Synchronized Activities among Retinal Ganglion Cells in Response to External Stimuli

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Abstract. Synchronized firing is an efficient way for retinal ganglion cells (RGCs) to encode visual stimuli. In the present study, we studied synchronized activities among RGCs in response to natural movie and pseudo-random checker-board flickering. The results showed that nearby RGCs tended to fire synchronously much more frequently than expected by chance, in response to both stimuli. Under our experimental conditions, synchronous groups could contain three or more cells in response to natural movie; but activities were more often observed between pair-wise cells in response to checker-board flickering. The correlation index calculated between neuron pairs did not have any significant tendency of increase or decrease when natural movie stimulation was lasted; however, it tended to increase when pseudo-random checker-board flickering stimulation was lasted.

Keywords: Synchronized activities; correlation index; dynamical; retinal ganglion cells.

1 Introduction

In vertebrates, the optic nerve is a severe bottleneck presented in the visual pathway; dynamic concerted firings are therefore critically required for conveying information effectively [1, 2]. Many lines of evidence from multi-electrode studies of retina have confirmed that adjacent RGCs of similar functional subtype tend to fire in synchrony in response to external stimuli [3-5]. Correlation index, the ratio between the observed concerted firings and that expected by chance, was proposed to quantify the strength of correlation within neuron groups [6].

Over the years, synchronized activities elicited by artificial laboratory stimuli have been studied [4, 6-7], and it was reported that RGCs tend to fire in synchrony more frequently than expected by chance in response to various laboratory stimuli, such as uniform illumination, pseudo-random checker-board stimuli, etc.[6, 8]. However, natural stimuli are usually more complex than artificial stimuli. In order to understand visual function under natural conditions, it is better to study neural responses to natural stimuli directly [9, 10].

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In the present study, we adopted information-theoretic algorithm [8] to study the dynamically synchronized activities among RGCs in response to natural movie and pseudo-random checker-board flickering stimulation. Correlation index was computed to estimate the strength of synchronous patterns in response to both stimuli. It was found that nearby RGCs tended to fire synchronously more frequently than expected by chance in response to both stimuli. During natural movie, many synchronous groups contained more than three cells; but in response to checker-board flickering; most of groups only contained two cells. For synchronous neuron pairs, correlation index did not show any significant change along with time during natural movie stimulation; but it tended to increase with time in response to pseudo-random checker-board flickering.

2 Materials and Methods

2.1 Electrophysiology Recordings and Visual Stimulation

Detailed extracellular-recording procedure can be found in our previous report [11]. Spikes from RGCs were recorded from retinas of newly-hatched chicks (about 1-3 weeks post-hatching) using multi-electrode array (MEA, 8×8) (MEA60, MCS GmbH, Germany) via a commercial multiplexed data acquisition system with a sampling rate of 20 kHz. Recorded data were stored in PC for off-line analyses.

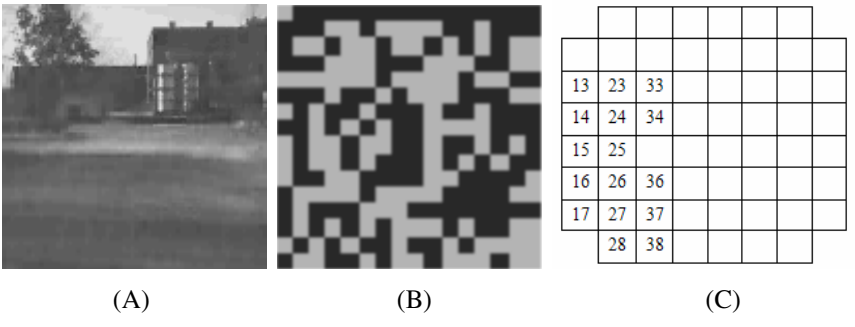

Fig. 1. Example frames and geometric position of eletrodes. (A) Natural movie; (B) Checker-board flickering; (C) Geometric position of 16 adjacent electrodes by which a group of RGCs were recorded from one example retina.

The following stimulation protocols were applied: (1) Full-field white light flashes with light-ON duration of 1 sec and light-OFF intervals of 9 sec were applied (lasted for 30 sec) to test the functional condition of the neurons being recorded; (2) Digitized grayscale video recording of natural movies (downloaded from the website of van Hateren's lab, http://hlab.phys.rug.nl/vidlib/index.html. [12]) were presented with a refresh rate of 10 Hz and lasted for 192 sec; (3) Pseudo-random binary checker-board flickering (16×16 grid) were applied at a refresh rate of 9.05 Hz and lasted for 221 sec [13]. Example frames of natural movie and checker-board flickering are shown in Fig. 1A and B. These images were of the same size when being presented on the screen and projected onto the retinal piece via an optical lens system.

2.2 Information-Theoretic Algorithm

In order to test whether the interactions among ganglion cells are limited to pair-wise neurons or extended to neuron groups containing more cells, information-theoretic algorithm based on entropy analysis was adopted [8]. Detailed procedures are as follows:

Firstly, the spike trains are symbolized into "0" and "1" with time bin of 2 ms, where "1" represents that there is a spike in the time bin and "0" represents that there is no spike in the time bin. Given two neurons *A* and *B*, a new symbolic neuron AB can be defined such that:

$$\begin{aligned} r_j^{(AB)} &= r_j^{(A)} r_j^B \\ &= \begin{cases} 1, \text{ if the neuron } A \text{ and neuron } B \text{ fired in time bin } j \\ 0, \text{ otherwise} \end{cases} \end{aligned} \tag{1}$$

Secondly, to see whether the neurons *A* and *B* are concertedly activated, the entropy is computed:

$$H_i = -(P_i \log_2 P_i + (1-P_i)\log_2(1-P_i)) \tag{2}$$

where P_i is the probability that symbolic neuron i has a spike in the time bin ($P_i = \frac{1}{N}\sum_{i=1}^{N} r_j^{(i)}$, N is the number of time bins in the data set). As for each individual neuron, usually only a small fraction of spikes are fired in synchrony with others, the net reduction in entropy can be calculated as:

$$\begin{aligned} \Delta H_{AB} &= H_A + H_B - H_{AB} \\ &\approx P_{AB} \log_2 (P_{AB} / P_A P_B) \end{aligned} \tag{3}$$

The identification of concerted neuron groups starts with computing ΔH for all the cell pairs. If the largest ΔH value is greater than a predetermined threshold (see below), we regard these two cells as a concerted group. We then further search for other synchronous neuron pairs or synchronous groups containing more cells. The process is repeated until the largest ΔH falls below the predetermined threshold. To define the threshold, all the spike trains are shifted by randomly chosen time delays, and the largest ΔH in the shuffled data set is defined as the threshold.

2.3 Correlation Index

Correlation index is the ratio between the observed frequency of synchronized activities and that expected by chance [6], which is used to estimate the strength of the synchronized firings. The correlation index is measured as follows:

The observed frequency of synchronized firings among *M* cells is:

$$P_{1\ldots M} = \frac{1}{N}\sum_{j=1}^{N}\prod_{i=1}^{M} r_j^{(i)} \tag{4}$$

The frequency of synchronized firings expected by chance can be calculated as:

$$P_1 \ldots P_M = \prod_{i=1}^{M} \frac{1}{N} \sum_{j=1}^{N} r_j^{(i)} \tag{5}$$

Then we can compute the correlation index as:

$$C_{1\ldots M} = P_{1\ldots M} / \prod_{i=1}^{M} P_i \tag{6}$$

3 Results

Most RGCs recorded in our experiments are of On-Off subtype [4], therefore in the present study, analyses were focused on this type of cells. Experiments were performed on 3 retinas. The locations of electrodes by which the neurons' activities were recorded are presented as an approximate indication of the locations of neurons. In the example given in Fig. 1C, the spike trains recorded from 16 adjacent electrodes were analyzed. To reveal dynamically changed population activities among RGCs in response to natural movie and pseudo-random checker-board stimuli, the analyses were performed on the 120-s data sets, and the synchronous groups and strength of the correlation in groups were calculated for each 500-ms period.

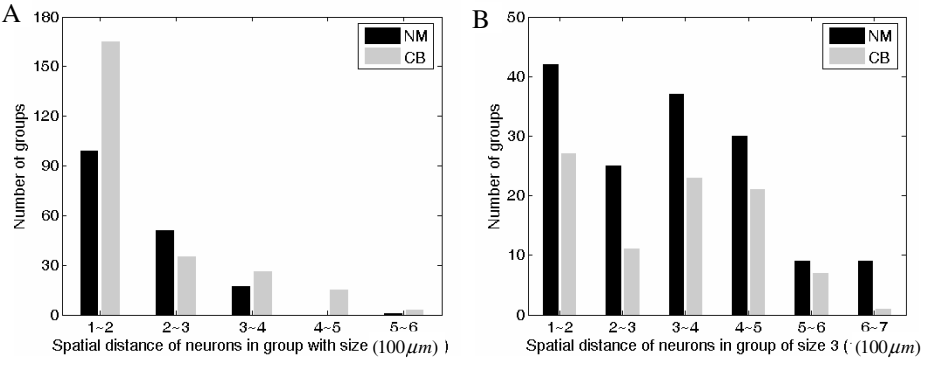

Fig. 2. Spatial arrangement of RGCs engaged in synchronized firing in one example retina (recorded by electrodes presented in Fig. 1C) in response to natural movie (NM) and checker-board (CB) stimuli. A, B. The relationship between number of synchronous groups and inter-neuronal distances, during natural movie (NM) and pseudo-random checker-board (CB) stimulations, with group sizes being 2 and 3, respectively.

3.1 Synchronous Groups

Previous studies have shown that synchronized activities are frequently recorded from adjacent cells [6, 8]. We defined the inter-neuronal distance of a synchronous group using the summation of distances between each neuron and their gravity center.

Fig. 2A (Pairs) and B (Triplet) illustrate the relationship between the inter-neuronal distance and the number of synchronous groups of neurons recorded by electrodes illustrated in Fig. 1C, in response to natural movie and pseudo-random checker-board stimuli from one example retina. It is clear that the number of groups was decreased with distance during both stimuli.

In order to investigate the firing patterns during both stimuli, data collected from three different retinas were analyzed. Table 1 shows the statistic of the group size under various conditions. It is notable that during natural movie, groups could contain three or more neurons; however, most of groups only contain two neurons during pseudo-random checker-board stimuli.

Table 1. Statistic of the number of cells per group

	Stimuli	Pair	Triplet	Quaternion
Retina 1	NM	145	104	22
	CB	242	63	3
Retina 2	NM	179	152	16
	CB	236	90	5
Retina 3	NM	151	145	18
	CB	278	80	3

3.2 Correlation Index

Correlation index represents how frequently a synchronous pattern is observed as compared to that expected by chance [8]. The probability distributions of correlation index for synchronous pairs and synchronous triplets from one example retina (same as presented in Fig. 2) are shown in Fig. 3A and Fig. 3B, for the cells' responses elicited by natural movie and pseudo-random checker-board stimuli. The distributions of synchronous groups in response to both stimuli were similar to each other. Consistent results were observed from the other two retinas.

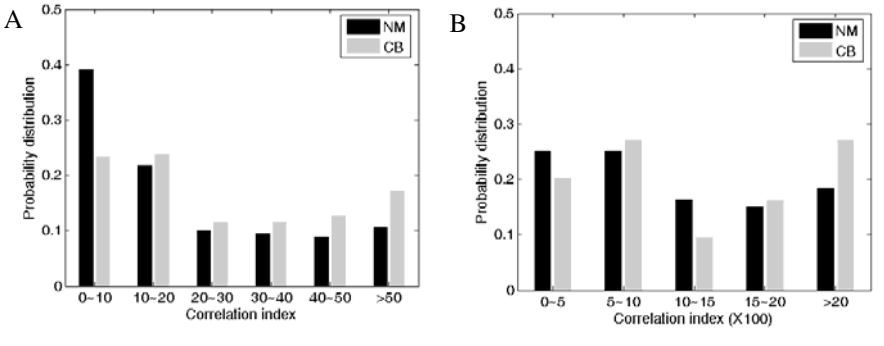

Fig. 3. Distribution of correlation index values from one example retina (the same as presented in Fig. 2) during NM and CB stimuli. A. For synchronous neuron pairs. B. For synchronous neuron triplets.

The results above were obtained by overall analyses perform on 120-s data sets. Actually synchronized activities among RGCs varied dynamically during both stimuli. In order to investigate the time-varying characteristics of correlation index, we analyzed the correlation index of pair-wise neurons by least-squares linear regression fitting. Fig. 4 gives an example pair (#17 and #27 in Fig. 1C). Although the correlation index was fluctuating, it did not have any significant tendency of increase or decrease, during natural movie stimuli (Fig. 4A); but it tended to increase in response to pseudo-random checker-board flicking stimuli (Fig. 4B). The results were observed in almost all the synchronous groups in the three retinas under investigation.

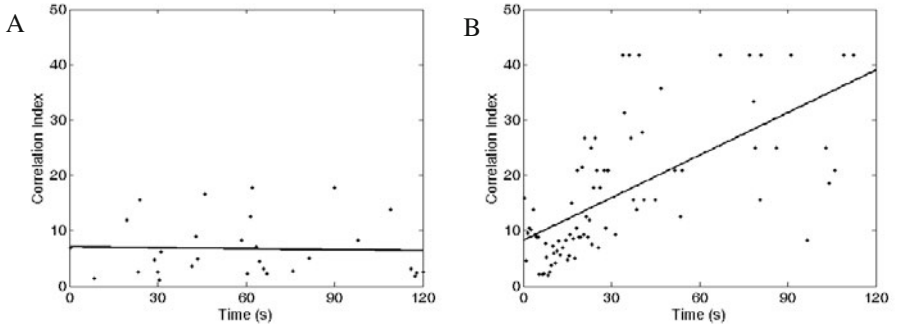

Fig. 4. An example of time-dependent changes of correlation index. The synchronous neurons were recorded by electrodes #17 and #27 in Fig. 1C during both stimuli. A. Duing natural movie stimuli. B. During pseudo-random checker-board stimuli.

4 Discussion

In the present study, we adopt information-theoretic algorithm [8] and correlation index [6] to investigate the concerted activities of neurons recorded by adjacent electrodes in response to natural movie and pseudo-random checker-board stimuli respectively. The results revealed that synchronized activities frequently occurred among adjacent RGCs (Fig. 2). Synchronous patterns elicited by natural movie stimuli were different from that elicited by pseudo-random checker-board stimuli, neurons tended to fire synchronously in larger groups during natural movie stimuli. The distributions of synchronous groups with different correlation index values were almost similar during both stimuli, but the time-varying characteristics of correlation index were very different. For synchronous neuron pairs, the correlation index did not show any significant change along with time in response to natural movie stimuli; however it tended to increase with time in response to pseudo-random checker-board flicking stimuli.

Natural stimuli are fundamentally different from pseudo-random checker-board flicking stimuli in a sense that natural stimuli contain intensive correlations [14, 15] and are spherically asymmetric [15]. It is more frequently that nearby neurons tend to fire synchronously in larger groups during natural movie stimuli. During pseudo-random checker-board stimuli, neurons adapt to the stimuli quickly, which make the

observed frequency of synchronized activities much higher than expected by chance. All of these may suggest that activity patterns among RGCs are different between natural movie and pseudo-random checker-board flicking stimuli and dynamically synchronized activities among RGCs are stronger in response to natural movie.

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