**Introduction to BSF Grant – Mossy-Fiber LTP and its Physiological Significance.**

The hippocampus has long been recognized as a key region for the formation and long-term storage of memories. It is roughly divided into three sub-regions – the dentate gyrus (DG) and Cornu Amonis 1 and 3 (CA1 and CA3 respectively) which are connected by unidirectional pathways to form a closed loop with the cerebral cortex. The Mossy-fibers (MF) pathway connects the DG and CA3 sub-regions, and is hypothesized to be the location in-which similar, yet distinct representations can be distinguished between one another, in a process termed “pattern separation” (Ref). This crucial ability to discriminate between similar patterns is ascribed to the MF pathway due to several unique properties it possesses; First, the granular cells of the DG are known for their ability to shift their firing-pattern between very-low firing frequencies to high firing frequencies upon subtle changes in the environment, in a process termed “rate re-mapping” (Ref). Second, the synapse formed between the mossy-fibers and their CA3 targets has the highest facilitation in the mammalian CNS, which allows it to perform as a very efficient high-pass filter for information transfer, allowing only high-frequency activity to be propagated to its downstream targets while filtering out low-frequency activity (Ref). In addition to its high facilitatory nature, the MF-synapse is also a very large synapse containing up to 40 active zones in a single mossy-fiber bouton (Rollenhagen & Lubke, 2010). The combination of both of these traits has led to consideration of this synapse as a ‘Detonator Synapse’, because a single MF-synapse, when firing in short high-frequency bursts, is able to induce spiking in its post-synaptic target, a trait which is rarely observed in other brain regions. (Ref).

 The MF-synapse also exhibits a unique form of long-term potentiation (LTP), which forms in response to prolonged activity of the synapse at a high frequency and manifests as a sustained increase in neurotransmitter release, which also leads to reduction in the facilitatory properties of this synapse and therefore to deterioration of its high-pass filter properties (Ref). Another non-trivial property of the MF-LTP is that it does not require any post-synaptic coordinated activity, as is the case in NMDA-dependent LTP which is the prevalent form of LTP in the hippocampus and is generally considered to be expressed post-synaptically as an increase in AMPA receptors responses (Ref, but see Jaffe & Johnston, 1990). The fact that the MF-LTP is non-associative suggests that it is not a suitable process to underlie memory storage, as it does not obey the hebbian learning rules (Ref). This is consistent with a recent study in which the researchers provided evidence that homeostatic plasticity processes are prevalent in the MF-synapse, and in-light of these observations, suggested a new role for this synapse as a gain-control device that helps keeping excitation levels in a certain physiological range (Lee et al., 2013).

Mainly due to technical reasons, most studies done so-far on MF-LTP have used non-physiological conditions for its induction. For example, most of the studies use LTP induction protocols that involve the simultaneous activation of many MF-axons that leads to the concurrent stimulation of many synapses, some of them converge on the same post-synaptic CA3 pyramidal cell (Ref). The probability of such an event under endogenous granular-cell firing patterns and their low connectivity to CA3 targets is very low (Unpublished data). Moreover, most researchers used the paired-pulse recording approach in-order to measure MF responses and to verify the pre-synaptic origin of LTP. However, there is ample evidence that the first two responses in a stimulation burst are unable to propagate their post-synaptic target, and thus are irrelevant to the information transfer through the hippocampal circuitry. This was shown in a seminal study in which the researchers tested the ability of one granular cell to induce spiking in its post-synaptic targets in the CA3, using *in-vivo* patch-clamp of DG granular cell combined with multi-unit activity measurements in the CA3 sub region. Consistent with the view of the MF-synapse as a high-pass filter, it was shown that only bursts of action-potentials, but not single action-potentials could induce spiking in the CA3 pyramidal cells. Furthermore, the researchers have shown that the higher the frequency of the pre-synaptic activity, the higher the chances to induce spiking in the post-synaptic targets (Henze, Wittner & Buzsaki, 2002). Furthermore, when researchers used a setup closely resembles the conditions of physiological activity …utilized organotypic slices and performed double-patch between DG granular-cell and CA3 pyramidal cell they observed that …, When they used high-frequency bursts that according to other e studies is capable of inducing LTP, they saw an initial decrease in failure rates of neurotransmission is response to single AP, but later, failure rates returned to baseline levels, which suggests that no significant LTP processes are evident under these conditions (Mori et al., ). Therefore, understanding under what physiological conditions does LTP take place, and what will be its consequences on later responses of a burst will be much more informative of LTP effects on information flow through this synapse, and might deepen our

This probably stems from technical reasons.

As new techniques has emerged in recent years that allow neuron-type specific control over.

First we want to understand what will be the consequences of MF-LTP on the synapse ability to propagate only high-frequency activity, Later we will pursue the physiological conditions under which MF-LTP is taking place and the way it supports information transfer.