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Review article

# Mature granule cells of the dentate gyrus—Passive bystanders or principal performers in hippocampal function?

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ABSTRACT

The dentate gyrus is the main entrance of highly processed information to the hippocampus which derives from associative cortices and it is one of the few privileged areas in the brain where adult neurogenesis occurs. This creates the unique situation that neurons of diverse maturation stages are part of one neuronal network at any given point in life. While recently adult-born cells have a low induction threshold for long-term potentiation several studies suggest that following maturation granule cells are poorly excitable and they exhibit reduced Hebbian synaptic plasticity to an extent that it was even suggested that they functionally retire. Here, we review the functional properties of mature granule cells and discuss how plasticity of intrinsic excitability and alterations in excitation-inhibition balance might impact on their role in hippocampal information processing.



**Contents**



## 1. The role of the dentate gyrus in hippocampal circuitry

The hippocampal formation comprises the dentate gyrus, the hippocampus proper and the adjacent parahippocampal cortices. It is organized in a laminar fashion and its connectivity is mostly unidirectional. This configures the classical trisynaptic hippocampal circuit model of information processing (Fig. 1) (Andersen et al., 1971; Andersen et al., 1966). The major excitatory input to the hippocampus arises from the entorhinal cortex via the perforant path to primarily terminate in the dentate gyrus. Dentate axons, the mossy fibers, project to the CA3 region and from there the Schaffer collaterals convey the processed input to the CA1 area (Fig. 1). This circuitry has led already very early to the idea that the dentate operates as a gate at the entrance to the hippocampus, filtering incoming excitation from the entorhinal cortex. However, the exact nature of its role is still a matter of debate (Treves et al., 2008).

Lesions to the dentate profoundly affect associative and spatial learning (Lee and Kesner, 2004; Nanry et al., 1989; Sutherland et al., 1983; Walsh et al., 1986) and the optogenetic re-activation of granule cells that were active during contextual fear conditioning evokes the stored memory, suggesting that they are indeed part of an engram formed (Liu et al., 2012; Ramirez et al., 2013). Early modeling work of hippocampal circuitry (Marr, 1971) proposed that the dentate gyrus is a key structure for pattern separation, the capacity to discriminate among similar events. Pattern separation is an

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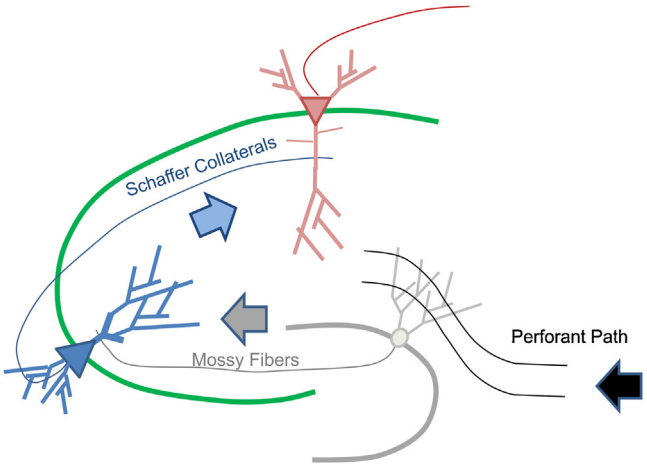


**Fig. 1.** The hippocampal trisynaptic circuit. Based on extensive anatomical and functional evidences the hippocampal circuit is classically described as a trisynaptic loop. However, nowadays, it is assumed that information does not only flow serially in the hippocampus but that there is also parallel processing. For instance, the entorhinal cortex sends projections as well to CA3 and CA1 areas, several associational/commissural connections among CA3 pyramidal cells have been identified and it has even been suggested that CA3 cells project back to the dentate gyrus. Nonetheless, although the concept of the trisynaptic loop is an oversimplification of functional connectivity of the hippocampus it captures many important hippocampal features.

indispensable cognitive feature and is thought to result from a non-overlapping representation of temporal and spatial traits of similar experiences. It requires that the encoding of the memories is done in a way that maximizes their independency and minimize mutual interferences. Granule cells have some features that predestine them for a function in pattern separation. They exhibit an unusual low firing rate (Jung and McNaughton, 1993; Pernia-Andrade and Jonas, 2014), theoretically increasing the probability that different granule cells will encode similar inputs, and they outnumber both their presynaptic entorhinal partners and their postsynaptic CA3 pyramidal targets by an order of magnitude (in rats there are around 112,000 principal cells in layer II of the entorhinal cortex, 250,000 CA3 pyramidal cells and 1,200,000 granule cells). A single granule cell also has synaptic contacts with a reduced number (like a dozen) of CA3 pyramids. This results in a divergence in the projection from the entorhinal cortex to the dentate gyrus and a convergence from the dentate to the CA3 (Amaral et al., 1990; Amaral et al., 2007; Schmidt et al., 2012) and it allows for an orthogonalization of the information that the dentate receives from the entorhinal cortex while it is relayed to the CA3 region (Aimone et al., 2011; Kesner and Rolls, 2015; Sahay et al., 2011b; Schmidt et al., 2012). Substantial experimental evidence supports this computational function of the dentate gyrus (Bakker et al., 2008; Gilbert et al., 2001; Goodrich-Hunsaker et al., 2008). Interestingly pattern completion, the ability to recall information from a reduced number of inputs and classically attributed to CA3 region, has recently also been related to the dentate gyrus (Kropff et al., 2015; Nakashiba et al., 2012; Temprana et al., 2015).

A highly controversial topic is the functional heterogeneity of the granule cell population (Table 1) that stems from adult neurogenesis. In rodents the first granule cells are born in the last stage of embryogenesis whilst the main period of granule cell neurogenesis extends throughout the first two weeks of postnatal development. Thereafter the rate of neurogenesis declines considerably (a drop of 90% in birth rate of neurons was reported in middle-aged rats and humans as compared to young animals) but adult-born cells are still constantly integrated into hippocampal circuitry (Kempermann, 2011; Knoth et al., 2010; McDonald and Wojtowicz, 2005; Schlessinger et al., 1975). This decrease in neurogenesis has been proposed to relate with the age-dependent decline in cognitive capabilities (Drapeau and Nora Abrous, 2008; Seib and Martin-Villalba, 2015). It is also thought to underlie the deficits in pattern separation seen during normal aging (Holden and Gilbert, 2012; Sahay et al., 2011a; Small et al., 2004; Yassa et al., 2011).

Granule cells of the dentate gyrus are born from neuronal stem cells located in the subgranular zone. During the first week, after committing to the neuronal lineage, the early neuroblasts migrate toward the inner granule cell layer and extend first processes; but they are not yet integrated into the trisynaptic network and are at this stage mainly activated by ambient γ-aminobutyric acid (GABA) and not glutamate (Esposito et al., 2005). The second week is characterized by rapid neurite growth as well as synaptogenesis and this week is crucial for the integration into the dentate gyrus synaptic network. More than 50% of the adult-born cells fail to integrate and subsequently undergo apoptosis (Dayer et al., 2003; Gould et al., 1999; Sierra et al., 2010). The first functional synaptic inputs onto young granule cells are GABAergic and only in the third week glutamatergic synapses with axons from the entorhinal cortex start to appear (Esposito et al., 2005; Overstreet Wadiche et al., 2005). Dendritic spines have been reported to start emerging in granule cells after the second postnatal week and the spine density continuously increases until reaching a plateau in the eighth postnatal week. However even after eight weeks the spines undergo further maturation thereby increasing the density of mushroom-like spines up to at least the eighteenth postnatal week. The motility of spines is also dynamically modulated. The maximum mobility is reached between the fourth and eight week, but it decreases afterwards (Zhao et al., 2006). Granule cell axons grow in parallel and establish synaptic contacts with CA3 postsynaptic targets at the beginning of the second postnatal week, but these contacts become only stable around the fourth week (Gu et al., 2012; Zhao et al., 2006). Eight weeks after birth granule cells are considered to be functionally and morphologically mature and at this stage they are practically indistinguishable from their developmentally-born peers (Ge et al., 2007; Laplagne et al., 2006; Mongiat et al., 2009). Several recent reviews cover in depth underlying mechanisms and functional implications of adult neurogenesis in the dentate gyrus (Abrous and Wojtowicz, 2015; Christian et al., 2014; Opendak and Gould, 2015; Yu et al., 2014). Immature newborn granule cells are thought to be the key players in learning and memory due to their high excitability and enhanced synaptic plasticity, which is surprising since the vast majority of the population, roughly 90%, can be considered mature (Cameron and McKay, 2001; Kempermann et al., 1997; Ninkovic et al., 2007). Mature granule cells, in contrast, are less excitable and poorly malleable (see below), which raises questions about their function. Nonetheless, several recent papers indirectly suggest that this cell population participates in learning and memory formation within the dentate gyrus (Liu et al., 2012; Ramirez et al., 2013; Redondo et al., 2014; Ryan et al., 2015). The relative contribution of young and mature granule cells is at present unclear but the engram-dentate neurons have electrophysiological characteristics of mature granule cells (Ryan et al., 2015) and also other lines of evidence point to mature cells as active players in dentate plasticity (Lemaire et al., 2012; Stone et al., 2011; Tronel et al., 2015a).

## 2. Distinctive intrinsic properties and GABAergic inhibition in mature granule cells

Distinctive features of mature granule cells are a hyperpolarized resting membrane potential below −75 mV and a relatively low input resistance (100–300 MΩ, which is one order of magnitude less than the input resistance of immature cells) (Staley

**Table 1**
Differences between mature and immature granule cells.

| Feature | Mature GC | Immature GC | References |
|---|---|---|---|
| Input resistance | ↓ | ↑ | Liu et al. (1996), Schmidt-Hieber et al. (2004) and Mongiat et al. (2009) |
| Rheobase | ↑ | ↓ | Schmidt-Hieber et al. (2004) and Mongiat et al. (2009) |
| Action potential amplitude | ↑ | ↓ | Liu et al. (1996) and Mongiat et al. (2009) |
| Action potential number | ↑ | ↓ | Mongiat et al. (2009) |
| Low-threshold calcium spike | – | + | Blaxter et al. (1989) and Schmidt-Hieber et al. (2004) |
| Dendritic complexity | ↑ | ↓ | Liu et al. (1996), Schmidt-Hieber et al. (2004) and Esposito et al. (2005) |
| Excitatory glutamatergic input | ↑ | ↓ | Mongiat et al. (2009) and Dieni et al. (2013) |
| GABAergic inhibition | ↑ | ↓ | Esposito et al. (2005) and Temprana et al. (2015) |
| Calcium buffering | ↑ | ↓ | Stocca et al. (2008) |
| Threshold for LTP induction | ↑ | ↓ | Wang et al. (2000), Schmidt-Hieber et al. (2004) and Ge et al. (2007) |
| LTP magnitude | ↓ | ↑ | Wang et al. (2000), Schmidt-Hieber et al. (2004) and Ge et al. (2007) |

*Abbreviations*: GC, granule cell; LTP, long-term potentiation; GABA, γ-aminobutyric acid.

et al., 1992). This results in a much higher threshold for excitation. Immature granule cells express a reduced repertoire of ion channels that are open at resting potentials like the inward rectifying potassium channel (Kir), and in conjunction with simplified dendritic and axonal processes this tremendously increases the input resistance of immature neurons, usually up to the gigaohm range (Liu et al., 1996; Mongiat et al., 2009; Schmidt-Hieber et al., 2004). With such high input resistance even small current injections lead to huge variations in voltage responses, *i.e.*, action potential firing. Another distinctive feature of immature granule cells is the transient expression of a T-type calcium conductance underlying a low-threshold calcium spike under physiological conditions. This low-threshold spike significantly boosts the initiation of a sodium spike in immature cells (Schmidt-Hieber et al., 2004). Mature granule cells in contrast do not generate low-threshold calcium spikes and when blocking T-type channels pharmacologically no evident changes take place in the sodium spike threshold (Martinello et al., 2015; Schmidt-Hieber et al., 2004). However, low-threshold calcium spikes can be observed in mature granule cells in the presence of potassium channel blockers (Blaxter et al., 1989) and mature granule cells, in contrast to immature ones, can under physiological conditions fire bursts of action potentials (Pernia-Andrade and Jonas, 2014; Staley et al., 1992) which enhances the chances to trigger spikes in their CA3 pyramid targets (Henze et al., 2002).

Mature granule cell dendrites receive and integrate inputs from many different sources, including the entorhinal cortex, mossy cells and diverse GABAergic interneurons (Fig. 2). Their characteristic cone-shaped dendritic arbor extends unidirectionally for about 270 μm through the molecular layer in rats and usually one to four primary dendrites arise from the soma. Most of the dendritic branching typically occurs in the proximal segments within the first third of the molecular layer. Up to eight order branches and an average of thirty dendritic segments have been described. These dendrites are very thin, with diameters of 1.5 μm in proximal segments and as thin as 0.7 μm in the distal parts (Claiborne et al., 1990; Hama et al., 1989; Schmidt-Hieber et al., 2007). Sodium action potentials evoke high-amplitude calcium transients in dendrites of both immature and mature granule cells (Hamilton et al., 2010; Kamijo et al., 2014; Krueppel et al., 2011; Schmidt-Hieber et al., 2007; Stocca et al., 2008). However, immature granule cells show longer transients in proximal and distal dendrites, which allows a more effective temporal summation of inputs. This seems to be due to a smaller endogenous calcium binding capacity and a slower extrusion rate (Stocca et al., 2008). The differences in calcium influx could in principle contribute to the differences in

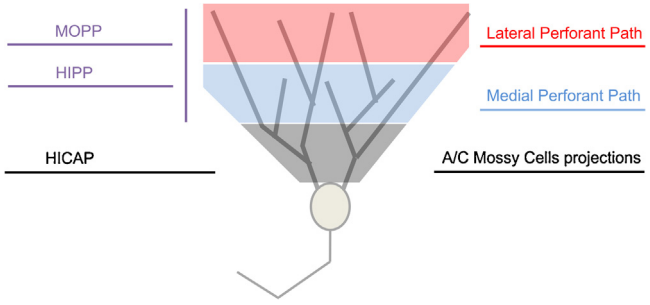


**Fig. 2.** Synaptic inputs to dendrites of mature granule cells. A schematic mature granule cell is represented. Dendrites of mature granule cells can be subdivided into three main regions according to the inputs they receive. In more distal dendrites, mature granule cells are contacted by axons from layer II of the entorhinal cortex, the lateral and medial perforant path coming from the medial and lateral entorhinal cortex. In the outer two-thirds, dendrites of mature granule cells also receive inhibitory inputs from GABAergic interneurons residing in the molecular layer (MOPP, molecular layer perforant path-associated cells) and the hilar region (HIPP, hilar perforant path-associated cells). In the most proximal dendrites, axons from associational/commissural (A/C) mossy cells make synaptic contacts. Inhibitory input from GABAergic interneurons from the hilar region (HICAP, hilar commissural-association pathway-related cells) is also received in the most proximal dendrites.

synaptic plasticity among immature and mature cells (see also below). Dendrites of mature granule cells has been described as passive linear integrators with a very strong attenuation of voltage signals (Krueppel et al., 2011). In consequence the backpropagating action potential amplitude seems to be severely attenuated in dendrites of mature cells and the amplitude of excitatory postsynaptic potentials (EPSPs) shows a steep decrease as it travels from dendrites to the soma. The contribution of single synapses to neuronal firing output is therefore relatively small. Moreover, mature granule cells seem to lack important active dendritic conductances and they also appear to lack dendritic spikes in response to synchronized synaptic inputs (Krueppel et al., 2011).

In addition to intrinsic membrane properties, GABAergic inhibition plays a key role in regulating the functional output of principal neurons. Even though GABAergic innervation takes place at early stages in a granule cell development, this innervation starts with a trophic function and is directed to the dendritic regions with slow kinetics. Perisomatic fast GABAergic inhibition, that exerts a powerful control on neuronal firing output, emerges only after cells reach three to four weeks of age (Esposito et al., 2005). But even granule cells of four weeks of age seem more likely to be recruited to fire action potentials by afferent stimulation than mature neurons,

which is due at least in part to a higher excitation/inhibition balance (Marin-Burgin et al., 2012). A recent study assessed in more detail the importance of GABAergic inhibition in mature granule cells capacity to fire action potentials after simultaneous electrical stimulation of medial and lateral perforant path *in vitro*. In conditions without pharmacological pre-treatment only 20% of the patched mature granule cells fired after afferent stimulation, though when blocking GABAergic inhibition all the cells were able to fire. Mature granule cells were classified as spiking or non-spiking according to their firing in conditions with intact inhibition but there are no apparent differences in the intrinsic and morphological characteristics of spiking and non-spiking cells. However the ratio of IPSC to EPSC amplitude differed markedly between both groups (Dieni et al., 2013). These results show the importance of GABAergic control of action potential output in mature granule cells.

Mature granule cells are not only tightly controlled by GABAergic inhibition, but they also contribute to the silencing of neighbouring mature cells by mechanisms involving feedback inhibition. Temprana et al. (2015) showed that immature granule cells of four weeks of age do not recruit and are not affected by GABAergic feedback inhibition. In stark contrast, mature granule cells exert a very powerful inhibition on surrounding mature neurons by means of parvalbumin positive GABAergic interneurons. Based on these results the authors suggest that granule cells could play different roles in pattern separation and completion. They propose that immature granule cells would have wide and unspecific receptive fields, while mature cells would sense more specific inputs and favour discrimination (Kropff et al., 2015).

## 3. Synaptic plasticity of mature granule cells

Functional synaptic plasticity, i.e. changes in the functional properties of synapses like the presynaptic release probability or modifications in the number or properties of postsynaptic AMPA-receptors, is considered as a standard cellular model of learning and memory (Takeuchi et al., 2014). The first description of the long-lasting potentiation of synaptic transmission, called nowadays long-term potentiation (LTP), involved the dentate gyrus (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973). However, after this pioneer work, some practical difficulties arose in subsequent attempts to induce LTP *in vitro* in the dentate in hippocampal slices. Consequently, the focus shifted to the very well investigated CA1 subfield as it is easier to induce LTP in this area than in the dentate. It has been argued that a very strong GABAergic inhibition significantly contributes to the constrained synaptic plasticity in the dentate (Arima-Yoshida et al., 2011; Wigstrom and Gustafsson, 1983). *In vivo*, synaptic plasticity has been quite extensively studied, however, strong induction protocols are often needed in order to elicit long-lasting changes in synaptic strength (Abraham et al., 2002; Frey and Frey, 2009; Pastalkova et al., 2006). Another issue is related to the measurement of the synaptic component of the potentiation. For instance, it is not rare that changes in the population spike, rather than changes in field-EPSP slope, are taken as an indicator of synaptic plasticity (Bergado et al., 2009; Frey et al., 1996; Gilbert and Mack, 1990; Kenney and Manahan-Vaughan, 2013). This latter measure, however, can be misleading since changes in population spike can be dissociated from synaptic changes like it was already reported in the first description of LTP (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973).

Early attempts to elucidate the role of mature and immature granule cells for the induction of LTP at perforant path-dentate synapses (Wang et al., 2000) took advantage of the differential distribution of granule cells across the granule cell layer according to their maturation (Crespo et al., 1986; Esposito et al., 2005). Thus, patch clamp recordings were performed from putative mature cells located towards the outer part of the layer and immature neurons in the inner layer close to the hilus. Mature granule cells did not show any LTP in normal ACSF, but in the presence of bicuculline half of the cells exhibited potentiation. This was different in young cells where LTP was always induced irrespective of GABAergic inhibition. Notably, even following dis-inhibition mature granule cells showed a higher induction threshold for LTP than immature neurons. Subsequent work used the immunoreactivity for polysialic acid neural cell adhesion molecule (PSA-NCAM, a marker of immature granule cells (Seki, 2002; Seki and Arai, 1993)), the dendritic morphology and the intrinsic membrane properties of the cells as criteria for classification. In the presence of bicuculline, mature granule cells presented a higher threshold for LTP induction than immature granule cells (Schmidt-Hieber et al., 2004). These results suggested that not only a stronger GABAergic inhibition was the underlying cause of the impaired synaptic plasticity in mature granule cells. With the help of retroviral birth-dating technique, the period of four to six weeks of age was identified as critical when immature granule cells exhibit decreased LTP induction thresholds and increased potentiation levels (Ge et al., 2007). It was proposed that elevated expression of GluN2B-containing NMDA receptors could be responsible for those differences, an idea that had its roots in earlier work (Snyder et al., 2001) and the well documented role of GluN2B in synaptic maturation (Erisir and Harris, 2003; Hestrin, 1992; Sheng et al., 1994). All of these comparative studies have been performed with stimulation of the medial perforant path. However, the dentate also receives prominent cortical input through the lateral perforant path (Kesner, 2007; Kesner, 2013; Witter, 2007) and medial and lateral perforant path synapses differ in their functional and plastic properties (Bramham et al., 1988; Bramham et al., 1991a,b; Colino and Malenka, 1993; Dahl et al., 1990; Hanse and Gustafsson, 1992; McNaughton, 1980; Witter, 2007). Also, in view of their relative and ordered positioning in the more medial or distal dendritic region and in view of the apparent lack of active properties of their dendrites (Krueppel et al., 2011), granule cells should be more easily excited by medial perforant path stimulation. All this raises the interesting possibility that the differences in the plastic properties of the lateral perforant path-granule cell synapses in granule cells of different maturation stages could be even more pronounced than the differences reported for the medial perforant path, due to the higher excitability of immature cells.

Finally, the plastic properties of the presynaptic output of mature granule cells, the mossy fiber synapse on CA3 pyramidal cells, are also constrained. Following maturation granule cells showed a much higher threshold for LTP induction and lower potentiation levels than younger cells at mossy fibers-CA3 synapses. Immature cells of four weeks were particularly sensible to theta burst stimulation and this enhanced plasticity was associated with a calcium T-type-like conductance (Gu et al., 2012).

## 4. Mature granule cells in learning and memory

At first glance it appears unlikely that mature granule cells based on their intrinsic properties, the strong GABAergic inhibition and the reduced synaptic plasticity play a major role in hippocampus-dependent learning. Indeed, several landmark studies showed that immature granule cells significantly contribute to learning and memory. Increases in the rate of neurogenesis, for example by exposing the animals to enriched environments or ablating the proapoptotic protein Bax selectively in neural stem cells, are accompanied by enhanced learning capabilities (Kempermann et al., 1998; Koo et al., 2003; Sahay et al., 2011a). On the other hand experimental manipulations decreasing neurogenesis, like prenatal stress exposure or overexpression of Bax in neuronal precursors, are associated with poor hippocampus-

dependent learning (Dupret et al., 2007; Koo et al., 2003; Lemaire et al., 2000). Complementary studies have evaluated the relative recruitment of immature and mature granule cells during learning and memory formation. In pioneering work, laboratory animals were injected with BrdU and were trained in a spatial task at different time points after the injection (Kee et al., 2007). A quantification of the ratio of activated neurons to the number of neurons of the same age, showed that young cells of around six weeks of age were preferentially recruited into spatial memory networks. When compared to "mature" granule cells, younger cells were two to four times more often engaged in the learned task. This disparity among granule cells was explained by the competitive advantage of immature cells due to their enhanced excitability and plastic properties (Kee et al., 2007). Stemming from this work it was proposed that mature granule cells, with a more stable connectivity, would be sensitive to features of memories that were formed when they were younger (Bischofberger, 2007). However, subsequent and more systematic analysis (Alme et al., 2010) did not provide definitive evidence for this hypothesis. Instead, during a restricted temporal window in the dentate a relatively small group of neurons, putative immature granule cells, was always active in response to many spatial stimuli, while the vast majority of cells were inactive most of the time contributing to the idea that after their critical period, immature cells become silent and unresponsive to environmental stimuli, *i.e.*, they become functionally retired (Aimone et al., 2010). The constant synaptic input from grid cells of the entorhinal cortex (grid cells fire action potentials at regularly spaced locations and serve to map the space, therefore a group of them is always active) together with a low firing rate of granule cells is thought to contribute to the generation of a large pool of unresponsive dentate neurons and neurogenesis could be a solution for keeping always a constant number of easily excitable granule cells (Lisman, 2011).

In contrast with the retirement idea a follow up study (Stone et al., 2011), using a more direct and precise approach than in previous work (Kee et al., 2007), came to the conclusion that after five weeks of age granule cells have equal chances to be integrated into memory networks irrespective of their age, which is not in strict correspondence with the reported transient period of enhanced plasticity and excitability (Stone et al., 2011). Separate cohorts of granule cells were labelled with thymidine analogues and their rates of integration into memory networks were assessed through the quantification of immediate early genes expression (Stone et al., 2011). This was technically at variance with the previous report (Kee et al., 2007) where a similar approach was employed, but where mature cells were identified by the neuronal marker NeuN. NeuN is expressed in granule cells just a few days after birth (Brandt et al., 2003) and it is therefore not an appropriate marker of granule cells maturity. This fact, contributed to an underestimation of the recruitment of "mature" granule cells. However the new findings (Stone et al., 2011) indicated that at least from the fifth until the tenth postnatal week (when granule cells are considered to have already reached maturity) there is no preferential recruitment of younger cells in spatial memory networks.

More recent work (Lemaire et al., 2012) did not find evidence of a critical time window for dendritic structural plasticity in granule cells after Morris water maze training. Granule cells dendrites and soma were profoundly modified as consequence of the spatial learning even when they were sixteen weeks old. Moreover, it was reported that ablation of mature granule cells that were eight or sixteen weeks old, but not the ablation of very young cells of one week of age, interfered with the learning of the spatial task. Later on the same group showed that both mature and immature granule cells are equally recruited in spatial memory encoding and retrieval (Tronel et al., 2015a). The experimental subjects received two thymidine analogues injections to label two different granule

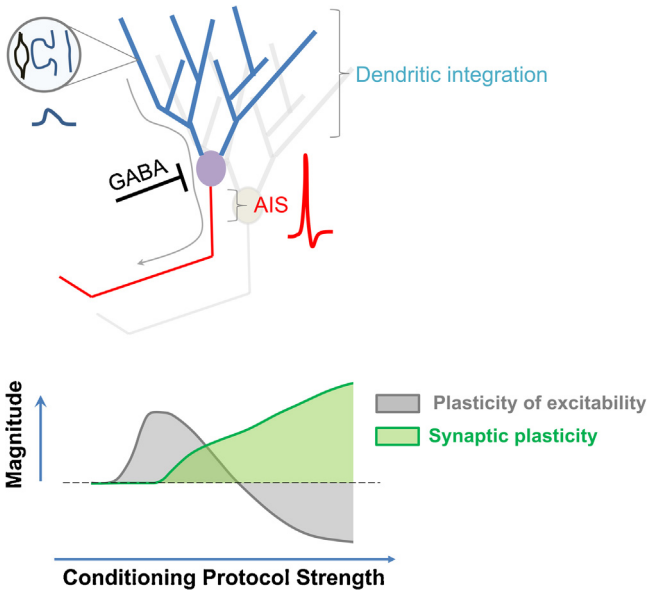


**Fig. 3.** Mature granule cell plasticity. Action potential output is not only influenced by the synaptic excitatory drive that a given neuron receives, but also by GABAergic inhibition and the intrinsic properties of the cell. All three levels of regulation together control plastic properties of mature granule cells. Plasticity of dendritic intrinsic excitability of mature granule cells as well as plasticity of the excitation/inhibition balance may play more dominant role in this particular cell type than in other hippocampal neurons. Mature granule cells might exhibit a lower threshold for changes in their excitability than for synaptic plasticity. Once the threshold for synaptic plasticity is reached, to moderate synaptic potentiation would correspond an increased excitability but high levels of synaptic potentiation would be accompanied with reductions in neuronal excitability. AIS: Axon initial segment. Schematic mature granule cells are represented.

cell cohorts in the same animal: a cohort of cells that was six weeks old before training and another cohort that was twelve weeks old. Subsequently the animals were trained in the Morris water maze and sacrificed at different time points. The results indicate that both, the encoding and retrieval, lead to a similar activation of immature and mature granule cells (as assessed by the expression of the immediate early gene Zif268), with no evidence of any preferential recruitment of immature cells (Tronel et al., 2015a).

Further indirect evidence for a role of mature cells in learning and memory comes from a recently published study (Ryan et al., 2015). Granule cells that were active during contextual fear conditioning were tagged with a fluorescence marker and channelrhodopsin. Those tagged cells were proved to be sufficient to elicit a fear response once re-activated through light. Very interestingly, the intrinsic electrophysiological properties of these 'engram-neurons' correspond to values characteristic of mature granule cells (*i.e.*, input resistance of 100–150 MΩ). All these results point to mature granule cells as active players in learning and memory.

## 5. Perspectives

As outlined above mature granule cells exhibit reduced excitability and a higher induction threshold for LTP and it has been therefore a matter of debate how these cells can be recruited in the formation of an engram. A long-standing hypothesis proposes that mature granule cells connectivity gets fixed during a plastic young stage and once they have matured their function is limited to contribute to the pre-existing memory trace. On the other hand it is also possible that mature granule cells are still plastic and that relatively under-investigated forms of plasticity under-

lie their contribution to newly formed memories (Fig. 3). Mature granule cells actually express voltage-dependent ion channels, like A-type potassium channels, in their dendrites (Serodio and Rudy, 1998; Sheng et al., 1992) that can be regulated in an activity-dependent manner (Monaghan et al., 2008; Tsaur et al., 1992). Given the low impact of synapses on neuronal firing output, due to the strong basal levels of dendritic voltage attenuation, changing the "EPSP-attenuation" levels by modifying dendritic excitability can plausibly more readily impact on the output of these cells than induction of synaptic potentiation. Indeed, we have recently found (Lopez-Rojas et al., 2016) that mature granule cells can increase their ability to fire action potentials in response to synaptic stimulation after weak but physiologically relevant conditioning protocols that did not even elicit any synaptic potentiation. Those changes are related to modifications in intrinsic dendritic excitability, most probably by modulation of A-type potassium channels allowing a more efficient voltage transfer from dendrites to the soma. Interestingly, with stronger induction protocols synaptic plasticity does occur and in these conditions intrinsic excitability changes according to the actual extent of synaptic potentiation. We therefore propose a plasticity-model for mature granule cells with a lower threshold for excitability changes and a higher induction threshold for synaptic plasticity (Fig. 3). These results suggest that intrinsic plasticity could underlie the role of mature granule cells in learning and memory. They also raise the question whether intrinsic changes can be seen as core elements of the engram. Another and not mutually exclusive possibility is that excitability changes reduce the threshold in mature granule cells for the induction of synaptic plasticity. Interestingly, it was recently reported that dopamine can decrease the threshold for LTP-induction in dentate granule cells, by means of functional down-regulation of A-type potassium channels (Yang and Dani, 2014). In addition, plasticity of GABAergic interneurons in the dentate gyrus is an area that has gained attention recently. Given the important role of inhibition on mature granule cells firing, the analysis of this topic could provide new insights into distinct functional properties of mature granule cells (Hadad-Ophir et al., 2014; Hainmuller et al., 2014). It is also unclear whether mature granule cells are indeed a homogeneous population. Some studies have addressed this issue by looking at potential differences among developmentally- and adult-born mature granule cells (Laplagne et al., 2007; Lemaire et al., 2012; Stone et al., 2011; Tronel et al., 2015b). Last but not least it is imperative to bridge the gap between *in vitro* electrophysiology and *in vivo* experimentation to address the functional relevance of excitability changes in mature granule cells for learning and memory in the intact alive animal.

Finally, emerging evidence suggests that maturation of granule cells is a key factor for mental health. An "immature dentate gyrus" has been associated with several neuropsychiatric pathologies such as schizophrenia and bipolar disorders (Hagihara et al., 2013). In animal models of such conditions, as well as in actual human patients, granule cells have been found to be in a predominant immature-like status: the rate of neurogenesis and the number of granule cells with an immature phenotype was increased, whereas the actual number of mature-like granule cells was reduced (Altar et al., 2005; Ohira et al., 2013; Walton et al., 2012; Yamasaki et al., 2008).

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