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Behaviorally Modulated Filter Model for the Thalamic Reticular Nucleus

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Abstract—**Incoming sensory information is first processed in the thalamocortical network. Previous studies showed that the responses generated in the nuclei of this network are behaviorally modulated, suggesting that the processing of the somatosensory information could be state dependent. Most theories, proposed to describe this response modulation have postulated that the thalamic reticular nucleus (TRN) plays a role in this response modulation. We suggest that the TRN acts as a bandpass filter whose bandwidth increases or decreases depending on the state of the animal. To test this idea, we used multineuron recordings and demonstrate, for the first time, that the responses of single neurons in the reticular nucleus are modulated by the behavior of the animal. This result, taken together with the anatomy of the thalamocortical network and previous studies on anesthetized rats, suggests that the modulation of the responses in the thalamus and cortex could be at least partially due to the TRN through a mechanism that is similar to that of a behavioral modulated filter.**

I. Introduction

Behavioral modulation of stimulus evoked responses in the thalamocortical loop is thought to be an integral component of the somatosensory processing [1]-[10]. In rat models, in fact, it has been observed that two major components of the thalamocortical network (Fig. 1), i.e. the cortex (CT) and the ventral posterior medial (VPM) nucleus of the thalamus, change their responses accordingly with the animal behavioral state [1]-[3]. It is also suggested that rats may exploit this responses modulation to tune the somatosensory system to detect different features of an incoming somatosensory stimulus [1]-[3]. In particular, during states in which the animal is actively moving its whiskers, both high and low frequency inputs are allowed to reach the CT, during state of rest immobility, instead, only low frequency inputs are able to reach the CT.

Different mechanisms have been proposed to describe this change in frequency response, following changes in the animal behavior, in the thalamocortical loop. On one hand, several studies [3], [5], [7] suggest that intrinsic cellular properties of the thalamocortical cells are responsible for this band pass modification. Namely, alterations in the spontaneous activity [2], [5] and thalamocortical synaptic depression with high frequency stimulation [7] could provoke the variation in frequency response during different behavioral states. On the other hand, the modulation may be caused by the interaction with external processes. Specifically, the ongoing motor activity during the whisking state can modulate the response of the thalamocortical network [1]. However, each of these theories postulates a role for the thalamic Reticular Nucleus (TRN) in shaping the response of the thalamus and consequentially of cortex.

Although, taken together, these observations suggest that the TRN has a principal role in the determination of the stimulus evoked response during different behavioral states, no study in awake freely moving rats has demonstrated that the output of the TRN is behaviorally modulated. We therefore recorded neural data from multiple and single cells in both TRN and VPM in awake freely moving rats while stimulating the whisker pad under different behavioral conditions. The analysis of these data reveals that the TRN is indeed behaviorally modulated. More importantly, these analysis together with anatomical and anesthetized studies, showing that the TRN provides the major inhibitory input to the VPM [11] and suppresses VPM activity modulating the signal-to-noise of the VPM [12], [13], allow us to propose a model for the role of the TRN in the early phase of the somatosensory processing. Therefore, we suggest that the reticular nucleus acts as a bandpass filter whose bandwidth increases or decreases depending on the state of the animal.

II. Materials and Methods

A. Surgery Procedures and Neuron Discrimination

Two 8 channels bundle Teflon-coated stainless steel microwires (Neurolinc Corp., New York, NY) were chronically implanted with stereotaxic techniques into the whisker region of the VPM and TRN.

After the implantation surgery, a rest period of 7–10 days was left. Analog signals from the electrodes were filtered and amplified using Multi-Neuron Acquisition Processor (MNAP) (Plexon Inc. Dallas, TX) and single neurons were discriminated on each electrode using commercial software Sort Client (Plexon Inc. Dallas, TX).

B. Whisker-Pad Implant

The rats were lightly anesthetized with Nembutal (35 mg/kg). Each whisker was stimulated by moving it forward approximately with an angle of 5 degree, with respect to the

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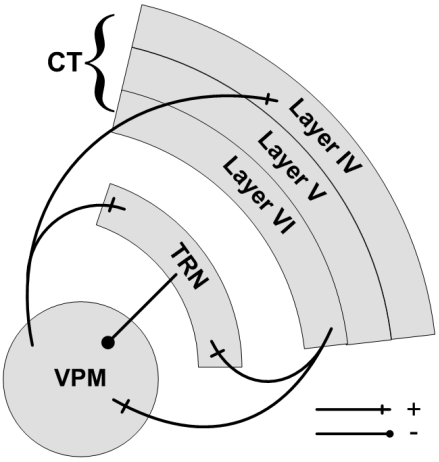

Fig 1. Schematic representation of the thalamocortical network. The legend in the right bottom corner of the picture shows which connection are inhibitory (-) or excitatory (+).

surface of the skin, using a fine tipped metal probe controlled by a Grass stimulator that simultaneously sent TTL pulses to the MNAP to record the precise time of stimulation. The whisker that showed the most responsive location considering the entire cell population was selected as the "target whisker". Then, supplemental doses of Nembutal (0.05 ml) were injected to ensure a suitable grade of anesthesia to implant the whisker-pad stimulator.

The whisker pad stimulator implant technique was similar to that described in [14]. In short, a twisted pair of Teflon coated stainless steel wires with a diameter of 0.004 in. (California Fine Wire Co., Ca) was tunneled with an 18 gauges needle from the original incision in the scalp to the whisker pad of the rat to stimulate sensory afferent. Prior to the implantation, the wire was inserted in an 18 gauges needle and the ends of the wires were stripped (1-2 mm on the needle tip side and 10-15 mm on the luer-lock side). The bare end on the needle tip side were offset of 2-3 mm and bent over the needle tip in order to form a hook to anchor the electrode at the base of a single whisker follicle. The wire was then tunneled to the whisker pad using the 18 gauges as a guide; when the whisker pad area was reached the wire was anchored to the base of the "target whisker" and the guide was gently removed. The bare ends of the wire on the implant side were inserted in a conductive grease filled connector. Finally, the whisker pad stimulator was tested applying a biphasic pulse of approximately 0.2 mA to evoke a whisker twitch and the connector was then cemented with acrylic on the implant.

C. Recording Sessions and Behavioral State Classification

After a week from the whisker-pad implantation surgery, neural responses from the animal were recorded while a biphasic pulse was delivered randomly through the whisker pad stimulator. During the same recording session the animal was allowed to move freely in a small box and videotaped throughout the session in order to allow off-line identification of time periods of different animal behavioral states.

Two different animal states were identified and utilized in this study: rest state, i.e. periods or epochs in which the animal stand still and no whisker movement were observed, and whisking state, i.e. periods or epochs in which the animal stand still and whisker movement is observed.

D. Data Analysis

Neural responses from each discriminated cell were sorted depending on the behavioral state of the animal, either rest or whisking and two different Peri-Stimulus Time Histograms (PSTHs) were obtained one for each behavioral state.

The changes in the spontaneous activity and the stimulus evoked response were quantified by extracting the pre-stimulus mean firing rate, integrated response and the response duration from PSTHs of the cells. The spontaneous activity firing rate was computed for each cell as its mean firing rate in a pre-stimulus interval of 100 ms. The integrated response was computed for each cell as its cumulated firing rate in a post-stimulus window ranging from 2 to 20 ms. Finally, in order to compute the duration of the neural response, the first and the last significant bin were found as the first and the last bin of the PSTH that showed a

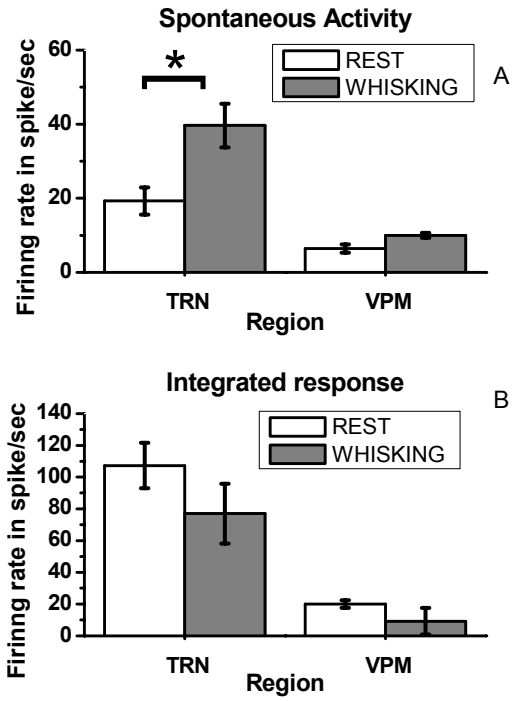

Fig 2. Spontaneous activity and integrated response in the TRN and VPM in different behavioral state. The top graph shows that spontaneous activity increased during whisking compared to quiet for both VPM and TRN ($p<0.05$ for TRN). The lower graph shows that the integrated response to a whisker pad stimulus decreased for both the VPM and TRN cells during whisking compared to quiet. Error bars denote the Standard Error of the Mean (SEM) whereas the star denotes a statistically significant difference ($p<0.05$).

firing rate greater than the 99% C.I. computed with respect to a uniformly random distribution of the spikes. Thus the response duration was computed as the temporal difference between the last and the first significant bin.

Each parameter extracted was then compared across the behavioral states and the regions using a 2 way ANOVA and the Tukey's honestly significant test when a post hoc comparison was needed. Responses were considered statistically significant for $p<0.05$.

III. Results

A. Spontaneous Activity

The results for the comparison of the mean spontaneous firing rates are shown in (Fig. 2).

Both the TRN and the VPM increased their spontaneous activity during whisking compared to rest. The activity of TRN cells increased by 105% while the activity of the VPM increased by 55% (20 and 2 spike/sec for TRN and VPM, respectively). The increase was observed in each cell for both the nuclei, but only the TRN showed a statistically significant increase ($p<0.05$).

B. Stimulus Evoked Response

The integrated response of each cell in response to the stimulation of the whisker pad decreased during whisking compared to rest. Both TRN and VPM showed a reduction in their integrated responses during whisking compared to rest, as can be observed in Fig.2. The decrease was consistently observed for each cell independently. On average the TRN cells deceased by 28% while the VPM cells decreased by 55% (30 and 10 spike/sec for TRN and VPM, respectively).

The duration of the stimulus evoked response in TRN and VPM was shorter during whisking compared to rest. The response in the TRN was reduced by 11.5 ms and the response in the VPM was reduced by 2 ms when the response during whisking compared to rest (Fig 3). The drop in the duration was consistent across all cells, but only the TRN cells showed a statistically significant ($p<0.05$) reduction of the response duration.

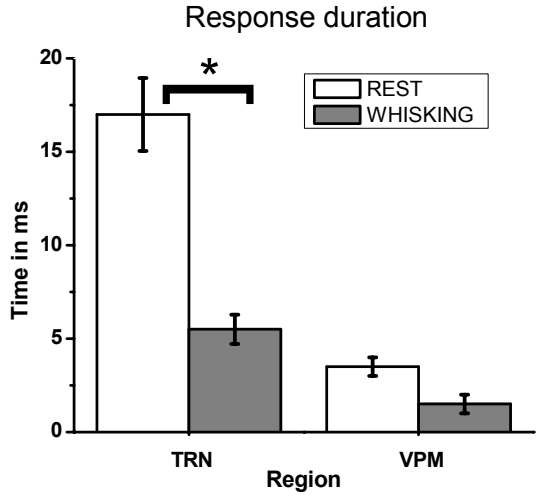

Fig. 3. Response duration for the TRN and VPM in different behavioral state. The graph shows the average value of the response duration for the TRN and VPM was reduced during whisking compared to rest. Error bars denote the Standard Error of the Mean (SEM) whereas the star denotes a statistically significant difference ($p<0.05$).

IV. Discussions

A. Behavioral Modulation of the TRN

The results presented in this paper denote that the activity of the TRN can be modulated in response to changes in the animal's behavioral state. The spontaneous activity increases as the animal transitions from rest to whisking for both cell types. The evoked response, measured by the integrated response of each cell decreases as the animal transitions from rest to whisking. Finally, the duration of the response of both the VPM and TRN cells decreases as the animals transitions from rest to whisking. These changes observed in the TRN suggest that activity in the TRN is behaviorally modulated just as activity in the VPM is behaviorally modulated.

We suggest that the ability of the TRN to modulate its responses is a key mechanism through which the TRN itself can express its powerful inhibition to the VPM on a state dependent base. This would create a different inhibitory state for the incoming somatosensory information during different behavioral states, thus controlling the flow of sensory information to the cortex depending on the state of the animal.

Previous studies assumed a behavioral modulation of the TRN [2], [3], [8] and this assumption, though not demonstrated, was critical for the interpretation of the system functioning including the role of neuromodulators. However, there were no data available from awake, freely moving animals to show the behavioral modulation of the TRN. The data presented here demonstrate for the first time that the TRN is indeed behaviorally modulated in awake freely moving animals.

B. TRN as Behaviorally Modulated Filter

Based on previous studies conduced in the VPM and CT [1], on the anatomical structure of the thalamocortical network and on the results presented here, we suggest that the TRN functions as a filter that changes its bandwidth accordingly with the animal behavior. During the rest state, since it has been shown that the VPM response to a second stimulus within 100 ms (frequency greater than 10 Hz) is attenuated compared to the response to the first stimulus, it is likely that the greater and longer lasting TRN response to the first stimulus keeps the VPM in this inhibited state. Thus, the TRN, during the rest state, could act as a low pass filter allowing only low frequency inputs to reach the cortex.

During the whisking state, since it has been shown that

the VPM response to a second stimulus within 100 ms (frequency greater than 10 Hz) is not attenuated compared to that of the first stimulus, it is likely that the smaller and shorter duration of the TRN response is responsible for lack of inhibition in the VPM compared to the rest state. This is true for frequencies up to 40 Hz. Thus the TRN, during whisking state, could act as low pass filter with a higher cut-off frequency, e.g. 40 Hz.

This could have important ramifications for cognitive processing and could give insights into several disease states such as schizophrenia. For example, normally, during quiet resting, humans respond to low frequency stimuli by suppressing the evoked response to the second stimulus. However, schizophrenic patients, who are known to have sensory gating problems [15], do not suppress the response to the second stimulus. Since the response of both the VPM and TRN can be affected by neuromodulators that are known to be disrupted in schizophrenia (e.g. serotonin), it is important to understand which nuclei are involved in sensory gating and, ultimately, how these neuromodulators affect the response of these nuclei. This work addresses the first issue and demonstrates that the response of the TRN is behaviorally modulated and involved in suppressing the response to high frequency stimuli during quiet rest.

ACKNOWLEDGMENT

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