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Interaction of Short-Term Neuronal Plasticity and Synaptic Plasticity Revealed by Nonlinear Systems Analysis in Dentate Granule Cells

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***Abstract*—Dentate granule cells receive inputs from the entorhinal cortex as the "perforant path". There are two components of the perforant path: the lateral component(LPP) and the medial component(MPP). LPP and MPP convey different sensory modality information. It remains elusive as to how signals from different inputs interact and integrate at the granule cell level. We attempted to address this issue by using nonlinear systems analytic methods. Granule cell EPSPs and action potentials were recorded intracellularly from in vitro hippocampal slices of the rat. MPP and LPP were activated simultaneously by two independent Poisson random trains. Poisson-Volterra kernel models were estimated using Laguerre expansion of Volterra kernel technique. In the kernel models, self-kernels represent the intrinsic input/output properties of each pathway, while cross-kernels quantify the interactions between the two inputs. Short-term plasticity (STP) was revealed by both 2nd order self and cross kernels. We reason that the underlying mechanisms of the STP are diffusely distributed along input-specific synapses, dendritic tree and soma. The plasticity held by the dendritic tree/soma and synapses can be divided and referred to as neuronal and synaptic plasticity respectively. We argue that the cross kernel properties are determined primarily by neuronal plasticity while the self kernel properties are controlled largely by synaptic plasticity. Our experimental data suggest that linear summation of the membrane potential of the postsynaptic neuron can only partially explain the neuronal plasticity. Both supra- and sublinear summations were observed. Thus, the neuronal plasticity is likely to be the product of passive and active processes of the postsynaptic neuron and plays a pivotal role in multiple inputs integration.**

I. INTRODUCTION

THE mammalian brain routinely and readily creates multi-modality representations. In the brain, every external event regardless of modality, is converted into a series of all-or-none, point-process electrical events (action potentials) by peripheral, transduction processes. Thus, all external events are transformed into a common code. In addition, there are multiple locations in the brain where inputs transmitting information about one modality converge with inputs transmitting information about other modalities, with fusion of the different modality inputs occurring naturally as a consequence of integration by the postsynaptic neuron membrane.

The first major extrinsic input to the hippocampus arises from the entorhinal cortex as the "perforant path", and terminates in the dentate gyrus. There are two components of the perforant path: the lateral component, which synapses onto the outer third of the dendrites of dentate granule cells, and the medial component, which synapses onto the middle third of it. Both pathways are excitatory, but the lateral perforant path transmits information primarily about auditory and olfactory modalities, while the medial perforant path is believed to transimt information primarily about visual and somatosensory modalities [1]. Thus characterizing nonlinearities of the medial and lateral perforant path is the first step in understanding how different sensory modalities are processed within the hippocampal memory system.

METHODOLOGY

A. Electrophysiology

Hippocampal slices were prepared from adult male Spraugue-Dawley rats (200-300g). Animals first were anesthetized with 5% halothane, and then were decapitated and the hippocampi were rapidly dissected. Both hippocampi were sectioned into blocks while being washed with cold, oxygenated medium and slices of tissue (400 microns thick) then were cut perpendicular to the longitudinal axis using a vibratome. Slices were incubated with medium consisted of (in mM): 128 NaCl; 3.5 KCl; 1.25 NaH2PO4; 26 NaHCO3; 10 glucose; 2 CaCl2; 1.0 MgSO4, aerated with 95% O2/5% CO2. Two bipolar nichrome stimulating electrodes were placed, based on anatomical cues, to activate either lateral (LPP) or medial (MPP) perforant path axons (Fig. 1A and B). Granule cell EPSPs and APs were evoked simultaneously by two independent Poisson random impulse trains (RIT), each having mean frequency of 2 Hz but with a different sequence of inter-impulse intervals (Fig. 1C) and were recorded intracellularly using a sharp pipette.

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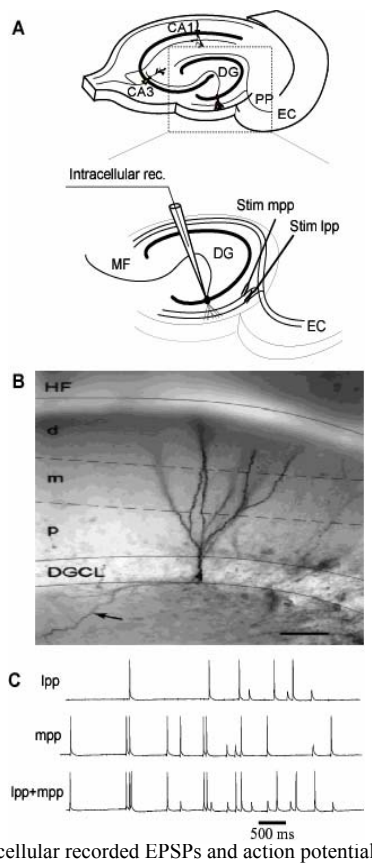

Fig.1. Intracellular recorded EPSPs and action potentials (APs) from the granule cell in dentate gyrus of the hippocampal slice. **A**. Transverse hippocampal slice. One stimulating electrode was placed in middle third and another was placed in outer third of molecular layer of dentate gyrus to activate medial (MPP) and lateral (LPP) perforant paths respectively. MF: mossy fiber; DG: dentate gyrus; EC: entorhinal cortex. **B**. a single granule cell is shown in dentate gyrus. DGCL: dentate granule cell body layer; p: proximal third (associational/ commissural), m: medial third (MPP), d: distal third (LPP) of molecular layer; HF: hippocampal fissure; arrow: granule cell axon; scale: 50 μM. **C**. EPSPs and APs were evoked by two independent Poisson random trains. The random trains, each having mean frequency of 2 Hz, were given to either LPP (upper trace) or MPP (middle trace) or both LPP and MPP simultaneously (lower trace). Note that in the third case the two random trains have a different sequence of inter-impulse intervals.

B. Nonlinear Systems Analysis

Self and cross Poisson-Volterra kernel models were estimated using both cross-correlation and Laguerre expansion of Volterra kernel techniques. Compatible results were obtained with these two methods.

III. RESULTS

When stimulus intensity is set to evoke EPSPs with amplitudes at which the membrane potential is depolarized close to action potential (AP) threshold, neuron firing will be probabilistic in nature (Fig. 2). The firing rate is set at approximately 50% during low frequency stimulation.

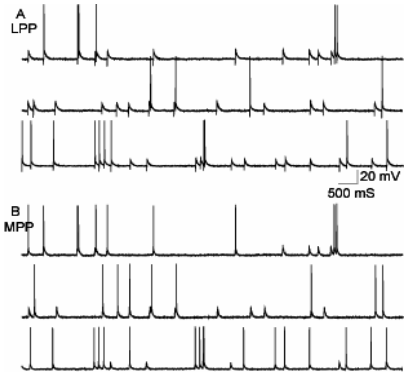

Fig.2. The same Poisson random train, each having mean frequency of 2 Hz was used to activate LPP (A) and MPP (B) separately showing the probabilistic nature of AP firing.

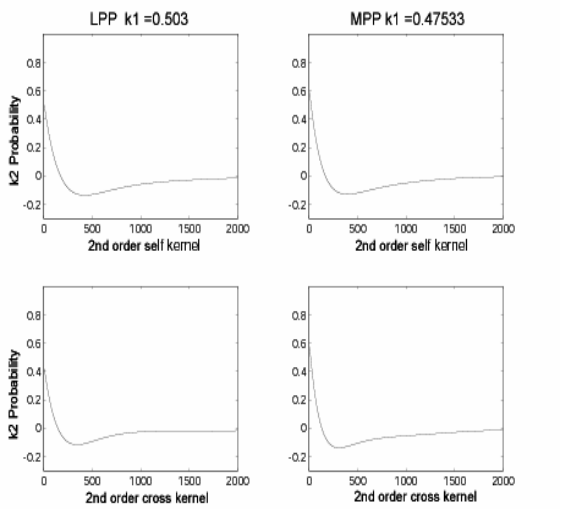

Fig.3. Representative 2nd order self and cross kernels. Left column: LPP; right column: MPP. Upper penal: self kernels; lower penal: cross kernels. 2nd order self and cross kernels were obtained by delivering random impulse trains simultaneously to LPP and MPP.

In the kernel model, self-kernels represent the intrinsic input/output properties of each pathway, while cross-kernels quantify the interactions between the two inputs. Short-term plasticity (STP) was revealed by both 2nd order self and cross kernels. Fig. 3 shows 2nd order self and cross kernels obtained by delivering two RITs simultaneously as described in the methodology section. The self kernels of LPP and MPP pathways demonstrated essentially the same dynamic input/output property as that when the RIT were delivered separately (not shown). The 2nd order cross kernel reflect the immediate interaction between these two inputs. Since the cross interaction is mostly among different synapses along the dendritic tree of the cell, the cross kernels mainly reflect the dynamic action of the postsynaptic component of STP.

The classical form of STP (frequency facilitation 1 and 2, post-tetanic potentiation) has been considered as presynaptic in origin [2]. If STP is purely presynaptic in origin,

however, one would expect that the cross kernel should have been flat. This is not the case in our results (Fig.4). A reasonable explanation is that some postsynaptic component is also involved in STP and is essential for dynamic interaction of inputs from multiple pathways. Interestingly, the difference in 2nd order self kernel between LPP and MPP is not statistically significant while the difference is significant between 2nd order self and cross kernels in both pathways (Table 1).

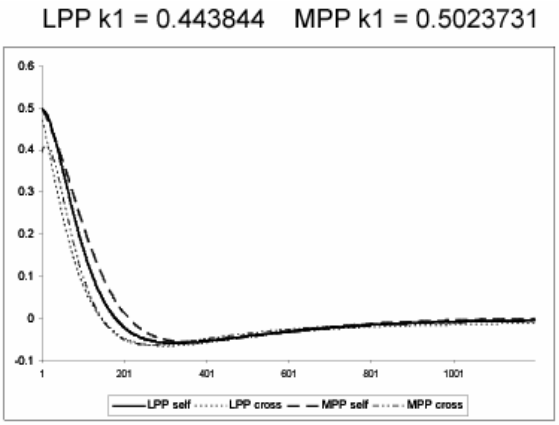

Fig.4. Averaged first and second order kernels from 9 experiments, one of which is shown in Figure 3. k1: first order kernel.

2nd order kernel differences	MPP self	LPP cross
LPP self	No (P>0.10)	Yes (P<0.05)
MPP cross	Yes (P<0.05)	No (P>0.10)

Table 1. In the first 200 mS period, there is no statistically significant difference between LPP and MPP 2nd order self kernels while the difference is significant between self and cross kernels of the same pathway for both pathways (n=9).

We observed that LPP-evoked EPSPs had a slightly slower rising and decaying course compared to MPP-evoked EPSPs. This can be explained by their geometrical locations relative to the soma of the granule cell where the recording electrode was placed. The slight difference could be accumulated to a greater magnitude as stimulation frequency was increased (Fig.5). Nevertheless, it did not seem to result in significant difference between LPP and MPP 2nd order self kernels.

IV. DISCUSSION

Marked difference in frequency facilitation between LPP and MPP evoked EPSPs was observed using high frequency stimulation. However, the difference only became obvious during high frequency and late in the 10 pulses train used suggesting that frequency facilitation of this magnitude is less likely to occur in dentate gyrus in physiological and in our experimental conditions in both of which the mean input frequency is only 2 Hz.

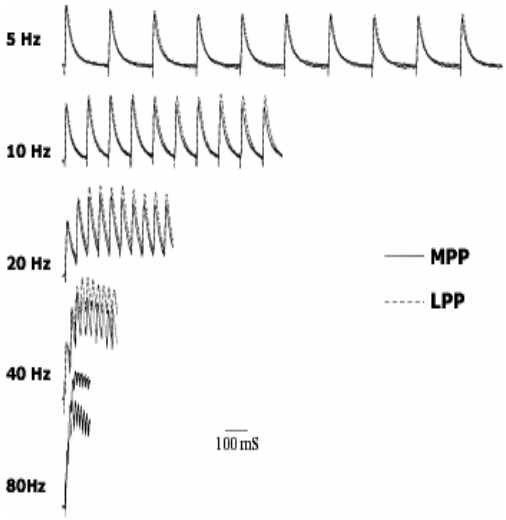

Fig.5. MPP and LPP demonstrated different degree of frequency facilitation. The difference became much more marked at higher stimulation frequencies. EPSPs were recorded at resting membrane potential and averaged from 6 cells.

Single input/output nonlinear functional property has been extensively studied in the past to characterize synaptic STP of different pathways in the hippocampus and other brain areas. The classical form of STP was demonstrated via input/output of a single pathway by stimulation with a high-frequency train and has been considered as presynaptic in origin. Using decomposition technique, previous studies in our lab have shown that feed forward and feedback inhibition played a role in a single input/output nonlinear dynamics through IPSPs modulation of postsynaptic membrane potential, suggesting that STP was also affected by postsynaptic neuron state. The single input/single output paradigm, however, makes it hard to reveal how EPSPs and postsynaptic spikes involve in STP. Membrane potential level and AP threshold ultimately determine whether or not a neuron fires an AP. It is reasonable to think that memory of the history of recent synaptic activity can also be held by changes in postsynaptic membrane potential or AP threshold level. Thus STP can be divided into presynaptic and postsynaptic components. It is also reasonable to believe that interactions may exist between these two components. This type of interactions has not been well recognized and characterized. In this study, we attempted to address this issue by using nonlinear systems analytic methods in an experimental preparation with double inputs and single output. Dentate granule cells receive inputs from the entorhinal cortex as the perforant path. There are two components of the perforant path: the LPP component and the MPP component. LPP and MPP more often than not converge onto the same granule cell. Thus the perforant-

granule cell pathways are proper to serve the purpose of our study.

V. CONCLUSIONS

1. Comparison of 2nd order self and cross kernels of the LPP/MPP-dentate granule cell pathways indicates that the STP seen in the cross interaction can be largely accounted for by the postsynaptic mechanism while the presynaptic mechanism barely plays a role.

2. Although the LPP/MPP-granule cell pathways display different electrophysiological properties, our kernel data suggest that AP output can discount such difference under physiological condition in which the average firing rate is low. As a result, no significant difference can be detected between these two pathways in terms of dynamic output given the same random input.

3. Thus, granule cells do not seem to be able to distinguish whether or not the incoming signals are from LPP or MPP. But they may be able to tell whether or not these signals are from a single input alone or from mixed inputs based on the different short-term dynamics revealed by comparison of self and cross kernels.

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