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Mini Review

Mossy cells of the dentate gyrus: Drivers or inhibitors of epileptic seizures?

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ABSTRACT

Mossy cells (MCs) are glutamatergic cells of the dentate gyrus with an important role in temporal lobe epilepsy. Under physiological conditions MCs can control both network excitations via direct synapses to granule cells and inhibition via connections to GABAergic interneurons innervating granule cells. In temporal lobe epilepsy mossy cell loss is one of the major hallmarks, but whether the surviving MCs drive or inhibit seizure initiation and generalization is still a debate. The aim of the present review is to summarize the latest findings on the role of mossy cells in healthy and overexcited hippocampus.

1. Mossy cells of the dentate gyrus

In the human brain, the hippocampus is located deep within the medial temporal lobes. Anatomists divide the hippocampus into two major parts, the hippocampus proper (Ammon's horn, or Cornu Ammonis) and the dentate gyrus. The Cornu Ammonis (CA) can be further divided into three subareas, namely the CA1, CA2 and CA3 subregions. The dentate gyrus (DG), which contains the hilar region as well, is regarded as the gateway to the hippocampus because it filters the information input from the neocortex [1]. Information flow within the hippocampus is largely unidirectional: it arrives from the entorhinal cortex to the granule cells of the DG, which project to the pyramidal neurons of the CA3, which in turn project to pyramidal neurons of the CA1, these cells project to the subiculum and then information flows back again to the entorhinal cortex [2].

In this review, we focus on the DG, which plays a crucial role in a wide range of cognitive functions, including learning, memory formation and exploration of the environment [3,4]. Furthermore, it is involved in the pathophysiology of various neuro-psychiatric disorders, such as the medial temporal lobe epilepsy (TLE) [5,6]. The two excitatory cell types of the DG that also implicated in seizure development are granule cells (GC) [5] and hilar mossy cells (MC) [6].

MCs were first described in 1934 by *Lorente de Nó* [7]. Later *Amaral* investigated the Golgi-stained rat hippocampus and found MCs as the most numerous and so-called "impressive" cells of the hilar region [8]. These neurons were named after the special moss like structures seen on their proximal dendrites (Fig. 1). These thorny excrescences build up relatively large and complex spines that receive excitatory inputs mainly from mossy fibers, the axons of GCs [6]. MCs innervate GCs directly via axons terminating in the inner molecular layer suggesting that MC activity may lead to GC excitation. However, MCs also project to both parvalbumin and somatostatin positive hilar inhibitory neurons [9,10] and therefore, they can indirectly inhibit GCs. These opposing effects of MC activation led to controversies whether the net effect of MC activation to GCs is inhibitory or excitatory. The first study proving that MCs were glutamatergic suggested that MC activation leads to a general excitation in the DG [11]. Another study later clarified that indeed MCs were excitatory neurons, which innervated not only GCs but also the inhibitory basket cells therefore, indirectly inhibiting GCs [9]. Furthermore, paired recordings from monosynaptically connected MCs and GCs showed that activation of MCs led to excitatory postsynaptic potentials, but only in the presence of the blockade of GABAergic inhibition, suggesting that the net effect of MC activation was rather inhibitory to GCs. In contrast, another study found that deletion of MCs in acute brain slices did not cause overexcitation of the dentate gyrus, questioning the inhibitory function of MCs [12]. To make this

Abbreviations: DG, dentate gyrus; GC, granule cell; iDREADDs, inhibitory Designer Receptor Exclusively activated by Designer Drugs; HIPP, hilar perforant path-associated cells; LTP, long term potentiation; MC, mossy cell; NSC, neural stem cell; SE, status epilepticus; TLE, temporal lobe epilepsy.

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controversial field even more complicated, few years later *Jinde* et al. described that that genetic ablation of MCs using Cre-LoxP system resulted in increased excitability of GCs in the acute phase (4–11 days after deletion), but interestingly, not anymore in the chronic phase (6–8 weeks after deletion) [13]. Furthermore, a recent study targeted MCs optogenetically and showed that stimulation of MC axons during parallel electrical activation of the perforant path led to increased bursting activity in the DG [14]. Finally, *Botterill* et al. also demonstrated that selective inhibition of MCs during status epilepticus (SE) decreases epilepsy severity, further supporting the hypothesis that MCs are excitatory to GCs [15].

Taken together, despite decades of high-quality research, the fundamental role of MCs is still highly debated in the healthy hippocampal network, and even more complicated under pathological conditions, for instance, in epilepsy where MC loss is a major hallmark.

2. Mossy cells in synaptic plasticity

MCs are also involved in synaptic plasticity of the DG. It was shown that GC input to MC exhibited long term potentiation (LTP) with similar characteristics as GC evoked LTP in CA3 pyramidal cells [16]. Early studies already suggested that mossy cell input to granule cells might also display LTP [17,18], while a recent paper clarified that indeed this is the case. *Hashimotodani* et al., described a special, non-hebbian (BDNF-dependent) presynaptic form of LTP on GCs [19]. Interestingly, similar LTP was not present on MC-GABAergic interneuron synapses. These findings are especially important in the context of the balance of hippocampal excitation and inhibition recruited by mossy cells. Indeed, a recent study (pre-publication, not yet been peer reviewed) showed that acute epileptic seizures, increased MC and GC activity and triggered a BDNF-dependent strengthening of MC-GC synaptic transmission [20]. For more detailed description on the role of MCs in synaptic plasticity see also the review by H.E. Scharfman [6].

3. Mossy cells in neural oscillation

Neural oscillations at various frequencies are important features of hippocampal activity in vivo. Oscillation in the theta range (4–8 Hz) are crucial in encoding spatial information and memory retrieval [21,22]. *Soltesz* et al. showed that MCs participated in generation of hippocampal theta oscillations by phase locking postsynaptic neuronal (granule cell) activity [23]. Furthermore, a recent study using more sophisticated

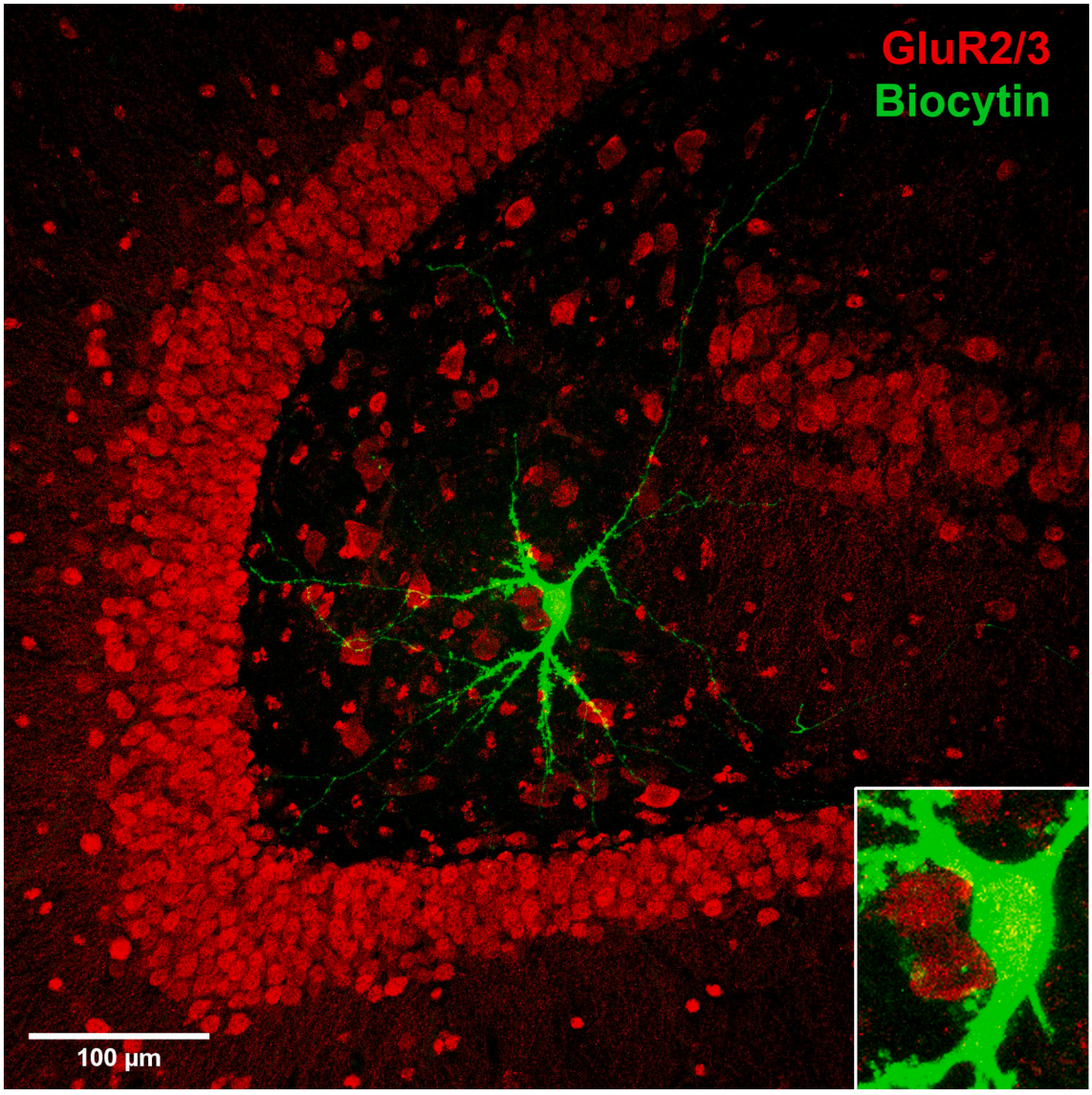

Fig. 1. Biocytin filled mossy cell and GluR2/3 immunostaining in a hippocampal slice from an adult mouse. The mossy cell was identified electrophysiologically and histologically as well. Insets shows the overlap (yellow) between Glur2/3 staining and biocytin filling. Authors unpublished data.

experimental approaches to distinguish MCs over GCs also concluded that MCs were phase-modulated, although to a lesser extent than GCs [24]. Finally, chronic elimination of MCs from the adult mouse resulted in increased theta power in the DG, further emphasizing the potentially underestimated role of MCs in hippocampal theta oscillation [13]. A recent study provided evidence that MCs are also involved in gamma oscillation and object learning. *Fernández-Ruiz* et al. showed the slow gamma oscillation from the lateral entorhinal cortex engaged MCs and CA3 pyramidal cells and this coupling is important in object learning tasks [25].

4. Mossy cells and adult neurogenesis

Beside few other brain regions [26] the dentate gyrus of the hippocampus continuously generates new neurons during adulthood [27]. Numerous studies investigated this form of neuroplasticity and it appears that adult-born neurons play an important role in hippocampal function [28]. Furthermore, they may play a significant role in the pathophysiology of various neuro-psychiatric disorders including the development of chronic epileptic seizures [29]. One of the most prominent features of newborn granule cell development is synaptic integration, a process that is believed to control the incorporation of new neurons into the pre-existing neuronal network in the DG. These early synapses are crucial in the activity-dependent maturation. *Chancey* et al. pointed out that MCs might be also important in the maturation and integration of newborn neurons by providing the first excitatory input to these cells [30]. Later, *Yeh* et al. demonstrated that MCs can regulate neural stem cell (NSC) quiescence or activation by providing direct excitatory or indirect inhibitory input to these cells [31]. Additionally, the same study found that genetic ablation of MCs resulted in a reduction of NSC pool and impaired hippocampal neurogenesis. These observation is in part contrary to previous findings showing rapid increase in the proliferation of newborn GCs after SE [32,33]. However, it has to be noted that these studies used different strategy to eliminate MCs. Furthermore, a recent study showed that Sonic hedgehog a multifunctional signaling protein produced by MCs might be important in neural precursor cell proliferation and their migration into the subgranular cell layer [34]. Finally, two recent studies highlighted that running can increase adult hippocampal neurogenesis and reorganize the newly developed excitatory and inhibitory circuitry including innervation of newborn GCs by MCs [35,36].

5. The role of mossy cells in pattern separation

It is well accepted that the DG plays a central role in pattern separation, a neuronal computation important for memory formation [37]. One possible way of computing pattern separation in the DG is remapping the spatial firing fields of MCs or GCs in response to contextual manipulation [38,39]. A crucial aspect of episodic memory encoding is to minimize the overlap between similar episodes. This computation is called pattern separation and GCs are key players in this process. They receive divergent sensory information from the entorhinal cortex via the performant pathway and GC-GC connections are sparse allowing the temporal separation of the information flow. This unique connection pattern ensures that GCs are widely accepted as the neurons responsible for pattern separation. Three recent independent studies tried to elucidate the potential role of MCs, besides GCs, in this process by investigating their firing properties in vivo [24,40,41]. These studies concluded that GCs exhibited extremely sparse firing pattern and showed either no space field or only one in an environment. In contrast, MCs were found to be very active and exerted several place fields. These findings supported the hypothesis that the low firing rate of GCs with no communication with each other may underlie pattern separation, but the question remains: what could be the role of MCs in this process? To answer this, all three studies investigated the remapping properties of GCs and MCs in new environment. All of them concluded that MCs showed clear remapping during contextual change, in contrast with GCs, suggesting that they might have a distinct but probably synergistic role in pattern separation. One interesting hypothesis is that MCs close to their soma activate mainly basket cells and therefore, inhibit GCs indirectly, while more distal from the soma they activate GCs directly [42]. Therefore, perforant path activation might lead to the subsequent inhibition of GCs by local MC axons. This local GC inhibition after perforant path activation might be important in pattern separation where the continuous firing would not be ideal [42].

6. Mossy cells in epilepsy

The main reasons that MCs are in the focus of intense research over the past decades is their extreme vulnerability to insults often leading to temporal lobe epilepsy (TLE). TLE is a form of focal epilepsy where seizures originate from temporal lobe of the neocortex. Pathological changes in TLE involve neuronal loss in the hippocampus, including MCs that has been observed in rodent models as well as in human patients [43]. Animal models of TLE confirmed that the two most vulnerable cell types in the hilar region are the MCs and the somatostatin-positive hilar interneurons (HIPP cells), while GCs and basket cells were significantly less affected [42].

MC vulnerability was mainly explained by their high susceptibility to excitotoxicity. The thorny excrescences found in the proximal dendrites of MCs receive input from the giant axonal buttons of GCs. These so-called “detonator” buttons can release large amount of glutamate, especially during seizures, resulting in long-lasting depolarization of MCs and eventually in excitotoxicity [44]. Since MCs have a depolarized resting membrane potential (−60–65 mV), relatively wide action potentials and display weak repolarization [45–47], one can speculate that this strong excitatory input may easily damage MCs. Furthermore, it has been suggested that MC vulnerability might be linked to the low expression of calcium binding proteins in these neurons including parvalbumin or calbindin [48]. Without these proteins MCs has poor calcium buffering capacity leading to cell death in overexcited conditions. However, this hypothesis has been challenged by a study showing that TLE phenotype in mice does not depend on calcium binding proteins [49]. Finally, it has been suggested that MCs display low level of autophagy. The decreased level of waste removal capacity during high metabolic demands may also the reason for their vulnerability [50].

These findings led to the hypothesis that MC loss may result in TLE development. It has to be noted however, that during TLE not only MCs are damaged and that selective deletion of MC did not necessarily result in disinhibition of GCs in slice electrophysiological studies [12] suggesting that MC loss alone may not be sufficient to cause TLE.

As discussed above, the role of MCs regulating excitation or inhibition in the dentate gyrus network in physiological or pathological conditions is still controversial. Moreover, the role of the surviving MCs in TLE is even more complicated. Two main hypotheses have been put forward. One of them suggested that MC loss may contribute to seizures because the hilar basket cells lose their excitatory MC input leading to the disinhibition of GCs (“dormant basket cell hypothesis”). Evidence showed that after intermittent perforant path stimulation the majority of basket cells in the DG were still present but lack their MC excitatory input [51] similar results has been found in the CA1 region in experimental TLE [52]. However, this hypothesis has been questioned by several subsequent papers. First of all, it has been shown that HIPP cells are also lost after seizures [53,54] and the lack of these GABAergic interneurons might also cause GC hyperexcitability. Furthermore, it has been shown that in TLE $GABA_A$ receptor expression of GCs are altered and this might play a role in hyperexcitability without the involvement of presynaptic mechanisms [55]. Taken together the dormant basket cell hypothesis faces now several potential limitations [56].

The other explanation is that the surviving MCs in TLE became overactive triggering GC hyperexcitability (“irritable mossy cell hypothesis”). *Santhakumar* et al. demonstrated that MC loss and GABAergic

cell loss were comparable in the hilar region in a traumatic brain injury model. Moreover, the surviving MCs were more excitable in slice electrophysiological experiments [57,58]. *Scharfman* et al. also found that not all the MCs are lost after pilocarpine induced SE and the surviving MCs display spontaneous burst discharges [59]. The generator of the burst activity was the CA3 region via the backprojecting axon collaterals [60].

The lack of selective in vivo MC manipulation in epileptic animals as the major technical bottleneck has been long hampered to answer which mechanism is dominant in TLE. Several molecular markers have been identified, however these markers are not always uniform between different species. For instance, MCs express GluR2/3 in humans, rats and mouse [40,61], calretinin in mice and non-human primates [62,63], and Cocaine- and amphetamine-regulated transcript peptide (CART) in humans [64]. With the help of MC specific Cre-lines, recent studies selectively activating or inhibiting MCs using optogenetic and chemogenetic tools aimed to clarify the pathophysiological function of mossy cells in TLE, however the outcome of these experiments generated an even more complicated picture [6,12,13].

7. Selective MC activation in an epilepsy model inhibits seizure development

Bui et al. attempted to clarify the role of MCs in the DG circuitry using elegant experimental approaches to selectively activate/inhibit MCs both in control and epileptic mice [65]. As we discussed earlier, MCs develop not only local but also commissural projections therefore targeting the contralateral DG using the wheat germ agglutinin (WGA-Cre) system, they were able to express archaerhodopsin in the ipsilateral MCs and by that they could selectively inhibit them. Furthermore, in another set of experiments they used the MC specific calcitonin receptor-like Cre (Crlr-Cre) mice and a virus containing the Cre-dependent channelrhodopsin to specifically activate MCs.

With the help of these advanced experimental approaches, the authors were able to show that activating the remaining MCs in the chronic phase of TLE can reduce the duration of non-convulsive seizures while inhibiting them had no effect. Furthermore, inhibition of MCs during the electrographic seizure onset facilitated the development of more severe convulsive seizures. Finally, inactivating MCs in healthy mice resulted in altered spatial memory encoding also present in epileptic rodents. In conclusion, these data clearly supported that surviving MCs in TLE are inhibitory to GCs and therefore MC activation can stop seizure generalization.

8. Selective MC inhibition decreases status epilepticus severity

In contrast to the findings that MC activation during spontaneous seizure onset mitigates the seizure generalization, *Botterill* et al. demonstrated that MC inhibition during status epilepticus (SE) led to a milder brain injury and alleviates spontaneous seizure frequency [15]. They used a pilocarpine-induced SE model in control and MC specific transgenic mice (DrD2-Cre) and the "inhibitory Designer Receptor Exclusively activated by Designer Drugs" (iDREADDs) technique. Selective inhibition of MCs in DrD2-Cre mice reduced SE onset development compared to wild type animals. Additionally, video-EEG recording confirmed that one day after the pilocarpine administration, iDREADDs mice exerted significantly reduced spontaneous convulsive behaviors and non-convulsive epileptiform-like activities. Finally, 4-weeks of video-EEG monitoring after pilocarpine injection revealed that selective MC inhibition during SE significantly reduced seizure frequency and seizure duration, thus overall epilepsy severity.

Histological data also supported these electrophysiological findings. Neuronal injury 3 days after the pilocarpine administration was assessed by FluoroJade B, a neurodegenerative marker in iDREADDs and wild type mice. Both ventral and dorsal hilar neuronal injury were significantly higher in wild type compared to iDREADDs mice. Importantly, exclusively the GluR2/3-immunoreactive MCs were damaged, not the somatostatin-positive hilar perforant path-associated (HIPP) cells, showing that selective MC-inhibition during SE played a protective role in hilar MC loss.

In vitro, optogenetic activation of MC axons during acute slice simulation failed to evoke paroxysmal depolarization shifts in GCs under standard recording conditions, whereas paroxysmal depolarization shifts were evoked in all GCs after simulated SE started. These results indicated that during SE initiation MCs could strongly activate GCs. Taken together, inhibiting MCs during SE could exert a neuroprotective and anti-epileptogenic effect.

9. Conclusion

Despite the decades of research investigating the role of MCs in the pathophysiology of epilepsy we still have to face an apparent paradox: the same cell population in certain studies inhibits while in others provokes the seizures onset or generalization. The opposing role of MCs in epilepsy are especially conspicuous in case of the two recent studies detailed above [15,65]. While *Bui* et al. demonstrated that during chronic epilepsy MC activation curtails seizures, in contrast, *Botterill* et al. showed that MC inhibition decreased SE severity. The most likely explanation that may solve this paradox is that the two studies investigated different stages of seizures. *Bui* et al. studied the spontaneous seizures in the chronic phase of experimental TLE, while *Botterill* et al. examined SE evoked by systemic pilocarpine injection. The main difference in the two experimental designs beside the type of seizure investigated, is that in the first study only the surviving MC were manipulated in the pathological hippocampus, while in the second study all the MC were inhibited in an essentially healthy hippocampus. These findings clearly suggest that surviving MCs in TLE exert different function on the DG excitability than intact MCs in a healthy hippocampus. It has to be noted however that the mouse lines used in the two studies are both not exclusively MC specific. Cre expression can also be found in CA3 region in case of the Crlr-mice and in hippocampal GABergic interneurons in the Drd2-mice [65,66].

What could be the explanation for the inconsistent results? One possibility is that after MC loss in TLE the surviving MCs change their connectivity pattern towards GCs and basket cells (possibly by axon sprouting like in case of GCs [67]) therefore their activation leads to inhibition rather than excitation. Other explanation could be that even in the healthy hippocampus MCs are not homogenous cell population regarding their connectivity with GCs. One can speculate that during TLE mostly MCs that are directly activating GCs are lost and the surviving MCs are rather inhibiting them via basket cells. This scenario may answer many conflicting results in previous studies, but hardly answers how MC loss in general can lead to GC overexcitation. Indeed, an early study already suggested that there is a subpopulation within MCs with a lower threshold for perforant path activation [68]. Furthermore, two recent independent studies clearly demonstrated that dorsal and ventral MCs differ in their axonal projection pattern therefore, likely have different functional roles [69,70]. Unfortunately, these studies did not investigated MC loss during TLE. Another explanation is that in normal condition MCs exert inhibitory effect on GCs via GABAergic cells but, during strong activation of MCs the excitation of GCs will become dominant. This could happen via the depletion of GABA stores during seizure [71,72] or because MC → GC synapse is potentiated preferentially when MCs discharge at high frequency [19]. This scenario would answer why MC inhibition during SE decreases seizure severity [15] while activating them at the onset of a spontaneous seizure curtails seizure duration [65]. This hypothesis is summarized in Fig. 2.

Despite the recent advances in MC research using cutting-edge technologies, further investigations are necessary to clarify the physiological role of different MC subpopulations which may also help us to understand the exact contribution of MCs to temporal lobe epilepsy. Detailed molecular characterization is needed -possibly with single cell

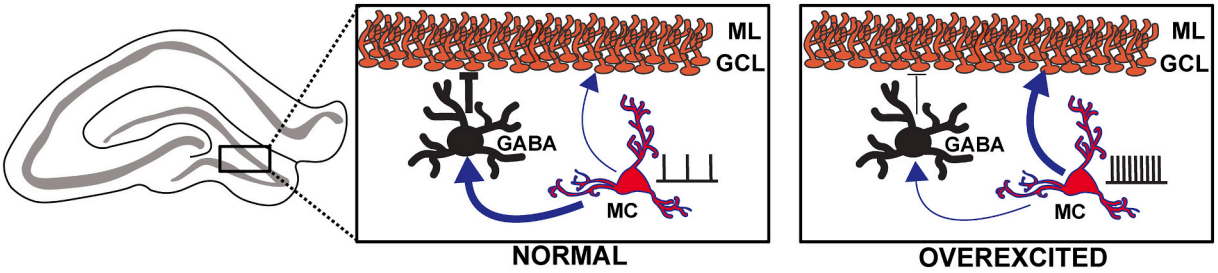

Fig. 2. Possible function of MCs in the DG circuitry in normal and overexcited conditions. In normal condition MCs exert net inhibitory effect on GCs via innervation of GABAergic neurons. However, during strong activation of MCs the excitation of GCs will become dominant by GABA depletion or by strengthening the MC → GC synapses.

RNA sequencing combined with electrophysiological recordings- to better distinguish sub-populations within MCs. With the help of this characterization, selective targeting of the sub-populations might become possible and we could obtain a more precise role of MCs in the overexcited hippocampus.

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Declaration of competing interest

The authors declare no competing interests.

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