Relationship between Dorsal Raphe Nucleus Neuronal Population Activity with Cortical Rhythms

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***Abstract*— Studies have shown that the firing activity of single neurons in the dorsal raphe nucleus (DRN) brain region is linked to slow wave oscillations in the cortex, especially the frontal cortex. However, most studies consist of either single DRN neuronal or single-channel electrocorticogram (ECoG) recording. Hence, it is unclear how a population of DRN neurons with electrophysiologically diverse characteristics can coordinate and relate to the oscillatory rhythms in different cortical regions. In this work, in anaesthetized mice, we simultaneously record extracellularly a group of DRN neurons and three cortical regions using electrocorticogram (ECoG). The cortical regions are the two bi-hemispheric frontal and one (right) occipital regions. Using coherence analysis, we investigate the relationship between DRN neurons and cortical rhythms. We then found the coherence between firing activities of DRN neurons to quantify the relationship. We found that most slow firing DRN neurons with regular and irregular spiking characteristics have significantly stronger relationship with cortical ECoG signals at frequencies of oscillation around 0.5-1 Hz and 3.5-3.8 Hz, especially with the frontal cortex. Moreover, the simultaneously recorded DRN neurons were generally found to be weakly correlated with each other. In summary, these findings suggest that slow firing DRN neurons, potentially 5-HT neurons, exhibit strong relations with frontal cortical activities even though the neurons have weak correlation with each other. Future work will investigate using more samples and to identify the specific types of DRN neurons, for example, whether they are serotonergic neurons.**

Keywords — Dorsal raphe nucleus, neuronal firing activity, cortical oscillations, cortico-subcortical coherence, neuronal spike correlation.

I. Introduction

Serotonin (5-HT) is a class of endogenous neurochemicals, called neuromodulators, that can modulate neural activities, which in turn can affect cognition, emotion and behaviour [1]–[4]. Sources of 5-HT in the brain largely arise from the raphe nuclei deep in the brain, including the dorsal raphe nucleus (DRN) located in the brainstem [1]. It has been shown that there is heterogeneity of DRN neurons in terms of electrophysiological and neurochemical characteristics [5]–[9].

The DRN receives several inputs from various parts of the brain[10], [11] including from the prefrontal cortex (PFC)[12]–[16]. There are evidences that indicate the prefrontal corticoraphe projection could be mediated by glutamatergic synapses [14], [17]. Further, high frequency stimulation of pyramidal neurons in the prefrontal cortex is shown to inhibit 5-HT activities in the DRN[12], [18]. State-of-the-art optogenetic stimulation of the prefrontal cortex has shown potent effects on the DRN activity and behaviour [17], [19], which may have implications in brain disorders, especially the dysfunctions in mood regulation and stress processing [17], [19], [20], as also reflected in abnormal neural activity oscillatory patterns[21].

At the other end of the PFC-DRN circuit, 5-HT-producing neurons from the DRN are known to innervate the cortex, providing major projection to the frontal cortex [13]. Electrical stimulation of the DRN releases 5-HT that modulates both the frequency and amplitude of cortical slow-wave oscillations in the prefrontal cortex (PFC) [13], [22]–[24]. This slow-wave activity is normally present during natural sleep but can also be induced by certain anaesthetics like urethane [25]. It has also been found that 5-HT1A receptors, a subtype of 5-HT receptors, decreases the firing rate of fast spiking interneurons in the PFC, whereas 5-HT2A increases the firing rate of the fast spiking interneurons in the PFC [26], but overall increases the signal power of cortical slow wave oscillations [13].

In [27], it reveals that most DRN 5-HT neurons, including those with clock-like and bursting firing activities, are found to have significant coherence with cortical oscillations. Specifically, these neurons typically fire more frequently during the inactive phase (trough) of the slow cortical oscillation. Interestingly, almost 50% of the bursting 5-HT neurons do not show any significant coherence with cortical rhythms. In contrast, the non-5-HT neurons in the DRN fire at a higher rate during the active phase (peak) of the slow cortical waves. Hence, within the DRN, electrophysiologically and neurochemically distinct neuronal groups exhibit distinct relations to cortical activity.

Overall, the abovementioned evidences indicate a tight reciprocal relationship between the cortex, especially the PFC, and the DRN. However, most of the studies typically involved single-cell recordings and/or focused on slow-wave cortical

activity. Moreover, previous studies did not take into account several cortical regions during ECoG recording. Thus, it is not clear how the DRN neuronal population as a whole work in concert with the cortex, and how different cortical regions are comparatively associated with the DRN activity.

To address these, we have performed simultaneous (extracellular) recordings of the DRN neuronal population firing activity in conjunction with the monitoring of ECoGs across multiple cortical regions. We computed pairwise coherence between DRN neuronal firing activities and the ECoGs. This was also done between the spike trains of the DRN. Overall, at least for the samples investigated, our study found that most slow firing DRN neurons (regular and irregular) have stronger relationship with cortical, especially frontal cortical, ECoG signals at frequency of oscillations around 3.5-3.8 Hz. Further, it has been found that the DRN neurons are sparsely correlated with each other.

II. METHODS

A. Experiment

The open-source Open Ephys tool[28] was used to record the electrocorticograms (ECoGs) in two urethane-anaesthetised SERT-CRE mice. We used anaesthetized animals because the data is more stable to analyse. Simultaneously, extracellular electrophysiological recordings were done using 32 channels using a silicon probe (Cambridge NeuroTech, 32 channels) stereotaxically implanted into the DRN (-4mm posterior to brema). The recordings were done continuously for 1-hour for each session with sampling rate, Fs=30 KHz.

ECoG electrodes (3 channels) were placed bilaterally over the frontal cortex and right occipital cortex to record brain state (frontal channels: +1 mm anterior and +- 1.5mm lateral to bregma; occipital channel: -2.5mm posterior and + 1.5mm lateral to bregma). The frontal cortices were selected based on previous studies showing their interactions with the DRN, while the (right) occipital cortex was selected based on previous study showing 5-HT influence in this brain region.[29] Further, the frontal cortex is well-known for high-level cognitive control [30]while the occipital cortex is more for sensory (visual) processing[31] very different functional roles.

B. Data Preprocessing

Raw neuronal spiking data acquired from the 32 channels were filtered and single units were identified automatically using Kilosort[32] and verified by manual clustering using the software package Phy[33]. Spike trains were further analysed to reveal spike waveform characteristics, firing rate and firing regularity.

The spiking activities of DRN neurons were labelled with their corresponding subtypes, namely, slow regular, slow irregular, fast regular, fast irregular, and clubbed together to form the spike trains. Instantaneous firing rates (IFR) of the DRN neurons were derived from the corresponding neuronal spike trains using non overlapping time bins of 5 ms, using the Elephant toolbox in Python 3.0[34].

The 3 ECoG signals were band limited to 25 Hz using a 5th order Butterworth high pass filter, because we were interested in low-frequency oscillations and the signals were then concatenated for analysis. No further filtration or average referencing methods were used, which would impart spurious results based on the nature of our dataset (low-density recording, and sensors were not close to each other).

Power spectral analysis of the ECoG signals showed that most of the signal powers were concentrated at the lower frequency components. This was consistent with the nature of our experimental data – the use of anaesthetized mice having brain waves in the delta band of frequency[27], [35]. Hence, we focused on the lower frequencies of 0.5 to 4 Hz in our analysis.

To assess the relationship between simultaneously recorded neuronal activities between two brain regions (cortex and DRN) we perform coherence analysis[27],[36]. We also computed the coherence between each DRN neurons to find whether the DRN neurons were correlated with each other. We then used statistical analysis to find the significance of our measures. These are described in detail below.

C. Data Analysis

Coherence analysis, which is performed in frequency space by applying Fourier transform, is a well-known method to compute the frequency dependent relationship (correlation) between two signals [37]. Coherence measures the degree of linear dependency of two signals by testing for similar frequency components. In our data, the sensors for acquiring the neural activities were neither too many in number nor were they spatially close to each other. Hence, volume conduction may not present a serious issue, and we shall use the magnitude of coherency (*COH*) to find the interactions between any two neurons Specifically, the coherence function, *COH*, at each given frequency *x* is mathematically described by

$$COH(x) = \frac{|S_{AB}(x)|^2}{S_{AA}(x).S_{BB}(x)} \quad (1)$$

Where $|S_{AB}(x)|$ is the cross-spectrum between signals A and B, $S_{AA}(x)$ is the autospectrum of signal A, and $S_{BB}(x)$ is the autospectrum of signal B.

E. Statistical Analysis

In order to test whether the interaction between the neurons as depicted by the coherence analyses are statistically significant, we calculated the threshold above which coherence level is considered to be statistically significant with $p<0.01$. To do this, suppose that $T_1, T_2, \ldots T_n$ are test numbers -and $P_1, P_2, \ldots P_n$ are the corresponding p-values, then the test corresponding to the maximum p-value is calculated as T_{max}.

While comparing two signals such as IFR and ECoG and to find the coherence estimates inferred from simultaneous trials, we first computed the distribution of T_{max}. This gives the original statistics of the coherence indices [38]. After that, the T_{max} for the surrogate data was computed in a similar manner by deriving the surrogate data from the original data. This was done by keeping one signal, e.g. the IFR to be the same as the original

while permuting the other signal (e.g. ECoG) randomly. The procedure was repeated for all the three combinations of the ECoG signals and the corresponding T_{max} values were calculated. The absolute value of these T_{max} was then found. This process was repeated for 1000 Monte Carlo resampling. The 99% percentile value of these T_{max}'s was taken as the threshold, which corresponds to p-value equals 0.01. The tests having $p<0.01$, were considered to be significant.

III. Results

As discussed earlier, the DRN consists of electrophysiologically distinct subgroups of neurons. Specifically, in our recordings, we have identified 4 different subgroups, namely: (i) fast and irregular spiking; (ii) slow and regular spiking; (iii) slow and irregular spiking; and (iv) fast and regular spiking DRN neurons. We then compute, within the 0.5-4 Hz frequency band, the the coherence of individual neurons with the 3 ECoG signals for each mouse. There were two mice in total, each with 1-hour recording.

Fig. 1 shows the coherence analysis for one mouse in one sample recording session breaking down into the individual neurons labelled by their electrophysiological (spiking) characteristics and the 3 ECoG channels. Coherence magnitudes are plotted against the frequencies to find the frequency at which the signals are more correlated. The channels are 43, 44 and 46 which are located on the left frontal, right frontal and right occipital cortices, respectively. In this session there are 37 neuronal activities. We can easily see that slow and regular, and slow and irregular neurons are the majority of neurons in the session. In general, one can observe that the right frontal cortex generally exhibits the highest coherence with the DRN neurons. This we have observed in the other mouse data as well.

For a more detailed evaluation of the coherences, we plotted in Fig. 2 for the same sample recording session the coherences across a continuous range of oscillation frequencies, up till 5 Hz. This is shown for all the 37 recorded neurons and their coherences with the left frontal cortex (Fig. 2A), right frontal cortex (Fig. 2B) and right occipital cortex (Fig. 2C). We found that the coherences between ECoG activities and DRN neuronal firing rates generally have statistically significant (Fig. 2, above black dashed lines) peaks at around 0.5-1 Hz and 3.5-3.8 Hz, with the former generally higher than the latter. This observation is also consistent with a previous work using extracellular single-cell recording [27]. Interestingly, we found a fast and regular firing DRN neuron to have very weak but significant coherence with the ECoG at a much lower frequency of 0.17 Hz (Fig. 2, blue).

For one slow and irregular neuron, the peak at 1 Hz is substantially higher (0.12) than that at 3.6 Hz (0.045). In terms of the contribution of the individual DRN neuronal types, other than the fast and irregular spiking DRN neurons, the slow and regular, slow and irregular, and fast and, at a more moderate level, regular spiking types, are found to have relatively significant coherence level with the right frontal ECoG signals (Fig.1). We found similar patterns, but weaker in coherence magnitudes, for the left frontal and right occipital cortices for the same recording session or mouse (Figs. 2A and 2C) With the second mouse or recording session, similar patterns were observed (Appendix).

We have shown the variability of coherences between the DRN neuronal subgroups and the ECoG signals, particularly more strongly with the right frontal cortex. To further understand whether the same simultaneously recorded DRN neurons are functionally linked to each other, *COH* is computed for the IFRs of every pair of DRN neurons within the same recording session. We found that the coherence matrix was relatively sparse (Fig. 3, blue region). Hence, the DRN neuronal connectivity was potentially sparse. Moreover, the maximum *COH* level within the frequency of 0.5 and 4 Hz was a weak 0.18 for only 2 pairs of neurons (Fig. 2, yellow range in colour bar). This might indicate very weak interactions among the DRN

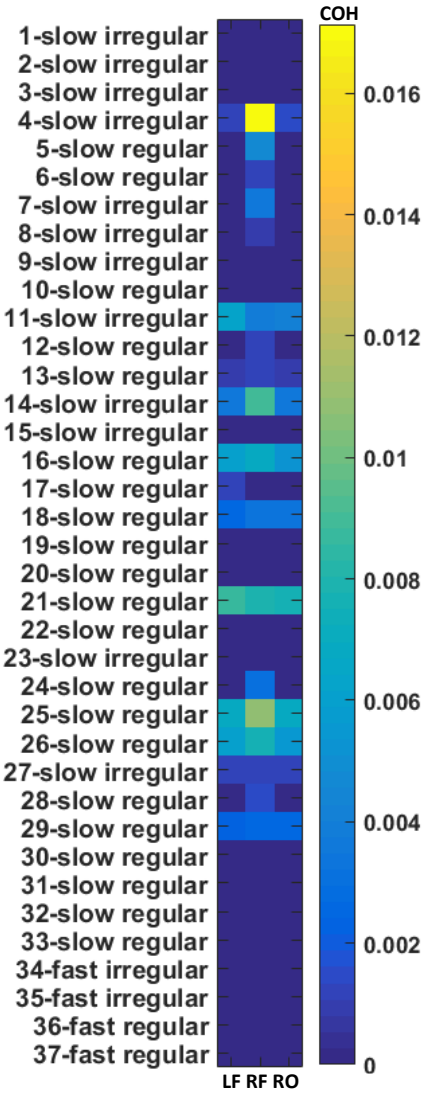

Fig. 1. *Significant interaction between DRN neuronal firing activities and 3 cortical regions*. Interactions, measured by the magnitude of coherence (*COH*), between different subgroups of DRN neurons (vertical axis) and ECoG signals (horizontal axis). Colourbar: *COH* level. LF (RF): ECoG from left (right) frontal cortices; RO: ECoG from right occipital cortex. DRN neuronal subgroups based on slow regular, slow irregular, fast regular, and fast irregular firing characteristics. Interaction is analysed for frequency range between 0.5 to 4 Hz.

neurons. Further, the relatively higher *COH* levels largely come more from interactions between the slow regular firing DRN neurons.

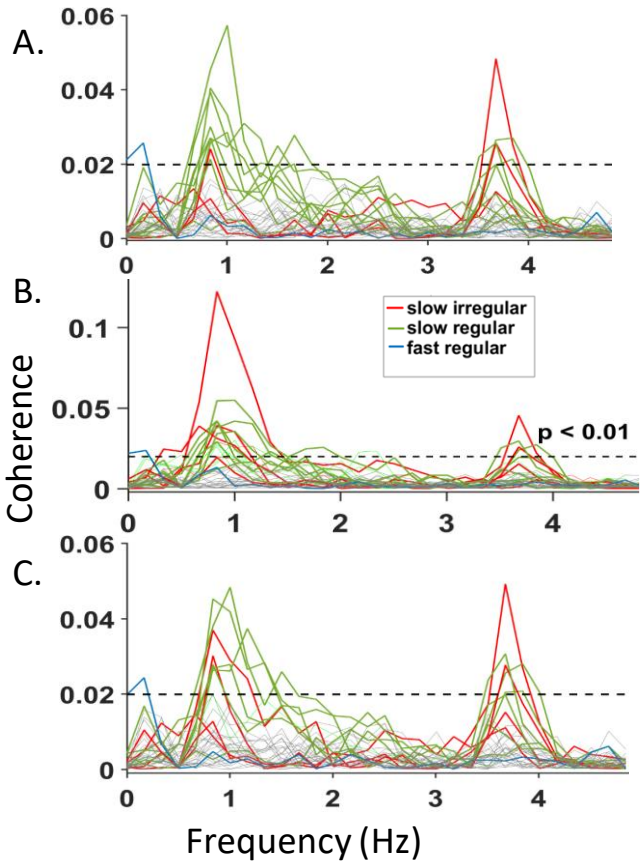

Fig. 2. *Double frequency peaks for significant COH between the DRN neurons and cortical ECoGs.* Only the slow regular, slow irregular, and fast regular firing neurons are shown. Threshold for significant coherence (0.02) is determined by maximum statistic (see Section II E). A. Figure shows the interactions between the DRN neurons and the ECOG signals of the left frontal cortex. B. Figure shows the interactions between the DRN neurons and the ECOG signals of the Right frontal cortex. Slow firing DRN neurons interacting more strongly at frequency peaks as those in A. ECoG from right occipital cortex.B. C. Figure shows the interactions between the DRN neurons and the ECOG signals of the Right Occipital cortex.

IV. Discussion

Previous studies have indicated a relationship between the frontal cortex, particularly the PFC, and the DRN neurons [12], [39]. However, most of these studies had investigated using either single-neuron recordings [24] or single ECoG channel [27]. Hence, it is not clear how the diverse DRN neuronal population work together to coordinate or communicate with the frontal cortical rhythms, and what are the relative contribution of the electrophysiologically distinct DRN neuronal types and the cortical regions.

In this work, we simultaneously recorded the activities of several neurons in the DRN and ECoG signals across 3 brain regions (left and right frontal, and right occipital cortices). The DRN neurons were classified into 4 categories, based on their spiking characteristics. Based on coherence analysis, we showed that the firing activities of the simultaneously recorded DRN neurons were linked to the slow oscillations in the cortex as reflected in the ECoG signals. In particular, we showed that the slow (regular and irregular) firing DRN neurons exhibited more strongly with the ECoG signals, especially around the neural oscillation frequencies of 0.5-1 Hz and 3.5-3.8 Hz. This is consistent with a previous work [27]. We also found that the right frontal cortex in particular has relatively stronger coherence than the other cortical regions. 5-HT neurons in the DRN typically exhibit slow regular or irregular firing characteristics [6], [40], [41], and so these DRN neurons could be putative 5-HT neurons. Future work will confirm this. Given that there were only a small proportion of the DRN neurons in every session to have significant coherence with the ECoG signals, we checked whether the same group of DRN neurons had low level of communications with each other. Computing using similar coherence analysis, our results showed that only a small proportion of the recorded DRN neurons were found to be correlated with each other. This finding is reminiscent of a recent work which indicated low correlation between pairs of neurons in the locus coeruleus brain region which consisted of another type of Monoaminergic neurons, the norepinephrine/noradrenergic neurons [23].

Future work would entail more recording sessions and mice, include more minority subgroup (e.g. fast irregular spiking) of neurons, and should identify, using e.g. neuroanatomical tracing methods [42], the internal microcircuit structure of the DRN neurons, and how they relate to the cortex, especially the frontal cortex. Also, given that the animals were anaesthetised, future challenge should seek to identify the interactions between DRN and cortex in different brain states in awake or behaving animals (see e.g. [19]. Taken together, our work has shed light on the heterogeneity and sparsity in terms of neuronal interactions or communications within the DRN and between the DRN and the cortex.

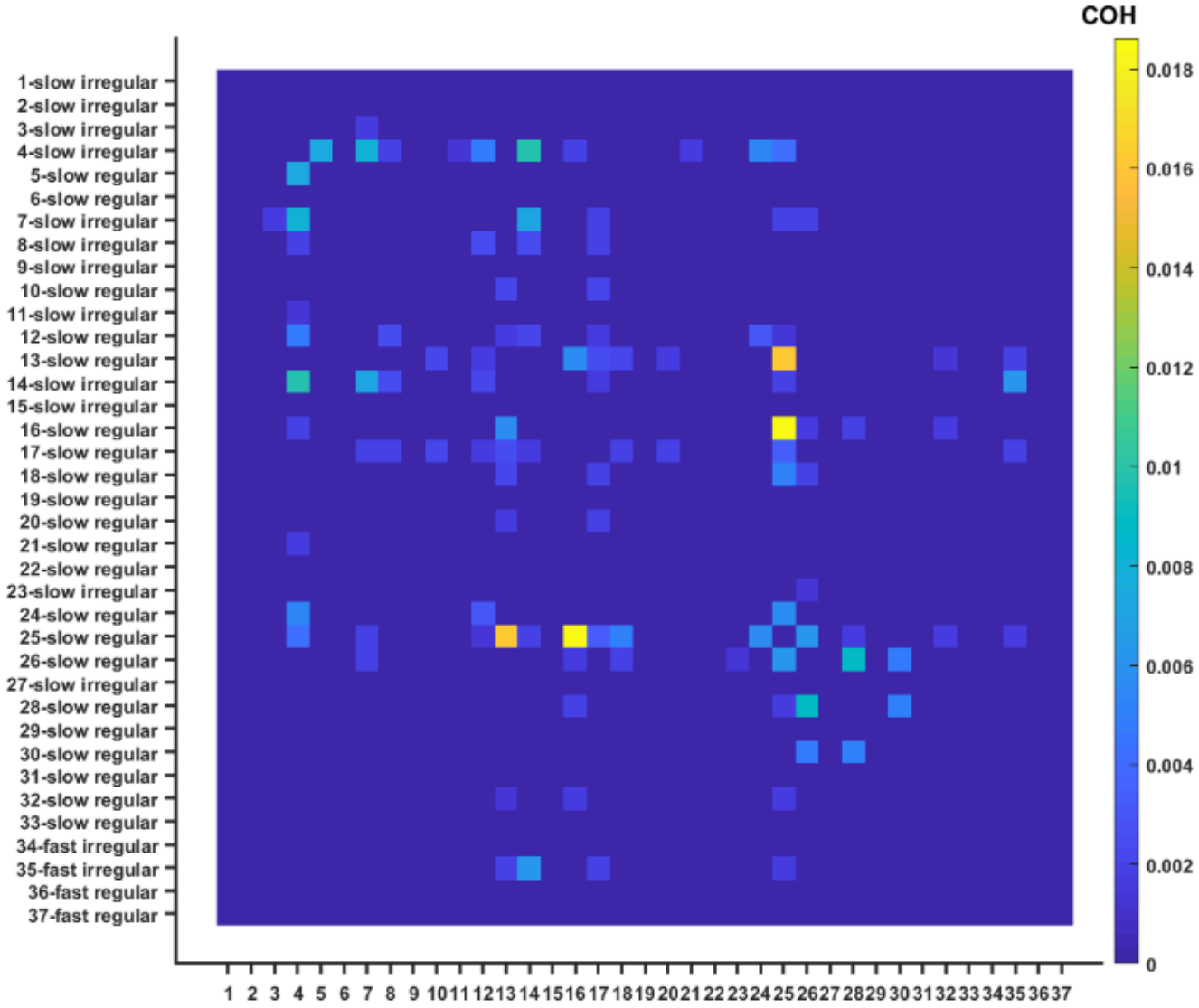

Fig. 3. *Sparse and very weak interactions among 37 simultaneously recorded DRN neurons based on magnitude of coherence*. Colourbar: *COH* level. Most pair of DRN neurons have very low coherence magnitudes (less than 0.018), indicating weak interactions. Threshold for significant coherence (0.02) is determined by maximum statistic (see Section II E).

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APPENDIX

Repeating the analysis for additional data from a different mouse and recording session are presented here. The outcomes here show a similar result as that observed in the data presented in the Results section.

As with the results from the previous data, the relatively higher coherence levels come from interactions between slow firing DRN neurons and the three cortical regions, compared to the fast firing DRN neuronal group (Fig. 4). Figs. 5A-C show significant interactions between DRN neurons and ECoG signals from the left and right frontal cortices (Figs. 5A and B) and the right occipital cortex (Fig. 5C). Again, the right frontal cortical ECoG shows the strongest interaction with the DRN neurons. However, with this data, the double frequency peaks for the high coherences are not as apparent (compare with Figs. 3). Further, as with our previous data, we observed that the DRN neurons are sparsely and weakly interacting with each other, with their very weak coherence magnitudes, and that the neuronal pairs with stronger interactions mainly consists of the slow regular firing neurons (Fig. 6).

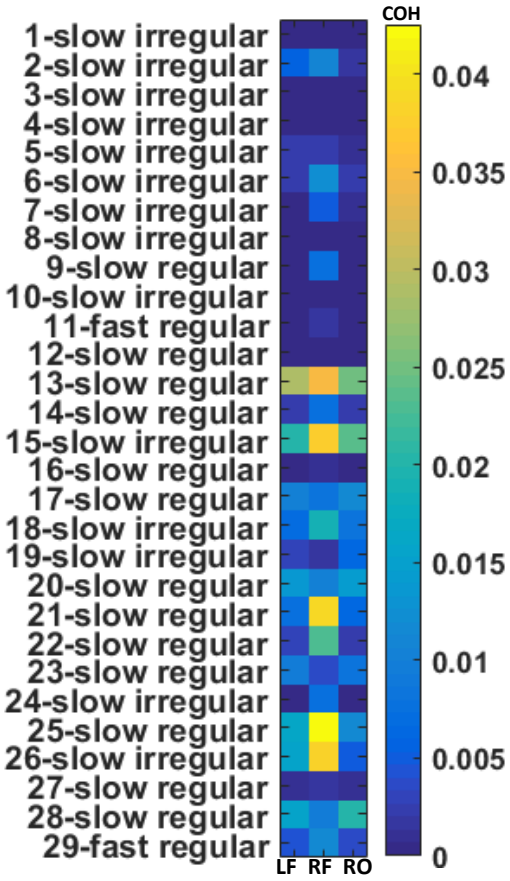

Fig. 4. *Significant interaction between DRN and 3 cortical regions.* 29 neurons in this recording session. Labels as in Fig. 1.

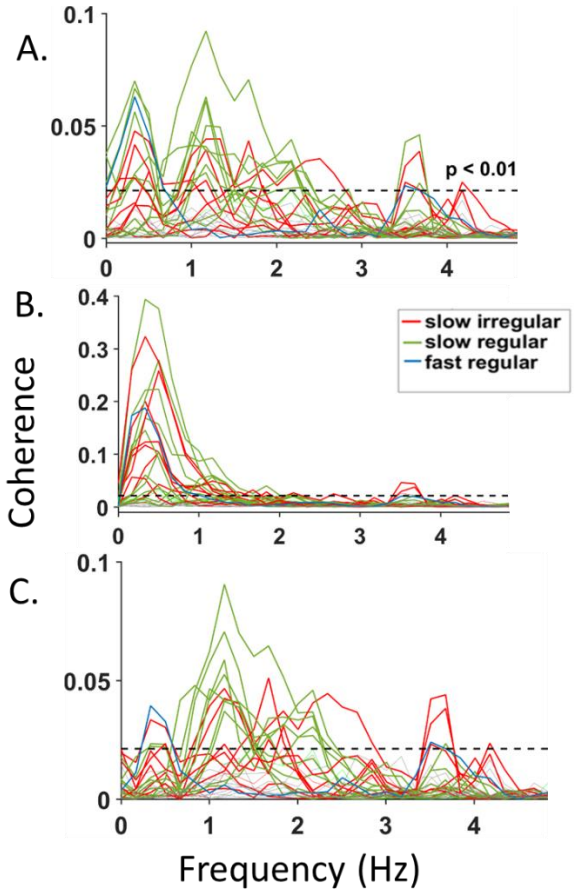

Fig. 5. *Majority of significant COH with ECoGs come from slow firing DRN neurons.* Labels as in Fig. 2.

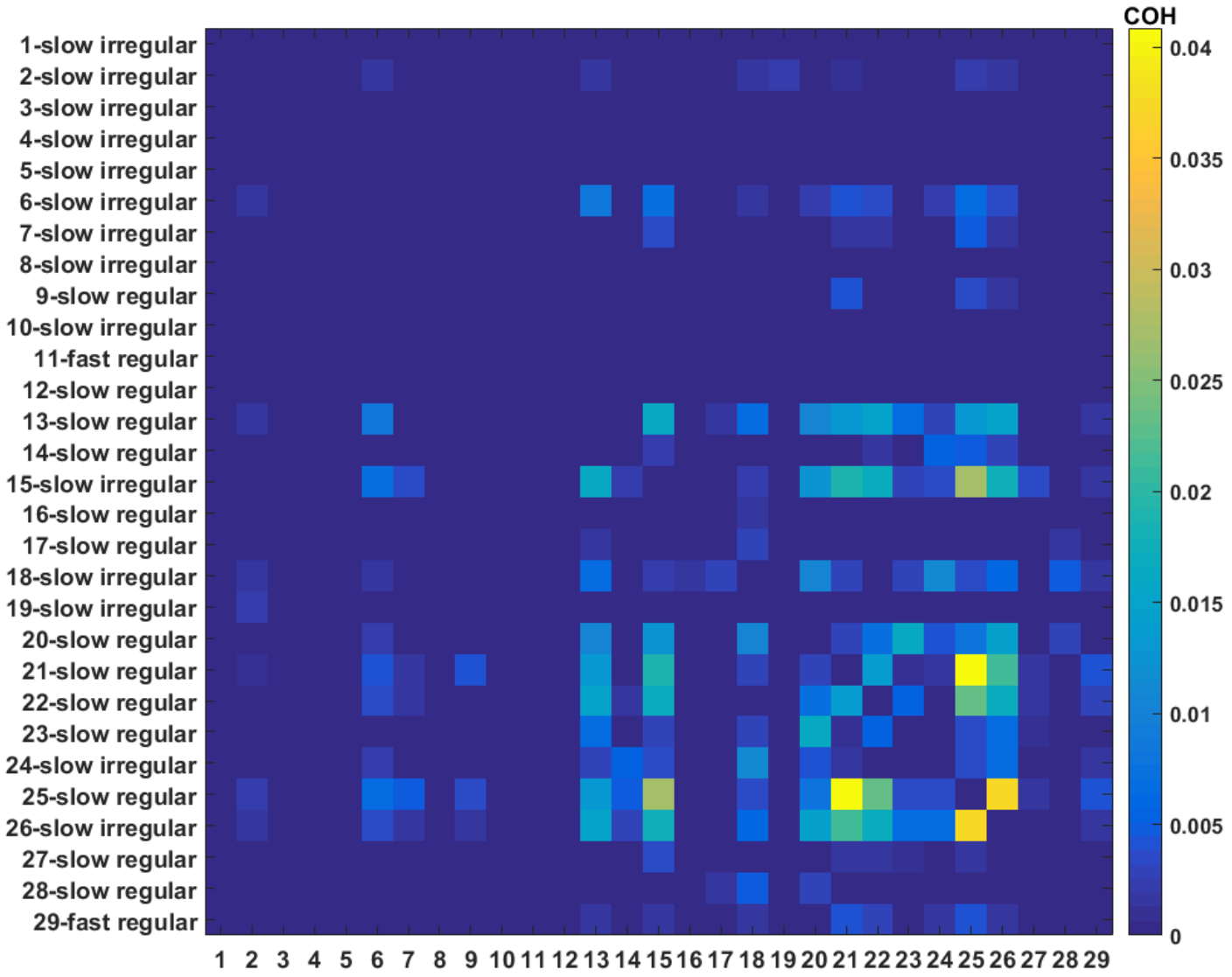

Fig. 6. *Sparse and very weak interactions among 29 simultaneously recorded DRN neurons based on magnitude of coherence*. Labels as in Fig. 3.