The hippocampus has long been recognized as a key region for the formation and long-term storage of memories. According to the ‘trisynaptic pathway’ model, the hippocampus 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 are the axons sent by the granular cells of the DG to the CA3 sub region, where they form large and complex synapses onto CA3 pyramidal cells (hereafter MF-synapses). Traditionally, the MF-synapse is considered to be a ‘detonator synapse’ because of the unique ability of a single MF-synapse to induce spiking in its post-synaptic target, when activated in short bursts of high-frequency. This ability of the MF-synapse is largely attributed to its special short-term plasticity – namely, its extremely high facilitation.

The high facilitatory nature of the MF-synapse makes it a very efficient high-pass filter of information transfer which allows it to propagate its incoming inputs only if they are compressed in bursts of high-frequency activity (Henze et al., 2002). This property, together with some additional features of the DG-CA3 circuit, such as the sparse activity of the DG-granular cells, and their low connectivity to the pyramidal cells of the CA3, led computational theorists to hypothesize an important role for the MF pathway in ‘pattern separation’ - the process that supports the orthogonalization of highly overlapping mnemonic representations (Yassa & Stark, 2011). Indeed, some studies provided support for this theory by showing that lesions and perturbations of the DG and its efferents led to reduced ability of the inflicted animals to distinguish between similar contexts (Gilbert et al., 2001; Morris et al., 2012).

In addition to these unique properties, the MF-synapse also exhibits a special form of long-term potentiation (LTP) which forms in response to prolonged activity of the synapse at high frequencies and manifests as a sustained increase in the probability of neurotransmitter release (Pr). In a seminal study that involved both modeling and experimental approaches, it was shown that presynaptic LTP, such as the MF-LTP, does not lead to a uniform amplification of post-synaptic responses to a given pre-synaptic train of stimuli, but rather to a redistribution of the post-synaptic responses relative to one another, termed ‘redistribution of synaptic efficacy’ (Tsodyks & Markram, 1997). In the case of the MF-synapse, the redistribution of synaptic efficacy, as a result of LTP, is manifested as a decrease in its synaptic facilitation, which also entails deterioration of its high-pass filter properties. The implications of such changes in the filtering properties of the MF-synapse on its ability to support pattern-separation are currently unknown.

As opposed to the NMDA-dependent LTP, which is the most-studied form of LTP and is generally considered to be expressed post-synaptically, MF-LTP does not require any coordinated post-synaptic activity for its induction (Ref, but see Jaffe & Johnston, 1990). The fact that the MF-LTP is non-associative might suggest that it is less suitable to underlie memory storage processes (Ref). Consistent with this notion are studies that tested knock-out mice in which MF-LTP and LTD are impaired and found no impairments in learning tasks (Huang et al., 1995; Yokoi et al., 1996). Another support for this idea comes from a recent study in which the researchers provided evidence that homeostatic plasticity processes are prevalent and centered in the MF-synapse in response to pharmacological perturbations to network activity. In-light of these observations, the authors suggested a new role for the MF-synapse as a gain-control device that helps keeping excitation levels in the hippocampal circuitry in a certain physiological range (Lee et al., 2013).

The many atypical features of the MF-synapse highlighted above make it an enigmatic neuronal device, that its contribution to memory encoding and pattern-separation is still shrouded in mystery. The uniqueness of the MF-LTP suggests that it might have different role than the one ascribed to the more prevalent NMDA-dependent LTP, and thus require to take into consideration its atypical features when trying to integrate it into a Specifically, the two main properties of the MF-LTP – its non-associativity and its pre-synaptic expression, raise some exciting questions regarding the MF-physiology and its contribution to mnemonic and cognitive processes. First, how did LTP in this synapse change its filtering abilities and what are the implications of such changes on cognitive functions. Second, What will be the