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Interactive report

Population coding in spike trains of simultaneously recorded retinal ganglion cells[1]

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Abstract

To achieve a better understanding of the parallel information processing that takes place in the nervous system, many researchers have recently begun to use multielectrode techniques to obtain high spatial- and temporal-resolution recordings of the firing patterns of neural ensembles. Apart from the complexities of acquiring and storing single unit responses from large numbers of neurons, the multielectrode technique has provided new challenges in the analysis of the responses from many simultaneously recorded neurons. This paper provides insights into the problem of coding/decoding of retinal images by ensembles of retinal ganglion cells. We have simultaneously recorded the responses of 15 ganglion cells to visual stimuli of various intensities and wavelengths and analyzed the data using discriminant analysis. Models of stimulus encoding were generated and discriminant analysis used to estimate the wavelength and intensity of the stimuli. We find that the ganglion cells we have recorded from are non-redundant encoders of these stimulus features. While single ganglion cells are poor classifiers of the stimulus parameters, examination of the responses of only a few ganglion cells greatly enhances our ability to specify the stimulus wavelength and intensity. Of the parameters studied, we find that the rate of firing of the ganglion cells provides the most information about these stimulus parameters, while the timing of the first action potential provides almost as much information. While we are not suggesting that the brain is using these variables, our results show how a population of sensory neurons can encode stimulus features and suggest that the brain could potentially deduce reliable information about stimulus features from response patterns of retinal ganglion cell populations.

Theme: Sensory systems

Topic: Retina and photoreceptors

Keywords: Neural coding; Visual system; Retina; Neural ensembles; Discriminant analysis; Multineuronal recording

1. Introduction

Most of the current knowledge about neurons and their functional properties has been based on single sequential recordings of their responses using microelectrode techniques. Although these tools have been very useful for understanding the cellular and molecular mechanisms underlying cell biophysics, it is clear that sensory and motor information is processed in a parallel fashion by populations of neurons working in concert [6,28]. Thus, in order to understand the coding, decoding, and information processing that occurs in the brain, many researchers are beginning to use techniques that allow them to perform simultaneous recordings of multi-neuronal activity. New imaging technologies such as multi-channel optical imaging [3,13,15,17] and multi-site extracellular electrode arrays [5,7,18,19,24,26,29,33,34,36] are being employed in order to record neural responses at many sites simultaneously. While the use of extracellular electrode arrays allows imaging of multineuronal responses with unprecedented spatial and temporal resolution, the development of tools used to analyze this multi-neuronal activity is generally lagging behind the development of the tools used to acquire this data.

One of the basic tools that has been used for the analysis

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of simultaneous recordings of neuronal cells is cross-correlational analysis [12,24,37,41]. This approach has mainly been useful for the analysis of synaptic connectivity using pairs of spike trains [41] and for the separation of individual neurons in multi-unit spike trains [24], but it cannot be directly used to obtain details about the important response features used in the stimulus discrimination task. Other approaches, such as artificial neuronal networks, are able to deal with data from large populations of neurons [9,23,34,38,40], but their behavior is highly dependent upon the models chosen. This dependency limits the application of artificial neural networks to the realistic analysis of simple ensembles or to the non-mechanistic analysis of complex systems. These techniques have been used to demonstrate that a population code can provide a more accurate prediction of performance than the individual elements that constitute the population [9,22,23]. However, these approaches do not provide a direct way to study how a population of neurons can collectively represent the complexities of a multi-dimensional stimulus like that used to excite the retina in this study.

This paper explores the question of how an ensemble of retinal ganglion cells might encode the wavelength and intensity of a variety of full field monochromatic stimuli. Specifically, the broad and highly overlapping spectral sensitivity curves of the cone photoreceptors, and their sigmoidal shaped intensity–response curves cause stimulus wavelength and intensity to be dependent variables. As the intensity of a monochromatic stimulus is changed, the differential excitation of the three classes of cone photoreceptors changes, changing the perceived hue and saturation of the stimulus. Thus, how groups of retinal ganglion cells encode a broad range of colors of differing intensities is a challenging and unresolved question.

Although the visual scene is conveyed to the brain in parallel by the spike trains of all ganglion cells, most of what we know about retinal cell signaling is derived from recordings of single retinal ganglion cells (see Ref. [23] for a review). The assumptions underlying this hypothesis are that the population code can be understood from the analysis of single cell responses, and that the brain decodes the stimulus features from the simultaneous firing of many neurons in the ganglion cell population that essentially operate independently of each other. Whether or not ganglion cells act as independent encoders is important because it bears on the experimental strategy one might use to deduce the retinal code. Thus the specific questions addressed in this study were: (1) how does the ability to estimate stimulus features based on populations of ganglion cells compare with estimation based on single cells? and (2) what response features are most important in estimation of stimulus wavelength and intensity?. We investigate these questions with the use of discriminant analysis, a tool developed to reveal complex dependencies between multivariate systems [10].

2. Methods

2.1. Experimental procedures

Extracellular ganglion cell recordings were made in the isolated superfused turtle *Pseudemys scripta elegans* retina using an array of 100, 1.5-mm long electrodes as reported previously [9,30,34]. After enucleation of the eye, the eyeball was hemisected with a razor blade, and the cornea and lens were separated from the posterior half. The retinas were isolated from the pigment epithelium and mounted on a glass slide photoreceptor side down. The retina was then superfused with ringer solution [32] and the electrode array was lowered into the tissue.

The electrode arrays contained 100 electrodes, and were built from silicon on a square grid with a 400μm pitch as described elsewhere [16]. The distal 50 μm of the needles, metallized with platinum, form the active site of each electrode. The remaining parts of the silicon array were insulated with polyimide. Impedance measurements were performed on the electrode array prior to each experiment to insure ensure the integrity of the polyimide coating. The electrode array was connected to a 100-channel amplifier (low and high corner frequencies of 250 and 7500 Hz) and a digital signal processor based data acquisition system [14]. For the present experiments, light stimuli were produced from a 100-W tungsten lamp. Flashes with a duration of 0.2 s, followed by a 0.24-s period of darkness, were used as typical stimuli. Wavelength selection (400, 450, 488, 514, 546, 577, 600, 633 and 694 nm) were achieved with narrow band interference filters, and intensities were controlled with neutral density filters. They were changed in steps of 0.5 log units from maximum intensity down to −4.0 log relative intensity, depending on the exact experiment. For each wavelength, the intensities were measured with a calibrated photodiode and expressed as log relative intensity. Maximum quantum fluxes (log. rel. int.=0) at the different wavelengths were: 400 nm, 1.3×10^{13} quanta/s per cm^2; 450 nm, 1.8×10^{13} quanta/s per cm^2; 488 nm, 1.7×10^{13} quanta/s per cm^2; 514 nm, 0.7×10^{13} quanta/s per cm^2; 546 nm, 1.2×10^{13} quanta/s per cm^2; 577 nm, 1.6×10^{13} quanta/s per cm^2; 600 nm, 0.8×10^{13} quanta/s per cm^2; 633 nm, 1.1×10^{13} quanta/s per cm^2; 694 nm, 1.3×10^{13} quanta/s per cm^2. The background was complete darkness. Each set of stimuli was presented 8 times.

The electrode array was lowered into the retina, and when responses were recorded on a maximal number of electrodes, the array's position was fixed. While stable recordings could be made using this preparation in retinas that had been isolated for over 8 h, the retinas used for these experiments were typically limited to 4 h post-isolation. In each experiment we recorded neural activity from about 80–90 electrodes. In general, multi-unit signals were obtained from most of the electrodes and often single unit separation was difficult so that we selected those

13–15 prototypes which were unequivocal in terms of both amplitude and shape [9,30]. All the selected channels of data plus one stimulus channel were digitized with a commercial multiplexed data acquisition system (Bionic Technologies, Salt Lake City, UT) and stored in a Pentium-based class computer. A custom analysis program sampled the incoming data at 30 kHz, plotted the waveforms on the screen, and stored the record for later analysis.

2.2. Discriminant analysis

Canonical discriminant analysis was carried out on simultaneously recorded neuronal spike activity (extracellular action potentials) in order to classify the luminosity, chromaticity and temporal aspects of the light stimuli that evoked the responses. From each individual presentation of the light stimuli, the number of spikes and the time of occurrence time of each spike were extracted for each of the identified and classified single units using a custom-designed program. For the present study we only used the number of spikes during the light-ON period (mean rate), the timing of the first and the second spike relative to the stimulus onset, and the time interval between the first two spikes as the discriminant variables. We did not use information from any other spikes evoked by the stimulus, because under our stimulus conditions, many responses showed at most two spikes after light onset. This procedure resulted in a data vector of 60 quantitative variables (four variables×15 cells) for each light presentation. Two additional elements, coding wavelength (nine categories) and intensity (nine categories) were also included in the data set.

Whereas detailed discussion of discriminant analysis and its application to the analysis of spike trains is available elsewhere [1,8,20,27,31,35], here we briefly describe for those unfamiliar with the technique, the basis of the method we have used throughout this study for those unfamiliar with the technique. Discriminant analysis allows us to effectively separate two or more groups of individuals (stimulus parameters in this study), given measurements of several variables for these individuals. The usual approach involves taking a linear combination of the X variables

$$Z = W_1X_1 + W_2X_2 + \cdots + W_pX_p + C$$

where the W_1, $W_2, \ldots W_p$ are discriminant coefficients reflecting the unique contribution of each variable (X_1, $X_2, \ldots X_p$) to the classification task and C is a constant.

Groups can be well separated using Z if its mean value changes considerably from group to group, with the values within a group being fairly constant. When this approach is used and there are more than two possible groups (as in our case), it turns out that it may be possible to determine several linear combinations for separating groups [20]. In general, if there are k groups, $k-1$ discriminant functions can be computed. They are all uncorrelated with each other and maximize the ratio of between groups to within groups sums of squares. The first function

$$Z_1 = W_{11}X_1 + W_{12}X_2 + \cdots + W_{1p}X_p + C$$

gives the maximum possible difference between groups. The second one,

$$Z_2 = W_{21}X_1 + W_{22}X_2 + \cdots + W_{2p}X_p + C$$

captures as much as possible of the group differences not displayed by Z_1; Z_3 reflects as much as possible of the group differences not displayed by Z_1 and Z_2; and so on. The hope is that the first few functions are sufficient to account for almost all the important group differences. Thus, information contained in multiple independent variables is summarized in a single index, called discriminant score, and serves as the basis for assigning cases to groups.

It should be stressed that usually the discriminant functions fit the sample from which they have been derived better than they will fit another sample from the same population. Thus, the percentage of cases classified correctly by the discriminant functions is an inflated estimate of the true performance in the population [31]. To overcome this bias we have used what is called ‘jackknife classification’. It involves allocating each individual light presentation to its closest group without using that individual (but the remaining $n-1$ cases) to calculate the discriminant functions, and then classify the left out case. Since the case which is being classified is not included in the calculation of the functions, the observed misclassification rate is a less biased estimate of the true one.

All the statistical analysis were performed using the SPSS/PC 8.0 software package (SPSS).

3. Results

For many stimulus conditions and many ganglion cells only a few spikes were evoked in response to light-ON. Fig. 1 shows an example of simultaneously recorded responses from 15 electrodes to eight consecutive flashes of 633 nm, 2.6 mm diameter, log. relative intensity = −0.5. For each electrode, close inspection of the firing patterns to repeated identical stimuli, showed some degree of variability, introducing uncertainty in the code. Thus it seems very unlikely that the features of a visual stimulus can be derived exclusively from the activity of single ganglion cells. This suggests that the concerted activity of many cells rather than individual activity of single neurons is encoding visual stimulus features.

Discriminant analysis is a useful procedure that allows one to study the percentage of correctly classified presentations of a given stimulus using single cells or a population of cells, as well as to quantify the more important variables in the classification task. Table 1 shows the percentage of

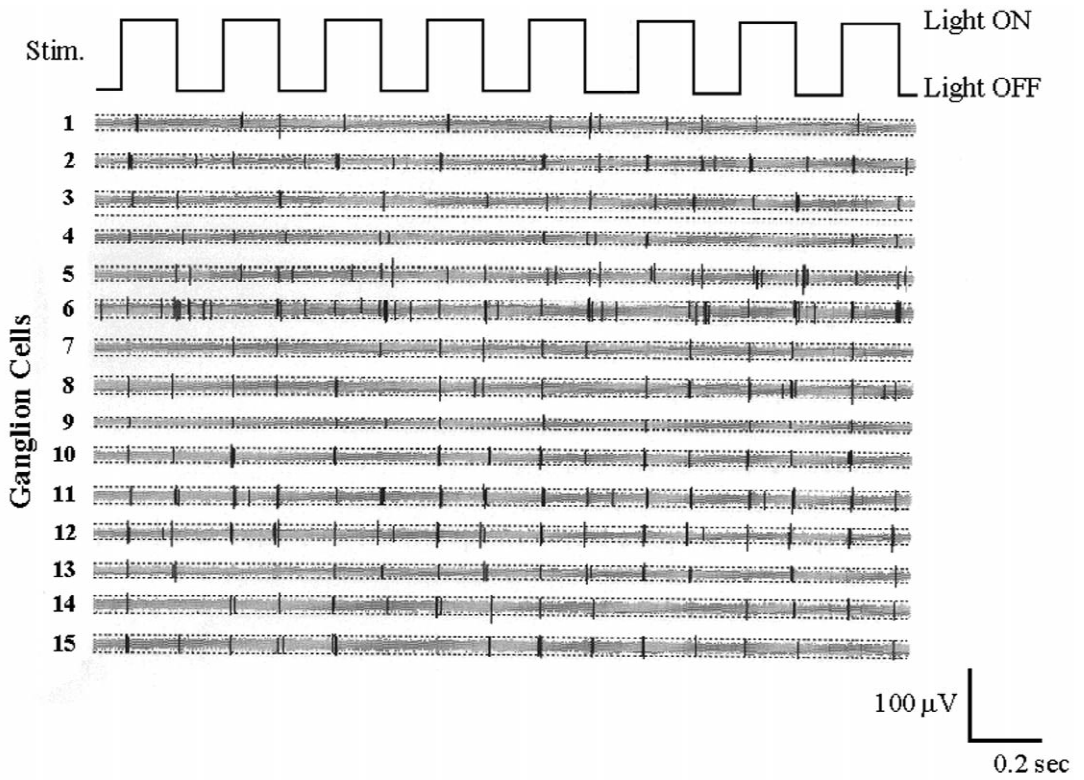

Fig. 1. Example of simultaneously recorded extracellular responses from 15 ganglion cells to eight consecutive and identical flashes of 633 nm, 2.6 mm diameter, intensity equal to 0.5 units of attenuation. The top trace shows the timing of light stimulus.

correct stimulus intensity discriminations in a typical experiment when the wavelength is kept constant. Correct classification using various coding models to estimate the intensity of the stimuli are showed separately. On average, all single units were far below ideal discrimination, although to a varying degree. All of the units were above chance level (12.5% in this case, since eight intensities were tested) and relatively good classification scores were achieved by using spike rate, spike timings or spike rate + spike timings.

Table 1
Percentage of correct stimulus intensity classification for single cells and for the 15-cell population for a fixed wavelength of 633 nm

Cell number	Percentage of correct classification using:		
	Spike rate	Spike timings	Spike rate + spike timings
1	33.0	31.3	36.6
2	32.1	29.5	38.4
3	21.4	24.1	33.0
4	23.2	23.2	35.7
5	29.3	36.6	31.3
6	24.1	30.4	33.9
7	19.6	23.2	29.5
8	25.9	25.0	31.3
9	22.7	27.7	38.4
10	23.2	27.7	39.3
11	28.6	32.1	46.4
12	23.2	22.3	38.4
13	19.6	18.8	26.8
14	21.4	22.3	26.8
15	27.7	30.4	29.5
All cells together	82.1	84.8	96.4

When we analyze all the recordings together, not one at a time, the discrimination improved significantly achieving 96.4% correct discrimination when all the variables were used (Table 1). For this classification, the analysis extracted seven discriminant functions (one less than the number of intensities being classified). Table 2 displays the amount of variance explained accounted for by each discriminant function. It can be seen that the first discriminant function accounts for 52.8% of the variance. The second function contributes with an additional 21.2% of the variance and so on. Thus, the first three discriminant functions taken together were able to explain most of the observed variance (86.4%). Table 2 also shows for each discriminant function the eigenvalue or ratio of between groups to within groups sums of squares and the canonical correlation that represents the proportion of total variability 'accounted for' by differences between groups.

To see how much different groups overlap and to examine the distribution of the discriminant scores, it is useful to plot the discriminant function scores for the groups. Fig. 2 plots 112 light presentations with a fixed wavelength of 633 nm against their values for the first two, most important discriminant functions using the full 60

Table 2
Amount of variance accounted for each canonical discriminant function for the intensity classification task

Discriminant Function	Eigenvalue	Amount of variance explained (%)	Cumulative variance (%)	Canonical correlation
1	22.636	52.8	52.8	0.979
2	9.066	21.2	74.0	0.949
3	5.496	12.8	86.8	0.920
4	2.586	6.0	92.9	0.849
5	1.641	3.8	96.7	0.788
6	0.783	1.8	98.5	0.663
7	0.632	1.5	100.0	0.622

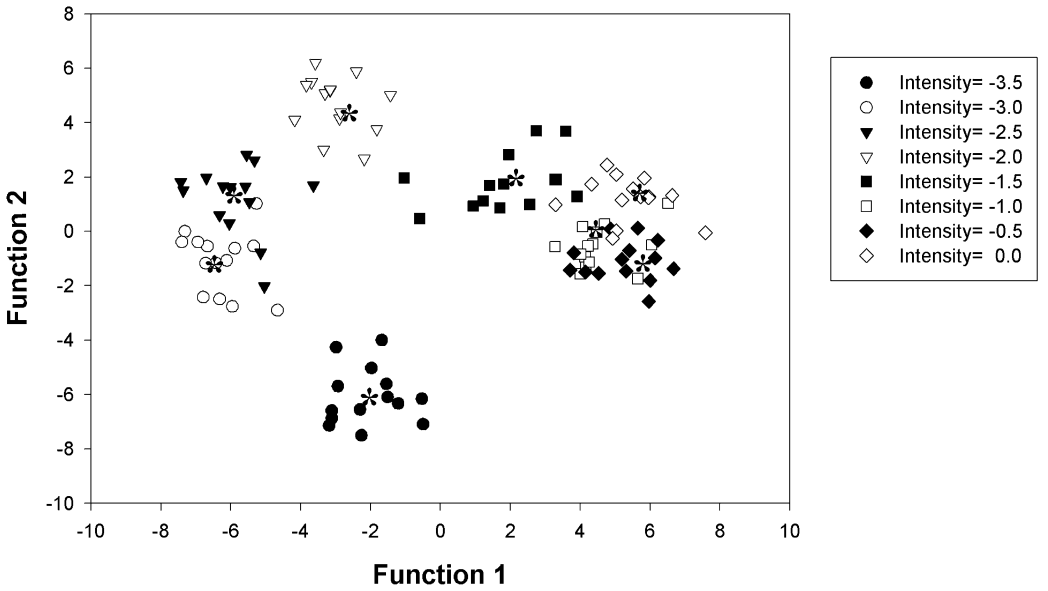

Fig. 2. Scatter plot values of the first two canonical discriminant functions for a fixed wavelength of 633 nm, showing the distances among different intensity groups. The average score for each group, named the group centroid, is indicated by an asterisk.

parameters. The higher intensities appear on the right-hand side, middle intensities in the center, and the lower intensities on the left-hand side of the figure. The average score for each group is called the group centroid and is indicated by an asterisk. Whereas these discriminant functions are good enough to separate low intensity groups, there are some overlaps, especially for high intensities, so that it is not possible to correctly classify all the groups on the basis of only these two functions and additional discriminant functions are needed.

To assess the contribution of each variable to the discriminant functions we can use their standardized coefficients. Another way to examine the contribution of the different variables to the classification task is to run the discriminant analysis with only some selected variables and compare their classification results. Table 3 shows the importance of the different variables for the discrimination of the intensity of the stimulus using the whole ganglion cell ensemble. The results show that all the variables tested were not of equal importance for the discrimination. Spike rate (rate in Table 3) was the most important variable for the discrimination task and 86.7% mean correct discrimi-

Table 3
Relative importance of various response parameters and combination of parameters for discriminating intensity (values are given in percentage)

Wavelength (nm)	Rate	$t1$	$t2$	Int.	Rate $+t1$	Rate $+t2$	Rate +Int.	$t1+t2$	Rate $+t1+t2$	Int. $+t1+t2$	All
400	93.5	97.8	65.2	56.5	97.8	95.7	97.8	100	100	100	100
488	89.3	75.0	67.9	67.9	94.0	96.4	96.4	89.3	98.8	96.4	98.8
546	83.5	76.9	61.5	54.9	95.6	91.2	91.2	90.1	98.9	95.6	98.9
600	80.6	78.6	55.1	41.8	91.8	93.9	83.7	95.9	99.0	98.0	100
694	86.7	78.3	72.3	60.2	100	96.4	98.8	92.8	100	97.6	100
Mean	86.7	81.3	64.4	56.2	95.8	94.7	93.5	93.6	99.3	97.5	99.5

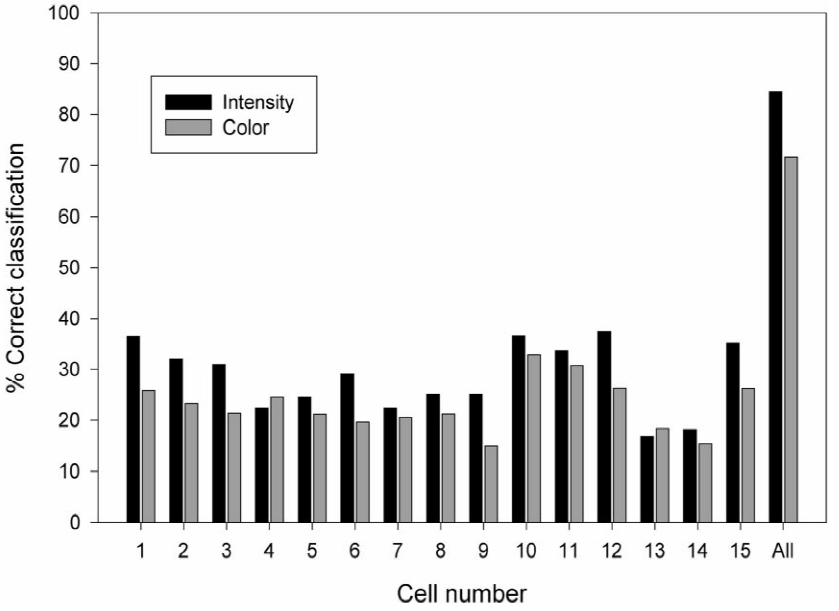

Fig. 3. Comparison of intensity and wavelength discrimination using the same set of ganglion cells.

nation was obtained using only this variable. The following next most important variable for the discrimination was the timing of the first spike ($t1$) so that 81.3% of the stimuli were correctly classify using only this variable. The timing of the second spike ($t2$) and the time difference between spike one and spike two (Int. in Table 3) were of less importance for the classification. The best performance was reached by using all variables together (99.5% correct classifications). An important finding was that the intensity of visual stimuli could be correctly classify by using either a rate code or a temporal code, which could imply some redundancy in the code.

Wavelength discrimination was more complex than intensity discrimination, because intensity, expressed as number of quanta/s per mm^2 cannot be kept exactly constant for all wavelengths at the level of the photoreceptors. Therefore, discrimination was based on a mixture of two changing stimulus parameters. In this sense, when we asked the discriminant analysis to correctly classify nine different wavelengths, classification could also be based on minor intensity differences. Fig. 3 shows the performance of the same set of ganglion cells for classifying all the intensities and wavelengths using the full 60 parameters. As can be seen, some neurons were better classifiers of intensity while others were better at classifying wavelength. Again the population discrimination was fairly good for this more complex classification task: 71% for wavelength discrimination and 86% for intensity discrimination.

Discriminant analysis can also allows be used to evaluating the misclassification results. Table 4 shows the performance of a network of 15 ganglion cells in classifying the wavelength of the stimulus. Correctly classified cases appear on the diagonal of the table since the predicted and actual groups are the same. For example the wavelength of 400 nm is classified correctly 75% of the

Table 4
Summary of the classification results for color wavelength classification (log intensity = −1)

Actual[a] color	Predicted group membership[b]								
	400	450	488	514	546	577	600	633	694
400	**75.0**	5.0	20.0	–	–	–	–	–	–
450	4.8	**90.5**	–	4.7	–	–	–	–	–
488	3.6	21.4	**75.0**	–	–	–	–	–	–
514	9.4	4.8	4.8	**81.0**	–	–	–	–	–
546	–	–	–	9.5	**76.2**	4.8	9.5	–	–
577	–	–	–	–	4.8	**85.7**	9.5	–	–
600	–	–	–	–	–	–	**90.5**	–	9.5
633	–	–	–	4.8	–	4.7	4.8	**85.7**	–
694	–	–	–	–	–	9.5	4.7	4.8	**81.0**

[a] Real wavelength.
[b] Predicted wavelength expressed as percentage of cases classified correctly.

times, although sometimes the analysis classifies a wavelength of 400 nm as being of 450 nm (5% of the times) or as being of 488 nm (20% of the times). Table 4 illustrates two important features. First, as the wavelength of the stimulus is increased, the analysis generally predicted that a higher wavelength was used to evoke the responses. Second, although sometimes there are misclassifications, the results are generally centered around the actual value.

4. Discussion

Relatively little is known about how the brain encodes and represents even single aspects of the outside world. Part of the reason is certainly the complexity of the many feedback and feedforward neural pathways. However, other important factors contribute, such as the necessity of collecting and analyzing large numbers of responses, and extracting from these responses the meaningful information that pertains to the stimuli [6]. Discriminant analysis is a mathematical method, that uses linear combinations of the predictor variables as the basis for separating two or more groups of individuals (see Ref. [27] for a review) and, as we have shown here, it can be very useful to in getting insights about how a population of retinal ganglion cells can encode certain stimulus features like intensity or wavelength.

In order to get as much information as possible about the nature of the neural code, raw data should be used. One needs to construct models based on data sets and not assume a priori the important variables nor the form of the models. It is not known in advance which of the possible variables are important for group separation and which are, more or less useless. In this context discriminant analysis provides an excellent exploratory tool. This tool allows one to analyze all the variables and recordings as a unified set, not one at a time. By considering all the variables simultaneously, we are able to obtain insights about their possible relationships. Since the data for a discriminant functional analysis do not need to be standardized to have zero means and variances prior to the start of the analysis, the outcome of a discriminant function analysis is not affected in any important way by the scaling of individual variables [20].

The discriminant analysis, as applied in the current study, detected patterns of covariance between neurons in the ensemble and determined which combination of neurons and variables were more effective for discriminating these patterns. Rate and spike timing were chosen as discrimination variables because was there is ample evidence from different neural systems that show that these are important variables for encoding [2,4,6,11,22, 25,27,28]. Although this does not mean that the brain is using these variables, and we do not know at present if indeed the brain used exclusively these variables, our results show at least that the brain can potentially deduce reliable information about stimulus features from response patterns of retinal ganglion cell populations [9,22,30]. Thus, the neural coding could be organized to seek covariation in its input, such as it is represented in parallel analyzers [21,39].

Since our stimulus intensities were not equated for quantum catch across the wavelength spectrum, our results for wavelength discrimination could be based, at least in part on changes on intensity. Although at present we could not entirely reject this possibility, under the stimulus conditions used in this study for wavelength discrimination, the quantum flux falling onto the retina was very similar for 400 and 694 nm (and very similar for 546 and 633 nm, and 514 and 600 nm, and other pairs and triples). Thus, if intensity were classified, these wavelengths should be largely confused. Since this is clearly not the case (see Table 4) our results support the view that the ganglion cells can effectively discriminate between lights of similar quantum flux, but different wavelengths.

Finally in this paper we report classification of intensity and wavelength based on a total of 15 well isolated retinal ganglion cells. However the conclusions have been substantiated in several other identical experiments, with best classification scores ranging from 70 to 99% [9,30]. These results demonstrate the utility and richness of knowledge obtainable from ‘many-neuron’ ensemble recording techniques and show that appropriate application of discriminant analysis can be used to analyze the large volume of data generated in these studies. We propose that discriminant analysis, in addition to the other approaches currently used (neuronal networks, information theory, principal component analysis, etc.) can be very useful in obtaining insights into the mechanisms underlying neuronal coding.

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