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FUNCTIONAL RELEVANCE OF 'EXCITATORY' GABA ACTIONS IN CORTICAL INTERNEURONS: A DYNAMICAL SYSTEMS APPROACH

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The non-classical, but frequently reported behavior of $GABA_A$ receptor-mediated excitation in mature CNS has long been regarded as a puzzle. We theorize that the function of cortical GABAergic interneurons, which might constitute a subsystem of brain's GABA interneurons, is their ability of switching from inhibitory action to excitatory action depending on the level of spatio-temporal activity in progress. From the perspective of a dynamical systems approach, such "excitatory" GABAergic responses may serve to temporarily invoke attractor-like memories when extensively activated by, for example, top-down signals as category information or attention, while an ongoing background state of GABA changes its action to inhibition, returning the dynamical nature of the memory structure back to attractor ruins.

Keywords: Attractor ruin; chaotic itinerancy; Milnor attractor; GABAergic interneuron; activity-dependent excitatory GABA action;

1. Introduction

GABA is known as the principal mediator of inhibition, but there exist numerous reports that GABA may play an excitatory role under some conditions.

First, it is known that $GABA_A$ acts as an excitatory transmitter during developmental stage, and it is after some maturation period that GABA transforms its functional action into inhibitory. The excitatory nature of $GABA_A$ in neonatal period may be due to the change of Cl^- homeostasis causing the upward shift of the

reversal potential E_{GABA}. What is the functional role of such GABA-mediated "excitatory" actions? Although there are controversies, it is argued that this may be due to the necessity of sculpting network circuits in developing period [9, 10, 11, 25]. After the maturation period, "GABA needs to become inhibitory in a hurry *to stabilize* the new neural nets" [66].

The puzzle surrounding the GABA action begins at this point. There are a number of findings indicating that $GABA_A$-receptors mediate a depolarizing action in *mature* CNS neurons [4, 8, 32, 48, 49, 57, 64, 84]. (See, also [27, 67].) It is reported that when intensively activated, dendritic $GABA_A$ receptors excite rather than inhibit post-synaptic neurons, which are normally hyperpolarized by brief $GABA_A$ receptor activation. For example, Staley *et al.* [64] showed that while a single distal orthodromic stimuli induces hyperpolarizing $GABA_A$ receptor mediated PSP_S (post-synaptic potentials), a train of 40 stimuli at 200 Hz yielded additional late depolarizing potential, and this depolarization is strong enough to modulate the voltage-dependent Mg^{2+} block of synaptic NMDA receptor activations. Staley *et al.* called this synapse-specific phenomenon as "activity-dependent $GABA_A$ receptor-mediated depolarization", and emphasized that this should be distinguished with the rapid activity-independent $GABA_A$ depolarizing responses during developmental period. We may abbreviate such activity-dependent excitatory GABA actions as "eGABA".

What is the functional consequence of this eGABA action? There could be several scenarios, but it appears that very few attempts have been made to systematically study the functional consequences of the phenomenon.

The purpose of this paper is, partly, to give a short review of the apparently strange GABA action, and then give possible theoretical implications on its functional consequences. A key might exist in its role of consolidating memory structure dynamics, and our hypothetical standpoint might present a key to solve the puzzle of eGABA action. We shall propose that the puzzle could be solved if viewed from a dynamical systems standpoint, and which could open a new prospect in memory dynamics. At the same time, we would like to address both experimental and theoretical significance of eGABA action in the organization of cognitive functions.

In the next section, we first introduce the concept of attractor ruins, and then in Section 3 we review the experimental data about eGABA actions. In Section 4 we turn to our main subject - functional consequences of eGABA actions, and propose a new scenario on the role of eGABA actions in mature CNSs.

2. Dynamical Systems View to Cortical Dynamics and Cognitive Functions

2.1. *Itinerant dynamics in brain activity*

Transitory chaotic phenomena have been observed in experimental brain studies, accompanied with behavioral and perceptual stages of the animal. In olfactory systems, Freeman and colleagues report the appearance of chaotic transitions between quasi-attractors with related to perceptive stages of odors [18, 19, 20, 63]. Transitory appearance of synchronized states among desynchronized states in local field potentials (LFP) of cat visual cortex is reported by Gray [26], where a synchronized state is postulated to be related to *binding* process of fragmentary visual information. Kay observed the propagation of wave packets of γ- and δ- range activity [37, 38] in different stages of olfaction perception, and the irregular appearance of synchronization of large phase difference [21]. A common feature of these phenomena is chaotic and itinerant transitions between behavioral states.

How should we interpret and describe transitory dynamics in the brain?

2.2. *Chaotic itinerancy among attractor ruins*

Brain activity, and memory dynamics in particular, have often been considered in terms of "attractors". Classical attractors, i.e., attractors in the geometric sense are primarily concepts in low-dimensional dynamical systems, and do not provide an appropriate language for the interpretation of those transitory dynamics observed in the brain. To describe such dynamics typically appears in high-dimensional dynamical systems, a non-classical concept of dynamical states which include both stability and instability is necessary.

The concept of chaotic itinerancy, proposed firstly by Ikeda [30], Kaneko [33] and Tsuda [72] describes the recurrent process of the genesis of ordered states and their collapses, where the notion of "attractor ruin" play the key role in the description of itinerant dynamics. Roughly, an attractor ruin is a "ruin" in that there are orbits approaching and stay there for a while, but may simultaneously possess repelling orbits from itself. Intuitively, an itinerant dynamics may appear as a composition of *ruins* of fixed points, limit cycles, tori and/or chaos, together with orbits that connect those "attractor ruins". In fact, those ruins are not attractors in the classical sense, and we shall redefine them later. Chaotic itinerancy may be characterized as a state of dynamics that transiently itinerates among attractor ruins. A chaotic itinerancy has particular characteristics in its structure and dynamics. For such materials, please refer to the papers [36], or [35].

Suppose that a dynamical system has multiple stable states. It means that the system has multiple-stable geometric attractors. The phase space is divided by basins of attraction, and the dynamics of the system is such that it asymptotically approaches one of the attractors in the phase space, which is determined by the initial

state. What would happen if such a system is *destabilized* so that all the attractors lose stability? In other words, what would be the dynamics in a phase space where *no* stable attractors exist but ruins? If the level of destabilization is strong enough, it would lead to a turbulent state. However, for some destabilization level, one would expect an intermediate state something between turbulent and ordered states, and which would transit among attractor ruins intermittently. It is now known that such itinerant dynamics appear in high-dimensional dynamical systems in a variety of areas, e.g., optical systems, electro-chemical systems, ecosystems, protein dynamics, acto-miosin systems, rat limbic system, and human EEG (see, Kaneko and Tsuda (eds.), *Focus Issue: Chaotic Itinerancy* [34]), and recognized that it is universally observed phenomena.

What characterizes "attractor ruins" in mathematical sense? At the present moment, it is not fully understood. However, attractor ruins must have unstable manifolds to some directions in its neighborhood. The*Milnor attractor* and its perturbed structures are eligible to be an attractor ruin. By definition, a Milnor attractor posseses *a positive measure* of attracted orbits, but simultaneously may possess repelling orbits from the attractor. A Milnor attractor may thus provide a mechanism of allowing both transition and reinjection to and from a state. For the detailed definition of the Milnor attractor, see e.g., [52].

It is noted that the concept of attractor ruins may include a wider class of non-classical attractors than the Milnor attractor, but the details of attractor ruins are not yet formalized. By this reason, we may use the term "attractor ruins" in this article to include possible but unknown classes of ruins.

An explicit example of a dynamical system was given by Tsuda and Umemura [76] where *no* stable geometric attractors exist. Their locally coupled circle maps each of which possesses an identical Milnor attractor transformed firstly to tori as the coupling strength is increased, and then there appear an itinerant chaotic dynamics connecting those tori.

Another example of a complete dynamical system in which a beautiful but complicated Milnor attractor inhabits is reported in Tsuda, Fujii and their colleagues ([77], *this issue*). The model is a system of class I^* neurons locally coupled by gap junctions, which exhibits chaotic alterations between synchronous and desynchronized states.

The significance of the concept of "attractor ruins" is in its potential ability of overcoming the conceptual difficulty of the attractor view to the memory, as how to cope with binding for novel stimuli, temporal or sequential aspects as episodic memory, etc., and also difficulty in interpreting those transitory dynamics in the brain. We claim that "memories" in the brain inhabit in the form of attractor ruins rather than conventional geometric attractors, which provides a contemporary framework on memory dynamics in the brain. An attractor ruin could be regarded as a shot of "memory trace", and an itinerant dynamics among a sequence of ruins as an episodic memory. One of the authors argued how an "episodic memory" is

organized in the hippocampal system, as well as the role of Cantor coding in category formation in the cortex [74, 75], while Aihara *et al.* [1, 3] studied possible role of itinerant dynamics in memory searching within chaotic network systems. For further discussions on cognitive roles of itinerant dynamics, refer to [74, 75].

2.3. *Principles of genesis of attractor ruins*

How is the itinerant dynamics organized in the brain? We are far from understanding the physiological and mathematical mechanism of memory formation, nor its form of existence in *in situ* brain. It is pointed out, however, that (at least) three principles may take part in the genesis of ruins.

(1) Delayed feedback: Delay-differential equations can, in principle, exhibit chaotic itinerancy as well as fully developed chaos [30]. This suggests that a delayed feedback loop in the cortical networks may produce chaotic itinerancy if the feedback yields a certain degrees of instability: strong enough for destabilizing attractors, but weak enough to suppress chaotic motion. Actually, Freeman [17] observed chaotic behaviors in the olfactory bulb, which possesses feedback connections with the olfactory cortices such as the prepyriform cortex and the anterior olfactory nucleus. Freeman found that the delayed feedback would be a necessary condition for the existence of chaos, investigating the system without feedback from the cortex by cutting off the lateral olfactory, where chaos disappeared and the system exhibited damped oscillations. Because this is not a sufficient condition for the existence of chaos, the term of delayed feedback does not necessarily guarantee the presence of chaos. However, chaos can appear under some restriction on parameters such as the strength of the feedback and the delay time. Furthermore, for the presence of chaotic itinerancy, some delicate conditions appear to be necessary. Actually, Freeman found a similar transitory phenomenon to chaotic itinerancy under a certain parameter condition, and also obtained essentially the same phenomenon in computer simulations of his model KIII on olfactory systems.

(2) Gap junction-coupled interneuron systems: Gap junction-coupled neuronal systems can, in principle, exhibit emergent spatio-temporal chaotic dynamics if neurons possess a certain condition on its ionic channel properties. In fact, gap junction-coupled class I^* [23, 77] neurons show a transitory dynamics of synchronized and desynchronized states even under a spatially and temporally constant injected background currents. The authors showed that this transitory dynamics could be regarded as being itinerant around a Milnor attractor possessing a beautiful internal structure ([77], *this issue*). The transient synchrony of local field potential observed by Gray [26] might be interpreted as a consequence of interplay of this interneuron dynamics and the pyramidal cell systems in the cortex.

(3) Inhibition of attractors: Inhibitory actions can turn an "attractor" into "attractor ruins", and which could be a dynamic trigger of switching between an "attractor" dynamics and itinerant dynamics among ruins. This is an expression of the general principle that inhibitory neurons may make the memory structure dynamical. (See, Section 4.) Prototypaical examples have been described by Tsuda [71, 73, 74] in the study of dynamic associative memory and episodic memory formation. In conventional neural network model of associative memory, an attractor embedded in recurrent connections of excitatory neurons is a representation of memory of an event or a pattern. Attractor networks may be regarded as an expression of the retrieval process of memory, in which its activity eventually reaches a stationary state represented by each attractor. An addition of *local or global* negative feedbacks via inhibitory neurons can in principle destabilize such attractors. In the balance between stability and instability, the attractors can become neutrally stable, which gives rise to the genesis of Milnor attractors, leading to emergence of itinerant dynamics.

Chaotic itinerancy among Milnor attractors can also be born in a system of coupled chaotic neurons [1, 2, 3]. This shows also switching of memory dynamics between attractor and itinerant motion. Mechanism of the chaotic itinerancy in globally coupled map is explained by the presence of crisis-induced intermittency and charge of stability along the direction of the orthocomplemnent on invariant subspaces [41]. Hierarchical structure among invariant subspaces in chaotic networks with associative dynamics is also clarified [40].

The view that "inhibition could turn an attractor into an attractor ruin under a certain condition" is a hypothetical statement derived from dynamical systems considerations, which might provide us a "theoretical link" between the concept of "itinerant dynamics" and "inhibition" in the brain. With this in mind, one may wonder what kind of physiological processes could "link" the two theoretical concepts of "itinerant dynamics" and "inhibition", and on which question this paper will focus.

3. Excitatory Actions of $GABA_A$ - Experimental Evidence

Two distinct processes of excitatory GABA actions have been reported, which occur under different conditions and on different time scales. One is the rapid *activity-independent* $GABA_A$ depolarizing responses during developmental period [14, 24, 25, 56, 62]. The other is *activity-dependent* $GABA_A$ receptor-mediated depolarization in adult [4, 8, 32, 48, 49, 57, 64, 84]. (See, also [27, 67].) The two phenomena are different in their ionic processes and time scales.

3.1. *Developmental stage*

The homeostasis of ionic concentrations between intra- and extra-cellular neurons, in particular for the Cl^-, is more dynamic than had been assumed. In fact, it is known that GABA is excitatory in the immature brain. Also, GABA-releasing synapses are formed first, and glutamatergic contacts appear later in the developing stage. In the neonatal period, the Cl^- importer NKCC1 expression, which transport Cl^- ions from the outside to the inside of the cell predominates as compared with the KCC2, the Cl^- exporter expression which transports Cl^- ions in the opposite direction. Thus because of the predominance of NKCC1, intracellular concentration of Cl^- is relatively high during the developmental stage, leading to depolarizing GABA reversal potential E_{GABA}. Activation of $GABA_A$ receptors generates efflux of chloride ions and an excitation. As GABAergic synapses are gradually formed with maturation, KCC2 increases, while NKCC1 decreases, resulting in net decrease of $[Cl^-]_i$, which turns the nature of GABAergic action into "inhibitory" [11].

Why such a complicated process is required ?

It appears that there are general agreements among physiologists in that this *subtle* series of processes may be due to the necessity of sculpting network circuits in the developing period. Ben-Ari [11] hypothesized that this is a solution to the difficulty of how to excite developing neurons to promote growth and synapse formation while avoiding the potentially toxic effects of a mismatch between GABA-mediated inhibition and glutamatergic excitation.

Fukuda [24, 25, 62] pointed out that constructing GABAergic circuits firstly as excitatory networks may be more advantageous for Ca^{2+} production which is necessary for LTP processes. In fact, the depolarization produced by GABA is strong enough to remove the voltage-dependent Mg^{2+} block from NMDA channels and inducing an increase in $[Ca^{2+}]_i$. Also the strategy to "transform" of GABA actions later to an inhibitory one does not necessitate to have a mechanism of synapse formation specially designed for inhibitory synapses. The critical role of GABA in the developmental stage of primary visual cortex has also been reported [16, 29].

Then why $GABA_A$ should be transformed to act as an inhibitory transmitter ?

This appears to be a trivial question since GABA has been regarded as the principal mediator of inhibition. In fact, agents that block GABA synapses generate seizures. Hence, it is a natural assumption that "GABA need to become inhibitory in a hurry *to stabilize the new neural nets*" (Staley and Smith, 2001 [66].)

3.2. *Activity-dependent excitatory* $\mathbf{GABA_A}$ *actions in mature CNS*

However, the story may not be so simple. There are numerous reports that $GABA_A$ receptors have a depolarizing action even in mature CNS neurons. It is reported that

when intensively activated, dendritic $GABA_A$ receptors excite rather than inhibit neurons. Initially hyperpolarizing postsynaptic $GABA_A$ responses $shift$ to depolarizing during prolonged GABA release.

Staley *et al.* [64] showed that while a single distal orthodromic stimuli produced hyperpolarizing $GABA_A$ receptor-mediated PSPs in a CA1 pyramidal cell, a train of 40 stimuli at 200Hz produced an additional late depolarizing potential. Moreover, GABA-mediated depolarization was sufficient to modulate the voltage-dependent Mg^{2+} block of synaptic NMDA receptor activation, and high-frequency stimuli evoked robust spiking.

The experiments reported by Kaila *et al.* [32] using both sharp microelectrodes and whole-cell-pipettes in the presence of ionostropic glutamate antagonists provided some measure about the time course of eGABA actions. A train of 40 pulses at 100Hz applied to the *stratum radiatum* in CA1 close to the intracellular recording site evoked a fused sequence of initially hyperpolarizing fast IPSPs. The hyperpolarizing phase of the fused response reached its peak amplitude of approximately -10 mV usually within 20-50 ms, and then turned promptly (within 200-300 ms) into a prolonged depolarization that often had an amplitude sufficient to trigger a burst of action potentials.

3.2.1. *Anionic gradient shift model*

The $GABA_A$ ionosphore is selectively permeable to anions of chloride Cl^- and bicarbonate $HCO_3{}^-$, and the mechanism of depolarization should involve the flux of these anions. Kaila and Voipio [31] showed in direct measurements of $[Cl^-]$ and $[HCO_3{}^-]$ in crayfish muscle fibers that prolonged activation of $GABA_A$ receptors can lead to accumulation of intracellular $[Cl^-]$ and $[HCO_3{}^-]$-dependent depolarization. Based on this work, Staley *etal.* [64] have proposed the anionic gradient shift model, which claims that the eGABA action is the result of an asymmetric, activity-dependent collapse of the opposing electrochemical gradients of Cl^- and bicarbonate. They [64, 65] proposed that the mechanism of the eGABA is an activity-dependent shift of the GABA reversal potential E_{GABA} toward E_{HCO3^-}.

The resting E_{GABA} is primarily determined by E_{Cl^-} because the permeability of Cl^- is five times that of $HCO_3{}^-$. However, by intense GABA activations, the Cl^- gradient decreases. Although the shift in the Cl^- gradient is eventually corrected, $HCO_3{}^-$ gradient is more rapidly compensated by the regeneration due to carbonate anhydrase H_2CO_3 catalysis. Thus, the electrochemical gradient for Cl^- collapses more significantly than does the $HCO_3{}^-$ gradient. As a result of these processes, E_{GABA} shifts toward E_{HCO3^-}. (-12 mv at physiological internal pH (7.0-7.2), which is more positive than resting membrane potential [32]).

Kaila *et al.* [32] argued that the postsynaptic $[HCO_3{}^-]$ alone cannot explain the activity -dependent positive shift of E_{GABA} in pyramidal cells. They stressed that eGABA actions are due to depolarizing effects of increased $[K^+]_o$ generated by a local network of GABAergic interneurons, although Staley and Proctor [65] argues

that $[K^+]_o$ effects are not necessary for eGABA actions.

The experimental data introduced above suggested that the activity-dependent eGABA actions are synapse-specific, and the depolarization is *dendritic*. (See, however, Gullege and Stuart [27].) The scenario of Staley *et al.* [64] explains why the shift of E_{GABA} toward E_{HCO3^-} is a slow process. The experimental data by e.g., Kaila *et al.* [32] shows that it may take a few hundred ms until eGABA actions due to high frequency stimulations trigger spike firings under the presence of glutamate antagonists. This time course could be shorter when excitatory AMPA spikes might work in concert with eGABAs as may be the case in *in situ* brains. This is almost equivalent to the time scale of "psychological time" for perception, and of synaptic NMDA receptor activations via removal of voltage-dependent Mg^{2+} blocks.

Staley *et al.* [64] emphasized that one of the functions of eGABA is to provide activity-dependent modulation of the Mg^{2+} block of the NMDA receptor, and to regulating NMDA depolarization mechanism of synaptic plasticity. Szalisznyo and Erdi [70] pointed out that the depolarizing/hyperpolarizing effects of $GABA_A$ synapse have a beneficial role in synaptic weight resetting in the hippocampus.

3.3. *Brain phenomena proposed to be related to "eGABA" actions*

Let us review the possible "role" or experimentally observed brain phenomena, which have been claimed to be related to eGABA actions.

Epileptogenesis has always been postulated to be a possible consequence of eGABA under a certain condition.

3.3.1. *Epileptogenesis*

Cohen *et al.* 2002 [15] showed that under a pathological condition depolarizing GABA actions may induce interictal epileptic activity in human temporal lobe.

Epileptogenesis appears not to be the unique function of eGABA actions, and there is evidence that they might work in higher cognitive functions in a non-pathological condition. There exist several arguments related to eGABA actions that may deserve special attention.

3.3.2. *Relation to up-down two state transitions*

The phenomenon of *up and down* two-state transition in *subthreshold* membrane potentials has long been observed both in neostriatum [39, 58, 59, 60, 68, 69, 82, 83] and neocortex [7, 45]. Anderson *et al.*, 2000 [7] wrote about how this phenomenon looked like experimentally as "when monitoring the membrane potential on individual trials, we were struck by the presence of large, low frequency, bistable fluctuations". The large, two-state fluctuations occur in neurons both in awake and anesthetized animals, which are not time locked to stimulus, and nearly synchronously in nearby neurons. Also, up-down timing was reported to be hardly regular [68]. Neuronal mechanisms, as well as functional meanings of these fluctuations

are not known. In neostriatum, $GABA_A$ actions from FS (fast spiking) cells onto MS (medium spiny) principal cells may play a role with an interplay with AMPA and NMDA activation in the transition to up state from down state [60, 67]. Also, GABA input to proximal apical dendrite during when an MS cell is in up state could promote action potential firing in response to both sub-, supra-threshold excitation of basal dendrites if V_{rest} (the resting potential) $< E_{GABA}$ [27]. Enhance of NMDA receptor activation in more distal dendritic compartments, in turn, influence synaptic plasticity and may enhance dendritic spike initiation.

What could be the functional significance of the two state transition? In view of the fact that spikes are generated only when the pyramidal cell is in up state, and that nearby cells are in up state almost synchronously [7], the group of pyramidal *cells in up state* might be regarded as a cell assembly related to some behavioral state of the animal.

3.3.3. *Collective, synchronized activity of interneurons due to eGABA*

Based on the experiments of Michelson and Wong [49, 50] on interactions among interneurons during strong population bursts in the hippocampus, Lämsä [46] proposed that eGABA actions primarily promotes firing in GABAergic interneurons rather than in glutamatergic principal cells in *gyrus dentatus*. Lämsä claimed that $GABA_A$ excitation provides, together with the gap junction couplings, a mechanism for self-sustained synchronous oscillations (e.g. at gamma frequency).

Lämsä concluded that eGABA actions may strengthen the net inhibition by interneurons to pyramidal cells. However, it remains the possibility as well that the resulting collective, synchronized activity of interrneurons would induce excitatory $GABA_A$ actions in the pyramidal cells. Further experimental studies are needed to clarify the role of eGABA and gap junctions in hippocampal/cortical synchrony generations.

3.3.4. *Connectionist standpoint - an associative memory model based on disinhibition*

Vogel [78, 79] appears to be the only researcher who studied a potential functional meaning of the eGABA action from the standpoint of associative memory. He considered an abstract memory model with a conceptual change to the conventional recurrent network model. The model depends on *disinhibition* of inhibitory links rather than long-term potentiation of excitatory projections. He investigated the problem of memory capacity of his own model. In his model, couplings between pyramidal cells are only via "interneurons" with eGABA actions, and no direct communications among pyramidal cells are assumed to exist. Interneurons play the role of switching *on and off* of the pyramidal cell connections through the functioning of eGABA - switching of "excitatory" and "inhibitory" actions. If an interneuron is extensively excited, it will "open" the communication channel between pyramidal

cells via disinhibition. Vogel constructed a large scale network based on his own disinhibition idea, and showed the basic possibility of performing a functional role of a certain level [80].

The study of Vogel is pioneering in the sense that he considered a functional consequence of eGABA from a system-level consideration. However, like other connectionist network models of memory there is little consideration on dynamical aspects of memory in the brain.

We shall discuss in the next section the functional significance of dynamic excitatory and inhibitory actions from dynamical systems standpoints, and propose a hypothetical role of the GABA behavior in the memory structure in the brain.

4. Role of Excitatory Actions of $GABA_A$ - A Dynamical Systems View

In order to understand the functional significance of "excitatory" actions that a subsystem of GABAergic interneurons is presumed to possess, one must first reconsider the functional meaning of inhibitory actions. In contrary to an intuitive image, it should be emphasized that GABAergic inhibitory systems may, under a certain condition, bring internal *instability* in the system. More precisely, inhibitions may destabilize *attractors* (as components of the memory structure in the brain). Here by the term "destabilization" we mean the "ruinization" of the memory structure under consideration.Attention should be made to the fact that the word "instability" appears in this paper with double meanings. The first one is due to Staley and Smith, 2001 [66], who claimed in Section 1 that "GABA need to become inhibitory in a hurry to stabilize the new neural nets", where "instability" means epileptic oscillations of the whole system. The second one, proposed by Nicolis and Prigogine [55], which is related to the present context of "ruinization", claims that instability is necessary to create a new structure and function in dissipative systems.

Although mathematical mechanisms of this destabilization are not fully understood yet, there are several examples that may suggest the existence of such destabilizing phenomena. This section is devoted to discussions of such examples, and the functional relevance of the eGABA action in the brain.

4.1. *GABA as dynamic regulator of memory structure*

Excitatory actions of GABAergic synapses during developmental period have been discussed in Section 3.1, where it was argued that the eGABA actions may be advantageous in sculpting basic network circuitry. Such a process should probably be taking place, and it seems consistent with the fact that in low level animals such as sea slugs -*Hermissenda Classicornis* [5] GABA may function as both inhibitory and excitatory transmitters.

Then, we need to ask again the reason why GABAergic neurons - fired from the job as sculptor or just its assistant - must find the new job as an inhibitor when the

brain system is matured.

Cohen *et al.* 2002 [15] showed that, during pathological conditions, the interictal activity in human temporal lobe epilepsy can be attributed to the eGABA actions. Hence, it is natural to assign the role of inhibiting such epileptic activity to GABA transmitters.

The puzzle lies in the fact that GABA, after the nervous system has matured, functions *again* as an excitatory transmitter. At least under certain conditions, activity-dependent excitatory GABA may be *invited* to play a role in sculpting a new memory structure in the interplay with AMPA and NMDA synapses. It is presumed that the strengthening of synaptic efficacy would happen at nearby AMPA synapses, although details are largely unknown. (Note also that GABAergic transmission efficacy itself would have LTP and LTD [43, 47, 61].) In summary, the eGABA activity may perform a *significant* or at least a *supplementary* role in constructing and re-organizing memory structures in a certain situation.

A series of questions may arise here. Is the supplementary role of organizing memory attractors the *only* function carried by the excitatory GABA action? As soon as a new memory structure is successfully built-in in the network as a new attractor, then GABA quickly changes its role to an "auditor" in order to check the enterprise not to go out of control. Why should only GABAs be both *excitatory* and *inhibitory* within a timescale of a few hundred ms? Why are AMPA and NMDA synapses not enough for inducing LTP? Why do not other GABAergic or non-GABAergic interneuorn systems work as an auditor?

In fact there is a huge diversity among interneurons in the hippocampus and the neocortex. Anatomy, ionic channel characteristics, pharmacological responses, spiking properties as fast or regular spiking, with/without adaptation and bursting etc. are well known factors of the diversity. Even there exist a number of interneurons with GABAergic synapses, with different projection sites as perisomatic, dendritic and so on. (See, e.g., [12].)

The secret may lie not in its excitatory nor in inhibitory aspect, but in its *switching* of excitatory and inhibitory actions - *a function that only* GABA *could carry*. Viewed from this standpoint, a few scenarios unveil in which GABA might act. GABA could be a dynamic regulator of the memory structure.

In the following we may pose a minimum scenario, as well as a maximum scenario in which the eGABA action may play a role in cognitive functions.

The *minimum scenario* assigns to GABA, firstly at the opening stage, the role of formation of *new* attractors in the network, in collaboration with AMPA and NMDA channels. Then, GABA changes at consecutive stages its role to an *inhibitor*. This *switching* transforms the newly organized "attractor" into an "attractor ruin". It seems significant that GABA plays an excitatory role jointly with AMPA and NMDA synapses. GABA, which is one of the *concerned* components that brought the membrane potential to fire, changes its activity from excitatory to inhibitory. This fact may constitute the critical factor in this *ruin genesis*.

This is a hypothetical scenario, and mathematical justification should be a subject of future study. However, the arguments of Tsuda [74] and of Nara *et al.* [54] may provide evidence.

Tsuda and his coworkers [42, 71] gave a model-theoretic argument that inhibitory neurons could play a significant role in making the memory structure dynamical. In a neocortical model with pyramidal and stellate neurons, together with Martinotti interneurons, they showed that the network exhibits itinerant behavior, repelling dynamically from one "attractor" and approaching another "attractor". The specific negative feedback supposed by the Martinotti cells may have resulted in the change of the nature of attractors. Although there are several possibilities for the function of the specific inhibitory neurons [74], the role of the inhibitory neuron is in all the cases to *temporarily hide* the information contained in the states of pyramidal cells during when the pyramidal cell system is in a steady state.

A similar effect can be obtained by the addition of only a *local* negative feedback to each pyramidal cell via an inhibitory neuron in the recurrent network of pyramidal cells. In this case, the masking effect is only due to continual inhibitions [42]. Similarly, a chaotic neuron model comprising the chaotic neural network has self-recurrent inhibition, that is one of the essential factors to generate chaotic dynamics at the level of the single neuron [2, 3].

Tsuda [74, 75] proposed the possibility that a similar principle may work in hippocampal CA1/CA3 systems. There are two inhibitory inputs - GABAergic and cholinergic to CA3 and also to CA1 from the septum [13] The septum sends inhibitory projections to CA1/CA3 via another GABAergic inhibitory cells located in CA1/CA3, which *in turn* inhibit pyramidal cells therein. Hence, the effect on CA3 of efferent spikes from the septum is *disinhibition*, which makes the memory structure "attractor-like". On the other hand, when the septum is in an *idling* state, CA3 exhibits an itinerant state due to inhibition. In this way, inhibition may play the role in switching between attractor and itinerant states.

In a series of papers Nara *et al.* [44, 51, 53, 54] constructed a recurrent network model of binary "neurons" with the synchronous updating rule, in which they built in several periodic (limit cycle) attractors. The network function as a conventional associative memory with multi-stable attractors. Then, they reduced the number of existing synaptic connectivity r, i.e., the fan-in number to each neuron. What they found was that as r tends smaller, each basin volume decreases. As r reaches a critical value r_c, the basins vanish and the attractors become unstable. The network dynamics appears to be itinerant among all the attractor "ruins", but stay in each attractor "basin" for considerably longer time steps. Such a dynamics may depend on the r-value and configuration of connectivity, and sometimes the network shows highly developed chaotic dynamics.

However, even in such cases, a one step application of a fragment (40 bits among 400 bits pattern) of an imbedded memory pattern could push the dynamics to make a quick transition to a very near state containing the target memory. Nara

et al. claim that dynamic correlation transiently appears in the chaotic memory dynamics, which may be the basic mechanism of rapid access to limit cycle attractors without searching among a memory store. As Nara refers, this may be in harmony with the Skarda and Freeman's statement [63] that "chaotic activities allows rapid and unbiased access to every limit cycle attractor on every inhalation, so that the entire repertoire of learned discriminanda is available to the animal at all times for instantaneous access." A similar quick response to memory fragment input is also observed in memory dynamics of the chaotic neural network [44].

4.2. *Perceptual role of inhibitory actions of* $\mathbf{GABA_A}$

The second scenario for the eGABA action is highly hypothetical, and remains naïve and conceptual.

The report of Kaila *et al.* on the time course of eGABA activity [32], (see, the argument in Section 3.2) may, however, suggest that it might carry some cognitive role even at the stage of *perception*. Top down signals as "attention", "categorical information" etc. may have the possibility to extensively excite a certain subsystem of GABAergic systems. In fact, in order that a *new* attractor be "registered" in the memory structure, the spatio-temporal activity pattern should at the same time be emerged to be perceived as a *unity*, whether consciously or not. This suggests that the eGABA might participate in the perceptual stage within the psychological time of a few hundreds ms at a certain situation.

To proceed further, we are obliged to use the two complementary concepts at the same time: "cell assembly" and "dynamical systems". A cell assembly is defined as a $functionally-organized$ group of cells to perform a particular task [22, 28, 81], and has a close relation with the attractor view of the memory. This is a concept in the *physical* space, and cannot describe dynamical systems concepts such as "transitions of states", or the metamorphosis of memory structure due to dynamical (activity-dependent) change of GABA behavior, while the dynamical systems language as "the phase space" does not have means to describe internal interactive processes and the process of learning.

How the perceptual process could be described within the framework of dynamical systems language? A $default$ (or, background) state with low activity may correspond to a point in the phase space far from any "attractor ruins". The role of input stimuli is to trigger a dynamic transition of "states" to some other state depending on the nature of stimuli. In particular, when a stimulus is a familiar one, it might bring the state immediately *near the center* of a "ruin", which is a memory structure organized throughout the sensory, temporal and/or frontal cortices. This might be considered as *Freeman's miracle*, which S. Amari has aptly called. This kind of *automatic* memory recalls might take place in the real brain.

However, the GABA's turn does not come at this stage. The potential role of eGABA is *not* to trigger the transition of orbits. It is postulated that the eGABA action changes the *landscape* of the memory structure. In other words, it temporarily

(re-)organizes potentially existing attractors.

Suppose that the brain encounters an externally driven stimulus, but since they are novel or unfamiliar, some kind of attention or reference to categorical information might be required to perceive it as a unity. In such an occasion, eGABA actions might play a role in internal dynamical processes as interactions with those top down signals. We postulate that such a state may correspond to a case where "local" fragmental cell assemblies (fCAs) are triggered by the external stimulus to excite, but are not bound to have a perceptual unity. In dynamical systems language, this may be a state where several "local orbits" are co-running with only weak interactions.[a] We may assume that this 'NO PERCEPT' state is due to the lack of coherent activation (e.g., synchrony) among activated fCAs, which a "global" attractor ruin should be expected to possess.

We hypothesize that the eGABA action temporarily "links" those locally activating fCAs by helping strengthen weak interactions between pyramidal cells. This may be done through interaction with top down signals as categorical information or attention, etc. (Even the possibility of *feedback* excitation of eGABA system from fCAs themselves might also be considered.) An interesting possibility may be that synchrony among gap junction-coupled GABAergic interneuron systems [23, 77] may help create correlated firings among fCAs. (See, also discussions in Section 3.4 [46].)

Thus, activation of excitatory GABA actions temporarily changes the attractor *landscape* of the memory system by temporal organization of "attractors". When GABA turns its activity *back* to inhibitory, the structure which formed a "temporal attractor" breaks down to fragmental cell assemblies, each of which may exhibit a low activity chaotic state. However, as such temporarily linked fCAs cause correlated (or, synchronous) firings for some time, NMDA channels eventually open causing consolidation of a new memory structure. This newly-born structure turns to an attractor ruin in a background state.

It might be possible to view the pool of fragmentally cell assemblies as a brain function prepared for flexible, dynamical organization of memory structure. FCAs that behave as "local" attractor ruins, are building blocks for potentially existing attractors. The role of excitatory GABA, as the dynamic regulator of memory structure, might be to broaden the diversity of representation to cope with higher brain functions, as Fukuda suggested.[b]

[a]The "global" phase space is now supposed to be consisted of several local but *dynamically organized* spaces with smaller degree of freedom, which may have weak interactions.
[b]Personal communication.

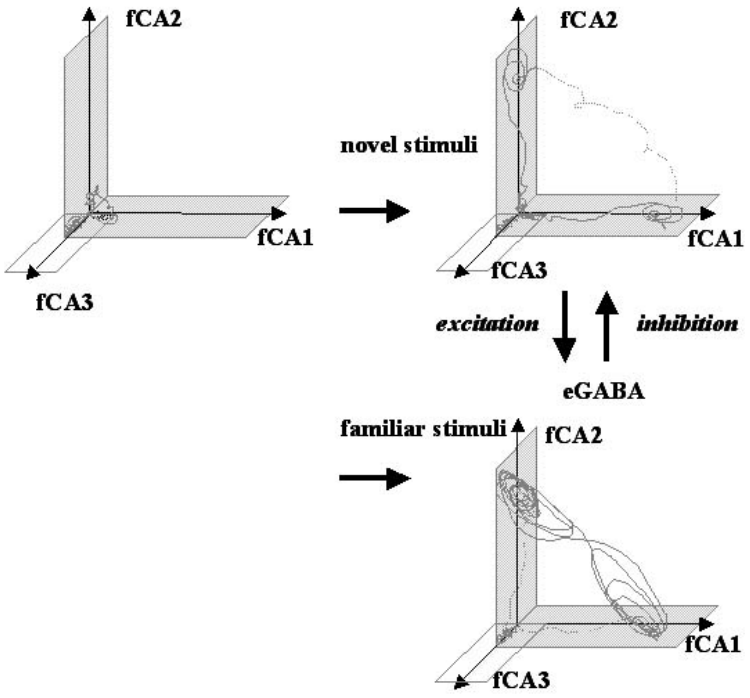

Fig. 1. Schematic Picture of Dynamics in the Phase Space.
When the brain system is in a background state (*top-left picture*), the three fragmentary cell assemblies (fCAs) exhibit low activities in "local" phase spaces; this is a state far from any attractor ruins. When a stimulus, which is composed of two local "features", corresponding to, say fCA1 and fCA2, comes in, the two fCAs are triggered to fire. If the stimulus is novel or unfamiliar (*top−right*), the two activated states are not perceived as a unity due to the lack of coherent (or, synchronous) activity between the two "local" states. The eGABA action may, booted up by, e.g., attention or top down categorical information, temporarily "link" the fCAs, to unveil or create temporarily a global attractor ruin, which possesses coherent activity (*bottom*). Note the possibility that fCAs may have further nest structures. Here, the three axes symbolically represent the "directions" of fCAs, and represents "local" phase spaces.

5. Concluding Remarks

The aim of this paper was to study the functional significance of the excitatory GABA (eGABA) action, the presence of which in *matured* CNS has frequently been reported. The functional role of this phenomenon has been argued by a number of researchers, but still it is regarded largely as a puzzle. It has also been known that there exists a "similar" - but distinct in their ionic processes and time scales, phenomenon of excitatory GABA action in neonatal period. The scope of this paper is to prepare a theoretical, but conceptual, perspective for investigating possible "role" of this eGABA action, rather than to write a flawless "answer paper" to solve the puzzling behavior. Along this line of presentation, we gave hypothetical scenarios which the eGABA action could play in the cognitive function. For this, we firstly

gave a short review about the known experimental data on the phenomenon, and also our theoretical framework on the memory dynamics, which is based on the concept of "attractor ruins" and "chaotic itinerancy". These contemporary concepts on the memory structure may, in principle, have the basic ability to overcome limitations of the classical attractor view.

Our basic standpoint is, although most of experimental data about eGABA are from hippocampal CA1 area and neostriatum, to investigate possible functional consequences of the phenomenon, assuming the universal presence, under some conditions, of the eGABA action in the hippocampus and the neocortex in view of the generality of the assumed ionic mechanisms (see, e.g., Staley *et al.* [64].)

The puzzle surrounding the action of eGABAs may be summarized as "why does GABA change its action so dynamically?" However, if we change our point of view and ask "what is the function that only "e-GABAergic" neurons could carry?", the answer would immediately be disclosed. That is, *a possible role of* eGABA *may not be "inhibition" nor "excitation", but "switching" between the two functions.* Such a viewpoint might be in harmony with the opinions such as: " GABA cannot simply be classified as "inhibitory" or "excitatory" [27, 67]" and the concept of "discriminative inhibition" described in CA1 pyramidal neurons by Andersen *et al.*, 1980 [6].

Functional consequences of such "switching" on the cognitive function are, as described in the previous sections, to make the memory structure dynamic, organizing attractor ruins. Thus, the role of GABA is a dynamic *regulator* of the memory structure. This eGABA function may serve to broaden the diversity of information representation underlying higher brain function.

In both the processes of learning and perception, there may be at least two phases of dynamics. One is a stable phase and the other is an unstable phase. In early stage of the processes, stable dynamics should be dominant, because restrictions are necessary for the formation of memories and sensory information processing. It is reasonable to think that unstable dynamics before the formation of the seeds of organization cannot yield diversity of memory systems and sensations. On the other hand, after the formation of such seeds, instability of the dynamics rather than the stability plays a role in ensuring diversity. The system will loose flexibility, if stable dynamics could be dominant at this late stage. The all of recent findings on activity of GABAergic interneurons are consistent with this two-fold of the roles of dynamics, and rather some findings suggest its plausibility.

Our hypothetical view on the role of "e-GABAergic" neurons, however, may be challenged by a number of questions. In view of the diversity of GABAergic interneurons in e.g., the neocortex, which systems may play the role we have assumed? Who may drive such GABAergic interneuron systems? Such experimental details are largely unknown at this moment. It is reported also that the activity-dependent eGABA actions are synapse-specific, and the depolarization is *dendritic.* Thus, the eGABA action depends on its spatio-temporal relationship to other depolarizing inputs. Both experimental and model-theoretic studies are indispensable.

At the same time, there exists a study [27], which suggests that GABA action is more dynamic than previously reported. They showed that GABA is always excitatory when it acts on dendrites. When injected to soma, the effective GABA action depends on the timing relative to AMPA excitatory input. If the GABA and (superthreshold) depolarizing AMPA input come together, then because of shunting mechanism, GABA acts as inhibitor, but if GABA arrives 2 ms before the (even subthreshold) AMPA input, the two stimuli together can make the cell to fire. The relation of this study to the activity-dependent excitatory GABA action appears to be not clear, the ionic mechanism of the latter has been reported, e.g., by Staley *et al.* [64]. Thus, further experimental and theoretical studies would be needed in this regard.

Although our hypothetical argument on the role of eGABA action and possible consequences to memory dynamics remain conceptual, we hope that it may motivate further studies on the phenomenon from both experimental and theoretical standpoints.

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References

[1] Adachi K. and Aihara K., Associative Dynamics in Chaotic Neural network, *Neural Networks* **10**:83-98, 1997.

[2] Aihara K., Chaotic Neural Networks, *Bifurcation phenomena in nonlinear systems and theory of dynamical systems*, ed. by Kawakami H. (World Scientific, Singapore, 1990), 143-161.

[3] Aihara K., Takabe T. and Toyoda M., Chaotic Neural Networks, *Phys. Lett. A* **144**:333-340, 1990.

[4] Alger B. E. and Nicoll R., Feed-forward dendritic inhibition in rat hippocampal pyramidal cell studied in vitro, *J. Physiol.-London* **328**:105-123, 1982.

[5] Alkon D.L., Sanchez-Andres J.V., Ito E., Oka K., Yoshioka T., and Collin. C., Long-Term Transformation of an Inhibitory into an Excitatory GABAergic Synaptic Response, *P. Natl. Acad. Sci. USA* **89**:11862-11866, 1992.

[6] Andersen P., Dingledine R., Gjerstad L., Langmoen I.A. and Laursen A.M., Two different responses of hippocampal pyramidal cells to application of gamma-amino butyric acid , *J. Physiol-London* **305**:279-296, 1980.

[7] Anderson J., Lampl I., Reichova I., Carandini M., and Ferster D., Stimulus dependence of two-state fluctuations of membrane potential in cat visual cortex, *Nature Neuroscience* **3**:617-621, 2000.

[8] Avoli M. and Perreault P., A GABAergic depolarizing potential in the hippocampus disclosed by the convulsant 4-aminopyridine, *Brain Res.* **400**:191-195, 1987.

[9] Ben-Ari Y., Khazipov R., Leinekugel X., Caillard O. and Gaiarsa J. L., $GABA_A$, NMDA and AMPA receptors: a developmentally regulated 'menage a trois', *Trends Neurosci.* **20**:523-529, 1997.

[10] Ben-Ari Y., Developing networks play a similar melody, *Trends Neurosci.* **24**:353-360, 2001.

[11] Ben-Ari Y., Excitatory Actions of GABA during Development: the Nature of the Nurture, *Nat. Rev. Neurosci.* **3**:728-739, 2002.

[12] Buhl E. H., Halasy K. and Somogyi P., Diverse sources of hippocampal unitary inhibitory postsynaptic potentials and the number of synaptic release sites, *Nature* **368**:823-828, 1994.

[13] Buzsaki, G., The hippocampo-neocortical dialogue, *Cereb. Cortex* **6**:81-92, 1996.

[14] Cherubini E., Gaiarsa J.L. and Ben-Ari Y., GABA: An excitatory transmitter in early postnatal life, *Trends Neurosci.* **14**:515-519, 1991.

[15] Cohen I., Navarro. V., Clemenceau S., Baulac M. and Miles R., On the Origin of Interictal Activity in Human Temporal Lobe Epilepsy in Vitro, *Science* **298**:1418-1421, 2002.

[16] Figiolini M., and Hensch T.K., Inhibitory threshold for critical-period activation in primary visual cortex, *Nature* **404**:183-187, 2000.

[17] Freeman W. J., Simulation of chaotic EEG patterns with a dynamic model of the olfactory system, *Biol. Cybern.* **56**:139-150, 1987.

[18] Freeman W. J., The creation of perceptual meanings in cortex through chaotic itinerancy and sequential state transitions induced by sensory stimuli. In *Ambiguity in Mind and Nature*, ed. by P. Kruse and M. Stadler. (Springer Series in Synergetics **64**:421-437, 1995.

[19] Freeman W. J., *Societies of Brains - A Study in the Neuroscience of Love and Hate.* (Lawrence Erlbaum Associates, Inc., Hillsdale. 1995).

[20] Freeman W. J., *How Brains Make up Their Minds* (Weidenfeld & Nicolson, London, 1999).

[21] Freeman W. J., Evidence from human scalp EEG of global chaotic itinerancy, *Chaos* **13**:1067-1077, 2003.

[22] Fujii H., Ito H., Aihara K., Ichinose N. and Tsukada M., Dynamical cell assembly hypothesis – Theoretical possibility of spatio-temporal coding in the cortex, *Neural Networks* **9**:1303-1350, 1996.

[23] Fujii H. and Tsuda I., Neocortical gap junction-coupled interneuron systems may induce chaotic behavior itinerant among quasi-attractors exhibiting transient synchrony, *Neurocomputing* **58**:151-157, 2004.

[24] Fukuda, A., Tanaka, M., Yamada, Y., et al., Simultaneous optical imaging of intracellu-

lar Cl^- in neurons in different layers of rat neocortical slices: advantages and limitations. *Neurosci. Res.*, **32**:363-371, 1998.

[25] Fukuda A., Roles of intracellular Cl^- regulation in the neural function of the brain, *Neuroscience* **22**:219-223, 2000. (*in Japanese*).

[26] Gray C., Engel A. K., Koenig P. and SingerW., Synchronization of oscillatory neuronal responses in cat striate cortex: Temporal properties, *Visual Neurosci.* **8**:337-347, 1992.

[27] Gulledge A.T. and Stuart G.J., Excitatory Actions of GABA in the Cortex, *Neuron* **37**:299-309, 2003.

[28] Hebb, D. O., *The Organization of Behavior - a Neurophysiological Theory* (John-Wiley, New York, 1949).

[29] Hensch T.K., Figioli M., Mataga N., Stryker M.P., Baekkestov S., and Kash S.F., Local GABA Circuit Control of Experience-Dependent Plasticity in Developing Visual Cortex, *Science* **282**:1504-1508, 1998.

[30] Ikeda K., Otsuka K. and Matsumoto K., Maxwell-Bloch turbulence, *Prog. Theor. Phys. Supp.* **99**:295-324, 1989.

[31] Kaila K. and Voipio J., Postsynaptic fall in intracellular pH induced by GABA-activated bicarbonate conductance, *Nature* **330**:163-165, 1987.

[32] Kaila K., Lämsä K., Smirnov S. Taira T. and Voipio J., Long Lasting GABA-Mediated Depolarization Evoked by High-Frequency Stimulation in Pyramidal neurons of Rat Hippocampal Slice Is Attributable to a network-Driven, Bicarbonate-Dependent K+ Transient, *J. Neurosci.* **17**:7662-7672, 1997.

[33] Kaneko K., Clustering, coding, switching, hierarchical ordering, and control in network of chaotic elements, *Physica D* **41**:137-172, 1990.

[34] Kaneko K. and Tsuda I., (eds.), Focus Issue: Chaotic Itinerancy, *Chaos* **13**:926-1164, 2003.

[35] Kaneko K. and Tsuda I., *Complex Systems: Chaos and Beyond - A constructive approach with applications in life sciences* (Springer-Verlag, 2001).

[36] Kaneko K. and Tsuda I., Chaotic itinerancy, *Chaos* **13**:926-936, 2003.

[37] Kay L., Shimoide K. and Freeman W. J., Comparison of EEG time series from rat olfactory system with model composed of nonlinear coupled oscillators, *Int. J. Bifurcat. Chaos* **5**:849-858, 1995.

[38] Kay L., Lancaster L. R. and Freeman W. J., Reafference and attractors in the olfactory system during odor recognition, *Int. J. Neural Syst.* **7**:489-495, 1996.

[39] Kita H., Kita T. & Kitai S. T. Active membrane properties of rat neostriatal neurons in an in vitro slice preparation. *Exp. Brain Res.* **60**:54-62, 1985.

[40] Komuro M. and Aihara K., Hierarchical structure among invariant subspaces of chaotic neural networks, *Jpn. J. Ind. Appl. Math.* **18**:335-357, 2001.

[41] Komuro, M., *Basic Dynamical Systems : from Bifurcation Theory to Chaotic Itinerancy*, Science-sha, 2002 (in Japanese).

[42] Koerner E., Schickoff K. and Tsuda I., Dynamic inhibitory masking by means of compensation learning in neural networks. In: *Neurocomputers and Attention*, I, ed. by A. V. Holden and V. I. Kryukov. (Manchester University Press, Manchester, 1991), 309-317.

[43] Komatsu Y. and Iwakiri M. (1993) Long-term modification of inhibitory synaptic transmision in developing visual cortex, *Neuroreport* **4**:907-910, 1993.

[44] Kuroiwa J., Matsutani N., Nara S. and Aihara K., Sensitive response of a chaotic wandering state to memory fragment inputs in a chaotic neural network model, *Int. J. Bifurcat. Chaos* **14**, 2004.

[45] Lampl I., Reichova I. and Ferster D., Synchronous Membrane Potential Fluctuations in Neurons of Cat Visual Cortex, *Neuron* **22**:361-374, 1999.

[46] Lämsä K., $GABA_A$ *Receptor-Mediated Excitation in the Hippocampus of Adult and Newborn Rats* (Dissertation, Faculty of Science, University of Helsinki, 2000).

[47] McLean H. A., Caillard O., Ben-Ari Y., and Gaiarsa J. L., Bidirectional plasticity expressed by GABAergic synapses in the neonatal rat hippocampus, *J. Physiol.* **496**:471-477, 1996.

[48] Mercuri N.B., GABA depolarize neurons in the rat striatum: an in vivo study, *SYNAPSE* **8**:38, 1991.

[49] Michelson H. and Wong R. K. S., Excitatory synaptic responses mediated by $GABA_A$ receptors in the hippocampus, *Science* **253**:1420-1423, 1991.

[50] Michelson H. B. and Wong R. K. S., Synchronization of inhibitory neurones in the guinea-pig hippocampus in vitro, *J. Physiol.-London* **477**:35-45, 1994.

[51] Mikami S. and Nara S., Dynamical responses of chaotic memory dynamics to weak input in a recurrent neural network model, *Neural Comput. Appl.* **11**:137-143, 2003.

[52] Milnor J., On the concept of attractor, *Commun. Math. Phys.* **99**:177-195, 1985.

[53] Nara S. and Davis P., Chaotic wandering and search in a cycle-memory neural network, *Prog. Theor. Phys* **88**:845-855, 1992.

[54] Nara, S., Davis, P., Kawachi, M. and Totsuji, H., Chaotic memory dynamics in a recurrent neural networks with cycle memories embedded by pseudo-inverse method. *Int. J. Bifurcat. Chaos* **5**:1205-1212, 1995.

[55] Nicolis G. and Prigogine I., *Self-Organization in Nonequilibrium Systems* (John-Wiley, 1977).

[56] Owens D., Boyce L., Davis M. B. E., Kriegstein A. Excitatory GABA responses in embryonic and neonatal cortical slices demonstrated by gramicidin perforated patch recordings and calcium imaging. *J. Neurosci.* **16**:6414-6423, 1996.

[57] Perreault P. and Avoli M., 4-Aminopyridine-induced epileptiform activity and a GABA-mediated long-lasting depolarization in the rat hippocampus, *J. Neurosci.*, **12**:104-115, 1992.

[58] Plenz D. and Aertsen A., Neural dynamics in cortex-striatum cocultures I. Anatomy and electrophysiology of neuronal cell types, *Neuroscience* **70**:861-891, 1996.

[59] Plenz D. and Aertsen A., Neuronal dynamics in cortex-striatum cocultures II. Spatiotemporal characteristics of neuronal activity, *Neuroscience* **70**:893-924, 1996b.

[60] Plenz D. and Kitai S.T., Up and Down States in Striated Medium Spiny Neurons Simultaneously Recorded with Spontaneous Activity in FS Interneurons Studied in Cortex - Striatum - Substantia Nigra Organotypic Cultures, *J. Neurosci.* **18**:4001-4005, 1998.

[61] Ross S.T. and Soltesz, Long-term plasticity in interneurons of thye dentate gyrus, *P. Natl. Acad. Sci. USA* **98**:8874-8879, 2001.

[62] Shimizu-Okabe, C., Yokokura, M., Okabe, A., Ikeda, M., Sato, K., Kilb, W., Luhmann, H.J., and Fukuda, A., Layer-specific expression of Cl^- transporters and differential $[Cl^-]_i$ in newborn rat cortex, *NeuroReport*, **13**(18):2433-2437, 2002.

[63] Skarda, C. and Freeman, W. J., How brains make chaos in order to make sense of the world, *Behav. Brain Sci.* **10**:161-195, 1987.

[64] Staley K. J., Soldo B. L. and Proctor, W. R., Ionic Mechanisms of Neuronal Excitation by Inhibitory $GABA_A$ Receptors, *Science* **269**:977-981, 1995.

[65] Staley K. and Proctor W., Modulation of mammalian dendritic $GABA_A$ receptor function by the kinetics of Cl^- and HCO_3^- transport, *J. Physiol.-London* **519**:693-712, 1999.

[66] Staley K. and Smith R., A new form of feedback at the $GABA_A$ receptor, *Nat. Neurosci.* **4**:674-676, 2001.

[67] Stein V. and Nicoll R.A., GABA generates excitement, *Neuron* **37**:375-378, 2003.

[68] Stern E. A., Kincaid A. E. and Wilson C. J. ,Spontaneous subthreshold membrane potential fluctuations and action potential variability of rat corticostriatal and striatal neurons in vivo. *J. Neurophysiol* **77**:1697-1715, 1997.

[69] Stern E. A, Jaeger D. and Wilson C. J , Membrane potential synchrony of simultaneously recorded striatal spiny neurons in vivo, *Nature* **394**:475-478, 1998.

[70] Szalisznyo K. and Erdi P., Depolarizing/hyperpolarizing effects of the $GABA_A$ synapse have a beneficial role in synaptic weight resetting in the hippocampus, *Neuroreport* **11**:3559-3563, 2000.

[71] Tsuda I., Koerner E. and Shimizu H., Memory dynamics in asynchronous neural networks, *Prog. Theor. Phys.* **78**:51-71, 1987.

[72] Tsuda I., Chaotic itinerancy as a dynamical basis of Hermeneutics of brain and mind, *World Future.* **32**:167-185, 1991.

[73] Tsuda I., Dynamic link of memories–chaotic memory map in nonequilibrium neural networks, *Neural Networks* **5**:313-326, 1992.

[74] Tsuda I., Toward an interpretation of dynamic neural activity in terms of chaotic dynamical systems, *Behav. Brain Sci.* **24**:793-847, 2001.

[75] Tsuda I. and Kuroda S., Cantor coding in the hippocampus, *Jpn. J. Ind. Appl. Math.* **18**:249-258, 2001.

[76] Tsuda I. and Umemura T., Chaotic itinerancy generated by coupling of Milnor attractors, *Chaos* **13**:937-946, 2003.

[77] Tsuda I., Fujii H., Tadokoro S., Yasuoka T., and Yamaguti Y., Chaotic itinerancy as a mechanism of irregular changes between synchronization and desynchronization in a neural network (*this issue*).

[78] Vogel D., Auto associative memory produced by disinhibition in a sparsely connected network. *Neural Networks* **11**:897-908, 1998.

[79] Vogel D., A biologically plausible model of associative memory which uses disinhibition rather than long term potentiation, *Brain Cognition* **45**:212-228, 2000.

[80] Vogel, D.,A neural network model of memory and higher cognitive functions in the cerebrum, BBS Online (2002) http://www.bbsonline.org/documents/a/00/00/11/77/index.html.

[81] Von der Malsburg, C., The Correlation Theory of Brain Function, *Internal Report* **81-2**, 1981, Max-Planck-Institute for Biophysical Chemistry, Goettingen.

[82] Wilson C. J., The generation of natural firing patterns in neostriatal neurons. *In Prog. Brain Res.* **99**, *Chemical Signaling in the Basal Ganglia*, ed. by G. W. Arbuthnott and P. C. Emson. (Elsevier, Amsterdam 1993), 277-297.

[83] Wilson C.J. and Kawaguchi Y., The origins of teo-state spontaneous membrane potential fluctuations of neostriatal neurons, *J. Neurosci.* **16**:2397-2410, 1996.

[84] Xie X. and Smart T. G. A physiological role for endogenous zinc in rat hippocampal synaptic transmission, *Nature* **349**:521-524, 1991.