Shifted encoding strategy in retinal luminance adaptation: from firing rate to neural correlation

Lei Xiao, Mingsha Zhang, Dajun Xing, Pei-Ji Liang, and Si Wu. Shifted encoding strategy in retinal luminance adaptation: from firing rate to neural correlation. *J Neurophysiol* 110: 1793-1803, 2013. First published July 17, 2013; doi:10.1152/jn.00221.2013.—Neuronal responses to prolonged stimulation attenuate over time. Here, we ask a fundamental question: is adaptation a simple process for the neural system during which sustained input is ignored, or is it actually part of a strategy for the neural system to adjust its encoding properties dynamically? After simultaneously recording the activities of a group of bullfrog’s retinal ganglion cells (dimming detectors) in response to sustained dimming stimulation, we applied a combination of information analysis approaches to explore the time-dependent nature of information encoding during the adaptation. We found that at the early stage of the adaptation, the stimulus information was mainly encoded in firing rates, whereas at the late stage of the adaptation, it was more encoded in neural correlations. Such a transition in encoding properties is not a simple consequence of the attenuation of neuronal firing rates, but rather involves an active change in the neural correlation strengths, suggesting that it is a strategy adopted by the neural system for functional purposes. Our results reveal that in encoding a prolonged stimulation, the neural system may utilize concerted, but less active, firings of neurons to encode information.

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Retinal ganglion cell; luminance adaptation; information coding; neural correlation; discrimination

Adaptation refers to a general phenomenon in which a neural system adjusts its response property according to the statistics of external inputs (Kohn 2007; Wark et al. 2007). It has been widely suggested that adaptation underlies the strategy for a neural system to utilize its resource efficiently to encode stimulus information (Fairhall et al. 2001; Gutnisky and Dragoi 2008; Lesica et al. 2007; Maravall et al. 2007). For instance, it was found that the tuning functions of sensory neurons are optimized to match the variance of inputs in a natural environment, so that high encoding accuracy for the whole range of stimuli is achieved (Laughlin 1981). In practice, adaptation can also occur very rapidly in response to sudden changes in the input statistics, so that the stimulus information is transmitted with high fidelity (Fairhall et al. 2001; Sharpee et al. 2006). A recent experimental work reported that in addition to enhancing information representation, adaptation can regulate information content transmitted in the sensory pathway (Wang et al. 2010). Thus, to fully understand how the brain processes stimulus information in a natural dynamical environment, it is critical to unveil the computational roles associated with adaptation.

Luminance adaptation, in which a neural system is exposed to a sustained stimulation with constant luminance, is a fundamental visual adaptation process whose biophysical mechanisms and potential computational roles have been intensively studied (Wark et al. 2007). However, the detailed time course as to how the stimulus information is encoded dynamically in the varying neural responses during adaptation remains largely unresolved (Kastner and Baccus 2011). In luminance adaptation, the firing rates of retinal ganglion cells (RGCs) first increase dramatically at the onset of the stimulation and subsequently decrease gradually to a low level close to spontaneous activity. The attenuation of firing rates may suggest that the neural system is ignoring the stimulus information, but there exists another possibility: the stimulus information is encoded by neuronal response features other than firing rates during the adaptation.

To address this issue, we simultaneously recorded the activities of a group of neurons (dimming detectors) in the bullfrog retina in response to sustained dark and gray luminance stimuli. Dimming detectors are known to encode escape-related information for bullfrog (Ishikane et al. 2005). A prolonged dimming stimulation could evoke adaptive responses in dimming detectors lasting for ~5 s, which enabled us to look into the detailed features of information encoding during the adaptation. We measured the correlation strengths between neurons connected by gap-junction and found a seemingly paradoxical phenomenon that the neural correlation increased during the adaptation, despite attenuating firing rates. To ascertain the functional meaning of this unusual behavior, we applied information analysis approaches to estimate the stimulus information contained in the neuronal responses. Interestingly, we found that at the early stage of the adaptation, neural correlation contains little stimulus information, whereas, at the late stages of the adaptation, neural correlation becomes more effective than firing rate for discriminating stimuli.

The role of concerted activities in neural information processing has long been debated in the field (Averbeck and Lee 2004). Some studies suggested that the firing rates of neurons conveyed the majority of the stimulus information, and that the contribution of neural correlation could be largely neglected (Meytis et al. 2012; Nirenberg et al. 2001; Oizumi et al. 2010), whereas others suggested that neural correlation played an indispensable role in neural computation (Dan et al. 1998;
Pillow et al. 2008; Schneidman et al. 2006; Schwartz et al. 2012). Here, our study reveals that the neural coding strategy is dynamic in nature and can vary in different time scales.

MATERIALS AND METHODS

Experimental Methods

Retinal recordings. Experiments were performed on isolated bullfrog retinas (Li et al. 2012). Bullfrogs were dark adapted for ~40 min before experiments. A piece of retina (~4 × 4 mm²) was placed on a multielectrode array (MEA; MMEP-4, CNNS UNT) with the ganglion cell side in contact with the electrodes. The retina was perfused with oxygenated Ringer solution (95% O₂ and 5% CO₂), containing the following (in mM): NaCl 100.0, KCl 2.5, MgCl₂ 1.6, CaCl₂ 2.0, NaHCO₃ 25.0, and glucose 10.0. The activities of neurons were recorded by the MEA, which consisted of 64 electrodes (8 μm in diameter) arranged in an 8 × 8 matrix with 150-μm tip-to-tip distance. Signals were amplified by a 64-channel amplifier (MEA workstation, Plexon), and each channel was sampled at a rate of 40 kHz, along with the stimulation. Well-isolated action potentials were sorted by the commercial software OfflineSorter (Plexon). All procedures strictly conformed to the humane treatment and use of animals, as prescribed by the Association for Research in Vision and Ophthalmology, and were approved by the Ethic Committee, School of Biomedical Engineering, Shanghai Jiao Tong University.

Stimulation protocols. Light stimuli were generated from a computer monitor (Iiyama, Vision Master Pro 456) and were focused on isolated retinas via a lens system. To adjust the sensitivity of ganglion cells to similar levels, full-field sustained white light (38.9 nW/cm²) was given for 30 s before stimulation protocols were applied.

In the protocol for investigating luminance adaptation behavior, flickering (frame refresh rate = 10 Hz) pseudorandom checkerboards consisting of 16 × 16 subsquares were first presented for 15 s, which was then followed by 15 s of darkness (~0.0015 nW/cm²). This process was repeated for 20 times (Fig. 1A). Each subsquare of the checkerboard covered an area of 66 × 66 μm² on the retina and was assigned a value either “+1” (white light, 77.7 nW/cm²) or “−1” (dark, ~0.0015 nW/cm²). The pseudorandom checkerboards were uncorrelated both temporally and spatially, and they can be regarded as background noises. The dark stimulation activated dimming detectors, a type of RGCs responding preferably to dimming stimulation.

In the protocol for investigating the discrimination performance, flickering pseudorandom checkerboards were first presented for 10 s, which was followed by a stimulation of either full-level darkness (~0.0015 nW/cm², referred to as the dark stimulus) or dimmed level (19.5 nW/cm², referred to as the gray stimulus) for 10 s. The order of the stimuli was random. This process was repeated for 40 trials.

Data Analysis and Modeling Study

Correlation measures. To quantify the characteristics of neural response, we divided time into small bins. The default bin size was 5 ms, unless stated otherwise. A spike train was discretized into “0” or “1” within each time bin, where \( r_i(n) = 1 \) means that the cell fired in the nth time bin, and “0” means that it did not fire. In this way, the spiking activities of \( N \) neurons can be represented as a matrix \( R = [r_{ij}] \), with each column representing a binary sequence. The cross-correlation function between two spike trains was calculated by (Liu et al. 2007),

\[
C_{ij}(m) = \frac{M}{M-2} \frac{\sum_{n=1}^{N-|m|} r_i(n) r_j(n + m)}{\sum_{n=1}^{M} r_i(n) \sum_{n=1}^{M} r_j(n)}
\]

where \( n = 1,..., M \) is the index of the bins.

We measured the neuronal correlation strength by the peak value of the cross-correlation function.

Modeling study on correlation strength. To demonstrate that the enhancement of neural correlation was not a trivial consequence of the decay of neuronal firing rates, we carried out a modeling study. We considered a pair of leaky integrate-and-fire neurons connected by gap-junction, whose dynamics are given by,

\[
\frac{dV_i}{dt} = -g_L(V_i - V_{\text{rest}}) + I_{\text{input}} + g_{\text{coupling}}(V_j - V_i), \quad i, j = 1, 2
\]

where \( C \) is the membrane capacitance, \( g_L \) is the leaky conductance, \( I_{\text{input}} \) is the input from bipolar/amacrine cells, and \( g_{\text{coupling}} \) is the coupling conductance between the neurons via the gap-junction.

Neurons have a resting potential of \(-70\) mV. If the membrane potential of a neuron \(V_r\) reaches a threshold \(-50\) mV, a spike is generated, and \(V_r\) is reset to \(-85\) mV.

The input to a neuron was set to be,

\[ I_{\text{input}} = \mu_i(t) + \sigma \xi_i(t) \]

where \(\mu_i(t)\) is the mean of the input, \(\xi_i(t)\) is the Gaussian white noise of zero mean and unit variance, and \(\sigma\) is the noise strength. The noise processes of the two neurons were independent of each other, i.e., \(\langle \xi_i(t) \xi_j(t) \rangle = \delta_{ij} \delta(t - t')\). We chose \(\mu_i(t)\) as decaying with time, mimicking the adapted input to a RGC from bipolar/amacrine cells (Baccus and Meister 2002; Denb 2008; Rieke 2001). Without loss of generality, we chose \(\mu_i(t) = \mu_i(t) = 0.8e^{-t/\tau}\), with \(t = 0\) denoting the onset of the stimulation. The parameters were chosen to roughly match the experimental data: \(\tau = 20\) s for the flickering checkerboard, and \(\tau = 0.85\) s for the dark stimulation.

We ran simulations for 20 repetitions with randomly generated noises in each trial and computed the correlation strength according to Eq.1. We observed that for a constant coupling strength (including \(g_{\text{coupling}} = 0\)), the neural correlation strength always decayed with time during the adaptation (data not shown), indicating that the increasing correlation strength observed in our experiment is not a passive process associated with attenuating firing rates.

**Information measures.** In the discrimination task, we let the stimulus set \(S\) take two values: dark stimulation and gray stimulation, with each occurring with equal probability, i.e., \(p(s) = \frac{1}{2}\). Denote \(p(rs)\) the conditional probability of observing the neuronal response \(r\) given the stimulus \(s\).

For two neurons, the total amount of the stimulus information in the neuronal data is given by the joint mutual information (Cover and Thomas 1991),

\[ I(S;R) = \sum_{r_i} \sum_{r_j} p(r_1, r_2) p(s) \log_2 \frac{p(r_1, r_2 | s)}{p(r_1, r_2)} \]

We calculated the amount of the stimulus information contained in a single time bin. The neuronal response was described by a binary variable, i.e., \(r_i = 0, 1\). Since the neuronal responses were highly noisy and the number of trials was limited, we used a moving-window approach to estimate the distributions of neuronal responses, namely, \(p(r)\) and \(p(rs)\) at time \(t\) were estimated by the statistics of spike trains in the time window from \([-500, t + 500]\) ms over \(N_{\text{trial}} = 20\) trials. The obtained probability distributions were then used to compute information quantities. Since the amount of data was limited, the estimation of the mutual information may be biased. We corrected this by subtracting the biased term, which was calculated by (Panzeri and Treves 1996),

\[ I_{\text{bias}} = \frac{1}{2 \log 2 N_{\text{trial}}} \sum \frac{\bar{R}_i - \bar{R} - (N_i - 1)}{N_{\text{trial}}} \]

where \(N_{\text{trial}} = 20\) is the number of trials and \(N_i = 2\) is the number of stimuli. \(\bar{R}_i\) and \(\bar{R}\) denote, respectively, the number of bins in which \(p(r)\) or \(p(r)\) is nonzero.

When two neurons fire independently, the joint mutual information equals the sum of the mutual information they convey separately, i.e.,

\[ I(S;R) = I(S;r_1) + I(S;r_2) \]

When two neurons’ firings are correlated, the joint mutual information can be larger than the sum of individual ones, and their discrepancy, called synergy information (Syn), measures the amount of the stimulus information contained in the neural correlation (Brenner et al. 2000; Panzeri et al. 1999; Schneidman et al. 2003). It is given by,

\[ \text{Syn}(r_1, r_2) = I(S;R) - I(S;r_1) - I(S;r_2) \]

The case \(\text{Syn} < 0\) corresponds to the fact that the stimulus information contained in individual neurons’ activities is larger than that contained in their joint responses, implying that some information is redundant (Schneidman et al. 2003).

We used the ratio, \(\text{Syn}(r_1, r_2)/I(S;R)\), i.e., the normalized synergy information, to measure the relative contribution of neural correlation in conveying the stimulus information.

**Surrogate data.** To eliminate the trivial consequence associated with attenuating firing rates, we calculated the stimulus information contained in the neural correlation of surrogate data. To estimate the response probability \(p(r_i, r_j)\) at time \(t\), we used the neuronal spike sequences in the time interval of \([t - 500, t + 500]\) ms (a moving-window). The surrogate data were constructed by shuffling the interspike intervals of neuronal spike sequences in this interval (Liu et al. 2011). The shuffling operation destroyed the correlation structure between neurons (i.e., the cross-correlation function) but did not change other characteristics, such as the firing rates and the interspike interval distributions.

**Classification by linear support vector machine.** To study the role of neural population in encoding the stimulus information, we applied the classifier approach to analyze the data. Specifically, we predicted the stimulus condition from the neuronal data using a linear support vector machine (SVM). The SVM is currently one of the most accurate pattern classification approaches. The SVM algorithm picks the classification boundary that maximizes the margin (i.e., the separation) between two classes of data (Chen et al. 2010; Vapnik 1995). The linear SVM is a version of the SVM that classifies using a linear boundary.

We divided the adaptation process into several time intervals (length \(1\) s) and calculated the firing rate of each neuron and the correlation strength between each neuron pair based on the neuronal spiking activities in each interval. The input to the classifier was either the firing rates of individual neurons or the correlation strengths between neuron pairs in a given time interval. To reduce the dimensionality of the inputs (which is critical to train a classifier that generalizes well when the amount of training data is limited), we applied principal components analysis (PCA) to preprocess the data. The final input features were the projections of the raw input data onto the first \(L\) principle components. The value of \(L\), which was 2 for firing rate and 3 for correlation strength, was optimized for best classification performance.

To quantify the classification performance, we used the cross-validation approach (Bishop 1995), that is, at each turn of training, 35 sets of data were chosen from the total 40 trials as training examples, and the leftover 5 sets were used as testing data to estimate the classification error. This division procedure was repeated eight times until all data had been used once as the test examples. The final classification accuracy was the averaged value of the accuracy obtained over the eight repetitions.

**Receiver operating characteristic analysis of discrimination performances.** We calculated the receiver operating characteristic (ROC) to analyze the accuracy of using either the firing rate of a single neuron or the correlation strength of a pair of neurons to discriminate the two stimuli (Zweig and Campbell 1993). For this analysis, discrimination was performed by comparing the firing rate or correlation strength with a threshold. A ROC curve is a graphical plot of the true positive vs. false positive rate as a function of the value of the thresholds. In our study, we defined the full-level dark stimulation as the positive stimulus. The true positive rate was then the empirical probability that the classifier predicted correctly the dark stimulus. The false positive rate was the empirical probability when the prediction was the dark stimulus when the actual stimulus was the gray one. The performance of classification was quantified as the total area under the ROC curve (AUROC). We divided the adaptation process into several time intervals (length \(1\) s), and the AUROC was calculated for each interval.
The amount of overlap in the distributions of the input features (firing rate, correlation strength) between the two stimuli classes substantially influences the accuracy of discrimination in the above analysis. We visualized the amount of overlap in the input features by fitting gamma distributions $\Gamma(\alpha, \lambda, \mu)$, where $\alpha$ and $\lambda$ are the shape and scale parameters, respectively. The parameters were estimated via the mean $\mu$, and variance $\sigma^2$ of the input features ($\alpha = \mu^2 / \sigma^2$ and $\lambda = \sigma^2 / \mu$). 

RESULTS

Adaptive Response to Sustained Stimulation

Experiments were performed on isolated bullfrog retinas. Based on their response properties, RGCs of bullfrogs can be categorized into four classes, namely, sustained contrast detectors, net convexity detectors, moving-edge detectors, and dimming detectors (Maturana et al. 1960). Dimming detectors are known to encode escape-related information: dimming indicates the potential approach of a predator from behind (Ishikane et al. 2005). Sustained darkening or dimming stimulation can evoke sustained responses in dimming detectors, but only elicit a few spikes transiently in other cell types (Ishikane et al. 2005; Maturana et al. 1960). In our experiments, the adaptive response of dimming detector to sustained dimming stimulation was analyzed.

To identify the key characteristics of neural responses during the luminance adaptation, we applied a full-field dark stimulation to induce repeatable and reliable adaptive responses. In the experiment, the retina was first exposed to 15 s of flickering pseudorandom checkerboards, followed by 15 s of full-field dark stimulation (Fig. 1A; see MATERIALS AND METHODS). Throughout this paper, the default bin size for presenting the results is 5 ms, unless it is stated otherwise. The activity of an example dimming detector to dark stimulation over 20 trials is plotted in Fig. 1, B1 and B2. At the onset of the stimulation, the firing rate of the dimming detector first increased dramatically and then decreased gradually to a low level that was close to the background activity level. Note that, since the sequence of pseudorandom checkerboards was identical over trials, the responses of the neuron also exhibited some degree of repetition over trials. This has also been observed in other studies (Berry et al. 1997; de Ruyter van Steveninck et al. 1997; Mainen and Sejnowski 1995).

The entire adaptation process lasted for ~5 s. Considering that a bullfrog has no eye movement (Dieringer and Precht 1982; Lettvin et al. 1959; Maturana et al. 1960) and typically responds very slowly to external stimulations in a natural environment [e.g., the time scale for bullfrogs’ escaping behavior in response to dark stimulation is in the order of 1 s (Ishikane et al. 2005)], we presume that neural information processing in these 5 s is relevant to bullfrogs’ behavior, and our study was focused on information representation during this interval. When fitted by an exponential decaying function, the time constant for the decay of firing rate after the onset of the dark stimulation was measured to be 0.8218 s. Other cell types recorded in our setup only fired transiently (less than 200 ms) after being exposed to the dark stimulation (Fig. 1C). Since our interest is on information encoding during the adaptation, only data from dimming detectors and not from other cell types were analyzed in this study. In the dark stimulation experiment, a total of 126 RGCs from 6 retinas were recorded, and 65 among them were dimming detectors exhibiting clear adaptive responses. The averaged time constant for the decay of firing rate after onset of the dark stimulation was $0.8528 \pm 0.0423$ s (mean ± SE).

Correlation Patterns of RGCs

The population activity of 10 neurons recorded in a single trial from an example retina is presented in Fig. 2A. The cross-correlation functions between all neuron pairs are shown in Fig. 2B (see MATERIALS AND METHODS). Concerted activity
between RGCs has been widely observed (Meister et al. 1995; Usrey and Reid 1999) and can be well-classified into two different patterns based on the time-lag distribution of the cross-correlation function (Brivanlou et al. 1998; DeVries 1999). If the cross-correlation function between two RGCs' firing sequences has a narrow peak (with time-lags in the cross-correlation function distributed within 10 ms), then the neurons' activities are "synchronized", referred to as SynCorr hereafter (Fig. 2C1). Note that, if the analysis time bin is sufficiently small, the cross-correlation typically exhibits a bimodal shape (the inset in Fig. 2C1). This is consistent with the property of gap-junction: the bimodal shape becomes visible when the bin size is comparable to the transmission delay of a gap-junction. Indeed, the bimodal shape of the cross-correlation function is an important criterion for judging whether two neurons are connected by gap-junction (Brivanlou et al. 1998; DeVries 1999; Shlens et al. 2008). In a few cases (21 out of 108 neuronal pairs recorded), the cross-correlation may only have a single peak around zero lag due to one-way signal transmission via gap-junction (Haas et al. 2011; Mann-Metzer and Yarom 1999). Note that asymmetric correlations do not necessarily imply asymmetric conductance, and they may occur due to asymmetric input resistances.

On the other hand, if the cross-correlation function of a neuron pair has widely distributed time-lags (between 30 and 100 ms), then the neurons' activities are merely "correlated" due to common presynaptic inputs. We refer to this situation as WeakCorr hereafter (Fig. 2C2 and the inset). We used the peak value of the cross-correlation function to measure the correlation strength between two neurons. Generally, under the same bin size, the correlation strength of a SynCorr-pair was much larger than that of a WeakCorr-pair.

We found that in the set of simultaneously recorded neurons, the pairwise correlation structure could be classified into two types, SynCorr and WeakCorr. Moreover, neurons typically formed groups such that intragroup correlations were of the type SynCorr and intergroup correlations were of the type WeakCorr. For the example retina presented in Fig. 2B, neurons could be divided into two groups (marked by dark and red colors, respectively).

Active Correlation Change During the Adaptation

As expected, firing rates of neurons attenuated during adaptation (Fig. 3, A and B). We wondered how the correlation strengths between neurons changed over time. We found that, for the 336 total simultaneously recorded neuron pairs from 6 retinas, the strengths of SynCorr- and WeakCorr-pairs exhibited consistent time-dependent changes as follows (Fig. 3C).

For neuron pairs with WeakCorr, i.e., the neurons that were correlated due to receiving common inputs rather than gap-junctions, correlation strengths were weakened during the adaptation (Fig. 3B). This is easily understandable, since the input from bipolar/amacrine cells to a RGC diminishes over time during the luminance adaptation, and hence the common-input-induced correlations are reduced. This is also the reason for the decay of RGCs' firing rates (Baccus and Meister 2002; Rieke 2001).

Surprisingly, however, we found that, for neuron pairs with SynCorr, i.e., the pairs connected by gap-junctions, correlation strengths were gradually enhanced during the adaptation (Fig. 3A). This is not a trivial property. In a normal situation when two neurons are unconnected or connected by a constant electrical/chemical synapse, their correlation strength should decrease with the firing rates (de la Rocha et al. 2007). A possible mechanism to generate this unusual consequence is that the electrical coupling between two neurons is facilitated during the adaptation (see DISCUSSION). Nevertheless, the focus of the present study was not on the biophysical mechanism underlying the active change of neural correlation, but rather the functional role of this change.

A Stimulation-Discrimination Task

To investigate the potential functional role of the temporal changes of neural correlations in encoding the stimulus infor-
mation during adaptation, we carried out another experiment in which two different stimuli were applied. In this experimental protocol, bullfrog retinas were first presented with flickering pseudorandom checkerboards for 10 s and then followed by either a full-field dark stimulation or a full-field gray stimulation (chosen randomly) for 10 s, and this process was repeated for 40 trials (see MATERIALS AND METHODS). The only difference between the dark and gray stimuli was the luminance level. Both stimuli triggered adaptive responses in dimming detectors (Fig. 4A) and also induced active changes in the neural correlation strengths. In this experiment, 16 out of 30 RGCs recorded from 2 retinas were identified as dimming detectors and selected for further analysis. Since only the strength of SynCorr pairs displayed interesting nontrivial time-dependent changes, our analysis was focused on the neuron pairs exhibiting SynCorr. Of 2 retinas inspected, we found that 24 neuron pairs in one retina and 6 in the other exhibited SynCorr.

Based on the recorded neuronal data, we constructed a luminance discrimination task with two alternatives: dark vs. gray. The maximum amount of stimulus information contained in neural data is, therefore, 1 bit. In the following, we explore how the luminance information (dark vs. gray) was encoded in the neuronal response features during the adaptation.

**Encoding the Stimulus Information in Neural Correlation**

Since the neuronal responses were highly noisy, we used information theoretic tools to analyze the stimulus information contained in the neuronal data. We computed the mutual information between the stimuli (dark and gray) and the neuronal response features (firing rates and correlations) to quantify the total amount of stimulus information contained in neuronal data. The stimulus information contained in neural correlation was measured by the synergy information, which is the difference between the joint mutual information and the sum of the individual mutual information (see MATERIALS AND METHODS) (Brenner et al. 2000; Panzeri et al. 1999; Schneidman et al. 2003).

We denote $p(r|s)$ the probability of observing the neuronal activity $r$ given the stimulus $s$. Since the data were noisy and limited in quantity, we took a moving-window approach to compute $p(r|s)$; that is, $p(r|s)$ at time $t$ was estimated by the statistics of neuronal responses between $t - 500$ and $t + 500$ ms.

The time course of the mutual information for two neurons with SynCorr is presented in Fig. 4B, which shows that the stimulus information contained in the neural responses did not change considerably during the adaptation. We further measured the stimulus information contained in the neural correlation by computing the synergy information. Interestingly, we found that synergy information increased over time during the adaptation (Fig. 4B). The relative contribution of the neural correlation to the encoding of the stimulus information (the other contributor being firing rates) can be measured by the ratio between the synergy and the mutual information (also called the normalized synergy information, see MATERIALS AND METHODS). Fig. 4C shows that the contribution of the neural correlation increased dramatically with time, from $\sim 0\%$ at 0.5 s to $\sim 60\%$ at 3 s, relative to the onset of the stimulation. This finding suggests that the active change in the correlation strength of a SynCorr-pair is associated with the increasing importance of the neural correlation for encoding the stimulus information.

To confirm that the increase of synergy information is not a trivial consequence of the attenuation of firing rate, we constructed a set of surrogate data in which the spike trains were randomly shuffled without affecting the values of the time-dependent firing rates (see MATERIALS AND METHODS). We found that in the surrogate data, the stimulus information contained in the neural correlation was negligible (Fig. 4B and C).

To ensure that our result is independent of the bin size adopted in our analysis, we computed information ratios under different bin sizes (1, 2, 5, and 10 ms). Figure 4D shows that the tendency that the information ratio increased over time kept consistent for each case. This is because both the mutual and
the synergy information increased linearly with the bin size (up to a certain value), and their ratio was unaffected.

**Classifying Stimuli Based on the Neural Population Activity**

Restricted by the experimental setup (which limited the number of trials and the amount of recorded data) and the nonstationary nature of adaptive neuronal responses, we could only compute the mutual and synergy information contained in the responses of up to two neurons at a time. To estimate the stimulus information contained in a neural population, we took a classifier approach. The idea of the classifier approach is straightforward: if the neural responses contain information about the stimuli, we should be able to train a classifier which can discriminate between the stimuli types. The performance of the classifier can then be related to the amount of information present in the neuronal responses. The classifier approach is increasing in popularity in the neuroscience field (Chen et al. 2010; LaConte et al. 2005; Norman et al. 2006; Schwartz et al. 2012). The linear SVM was adopted as the classifier in this study.

By applying either the firing rates of neurons or the correlation strengths of neuron pairs as the input features to the classifier, we tested which neural feature was more informative for discriminating the dark from the gray stimuli. To reduce the dimensionality of the inputs (which is critical to train a classifier that will generalize well when data is limited in quantity), we applied PCA to preprocess the data (see MATERIALS AND METHODS). In our study, for the firing rates, ~81.26% of the variance of the data can be accounted for by the first two principal components; for the correlation strengths, 83.04% of the variance of the data can be accounted by the first three principle components. Thus we projected the raw data onto these components to reduce the dimensionality of the inputs. Using more PCA components leads to reduced classifier performances due to over-fitting with a limited amount of data. The details of how we applied the classifier approach can be found in MATERIALS AND METHODS.

To get an intuitive idea on whether neural population activity contained stimulus information, we calculated the differences in firing rates and differences in correlation strengths between the responses to the dark and the gray stimuli. The absolute values of the differences were normalized to be in the range of [0, 1] for the convenience of comparison. Figure 5A shows that, over time, the differences between neuronal firing rates in response to the dark and gray stimuli gradually decreased; whereas the differences between correlation strengths gradually built up, implying that a classifier using correlation strengths as input will become more effective at discriminating the two stimuli at the later stages of the adaptation.

By choosing a 5-neuron group for input, we applied the classifier approach and observed that the classification accuracy based on firing rate decreased over time during the adaptation, whereas the accuracy based on neural correlation increased (Fig. 5B). This is consistent with the above finding that, during the adaptation, the contribution of neural correlation to the encoding of the stimulus information increased over time.

We further analyzed how the classification accuracy varied with the number of neurons. The neuronal data in two time intervals, [0, 1] s and [3, 4] s, was inspected. We found that the classification accuracy based on neural correlation always increased with the number of neurons, and it reached ~80% when the number of neurons used for classification was 6 (Fig. 5C). On the other hand, the classification accuracy based on firing rate only increased with the number of neuron at the early stage of the adaptation, [0, 1] s, and did not do so at [3, 4] s (Fig. 5C). This agrees with the above finding that at the late stages of the adaptation, firing rate is no longer a dominating factor in the encoding of the stimulus information.

**Discriminating Stimuli Based on Neural Correlation**

To further support our hypothesis that the encoding properties of neurons are shifted from firing rates to correlations during adaptation, we applied ROC analysis to quantify the
discrimination power of neural correlation. Since the two stimuli were quite similar and neuronal responses were highly noisy, the discrimination process involved an element of chance. We applied the ideal observer approach from the framework of classical signal detection theory to measure the discrimination capacity. The ideal observer makes a decision based on a classification threshold and assigns the stimulus class according to whether the observed feature value is larger or smaller than the threshold. The overall performance of the observer was quantified by ROC analysis, which plots a curve of the true positive rate vs. the false positive one as a function of the threshold (see MATERIALS AND METHODS). The AUROC curve measures the discrimination capacity associated to a neural feature. Larger AUROC implies better discrimination capacity (a value of 0.5 corresponds to chance level, and a value of 1 corresponds to perfect discrimination).

The overlap between the distributions of neural features generated by different stimuli is the key aspect determining the performance of the ideal observer. That is, the larger the overlap, the more difficult it is to separate the two stimuli. The changes in the distributions of firing rate and correlation strength generated by two stimuli in the first 3 s of the adaptation were analyzed. We divided the time into three intervals and fitted gamma distributions to the empirical distributions of firing rate and correlation strength in each interval (n = 20 trials) to aid visualization (see MATERIALS AND METHODS). We observed that the overlap between the firing rate distributions under different stimuli increased over time, indicating that it became more and more difficult to distinguish the stimuli based purely on the firing rates (Fig. 6A). The value of AUROC decreased from 0.6387 ± 0.0164 at the 1st s to 0.5432 ± 0.0180 at the 2nd s and to 0.5391 ± 0.0162 at the 3rd s (Fig. 6C). On the other hand, the overlap between the distributions of correlation strength gradually decreased with time, indicating that the neural correlation became more and more effective in discriminating stimuli (Fig. 6B). Consequently, the AUROC value increased from 0.5258 ± 0.0126 at the 1st s to 0.5937 ± 0.0230 at the 2nd s and to 0.6556 ± 0.0222 at the 3rd s (Fig. 6C; n = 24; ANOVA, P < 0.001). This result supports the above finding that neural correlation became more important in the encoding of the stimulus information at the late stage of the adaptation.

DISCUSSION

Luminance adaptation is one of the fundamental adaptive phenomena observed in the neural system. In the present study, we investigated how stimulus information is encoded dynamically in the changing neuronal responses during adaptation. Several authors also studied the related issues, but with different purposes and concerning different aspects of how neural encoding properties may change over time (Mechler et al. 1998; Reich et al. 2001; Schwartz et al. 2012). Here, motivated by the observation that neuronal correlations mediated by gap-junctions were enhanced during adaptation, we inspected the dynamic role of neural correlation in conveying stimulus information. We applied three complementary information analysis approaches, aiming to resolve this issue from different perspectives. We found that at the early stage of the adaptation, the stimulus information was mainly encoded in the neuronal firing rates, whereas at the late stage of the adaptation, the stimulus information was more encoded in the neuronal correlations. Thus our results reveal that there exists a shift in the encoding properties of neurons during the adaptation. Furthermore, the attenuation of firing rates, a typical phenomenon associated with neuronal responses to sustained stimulation, is not a simple consequence of ignoring constant input, but rather is part of an active strategy for the nervous system that uses concerted neuronal firings to encode stimulus information.

Adaptive neural responses have been widely observed in sensory systems, including the luminance and contrast adaptations in the visual system (Baccus and Meister 2002; Kaplan and Benardete 2001; Kohn 2007), and the stimulus-specific adaptations in the auditory (Neuweiler 1990; Ulanovsky et al. 2004), olfactory (Dalton 2000), and tactile systems (Wang et al. 2010). It has been reported that neurons can continually adjust their response characteristics, including the sensitivity, gain, and receptive field properties during adaptation (Baccus and Meister 2002; Li et al. 2012; Rieke 2001), suggesting that adaptation encompasses some general principles used by the neural system to process information efficiently in changing environments (Demb 2008; Shapley and Enroth-Cugell 1984). Here, our study contributes evidence to this theory by unveiling that luminance adaptation underlies a strategy for the neural system to use the concerted, but less active, firing of neurons to encode stimulus information. A recent study re-
ported that there exist two groups of RGCs, and when one group adapts to high-contrast inputs, the other group compensates for the information loss due to adaptation by maintaining high sensitivity to weak signals (Kastner and Baccus 2011). Our study suggests another mechanism to compensate for information loss, that is, by using concerted neuronal responses to encode the stimulus information.

We used synergy information to quantify the amount of the stimulus information contained in neural correlation. Alternatively, one may use other correlation measures. Nirenberg and Latham proposed such a measure, the Kullback-Leibler divergence between true encoding model \( [i.e., p(r|s)] \) and a mismatched one that neglects neuronal correlation (Nirenberg et al. 2001). Recently, a measure called \( I^u \), which is directly linked to the decoding error of a maximum likelihood inference based on a mismatched model (Oizumi et al. 2010; Wu et al. 2001), was applied to analyze neural data. There is a standing debate over which measure better quantifies the stimulus information conveyed by neural correlation (Latham and Nirenberg 2005; Schneidman et al. 2003). Nevertheless, for the shifted encoding properties investigated in this work, these three measures gave similar results (Fig. 7).

The shift in the neuronal encoding properties was accompanied by an active change in neuronal correlation strengths. If the neural data were shuffled (i.e., the correlation structure of spike trains was destroyed without affecting neuronal firing rates), the stimulus information contained in neural correlation also became negligible. In the present study, we have not explored the biophysical mechanism underlying the enhanced neuronal synchrony. One candidate mechanism, we speculate, is the short-term facilitation of gap-junction between RGCs. Our computational study showed that short-term facilitation of gap-junction could induce enhanced synchrony between a neuron pair, even though the neuronal firing rates attenuate (data not shown). The activity-dependent modification of gap-junctions has been observed in the cortex (Landsman and Connors 2005). Although there has been no direct observation of activity-dependent modifications of gap-junction between RGCs, some studies suggested that gap-junction strength could be modulated by dopamine, the activity of which is influenced by the luminance of the environment (Bloomfield and Volgyi 2005). Also, luminance- and activity-dependent modifications of gap-junctions between amacrine cells have been found in the retina (Bloomfield et al. 1997; Kothmann et al. 2012). Alternatively, there may exist other mechanisms which could generate the observed enhanced synchrony behavior. For instances, the behavior could be due to the intrinsic dynamic properties of individual neurons as studied in Pfetleuy et al. (2003), or it could be due to some subtle changes in the synaptic input during adaptation (e.g., a decrease of the mean input contributes to attenuation of firing rates, while increased common noise leads to enhanced synchrony). These possibilities are worth investigating in future study.

Our finding in this study has also far-reaching implications on the computational role of neural correlations. Concerted activities widely exist in RGCs of various species (DeVries 1999; Ishikane et al. 2005; Mastronarde 1983; Meister et al. 1995; Shlens et al. 2008; Usrey and Reid 1999). Synchronized firing among neurons in response to external stimuli has been observed in experiments (Brivanlou et al. 1998; DeVries 1999; Shlens et al. 2008). However, there is a long-standing debate over the role and significance of concerted activity in neural information processing (Averbeck and Lee 2004). A number of studies have revealed that concerted neuronal activity encodes extra stimulus information which cannot be extracted by the responses of single neurons, and they play important roles in animal behaviors (Dan et al. 1998; Ince et al. 2010; Ishikane et al. 2005), whereas other work suggested that neuronal correlation conveys little information and can be largely neglected (Meytlis et al. 2012; Nirenberg et al. 2001; Oizumi et al. 2010). In this study, we observed the changes in information representation throughout the process of adaptation. Our results show that, at the early stage of the adaptation, the firing rates of neurons conveyed the majority (more than 90%) of the stimulus information, which is in agreement with findings reported by other authors (Meytlis et al. 2012; Nirenberg et al. 2001; Oizumi et al. 2010), whereas at the later stage of the adaptation, the contribution of neuronal correlation increased remarkably and became the dominant factor, which is in accordance with other research (Schneidman et al. 2006). Thus our results reconcile the two different views in the literature and reveal that the contribution of neuronal correlation in conveying the stimulus information can vary with time during adaptation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


