Cortical Modulation of Synaptic Efficacies through Norepinephrine

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Abstract

I propose a norepinephrine- (NE-) neuromodulatory system, which I call "enhanced-excitatory and enhanced-inhibitory (E-E/E-I) system". The E-E/E-I system enhanced excitatory and inhibitory synaptic connections between cortical cells, modified their ongoing background activity, and influenced subsequent cognitive neuronal processing. When stimulated with sensory features, cognitive performance of neurons, signal-to-noise (S/N) ratio, was greatly enhanced, for which one of the three possible S/N enhancement schemes operated under the E-E/E-I system, namely; i) signal enhancement more than noise increase, ii) signal enhancement and noise reduction, and iii) noise reduction more than signal decrease. When a weaker (or subthreshold) stimulus was presented, the scheme (ii) effectively enhanced S/N ratio, whereas the scheme (iii) was effective for enhancing stronger stimuli. I suggest that a release of NE into cortical areas may modify their background neuronal activity, whereby cortical neurons can effectively respond to a variety of external sensory stimuli.

1 Introduction

It is well known that a release of norepinephrine (NE) into target brain areas through noradrenergic (e.g., locus coeruleus (LC)) pathways facilitates the efficacies of excitatory and inhibitory synaptic transmissions within the targeted neuronal circuits [1]. NE binds to α and β adrenoceptors of neurons, activates second messenger systems, and augments the efficacies of excitatory (e.g., glutamatergic) and inhibitory (e.g., GABAergic) synaptic transmissions [2]. Such NE-induced neuromodulation has been well demonstrated for cortical pyramidal cells [3]. Although many experiments have demonstrated that NE-release in certain cortical areas modifies neuronal excitation and/or inhibition, little is known about how these neuronal modulations affect the cognitive performance of the cortices [2,3].

The purpose of the present study is to propose a neural network model whose dynamic behavior is altered when dosed with NE. By simulating the model, I investigate how NE modulates the dynamic behavior of neurons and what neural mechanisms are essential for NE-mediated cognitive enhancement. We use "signal-to-noise (S/N)" ratio as a cognitive performance measure.

2 Neural Network Model

I construct a neural network model for the cortex (Figure 1a). The model consists of an input (IP) and an output (OP) network. Feature stimuli Fn (n = 1, 2, 3, 4, 5) activate their corresponding groups of IP neurons ("ellipses"), whose action potentials are sent to the OP network via divergent/convergent feedforward projections ("solid lines") and activate corresponding cell assemblies ("circles"). As shown in Figure 1b, the OP network consists of neuron units, each of which contains a pyramidal cell (PYC) ("large triangle"), a small basket cell (SBC) ("small circle") and a large basket cell (LBC) ("large circle"). In each unit, the PYC and the SBC are reciprocally connected via a positive (PYC-to-SBC) and a negative (SBC-to-PYC) synapse. The PYC positively synapses on the LBC. Groups of PYCs form cell assemblies. PYCs within cell assemblies are connected with each other via positive synapses, and there is no

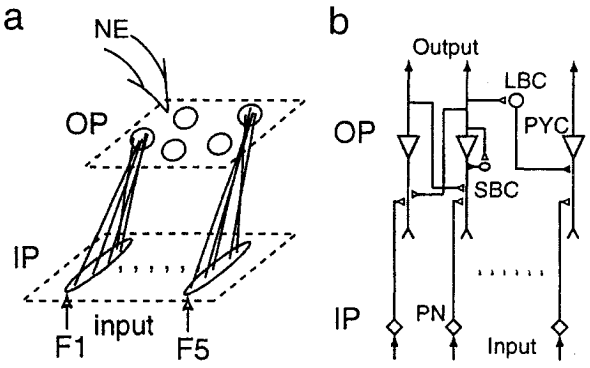

Fig. 1. Structure of the neural network model. (a) Feature stimuli Fn (n = 1, 2, 3, 4, 5) are applied to corresponding groups of IP neurons ("ellipses"), whose action potentials are sent to the OP network via divergent/convergent feedforward projections ("solid lines") and activate corresponding cell assemblies ("circles"). NE (norepinephrine) is dosed into the OP network. (b) PYC, SBC and LBC denote, respectively, pyramidal, small basket and large basket cell. "Open" and "filled" small triangles denote excitatory and inhibitory synapses, respectively.

connection between PYCs across cell assemblies. LBCs negatively synapse on the PYCs of the other cell assemblies through lateral (LBC-to-PYC) connectios.

I assume here a primary cortical area whose neurons have tuning properties to specific sensory features. To make the PYCs feature-selective, I create in the output (OP) network multiple dynamic cell assemblies that are spatially separated from each other (see Figure 1a). Due to such separable property, the dynamics of the OP network allows a given cell assembly to be selectively activated against others when its corresponding feature stimulus is presented to the input (IP) network. For simplicity, the IP network contains only projection neurons (PNs) between which there is no connection. That is, the IP network works exclusively as an input layer. These neurons are an integrate-and-fire type of neurons (for detail, see ref. [4]).

The efficacies of both excitatory and inhibitory synapses are enhanced as a function of a dose level of norepinephrine, or concentration of NE ([NE]). Neuromodulation of excitatory ($w_{ij}^{PY,PY}$: PYC-to-PYC) and inhibitory ($w_{ij}^{PY,LB}$: LBC-to-PYC, $w_{ij}^{PY,SB}$: SBC-to-PYC) synaptic efficacies are described by the following equations.

$$\frac{dw_{ij}^{PY,PY}}{dt} = \alpha_{PY}([NE]_0 - [NE])[NE] - \beta_{PY}(w_{ij}^{PY,PY} - w_0^{PY,PY}) \quad (1)$$

$$\frac{dw_{ij}^{PY,LB}}{dt} = \alpha_{LB}[NE] - \beta_{LB}(w_{ij}^{PY,LB} - w_0^{PY,LB}) \quad (2)$$

$$\frac{dw_{ij}^{PY,SB}}{dt} = \alpha_{SB}[NE] - \beta_{SB}(w_{ij}^{PY,SB} - w_0^{PY,SB}) \quad (3)$$

Equation 1 defines the excitatory synaptic modulation between PYCs, which is based on observed results [5]. Equations 2 and 3 define the inhibitory synaptic modulation from LBC to PYC and from SBC to PYC, respectively, which are simple hypothetical representations based on observed results [2]. In the present study, I focused especially on the postsynaptic (PYC-to-PYC, LBC-to-PYC and SBC-to-PYC) actions of NE on the activities of PYCs that play, in general, major roles in cognitive information processing in the cortex. For simplicity, I did not modulate the other excitatory synapses, PYC-to-LBC and PYC-to-SBC. Unless otherwise stated elsewhere, $w_0^{PY,PY} = 7.0$, $w_0^{PY,LB} = 0.1$, $w_0^{PY,SB} = 30.0$, $\alpha_{PY} = 3.0$, $\alpha_{LB} = 0.8$, $\alpha_{SB} = 60.0$, $\beta_{PY} = \beta_{LB} = \beta_{LB} = 1.0$ and $[NE]_0 = 2.0$.

3 Results

As shown by the raster plots of action potentials in Figure 2a, the PYCs have ongoing (background) activity, when no external stimulus and no dose of NE are applied. The random and brief emergence of the five (F1-5) dynamic cell assemblies, or population activation of PYCs, characterizes the present ongoing neuronal activity. The temporal formation of each dynamic cell assembly arises from mutual excitation between the PYCs within cell assemblies. The brief nature of the dynamic cell assemblies arises largely from the self-inhibition mediated through their accompanying SBCs. Due to such a self-inhibitory mechanism, the more the PYCs emit action potentials, the greater the activities of the PYCs tend to be suppressed.

When the IP network is stimulated with a sensory feature (F2), whose duration is indicated by a "horizontal bar" in Figure 2a, the PYCs of the cell assembly

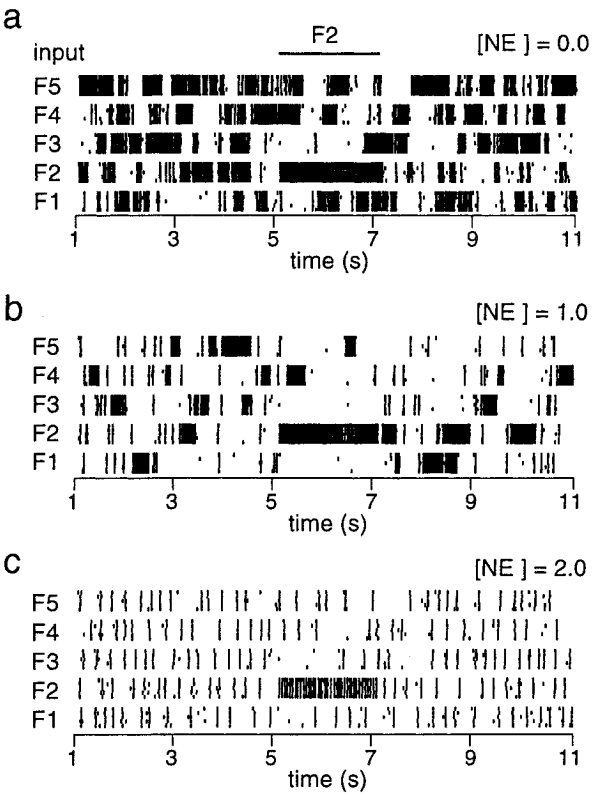

Fig. 2. Dependence of the dynamic behavior of the OP network on dose levels of NE ([NE]). Raster plots of PYC action potentials of cell assemblies that are sensitive to features F1-5 are shown. (a) NE is not dosed, or [NE] = 0.0. A "horizontal bar" indicates a stimulation (F2) presentation period. (b)-(c) NE-induced neuromodulation operated under the E-E/E-I system.

corresponding to the stimulus are activated and emit a long burst of action potentials. After switching off the input, the state of the OP network returns to the ongoing state. Note that the other dynamic cell assemblies (F1, F3, F4 and F5) tend to frequently emerge during the stimulation period. This indicates that the lateral inhibition across dynamic cell assemblies, which is mediated through LBC-to-PYC inhibitory connections, is not so strong under the original condition, or at [NE] = 0.0.

Figure 2b-c shows how the dynamic behavior of the network is modulated by the E-E/E-I system. The period of each brief burst under the ongoing state is deceased as the dose level of NE ([NE]) increases (Figure 2a → 2b → 2c), which is due largely to the enhanced self-inhibition of PYCs through SBC-to-PYC feedback connections. Note that the activation of the dynamic cell assemblies tends to be temporally separated from each other as [NE] increases, that is, they are not likely to overlap in the time course. This is due largely to the enhanced lateral inhibition through LBC-to-PYC connections.

Such temporal segregation of dynamic cell assemblies is essential for processing the applied feature stimulus (F2) in that as "feature-detection neurons" of an early sensory cortex the PYCs must respond selectively to a specific feature stimulus, while the other PYCs are not allowed to respond, or emit fewer action potentials. Note that although the ongoing PYC activity is decreased as [NE] increases, the synchronous PYC activity within cell assemblies is well preserved (e.g., see Figure 2c). The term, "synchronous activity", implies that the PYCs within cell assemblies generate action potentials almost at the same time.

I evaluated the cognitive performance of the network in terms of "evoked-to-background" PYC activity ratio, or [stimulus-induced firing rate of PYCs]/[ongoing firing rate of PYCs]. I applied the same feature (F2) stimulus with various stimulus intensities; ε = 0.3 (strong: Figure 3a), ε = 0.05 (weak: Figure 3b) and ε = 0.02 (too weak: Figure 3c). In Figure 3a-c, the ongoing ("circles") and stimulus-induced ("triangles") PYC activities are shown ("left"). The evoked-to-background activity is shown ("right"), which I call here signal-to-noise (S/N) ratio in a practical sense.

Background neuronal activity itself could contain significant information as internal representations. Hence, we cannot straightforwardly call the background activity as "noise", and therefore should use the term "evoked-to-background" activity ratio rather than "signal-to-noise" ratio (S/N ratio) in a strict sense. The reason why I used the term S/N ratio instead of evoked-to-background ratio is to evaluate the present simulation results in relation to experimental (neurophysiological) observations [1,2,3,5], in which evoked-to-background activity ratio was preferentially called S/N ratio. Nevertheless, such a use of S/N ratio is unusual in such a field of engineering, because noise is not allowed to involve any significant information (or signal). I understand that the term "signal-to-noise" ratio in experimental neuroscience might be used in a more practical sense than in engineering. In the present study, I employed these terms (signal, noise and S/N ratio) based on a neurophysiological use but not on an engineering use.

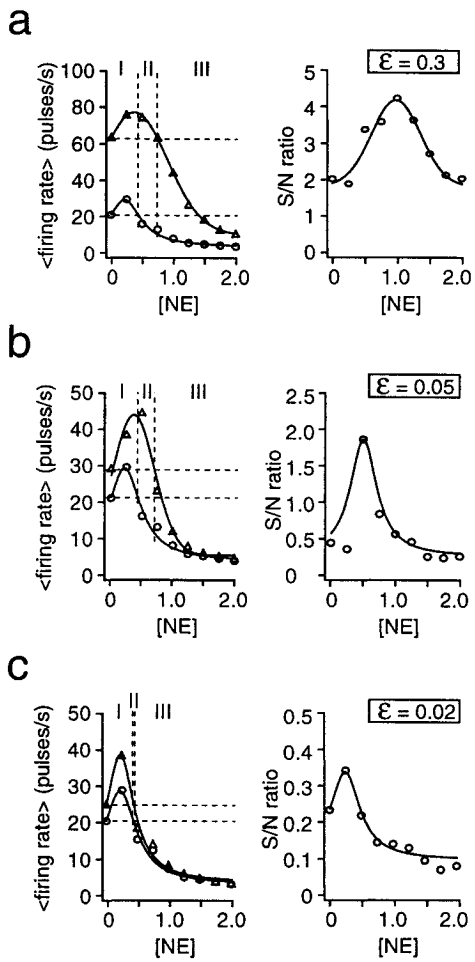

Fig. 3. Neuronal behavior (left) and S/N ratio (right) of PYCs. The model is presented with a feature stimulus with strong (a), weak (b) and too weak (c) intensity. In each figure, the left shows the ongoing firing rate ("circles") and stimulus-induced firing rate ("triangles") of a PYC. Regions marked by "I", "II" and "III" indicate that three distinct types of S/N enhancements take place.

For stronger stimuli (see the right of Figure 3a), S/N ratio is enhanced at an intermediate level of [NE] ([NE] = ~1.0). The stimulus-induced PYC-activity is progressively depressed at [NE] = ~1.0 (see the "triangles" of Figure 3a). This implies that S/N enhancement is possible provided that noise (or background PYC activity) is reduced more than signal (or evoked PYC activity). That is, noise reduction is as fairly effective as signal enhancement for improving S/N ratio. For weaker stimuli (see the right of Figure 3b), S/N ratio is enhanced at lower levels of [NE]. Figure 3c (right) shows fewer S/N enhancements for too weak stimuli.

Fig. 4 shows NE-mediated S/N enhancement for the same stimulus whose intensity is changed between 0.02 and 1.0. There are few S/N enhancements for too weak intensities ($\varepsilon < 0.03$). A greater S/N enhancement occurs for weaker intensities ($0.03 < \varepsilon < 0.1$) at lower levels of NE ("arrow" of Fig. 4). For strong intensities ($\varepsilon = \sim 1.0$), significant S/N enhancement occurs at higher levels of NE, [NE] = ~1.5.

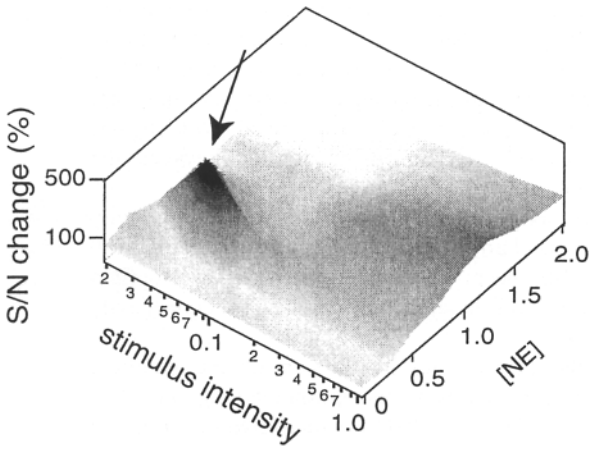

Fig. 4. Dependence of S/N enhancement on stimulus intensity and the dose level of NE, [NE]. An "arrow" indicates a peak in S/N enhancement.

It might be that scheme (ii), or signal enhancement and noise reduction, is quite effective for improving the S/N ratio for the weak stimulus. For the strong stimulus, scheme iii), or noise reduction that surpasses signal decrease, might work. Although the level of S/N enhancement is low for the too weak stimulus (see Fig. 2a), scheme (i) (or signal enhancement that surpasses noise increase) contributes to S/N enhancement.

4 Conclusions

I have proposed here a NE neuromodulatory system, investigated how NE alters ongoing background cortical activity and influences subsequent cognitive performance. The efficacies of the excitatory and inhibitory synaptic connections among pyramidal cells, small basket cells and large basket cells were modulated depending on the concentration of NE. I have found three possible schemes for S/N enhancement, namely; i) signal enhancement that surpasses noise increase, ii) signal enhancement and noise reduction, and iii) noise reduction that surpasses signal decrease. For weaker (or subthreshold) stimuli, signal-enhancement and noise-reduction scheme worked well, where NE application at lower concentration effectively improved the cognitive performance (S/N ratio) of the cortical network.

In these schemes, noise reduction played an essential role for the enhancement of S/N ratio. The reduction of noise could be established through neuromodulation of the inhibitory synaptic (SBC-to-PYC and/or LBC-to-PYC) efficacies. The SBC-to-PYC synapses contribute to suppressing PYC activity through feedback inhibition, and therefore reduce the ongoing PYC activity as [NE] increases. The LSBC-to-PYC synapses contribute to suppressing other PYCs through lateral inhibitory connections. This means that when one PYC assembly is active, the other assemblies tend to be suppressed, whereby the overall firing rate of the PYCs (or the ongoing PYC activity) can be reduced.

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