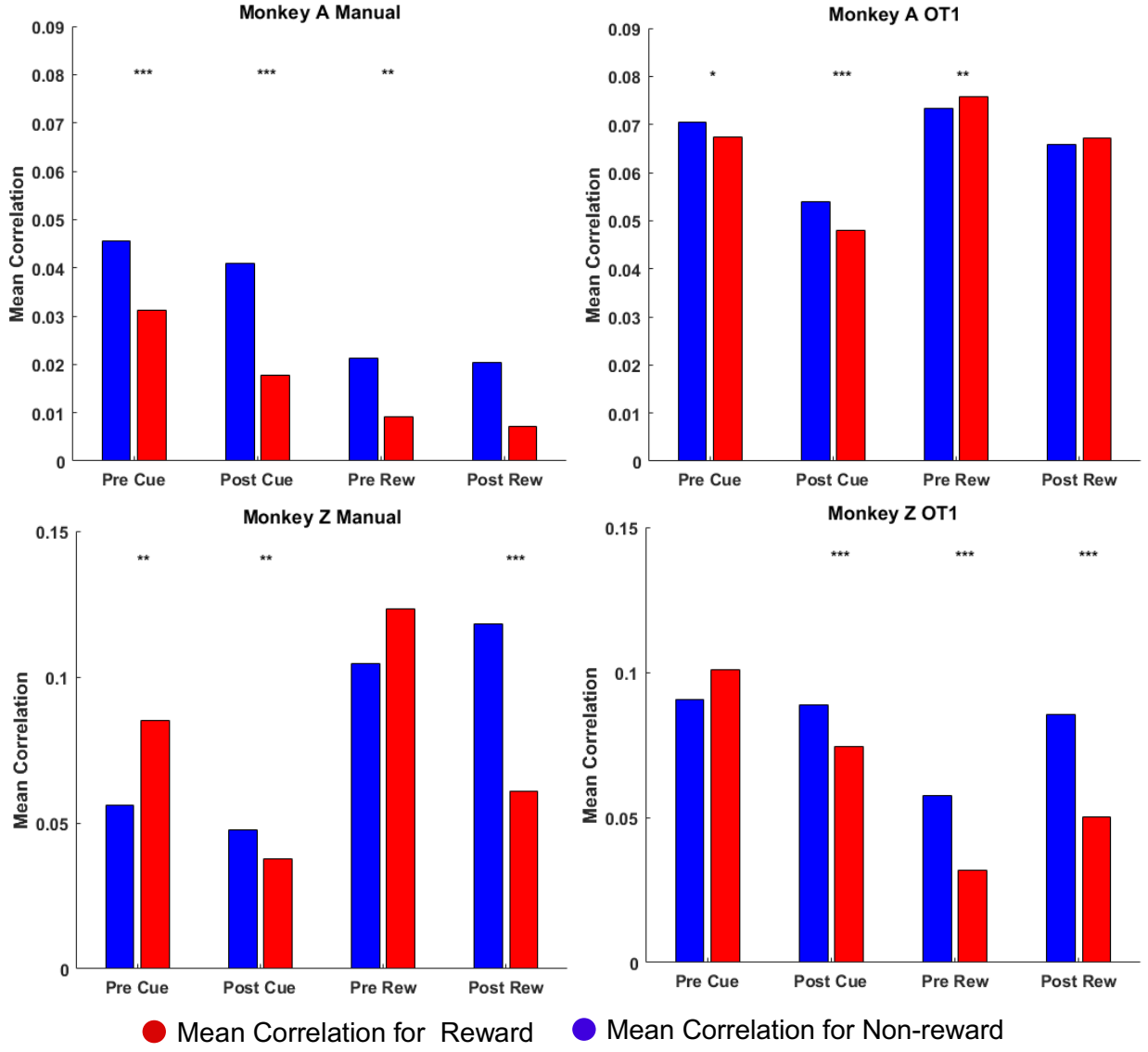

Figure 4. Mean correlation for rewarding (red) and non-rewarding (blue) with significant differences determined by Wilcoxon rank sum ($p < 0.05$, $p < 0.01$, and $p < 0.001$ denoted by *, **, and *** respectively). All values were determined after firing rate mean matching as described in the methods.

Effects of firing rate

Previous work indicates that an increase in firing rate causes an increase in correlation (de la Rocha et al., 2007). Understanding how firing rate and noise correlation are related in these tasks can reveal information about the underlying cortical networks. Both NHP A and Z demonstrate higher correlation for non-rewarding trials regardless of the relationship between evoked response and correlation coefficient. The relationship between noise correlation and firing rate differs between the trial types and NHPs (Figure 5). In NHP A, noise correlation showed a strong, positive linear relationship with firing rate during the manual task (Figure 5A). However, for NHP A observation task, there was an inverse effect on non-rewarding trials that resulted in a sharp decrease in correlation at higher firing rates (Figure 5B). For NHP Z, there was a negative linear relationship during low evoked responses for both the manual and observation tasks (Figure 5C and 5D). However, in general there is higher correlation during non-rewarding trials as compared to the corresponding rewarding trials bins.

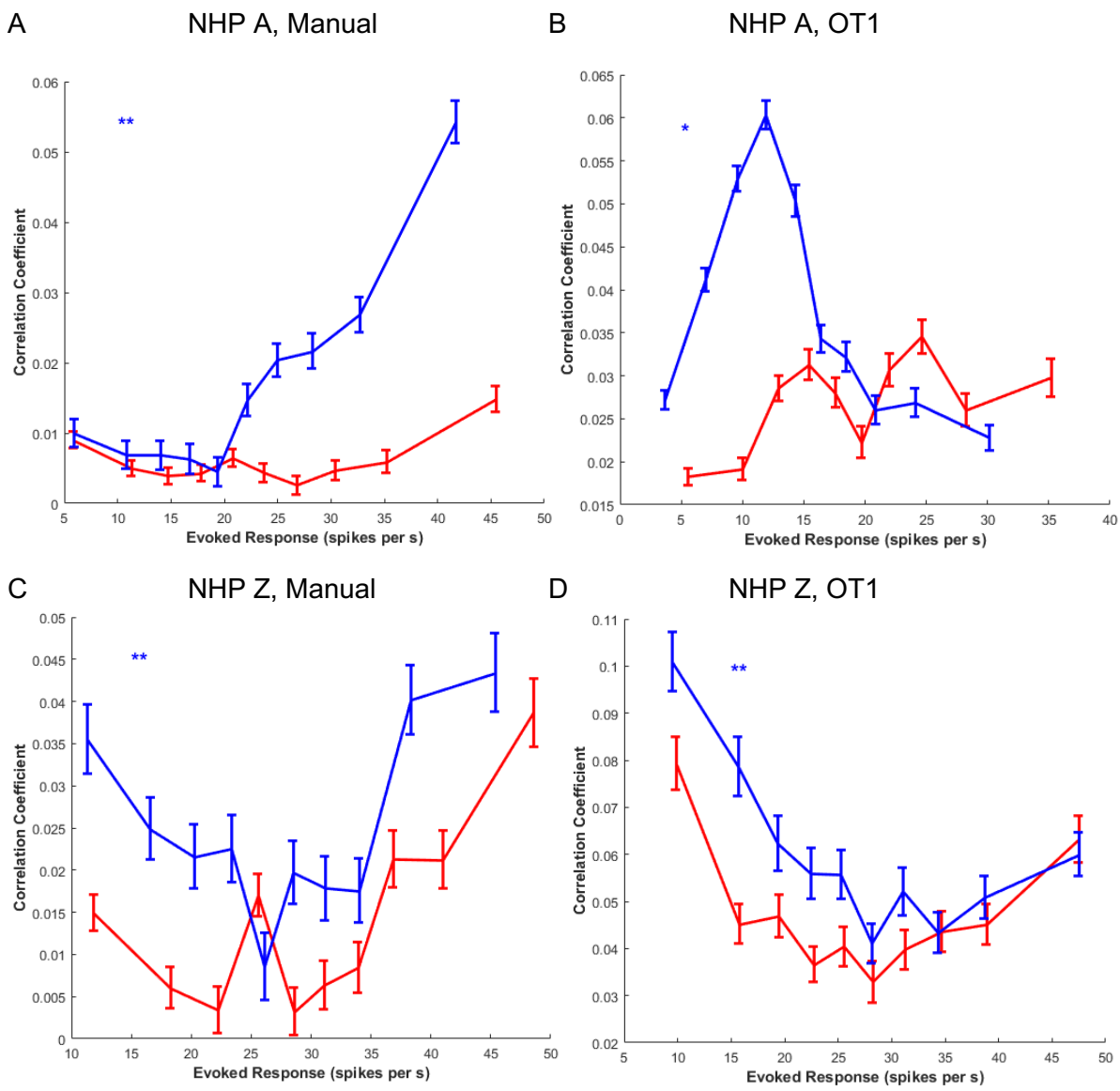

Figure 5. Correlation coefficient plotted against evoked response for (A) NHP A manual task, (B) NHP A OT1 task, (C) NHP Z manual task and (D) NHP Z OT1 task for rewarding (red) and non-rewarding (blue) trials.

Sign (+/-) of the correlation

Figure 6 shows the separation of mean positive and negative noise correlation. Positive (gray) and negative (black) correlations are shown with red dashed lines indicating the mean value for rewarding and non-rewarding trials. Previous studies have related lower information encoding capacity to increases in positive correlation, referring to the mean response of a population of neurons (Zohary, Shadlen, and Newsome 1994). Dissecting the distribution of these coefficients by separating positive and negative correlations may explain discrepancies between subjects and task types and reveal additional information about the role of noise correlation (Chelaru and Dragoi 2016). For NHP A manual task, the positive and negative coefficients are both greater in absolute value for all time periods for non-rewarding trials. This aligns with the mean correlation which is higher for non-rewarding trials (Figure 6). For NHP A observation task there is increased negative correlation for rewarding trials during the post cue and pre reward periods (Figure 6). Although both periods share this higher negative correlation for rewarding trials, the post cue and pre reward periods have different mean correlations. The post cue period has a higher mean correlation for non-rewarding trials while the pre reward period is higher for rewarding trials. The positive correlation reflects the trends observed in the mean correlation changes (Figure 6).

The positive correlation also better represents the mean correlation distribution for NHP Z manual and observation tasks (Figure 6). NHP Z manual task has increased positive correlation and decreased negative correlation during rewarding trials in both the pre cue and pre reward periods. All other periods show greater correlation during non-rewarding trials for both negative and positive coefficients. Lastly, the NHP Z observation task displays similar trends to NHP A manual data with all periods demonstrating higher negative coefficients for non-rewarding trials. The differences between rewarding and non-rewarding trials in the overall correlation distribution reflect the changes in the positive correlation distribution, regardless of the changes in the distribution of negative coefficients.

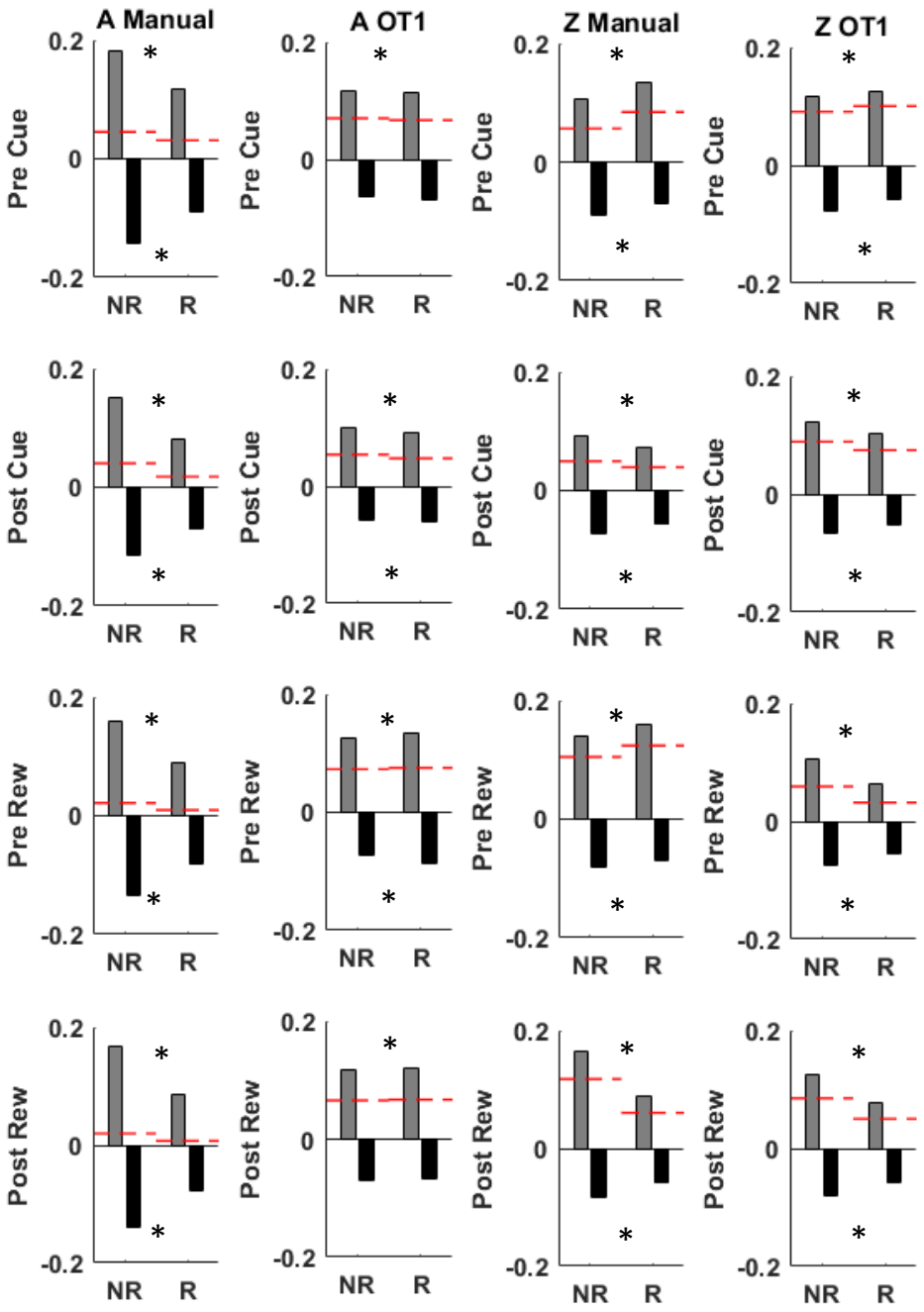

Figure 6. Mean correlation of positive (gray) and negative (black) correlation coefficients for non-rewarding (NR) and rewarding (R) trials. Red lines indicate overall mean. Significant differences between rewarding and non-rewarding were determined by Wilcoxon rank sum ($p < 0.05$ denoted by *).

Percent of Population

Considering only unit pairs with significant correlation coefficients, the significance of the difference between rewarding and non-rewarding correlation was determined by Wilcoxon rank sum (p-value < 0.05) for each unit pair. Unit pairs were classified as either having a higher noise correlation during rewarding (red) or during non-rewarding trials (blue) (Figure 7). NHP A shows a greater percentage of unit pairs with higher non-rewarding noise correlation in all time periods. This indicates that during a non-rewarding trial, there will be more unit pairs that increase their correlation in comparison to the correlation exhibited during the rewarding trial. A large percentage of unit pairs that show significant noise correlation, do not demonstrate a difference between rewarding and non-rewarding trials (gray). These results provide additional evidence that differences between rewarding stimuli correspond to differences in noise correlation in only a subset of unit pairs. NHP A observation, NHP Z manual, and NHP Z observation data all follow a similar trend with more unit pairs showing higher noise correlation for non-rewarding trials (Figure 7). The post cue period consistently shows a higher number of unit pairs with increased correlation for non-rewarding trials across all NHPs and tasks.

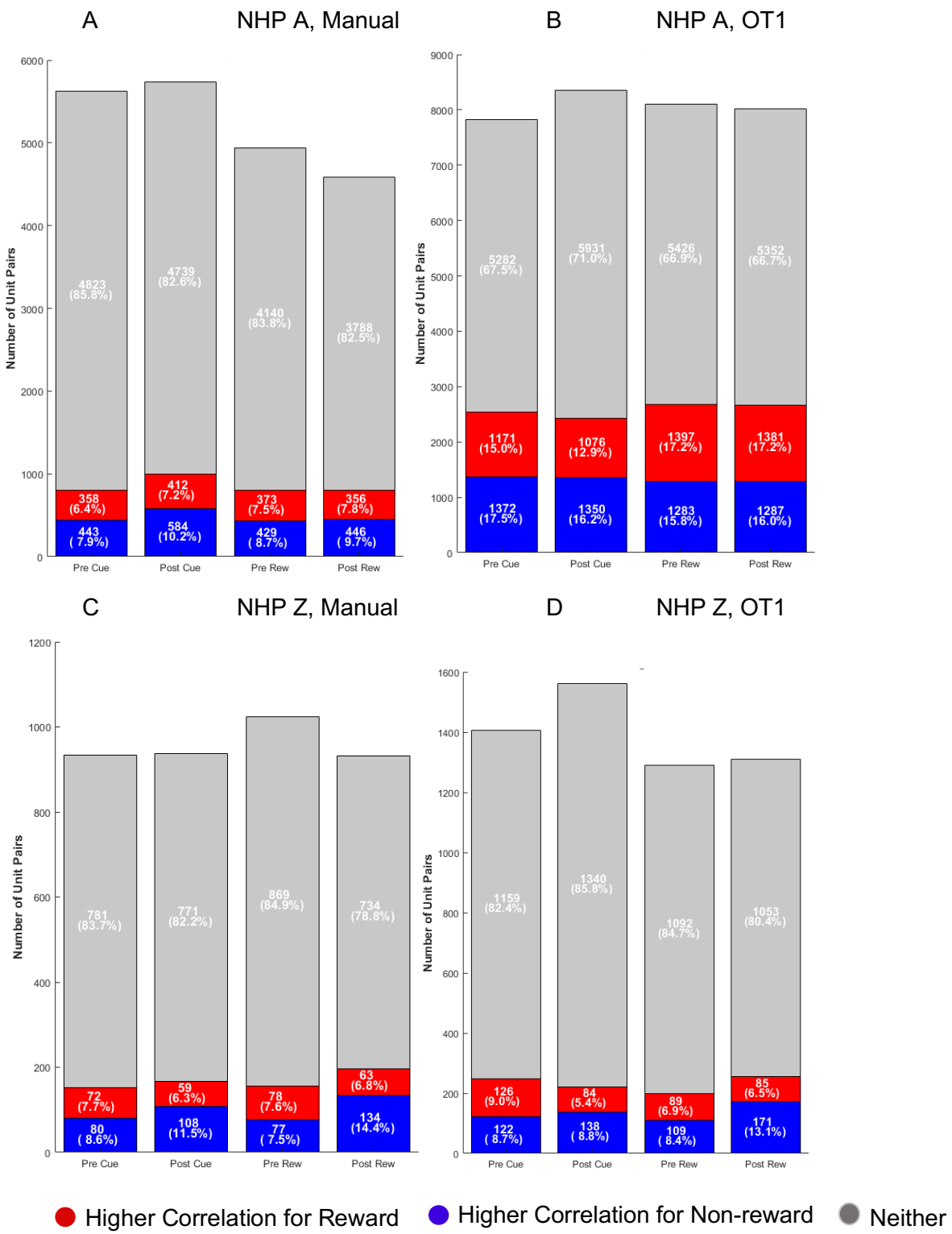

Figure 7. Percent of unit pairs that have higher correlation for rewarding (red), non-rewarding (blue), or neither (gray) trial type for (A) NHP A manual, (B) NHP A observation, (C) NHP Z manual, and (D) NHP Z observation tasks.

Reward Modulating Subpopulations

While it is apparent that noise correlation differences in response to reward are present in only a subset of unit pairs, the defining features of these subpopulations is still unclear. To use noise correlation as an indicator of reward, selecting subpopulations that are known to modulate for reward through firing rate provides a more direct comparison between these two factors. Figure 8 shows the mean correlation for rewarding and non-rewarding trials for each subpopulation, which are units with rates that are upmodulated during rewarding trials (High Positive), units with rates that are downmodulated during rewarding trials (High Negative) and units not modulated by reward (Non-Responsive, see methods). For NHP A manual task, the High Positive group shows significant differences in the correlational structure of the network (Fig.8) between rewarding and non-rewarding trials only during the post cue period, however, the High Positive subpopulation is significantly different from the Non-responsive subpopulation in almost all time periods and trial types. The High Negative subpopulation shows significantly higher correlation for rewarding trials during the post reward period. For NHP A observation task, the High Positive subpopulation has significantly lower correlation for rewarding trials during the pre cue and post cue periods, while the High Negative population shows significantly higher correlation for rewarding trials during the pre reward and post reward periods.

For NHP A, the behavior of the High Positive and High Negative populations supports the hypothesis that reducing correlation improves encoding accuracy. For all periods with significant differences, the High Positive modulating units, which increase firing rate during rewarding trials, showed a decrease in noise correlation during reward. Similarly, the High Negative modulating units showed a decrease in noise correlation during the non-rewarding trials.

Figure 8.C-D depicts the mean correlations for NHP Z. Only the Negative subpopulation shows significant differences between rewarding and non-rewarding trails. Contrary to the trends seen in the NHP A data, the NHP Z Negative subpopulation shows decreasing noise correlation during rewarding trials during the post cue and post reward periods for both the manual and

observation tasks. This opposite relationship between firing rate modulation and noise correlation modulation may be related to the different recording sites. The ipsilateral placement of the NHP Z implants might be the cause of the differences observed. In addition, NHP Z is a female while NHP A is a male, further work is needed to determine if this is true.

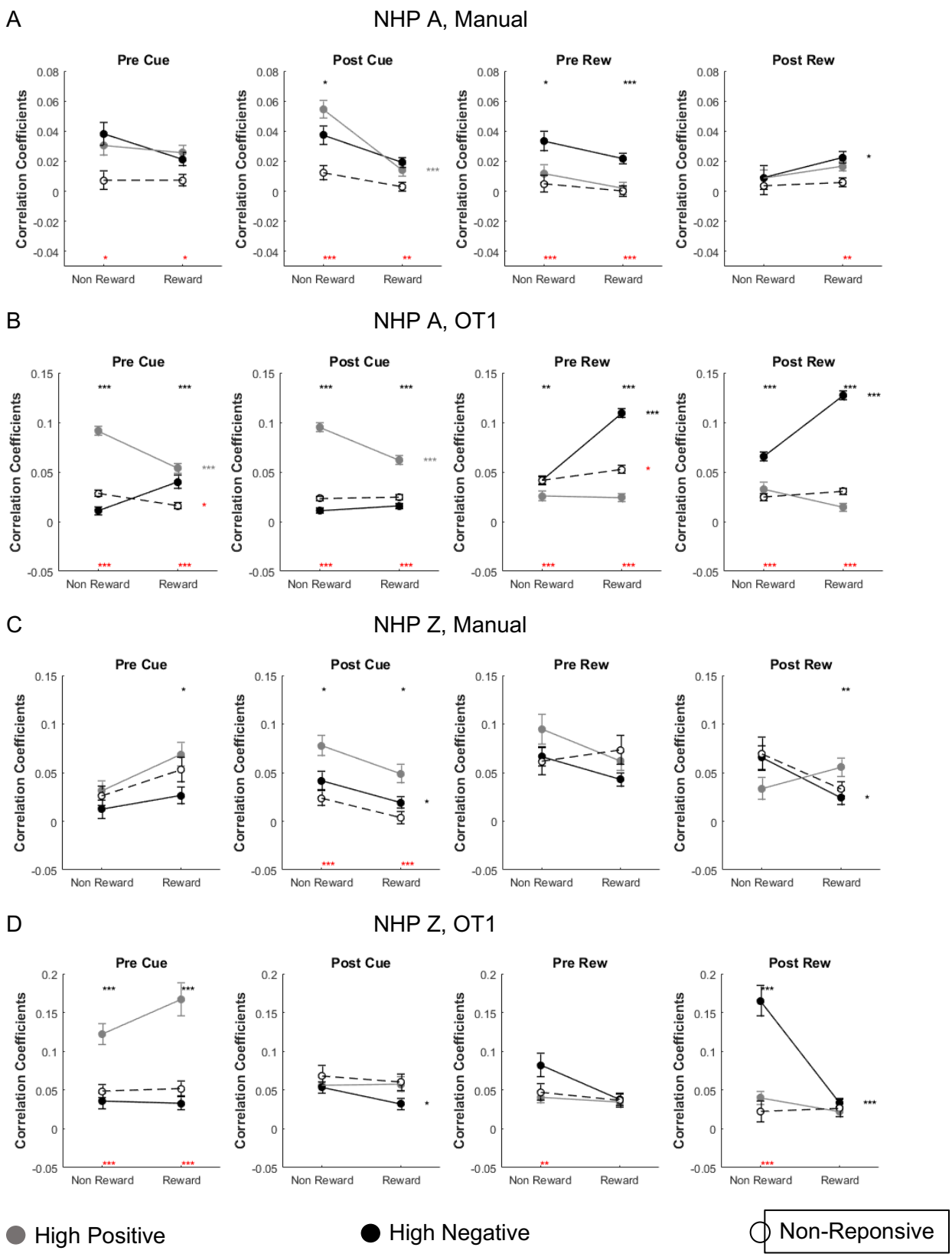

Figure 8. Mean correlation coefficient for the High Positive, High Negative and Non-responsive subpopulations for (A) NHP A manual task, (B) NHP A observation task (C) NHP Z manual

task and (D) NHP Z observation task. Black asterisks located at the top of the graph indicate if there is a significant difference between the High Positive and High Negative subpopulations. Red asterisks at the bottom of each graph indicate if either reward modulating population (High Positive or High Negative) has significantly different correlation coefficients than the Non-responsive subpopulation. The asterisks to the right of the graph indicate if there is a significant difference between the rewarding and non-rewarding correlations for each subpopulation (red for non-responsive, black for high negative and gray for high positive). Significance determined using Wilcoxon rank sum ($p < 0.05$, $p < 0.01$, and $p < 0.001$ denoted by *, **, and *** respectively).

Discussion

The primary goal of this analysis was to determine if significant differences in noise correlation exist between cued rewarding and non-rewarding trials, and if so, to what extent might these differences relate with reward modulation of firing rates. As previously described, firing rate reward modulated units are present in these data sets (Tarigoppula et al. 2018a; Marsh et al. 2015), with one subset of M1 units demonstrating increased firing rates during rewarding trials and one subset showing increased rate during non-rewarding trials (Figure 3). Because of the capacity for reward modulation demonstrated by these M1 units during both manual and observation tasks, it was predicted that there would be significant differences in noise correlation between rewarding and non-rewarding trials.

The noise correlation was determined from the Pearson correlation coefficient of normalized trial-by-trial variations. When considering all unit pairs with significant correlation, non-rewarding trials showed significantly higher noise correlation. Although this trend is present in multiple time periods, it is only consistently present in both NHPs and during both manual and observational tasks during the post reward level cue period (Figures 4). The post cue period also showed the greatest difference in the mean correlation between trial types for NHP A, while the post reward period shows the greatest difference in mean for NHP Z (Figure 6). The learned association between cue and reward through operant and classical conditioning shifts the increased firing rate response from the post reward to the post cue period and has been demonstrated in these data sets (Tarigoppula et al. 2018a). Likewise, we have previously shown

increases in spike field coherence (SFC), phase amplitude coupling (PCA) and power in these data sets in the alpha frequency band that seems more consistent from NHP to NHP and dataset than the current noise-correlation results, but follows the same pattern that these measures are all increased during non-rewarding trials (An et al. 2019), and allow for high trial type classification on a trial by trial basis (An et al. 2018).

There are several possible explanations underlying the increase in correlation during the post cue period of non-rewarding trials including changes in attention, firing rate, or, as previously mentioned, reward. The first relies on changes in visual attention, where attention may either be a coexisting, driving factor of correlation or a separable, but resembling factor that produces similar dynamics to those induced by reward or motivation. Given the predictable nature of the trial reward value sequence (NHP A observation), visual attention could be a confounding factor when discussing the relationship between reward and noise correlation. It is possible that the subjects' ability to anticipate a lack of reward resulted in a shift to an unattended state during non-rewarding trials, even before the trial started. Unattended trials show increases in correlation (Cohen and Maunsell 2009; Herrero et al. 2013; Mitchell, Sundberg, and Reynolds 2009) and could account for the higher correlation coefficients seen in the non-rewarding trials of the present study. In support of this hypothesis, the OT tasks produce mean noise correlations higher than the manual tasks during the post cue period. Although this may be related to the lack of physical movement during action observation, it is possible that reduced attention is also an influence. However, the significant differences in noise correlation are also present in manual tasks which indicates that the effects of attention are not sufficient to describe the observed trends as the NHPs still had to attend to the task in order to complete it properly. However, we can't state that there wasn't less attention for non-rewarding trials than for rewarding manual trials. We have shown previously that using a task with multiple levels of reward leads to both linear trends in firing rate with value (Tarigoppula et al. 2018), as well as non-linear gain modulated activity

patterns (Hessburg, Zhao, and Francis 2019), making it seem unlikely that all of our results are attributed to attention alone.

The second potential factor impacting increased non-rewarding correlations is firing rate. Previous studies have demonstrated that increases in firing rate are related to increases in correlation (de la Rocha et al. 2007). “Integrate-and-fire” models indicate that output correlation increases in response to increasing firing rate when the input correlation remains unchanged (de la Rocha et al. 2007). This pattern is illustrated by the increase in noise correlation with increasing evoked response rates in NHP A manual task and to a lesser extent, in NHP A observation task (Figure 5). However, despite the relationship with firing rate, non-rewarding trials continue to exhibit higher noise correlation than rewarding trials. The response to changes in rewarding stimuli is similar to the pattern seen in attention, with higher evoked rates leading to greater differences between the two states (Cohen and Maunsell 2009). With increases in evoked response, the difference between non-rewarding and rewarding noise correlation increased for NHP A manual data. However, there are conditions where this relationship does not hold true. NHP Z, during both the observation and the manual task, showed a decrease in correlation with an increase in evoked response with non-rewarding trials maintaining a higher correlation coefficient regardless of rate changes (Figure 5).

Attention, stimulus contrast (Kohn and Smith 2005), learning (Gu et al. 2011; Jeanne, Sharpee, and Gentner 2013), and global cognitive factors (Ruff and Cohen 2014) have been shown to decrease noise correlation in neurons within the same cortical area. Given the wide variety of factors impacting correlation, the increases during the non-rewarding trials could be the result of independent modulatory influence of reward on noise correlation. Previous studies provide insight into the ways in which this difference in correlation between states serves to improve information encoding. High levels of positive correlation can be detrimental to the coding accuracy of a similarly tuned population of neurons (Zohary, Shadlen, and Newsome 1994). Cohen and Maunsell determined that the “modulation of noise correlation accounts for the

majority of the attentional improvement in population sensitivity", with modulation of firing rate and single unit variabilities accounting for a much smaller portion of the change (Cohen and Maunsell 2009). Similarly, high correlation limits signal-to-noise ratio (SNR), with higher correlations leading to lower saturation of SNR as a function of neuronal pool size (Mitchell, Sundberg, and Reynolds 2009). Much like the trends seen in this research, Mitchell et al., notes that the effects of firing rate on the SNR saturation point does not adequately account for the differences in SNR ratios observed between units with high or low correlation (Mitchell, Sundberg, and Reynolds 2009).

There is strong evidence that increases in non-rewarding trial noise correlation is related to reward modulation. However, the mean correlation does not provide a complete picture of the correlation activity in the population. An additional factor that may be impacting reward modulation is the distribution of positive and negative correlation coefficients. A mean positive correlation reduces the coding capacity of similarly tuned neurons by reducing the beneficial effects of adding or averaging responses, a limitation not present with units showing negative correlation (Zohary, Shadlen, and Newsome 1994). There are more unit pairs that share a positive correlation and the change in the positive correlation coefficients between non-rewarding and rewarding trials shows a greater impact on the mean correlation. This aligns with previous evidence that changes in positive correlation specifically are the primary cause of the overall change in mean correlation. In the visual cortex, changes in orientation have been found to decrease positive correlation while negative correlation remained stable with shifts in preferred direction (Chelaru and Dragoi 2016). In a recurrent network model, a lower firing rate and decreased negative noise correlation is generated with increased local inhibition and reduced excitation, resulting in an increased SNR (Chelaru and Dragoi 2016). Our results show that rewarding trials have decreased positive correlation and a negative correlation that most often either decreases or remains unchanged (Figure 6). The combined effect typically results in a decrease in mean correlation, as described above (Figure 6). These results could be adhering to the trends seen in tuning direction, where the negative correlation is unchanged in response to changes in condition. It could also be

asserted that the instances where negative correlation are decreased for rewarding trials serve as a counter mechanism to the positive correlation, using negative correlation changes to improve encoding during non-rewarding trials. However, there is not enough evidence to support this claim based on the current analysis.

The results support the hypothesis that non-rewarding trials will have higher noise correlation coefficients. The separate analysis of reward modulatory subpopulations provides additional evidence that these changes in correlation are related to shifts in reward state rather than to changes in attention, learning, or motor behavior (Figure 8). The lower overall correlation values during rewarding trials aligns with previous research suggesting that decreases in correlation correspond with increased encoding capacity in similarly tuned neurons and homogeneous populations. Based on this information, it is possible to conclude that noise correlation plays a significant role in reward modulation in the motor cortex. Moving forward, this work has applications in the improvement of brain computer interfaces. Incorporating the context-dependent changes in noise correlation into neural models may improve decoding efficiency and increase BCI performance. Likewise, incorporating noise correlation into the neural state representation for a neural critic to be use in a reinforcement learning (RL) BCI should help improve the performance of such RL-BCIs (An et al. 2018; Sanchez et al. 2011; Prins, Sanchez, and Prasad 2017).

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