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REVIEW

Role of adult-born granule cells in the hippocampal functions: Focus on the GluN2B-containing NMDA receptors

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Abstract
Adult-born granule cells constitute a small subpopulation of the dentate gyrus (DG) in the hippocampus. However, they greatly influence several hippocampus-dependent behaviors, suggesting that adult-born granule cells have specific roles that influence behavior. In order to understand how exactly these adult-born granule cells contribute to behavior, it is critical to understand the underlying electrophysiology and neurochemistry of these cells. Here, this review simultaneously focuses on the specific electrophysiological properties of adult-born granule cells, relying on the GluN2B subunit of NMDA glutamate receptors, and how it influences neurochemistry throughout the brain. Especially in a critical age from 4 to 6 weeks post-division during which they modulate hippocampal functions, adult-born granule cells exhibit a higher intrinsic excitability and an enhanced long-term potentiation. Their stimulation decreases the overall excitation/inhibition balance of the DG via recruitment of local interneurons, and in the CA3 region of the hippocampus. However, the link between neurochemical effects of adult-born granule cells and behavior remain to be further examined.

1. Introduction

Adult hippocampal neurogenesis (AHN) is a phenomenon that has been recently discovered, as it was first mentioned in the literature in 1965 (Altman and Das, 1965). It was demonstrated that neurogenesis occurs in the DG under physiological conditions throughout life, and can be enhanced by living in an enriched environment (Kempermann et al., 1998).

AHN is the process by which adult-born granule cells are continuously generated from a residential population of neural precursors (Alvarez-Buylla and Lim, 2004; Gage and Temple, 2013; Ming and Song, 2011), found in the subgranular zone of the dentate gyrus (DG) in the hip-

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pocampus. The hippocampus is composed of several interconnected subregions, including the DG and the cornu ammonis (CA). Only a small number of adult-born granule cells are added in each DG: about 700 neurons per day in adult humans (Boldrini et al., 2018; Eriksson et al., 1998; Kempermann et al., 2003; Spalding et al., 2013) and a few thousand per day in mouse and rat hippocampus (Bordiuk et al., 2014; Cameron and McKay, 2001; Jacobs et al., 2000), depending on numerous environmental factors such as the gender, diet or exercise. Indeed, many studies have shown sex differences in AHN in numerous mammalian (Koss and Frick, 2017), which are linked to steroid hormones (Duarte-Guterman et al., 2015). However, how neurogenesis differs between sexes is still under debate (Chow et al., 2013; Duarte-Guterman et al., 2015; Hillerer et al., 2013). Diet is also a major influence on AHN (Heberden, 2016). Dietary restriction increases the number of neurons added per day in the DG in mice and in rats (Lee et al., 2000, 2002). Conversely, overnutrition or high-fat diets decrease this number (Lindqvist et al., 2006; van der Borght et al., 2011). Another environmental factor influencing the number of neurons added daily in the DG is voluntary exercise. Voluntary exercise has been shown to double the number of surviving adult-born neurons in the hippocampal circuitry in mice (van Praag et al., 1999). In a trial with elderly humans, aerobic exercise increased selectively anterior hippocampal volume; this increase being associated with greater serum levels of BDNF, a mediator of neurogenesis in the DG (Erickson et al., 2011). Thus, the number of neurons added per day is multifactorial and regulated by many factors, which are important to consider.

Yet, this minor population of the hippocampus is able to influence specific brain functions to ultimately impact behavior. In particular, the role of the hippocampus in memory has been extensively studied for decades (Danielson et al., 2016; Deng et al., 2010; Sheldon and Levine, 2016; Song et al., 2012a). The understanding of memory organization was revolutionized after the myriad discoveries obtained from the classic case report of a patient known as H.M., who was admitted to surgery to cure his epilepsy. The bilateral hippocampal lesions he underwent led to a persistent impairment to form new memories; yet, he retained intact memory for events prior to the surgery (Scoville and Milner, 1957, 2000), or procedural memory (Squire, 2009). Then, studies in monkeys suggested that damage to the hippocampal formation (including perirhinal cortex) delayed retention of object discriminations, concurrent discrimination (Zola-Morgan et al., 1989a, 1989b) and impaired recognition memory, but not associative memory (Zola et al., 2000). Other experiments narrowed the role of the hippocampus as contributing to specific forms of memory (Squire, 1992). Indeed, studies in rodents with hippocampal lesions indicated that the hippocampus is involved in memory retrieval (Fortin et al., 2004), spatial discrimination (Clark et al., 2005) and working memory (Gilbert and Kesner, 2006). As previously mentioned, the integration of adult-born granule cells plays a crucial role in learning and memory. In two studies contributing to this notion, inducible transgenic strategies were used either to increase (Sahay et al., 2011b) or to suppress AHN (Dupret et al., 2008). Mice with increased AHN showed an increased ability to context discrimination in a pattern separation task. Conversely, suppressing AHN in mice impaired their ability to retain spatial relational memory (Dupret et al., 2008). Likewise, the suppression of AHN due to focal X-irradiation of newborn neurons induced a deficit in pattern separation (Clelland et al., 2009), but it did not affect learning in very different contexts (Clelland et al., 2009; Dupret et al., 2008). Other studies have revealed the inconsistency of the adult-born granule cells' role in learning and memory (Cameron and Glover, 2015; Deng et al., 2010). This inconsistency could be explained by the less complex forms of learning studied. These studies did not use the same specific ablation system of AHN and did not evaluate these complex forms of learning or memory (Cameron and Glover, 2015; Deng et al., 2010). The hippocampus is also a key region in mood regulation (Anacker and Hen, 2017). Patients suffering from depression have a reduced hippocampal volume (Campbell et al., 2004; Frodl et al., 2006; Videbech and Ravnkilde, 2004). Moreover, studies in rodents have demonstrated the functional dissociation along the dorsoventral axis of the DG: ventral hippocampal lesions affect mood regulation, while dorsal hippocampal lesions affect memory function (Bannerman et al., 2003; Fanselow and Dong, 2010; Pothuizen et al., 2004; Wu and Hen, 2014). Chronic antidepressant drug treatments stimulate AHN proliferation, survival and neuronal differentiation (Banasr et al., 2004; Malberg et al., 2000; Santarelli et al., 2003; Wang et al., 2008). In mouse models of anxiety/depression, neurogenesis ablation partially suppresses antidepressant effects and affects several behavioral tasks, including notably the Novelty Supressed Feeding paradigm (David et al., 2009; Mendez-David et al., 2013; Perera et al., 2011; Santarelli et al., 2003; Surget et al., 2008; Tsai et al., 2015). Thus, stimulation at each step of AHN is considered necessary to achieve a complete response for antidepressant treatment (Anacker and Hen, 2017; Mendez-David et al., 2013). These data demonstrated that AHN affects hippocampal functions.

This review focuses on how adult-born granule cells influence hippocampal functions by their unique characteristics and aims to summarize data on neurochemistry of adult-born granule cells and their functions. In particular, we focus on a specific element of adult-born granule cells: the GluN2B subunit of the *N*-methyl-D-aspartate (NMDA) glutamate receptor. First, we will focus on the electrophysiological properties of the adult-born granule cells. We note that there is a critical window during which adult-born granule cells have enhanced plasticity, especially through the GluN2B subunit expression of their NMDA receptors. Second, we will highlight how adult-born neurons impact brain function during this critical period, as well as the role the GluN2B-containing NMDA glutamate receptors play in these brain functions. Third, we will describe adult-born granule cells' integration into the hippocampal circuitry. Finally, we will discuss neurochemical mechanisms affected by the AHN and that are linked to behavior regulation.

2. Adult-born granule cells possess distinct electrophysiological properties

First of all, adult-born granule cells are neurons with unique properties throughout their developmental stages (Ming and Song, 2011). Once mature, they migrate into the

granular layer of the DG. Within the adult-born granule cell population, there are different subpopulations depending on their age. Beyond 6 weeks post-division, adult-born granule cells become indistinguishable from mature granule cells in terms of physiological and electrophysiological properties (Ge et al., 2007). However, studies have shown that before 6 weeks post-division, adult-born granule cells differ substantially from mature granule cells, especially from an electrophysiological point of view. Two distinguishable populations with distinct electrophysiological properties have been identified: one up to around 3 weeks post-division, and another from 4 to 6 weeks post-division. Up to 3 weeks post-division, granule cells have a depolarizing response to GABA as occurred during the development process (Wang and Kriegstein, 2009). Four to 6-week-old granule cells display higher intrinsic excitability. This seems specifically due to the presence of the GluN2B subtype in their NMDA receptors subunit composition.

2.1. Up to approximately three weeks post-division, adult-born granule cells are depolarized by GABA

As soon as they have divided, adult-born granule cells are exposed to ambient GABA, which can produce a tonic current before any synaptic activation is detected (Ge et al., 2006). Then, from 2 weeks post-division onward, they receive an initial GABAergic spontaneous postsynaptic current inducing low frequency as well as long rise and decay times (Esposito et al., 2005). This GABAergic input comes from local GABAergic interneurons (Liu et al., 1998). The same phenomenon was observed in postnatal development in granule cells (Hollrigel and Soltesz, 1997). These GABAergic spontaneous postsynaptic currents are due to $GABA_A$ receptors, as they were completely blocked by a selective $GABA_A$ receptor antagonist, bicuculline (Esposito et al., 2005). The same results were obtained with another $GABA_A$ receptor antagonist, SR95531 (Overstreet-Wadiche et al., 2006). Adult-born granule cells are akin to neurons during brain development (Ben-Ari, 2002; Chen et al., 1996; LoTurco et al., 1995; Owens and Kriegstein, 2002) in that GABAergic input also enhances depolarizing tonic currents. This GABAergic depolarization is concomitant with DCX expression, which labels adult-born granule cells aged up to about 3 weeks (Heigele et al., 2016), indicating that this phenomenon is restricted to this timing. Perforated-patch recordings confirmed depolarized GABA responses in adult-born granule cells (Overstreet-Wadiche et al., 2005). Tonic currents were highlighted in this study by using a specific GABA transporter inhibitor, NO-711, which exacerbates the depolarization. By contrast, adult-born granule cells tonic currents were abolished by using a selective $GABA_A$ receptor antagonist, bicuculline; this demonstrated that $GABA_A$ receptors, as GABA-activated chloride channels (Olsen and Tobin, 1990), are responsible for the depolarizing effect of GABA (Ge et al., 2006). In order to obtain a depolarizing effect with an opening of chloride channels, chloride ions need to present an efflux from the cells. Contrarily, the opening of such channels in mature granule cells leads to the opposite effect: a chloride influx. Adult-born granule cells possess high cytoplasmic chloride ion contents (Delpire, 2000; Owens and Kriegstein, 2002; Payne et al., 2003) owing to high levels of NKCC1 (Na-K-Cl cotransporter 1) expression. These GABAergic tonic currents were not demonstrated to induce action potentials. However, they are likely to participate in maintaining a resting membrane potential in a less hyperpolarized state corresponding to levels that enable the generation of action potentials (Ben-Ari, 2007; Chancey et al., 2013). As a consequence, the resting potential of adult-born granule cells is higher than in mature granule cells. The measure revealed a value of approximately −48 mV in the earliest stages and a value of approximately −78 mV in fully differentiated adult-born granule cells (Esposito et al., 2005; Mongiat et al., 2009). This negative shift in the resting potential during development participates in the shift in the reversal potential of the GABA-mediated chloride currents (Chen et al., 1996). These particular GABAergic currents seem to be crucial; they have been demonstrated to be necessary in the normal maturation of adult-born granule cells regarding their dendritic development (Ge et al., 2006).

By the third week post-division, GABA becomes hyperpolarizing through a chloride influx into neurons (Brumback and Staley, 2008; Ge et al., 2006; Payne et al., 2003; Rivera et al., 1999). This change is mainly due to differential neuron expression in the cotransporters KCC2 (K-Cl cotransporter 2) and NKCC1. Immunohistochemical studies revealed that, at this time, adult-born granule cells express higher levels of the chloride exporter KCC2 and lower levels of NKCC1. Even if the selectivity of KCC2 and NKCC1 antibodies could be questioned (Lytle et al., 1995), the mRNA levels and the mRNA silencing of the NKCC1 tend to confirm these immunohistochemical observations (Ge et al., 2006; Rivera et al., 1999). Other elements can participate in the alteration of the effect of GABA in granule cells. Particularly, this timing also corresponds to the onset of glutamatergic input to these cells (Esposito et al., 2005). During the same period, GABAergic spontaneous postsynaptic currents with fast kinetics appear and progressively replace the ones with slow kinetics (Esposito et al., 2005). This increase in the kinetics is also found in postnatal development in granule cells (Hollrigel and Soltesz, 1997). Altogether, for these 3 first weeks post-division, it seems that adult-born granule cells recapitulate the steps observed during the postnatal development.

2.2. From four to six weeks post-division, adult-born granule cells exhibit enhanced plasticity

Excitability, or the ability of a neuron to generate an action potential, is a critical point considering that action potentials are the most common way a neuron propagates information. In one study (Marin-Burgin et al., 2012), hippocampal slices were prepared 4 weeks after the retroviral labeling of adult-born granule cells to express a red fluorescent protein, in order to target 4-week-old neurons in mice. Current pulses ranging from 5 to 150 μA (duration 100 μs) were applied on the molecular layer of the DG, where the perforant path axons from the entorhinal cortex connect onto spines and dendrites of granule cells. By using time-lapse calcium imaging, the authors observed that the number of active immature and mature granule cells

increased with stronger electrical stimuli. Each stimulus was able to elicit a higher number of spikes in immature granule cells as compared to mature ones, suggesting that immature neurons require weaker inputs to trigger a spike (Marin-Burgin et al., 2012). In most mature neurons, spikes are generated in response to excitatory postsynaptic currents (EPSCs), activating Na^+ voltage-dependent channels (Vacher et al., 2008). By contrast, in rat hippocampal slices, current stimulations below the threshold for Na^+ action potential initiation (pulse duration 200-μs at a frequency of 0.05 Hz) generated transient low-threshold spikes (Schmidt-Hieber et al., 2004), which are membrane depolarizations generated by the transient Ca^{2+} current (Puil and Carlen, 1984; Wang et al., 1991). These low-threshold spikes have been demonstrated to be Ca^{2+} dependent. Indeed, these low-threshold spikes were insensitive to 1 μM tetrodotoxin, a Na^+channel blocker, but were blocked by 50 μM Ni^{2+}, an inhibitor of calcium channels, showing that they were independent of Na^{2+}, but mediated by Ca^{2+} channels (Schmidt-Hieber et al., 2004). Altogether, it seems that 4-week-old neurons require weaker input to trigger a spike than mature granule cells due to Ca^{2+} currents.

Even if excitability of 4-to-6-week-old adult-born granule cells is higher than the excitability of mature granule cells, they still represent only a small subpopulation within the granule cells of the DG. Then, the question becomes whether and how this minor subpopulation is able to modulate the excitability of the whole DG. In order to begin to address this question, one study assessed the effect of AHN ablation on perforant-path responses, since this path from the entorhinal cortex is the major input to the DG. X-ray irradiation, known to suppress AHN, decreased field evoked responses following a perforant path stimulation (Lacefield et al., 2012). Likewise, excitatory postsynaptic potentials and population spike amplitude were analysed in X-ray irradiated mice after a spatial learning behavioral experiment. Irradiated mice also had decreased responses to perforant path stimulation (Park et al., 2015). The opposite approach was also employed: DG excitability was examined in mice with increased adult neurogenesis (Ikrar et al., 2013). Such an increase was obtained with the ablation of Bax, a pro-apoptotic gene, in neural progenitors (Sahay et al., 2011a). In view of the previous results (Lacefield et al., 2012; Park et al., 2015), increasing AHN would be expected to increase the excitability of the DG. However, using fast voltage-sensitive dye imaging, a decrease in DG excitability was observed, and the excitation spread was restricted to the granule cell layer (Ikrar et al., 2013). The results obtained by Ikrar et al. (2013) seem to be in opposition with the ones obtained by others (Lacefield et al., 2012; Park et al., 2015). The decrease in the excitability of the DG observed in Bax mice corresponds to a decrease in mature granule cell population activation. This decrease in excitability might be explained by the feedback inhibition of highly excitable adult-born granule cells on mature granule cells, through GABAergic hilar interneurons (described in detail below) (Kheirbek et al., 2012a; Lacefield et al., 2012; Sahay et al., 2011b). This hypothesis was further explored by the use of picrotoxin, a $GABA_A$ receptor antagonist, in Bax mice in order to overcome feedback inhibition (Adlaf et al., 2017). In these conditions, perforant path stimulation still decreased ESPCs in mature granule cells and reduced their excitatory transmission (Adlaf et al., 2017). This indicates that feedback inhibition is not the only element contributing to the counter-intuitive finding that the number of adult-born granule cells is inversely correlated to the excitability of the mature network. Another element that may be contributing to this phenomenon, in addition to AHN increase, is the fact that the Bax model also increases synaptogenesis in adult-born granule cells, which is much higher in these mice than in control mice. A decrease in spine density in mature granule cells was also observed with Bax deletion (Adlaf et al., 2017). This would lead to a competition between adult-born and mature granule cells to receive the inputs in their respective dendritic trees (this phenomenon will be further described below). Following perforant path stimulation in mice with an enhanced AHN, adult-born granule cells may usurp pre-existing synapses from mature granule cells to receive the inputs from the perforant path, resulting in a decrease in EPSCs. It seems that the increase in the spine density of adult-born granule cells does not compensate for the decrease in spine density from mature granule cells. This lack of compensatory effect could be explained by a high fraction of adult-born granule cell synapses being silent in the absence of GABA input (Chancey et al., 2013). This absence of GABA input may explain the decrease in excitability after perforant path stimulation, in presence of picrotoxin (Adlaf et al., 2017). Moreover, the diverging results obtained by Ikrar et al. (2013) are likely due to their protocol of stimulation. Indeed, contrary to the other studies using perforant path stimulation, Ikrar et al. (2013) used a direct stimulation of the granular layer, which stimulates adult-born and mature granule cells without considering the competition between adult-born and mature granule cells to receive perforant path inputs that promote adult-born granule-cell-mediated feedback inhibition. Altogether, Bax deletion induces AHN, but dramatically changes dendritic spine distribution in adult-born and mature granule cells. These results highlight the crucial role of competition in the dendritic tree of these two neuronal populations. Overall, the Bax model leads to diverging results regarding granule cell layer excitability: the Bax model increases the AHN and decreases the excitability whereas the X-ray irradiation suppresses the AHN and decreases also the excitability in the DG. Finally, adult-born granule cells from 4 to 6 weeks post-division increases DG excitability through interactions with the mature granule cells. However, they also influence mature granule cells through both of these phenomena: feedback inhibition and competitive processes (Fig. 1).

The AHN-mediated excitability requires the NMDA receptor. This glutamate receptor is a tetramer, which is typically composed of 2 obligatory GluN1 subunits and 2 GluN2 subunits (Laube et al., 1998). Four GluN2 subunits have been described. In particular, *in situ* hybridization of mRNAs encoding NMDA receptor subunits in the developing rat revealed that in the hippocampus, only GluN2A and GluN2B are expressed and able to form complexes with GluN1 (Haberny et al., 2002; Monyer et al., 1994). The GluN2B subunit is the predominant GluN2 subunit in neurons during development and subsequently, the GluN2A subunit becomes the predominant one (Dumas, 2005). Interestingly, the GluN2B-containing NMDA receptors present a lower rate of deactivation than GluN2A-containing NMDA receptors (Erreger et al., 2005). Thus, the presence of GluN2B on

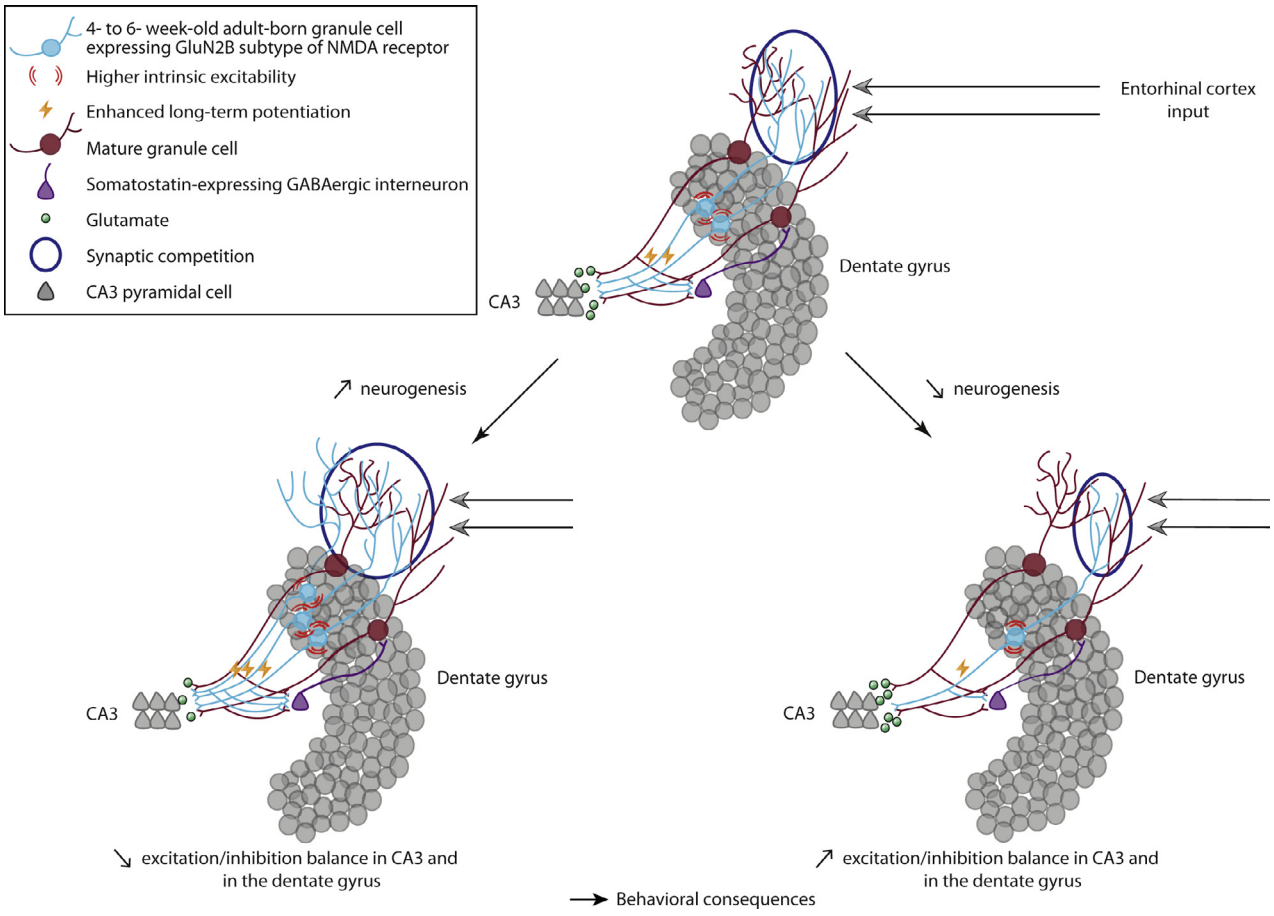

Fig. 1 Adult-born granule cells, at the critical age of 4 to 6 weeks, affect network activity in the DG and in CA3 area of the hippocampus and influence specific hippocampal functions.
In their critical stage of development from 4 to 6 weeks, adult-born granule cells have particular electrophysiological properties; more precisely, they demonstrate higher intrinsic excitability and a lower threshold for long-term potentiation. By their integration in the DG network, they compete with mature granule cells for entorhinal cortex stimulation. Then, they notably stimulate cells in CA3 and SST^+ hilar interneurons via a glutamate release. These interneurons are responsible for feedback inhibition and provide homeostatic control in the excitation/inhibition balance in CA3. Through their neurochemical implications in the hippocampus, adult-born granule cells that preferentially express GluN2B-containing NMDA receptors influence hippocampus-dependent behavior. With increased adult hippocampal neurogenesis, less mature granule cells receive perforant path stimulation, and SST^+ interneurons are more stimulated. As a result, glutamate levels are decreased in CA3, and the excitation/inhibition balance in the DG is also decreased. In contrast, a decrease in adult hippocampal neurogenesis leads to more mature granule cells receiving the cortex entorhinal inputs and less SST^+ interneurons are stimulated. In these conditions, glutamate levels are increased in CA3, and excitatory postsynaptic current amplitude in the DG is increased.
Although the precise mechanisms of how adult-born granule cells influence neurochemistry have not yet been fully elucidated, neurochemical modulation generated by adult-born granule cells lead to the changes in neurogenesis-dependent hippocampal behavior.

these adult-born granule cells could explain the AHN-mediated higher intrinsic excitability. To our knowledge, no study has been performed to assess directly the time-course of expression of GluN2B in adult-born granule cells. However, indirect evidence have shown GluN2B expression in adult-born granule cells (Cull-Candy and Leszkiewicz, 2004; Ge et al., 2007; Kheirbek et al., 2012b; Kim et al., 2005; Snyder et al., 2001; Tang et al., 1999; Tannenholz et al., 2016); notably selective GluN2B suppression in adult-born granule cells affects antidepressant response in the Novelty Suppressed Feeding (Kheirbek et al., 2012b) or impairs the context discrimination (Tannenholz et al., 2016) both behaviors are AHN-dependant. Concerning the implication of GluN2B in the adult hippocampal higher intrinsic excitability, the expression of c-fos, an immediate-early gene, following the exploration of a novel environment was measured in GluN2B knockdown and control mice using small interfering RNA (siRNA). The expression of c-fos was increased in mice exposed to a novel environment, but a smaller increase was observed in GluN2B knockdown mice, suggesting that there is less excitability with lack of GluN2B in adult-born granule cells. Furthermore, the suppression of GluN2B in adult-born granule cells significantly decreased neural activity of newborn neurons as compared to control

mice (Li et al., 2013). Thus, these studies suggest that adult-born granule cell excitability depends on the GluN2B subunit of NMDA glutamate receptors.

Due to adult-born granule cells' higher intrinsic excitability, there is a potential for synaptic strength modification. One study aimed to test this possibility by applying electrophysiological recordings on hippocampal slices. In particular, they used low-frequency perforant path stimulation ranging from 100 to 400 μA (20 μs), and paired 2 Hz afferent stimulation with postsynaptic depolarization to -20 mV. This experiment revealed that adult-born granule cells produced consistent, robust long-term potentiation (LTP), but not mature ones; this suggests that the threshold for LTP induction is raised in mature granule cells (Wang et al., 2000). Thereafter, it was demonstrated that the threshold for LTP induction in adult-born granule cells is lower than in mature neurons. Presynaptic bursts (10 stimuli at 100 Hz) at theta frequency (5 Hz) were applied at the granule cells' border. Unlike what is observed in mature granule cells, this stimulation paradigm was sufficient to induce LTP in adult-born granule cells (Schmidt-Hieber et al., 2004). Adult-born granule cells' threshold for LTP in the DG was also studied by electrophysiological recordings in X-irradiated rats (after a dwell time of three weeks). In this experiment, the adult neurogenesis ablation showed an unequivocal reduction in LTP in DG (Snyder et al., 2001). Two complementary strategies of ablation were used to study the change in electrophysiological responses. X-irradiation was also used for spatial specificity, and a genetic neural progenitor cell ablation targeting the glial fibrillary acidic protein (GFAP) with ganciclovir (GFAP-TK model) for cellular specificity. In each of these ablation procedures, LTP evoked by a 100 Hz perforant path stimulation was completely abolished (Saxe et al., 2006). In rat hippocampal slices, induction of LTP by perforant path stimulation was not affected by an NMDA receptor antagonist, APV, but was completely prevented by ifenprodil, a selective antagonist of GluN2B-containing NMDA receptors (Ge et al., 2007; Snyder et al., 2001). Moreover, slice electrophysiology was conducted in hippocampal slices of mice 6-7 weeks after deletion of the GluN2B subunit selectively in adult-born granule cells (Kheirbek et al., 2012b). Similarly to experiments led on neurogenesis ablation models (Saxe et al., 2006), high frequency stimulation (four trains of 1 s, 100 Hz, trains every 15 s) failed to induce LTP in the adult-born granule cells lacking GluN2B (Kheirbek et al., 2012b). This indicates that the GluN2B subunit is critical to adult-born granule cell synaptic strength. Finally, the amplitude of LTP was studied in adult-born neurons from 2-week-old neurons to 8-week-old neurons in hippocampal slices of mice. A critical window with enhanced LTP between 4 weeks and 6 weeks was identified, whereas between 2 and 4 weeks and after 6 weeks, LTP was not significantly different from mature granule cells' potentiation (Ge et al., 2007). It confirms that the 4-to-6-week-old granule cells are in a critical stage of development that enables them to affect the whole DG function. Moreover, the application of ifenprodil in 4-week-old neurons reduced EPSCs by 72%. In 8-week-old neurons, the same treatment led to only 25% reduction (Ge et al., 2007). After the critical period of 4 to 6 weeks, there is a shift from GluN2B to GluN2A corresponding to the shift of particular properties of adult-born granule cells to the standard properties of mature granule cells (Cathala et al., 2000; Selemon, 2013). Electrophysiological recordings were obtained in hippocampal slices, transfected with GluN2A/GluN1 in order to test the effects of this replacement of GluN2B by GluN2A. Synaptic currents in transfected cells were similar to those in nontransfected cells, indicating that the switch of GluN2B to GluN2A reduced plasticity (Barria and Malinow, 2005).

Around 4-6 weeks post division, adult-born granule cells have lower thresholds for generating action potentials, leading to higher intrinsic excitability. At that same moment, adult-born granule cells also have a lower threshold for LTP. By these mechanisms, adult-born granule cells exhibit a period of heightened plasticity 4-6 weeks post-division (Table 1). Furthermore, an electrophysiological study showed that the lack of young granule cells increases the magnitude of spontaneous gamma bursts promoted by perforant path input, although this perforant path input was reduced (Lacefield et al., 2012), demonstrating the involvement of AHN in the whole hippocampal functions. Adult-born granule cell plasticity could play a key role in adult-born granule cell involvement in forming new memory (Aimone et al., 2006, 2009; Cahill et al., 2017; Tashiro et al., 2007) and in flexibility using memories (Park et al., 2015). The pathophysiology of depression also involves dysfunction in synaptic plasticity (Perlman et al., 2012; Zeng et al., 2012) and an antidepressant-like effect is associated with an induction of synaptogenesis as well as an increase in AHN in rats (Li et al., 2010, 2011).

As seen with excitability and LTP induction, adult-born granule cells modulate network activity in the DG. This could be linked to a competition between adult-born granule cells and mature granule cells to receive the neuronal input. Spontaneous electric activity in the DG is constituted of gamma bursts, which are normally driven by mature granule cells. Competition with mature neurons for the perforant path connections would then explain why elimination of adult-born granule cells increased gamma bursts (Lacefield et al., 2012). This competition hypothesis is also supported by a cellular compartment analysis of temporal activity using fluorescence *in situ* hybridization in mice. This analysis is based on the localization of c-fos transcripts and is used to visualize cellular networks repeatedly activated in the DG. This work demonstrated that the expansion of a cohort of 5-to-8-week-old adult-born granule cells enhances global remapping in the DG (McAvoy et al., 2016). Moreover, in mice, neurogenesis enhancement through an enriched environment (Fabel et al., 2009; Olson et al., 2006) increases the frequency of EPSCs in hippocampal slices compared to mice under standard conditions. As there was no difference between mice under enriched environment and mice under standard conditions in the paired-pulse ratio – a measure of presynaptic release probability – enhanced synaptic transmission is likely to result from a greater number of functional synapses (Adlaf et al., 2017). This hypothesis would be consistent with a synaptic redistribution model wherein adult-born neurons have existing terminals that synapse onto mature granule cells and thus modify synaptic input on mature granule cells. The GluN2B subunit seems to contribute to the synaptic redistribution. Indeed, the deletion of this subunit from NMDA receptors of adult-born granule cells prevented the increase in the number of intersections

Table 1 Distinct electrophysiological properties of adult-born granule cells from 4 to 6 week-old.

	Species (Rats or mice) and strains	Sex	Population studied	Stimulation	Neurogenesis (intact i or suppressed s)	Method	Results	References
Adult-born granule cells increase dentate gyrus excitability	Wistar rats	♂	1- to 3-week-old granule cells	Perforant path stimulation	i		↘ threshold for spikes induction of immature granule cells than mature ones (due to calcium channel)	Schmidt-Hieber et al. (2004)
	C57Bl/6 J mice	♀	4-week-old granule cells		i		Activation of a larger population of immature granule cells than mature ones	Marin-Burgin et al. (2012)
	C57Bl/6 J mice	♂			s	Irradiation 3 × 5 Gy - 6 to 10 weeks prior experiments	↘ field evoked responses	Lacefield et al. (2012)
	C57Bl/6 J mice	♀♂	dividing granule cells	Open field	i	small interfering RNA-GluN2B-GFP	↘ c-fos/GFP ratio	Li et al. (2013)
	129 Sv/Ev mice	♂		Perforant path stimulation	s	Irradiation 3 × 5 Gy - 3 to 4 months prior experiments	↘ field EPSP and population spike responses	Park et al. (2015)

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Table 1 (*continued*)

	Species (Rats or mice) and strains	Sex	Population studied	Stimulation	Neurogenesis (intact i or suppressed s)	Method	Results	References
Adult-born granule cells affect long-term potentiation	Wistar rats	♂	adult-born granule cells expressing TOAD-64 < 12 days	Perforant path stimulation	i		Consistent 77% enhancement of the EPSCs at −80 mV (*vs* 3% in mature neurons)	Wang et al. (2000)
	Wistar rats	♂			s	Irradiation 2 × 5 Gy - 3 weeks prior experiments	LTP blocked	Snyder et al. (2001)
	Long-Evans rats	♂			s	Irradiation 2 × 5 Gy - 3 weeks prior experiments	LTP blocked	Snyder et al. (2001)
	Wistar rats	♂	1- to 3-week-old granule cells		i		Stimulation lead to LTP only in young granule cells	Schmidt-Hieber et al. (2004)
	129 Sv/Ev mice	♂			s	Irradiation 3 × 5 Gy - 3 months prior experiments	↘ field EPSP (abolished LTP)	Saxe et al. (2006)
	C57Bl/6J-BALB/c mice	♂			s	Genetic modulation (GFAP-TK transgene - 6 weeks prior experiments)	↘ field EPSP (abolished LTP)	Saxe et al. (2006)
	C57Bl/6 J mice	♀	4- to 8-week-old granule cells		i	Application of ifenprodil	LTP blocked (4 week-old)	Ge et al. (2007)
	C57Bl/6 J mice	♀	2- to 8-week-old granule cells		i		↗ LTP amplitude (4- to 6-week-old adult-born granule cells)	Ge et al. (2007)
	NestinCreERT2;GluN2B C57Bl/6 J mice	♂			i	Tamoxifen injections – 6–7 weeks prior experiment	LTP blocked	Kheirbek et al. (2012a, b)

of adult-born granule cell dendrites following fluoxetine treatment (Kheirbek et al., 2012b; Tannenholz et al., 2016). This finding supports the hypothesis that the GluN2B subunit is implicated in adult-born granule cell dendritic changes.

Altogether, 4-to-6-week-old adult-born granule cells display a higher excitability regarding the low input they need to trigger a spike as compared to mature granule cells (Schmidt-Hieber et al., 2004). This property implicates the GluN2B subunit of the NMDA receptor (Li et al., 2013) and affects the excitability of the whole DG trough feedback inhibition and competitive processes (Adlaf et al., 2017; Lacefield et al., 2012; McAvoy et al., 2016). As consequences, the induction of LTP in the DG is facilitated in 4-to-6-week-old granule cells (Schmidt-Hieber et al., 2004; Snyder et al., 2001; Wang et al., 2000).

3. Adult-born granule cells from 4 to 6 weeks post-division are necessary for specific hippocampal functions

After having identified a period during which adult-born granule cells exhibit heightened plasticity, the next step was to determine whether adult-born granule cells during this critical period could contribute to hippocampal function and behavior. As mentioned above, the ablation of adult neurogenesis impaired memory discrimination in active place avoidance training (Park et al., 2015). In order to determine if adult-born granule cell age also affects cognitive behavior, immunohistochemical approaches were coupled with a spatial memory test, the Morris Water Maze. The 5-bromo-2′-deoxyuridine (BrdU) proliferation marker and the neuronal specific nuclear protein (NeuN) were used as a mature neuronal marker to label adult-born granule cells and to evaluate the total number of neurons in the granule cell layer in mice. In addition, the expression of two immediate-early genes, c-fos and arc, were quantified to identify how granule cells process spatial memory. The incorporation of 1-, 2-, 4-, 6- or 8-week-old adult-born neurons into spatial memory circuits in the DG was examined. Neuronal activation (revealed by early protein expression) of adult-born granule cells did not occur until they were at least 2 weeks. Moreover, the activation of these cells was higher in adult-born granule cells beyond 4 weeks than in mature granule cells. This analysis indicated that adult-born granule cells from 4 to 8 weeks are preferentially recruited into circuits supporting spatial memory, compared to mature neurons (Kee et al., 2007).

In order to further characterize the functional involvement of these adult-born granule cells, they were optogenetically inhibited using a viral construction; selectively at 2-, 4-, or 8-weeks of age during the Morris Water Maze and a classical contextual fear conditioning paradigm. Adult-born neurons formed functional synapses on CA3 pyramidal neurons as early as 2 weeks after birth, and this projection to CA3 became stable by 4 weeks. Silencing 4-week-old adult-born granule cells projecting to CA3 pyramidal neurons caused deficits in spatial memory retrieval and impaired context fear memory. The same inhibition was not effective at 2 or 8 weeks post-infection (Gu et al., 2012). Thus, this study suggests that the preferential recruitment of adult-born granule cells from 4 weeks impacts cognitive behavior and more precisely spatial memory. This work identified a restricted time window for adult-born neurons essential in hippocampal memory retrieval. However, it would have been interesting if this study evaluated the involvement of 6-week-old granule cells in spatial memory, considering that this age is also critical. Yet, conflicting evidence from another study using X-irradiated mice demonstrated that behavior was unaffected in the Morris Water Maze and in the Y Maze as compared to sham mice (Saxe et al., 2006). Yet, in this study, the X-irradiation was performed 3 months prior to functional analyses, and the 4-week-old granule cell population was not the only one suppressed, which could explain the diverging results. Regarding the mechanisms underlying this memory effect, the role of the GluN2B subunit in memory was also assessed. One group used transgenic mice that over-expressed GluN2B, and placed these mice in the Morris Water Maze. These mice displayed enhanced spatial memory as compared to wild type mice in the time they spent in the target quadrant as well as the time to escape to the platform. This indicates that GluN2B-containing NMDA receptors enhanced spatial learning (Tang et al., 1999). However, in the same test in a separate study, mice treated with a selective antagonist of GluN2B-containing NMDA receptors, Ro25-6981, displayed an improvement of their spatial learning and memory (Hu et al., 2008). Ro25-6981-treated mice notably improved their ability to locate the hidden platform. The subunit blockade of GluN2B-containing NMDA receptors facilitated the formation of spatial memory in the adult mice, demonstrating that the GluN2B subunit affects memory. These two contradictory results (Hu et al., 2008; Tang et al., 1999) could be explained by the fact that GluN2B negatively regulates neurogenesis. Thereby, Ro25-6981 administration may stimulate neurogenesis, which might possibly explain the spatial memory improvement of Ro25-6981-treated mice. Indeed, this hypothesis was confirmed by the use of AZT, a telomerase inhibitor that inhibits neurogenesis, which reverted the enhancement of spatial memory induced by Ro25-6981 (Hu et al., 2008). The facilitated formation of spatial memory by blocking GluN2B would be caused by the up-regulation of neurogenesis (Gruden et al., 2018; Hu et al., 2008). However, it should be noted that the administration of Ro25-6981 is systemic, and not specific to the adult-born neurons, and thus, it cannot be concluded that Ro25-6981 directly modulates these cells specifically and not through an indirect mechanism.

Beyond spatial or fear memory, the ability of the hippocampus to identify novelty was investigated using a variety of different ablation approaches. First, one study examined the alteration of hippocampal-dependent behavior by adult neurogenesis suppression. X-irradiation or genetic ablation of AHN significantly decreased freezing in contextual fear conditioning, while a form of LTP was abolished (Saxe et al., 2006). Then, the contribution of adult-born neurons 2, 4, or 6 weeks following hippocampal X-irradiation was studied by a separate group (Denny et al., 2012). At 4 weeks post-irradiation, mice tended to investigate the novel object more than sham mice (though the difference was not significant). Yet, after 6 weeks, irradiated mice explored the novel object significantly more than sham mice. This result demonstrates that the critical age of 4 to 6 weeks is critical for memory. The

authors subsequently investigated novelty processing and context learning in the GFAP-TK model. Genetic suppression of adult neurogenesis in this model increased novel object recognition and impaired behavior in contextual fear conditioning at 4–6 weeks after the suppression of neurogenesis (Denny et al., 2012). The fact that the ablation of neurogenesis leads to an increase in novel object recognition performance instead of a decrease could be explained by compensatory extra-hippocampal processing resources competing with the hippocampus for dominance (Poldrack and Packard, 2003), such as parahippocampal regions of the temporal lobe. A separate group used mice in which GluN2B subunit was deleted in DG adult-born granule cells, and tested them in a battery of behavioral assays (Kheirbek et al., 2012b). The transgenic mice did not differ from controls in baseline anxiety-like behavior (open field, forced swim test, novelty suppressed feeding, elevated plus maze). However, in a fear discrimination task, transgenic mice required 8 days to significantly discriminate between two highly similar contexts, whereas control mice needed only 4 days (Kheirbek et al., 2012b). Thus, the authors concluded that the GluN2B subunit participates in fine contextual discrimination. Then, the same team assessed mood regulation by adult-born granule cells. In the same mouse model and using the same approach, the behavioral response to fluoxetine was evaluated (Tannenholz et al., 2016). Conditional deletion of the GluN2B subunit in adult-born granule cells 6 weeks prior to the onset of antidepressant administration revealed that GluN2B impacted the effect of fluoxetine in the Novelty Suppressed Feeding paradigm, which is considered a neurogenesis-dependent behavioral task (David et al., 2009; Surget et al., 2008). By contrast, in the same animals, GluN2B deletion in adult-born granule cells did not impact fluoxetine response in neurogenesis-independent tasks, the tail suspension test and the elevated plus maze (Tannenholz et al., 2016). Thus, adult-born granule cells with GluN2B-containing NMDA receptors make a unique contribution to hippocampus-dependent behavior. Thus, immature neurons in the 4-to-6-week-old range modulate information processing. Again, this period corresponds to the one in which adult-born neurons exhibit enhanced excitability and plasticity, with the involvement of the GluN2B subunit.

It is critical to note that discrete regions rather than the whole hippocampus regulate memory and mood in distinct ways. For instance, it was recently demonstrated using calcium imaging and optogenetics in freely moving mice that ventral CA1 is enriched in cells activated by anxiogenic environments (Jimenez et al., 2018). Functional dissociation of adult-born granule cells in the DG was also studied in a chronic stress model after focal X-irradiation directed to the dorsal or ventral DG in mice. Adult-born granule cells in the ventral DG are necessary for anxiolytic/antidepressant-related effects, whereas those in the dorsal DG are required for acquisition of contextual discrimination (Wu and Hen, 2014).

These experiments suggest that newborn neurons are recruited into hippocampal memory circuits, playing an essential role in memory and mood regulation. This essential role during the 4-to-6-week-old range relies on GluN2B-containing receptors of adult-born granule cells (Table 2). Under-expressing or over-expressing this specific receptor subunit influences hippocampal functions. However, to do so, 4-to-6-week-old adult-born granule cells must integrate into behavioral networks in the hippocampus and then modify neurochemical circuits.

4. Adult-born granule cells integrate into a di-synaptic circuit, and synapse with somatostatin interneurons to regulate neurochemistry

In order to understand neurochemical mechanisms underlying the adult-born neuron involvement in memory and in mood regulation, it is necessary to investigate the circuits in which they integrate, more specifically their targets (Fig. 1).

Like mature granule cells, adult-born granule cells in the hippocampus receive major synaptic inputs from the entorhinal cortex and local GABAergic interneurons (Overstreet-Wadiche et al., 2005; Vivar et al., 2012). As pointed out by anatomical studies using confocal and electron microscopies and live imaging in mouse hippocampal slices, adult-born granule cells seem to compete with mature granule cells for entorhinal cortical inputs (Toni et al., 2007). This competition hypothesis has also been demonstrated in several other studies mentioned above (Adlaf et al., 2017; Lacefield et al., 2012; McAvoy et al., 2016). To further the understanding of how these granule cells compete, it was crucial to determine whether adult-born granule cells connect to the existing network with synapses and whether they follow the same pattern of connection as mature granule cells. Using retrovirus-mediated birth-dating and labeling with electron microscopic reconstruction, it was reported that adult-born granule cells form initial synaptic contacts with CA3 pyramidal cells within 2 weeks post-division, forming a part of the mossy fibers (Faulkner et al., 2008). The reconstruction of axonal and dendritic processes of adult-born granule cells with a serial end-block imaging technique showed that their axons are fully developed 3 weeks post-division (Sun et al., 2013). Optogenetic stimulation was then used by another group to compare responses of axonal and dendritic targets of 4-week-old and mature granule cells. Both generated identical output responses in CA3 networks in terms of glutamatergic EPSCs and GABAergic inhibitory postsynaptic currents (IPSCs), resulting from feedforward recruitment of interneurons (Bergami et al., 2015; Restivo et al., 2015). This result indicates that at 4 weeks post-division, adult-born granule cell axons already make functional synapses onto CA3 interneurons and CA3 pyramidal cells (Temprana et al., 2015; Toni et al., 2008). These results indicate that regarding projections to the CA3, 4-week-old adult-born granule cells already displayed the same functional properties as mature granule cells ones.

Direct or indirect interactions between adult-born granule cells and mature granule cells were then explored. Voltage clamp recordings in mature granule cells showed weaker IPSCs after 4-week-old granule cell stimulation than after mature granule cell stimulation (Temprana et al., 2015). Thus, these data suggest that 4-week-old granule cells activate proximal GABAergic hilar interneurons. The

Table 2 Four to six week-old granule cells affect memory and mood regulation.

Species (Rats or mice) and strains	Sex	Population studied	Behavioral tests	Neurogenesis (intact i or suppressed s)	Method	Results	References
CaMKIIGluN2B C57B/6-B6/CBF1 mice			Water maze	i		↗ time in target quadrant	Tang et al. (1999)
C57Bl/6J-129 Sv/Ev mice	♂	1-, 2-, 4-, 6- or 8-week-old granule cells	Water maze	i		↗ of Fos expression from 4- to 8-week-old	Kee et al. (2007)
129 Sv/Ev mice	♂		Fear conditoning	s	Irradiation 3 × 5 Gy - 3 months prior experiments	↘ context-elicited freezing	Saxe et al. (2006)
C57Bl/6J-BALB/c mice	♂		Fear conditoning	s	Genetic modulation (GFAP-TK transgene - 6 weeks prior experiments)	↘ context-elicited freezing	Saxe et al. (2006)
C57Bl/6 J mice	♂		Water maze	i	Injection of Ro25-6981	↗ time in target quadrant	Hu et al., (2008)
129 Sv/Ev mice	♂	2-, 4- or 6-week-old granule cells	Fear conditoning	s	Irradiation 3 × 5 Gy - 8 weeks prior experiments	↗ time exploring novel object (6 week-old)	Denny et al. (2012)
129 Sv/Ev mice	♂		Novel object recognition paradigm, Fear conditoning	s	Genetic modulation (GFAP-TK transgene - 6 weeks prior experiments)	↗ time exploring novel object, ↘ context-elicited freezing	Denny et al. (2012)
C57Bl/6 J mice	♀	2-, 4- or 8-week-old granule cells	Water maze, Fear conditioning	i	Oncoretrovirus (Archaerhodopsin) and optogenetic inhibition	↘% time searching the target quadrant (4 week-old), ↘ context-elicited freezing	Gu et al. (2012)
NestinCreERT2;GluN2B C57Bl/6 J mice	♂		Fear discrimination tasks	i	Tamoxifen injections - 8 weeks prior experiment	↗ time to learn fine discrimination task	Kheirbek et al. (2012a, b)
NestinCreERT2;GluN2B C57Bl/6 J mice	♂		Novelty suppressed feeding	fluoxetine induced	Tamoxifen injections - 10 weeks prior experiment	attenuates the ↘ in latency to feed	Tannenholz et al. (2016)

activation of local inhibitory circuits in the hilus of the DG by adult-born granule cells was also studied by Drew and colleagues (Drew et al., 2016). In their study, optogenetic stimulation of young granule cells was performed at different stages of maturation, ranging in age from 0 to 6-7 weeks post-division in mice kept under standard housing conditions and in mice housed in enriched environments, increasing the number of adult-born granule cells in the DG (Fabel et al., 2009; Olson et al., 2006). Currents in the DG were studied in hippocampal slices. Following enriched environments, the ratio of IPSCs to EPSCs still heavily favored inhibition as observed in slices from control mice, but IPSCs had greater amplitude when the number of adult-born neurons was increased through the enriched environment (Drew et al., 2016). Previous diverging results (Temprana et al., 2015), indicating that stimulating 4-week-old granule cells led to weaker IPSCs, may be due to the selectivity of the adult-born granule cell population that was stimulated. The adult-born granule cells from 4 weeks and up to 6 weeks of age in the granule cell cohort would be responsible for the bulk of synaptic inhibition in mature granule cells. Moreover, light-activated IPSCs were substantially reduced following application of glutamate receptor antagonists (NBQX + APV), suggesting a di-synaptic circuit mediating inhibition. A residual IPSC remained after using the antagonists, denoting a direct release of GABA onto mature granule cells (Drew et al., 2016). A recent study showed a direct connection between adult-born and mature granule cells. Moreover, a weak excitation of immature granule cells inhibited mature granule cells via GIRK potassium channels coupled to group II metabotropic postsynaptic receptors. By contrast, a strong excitation of adult-born granule cells activated mature granule cells via ionotropic NMDA postsynaptic glutamate receptors (Luna et al., 2019). To summarize, it seems that adult-born granule cells over 4 weeks of age establish a glutamatergic synapse on a hilar GABAergic interneuron leading to an IPSC on the mature granule cells.

To explore the pathway leading to the synaptic inhibition after adult-born granule cell stimulation, optogenetic stimulation of adult-born granule cells was combined with patch-clamp recordings in hippocampal slices of parvalbumin (PV)- and somatostatin (SST)-expressing interneurons, the two major subpopulations of hilar GABAergic interneurons (Freund and Buzsaki, 1996; Maccaferri and Lacaille, 2003). GABAergic responses, resulting from stimulation of granule cells, were recorded. Currents from SST^+ interneurons, and not from PV^+ interneurons, were similar to those produced after granule cell stimulation. This result suggests that SST^+ interneurons are likely responsible for feedback inhibition that leads to attenuation of granule cell layer activity (Stefanelli et al., 2016). The increase in IPSCs following the enhancement of neurogenesis may result from SST^+ interneuron activation (Raza et al., 2017; Yuan et al., 2017). PV^+ interneurons do not seem to be involved in adult-born granule cell output responses, though they are involved in their input (Bao et al., 2017; Moss and Toni, 2013; Song et al., 2012b).

Furthermore, *in vivo* electrophysiological recordings were performed while conducting optogenetic inhibition of adult-born granule cells to study their projections outside the mossy fibers. Silencing of these cells increased local field potentials in the contralateral CA1 region with no effect in the contralateral CA3 region, supporting the hypothesis that adult neurogenesis recruits the former CA1 neural network (Zhuo et al., 2016). Finally, the adult-born granule cell incorporation in the circuitry may change in response to experience. Adult-born neurons were exposed to environmental enrichment at different times following their division, and starter cells were transduced with the rabies virus one week prior to sacrifice in order to specifically trace neuronal connections (Ugolini, 2011). There was a significantly higher proportion of local projections in the DG when environmental enrichment was provided between the second and sixth week of the neuron's life. Long-range projections were also selectively increased in number following the exposure to environmental enrichment during the same specific time window (Bergami et al., 2015). Thus, environmental enrichment increases the number of adult-born granule cells and their connectivity, notably with SST^+ interneurons.

5. Adult-born granule cells influence hippocampal functions through a decrease in the excitation/inhibition balance

Considering adult-born granule cells integrate in the hippocampus connectivity and affect electrical activity of neighboring cells as well as long-range projection, it is likely that they influence neurotransmitter release (Table 3 and Fig. 1).

The identification of a potential neurotransmitter released by adult-born granule cells was first examined. Adult-born granule cell targets and neurotransmitter release were studied in hippocampal slices by recording postsynaptic responses evoked by optogenetic stimulation of adult-born granule cells. EPSCs and IPSCs were obtained with these stimulations; they were reversibly abolished with kynurenic acid, a mixed AMPA/NMDA receptor antagonist. By contrast, the $GABA_A$ receptor antagonist bicuculline elicited no changes in postsynaptic currents. These experiments demonstrate that adult-born granule cells establish synaptic connections with mossy cells, with interneurons in the hilus, and more specifically with SST^+ interneurons as previously demonstrated (Stefanelli et al., 2016), as well as with pyramidal cells (Toni et al., 2008). They also release glutamate as their main neurotransmitter (Toni et al., 2008). Then, the contributory role of young granule cells in regulating mossy fiber-CA3 excitation via glutamate levels was established in a GFAP-TK mice model, where adult neurogenesis was inducibly suppressed. *In vivo* microdialysis was used to monitor extracellular glutamate levels into CA3. Loss of adult-born neurons resulted in increased glutamate levels in CA3 in response to an acute stress (Schloesser et al., 2014). Loss of adult-born granule cells would be responsible for a decrease in SST^+ interneuron stimulation leading to a decrease in GABA release. This disinhibition would be consistent with the possibility that innervation of SST^+ interneurons by adult-born granule cells would provide homeostatic control over mossy fiber-CA3 excitation. Contrariwise, an electrophysiological study showed that 4-week-old granule cells first send mossy fiber projections onto distal CA3 inducing an excitatory effect on the CA3 pyramidal cells. The adult-born granule cells connection with SST+ interneurons

Table 3 Adult-born granule cells release glutamate, activating somatostatin GABAergic interneurons, and thus reduce the overall excitability of the dentate gyrus.

Species (Rats or mice) and strains	Sex	Population studied	Stimulation	Neurogenesis (intact i or suppressed s)	Method	Results	References
C57Bl/6 J mice	♀		Optogenetic stimulation Application of kynurenic acid (4–10 mM)	i	Retroviral injection (CAG-Channelrhodopsin) - 3–4 months prior optogenetic stimulation	evoked PSCs reversibly abolished by kynurenic acid	Toni et al. (2008)
C57Bl/6 J mice	♂		Microdialysis	s	Genetic modulation (GFAP-TK transgene - 16 weeks prior experiments)	↗ glutamate levels in CA3	Schloesser et al. (2014)
C57Bl/6 J mice	♂	6-week-old granule cells	Voltage-clamp	Increased	Environmental enrichment	↘ EPSCs frequency	Bergami et al. (2015)
NestinCreERT2;Baxfl/fl C57Bl/6J-129 Sv mice	♂	4- to 6-week-old granule cells	Perforant path stimulation	Increased	Tamoxifen injections - 4–6 weeks prior experiment	↘ EPSCs frequency from mature granule cells	Adlaf et al. (2017)
NestinCreERT2;iDTR C57Bl/6J-129 Sv/Ev mice	♂		Field and whole-cell recordings	s	Tamoxifen injections - 6 weeks prior diphteria toxin injections	↗ EPSCs amplitude from mature granule cells	Adlaf et al. (2017)
SSTCre;ɤ2fl/fl C57Bl/6J-129 Sv mice	♀♂		Elevated plus maze, Novelty suppressed feeding, Forced swim test, Learned helpless-ness	i		↗ open arms entries (Elevated plus maze ♀♂), ↘ latency to feed (Novelty suppressed feeding ♀), ↗ time to first immobility ↘ time immobile (Forced swim test ♀♂), ↘ escape failures (Learned helplessness ♂)	Fuchs et al. (2017)

would then appear later (Temprana et al., 2015). These points need to be further explored.

Regarding the DG, an interesting element was pointed out in the study by Bergami et al. (2015); their main goal was not to study electrical recordings of adult-born granule cells in the DG. Yet, the authors used voltage-clamp recordings from hippocampal slices of control and environmental enriched 6-week exposed mice and revealed a reduction in EPSCs frequency (Bergami et al., 2015), which could be related to a decrease in glutamatergic transmission. Likewise, EPSCs from mature granule cells were recorded after stimulation of the perforant path. Mature granule cells had reduced excitatory transmission in slices where neurogenesis was enhanced with the conditional Bax deletion in Nestin-expressing progenitors. In those slices, frequency of spontaneous EPSCs was also decreased, suggesting a diminution in the number of active synapses, causing the reduction in excitatory transmission. It was confirmed with biocytin spine analysis showing a robust reduction in spine density in mature granule cells in mice with stimulated neurogenesis compared to controls (Adlaf et al., 2017). This suggests that adult-born granule cells integrating

into the DG network lead to a decrease in the number of stimulated mature glutamatergic granule cells (Tashiro et al., 2006), and thus a decrease in glutamate release in the DG. Conversely, using diphtheria toxin-induced ablation in Nestin-expressing progenitors (Buch et al., 2005) to ablate adult-born granule cells increased EPSC amplitude (Adlaf et al., 2017), but whether it resulted from pre- or postsynaptic mechanisms remains to be elucidated. However, knowing the circuits in which adult-born granule cells integrate, it is very likely that adult-born granule cells decrease EPSCs via a di-synaptic circuit, certainly with SST^+ GABAergic interneurons responsible for feedback inhibition, leading to a decreased excitation/inhibition balance in the DG, and a decrease in glutamate transmission in CA3 (Schloesser et al., 2014). Moreover, increasing excitability of SST^+ interneurons in genetically modified mice led to an anxiolytic- and antidepressant-like behavioral phenotype (Fuchs et al., 2017), supporting the importance of these SST^+ interneurons in the regulation of hippocampal functions.

Adult-born granule cells release glutamate and stimulate several types of cells, including GABAergic interneurons and glutamatergic pyramidal cells in CA3 or SST^+ neurons in the hilus of the DG. In CA3, adult-born granule cells decrease the overall glutamate release. In contrast, no data on neurotransmitter release in the DG is available yet. It would then be highly relevant to study in detail neurotransmission changes in the DG related to AHN and neurogenesis-dependent tasks. These observations would enlighten the underlying mechanisms linking AHN and specific tasks associated with this phenomenon.

6. Conclusions

The present review aimed to summarize electrophysiological properties of adult-born granule cells and neurochemical data that would explain underlying mechanisms of the involvement of adult-born granule cells to behavioral outcomes. With their enhanced plasticity during 4–6 weeks post-division, adult-born granule cells exhibit an essential role in hippocampal structural plasticity. At this specific age, they influence memory and mood regulation as well as antidepressant response. The GluN2B subunit of the NMDA receptor in particular seems to play a crucial role in controlling the particular properties of adult-born granule cells. Adult-born granule cells also contribute to a strong inhibitory tone through activation of SST^+ interneurons. Furthermore, they influence large neural networks, including their proximal mature granule cells, CA3, and also the contralateral hippocampus. In CA3 specifically, glutamate release is decreased by adult-born granule cells. In the DG, the increase in AHN leads to a modification of the excitation/inhibition balance, through an excitation decrease. The consequences at this level remain to be evaluated, especially *in vivo*. Elucidating the role of adult-born granule cells by deepening their neurotransmission modulation in the DG should bring a better understanding of their importance in hippocampal functions. The role of the GluN2B-containing NMDA receptors in hippocampal neurotransmission modulation should also be explored in future studies. Only a few studies so far have explored selectively GluN2B's role in the adult-born granule cells. It is possible that targeting 4-to-6-week-old GluN2B-containing adult-born granule cells may represent a novel antidepressive strategy. Overall, uncovering how adult-born granule cells function and how they contribute to behavior will lead to new therapeutic strategies to treat neuropsychiatric diseases such as depression.

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Declaration of Competing Interest

None regarding this work.

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