2004 International Symposium on Nonlinear
Theory and its Applications (NOLTA2004)
Fukuoka, Japan, Nov. 29 - Dec. 3, 2004

Effects of norepinephrine on dynamic behavior of a cortical neural network

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Abstract—I propose two distinct types of NE-neuromodulatory systems; i) enhanced-excitatory and enhanced-inhibitory (E-E/E-I) system, and ii) depressed-excitatory and enhanced-inhibitory (D-E/E-I) system. In both systems, inhibitory synaptic efficacies are enhanced, but excitatory ones are modified in a contradictory manner. Namely, the E-E/E-I system enhances excitatory synaptic efficacies, whereas the D-E/E-I system depresses them. I found three possible schemes for S/N enhancement in the E-E/E-I system; i) signal enhancement more than noise increase, ii) signal enhancement and noise reduction, and iii) noise reduction more than signal decrease. For weaker (or subthreshold) stimuli the neural network operated based on scheme (ii), where a low dose of NE effectively improved S/N ratio. D-E/E-I system was advantageous for processing stronger (or suprathreshold) stimuli. I suggest that depending on external circumstances, the brain may adopt the most appropriate NE-neuromodulatory system and S/N enhancement scheme among possible candidates for improving cognitive performance of cortical networks.

1. Introduction

It is well known that neurotransmitters such as norepinephrine, 5-HT, ACh and histamine affect dynamic properties of cortical neurons, and influences the cognitive performance of the brain [1]. The locus coeruleus (LC) is believed to be involved in the regulation of cognitive processes, in which a release of norepinephrine (NE) through rich efferent projections to relevant cortical areas plays an important role. 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 by NE application. By simulating the model, I investigate how NE modulates the dynamic behavior of neurons and what neural mechanisms are essential for NE-mediated enhancement of cognitive performance. We use S/N ratio as a cognitive performance measure.

2. Model

The model consists of an input (IP) and an output (OP) network (Figure 1a). As shown in Figure 1b, the OP network consists of neuron units, each of which contains a pyramidal cell (PYC), a small basket cell (SBC) and a large basket cell (LBC). 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 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 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.

Dynamic evolutions of the membrane potentials of PNs, PYCs, LBCs and SBCs are, respectively, defined by

$$\tau_{PN}\frac{du_i^{PN}(t)}{dt} = -(u_i^{PN}(t) - u_{rest}^{PN}) + \epsilon I_i^{PN}(t), \quad (1)$$

$$\begin{aligned}\tau_{PY}\frac{du_i^{PY}(t)}{dt} &= -(u_i^{PY}(t) - u_{rest}^{PY}) \\ &\quad + \sum_{j=1}^{N_{OP}} w_{ij}^{PY,PY}(t) S_j^{PY}(t) \\ &\quad - \sum_{j=1}^{N_{OP}} w_{ij}^{PY,LB}(t) S_j^{LB}(t) \\ &\quad - w_i^{PY,SB}(t) S_i^{SB}(t) \\ &\quad + \sum_{j=1}^{N_{IP}} L_{ij}^{OP,IP} S_j^{PN}(t), \end{aligned} \quad (2)(3)$$

$$\begin{aligned}\tau_{LB}\frac{du_i^{LB}(t)}{dt} &= -(u_i^{LB}(t) - u_{rest}^{LB}) \\ &\quad + w_i^{LB,PY} S_i^{PY}(t), \end{aligned} \quad (4)$$

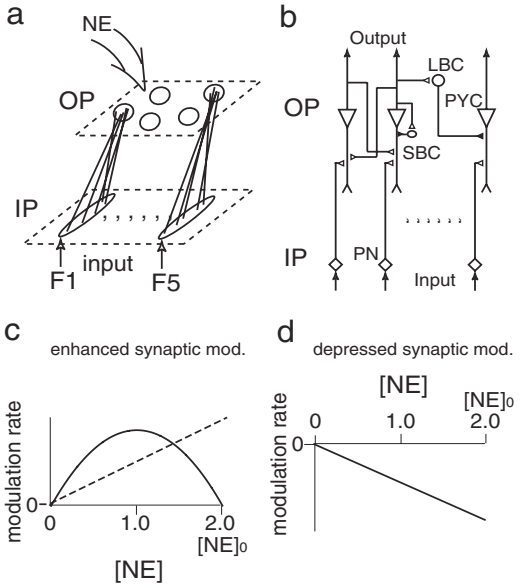

Figure 1: (a)-(b) Structure of the neural network model. (a) Feature stimuli Fn (n = 1, 2, 3, 4, 5) are applied to the corresponding groups of IP neurons ("ellipses"), whose action potentials are sent to the OP network via divergent/convergent feedforward projections ("solid lines") and activate the corresponding cell assemblies ("circles"). NE (norepinephrine) is dosed into the OP network. (b) The OP network consists of neuron units, a PYC ("large triangle"), a SBC ("small circle") and a LBC ("large circle"). "Open" and "filled" small triangles denote excitatory and inhibitory synapses, respectively. (c)-(d) Schematic drawings of synaptic modulation rates as a function of the dose level of NE ([NE]). (c) Enhanced modulations for excitatory ("solid line") and inhibitory ("dotted line") synaptic efficacies. (d) Depressed modulation for excitatory synaptic efficacies.

$$\tau_{SB}\frac{du_i^{SB}(t)}{dt} = -(u_i^{SB}(t) - u_{rest}^{SB}) + w_i^{SB,PY} S_i^{PY}(t), \quad (5)$$

and their action potentials are generated according to

$$Prob[S_i^Y(t) = 1] = f_Y[u_i^Y(t)], \quad (Y = PN, PY, LB, SB), \quad (6)$$

$$f_Y[u] = \frac{1}{1 + e^{-\eta_Y(u-\theta_Y)}}, \quad (7)$$

where $u_i^Y(t)$ is the membrane potential of the ith Y (Y = PN, PY, LB, SB) neuron at time t, whose time constant is τ_Y. u_{rest}^Y is the resting potential of Y neuron. $I_i^{PN}(t)$ is an external input to the ith PN with an intensity ϵ (positive constant). N_{OP} and N_{IP} are the numbers of neuron units of the OP and IP networks, respectively. $w_{ij}^{X,Y}$ is a synaptic strength from the jth Y neuron to the ith X (X = PY, LB, SB) neuron. $w_i^{X,Y}$ is a synaptic strength from neuron Y to X of unit i. $L_{ij}^{OP,IP}$ is a connection strength of the divergent/convergent feedforward projections from the jth PN to the ith PYC. Equations 6 and 7 define the probability of neuronal firing, that is, $S_i^Y(t) = 1$ is given by f_Y, otherwise $S_i^Y(t) = 0$. η_Y and θ_Y are, respectively, the steepness and the threshold of sigmoid function f_Y for Y neuron. When the ith neuron fires, $S_i^Y(t)$ takes on a value of "1" for one msec, which is followed by "0" for another one msec. After firing, the membrane potential is reset to the resting potential.

As schematically shown in Figure 1c, the efficacies of both excitatory ("solid line") and inhibitory ("dotted line") synapses are enhanced as a function of a dose level of norepinephrine, or concentration of NE ([NE]). The enhanced excitatory ($w_{ij}^{PY,PY}(t)$) and inhibitory ($w_{ij}^{PY,LB}(t)$, $w_i^{PY,SB}(t)$) synaptic modulations are described by the following equations.

$$\frac{dw_{ij}^{PY,PY}(t)}{dt} = \alpha_{PY}([NE]_0 - [NE])[NE] - \beta_{PY}(w_{ij}^{PY,PY}(t) - w_0^{PY,PY}), \quad (8)$$

$$\frac{dw_{ij}^{PY,LB}(t)}{dt} = \alpha_{LB}[NE] - \beta_{LB}(w_{ij}^{PY,LB}(t) - w_0^{PY,LB}), \quad (9)$$

$$\frac{dw_i^{PY,SB}(t)}{dt} = \alpha_{SB}[NE] - \beta_{SB}(w_i^{PY,SB}(t) - w_0^{PY,SB}). \quad (10)$$

The depressed excitatory synaptic modulation between PYCs is schematically depicted in Figure 1d and described by

$$\frac{dw_{ij}^{PY,PY}(t)}{dt} = -\alpha_{PY}[NE] - \beta_{PY}(w_{ij}^{PY,PY}(t) - w_0^{PY,PY}). \quad (11)$$

The "inverted-U" ("solid line" of Figure 1c) and the "monotonic-decrease" (Figure 1d) shapes for the excitatory synaptic modulation between PYCs are based on observed results [2]. The "monotonic-increase" shape for the inhibitory synaptic modulation ("dotted line" of Figure 1c) is a simple hypothetical representation that is based on observed results [4].

3. Results

As shown by the raster plots of action potentials in Figure 2a, the PYCs have ongoing (background) activity, where no external stimulus is applied. When the

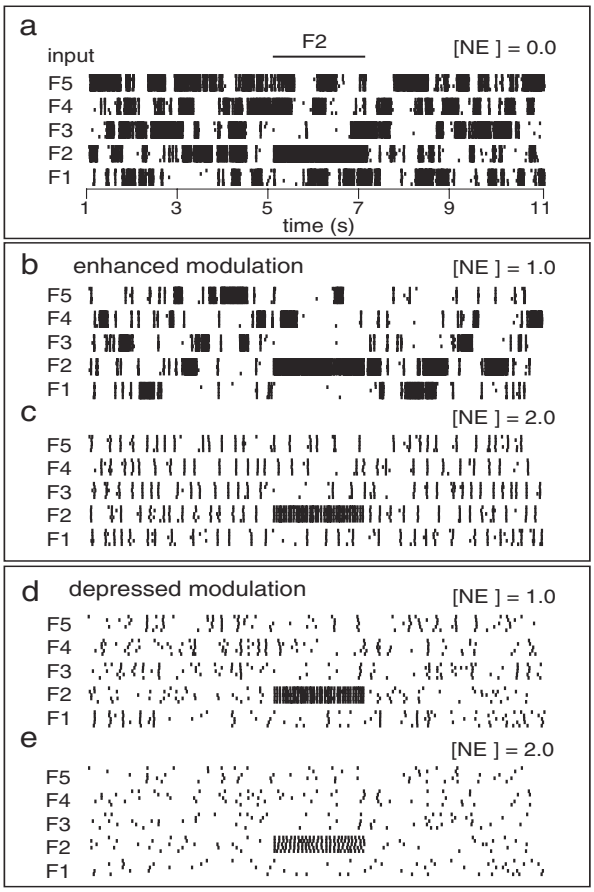

Figure 2: Dependence of the dynamic behavior of the OP network on dose levels of NE ([NE]). Raster plots of PYC action potentials of cell assemblies that are sensitive to features F1-5 are shown. (a) NE is not dosed, or [NE] = 0.0. A "horizontal bar" indicates a stimulation (F2) presentation period.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

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 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.

Figure 2d-e shows how the dynamic behavior of the network is modulated by the D-E/E-I system. Both the ongoing and the stimulus-induced activities tend to be decreased as [NE] increases (Figure 2a → 2d → 2e), where synchronicity among action potentials within cell assemblies progressively disappears. Such desynchronization in PYC activity is due largely to the depression of excitatory synaptic connections between PYCs.

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; $\epsilon = 0.3$ (strong: Figure 3a), $\epsilon = 0.05$ (weak: Figure 3b) and $\epsilon = 0.02$ (too weak: Figure 3c). In Figure 3a-c, the ongoing ("circles") and stimulus-induced ("triangles") PYC activities are shown for the E-E/E-I (left) and D-E/E-I (center) neuromodulatory systems. The evoked-to-background activity ratio, which I call here signal-to-noise (S/N) ratio in a practical sense, is indicated by "circles" and "triangles" (right) for the E-E/E-I and D-E/E-I systems, respectively. For stronger stimuli (see the right of Figure 3a), S/N ratio is enhanced at an intermediate level of [NE] ([NE] = ∼1.0) under the E-E/E-I system ("circles"), and enhanced at a higher level of [NE] ([NE] = ∼1.75) under the D-E/E-I system ("triangles").

In both systems, stimulus-induced PYC-activity is progressively depressed at [NE] > ∼1.0 (see the "triangles" at the left and center of Figure 3a), where S/N

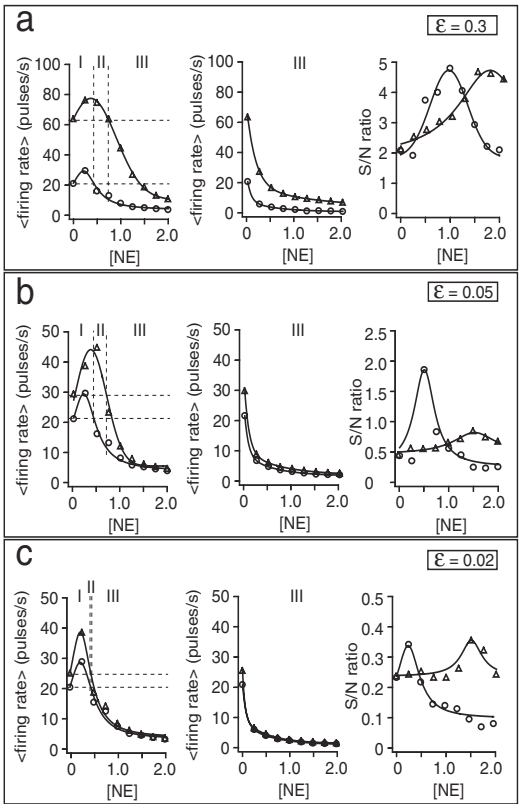

Figure 3: Neuronal and cognitive behaviors of PYCs. The model is presented with a feature stimulus with strong (a), weak (b) and too weak (c) intensity. In each figure, the left shows the ongoing firing rate ("circles") and stimulus-induced firing rate ("triangles") of a PYC operated under the E-E/E-I system. The center is for the D-E/E-I system. The right is S/N ratios for the E-E/E-I ("circles") and the D-E/E-I ("triangles") systems. Regions marked by "I", "II" and "III" indicate that three distinct types of S/N enhancements take place.

enhancement takes place provided that noise (or background PYC activity) is reduced more than signal (or evoked PYC activity). This result implies that 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] under the E-E/E-I system ("circles"), and is not likely to be enhanced under the D-E/E-I system ("triangles"). Figure 3c (right) shows fewer S/N enhancements for too weak stimuli under both systems.

4. Conclusions

I have proposed here two NE neuromodulatory systems (E-E/E-I and D-E/E-I), 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. One of the interesting findings might be that there have been three possible schemes for S/N enhancement; i) signal enhancement more than noise increase (see region "I" of Figure 3), ii) signal enhancement and noise reduction (region "II"), and iii) noise reduction more than signal decrease (region "III").

It has been found out that scheme (ii), or "signal enhancement and noise reduction", is quite effective for detecting weaker stimuli when operated under the E-E/E-I system, where lower doses of NE greatly improve S/N ratio. When a stronger stimulus is applied, scheme (iii), or "noise reduction more than signal decrease", effectively operates to detect the stimulus when operated under D-E-/E-I systems, where higher doses of NE greatly improve S/N ratio. It might be that a release of NE into cortical areas may modify their background neuronal activity as well as stimulus-induced neuronal activity, whereby cortical neurons can effectively respond to a variety of external sensory stimuli.

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