Critical periods regulating the circuit integration of adult-born hippocampal neurons

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Abstract

The dentate gyrus (DG) in the adult brain maintains the capability to generate new granule neurons life-long. Neural stem cell-derived new-born neurons are emerging for playing key functions in the way information is processed in the DG and then conveyed to the CA3 hippocampal area, yet accumulating evidence indicates that both the maturation process and the connectivity pattern of new granule neurons are not prefigured, but can be modulated by the activity of local microcircuits and, on a network level, by experience. Although most of the so-far described activity- and experience-dependent changes appear to be restricted to critical periods during the development of new granule neurons, it is becoming increasingly clear that the surrounding circuits may play equally key roles in accommodating, and perhaps fostering, these changes. Here, we review some of the most recent insights into this almost unique form of plasticity in the adult brain by focussing on those critical periods marked by pronounced changes in structure and function of the new granule neurons, and discuss how the activity of putative synaptic partners may contribute to shape the circuit module in which new neurons become finally integrated.

Key words: adult-born neurons, critical periods, synaptic plasticity, experience, circuit connectivity

Abbreviations:

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	brain-derived neurotrophic factor
CREB	cAMP response element binding protein
DG	dentate gyrus
EC	entorhinal cortex
EE	enriched environment
GABA	γ-Aminobutyric acid
LTP	long-term potentiation
ML	molecular layer
NMDA	N-methyl-D-aspartate
NR2B	N-methyl-D-aspartate receptor subtype 2B
POMC	pro-opiomelanocortin

Critical periods during the early development of adult-born DG neurons: the first two weeks

Once generated by transient-amplifying progenitor cells located in the sub-granular zone of the adult DG, immature neurons undergo a step-wise morphological and functional maturation process that gradually promotes their integration into the pre-existing DG network. Morphologically, this requires a continuum of structural changes involving the establishment of neuronal polarization, extensive neurite growth and branching, alongside with the formation and subsequent consolidation of synaptic structures (spines and axonal boutons) (Figure 1). Although the temporal evolution of these events and the maturation process of adult-generated neurons is possibly modulated by the age of the animal, very little is known on this aspect, in contrast to a well documented age-dependent decline in the overall rate of neurogenesis itself (Lee et al., 2012). In this manuscript we will therefore exclusively focus on studies largely conducted on young-adult rodents (about 2 to 4 months of age), in which the steps underlying newborn neuron maturation, synaptic integration and plasticity have been mostly investigated. These works collectively indicate that the maturation of adult-born neurons is a slow process occurring over the course of several weeks since the new neuron birth (Zhao et al., 2006), yet distinct periods of overt structural and functional plasticity have been identified that mark the achievement of key steps in the differentiation of new DG granule neurons. Right at the transition between transient-amplifying progenitor cells and post-mitotic new neurons, and continuing for the following few (1 to 4) days after birth, a pronounced peak of apoptotic cell death is observed in the sub-granular zone, reflecting the earliest of the critical periods of survival faced by a newborn granule neuron during its maturation stage (Sierra et al., 2010) (Figure 2). During this early period alone, more than 50% of the overall pool of newly-generated neurons is negatively selected via programmed cell death (Sun et al., 2004; Sahay et al., 2011), possibly indicating the existence of mechanisms of competition restricted to this very early stage within the neurogeneic niche. The surviving immature neurons thus enter another period marked by pronounced structural plasticity occurring shortly after axon specification (Zuccaro et al., 2014), between the end of the first and beginning of the second week of post-mitotic age, when the new neurons undergo considerable axonal elongation and

branching towards the CA3 region (Zhao et al., 2006). Around this time, one thicker process opposed to the newly-specified axon starts redirecting its growth towards the molecular layer (ML) of the DG, where it gives rise to the very first apical branches doomed to become the future dendrites (Zhao et al., 2006). Interestingly, the switch from the first to the second week of age in post-mitotic new neurons not only marks the morphological establishment of axon/dendrite polarity and the visible growth of neurites, but also the appearance of their first synaptic inputs, which are slow and GABAergic in nature, therefore believed to be dendritic in their origin (Esposito et al., 2005; Deshpande et al., 2013) (Figure 1). Before the onset of these early synapses, e.g. by day 3 after their generation, new-born neurons appear to be uniquely exposed to ambient GABA (Ge et al., 2006), yet at an even earlier step in the lineage (i.e. in transient-amplifying or type-2 cells) some extent of synaptic GABAergic input has been reported (Tozuka et al., 2005), suggesting the existence of highly dynamic processes regulating synapse formation/pruning in the transition towards post-mitotic cells. GABA signalling both in type-2 and early post-mitotic neurons is believed to exert a depolarizing action, and this lasts for almost the entire first two weeks of neuronal age owing to a high cytoplasmic chloride concentration in the new neurons (Ge et al., 2006). Disruption of this chloride concentration or deletion of GABA-A receptors during this early phase results in clear impairments in dendritic arborisation and synaptogenesis (Ge et al., 2006; Duveau et al., 2011), an effect which is at least in part mediated by activation of the transcription factor CREB (Jagasia et al., 2009), highlighting the essential role played by (tonic) GABA signalling from the very initial stages in new-born DG neurons. It may therefore be suggested that the earliest period in a new-born granule neuron life in which GABA signalling is critical for neuronal development (and presumably survival) covers the transition from the first to the second week of neuronal age (Figure 2). Supporting this notion, optogenetic manipulation of parvalbumin+ interneurons in the DG, which are considered to be amongst the main suppliers of ambient GABA within the neurogenic niche, alters the survival of immature neurons at the end of their first week of life (Song et al., 2013).

It is likely that these very same parvalbumin+ interneurons, alongside with Ivy/neurogliaform cells, also provide some of the first synaptic inputs onto new neurons once these mature into their second week of age, as revealed by electrophysiological and tracing experiments (Markwardt et al., 2011; Deshpande et al., 2013). At this stage, depolarizing GABA signalling exerts important yet somewhat different roles in young granule neurons, and in particular it appears to critically regulate the formation of new glutamatergic synapses. By utilizing POMC-GFP mice (in which GFP is driven by the pro-opiomelanocortin promoter and results in reliable GFP expression in immature DG neurons of approximately 10-12 days of age), Chancey et al. made the interesting observation that GABA-mediated synaptic depolarization in new neurons promotes their initial glutamatergic synaptic integration, an effect which is induced by the incorporation of AMPA receptors into "silent" NMDAR-only-containing synapses present at this stage (Chancey et al., 2013) (Figure 2). Importantly, this effect could be elicited both *ex vivo,* by stimulating protocols meant to enhance synaptic activity, and *in vivo* by brief (as short as 2 hours) exposure of the animal to environmental enrichment (EE) (Chancey et al., 2013), thus providing direct evidence for an early period of experience-dependent "unsilencing" of the first glutamatergic synapses in immature adult-born DG neurons. Interestingly, a recent work confirmed this narrow time-window of few days (i.e., 9-to-11 post-mitotic days) during the second week of age of the new neurons to be critical for regulating their maturation in response to experience (Alvarez et al., 2016), an effect which is reminiscent of earlier studies in which either EE or high-frequency stimulation of the medial perforant path leading to LTP induction in the DG *in vivo* produced a measurable increase in the survival of 1-to-2 week old new neurons (Bruel-Jungerman et al., 2006; Tashiro et al., 2007; Kitamura et al., 2010). In fact, short exposure to EE particularly during these days is sufficient to accelerate morphological maturation in new granule neurons, including their dendritic and spine growth and, ultimately, their glutamatergic synaptic integration into the pre-existing circuit (Alvarez et al., 2016) (Figure 2). Mechanistically, this requires the coordinated activation of mature granule neurons and the subsequent recruitment of parvabumin+ interneurons that in turn feed-back onto the immature new neurons (Alvarez et al.,

2016). Whether other microcircuits may play either similar or opposite roles in regulating the early maturation of new granule neurons is not yet clear, however this seems a likely possibility given that, at this developmental stage, the actual extent of presynaptic GABAergic interneuron activity can exert differential effects on immature neuron excitability, by either promoting action potential generation or shunting inhibition (Heigele et al., 2016), thereby suggesting that neuronal network-dependent modulation of GABA signalling may therefore produce very distinct effects on immature new neurons of this particular age. Intriguingly, modulatory cholinergic innervation arising from sub-cortical regions of the medial septum/nucleus diagonal band of Broca can be detected by tracing techniques already at this early stage of granule neuron development (Deshpande et al., 2013) (Figure 1), indicating that at least this type of long-range projection may also play an important role in the maturation of the young neurons, for instance by regulating the time interval during witch GABA exerts its depolarizing action (Campbell et al., 2010). Thus, GABA signalling during the first weeks of life of a new DG granule neuron mediates fundamental roles by promoting the early survival and initial incorporation of the neuron into local circuit modules.

Critical periods during the third and fourth weeks of life of a new DG granule neuron

By the end of the second/beginning of the third week of age the first glutamatergic inputs can be detected in adult-born granule neurons (Ge et al., 2006; Kumamoto et al., 2012; Chancey et al., 2014) (Figure 1). Interestingly, their origin has been identified by several recent studies to be the hilar mossy cells (Kumamoto et al., 2012; Deshpande et al., 2013; Chancey et al., 2014), which elaborated axons are known to provide translaminar excitatory innervation to both the ipsi- and contra-lateral DG. The onset of these glutamatergic synapses only shortly anticipates the morphological appearance of the first spines onto new-born neuron dendrites, which occurs around 16-18 days of age (Zhao et al., 2006), as well as the stable innervation by afferents originating from the entorhinal cortex (EC), which takes place only at the end of the third post-mitotic week (Deshpande et al., 2013; Chancey et al., 2014). Conspicuously, the temporal window during which these two (mossy cell and EC) main

excitatory inputs arise, i.e. between 14 and 21 days of neuronal age, matches with the previously described critical period of competitive survival mediated by NMDA receptors in adult-born DG neurons (Tashiro et al., 2006), which has been hypothesized to underlie at least some of the activity- and experience-dependent survival effects observed following, e.g., voluntary exercise, EE and spatial learning (Kempermann et al., 1997; Gould et al., 1999; van Praag et al., 1999) (Figure 2). Likewise, during this still immature stage (approximately between post-mitotic weeks 2 and 3) new neurons exhibit a lower threshold for the induction of long-term potentiation (LTP) than fully mature granule neurons, indicating that already at this stage, immature neurons are characterized by a somewhat pronounced plasticity of their newly-formed glutamatergic synapses (Wang et al., 2000; Schmidt-Hieber et al., 2004) (Figure 2). This is also the time when spine genesis steeply increases during the development of new-born neurons, and precisely at 21 post-mitotic days exposure to voluntary exercise significantly intensifies the motility of newly-formed spines (Zhao et al., 2006), an effect which might greatly facilitate their subsequent stabilization into/from multi-synaptic complexes in the ML, in which spines of both new and pre-existing granule neurons are (transiently) connected with the same afferent axonal bouton (Toni et al., 2007). Exposure to voluntary exercise (i.e., running) for the entire first 3 weeks of life of the new-born granule neurons also accelerates their dendritic spine growth, although this effect appears distinctly more pronounced in the temporal rather than the dorsal/septal hippocampus, likely reflecting different levels of basal network activity in these two regions which results in an overall intrinsically slower maturation pace of new neurons in the temporal DG (Piatti et al., 2011). Conspicuously, the effects of experience (in this case, EE) appear to also influence dendritic branching in new-born granule neurons. By taking advantage of a cranial window implant into the hippocampal fissure to chronically image retrovirally-labelled adult-born neurons *in vivo*, a recent study demonstrated that a period of over-branching that peaks by 21 days after cell birth is then followed by branch pruning to match the final dendritic tree complexity observed in fully mature new granule cells (Goncalves et al., 2016). Interestingly, EE provided from post-mitotic day 7 onwards induced an earlier (by post-mitotic day 17) and even greater addition of

new dendritic branches in new neurons, which on the other hand was counteracted by a more pronounced pruning during the following weeks, presumably as part of an homeostatic mechanism required to balance the final neuronal dendritic structure (Goncalves et al., 2016). Similarly, measurable dendritic pruning specifically in adult-born neurons was described in animals undergoing EC-perforant path stimulation to induce LTP in the DG, however this effect was only detected during a specific time window between 28 and 35 post-mitotic days (Beining et al., 2017), suggesting that the precise extent of dendritic remodelling induced by network activity and/or experience is strictly dependent on the maturational stage of the new neurons (Figure 2). The third week of a new neuron's life in the adult DG is therefore not only marked by an important period of enhanced structural and functional plasticity, in which the sequential onset of glutamatergic inputs of dual origin (mossy cells and EC) is mirrored by the development of dendritic spines, but it also identifies a critical period during which the effects produced by concurrent or even earlier experiences become manifest, in particular with respect to the synaptic integration process of the new neurons into the pre-existing circuitry. Notably, maturation of functional pre-synaptic axonal (mossy fiber) terminals in adult-born neurons also commences during their third week of age, around 17 post-mitotic days (Toni et al., 2008), concurrently with the formation of the first dendritic spines. This suggests the existence of a tight developmental coupling between the pre- and post-synaptic compartments in newly-generated neurons (Sun et al., 2013), which may be required to ensure their functional integration into pre-existing local networks.

The fourth week of age in adult-born DG neurons marks their transition into a period of particularly high excitability, yet as the neurons have by the end of this week established numerous contacts with their synaptic partners and thus have been functionally incorporated into local and hippocampal circuit modules (Figure 1 and 3), their excitability is believed to significantly modulate hippocampal information processing (Marin-Burgin et al., 2012; Nakashiba et al., 2012). Although 4-week old granule neurons are not yet fully mature, and the maturation of their synapses still progresses for additional weeks (Zhao et al., 2006; Toni et al., 2007; Toni et al., 2008), these immature

neurons can be reliably activated by an excitatory drive in acute brain slices (i.e., the stimulation of EC-derived perforant path fibres) owing to a transiently expressed high excitation/inhibition synaptic balance (Mongiat et al., 2009; Marin-Burgin et al., 2012) (Figure 2). Interestingly, 2-photon live Ca^{2+} imaging of the DG in awake, behaving mice showed that adult-born cells within this period of higher excitability are indeed more active than pre-existing mature neurons, although less spatially tuned (Danielson et al., 2016). Yet, their actual "recruitment" by EC fibres (in *ex vivo* preparations) seems to depend upon the actual strength of the imposed electrical stimulation suggesting that, in spite of their higher excitability, 4-week old granule neurons may still be characterized by a somewhat low cortical innervation (Dieni et al., 2016). Supporting this notion, tracing and ultrastructural experiments showed that EC innervation indeed keeps increasing until at least 12 weeks of age in adult-born granule neurons, alongside with their dendritic spine density (Toni et al., 2007; Vivar et al., 2012; Deshpande et al., 2013). Nonetheless, by 4 weeks of age the new neurons already receive a rich variety of local, subcortical and cortical inputs which identity is, to large degree, maintained until complete maturation is achieved (Vivar et al., 2012; Deshpande et al., 2013; Li et al., 2013) (Figure 3). Interestingly, with respect to dendritic spines the 4-week time point appears to match with the stage in which new neurons may maximally compete with pre-existing mature granule neurons for their pre-synaptic innervation in the ML. The first evidence in this regard originates from an ultrastructural study performed by Toni et al, in which the authors systematically assessed the density and morphology of spines in adult-born neurons of different ages (Toni et al., 2007). Intriguingly, neurons of 4 weeks of age were found to display a higher incidence of dendritic spines forming multi-synapse boutons, indicating that the newly-formed spines of immature neurons may preferentially associate with pre-existing synapses between (presumable) EC axonal boutons and spines of mature granule neurons (Toni et al., 2007). As the percentage of new spines being part of these multi-synaptic complexes significantly decreases with further maturation of the new neurons, these data strongly support the idea that a multi-synapse stage may be an important albeit transient step for the formation/stabilization of new spines and thus the stable integration of new neurons into the classic

"tri-synaptic" hippocampal circuitry. Mechanistically, this process might be mediated by the regulated (activity-dependent) release of neurotransmitters (Tashiro et al., 2006; Mu et al., 2015), gliotrasmitters released by perisynaptic astrocytic processes such as D-serine (Sultan et al., 2015) or even growth factors such as brain-derived neurotrophic factor, which is known to be required for spine growth in 4-week old new-born neurons (Bergami et al., 2008). However, these ultrastructural data also suggest the likely possibility that competition dynamics may exist between spines of newly-born and mature neurons, a concept which has been addressed by a recent study showing that transient spine elimination in mature neurons (achieved via chemogenetic manipulation) leads to a greater spine density (and successful stable integration) specifically in adult-born neurons of this immature age (McAvoy et al., 2016). To which extent similar or distinct competition mechanisms for post-synaptic targets may also regulate the maturation of efferent terminals in newly-born granule neurons is not completely understood (Yasuda et al., 2011; Lopez et al., 2012), however recent evidence suggests that by 4 weeks of age, the new neurons show heightened plasticity at their CA3 terminals synapsing onto pyramidal cells, which translates into a lower threshold for LTP induction and a higher amplitude of potentiation compared to either younger (3 weeks) or older (8 weeks) neuronal ages (Gu et al., 2012). This particular time of 4 weeks of age corresponds to the period when new neurons' terminals establish extensive connections with CA3 target cells (Toni et al., 2008; Restivo et al., 2015), thus supporting their heightened synaptic (and potentially structural) plasticity. Intriguingly, this capability of 4-week old neurons to efficiently drive distal CA3 targets appears opposed to a developmentally delayed activation of proximal GABAergic interneurons located in the DG, leading to a somewhat poor activation of feedback loops onto mature granule cells (Temprana et al., 2015). As new neurons mature, their capability to recruit (and respond to) inhibitory feedback loops also increases (Temprana et al., 2015; Drew et al., 2016), thus creating the presumed conditions for exiting their own critical period of higher excitability (Marin-Burgin et al., 2012).

Periods of enhanced synaptic plasticity in adult-born granule neurons older than 1 month

During their second month of life, adult-born DG neurons continue their maturation process until acquiring structural and functional features that, around 8 weeks of age, render them virtually undistinguishable from pre-existing granule neurons (Laplagne et al., 2006; Zhao et al., 2006; Toni et al., 2007; Mongiat et al., 2009). Yet, a 2-week long time-window between 1 and 1.5 months after their cell birth defines a classic critical period during which these neurons display enhanced plasticity at their post-synaptic sites (Ge et al., 2007) (Figure 2), which is somewhat mirroring (albeit with a slight delay) the transient heightened plasticity occurring at their output synapses (Gu et al., 2012). In fact, specifically during this period, new neurons respond to high frequency stimulation of the medial perforant path with a considerably higher potentiation of their synaptic efficacy (LTP), which is mediated by a developmentally-regulated expression of NR2B containing NMDA receptors (Ge et al., 2007; Kheirbek et al., 2012). This extent of synaptic plasticity is highly reminiscent of classic critical periods of plasticity during early postnatal development, which have been proposed to underlie neural circuit shaping in an activity- and experience-dependent manner (Maffei and Turrigiano, 2008; Takesian and Hensch, 2013). Intriguingly, this same period of enhanced synaptic plasticity in adult-born neurons matches with the time window during which they start becoming maximally recruited into hippocampal memory networks (Stone et al., 2011) (Figure 2), an effect which may be greatly facilitated by their heightened synaptic plasticity, although this degree of plasticity would not necessarily support their preferential integration when compared with pre-existing granule neurons (Kee et al., 2007). Overlapping with this same period is also a window during which experience may induce a reorganization of the pre-synaptic connectivity of adult-born neurons in an input-specific manner. Experiments conducted utilizing a rabies virus-based tracing technique have indeed shown that the pattern of synaptic innervation onto adult-born neurons is influenced by a combination of EE and running (in contrast to a somewhat marginal rewiring induced by running alone) (Deshpande et al., 2013; Bergami et al., 2015; Vivar et al., 2016), yet the extent and stability of these modifications appear to be differentially adjusted according to the type of synaptic input, with EC inputs amongst those few changes being retained even after returning the

mice to standard housing for several additional weeks (Bergami et al., 2015). Interestingly, the measured increase in EC inputs was mirrored by a corresponding increase in mushroom dendritic spines in EE-exposed adult-born neurons, supporting the notion that EE alone promotes spine morphogenesis and stabilization around this age (Zhao et al., 2014) (Figure 2). Lastly, a substantial portion of the traced synapse remodelling induced by EE involved distinct types of GABAergic inputs, which changes were, however, largely transient in nature (Bergami et al., 2015). These data add up to previous reports indicating that certain classes of GABAergic (e.g., parvalbumin-expressing) interneurons in the adult hippocampus respond differentially to specific experiences with pronounced but reversible forms of synaptic plasticity having direct implications for circuit information processing and cognition, including learning and memory (Donato et al., 2013; Pieraut et al., 2014). Thus, it is tempting to speculate that while one the one hand DG/hippocampal interneurons recruited by specific experiences might modulate (e.g., facilitate or even accelerate) the final integration steps of adult-born neurons into the pre-existing network, on the other they may regulate how the connectivity pattern of the new cells becomes stabilized once sculpted by experience. Inhibitory interneuron plasticity and the selective interaction between different types of interneurons and principal neurons are emerging as key players in regulating circuit development during early postnatal critical periods (Takesian and Hensch, 2013). Whether and to which extent the same principles also hold true for neurogenic circuits in the adult hippocampus is incompletely understood, however it is becoming increasingly clear that GABAergic interneuron activity controls several critical periods of plasticity in adult-born neurons, and therefore may play equally key roles in accommodating the experience-dependent changes that shape the evolving connectivity pattern of a new granule cell.

Concluding remarks

Despite growing evidence for an important role played by adult-born DG neurons in circuit function and information processing, still little is known about the rules that govern the incorporation

of these new neurons into the pre-existing network. Current evidence suggests that their synaptic integration process is tightly regulated by a progression of critical periods that not only shapes the morphological development of these cells, but also sets the pace for their functional maturation (Figure 2). Recent advances in imaging, tracing and optogenetics techniques have begun to reveal the existence of additional periods during which the survival and synaptic plasticity of new granule neurons is regulated in an activity- and experience-dependent manner. The emerging picture suggests that the onset and termination of many of these periods during the development of the new neurons might be controlled by the concerted activity of microcircuits, as evidenced by the key role played by (but not restricted to) DG parvalbumin interneurons. Yet, the rich variety of interneuron types in the DG (and in the rest of the hippocampus) raises the questions whether and how their specific patterns of innervation may regulate the experience-dependent maturation of adult-born granule neurons (Figure 3). Finally, it will be important for future studies to continue dissecting the exact contribution of other key partners in potentially shaping the evolving connectivity of adult-born neurons, as for instance mossy cells, which involvement in spatial memory encoding and pattern separation has been recently proposed (Danielson et al., 2017; GoodSmith et al., 2017; Senzai and Buzsaki, 2017).

Funding

This work was supported by the European Research Council (ERC-StG-2015, grant number 67844) to M.B.

Conflict of interest

No potential conflicts of interest were disclosed.

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Figure legends

Figure 1: Development of afferent inputs and efferent mossy fiber outputs in adult-born DG granule neurons. The upper panel illustrates the morphological lineage progression from a radial glia-like neural stem cell to a mature new granule neuron. Depicted structural changes are accompanied by the main evolving pre- and post-synaptic connectivity of newly-born granule neurons. At very early time points, the immature granule neurons are synaptically silent and only responsive to ambient GABA released by parvalbumin+ interneurons. During their second week of age they start receiving synaptic inputs, at first of GABAergic nature mediated by local interneurons (slow GABA), closely followed by glutametergic and cholinergic inputs from hilar mossy cells and projections arising from septal neurons, respectively. Finally, at later stages other classes of interneurons convey fast GABAergic signals, while glutamatergic inputs from the EC impinge onto granule cell dendrites. Secondary inputs originating from, e.g. mammillary bodies, subiculum, other hippocampal and sub-cortical areas are not depicted here. The bottom panel shows the maturation of adult-born neuron axonal terminal main outputs. Mossy fibers first innervate CA3 target cells while only in a second moment they are believed to stably connect to proximal targets (i.e., mossy cells and DG interneurons).

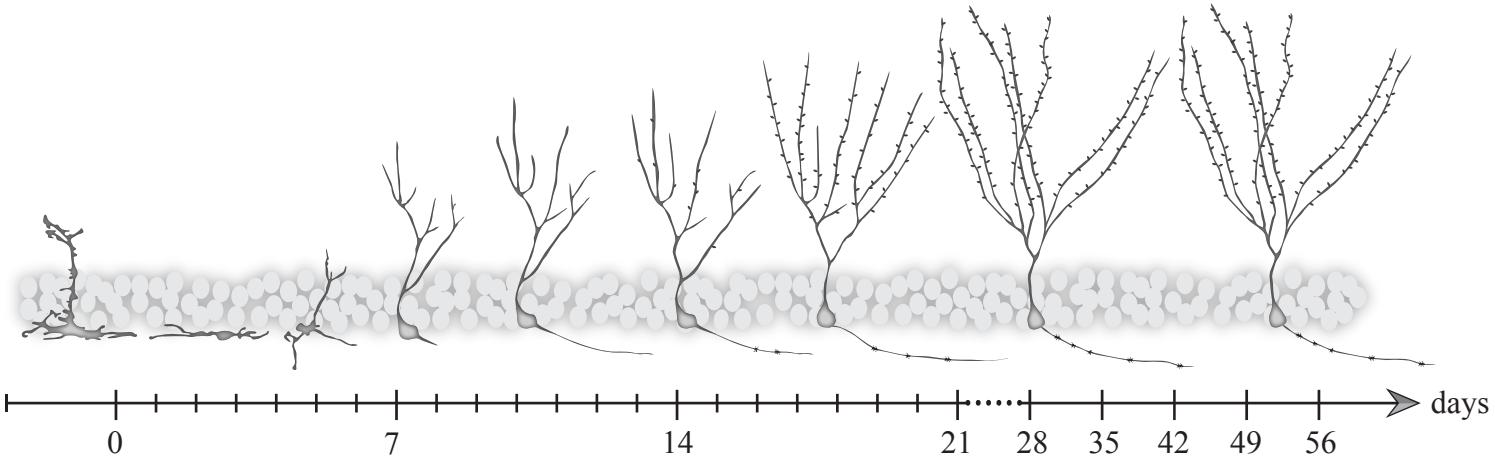
Figure 2: Critical periods regulating the survival, maturation and functional integration of a new DG granule neuron. The upper panel shows the time course of morphological maturation of a newly-generated granule neuron. Early and late developmental stages are regulated by critical periods in which neuronal survival is regulated via programmed cell-death and depends upon signalling initiated by neurotransmitters and growth factors (GABA, NMDA and BDNF-TrkB mediated signalling). Highlighted in red are the periods in which survival is modulated by network activity or experience (i.e., EE, exercise, learning). In the middle panel, the periods of highest structural plasticity during the development of the new neuron are shown. These include axon specification, periods of extensive neurite elongation, dendritic branching and maturation of synaptic terminals. A

growing number of activity- and experience-dependent changes affecting these periods of structural plasticity are reported in red colour. The lowest panel depicts the critical periods of synaptic plasticity of a new-born neuron and the changes (in red) potentially induced by network activity/experience.

Figure 3: Connectome of a fully integrated adult-born DG granule neuron

Cartoon summarizing the overall connectome of a newly-gerated granule neuron (in red) by several weeks after its generation, when synaptic maturation has been achieved. The cartoon illustrates the main inputs arising from local (DG) neurons, including mossy cells and several classes of GABAergic interneurons, as well as innervation from neurons located in the CA3/CA1 hippocampal sub-regions. On the left side the main long-range inputs originating from several cortical and sub-cortical areas are illustrated. With regard to synaptic outputs, the new granule neuron establishes connections with CA3 pyramidal neurons, mossy cells, and several GABAergic interneurons distributed between the hilus and the CA3 area.

Figure 1



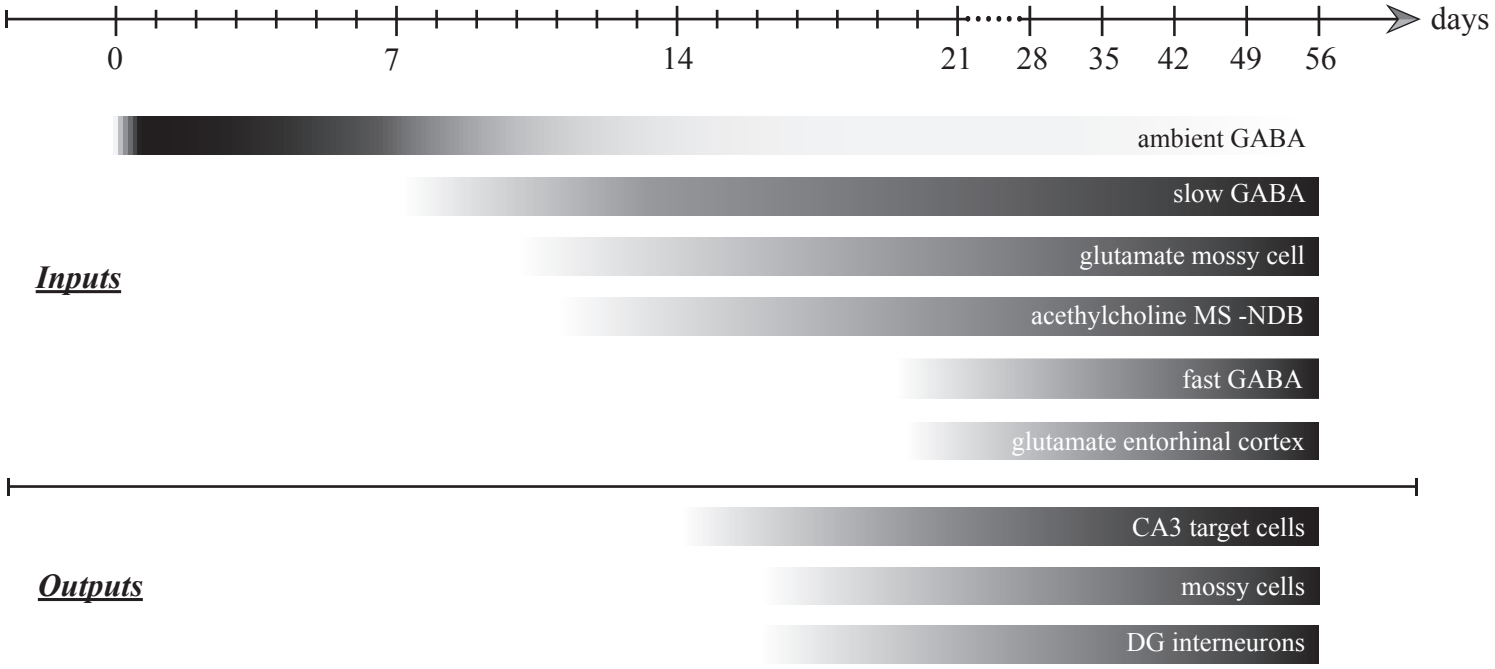
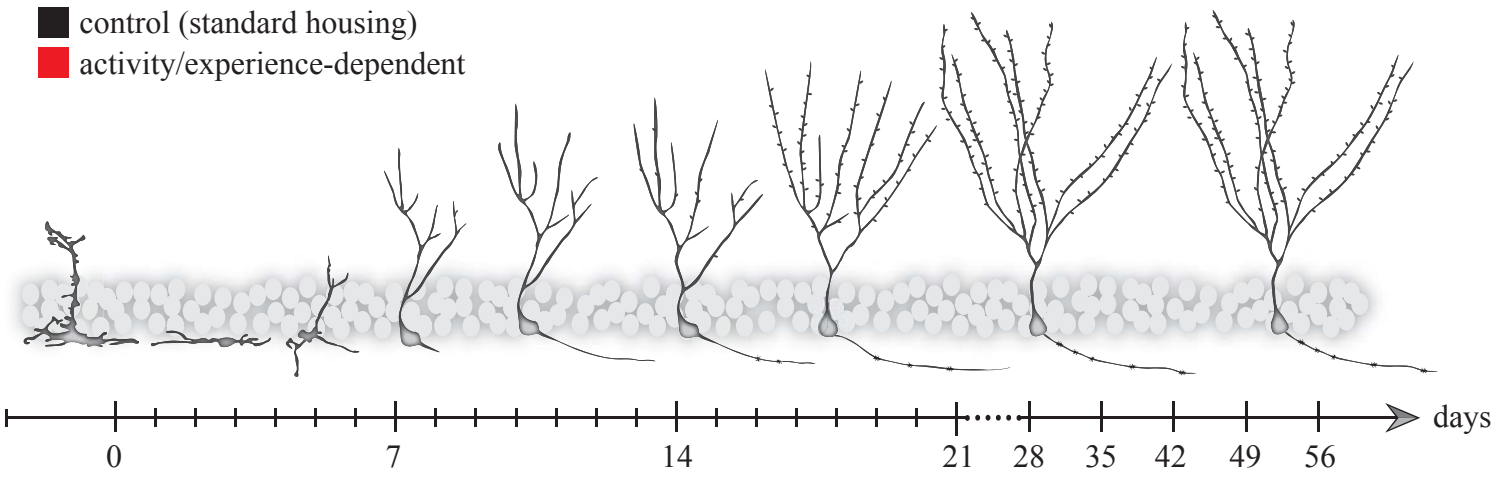

0
7
14
21
28
35
42
49
56
days
ambient GABA
slow GABA
glutamate mossy cell
Inputs
acethylcholine MS -NDB
fast GABA
glutamate entorhinal cortex
CA3 target cells
Outputs
mossy cells
DG interneurons

Figure 2



apoptosis

GABA

NMDAR

Survival

TrkB

running

enriched environment

high frequency stimulation

axon/dendrite specification

axon and dendrite elongation

max. dendritic branching

maturation of axonal terminals

Structural plasticity

spinogenesis

maturation

enhanced dendritic branching

pruning

spine motility

mushroom spines

presynaptic connectivity remodeling

higher excitability

lower threshold for LTP

Functional plasticity

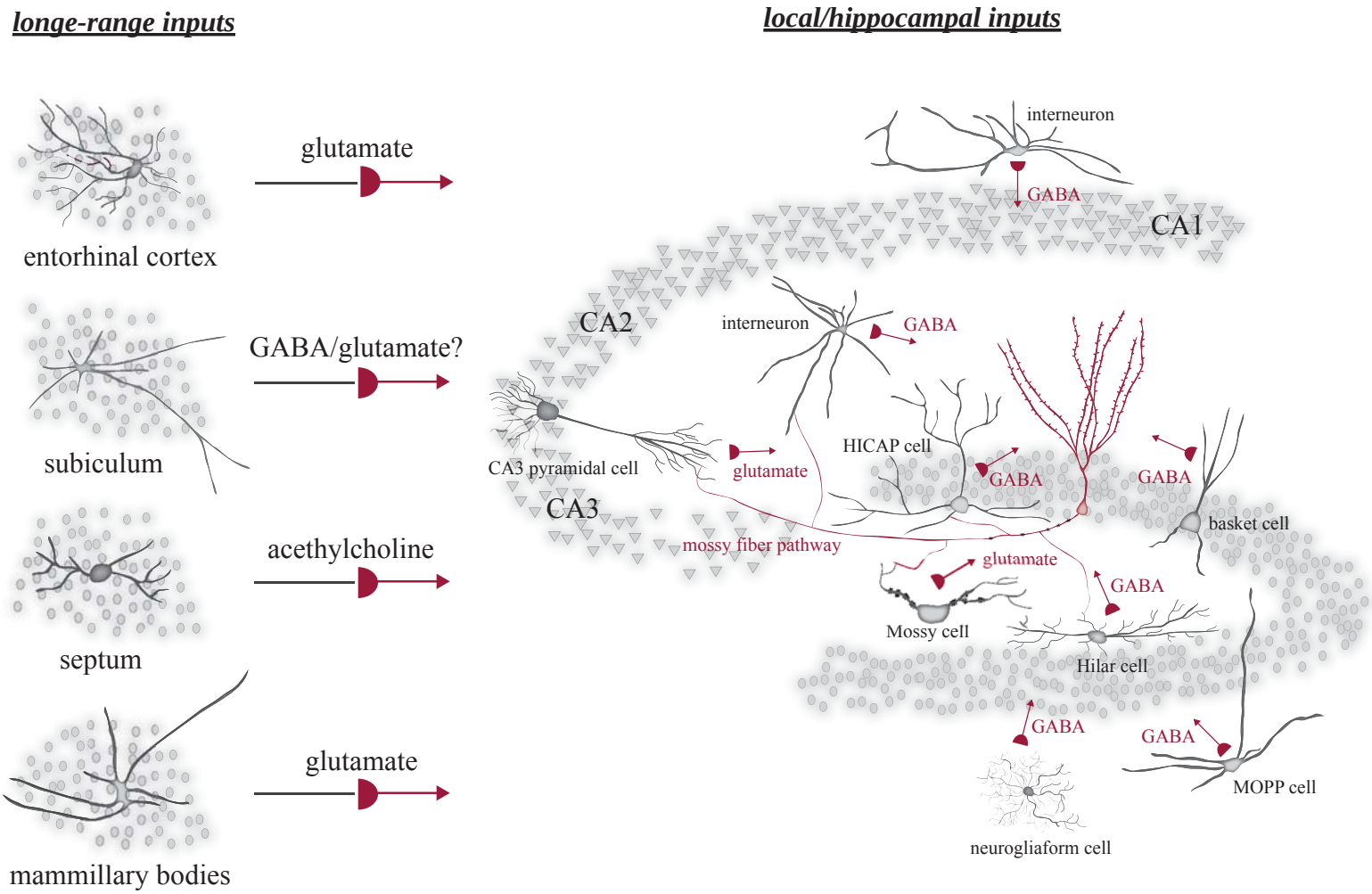
enhanced NR2B-dependent LTP

network recruitment

synapse silencing/priming

short term plasticity

Figure 3


longe-range inputs
local/hippocampal inputs
glutamate
entorhinal cortex
GABA/glutamate?
subiculum
acethylcholine
septum
glutamate
mammillary bodies
interneuron
GABA
CA1
CA2
interneuron
GABA
HICAP cell
CA3 pyramidal cell
glutamate
GABA
GABA
CA3
basket cell
mossy fiber pathway
glutamate
GABA
Mossy cell
Hilar cell
GABA
GABA
MOPP cell
neurogliaform cell