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Abstract

In mammals, the selective transformation of transient experience into stored memory occurs in the hippocampus, which develops representations of specific events in the context in which they occur. In this review, we focus on the development of hippocampal circuits and the self-organized dynamics embedded within them since the latter critically support the role of the hippocampus in learning and memory. We first discuss evidence that adult hippocampal cells and circuits are sculpted by development as early as during embryonic neurogenesis. We argue that these primary developmental programs provide a scaffold onto which later experience of the external world can be grafted. Next, we review the different sequences in the development of hippocampal cells and circuits at anatomical and functional levels. We cover a period extending from neurogenesis and migration to the appearance of phenotypic diversity within hippocampal cells, and their wiring into functional networks. We describe the progressive emergence of network dynamics in the hippocampus, from sensorimotor-driven early sharp waves to sequences of place cells tracking relational information. We outline the critical turn points and discontinuities in that developmental journey, and close by formulating open questions. We propose that rewinding the process of hippocampal development helps understand the main organization principles of memory circuits.

Graphical abstract

CLINICAL HIGHLIGHTS

- Hippocampal circuits produce cognitive maps in the form of sequences of neuronal activation representing space and time.

- Internal dynamics are important for hippocampal function and partly preconfigured, possibly during development.

- The functional organization of the adult hippocampus is not only formed through experience-dependent plasticity, but partly hardwired at the earliest stages of development, including embryonic neurogenesis.

- The emergence of recurrent connectivity is a critical step in the development of the hippocampal structure

- Activity-dependent wiring of hippocampal circuits is supported by a sequence of early spontaneous activities progressively emerging during the first postnatal month in rodents, which corresponds to the last trimester of gestation.

- Self-generated movements trigger hippocampal activity in a bottom-up fashion at early perinatal stages

- The hippocampus may perform generalization based on statistical learning from the sensory world before being able to support egocentric episodic memory.

- The study of hippocampal development in the context of circuit physiology will open the way for cracking memory circuits in the brain in health and disease

Introduction

The fundamental and clinical research in the hippocampal field over the past seventy years has significantly contributed to our understanding of the circuit basis of memory. Indeed, it is now well accepted that the hippocampus is not only a region for place representation and navigation, but also a key brain structure involved in episodic memory and planning (42, 206, 224). All these processes rely on the ability of hippocampal networks to form cognitive maps stored as sequences of related experienced events and visited places that can be mentally traveled through in space and time. This review aims at describing how and when these circuits emerge during development and signifying how early development scaffolds our memory networks.

Hippocampal cognitive maps are produced by sequences of transient neuronal activation that keep track of and order spatial and non-spatial information (continuously varying) in an allocentric or egocentric reference frame (15, 92, 147, 208). They may unfold at various temporal scales, from several seconds, the timescale of behavior, to a few milliseconds, nested and compressed within the period of the theta rhythm (~8Hz) or within sharp-wave ripples (~200Hz) (43, 80). Interestingly, hippocampal sequences do not simply represent serially ordered external information, rather, they arise from the interaction between environmental inputs and internal dynamics supported by the intrinsic functional properties of the hippocampal network (43, 135). The internal functional organization of hippocampal circuits is indeed a major contributor to sequence generation. The sequential activation of hippocampal neurons can be disengaged from external signals at all timescales. Hence, hippocampal sequences unfolding at the behavioral timescale have been recorded in the absence of changing sensory or feedback cues, mainly during running behavior (79, 127, 148, 208, 260). Similarly, still during exploration, but nested within the period of a theta cycle, sequences representing the ongoing trajectory in space at an accelerated rate that are involved in decision and planning also emerge from the integration of sensori-motor information into internal dynamics (80). Most notably, hippocampal sequences critically involved in memory encoding and consolidation are also observed offline during quiet rest or sleep, when body or environmental control over dynamics are minimal (156, 230, 266). In addition, hippocampal sequences are rooted within functional circuits that are remarkably rigid against transient perturbation (260, 278) and stable across days (109). It is possible

that hippocampal sequences originate from a reservoir of predefined sequences wired prior to experience, as evidenced by the "preplay" phenomenon (50, 77, 107, 159). Finally, the development of hippocampus-dependent memory is protracted and reflected by the late emergence of internally-generated sequences (91, 197, 216).

In sum, sequences of neuronal activation, a basic circuit motif of hippocampal function in memory, are produced by specific functional connectivity schemes which are partly prewired. This basic prewiring may originate throughout the construction of hippocampal circuits during development. This review will illustrate how early development, from embryonic neurogenesis to perinatal neuronal maturation and postnatal formation of local and long-range connections, provides an interesting framework to gain understanding of hippocampal function at circuit level. We will mainly focus on CA1, however, when possible, we will use examples from other hippocampal sub-regions to illustrate how general principles can be extended. First, we will summarize the growing body of literature indicating that many developmental traces remain in adult hippocampal circuits at various levels of analysis and different spatial scales. In other words, early developmental programs, prior to experience, seem to provide a strong scaffold on the organization of adult hippocampal networks. One way to understand the circuit basis of sequence prewiring is to deconstruct circuits as they mature, given that development offers natural sequential time windows on distinct circuits as they develop and progressively give rise to different dynamics and function. We will thus review the emergence of hippocampal structure. Next, we will present the progressive emergence of hippocampal dynamics. We will show how different dynamics emerge sequentially, further demonstrating how development offers natural dissection of hippocampal circuits. Last, we will show how the progressive emergence of hippocampus-dependent cognitive functions reflects the developmental timelines reviewed in the other sections. This review will outline the early postnatal period as a major time window of hippocampal development, including critical activity-dependent turn points. We will close this review by formulating open questions.

Lasting traces of early development in adult hippocampal circuits

The hippocampus is an elongated brain structure spanning three main anatomical axes (Figure 1A): (i) a longitudinal axis from the septal (dorsal) to the temporal (ventral) pole; (ii) a

150 transverse axis following the path of the trisynaptic circuit, from Dentate Gyrus to CA3c, b, a
151 to CA1c, b, a; and (iii) a radial axis, from deep (closer to the alveus) to superficial (closer to the
152 fissure). Numerous studies indicate that the intrinsic morpho-physiological properties of
153 principal neurons (47, 75, 76, 122, 158, 176, 181, 257), their gene expression (47, 74),
154 local and long-range connectivity, and ultimately their function often segregate along these
155 axes in the adult. We argue that embryonic temporal origin or neuronal "birthdate" (final cell
156 division), likely acts as a major segregating factor contributing to most of the diversity.
157 Indeed, several functional traits of regional specializations can be predicted from temporal
158 origin (Table 1). Before reviewing how the hippocampal structure develops in detail in the
159 next section, we will briefly summarize the temporal order of neurogenesis along the three
160 hippocampal axes mentioned above. Most of what we know about the main gradients of
161 formation of different hippocampal circuits comes from early studies using ^{3}H-thymidine
162 autoradiography. In mice, hippocampal neurons are born between E10 and birth (with the
163 exception of the Dentate Gyrus). We will mainly focus on CA1 but use examples from other
164 hippocampal sub-regions to illustrate how this general principle can be extended to all
165 hippocampal regions. The two hippocampal axes displaying the most significant differences in
166 their time of origin are the transverse and radial axes (46). CA2 neurons (and subiculum) are
167 born first, followed by distal CA1 (CA1a and b, i.e. closer to subiculum, see Figure 1A) and
168 distal CA3 (CA3 a-b, i.e. closer to CA2) (22, 46). In the transverse axis, CA1c (closer to CA2)
169 and CA3c (closer to the Dentate Gyrus) are the last regions of Ammon's horn to be born, just
170 before the Dentate Gyrus, which continues adding new neurons into adulthood(46). The
171 peak of neurogenesis in mice in CA3 (E14) occurs one day before CA1 (E15) (12). In the radial
172 axis, as in the neocortex, successive generations of glutamatergic neurons occupying the
173 principal pyramidal and granule cell layers of the hippocampus migrate past the existing
174 earlier born neurons thus creating layers in an ''inside-out'' fashion. Therefore, superficial
175 neurons (closer to the *stratum radiatum*) are in general born later than deep neurons (closer
176 to the *stratum oriens*). It is of note that this deep to superficial gradient is less pronounced in
177 CA3 than CA1 (22). In contrast, there is no obvious developmental gradient of neurogenesis
178 along the dorsoventral axis in the CA1 region, unlike CA3 or entorhinal cortex, where ventral
179 neurons are born significantly later that dorsal ones (22, 73). In sum, in CA1, earlier born
180 (eb) neurons are preferentially found throughout the dorsoventral axis, in CA1a,b (distal), and
181 in deep radial positions, whereas later born (lb) neurons are located in CA1c and closer to the

stratum radiatum (Figure 1A). This gradient matches the quantitative differences in the passive and active electrophysiological properties of pyramidal neurons (PN) in the adult CA1. Indeed, adult CA1 PNs occupying regions where PNs are presumably born earlier display a smaller HCN-mediated h-current (Ih) (176, 181), a lower membrane resistance (Rm) (103, 181)) as well as higher excitability (47, 189) and bursting propensity (see Table 1 and Figure 1B). Interestingly, cells located in the *subiculum* or CA2, two subregions with an earlier temporal origin than CA1, also display a smaller Ih (163) (but see (234)), a lower Rm (129, 163, 234), higher excitability (207), and burst propensity (69). It should be noted that CA2 itself was recently shown to display significant heterogeneity along the proximo-distal axes (93), despite its overall earlier temporal origin compared to CA1 and CA3, possibly indicating the need for in depth examination of its embryonic developmental schedule. The diversity of intrinsic electrophysiological properties among CA3 PNs also distributes along the proximo-distal axis, revealing a similar trend for Rm with the earlier born distal CA3 (CA3a) displaying a lower Rm than proximal CA3 cells (234). Different trends for Ih and excitability have been reported with earlier born regions (CA2, CA3a) displaying a larger Ih and lower excitability, but higher burst propensity (20, 69, 234). We will see in the next section how these cellular properties follow a stereotyped schedule during development, serving as ideal proxies of neuronal maturation stage, as if the delays in maturation originating from different neuronal birthdates partly remained in the adult. As expected from the lack of clear developmental gradient in CA1 along the longitudinal axis, the dorso-ventral segregation of these properties is not as clear, while a continuous genetic gradient has been observed (47). That said, PNs located in the dorsal part of CA1 (possibly slightly older than the ventral region), display less Ih, a lower Rm and a lower action potential threshold (9, 12, 22, 73). The link between birthdate and integration into adult hippocampal circuits is particularly striking when considering connectivity. This was already evident in seminal early studies that noted how the order of neurogenesis in the entorhinal cortex, proceeding from lateral to medial, also strictly correlated with the order of its termination on CA1 PNs, with afferent fibers from older cells of origin (lateral entorhinal cortex) projecting to older CA1 pyramidal cells (CA1a), while afferent fibers from younger cells (medial entorhinal cortex) projected to younger CA1 pyramidal cells (CA1b,c, (22)). This isochronic patterning of entorhinal projections has been recently further dissected at functional level across the transverse and radial CA1 axes (180) and also applies to the inputs from the early generated CA2 region, projecting onto deep

CA1PNs (145, 202, 257). Similarly, in the dorsal CA3, entorhinal inputs (early born) are more abundant in the earlier born distal CA3 region (CA3a&b) whereas the opposite trend is observed for the later generated mossy fiber inputs that are more abundant in the later born proximal CA3, again following a temporal matching rule (234). Interestingly, the distal dendritic length of pyramidal neurons in CA2 and CA3 correlates with their burst propensity and their response to *stratum lacunosum* stimulation (69, 116) . As observed for entorhinal afferents, output fibers from presumably early-born or late-born hippocampal regions also target older versus younger laminae of the lateral septum and mamillary body pars posterior, respectively (10). In addition, superficial CA1 pyramidal cells are more likely to project to the entorhinal cortex than deep cells which preferentially target earlier-born reward-related structures such as the striatum (231). This rule by which the temporal order of neurogenesis imposes the patterning of connectivity to form isochronic circuits has been more recently directly evidenced at the single-cell level throughout the hippocampal glutamatergic trisynaptic circuit (63). This again may be a direct consequence of the mechanisms by which these circuits form during development (see below).

Maybe even more than for local excitatory glutamatergic circuits, the overall mesoscopic organization of adult GABAergic inhibitory circuits is particularly interesting to revisit from the perspective of developmental timing (Figure 1C). Indeed, both along the radial and transverse axes of development, it appears that late born PNs (superficial) and subregions (CA3c) are more likely to drive CA1 interneurons, while early born regions (CA2, CA3a) and cells (deep) receive stronger inhibitory inputs (72, 158, 207, 234, 257). In addition, the fine temporal pairing rule of connectivity also seems to apply to GABAergic circuits, since early born PV cells target deep CA1 cells while late born PV cells target superficial CA1 cells (72). The equation between birthdate and laminar position also holds for hippocampal GABAergic neurons, where neurons born in the Medial Ganglionic Eminence (MGE), generated earlier, distribute in deep layers (*stratum oriens and pyramidale)*, while cells born in the Caudal Ganglionic Eminence (CGE) mainly locate in superficial layers (*stratum lacunosum moleculare)* (245). This fine organization of inhibitory and excitatory circuits according to birth order may be predetermined at the earliest stages of development given that glutamatergic ensembles sharing a common clonal origin also share common presynaptic perisomatic GABAergic inputs (271).

The pre-existing differences in excitability or connectivity rooted in the different temporal origins of hippocampal neurons should result in functional differences (89). Interestingly, linked to the advent of large-scale approaches to record neuronal activity there has been a recent rise of interest in the analysis of the heterogeneity in place field properties among hippocampal neurons. These recent studies mostly use extracellular recordings and/or head-fixed preparations, which should be taken into account when interpreting the findings given the unprecise spatial resolution of the former and the difference in place cell properties reported in the latter (2, 49, 217). Regardless, when combining the information of many recent reports a clear picture emerges by which early born subregions and PNs (i.e. CA2, CA3a, CA1a,b, and deep CA1) are comprised of a higher fraction of place-modulated neurons (59, 189), however, their spatial coding specificity is poorer (59, 97, 113, 119, 207) as they are more likely to display multiple and/or wider and less stable place fields than their younger counterparts (CA1c, CA3c, superficial CA1, Figure 1D). The latter not only display highly selective and stable place fields, but are also better at discriminating transient tactile, olfactory or object information (97, 163). One interesting possibility could be that PNs located in the deep CA1 sublayer, although place-modulated, comprise cells representing contextual identity rather than a spatial map. Indeed it was recently established that "engram cells" (cells expressing cfos after presentation of a novel context), like many deep CA1 PNs (189) and unlike other place cells, exhibit higher firing rates, larger place fields with poorer information content, and higher modulation by entorhinal inputs (241). In other words, hippocampal function may be roughly divided into two functional categories according to birthdate, where regions and cells generated early would serve a generalizing function and later ones would assist content discrimination. This is a general rule that may even extend to the function of the late-generated dentate gyrus and CA3c (157, 178, 234). More particularly, in CA1, older PNs are presumably better tuned to receive external sensory inputs as their firing is more anchored to external landmarks while later born PNs, would be more likely to convey an internal "memory stream", more likely to participate in SWRs, and more likely to convey self-referenced information, with slower if any remapping and more stable place maps (59, 97, 107, 145, 189). This hypothesis agrees with the earlier maturation of unstable landmark-based place cells (223, 265), the "overgeneralizing" infantile memory, and protracted emergence of episodic memory and idiothetic navigation (216).

While neuronal physiology and function seem to match well the temporal schedules of development across the main hippocampal axes at the population level (Figure 1), there are exceptions to this statement. For example, resting membrane potential, action potential threshold or dendritic morphology do not seem to segregate that well along the radial and transverse axes as a function of temporal origin (47, 75, 158, 163, 181). The distribution of soma position itself can diverge from developmental axes at the population level when examining specific neuronal subtypes (as reported for stellate cells in EC LII vs. pyramidal cells in EC LIII, (73)). Hence, hippocampal cells originating from the earliest stages of neurogenesis (around E10) are often uniformly distributed rather than anatomically clustered at specific locations (46, 221). Altogether, this indicates that the link between developmental origin and adult position and function may also need to be examined at single neuron level. Various fate-mapping approaches have been developed to permanently label individual neurons at the moment they exit cell division. With these methods, it has been shown that the adult phenotype of the diverse population of hippocampal GABAergic neurons is rooted in their spatio-temporal embryonic origins (16, 51, 126, 211, 244, 245, 259). A particularly appealing population of cells are those pioneering hippocampal neurogenesis, the earliest cohorts of GABAergic and glutamatergic neurons (Figure 2). Using inducible genetic fate-mapping that allows for the labelling of neuronal precursors according to the developmental schedule at which they express specific sets of transcription factors, pioneer GABAergic cells develop into a network of long-range projecting GABAergic neurons linking the adult hippocampus to the septum and entorhinal cortex (259). These cells are morphologically and neurochemically diverse but share this major distinctive anatomical feature. In addition, pioneer GABA cells display specific intrinsic excitability and connectivity schemes (30), including a bias for long-range targets and local excitatory inputs. *In vivo*, they signal a variety of network states (30), thus sharing this generalization function with their glutamatergic early born counterparts. A similar approach has been applied for glutamatergic neurons in CA3 and DG (175, 221). Like pioneer GABA cells, the earliest born glutamatergic neurons display distinctive neuronal physiology but diverse morphologies, with a lower excitability in early born DG neurons (221) and a higher propensity to trigger network bursts in the absence of fast inhibition (175) or to control local network transfer function (151, 221). Interestingly, both early born GABA and glutamatergic neurons share a stronger network influence than other cells, in CA1, CA3, Dentate Gyrus and entorhinal cortex (8, 30, 100, 175, 211, 221).

It is thus becoming increasingly clear that development provides a significant scaffold to hippocampal circuits that can be revealed at both the single-cell and population levels. Therefore, studying the developmental establishment of functional circuits should provide a unique tool to dissect the rules governing adult hippocampal organization. The next sessions will review the emergence of a mature hippocampus at the structural and functional level.

Emergence of the hippocampal structure

One mechanism by which temporal origin may structure neuronal phenotypes in the hippocampus is by providing the opening step in a chain of stereotyped processes involving preset sequences of transcription factor signaling (242) and activity-dependent regulations occurring during migration, early postnatal cellular maturation and later integration into functional networks. There is indeed a tight correlation between several markers of development and the age of individual cells (8, 73, 175). We will now describe the timing of all of these early steps, focusing on rodent literature and on events that are more prominent or different in the hippocampus.

Hippocampal neurogenesis

Molecular signals from the cortical hem, a source of Wingless-related (WNT) and bone morphogenetic protein (BMP) signaling located in the embryonic dorsomedial telencephalon, instruct the formation of the hippocampus as opposed to the neocortex (98, 173). Similar to their counterparts in the neocortex, excitatory glutamatergic neurons in the hippocampus are produced locally by progenitors in the ventricular zone of the primordial hippocampal area, adjacent to the cortical hem (12, 22, 205, 277), while prospective inhibitory GABAergic neurons originate from the medial and caudal ganglionic eminences in the ventral telencephalon (212, 245). The time span of hippocampal neurogenesis in rodents is compressed within less than ten embryonic days, from day 10 to 18. In humans, hippocampal neurogenesis occurs within 2 weeks, from Gestational Week (GW) 16 to 18 (277). In the mouse, pyramidal cells are generated between E10 and E18, with a peak at E14 in CA3 and E15 in CA1 (Figure 3). Subiculum and CA2 terminate neurogenesis earlier (E15) than CA1 and CA3 (E16). As in the neocortex, the peak of neurogenesis for GABAergic neurons occurs earlier (around E12) than for glutamatergic cells. GABAergic neurons are born

between E9 and birth and the timing of their birth has a significant impact on their adult fate. In the hippocampus, MGE-derived GABAergic neurons are globally born earlier than CGE-derived neurons. Interestingly, hippocampal MGE-derived interneurons are generated earlier and within a narrower temporal window than their neocortical homologs (210). MGE-derived interneurons include PV-expressing GABA neurons (basket cells, axo-axonic, bistratified cells), Ivy cells, SST-expressing GABA cells (like OLM cells or long-range GABA cells), and a subset of Neurogliaform cells (210). The earliest born GABA cells (E9), presumably of MGE origin, operate as hub neurons during early postnatal development and later become a diverse population of GABA neurons, including a subset of somatostatin-expressing cells, with an extrahippocampal target (30, 259). The peak of neurogenesis of SST and PV interneurons in CA1 occurs at the same time, two days after the earliest cells are born, at E11.5, which contrasts with the neocortex, where PV neurogenesis is delayed from SST by about 2 days. Two days later (E13.5), the peak of neurogenesis for nNOS-expressing interneurons occurs, and later still (E15.5), that of PV-expressing chandelier cells. In other words, there seems to be a paced wave of neurogenesis among MGE-derived interneurons, initiated by long-range hub neurons, followed by basket and O-LM cells, nNOS interneurons and closed by chandelier cells (Figure 3). Hippocampal CGE-derived interneurons include CCK-, VIP-, CR-, reelin-M2R- and some SST-expressing interneurons as well as a subset of Neurogliaform cells. These are generated later than MGE-derived cells, with CCK-, VIP-, and M2R- interneurons generated at around E13 followed at E16 by CR- cells. In contrast, reelin- and CoupTFII- expressing cells are produced consistently throughout this developmental period. We will see below how the emergence of a recurrent network provided by local interneurons is a critical step in the patterning of internal hippocampal dynamics. We will also see how hippocampal developmental studies may receive inspiration from studies performed in the neocortex, where the circuit maturation and fate-mapping of interneurons is more advanced than in the hippocampus, where most of the information described above comes from a single study by McBain and colleagues (245).

Migration of hippocampal cells

The hippocampus is quite different from the neocortex regarding neuronal migration. Interestingly, multiple migration modes, speeds and routes have been reported depending on birthdate. In mice *Cornus Ammonis (CA)*, migration occurs from embryonic neurogenesis to

the end of the first postnatal week, when the last interneurons find their final position. Hippocampal migration is a slower process than in the neocortex (about one week for CA glutamatergic neurons and two days for GABA neurons, Figure 3). As in the neocortex, hippocampal glutamatergic cells and GABAergic neurons follow different routes. In contrast to their neocortical counterparts, hippocampal pyramidal neurons do not migrate straight along a single radial glial fiber, but instead can spend some days in a multipolar state above the ventricular zone and later migrate in a "climbing mode" along different radial processes (144), which eventually even bend perpendicularly to the radial axis (271). Early-born pyramidal neurons migrate faster than later-born ones, which take 7–9 days to reach their final destinations, as they remain frozen for about 3 days in CA1 and 4 days in CA3 in the multipolar state (114, 144) . One major difference with the neocortex, related to these peculiar migration modes, is the fact that clonally related glutamatergic neurons in the CA1 region are arranged horizontally rather than vertically, due to their migration along horizontally bending radial glia (271).

Migration is also longer for hippocampal GABA neurons (48–72 h) than neocortical ones (24–48 h), maybe due to the longer distance to be traveled (245). They invade the hippocampus when pyramidal neurons are already settled and acquire their final position within the first postnatal week. Again, migration depends on birth order, with early born GABA cells migrating at a slower pace (more than 2 days to reach the hippocampus) than later born ones (Figure 3) (245). Interestingly, the first GABA cells colonize CA1 (from the subiculum) one day before CA3 (at around E14) through the superficial tangential migratory stream (closer to the alveus), whereas the deep stream stops at the CA1/CA3 border (172). Only after E16 do interneurons reach CA3 from the superficial migratory stream only, and by E17 the Dentate Gyrus (172). Overall, interneurons are present in CA1 as early as E17, before pyramidal cells (83). Interestingly, in contrast to the neocortex, hippocampal interneurons migrate primarily through the superficial path (from the pia in the neocortex), then radially to their final position. This process depends on AMPA-R activation (172), whereas migration of glutamatergic neurons depends on $GABA_A$-R activation (171). This indicates a possible crosstalk during migration between these two main cell-types which may result in the precise orchestration of their final positioning and wiring. It should be noted that migration still operates at a time when the first coordinated neuronal activity patterns emerge in the hippocampus (see below).

Maturation of the cellular properties of hippocampal cells

Maturation, the progression of cellular properties to their adult values, is a long process as revealed by the late transcriptional diversification of the dorsal and ventral parts of the hippocampus between P28 and P45 (155), or by the continuous growth of hippocampal volume until at least 5 years of age in non-human primates (152). It was recently proposed that the maturation of the entorhinal-hippocampal network, as indirectly revealed by the expression of specific anatomical markers (73), occurs sequentially along the main direction of information flow through the circuit with stellate cells in layer 2 of the medial entorhinal cortex being the first to display adult-like markers (P14), followed by CA3 (P20) then CA1 (P23) and 3 days later by dentate gyrus, subiculum, layer 5 of the medial and lateral entorhinal cortices, and, last layer 2 of the lateral entorhinal cortex (> P30). This order of maturation tracking the main information route in the hippocampus does not exactly match the chronological order of neurogenesis described above, as the subiculum or LEC are generated earlier than CA1 and CA3, which are both generated roughly at the same time. In fact, in humans, CA1 neurons were recently shown to be "more mature" than CA3 neurons at GW22 based on single-neuron transcriptomic data (277). Similarly in the rhesus macaque monkey, quantification of structural and molecular markers reveals that CA1 reaches adult-like volumes and levels of gene expression 6-months earlier than CA3, which only displays mature properties after one year of age (152). In fact, these conclusions depend on the biomarkers used to track cellular maturation. The previous study (73) used immunohistochemical analysis of doublecortin, parvalbumin and bassoon expression. All three markers are developmentally regulated but may not necessarily reflect the maturation of functional neuronal properties. Rather, there seems to be a good match between birthdate and cellular maturation. Indeed, the development of morpho-physiological intrinsic properties, connectivity or membrane expression of KCC2 in fate-mapped glutamatergic and GABAergic hippocampal neurons depends on their time of birth (8, 63, 175, 259). Furthermore, this relation between maturation and birth date translates functionally in the spontaneous activity observed at single-cell level (Figure 4C). Hence, developing hippocampal neurons are sequentially involved in spontaneous activities coordinated first by electrical synapses in the form of Synchronous Plateau Assemblies (SPA, Figures 4C&7), and later by

GABAergic synapses (7, 55) within Giant Depolarizing Potentials (GDPs, (24), Figures 4C,7&8).

Interestingly, these activities, described in slices, therefore isolated from extra-hippocampal and sensory influences, most likely reflect self-organized hippocampal dynamics emerging from the global maturation stage of the neuronal population. Within a given slice, individual cells will be either involved in SPA or GDP networks depending on their birthdate (8). In sum, the spontaneous activity of a given cell will reflect its birthdate, which in turn should contribute to its integration into functional networks with age-matched cells displaying similar activities, ultimately forming temporally-matched circuits as observed in adults (63). We have seen above that the two physiological cellular metrics that best segregated adult GABA and glutamatergic hippocampal neurons according to their presumed birthdate were Ih and Rm. Interestingly, the expression of both is tightly regulated during development. Membrane resistance and Ih typically linearly decrease as a function of age (at least until P35, Figure 4B (25, 76, 237)). Accordingly, all neurons involved in SPAs display a larger sag current than more mature cells involved in GDPs (55). Altogether, more mature neurons in the developing hippocampus have a lower sag and lower Rm, which is exactly the same difference as observed in the adult, once development is complete, between neurons with a putative older temporal origin and their peers. This is almost as if younger neurons never caught up with their older peers. In other words, the differences between hippocampal neurons seen in the adult may result from the naturally arrested maturing process of all cells following the same developmental journey from different starting points. This concept may even extend to connectivity patterns.

Developmental cell death

Most of the maturing hippocampal neurons end up wiring into functional networks, however a significant fraction of them are eliminated by cell death. This physiological process by which excess cells are removed through programmed apoptotic death is essential for the development of balanced networks (130, 199, 232, 268). Developmental apoptosis has been the recent focus of several excellent studies (29, 81, 213, 232, 268) in the developing neocortex (see (45, 269) for review). This phenomenon has not been reexamined as thoroughly in the hippocampus as in the neocortex. However, the hippocampus is known to display similar features. As in the neocortex, developmental apoptosis is mainly observed

during the first postnatal week in rodents and affects both glutamatergic and GABAergic cells. In the neocortex, cell death occurs in excitatory cells between birth and P5 and between P5 and P10 in interneurons (268) and results in the disappearance of more than one third of both cell types (45, 232, 269). As in the neocortex, developmental apoptosis involving hippocampal principal cells and interneurons is strongly stimulated by ethanol (124, 167). The temporal schedule and the intensity of developmental cell death also depends on the cell type in the hippocampus and it displays regional differences. For example, the hippocampal subregions that appear to display most signs of apoptosis are the CA1 stratum oriens and the distal CA1 (94). The density of apoptotic cell debris peaks at around P4 in the mouse CA1 , together with microglial cell density (90) while fragmented DNA was preferentially observed at P1 in rat pups (264). Some subpopulations like CGE-derived hippocampal interneurons decrease by up to 80% between birth and P10 (246). In contrast to the neocortex, the population of pioneer Cajal-Retzius cells residing in the hippocampus displays a delayed cell death, independent from caspase 3 activity and with almost twice as many surviving cells compared to the neocortex (14, 45). Cell death does not simply coincide with periods of high levels of spontaneous neuronal activity, it is an activity-dependent process (whereby increased activity generally promotes survival) (45, 167, 199, 269). The molecular mechanisms linking electrical activity to developmental apoptosis are starting to be elucidated (198, 213, 269). Interestingly, apoptosis seems to depend on the precise dynamics and mechanisms supporting spontaneous activity (29, 81, 198). It will be of great interest to determine the type of spontaneous activity preferentially regulating cell-death in the hippocampus. The time course and distribution of apoptosis in the hippocampus as well as the coupling between maturation and cell death through calcineurin (213) suggest involvement of SPAs (55). Future work is needed to gain a better understanding of the mechanisms and developmental profile of programmed cell death in the hippocampus.

Wiring of hippocampal circuits

Local recurrent connectivity and long-range extrahippocampal inputs differ in their developmental profile, the former globally emerging later (postnatally, (99, 179)) than the latter (before birth, see below and Figure 5). Most sensory information is conveyed to the hippocampus through the entorhinal cortex. The LEC matures before MEC and projects onto older CA1 pyramidal cells (CA1a) while MEC targets CA1b and c (22). In rats, axons emerging

499 from pyramidal-like cell bodies located in the entorhinal cortex are first found in the *alveus* of
500 CA1 as early as E16 (alvear and commissural pathway) and one day later in the *lacunosum*
501 *moleculare* (temporoammonic pathway), almost a week before the EC innervates the outer
502 molecular layer of the DG (from P2, Figure 5 (68, 236)). This early innervation of CA1
503 contrasts with the fact that layer 2 stellate cells contacting the DG were shown to mature
504 earlier than pyramidal cells (73). Therefore, axons originating from the EC innervate CA1
505 before birth in the oriens and lacunosum moleculare, and GABAergic neurons, in particular
506 neurons with an extra-hippocampal target (259) together with Cajal-Retzius cells (13, 14,
507 48, 235) are the first candidate postsynaptic targets to be present (83). In turn, CA1 and DG
508 Cajal-Retzius cells send axonal projections to the EC as early as E17. Next, a notable increase
509 in the density of entorhinal axons terminating in the hippocampus is observed at birth and
510 maturation of these afferents extends until P5 (Figure 5) (236). Interestingly, this early
511 innervation of CA1 by the EC is functionally reflected by the fact that EC activation precedes
512 early sharp waves in the hippocampus at perinatal stages (see below, (254)). The septum,
513 which in the adult is critically involved in generating theta sequences and organizing internal
514 hippocampal dynamics (262) but also in conveying unexpected sensory inputs (276), sends
515 inputs to the hippocampus before birth in rodents, with putative CA1 interneurons being
516 targeted as early as E16 (236), followed by pyramidal cells (E17, Figure 5). Interestingly,
517 hippocampal GABAergic projections may pioneer the hippocampo-septal circuit by sending
518 axons to the medial septal region, thereby guiding outgrowing septohippocampal fibers (236,
519 259). Like for EC inputs, septal projection continues to mature after birth, in particular the
520 projections to the *strata radiatum* and *lacunosum*, but reaches adult patterns as early as P10.
521 Thus, a general sketch emerges by which inputs from the EC and septum reach CA1 a few
522 days before birth and target GABAergic interneurons, including those with a long-range extra-
523 hippocampal projection. Reciprocal long-range GABAergic connections may thus critically
524 pioneer interactions between the hippocampus and other brain areas, in particular those
525 conveying sensory information. In this framework, the perinatal development of one
526 particularly interesting GABAergic input originating from the nucleus incertus in the
527 brainstem, with a function in memory encoding (239), remains to be further examined.
528 Commissural projections, connecting hippocampi from both hemispheres seem to develop
529 slightly later, with dorsal ones developing earlier than ventral ones, and the DG being
530 innervated only after P5 (236). Just after birth, projections onto the intermediate/ventral CA1

from the *nucleus reuniens* in the Ventro Medial Thalamus, a major hub in reciprocal hippocampo-prefrontal interactions, have been described as early as P1, whereas the hippocampus sends projections back to *nucleus reuniens* only at P5 (Figure 5) (112). Besides extrahippocampal GABAergic and glutamatergic inputs, acetylcholine, dopamine and serotonin releasing afferents develop at early postnatal stages, where they also influence local circuits (35, 37, 153, 194).

While long-range inputs seem to settle before birth, the first postnatal week is the time when local recurrent connectivity emerges (Figure 5). Dendritic GABAergic innervation develops before the perisomatic GABAergic coverage (58, 179, 251), and most likely after long-range GABAergic connectivity (259) (Figure 5). In general, the intrinsic morpho-physiological properties of GABA neurons develop according to their birthdate, following a stereotyped sequence (8), with early born interneurons contributing to a significant fraction of local axonal coverage (211). Interestingly, the end of the first postnatal week marks an abrupt surge of recurrent connectivity with the emergence of perisomatic GABAergic innervation in the CA1 pyramidal layer and the exuberant branching of CA3 axon collaterals (99, 111, 179, 238). This is also the time when connectivity between CA3 and CA1 develops, starting from P2 (Figure 5) (84). A similar phenomenon has been reported in the neocortex, including recently through imaging of perisomatic GABAergic domains in the barrel cortex (195). Interestingly, in that region, transient targeting of deep layer somatostatin interneurons by early thalamic inputs contributes to the emergence of perisomatic inhibition (177, 249). Following that idea, one could speculate that hippocampal somatostatin interneurons, activated by extrahippocampal inputs, whether or not of thalamic origin, would directly support the development of perisomatic GABAergic synapses, as in the neocortex. We would thus like to propose a general scheme by which early bottom-up inputs, conveyed through canonical or non-canonical paths would foster the emergence of recurrent connectivity in an activity-dependent manner. Such recurrent connectivity, emerging at the end of the first postnatal week, before active exploration, gives birth to “smart networks” capable of learning and sustaining self-organized internal dynamics (204).

Early hippocampal dynamics

562 We will focus here on the first postnatal month in rodents since that is the time it
563 takes for the emergence of the mnemonic and navigational functions of the hippocampus
564 (Figure 6,9,11&12). Reconciling prior studies on the emergence of hippocampal dynamics into
565 a unified picture is a difficult task for three main reasons. First because the menagerie of
566 hippocampal dynamics described during the first postnatal month were obtained using either
567 electrophysiological recordings or calcium imaging, with only a few studies performing both
568 simultaneously (not *in vivo*); it is therefore difficult to bridge that experimental gap. Second,
569 because early hippocampal network activities were most often dissected mechanistically in
570 slices (or even cultures) and their *in vivo* counterpart is not always known. Third, early
571 hippocampal dynamics have been studied along two different perspectives, either looking at
572 patterns that are thought to be important for the maturation of functional circuits (usually
573 referred to as *spontaneous activity*) or tracking the emergence of "typical" hippocampal
574 patterns observed in the adult such as theta sequences and ripples, in the context of gaining
575 understanding about hippocampal function.
576
577 *Spontaneous activity*
578 The now classical paradigm by which the brain is thought to operate as it develops,
579 was first evidenced in a pioneering work on prenatal development of the visual system in
580 primates by Rakic (214, 215)) and formulated in a seminal review by Katz and Shatz (134) as
581 follows:
582 *"Early in development, internally generated spontaneous activity sculpts circuits on the basis*
583 *of the brain's "best guess" at the initial configuration of connections necessary for function*
584 *and survival. With maturation of the sense organs, the developing brain relies less on*
585 *spontaneous activity and increasingly on sensory experience. The sequential combination of*
586 *spontaneously generated and experience-dependent neural activity endows the brain with an*
587 *ongoing ability to accommodate to dynamically changing inputs during development and*
588 *throughout life."*
589 This developmental paradigm has been verified through a prism of various systems and
590 species, and was largely elaborated in:
591 - the visual system of rodents, which are born blind and in which spontaneous waves of
592 activity in the light-insensitive retina drive most of the activity in the visual thalamus, cortex

and superior colliculus during the neonatal period, which is also a critical period for activity-dependent formation of retinotopic maps (1, 17, 28, 54, 106, 110).

- the auditory system of rodents, where spontaneous activity in the sound-insensitive cochlea similarly drives activity in auditory relay centers and auditory cortex during the period of "deafness of immaturity" (19, 186, 247, 261)

- in somatosensory circuits, in which sensory feedback from spontaneous myoclonic movements triggers activity, in a somatotopic fashion, in somatosensory regions of the spinal cord, thalamus and cortex, and most likely participates in the activity-dependent formation of cortical sensory maps during the critical period of thalamocortical plasticity (125, 143, 184, 273).

Together, these studies across three different sensory cortical areas show that early perinatal cortical dynamics are not strictly generated locally but rather driven by spontaneous activity originating from the sensory periphery which itself is still insensitive to environmental sensory stimuli (visual, auditory) or from spontaneous movement feedback in the somatosensory system. The latter system formally violates the theory of "internally-generated spontaneous activity in sensory organs" as it responds to external stimuli before birth and can be driven by tactile stimulation from the mother or the siblings (6, 188), probably reflecting the vital implication of somatosensation in survival including feeding behavior. In the same way, early activity in the olfactory-processing lateral entorhinal and piriform cortices and olfactory bulb is patterned by olfactory stimuli - dependent theta oscillations in olfactory bulb (105), and is thus not internally-generated, in strict terms, again probably due to the vital role of olfaction in survival as required for mother recognition without visual and auditory abilities.

In the hippocampus, a variety of *spontaneous activity* patterns have been documented at various developmental stages *in vivo* and *in vitro* using electrophysiological and imaging approaches (Figure 6 and Table 2). We will review these early hippocampal activity patterns in chronological order with an attempt to propose a unified classification, mechanism and function. We will also discuss whether these early patterns are transient in development, or whether they are early precursors of adult patterns (Figure 9).

Spontaneous uncorrelated activity

Spontaneous uncorrelated activity is the earliest form of activity, characterized by sporadic calcium spikes poorly correlated between neurons and reported in hippocampal slices *in vitro*

(Figures 6B&A&B7) during embryonic stages (55). This form of activity has been also reported in the neocortex (7, 34) and cerebellum (146) and it reflects the absence of functional electrical or chemical synapses between neurons. These earliest developmental stages are also characterized by very slow non-synaptic activity transients which are driven by the paracrine actions of glutamate and GABA (67). None of these patterns have been reported *in vivo* so far and their physiological functions are thought to involve neuronal differentiation and migration.

Synchronous plateau assemblies (SPA): spontaneous gap-junction mediated activity

These emerge at birth and represent the earliest form of spontaneous coordinated activity in the hippocampus (Figure 7). SPAs are local synchronizations recorded in slices, and likely a general step in the evolution of spontaneous neuronal activity, since similar patterns have been reported in the developing neocortex (7, 82) and striatum (64). SPAs are characterized by recurring membrane potential oscillations (1Hz) producing action potential firing and a sustained calcium plateau for periods of about ten seconds (55). They are highly voltage-dependent as they involve Ih and L-type calcium channel activation, and are synchronized across small groups of neurons via electrical synapses (Figure 7C&D) (55). Both GABAergic and glutamatergic neurons are involved in SPAs. One appealing possibility is that SPAs transiently synchronize clonally-related neurons, as shown in the neocortex (275); this remains an open question since hippocampal sister PNs have not yet been recorded at early postnatal stages (271). SPAs are modulated by oxytocin and peak at birth (55). They are progressively and actively shut-down by the emergence of GABAergic inputs, in particular GDPs (Figure 7C). The transition between SPAs and GDPs appears as a critical developmental checkpoint for each CA1 neuron (55). For a few days around birth, SPA and GDP circuits co-exist, and it is likely that for each individual neuron the time course of its recruitment into SPAs and then GDPs is intrinsically determined by its birthdate (Figure 4A) (8). SPAs have not yet been reported *in vivo*. Given that SPA assemblies are sparse and scattered, and that the electrophysiological signal associated with them is comprised of slow depolarizations, one would not expect them to produce any prominent extracellular electrophysiological event. Therefore, SPAs can be easily overlooked during *in vivo* extracellular recordings and calcium imaging would be needed. The traces left by SPAs at later stages remain to be determined. One interesting hypothesis is that the large calcium transients associated with SPAs guide the

formation of common excitatory and inhibitory inputs (84, 271) onto subsets of neurons that later form stable assemblies in the adult hippocampus. The filopodia and giant miniature events displayed by SPA cells indirectly support this role of SPAs in local circuit wiring(11).

Giant Depolarizing Potentials (GDPs): spontaneous synapse-driven activity

Giant Depolarizing Potentials (GDPs) are historically the first population activity pattern described in hippocampal slices of neonatal rodents (24, 96, 111, 142) (Figure 8A&B). GDPs can be observed in hippocampal slices and the intact hippocampal formation *in vitro* starting from the perinatal period and vanish at the end of the second postnatal week (Figures 6&8). GDPs are associated with population bursts and elevations of intracellular calcium lasting several hundreds of milliseconds and occurring at a frequency of ~10/min. Participation of neurons in GDPs decreases along with a reduced number of neurons excited by GABA during the second postnatal week (96, 142, 250). GDPs typically originate from the CA3 region of the hippocampus which operates as a GDP-generator because of: (i) a relatively high amount of recurrent excitatory glutamatergic connections between PNs, (ii) spontaneous bursting of many CA3 PNs supported by non-inactivating sodium conductance and low expression of potassium channels involved in I_m (185, 228, 229, 253) and (iii) the presence of highly connected GABAergic hub neurons (33). From CA3, GDPs typically propagate to CA1 and to DG, but they may also originate in CA1 and backpropagate to CA3 (32, 185, 228, 253, 263). Backpropagation of GDPs may be supported by CA1 GABAergic hub cells with extended axonal morphology (30). In the preparation of interconnected hippocampi *in vitro* (136), GDPs propagate to the contralateral hippocampus via the ventral hippocampal commissure and medial septum and EC (138, 160). Interestingly, in EC-hippocampal slices, spontaneous bursts of activity in EC fail to propagate to the hippocampus (62, 201). In the longitudinal axis, GDPs typically originate in the septal (dorsal) part of the hippocampus and propagate relatively slowly (7-10 mm/min) towards the ventral hippocampus (160). This may reflect the earlier birthdate of dorsal CA3 neurons than ventral ones.

GDPs are generated by the collective discharge of PNs and INs whose excitation is supported by complex interactions between depolarizing/shunting GABA and glutamate–activated synaptic conductances (140, 162, 185). GDPs are only observed during the period when GABA exerts depolarizing and excitatory actions, and they are completely suppressed by the NKCC1 antagonist bumetanide, which also suppresses the depolarizing and excitatory

effects of GABA (85, 253). Yet, the action of GABA at the network level also involves inhibitory shunting effects and dynamic changes in the driving force acting on currents through GABA channels during GDPs. For example, GABA may exert depolarizing action at the GDP onset but switch polarity to hyperpolarizing at the GDP peak (140) (Figure 8C). In addition, intracellular chloride concentration and thus GABA actions not only significantly vary between neurons, but also change during GDPs (165, 166). This dualism in GABA action explains the diverse effects of drugs modulating GABA(A) receptor functions and manipulations with INs excitability. In line with excitatory GABA actions, GDPs are promoted by positive allosteric GABA(A) modulators and agonists (137) and by optogenetic stimulation of SOM-INs (95), and suppressed by optogenetic inhibition of MGE-derived INs (including SOM-INs; interestingly, inhibition of CGE-derived INs affects GDPs less) (Figure 8G) (263). On the other hand, GDPs are transformed to epileptiform discharges after blockade of GABA(A) receptors (137, 253). The dualism in GABA actions also involves inhibitory effects of GABA mediated by presynaptic (183) and postsynaptic (139) GABA(B) receptors, which contribute to the termination of GDPs similarly to the GABA(B) receptor mediated termination of SPWs in adult animals (88).

GABAergic hub cells are likely important players in the coordination of hippocampal dynamics at the end of the first postnatal week in rodents. They are characterized by :(1) high output functional connectivity (i.e. they are active before most cells in the network); (2) high effective connectivity since their stimulation significantly affects network dynamics; (3) high anatomical connectivity with widespread axonal arborization crossing subfield boundaries; and (4) they receive more excitatory postsynaptic potentials and have a lower threshold for action potential generation than other INs (33). Hub neurons are most likely involved in the coordination of GDPs, however, their exact role is more complex than acting as pacemakers. Indeed, even though hub cells are spontaneously active at the onset of GDPs and have many postsynaptic targets (33), their stimulation may trigger GDPs (Figure 8E) but most often results in desynchronization (i.e. a decrease in the frequency of GDPs or a progressive phase delay in the period of GDPs (33), Figure 8F). Such desynchronization may have several causes, including a shunting or inhibitory action of GABA in some cells or an out of phase stimulation of intrinsic pacemakers. In addition, genetic fate mapping experiments showed that early-generated GABA cells form a sub-population of hub neurons (211). Accordingly, the maturation of the intrinsic morpho-physiological properties of early born hub cells as well as

their functional network integration, nicely parallel the developmental emergence of GDPs (259).

The age of non-hub cells also influences their participation in GDPs. As discussed above, the date of transition from an SPA to GDP network depends on the age of the cell (8, 175). This is also supported by clear correlation between the emergence of synaptic currents (that marks a transition from SPAs to GDPs) and the level of morphological differentiation of PNs and INs (118, 251), also seen in fetal macaque hippocampal slices (141). It is equally possible that the developmental excitatory to inhibitory switch in the action of GABA is set by birthdate as shown for early-born GABA cells (259). Thus, the dates of both entry to and exit from GDP-circuits could be individually determined for each neuron according to its age.

GDPs have been suggested as instrumental for synaptic plasticity and to guide the formation of intrahippocampal circuitry including a transition from silent NMDA receptor -mediated synapses to functional AMPA/NMDA receptor-mediated synapses, and the for maturation of GABAergic synapses (133, 190). Interestingly, the peak of GDP expression in CA1 matches the emergence of local recurrent connections (both CA3 and local GABAergic networks around P7), suggesting they could serve as a biomarker of this stage of circuit development. As such, it seems important to know whether a homologous pattern involving similar circuits and dynamics, can be observed *in vivo*. A major feature of GDPs is their internal generation in the hippocampal circuit in the absence of any input and their main generative mechanism involving recurrent excitation within the CA3 network similar to adult SPWs. Below, we provide evidence that early Sharp Waves (eSPWs) are the activity pattern during which the internal circuit of the hippocampus is first rehearsed, as observed with GDPs, but within a large-scale network involving the EC, the hippocampus and sensory-motor circuits.

Early Sharp Waves and tails in vivo

Early sharp waves (eSPWs) frequently followed by afterdischarges (so-called “tails”) are the earliest coordinated activity pattern reported *in vivo,* starting from P1 in the rodent CA1 (Figures 6&9). Based on their developmental timeline and their significant association with polysynaptic GABAergic events, eSPWs were initially described as the *in vivo* counterpart of GDPs (161). However, this equation may need to be slightly revised according to recent findings.

752 Overall, eSPWs are very similar to the electrophysiological phenotype of adult SPWs (besides
753 the absence of ripple oscillations, Figure 9B, C & Figure 11B). Like adult SPWs, they are highly
754 synchronized bilaterally between the left and right hippocampi (255), and along the
755 longitudinal axis (256), with a higher initiation probability in the septal pole and a speed of
756 propagation (250 mm/s) slightly lower than in adult animals (350 mm/s, (209)), but much
757 higher than the speed of GDP propagation in the intact hippocampus in vitro (7–10 mm/s,
758 (160)). However, while adult SPW-Rs are spontaneous top-down events, which are self-
759 generated in the hippocampal circuit, eSPWs are mainly bottom-up events involving the
760 inputs from EC, which are activated during myoclonic movements (startles and twitches,
761 Figure 9B&D). Therefore, eSPWs are distinct from adult SPWs despite the similarity in
762 electrophysiological traits. This is typical for many developmental activity patterns such as
763 neocortical delta waves, spindle-bursts and early gamma oscillations, which look similar to
764 but are mechanistically different from adult delta-waves, sleep spindles and gamma
765 oscillations (143, 187, 272).
766 The current source density profile of eSPWs in CA1 is characterized by two prominent sinks
767 located in strata radiatum and lacunosum-moleculare reflecting a co-activation of
768 intrahippocampal inputs from CA3 together with EC inputs (Figure 9B) (174, 255, 256). Both
769 superficial MEC and hippocampal units fire during eSPWs, with MEC L2/3, DG and CA1 units
770 showing the highest participation rates, and with MEC neurons firing before hippocampal
771 neurons (255). In addition, MEC burst-driven eSPWs are reliably preceded by myoclonic
772 movements (Figure 9D) (255), characteristic of active sleep during the neonatal period in
773 rodents (and fetal stages in humans). Based on these observations, the following network
774 model of eSPWs has been proposed (Figure 9B) (255). First, myoclonic movements generate
775 sensory feedback, which triggers activity bursts (early gamma and spindle-burst oscillations)
776 in the primary somatosensory cortex (S1) (6, 125, 143, 192, 273). S1 activity is further
777 conveyed to the MEC where it ignites an activity burst consisting of a sharp potential and a
778 beta-gamma oscillation. MEC L2/3 bursts are further conveyed from the MEC to the
779 hippocampus through two streams: (i) the temporoammonic pathway from MEC L3 to the
780 distal apical dendrites of CA1 pyramidal cells and (ii) the perforant path from MEC L2 to the
781 DG and CA3. Neuronal excitation in CA3 is amplified by a recurrent excitatory CA3 network
782 similarly to what occurs during adult SPWs (44, 57, 274) and GDPs in vitro (162) and
783 activates Schaffer collateral input to CA1. Thus, both inputs from EC and CA3 are co-activated

784 during MEC bursts/ eSPWs and their co-activation drives excitation of CA1 neurons. Notably,
785 the first functional glutamatergic synapses at P0 were only observed in CA1 PNs with apical
786 dendrites reaching the stratum lacunosum-moleculare (251). This raises the hypothesis that
787 the first glutamatergic synapses on CA1 PNs are of MEC L3 origin. The development of CA3-
788 CA1 synapses is delayed: they are absent at P0-1, and start to form only from P2 initially
789 mainly as NMDA receptor based "silent" synapses (84). This suggests that temporoammonic
790 EC inputs to CA1 mature earlier than Schaffer collateral inputs from CA3, and that the direct
791 EC – drive is pivotal for the generation of eSPWs in CA1. In agreement with this hypothesis,
792 severing the connections between the EC and the hippocampus suppresses CA1 unit
793 activation following movements (192). How S1 conveys sensory feedback from movements
794 to EC is less clear, however. As there is no direct input from S1 to EC, this should involve some
795 intermediate areas/structures such as the perirhinal cortex (39, 60, 267). In addition to the
796 cortico-cortical interactions, the link between movements and eSPWs may also involve
797 subcortical pathways such as projections from the nucleus reuniens from the higher order
798 ventromedial thalamus directly to CA1 (258) or projections from the medial septum to the EC
799 (276). Importantly, eSPWs become less frequent and dissociate from myoclonic movements
800 but persist in the "cerveau isole" preparation after severing external inputs through a
801 supracollicular transection (132), indicating that they are also internally-generated events
802 and that sensory input plays only a triggering role by analogy to S1 and V1 spindle-bursts (6,
803 110, 143). It would be of interest to test whether sensory inputs or spontaneous activity
804 from other modalities (retinal wave driven spindle-bursts and Slow Activity Transients (SATs)
805 in the visual system, cochlear-driven bursts in the auditory system, and olfactory bulb- driven
806 activity in the olfactory system) are also capable of triggering eSPWs. In addition, the
807 hippocampus is likely not the end-point but rather an intermediate station in the large-scale
808 bottom-up network activated by sensory feedback from myocloni Excitation during eSPWs is
809 further broadcasted from CA1 to the prefrontal cortex (3) and probably to other output
810 targets including the subiculum, the deep layers of EC, and the supramamillary nucleus of the
811 hypothalamus.
812
813 *Intermittent beta-gamma and theta oscillations*
814 While eSPWs are the amplest electrographic events in the neonatal hippocampus,
815 neuronal firing can also be observed during intermittent 1-5 s long population bursts. In about

half of the cases, these bursts are observed following an eSPW and are called "Sharp-and-tail" events (161). In CA1, population bursts are often associated with transient oscillations at a frequency of 20-30Hz (so-called *hippocampal beta* (174), or *gamma* (132, 191) oscillations). Similar bouts of short-lived oscillations were also found in CA3 starting from P5 (149, 248). These *beta/gamma* Hippocampal Network Oscillations (HNOs) increase in amplitude and frequency (towards the gamma frequency range) with age, and become modulated by theta rhythms starting from P8 (191). The activity bursts in which beta/gamma oscillations are intermingled with theta oscillations are often referred to as theta-bursts (3, 36, 65, 112). HNOs are characterized by current-source density profiles similar to eSPWs with sinks in CA1 *strata lacunosum-moleculare* and *radiatum* (174). Like eSPWs, HNOs co-occur with movements (174, 191) suggesting that they may also be driven by EC. Moreover, activity coherence between S1 and CA1 is higher in the beta (20-30 Hz) frequency range and is significantly reduced after lesion of the follicular (branch of CN-V) nerve (66). Since neonatal EC activity is organized in sharp potentials and *beta-gamma* bursts (201, 227, 252, 255), both types of EC activity likely contribute to the transfer of movement-triggered sensory feedback to the hippocampus. However, the EC is not the only driver of CA1 activity. Indeed, the intrahippocampal CA3 recurrent network may also be involved in the generation of HNOs, at least from the end of the first postnatal week, as indicated: (1) by the presence of a sink in *stratum radiatum* for Hippocampal Beta Oscillations (HBOs) (174); and (2) the parallel development of oscillatory activity at the beta frequency in CA3 and an increase in HNO frequency, amplitude and theta-modulation (149, 248). We propose that HNOs may not be a developmentally transient network activity pattern but rather precursors of mature slow/fast gamma oscillations, whose generation involves CA3 and EC as in adults, but display a lower fundamental frequency due to slower conduction delays in developing circuits and immature inhibition.

One last major subtype of hippocampal network activity patterns are theta oscillations, which in the adult rodent are observed during episodes of locomotion, active engagement, or REM sleep and provide an internal clock distributing CA1 dynamics into spike sequences (80, 262). It should be noted that theta oscillations do not necessarily generalize across species. Indeed, LFP fluctuations in humans, non-human primates, and bats tend to be either non-rhythmic, or concentrated in short oscillatory bouts as well as being task and cognitive state-dependent (40, 41, 86, 101, 128). However, the absence of a continuous theta rhythm, as reported in

bats, does not necessarily imply that the temporal phase coding thought to be intrinsically linked to theta in rodents is absent (86). Furthermore, the dissociation between the LFP signal periodicity, cell assembly synchronicity and phase coding may need to be considered when studying the development of theta oscillations, even in rodents.

In the adult rodent, CA1 theta oscillations are supported by the interplay between inputs from the septum, MEC, and CA3 with local and long-range GABAergic neurons and resonant intrinsic firing properties. The development of theta oscillations in the hippocampus was first described by LeBlanc and Bland in the form of intermittent bursts of activity within the theta frequency range occurring in CA1 and DG from P8-9 during movement and starting from P10 during RUN/REM-states or following cholinergic-agonist application (154). Starting from P8-10, theta-coherent activities synchronize the hippocampus, red nucleus, LEC, prefrontal cortex and ventromedial thalamus (3, 36, 65, 112). Notably, pharmacological inactivation of the medial septum blocks hippocampal theta oscillations at P12 (3, 36, 65, 112). From P10 to P23-28, theta oscillations increase in amplitude and frequency from 4 to 7 Hz. This developmental profile for theta oscillations has been confirmed by several studies (65, 161, 191), with a few reports suggesting an earlier emergence at P1-2 in the form of short bouts at 7-8 Hz frequency (36, 131). These events in younger animals may well result from the passive propagation of cortical spindle-bursts to the hippocampus (132). The exact network mechanisms underlying emergence and developmental changes in hippocampal theta oscillations, which likely involve maturation of theta-generative properties in CA3 and EC networks, local, notably inhibitory CA1 circuits, as well as cholinergic and noradrenalinergic control remain an open question for future investigations.

Role of GABAergic circuits in coordinating early hippocampal dynamics

While previous research has clearly identified instrumental roles of GABAergic neurons in the generation of GDPs *in vitro*, data on how interneurons shape network activity in the neonatal hippocampus *in vivo* remain sparse. On the one hand, barrages of synaptic GABAergic currents have been recorded during eSPWs and tails in CA1 PNs at P3-6 (161). Yet, manipulating interneuron activity did not provide consistent results (153). Lowering the excitability of hippocampal INs decreased the amplitude and frequency of eSPWs, while enhancing IN excitability did not affect eSPWs at P3 (Figure 10). At P7, manipulating GABAergic neuron excitability in either direction did not substantially affect eSPWs (200). In

880 contrast to these findings, immunotoxic lesion of CA1 INs decreased the occurrence of eSPWs
881 in P7-8 pups (26). Also, manipulation of depolarizing GABA actions through NKCC1 deletion
882 from telencephalic glutamatergic neurons decreased in-vitro excitatory GABA actions and
883 impaired GDPs in neonatal hippocampal brain slices but had a minor impact on correlated
884 spontaneous activity (eSPWs and HBOs) in the hippocampus of P3-4 mouse pups (102).
885 Optogenetic activation of Dlx5/6 interneurons inhibited theta-bursts, whereas their activation
886 boosted hippocampal activity in P8-10 mice (3). Thus, the roles of INs in shaping eSPWs and
887 early oscillatory activity in the neonatal hippocampus are far from being understood. Further
888 studies with the recording and targeted manipulation of specific subclasses of interneurons,
889 including hub cells, are needed. In particular, the functional and structural wiring of CA1
890 GABAergic neurons remains to be described, including the nature of their extra-hippocampal
891 inputs, the possible identification of transient scaffolds (177, 249), and their
892 interconnectivity schemes. This needs to be examined in detail with a high sampling rate
893 given the rapid changes occurring in the circuitry during the postnatal period. There are
894 however some facts that can help in this endeavor. First, as discussed above, the
895 development of perisomatic GABAergic innervation occurs quite late during cortical
896 development (61, 70, 179, 187, 193). Second, eSPWs lack ripple-oscillations, whose
897 generation involves perisomatic inhibition and which emerge during the second postnatal
898 week and attain adult-like features by P20 (Figure 11B) (38, 130, 161). Third, inhibition
899 based kainate-induced gamma CA3 oscillations also emerge during the second postnatal
900 week (in a form of beta oscillations) and acquire an adult-like phenotype by the third
901 postnatal week (248). Finally, while in adults EC inputs exert a global tonic inhibitory
902 influence on hippocampal activity, in neonates, activation of the EC excites all neurons within
903 the trisynaptic (EC layer 2 – DG – CA3 – CA1) and monosynaptic (EC layer 3 – CA1) EC-
904 hippocampal circuits during eSPWs (254). These findings support the hypothesis that
905 neonatal EC-hippocampal circuits operate without efficient feedforward inhibition during
906 eSPW to assist the integration and plasticity of excitatory inputs from major pathways. CA1 is
907 thus primarily driven by feedforward bottom-up excitation (Figure 9B). This is consistent with
908 an activity-dependent instructive signal provided by MEC to drive maturation sequentially and
909 unidirectionally through the intrinsic circuits of the entorhinal–hippocampal network during
910 the postnatal period (73). We further hypothesize that the transformation from eSPWs to
911 adult SPWs involves the maturation of the feedforward inhibitory circuits, with the

internalization of the primary SPW generator from EC to CA3 (also involving the development of the excitatory recurrent CA3 circuitry), the dissociation of eSPWs from movements together with a loss of EC drive to SPWs, and the emergence of ripple oscillations (Figures 6 and 9). Whether eSPWs themselves play a direct instructive role in the emergence of perisomatic axonal coverage is an open question.

Emergence of hippocampal sequences

The second postnatal week is the time when bottom-up driven eSPW and HNOs are progressively replaced by endogenous events in the form of SW-associated ripples and theta nesting gamma oscillations. As reviewed above, the emergence of these patterns is most likely supported anatomically by the appearance of recurrent networks comprising perisomatic inhibition and Schaffer Collateral CA3 inputs. At this stage, CA1 circuits switch from being mainly bottom-up driven by spontaneous activity originating from the sensory organs to displaying spontaneously recurring internal dynamics supported by intrahippocampal circuits, as revealed by the observation of recurring network bursts in the form of GDPs in preparations disconnected from external inputs such as slices. During this period, active exploration of the environment is limited, these spontaneous activities are therefore probably limited in their informational content and rather serve local network calibration purposes. The second postnatal week to a large extent remains a black box of hippocampal development that ends with the emergence of landmark-modulated place cells and stationary sequences (Figures11&12). The early appearance of place cells bound to external cues together with reactivation of stationary places (91, 197) suggests an earlier development of allothetic (i.e. cue-based) representation in CA1 (Figure 12). Accordingly, CA1PNs coding for cue-enriched environments in the adult were preferentially found in the deep part of the CA1 *stratum pyramidale,* where older cells should eventually locate (92, 225).

Since mice do not yet actively navigate during the second postnatal week it is difficult to know whether sequences of events are replayed. The fast oscillations characteristic of the sharp wave-associated ripples , observed both during the sleep and awake states, with their sink in the stratum radiatum indicative of CA3 input, are not seen before the end of the second postnatal week (P14 in rats (38)). Whereas the power of the SWRs gradually

increased with age during the third postnatal week (Figure 11B), the intraripple frequency was reported as constant (38, 44). As detailed in many excellent reviews including (44), SWRs are often associated with the compressed reactivation of place cell spike sequences occurring during navigation, with a major role in memory processes. Although place cells and SWRs were reported to emerge roughly at the same time (150, 265), recent evidence indicates that reactivation of traveled paths is not observed until one week later (around P23, Figure 11D (91, 197)), the time when grid cells appear in the MEC (150). The same is true for theta sequences observed during navigation (91, 197) (Figure 11D). This would indicate that the circuits necessary for binding together discontinuous events (relational information) are still immature at the end of the second postnatal week (Figure 11&12). However, at the beginning of the third week, cell pairs that fire together a significant amount of time during running are also more likely to be coactive during sleep, indicating that some form of post-experience Hebbian plasticity, with a higher co-activity threshold, is likely to occur as soon as place cells emerge(197). In addition, phase precession, the phenomenon by which the timing of spikes within a theta cycle is progressively delayed as the animal traverses a given place field, is also already present at this time(197). Both phenomena suggest that internal CA1 dynamics begin to keep track of experience within proto-sequences.

Two lines of findings diverge regarding the emergence of experience-dependent sequences during the third postnatal week. Some report that sleep replay and theta sequences emerge in a coordinated manner and progress from reactivating single locations, then short paths to longer trajectories between P17 and P32 (197). Others (91), observe a prior emergence of sequences unrelated to experience in the form of "preplay". The latter would indicate that a reservoir of preconfigured sequences is formed through an innate developmental program, serving as a backbone onto which future experience is mapped and encoded (Figure 11). These two views are comprehensively developed in recent reviews (78, 240). A three stage development of sequential activity patterns has thus recently been proposed (78): (1) end of second postnatal week: representation mode with "rate coding" of discrete locations (150, 265); (2) during the second postnatal week: emergence of preconfigured sequences, observed during rest or sleep in an age-dependent but experience-independent manner (but see (197)); (3) third postnatal week: age- and experience-dependent sequences of trajectories or episodes (theta sequences) are observed in higher proportions than preplay (91, 197). The earlier emergence of *rate coding* prior to *phase*

coding is somehow at odds with the recent finding that cells displaying a *rate code* are found in superficial layers and therefore born and mature after deep cells (225). Still, the fact that deep CA1 PNs comprise a higher proportion of place cells may partly explain this possible contradiction (189). It is also somehow inconsistent with the fact that spontaneous self-triggered body movements would tend to favor the initial development of *idiothetic* (i.e. based on self-referenced information) rather than *allothetic* (i.e. based on external landmarks) representations. Future work is needed to nail down these apparent discrepancies.

In conclusion, experience-dependent sequences would be the latest hippocampal pattern to mature during development (Figures11&12). Whether internal preconfigured sequences emerge before remains a debated issue. That sequences reactivating non-spatial contents of experience appear earlier is also an open possibility. Indeed, the observation of place cells requires the animal to move in an environment, which is delayed compared with the development of other senses such as olfaction. It is now well established that the hippocampus also encodes non-spatial features (eg. time, odors, sound frequencies, conspecifics) (15, 148, 168) and ripples may therefore reactivate content other than spatial information (18).

Development of hippocampus-dependent cognitive functions

This section does not aim to provide a comprehensive review of the ontogeny of spatial cognition and episodic memory, the two cardinal hippocampal functions, since many excellent recent reviews are dedicated to this very matter (see for example (71, 123, 136, 152, 216, 226, 240)). Instead, our objective is to interpret the emergence of these functions in the light of the developmental origin of hippocampal diversity. One particularly appealing concept towards this goal is the idea that navigation across autobiographical events (episodic memory) and in the real world (spatial navigation) relies on two mechanisms of hippocampal representation, one that is map or schema-based and depends on external multisensory landmarks (allocentric) and the other that is self-referenced and often requires body movement (egocentric) (42). In the adult, both representations work together but one may dominate according to the availability of external cues (for example in the dark, egocentric navigation dominates). Besides, these representations differentially contribute to a given

cognitive function. Hence, it has been proposed (42) that map-based navigation would support allothetic navigation and semantic memory (i.e. generalization of knowledge independent from context) while self-referenced information would be central to path-integration and episodic memory (i.e. 'mental travel' in time and space in reference to self). Given that earlier born CA1 pyramids are better tuned to cue-based representation and generalization while those born later encode self-referenced information (see section "Lasting traces of early development in adult hippocampal circuits"), episodic memory would be expected to develop later than allothetic navigation and semantic memory.

The development of episodic memory has been the focus of many cognitive studies in humans. Infants both lack knowledge of the self as an independent entity (121) and are unable to form or store memories for recall later in life, a phenomenon termed *infantile amnesia* until roughly two years of age (71, 216). Neither is spatial memory mature in infants before 20 months of age (203). In rodents, the onset of hippocampus-dependent spatial memory is delayed with respect to the emergence of place cells as assessed using different behavioral tasks that include the Morris Water Maze (5, 219), spatial alternation (104), Barnes maze, (182) or object location (56). It likely relies on environmental cues (5, 219), the same way place cells from young animals are stabilized by boundary information (196). In addition, grid cells, critical elements for path integration mature later than hippocampal place cells (150), which display distance coding based on self-motion (27). In addition, episodic aversive events elicited in rodents at the beginning of the third postnatal week create a latent trace in the hippocampus (108, 243).

While the emergence of complex forms of episodic memory and self-based navigation may be protracted, some aspects of hippocampus-dependent learning and memory are present early in life in infants. Besides its classic role in episodic memory, the hippocampus was recently proposed, based on human data, to be involved in statistical learning, i.e. the ability to extract regularities from the sensory environment and therefore segment a continuous sensory flow into sequences of cognitive units (117, 226). Statistical learning develops much earlier than episodic memory, as early as at 8 months in infants (220). Therefore, one appealing possibility would be that the first hippocampus-dependent cognitive function is statistical learning. This would culminate, once rodents or infants are able to travel in space, in the formation of place fields (150, 265), i.e. the chunking of a space continuum into segmented units. Statistical learning should inform predictive models and

allow more abstract, generalized and semantic knowledge. In this respect, infantile generalization (136, 216, 218) may be envisaged as a consequence of the early dedication to statistical learning of the hippocampus.

Recent modelling work suggested that the hippocampus supports the computations of both episodic memory and statistical learning via two pathways, the trisynaptic pathway (EC>DG>CA3>CA1) supporting episodic memory with the temporoammonic pathway enabling statistical learning (222). Experimental work in rodents indicates that early network dynamics in CA1 are mainly driven by direct EC inputs(255), while anatomical evidence in macaques (152) and rodents suggests protracted development of CA3, DG and consequently of the trisynaptic pathway (see section above). Both findings therefore give functional and anatomical support to the early development of the temporoammonic pathway (before the trisynaptic circuit) and the possible early commitment of the hippocampus to statistical learning. Given the correspondence of the developmental timelines between rodents and humans, this would start during the third trimester of gestation and certainly extend postnatally. A consequence of statistical learning is predictive abilities. It was also proposed that, in the adult, the predictive ability of the hippocampus and its role in retrieving memories are embedded in separate output pathways (21). Interestingly, in that framework, long-range hippocampal GABAergic neurons could function as an anatomical support to broadcast a predictive error signal (21). These cells are among the earliest to be generated (see previous section), again supporting the idea of an early wiring of intra and extra-hippocampal circuits for learning regularities and predictive coding.

In summary, we would like to propose that the hippocampus performs generalization based on statistical learning from the sensory world before being able to support egocentric episodic memory. This sequence in cognitive abilities nicely mirrors developmental schedules both at cellular and circuit level, with earlier born cells displaying a generalizing function, and the monosynaptic pathway maturing before the trisynaptic circuit. Future work in rodents is needed to confirm the possible implication of the hippocampus in statistical learning and its circuit basis, and in particular, to compare the developmental timelines for cue-based vs. internal hippocampal sequences.

Summary and conclusion

Hippocampal circuits emerge through a long developmental journey with several episodes and milestones. The first phase is neurogenesis and migration. Indeed, despite its fundamental role in learning and memory, the functional organization of the adult hippocampus is not only formed through experience-dependent plasticity, but is partly hardwired at the earliest stages of development, including embryonic neurogenesis. This is reflected in the dynamics of the adult CA1, which operates through a combination of plastic and rigid cells, bound together within segregated functional assemblies that support stable internal dynamics (107, 170). The propensity of individual cells to keep track of experience through intrinsic or synaptic plasticity may be rooted in their temporal origin, as indicated in several recent studies, with early born neurons serving a generalizing function and later born neurons assisting content discrimination. Future studies combining fate-mapping and in vivo physiology are needed to bridge the gap between neurogenesis and adult hippocampal function. Whether the final contour of hippocampal assemblies is set early in ontogenesis and stabilized through activity-dependent processes (eg. SPA), as described for cortical columns, remains an open question. Addressing this major issue should contribute to unraveling the topological logic of hippocampal functional maps.

Following neurogenesis and migration, the second phase starts at birth, when hippocampal circuits integrate into a large-scale bottom-up network that processes somatosensory feedback triggered by neonatal movements (Figure 12). This period is dominated by recurring network bursts, in the form of early sharp-waves and/or beta-gamma oscillations. While the exact circuit mechanisms and spatial organization of these bursts remain partly unknown, they certainly mirror the fact that extra-hippocampal inputs develop before intrahippocampal connectivity schemes, including feedforward inhibition. Future work is needed to reconcile the descriptions of early hippocampal dynamics *in vitro* and *in vivo* and in particular to probe the early synaptic function of GABAergic transmission. At present some *in vitro* patterns like SPAs lack an in vivo counterpart. Work is also necessary to describe the calcium dynamics associated with early electrophysiological activity patterns. Regardless, we propose that this period, which corresponds roughly to the third trimester of gestation in humans (53, 270), ends with the first postnatal week in rodents followed by a transition period with an emergence of adult activity patterns (theta and gamma oscillations, adult SPWs and ripples) during the second postnatal week. This is a critical period of structural

plasticity that terminates with the emergence of hippocampal recurrent connectivity, including feedback inhibition supporting the segregation of hippocampal assemblies, possibly along the radial axis (Figure 12). This is likely an activity-dependent but experience-independent process through which hippocampal "receptive fields" and local circuits calibrate local inhibition to the statistics of the external world. In other words, this second episode is likely the period when hippocampal circuits start building an internal model based on spontaneous and content-free activity from sensory organs and sensory feedback from myoclonic movements (Figure 12). This would fit the hypothesis that the hippocampus would initially support statistical learning. Future experiments are needed to test this hypothesis, either in rodents performing novel tasks aiming at probing statistical learning or in human babies for example using MEG (117). Addressing this critical question would enable the gap between species to be bridged. However, it requires a closer collaboration between cognitive and systems developmental neuroscience.

Towards the end of that period, both an "internalization" and a "sparsification" of activity are observed, most likely reflecting the emergence of a powerful inhibitory landscape and the consolidation of CA3 inputs. This period of structural plasticity is then followed by a period of internal spontaneous activity within the hippocampal formation supporting the emergence of circuits capable of comparing CA3 and EC inputs prior to active exploration. This period of functional plasticity ends with the emergence of place fields, first unstable (223) and landmark-based (265), followed by sequences integrating internal dynamics and external environmental cues. There are still many open questions, including those regarding the role of early network oscillations in the maturation of specific circuits and their link with adult network patterns or the role and function of specific GABAergic circuits. Nevertheless, we believe that the study of hippocampal development in the context of circuit physiology will pave the way for understanding memory circuits in the brain by watching the assembly of its building blocks.

Figure Legends

Figure 1: Possible link between the timing of neurogenesis and the diversity within CA1 pyramidal cells in the adult hippocampus as reflected by their anatomical distribution.

A: schematic cartoon illustrates the distribution of CA1 pyramidal neurons (PN) along the transverse and radial (inset) axes according to their presumed birthdate (from E12.5 to E18.5). Early born PNs (ebPNs) are represented in pink and later-born PNs (lbPNs) in green. ***B-D:*** Physiology ***(B)***, Connectivity ***(C),*** and Function ***(D)*** segregate along these two axes matching the timing of neurogenesis as illustrated below. ***B***: Input resistance (Rin) is smaller in deep or distal CA1PNs (pink) than in superficial or proximal ones (green). ***C***: Integration within perisomatic GABAergic inputs (red circles) also differentiates between eb and lbPNs, with lbPNs (located superficially or proximally) preferentially connecting onto interneurons and ebPNs preferentially contacted by perisomatic GABAergic inputs. ***D***: Distal and deep PNs are more likely to display multiple place fields than proximal or superficial ones. *B* from Ref. (129), with permission from *Journal of Comparative Neurology; C* from Ref. (207), with permission from *Hippocampus;* Ref. (158), with permission from *Journal of Neuroscience; D* from Ref (119), with permission from *Neuron* and Ref. (97), with permission from *Nature Communications.*

Figure 2. Early born GABAergic neurons (ebGABA) display characteristic physiology, connectivity, and function in the adult CA1. ***A****:* Fate-mapping experiments demonstrated that ebGABAs (born at E9.5) adapt their firing in response to long current injections ***(B)***, receive less local GABAergic inputs (lower putative PV contacts) ***(C),*** and display high functional connectivity ***(D)****. B-D* from Ref. (30), with permission from *Nature Communications.*

Figure 3. Developmental timeline of the neurogenesis and migration of CA1 neurons.

CA1 pyramidal neurons (PNs) and GABAergic Interneurons (INs) are born and migrate into their final positions from E10 until postnatal day 5 (P5) with different schedules for early-born (eb, red) versus late-born (lb, green) cells. The timing of neurogenesis is indicated for a few subtypes of INs. SOM: somatostatin, PV: parvalbumin; nNOS: Nitric Oxide, Chand.: chandelier, CR: Calretinin.

Figure 4: Developmental sequences for the maturation of morpho-physiological properties of CA1 neurons. ***A****:* Schematic description of postnatal changes in the morpho-functional properties of CA1 neurons. ***B****:* Input resistance and Ih decrease as postnatal age increases. ***C****:* Spontaneous activity shifts from gap-junction mediated Synchronous Plateau Assemblies (SPA, red) to synapse-driven Giant Depolarizing Potentials (GDP, blue) while the morphophysiological properties of GABAergic cells change from displaying filopodia, adaptive firing, and large miniature events to smooth cell bodies, firing diversity and small amplitude minis. ***D****.* The expression of KCC2 at the membrane is also developmentally regulated according to age with ebINs displaying membrane KCC2 as early as P3. *B* from Ref. (76), with permission from *Hippocampus; C* from Ref. (8), with permission from *Journal of Neuroscience; D* from Ref. (259), with permission from *Journal of Comparative Neurology*

Figure 5: Developmental timeline describing the wiring of CA1 hippocampal circuits. Long-range glutamatergic (top) inputs from the entorhinal cortex and septum as well as long-range GABAergic inputs reach CA1 first as early as the late embryonic stages. In turn, CA1 interneurons with a long-range projection to the septum mature before dendritic inhibition while somatic GABAergic inputs develop towards the end of the first postnatal week.

Figure 6: Global timeline for the development of hippocampal network activity patterns.
A, *in vivo* and *B,* in hippocampal slices and intact hippocampus preparation *in vitro*. Green indicates transient immature patterns, orange indicates emerging adult patterns. eSPW, early Sharp Waves; SPW, adult sharp waves; SPA, Synchronous Plateau Assemblies; GDP, Giant Depolarizing Potentials.

Figure 7: Emergence of correlated neuronal activity in the developing hippocampus *in vitro*. ***A****:* Developmental timeline of expression of hippocampal network activity patterns in vitro. ***B:*** Uncorrelated calcium spikes (black) are observed until birth when they are replaced by gap-junction mediated Synchronous Plateau Assemblies (SPA, red). In turn, SPAs are progressively replaced by Giant Depolarizing Potentials (GDP, blue) as illustrated by the histogram plotting the fraction of cells involved in either pattern as a function of time. These three patterns are associated with characteristic calcium fluorescence transients. ***C****:* GDPs actively shut down SPAs as shown by the example of a GDP terminating a calcium plateau and the associated

membrane potential oscillations measured in current-clamp mode. ***D:*** Neurons involved in SPAs are connected by electrical synapses as revealed by the spikelets recorded in current clamp (bottom right trace) and by multiple neuron labelling with neurobiotin. *B and D* from Ref. (55), with permission from Neuron; *C* from Ref. (8), with permission from *Journal of Neuroscience*.

Figure 8: Giant depolarizing potentials in hippocampal slices in vitro. ***A***: Timeline of GDPs. ***B***: Example traces of gramicidin perforated patch recordings from a CA3 pyramidal cell, multiple unit activity (MUA) and local field potential (LFP) recordings from the CA3 pyramidal cell layer in a P6 rat hippocampal slice. ***C***: Dynamic changes in GABAergic and glutamatergic currents in P5-6 CA3 pyramidal cells during GDPs. Note that GABAergic currents transiently switch their direction from depolarizing to hyperpolarizing at the peak of GDPs. ***D***: GDP network model. GDPs are initiated in CA3 recurrent network (1) with support of GABAergic INs (2), and further conveyed to CA1 via Schaffer collaterals and GABAergic projections (3), and to dentate gyrus via GABAergic projections. ***E***: Top, neurolucida reconstruction of the hub-IN (axon, red and dendrites, black) on a schematic drawing of the hippocampus. Left, Current-clamp recordings from the stimulated (grey box) hub-IN for six consecutive stimulations (gray). Four out of six trials triggered GDPs. Right, fraction of cells active as a function of time after repetitive hub-INs stimulation and corresponding peristimulus time histogram. ***F***: Top, histogram displaying the percentage of active cells (black) during stimulation of an early born IN (ebGABA) that was patched and stimulated by injecting suprathreshold depolarizing current steps (green trace). Bottom, box plots of "Inter GDP intervals" of a representative ebGABA cell (left) ***G***: Arch-mediated optogenetic inhibition of MGE-derived INs with a 10 s light stimulus (green) suppresses spontaneous GDPs and generates rebound GDPs in CA1. Left, Recording configuration with focus of yellowgreen light stimulus in CA1 to inhibit MGE-derived interneurons. Right, Example of simultaneous recordings in an MGE-derived IN (gray) and a neighboring PN (black). Activation of the Arch-current greatly reduced the frequency of spontaneous GDPs in both cells, which returned once the light was turned off. *B* and *C* from Ref. (140), with permission from *Journal of Neuroscience*; *E* from Ref. (33), with permission from *Science*; *F* from Ref. (30), with permission from *Nature Communications; G* from Ref. (263), with permission from *Journal of Neuroscience*.

Figure 9. Comparison of early sharp waves (eSPWs) with adult sharp waves (SPWs). *A*: Timeline of eSPWs and SPW/ripples. ***B***: Left, Example traces of the forelimb twitch (green circle), population burst in MEC-L3 (blue circle) and eSPWs (red triangle) recorded from the CA1 pyramidal cell layer (pcl), stratum radiatum (sr) and stratum lacunosum-moleculare (slm) in a P5 rat pup. Vertical color bars above traces indicate single unit activity. Middle, corresponding current-source density of eSPWs with the most prominent sinks in *sr* and around the hippocampal fissure. Right, eSPW network model. Note that sequential activation of various structures in this scheme follows the bottom-up information transfer from the spinal cord to hippocampus. ***C***: Left, Example traces of adult SPW/ripple in CA1 pcl and sr. Middle, current-source density of SPWs with the most prominent sink in CA1 *sr*. Right, SPW network model. Note that SPWs are internally generated in the hippocampus and support top-down information transfer from the hippocampus to the extrahippocampal targets. ***D***: Left, eSPWs are preceded by activation of MEC-L3 units in neonatal rat pups, whereas adult SPWs are associated with activation of neurons only in the hippocampal output deep EC layers. *B* from Ref. (254), with permission from Cerebral Cortex; *C* from Ref. (44), with permission from *Hippocampus* and Ref. (233), with permission from *Journal of Neuroscience*; D from Ref. (254), with permission from Cerebral Cortex and Ref. (52), with permission from Journal of Neuroscience.

Figure 10: Pharmacogenetic silencing of interneurons inhibits hippocampal activity in P3 mice. ***A****:* Representative recording for P3 reduction of GABAergic neuron excitability. MUA of spontaneous activity in CA1 hippocampus, along with associated *sr* LFP and thoracic movement detection and electromyography. Activity is dominated by eSPW whose spike density is reduced following subcutaneous SalB (KORD agonist) injection. ***B****:* Quantification of KORD-induced suppression of GABAergic neuron excitability and control conditions. *A* and *B* from Ref. (200), with permission from *Science Advances*.

Figure 11. Developmental timeline for the emergence of cognitive sequences in the CA1 region of the hippocampus *(A)*. ***B****:* Sharp-Wave-associated Ripples (SPW-Ripples) start being observed at P12 and their power progressively increases until the end of the third postnatal week. ***C:*** At P15, the first internal representations are observed in CA1 in the form of unstable place cells as illustrated by the heatmaps of the firing of three place cells across three recording

1259 sessions (S1, S2, S3). After P17, *preplay* and SWRs replaying single locations start being
1260 observed as illustrated by the heatmaps showing time-by-position probability using Bayesian
1261 decoding of position, based on event spiking. A few days later, the trajectories depicted
1262 within *replay* and *preplay* progressively represent longer trajectories and occur with similar
1263 incidence. ***D:*** After P24, experience-dependent sequences can be observed in the form of
1264 theta sequences and replay. Right plot shows a probability posterior derived from a single
1265 RUN session, where the x axis shows the proportion of time elapsed during the theta cycle
1266 and the y axis shows position on the track relative to the current location of the rat. The
1267 horizontal white line shows current rat location, and the vertical white lines demarcate one
1268 theta cycle. Hot colors show high decode probabilities. Numbers above the plots show theta
1269 sequence score, defined as the circular-linear weighted correlation of the probability
1270 posterior. *B* from Ref. (38), with permission from *Neuroscience*; *C* from Ref. (223), with
1271 permission from Hippocampus, Ref. (197), with permission from *Current Biology* and Ref.
1272 (91), with permission from *Science*. *D* from Ref. (197), with permission from *Current Biology.*
1273

1274 Figure 12. The main steps in the development of CA1 internal dynamics

1275 Schematic representation of the three main phases leading to the development of CA1
1276 internal dynamics. Phases 1 and 2 are periods when activity is generated spontaneously, first
1277 in a bottom-up fashion by spontaneous sensorimotor activity conveyed to CA1 by inputs from
1278 the entorhinal cortex (EC). At this time, local circuits are likely connected by gap-junctions and
1279 produce SPAs. EC inputs are more likely to innervate early born pyramidal neurons (ebPNs,
1280 pink) as well as eb Interneurons (Ins). This period terminates around the end of the first
1281 postnatal week (week#1) with the emergence of perisomatic inhibition (putatively originating
1282 from ebINs and contacting ebPNs which are decoupled from their electrical synapses) and
1283 CA3 collateral inputs. After this time, CA1 is also driven by spontaneous activity generated
1284 within the hippocampus (internally-driven and local), most likely through CA3 inputs. These
1285 are more likely to target late-born (lb) PNs (green) and lbINs (green), which may still be
1286 connected through electrical synapses. This period ends around the end of the second
1287 postnatal week (week#2) with the emergence of landmark-based internal representations in
1288 the form of place cells. This opens a period of about two weeks (weeks 3&4) during which the
1289 internal CA1 model is calibrated to sensory inputs through experience-dependent plasticity.

This period ends with the emergence of internal sequences (stage 4) integrating experience into internal dynamics.

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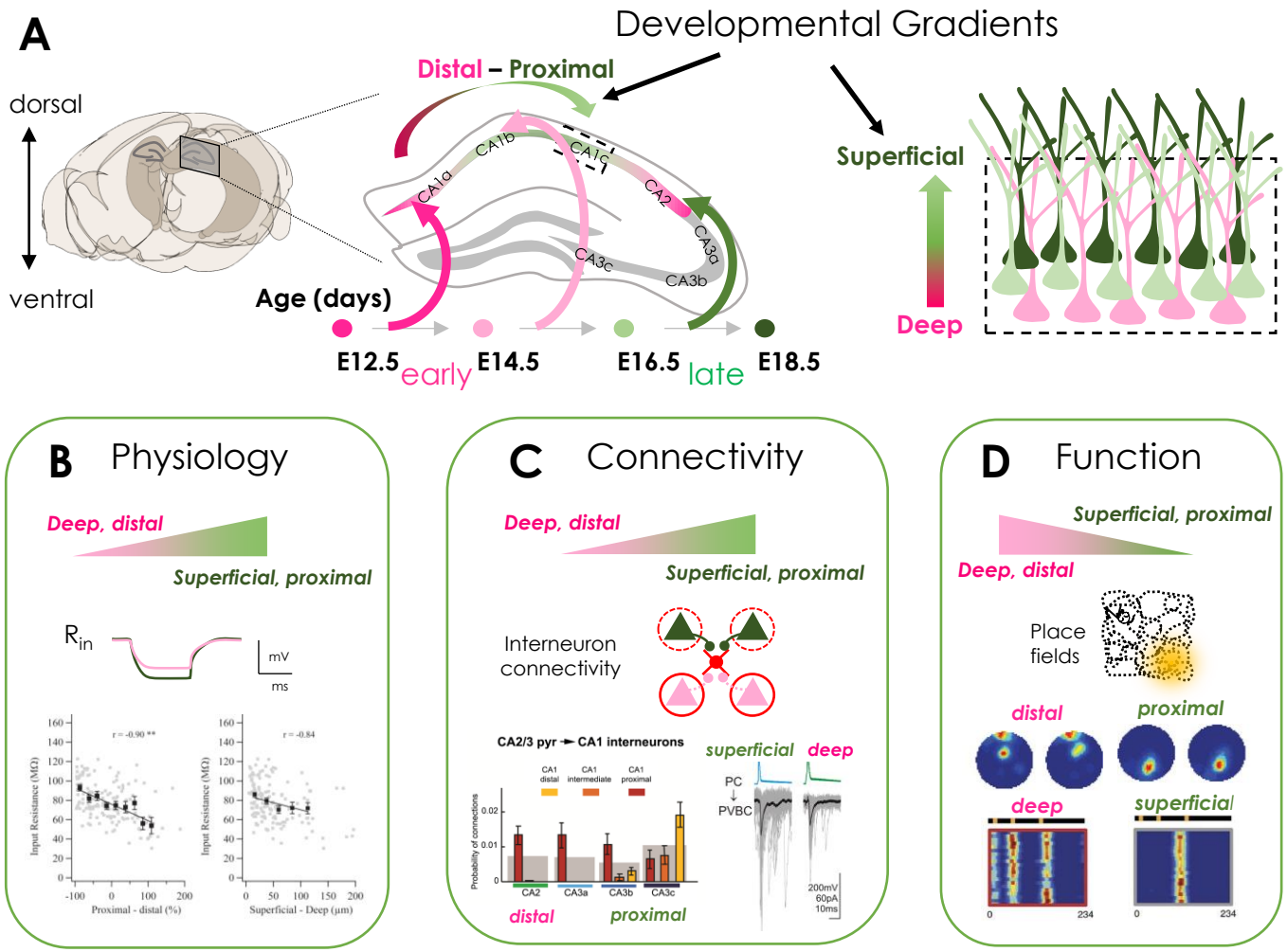

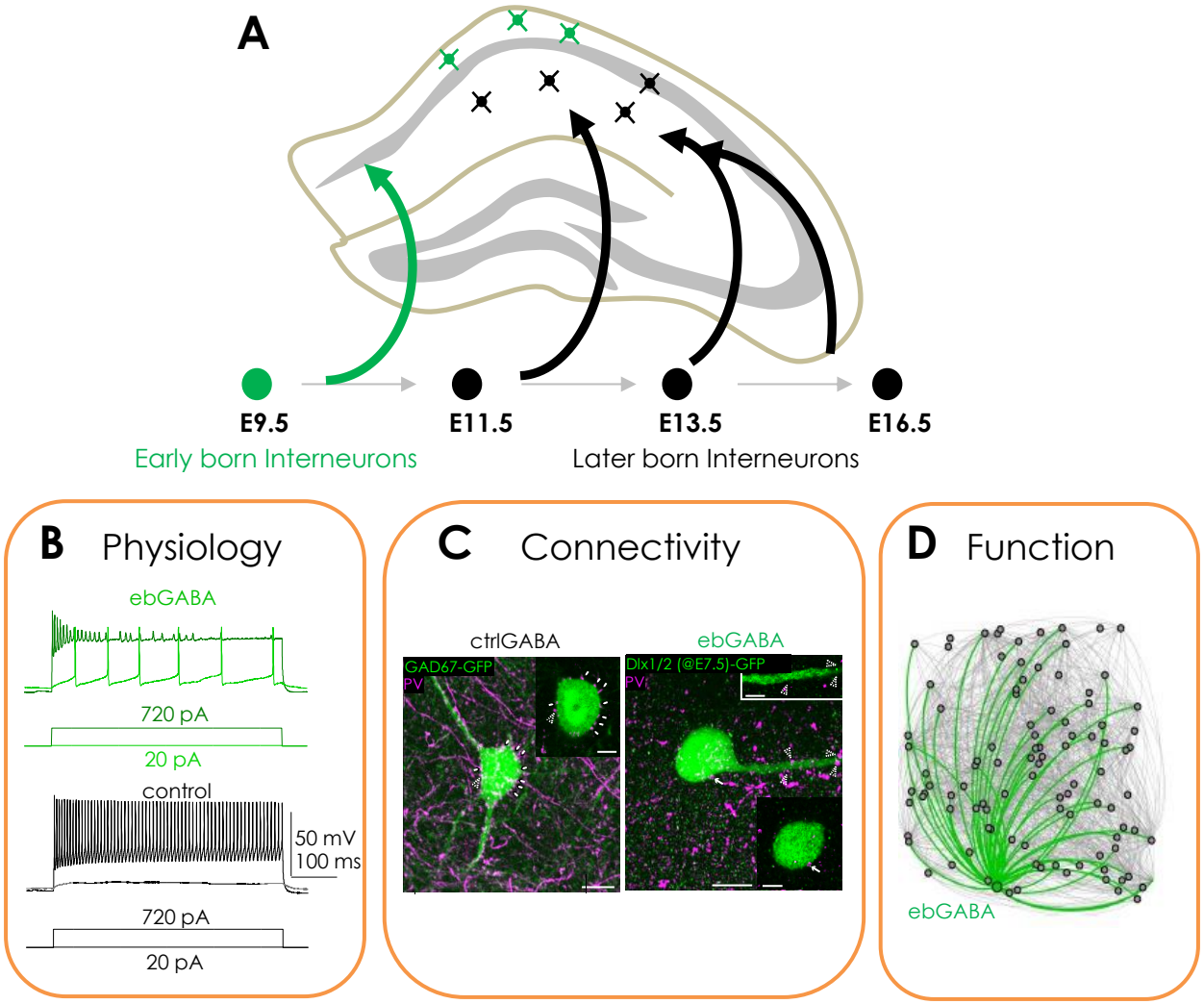

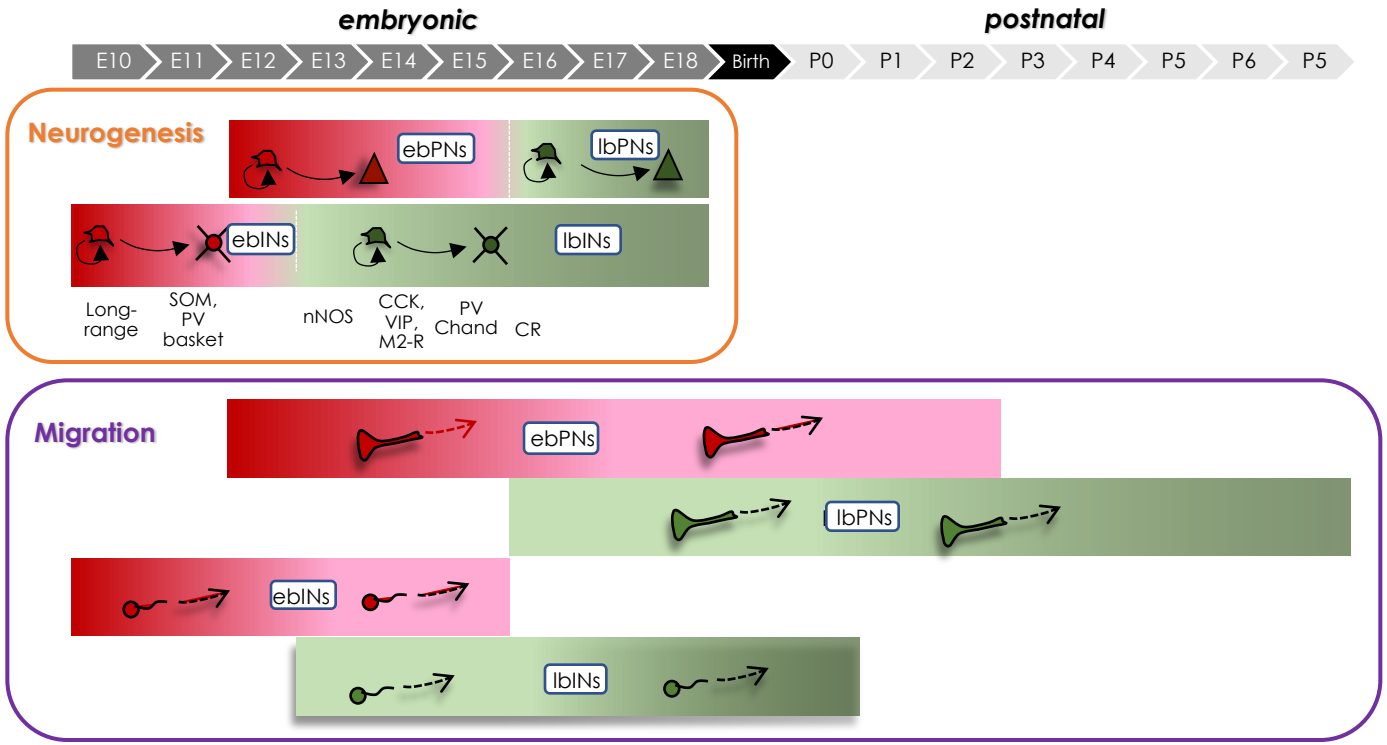

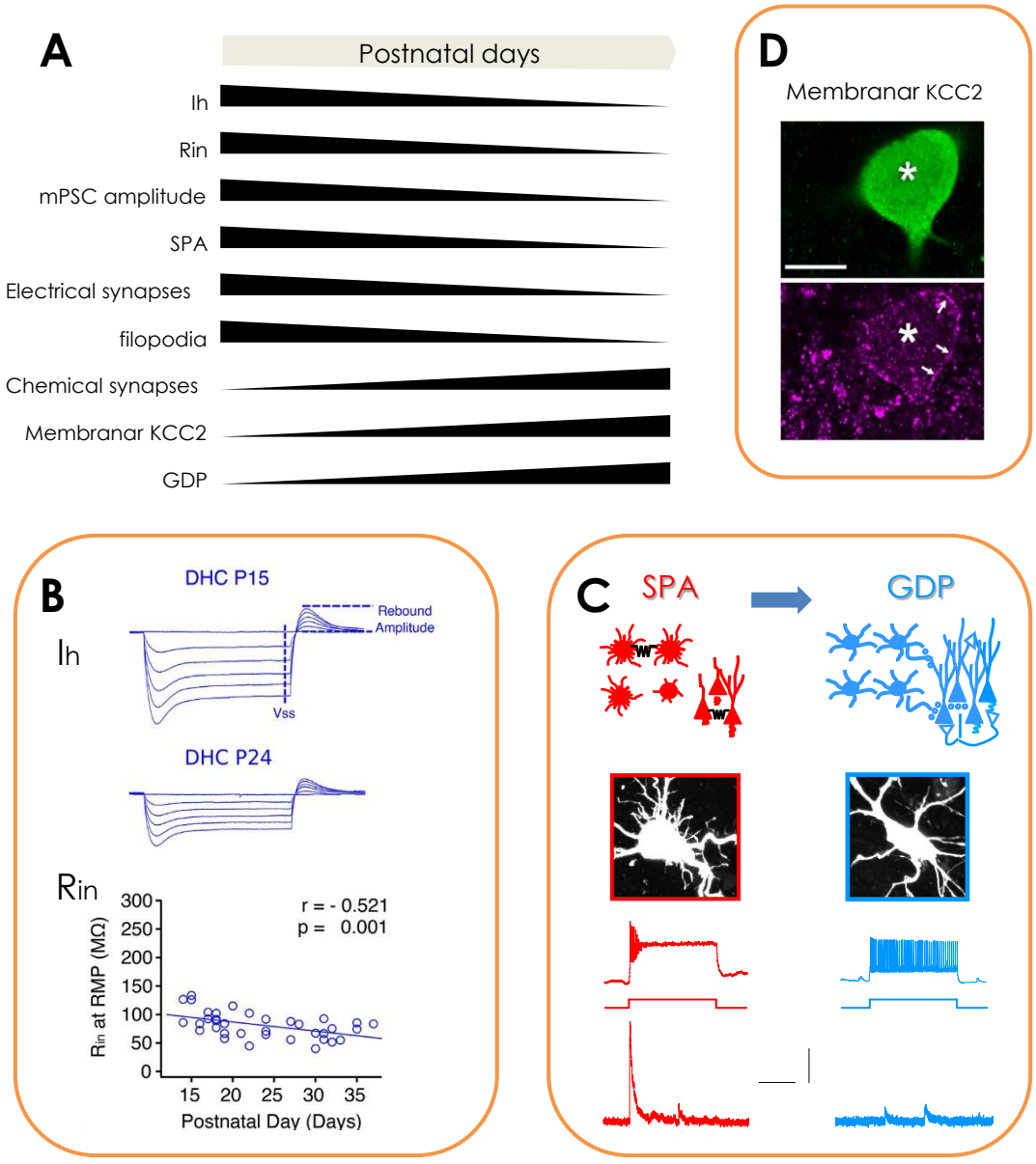

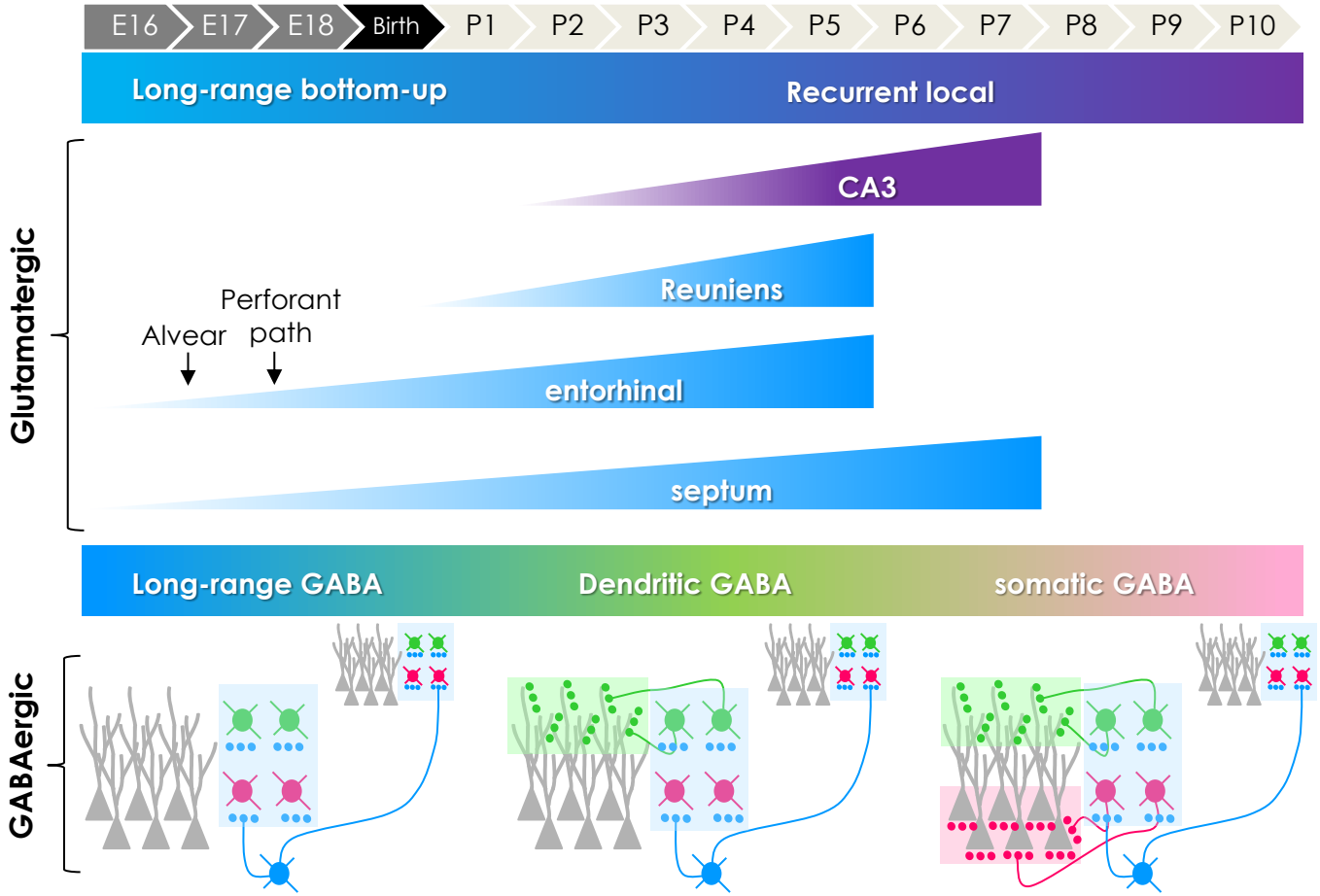

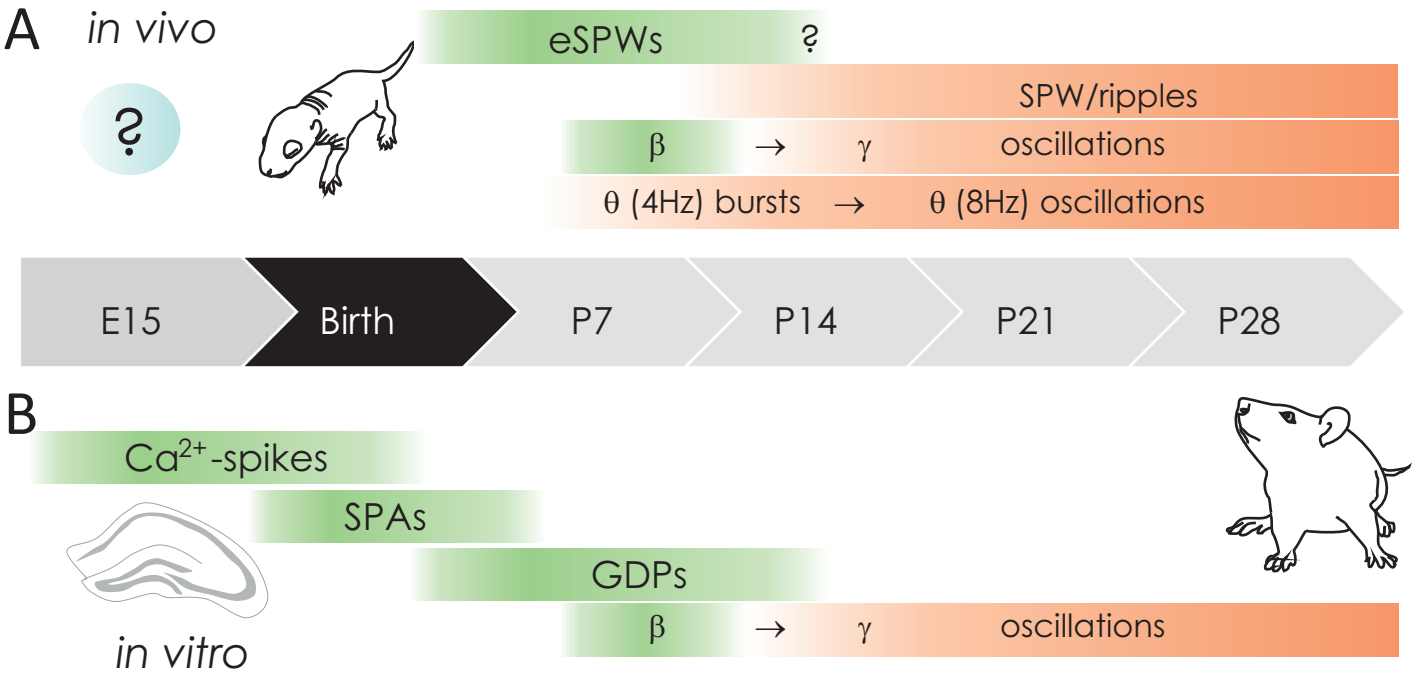

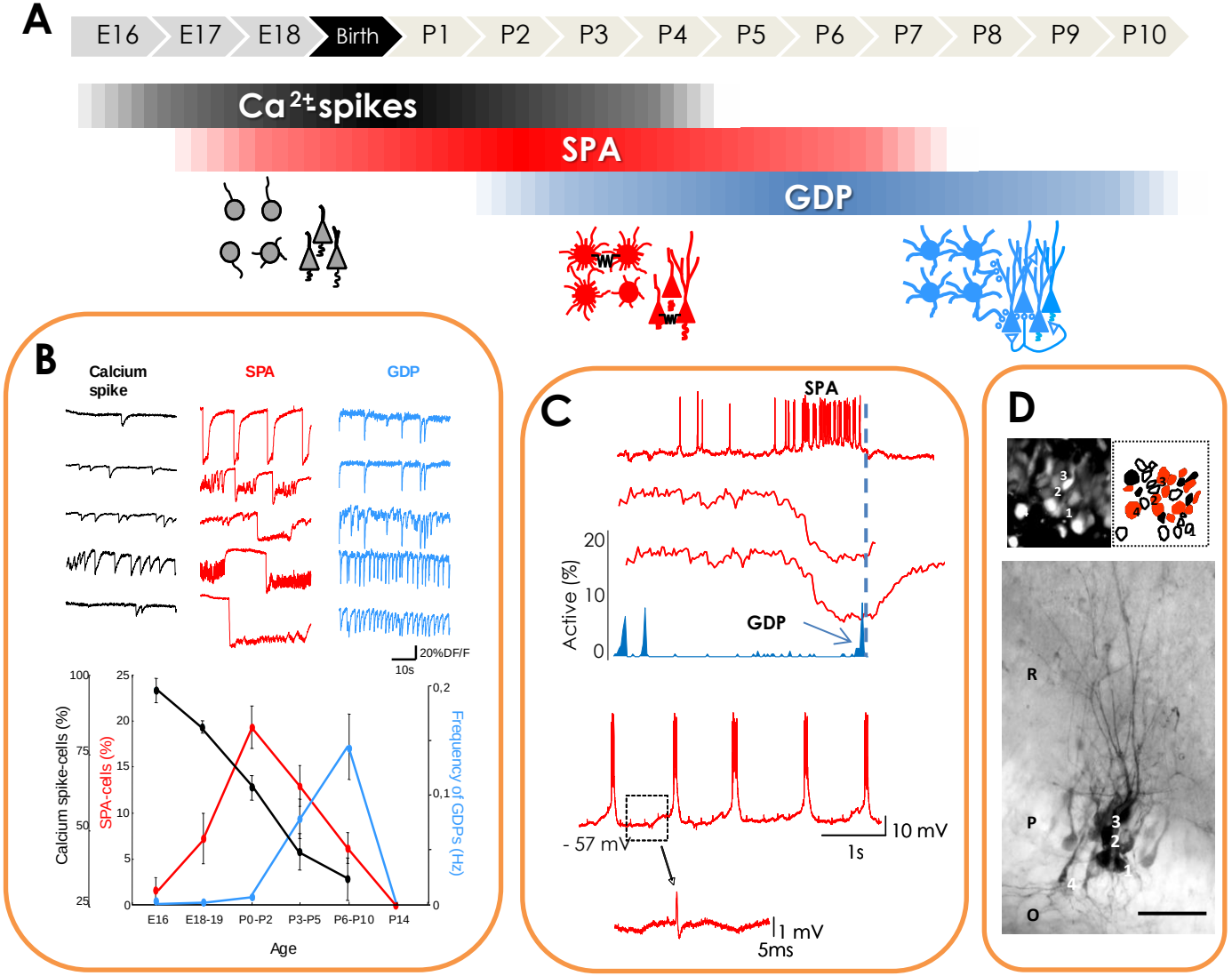

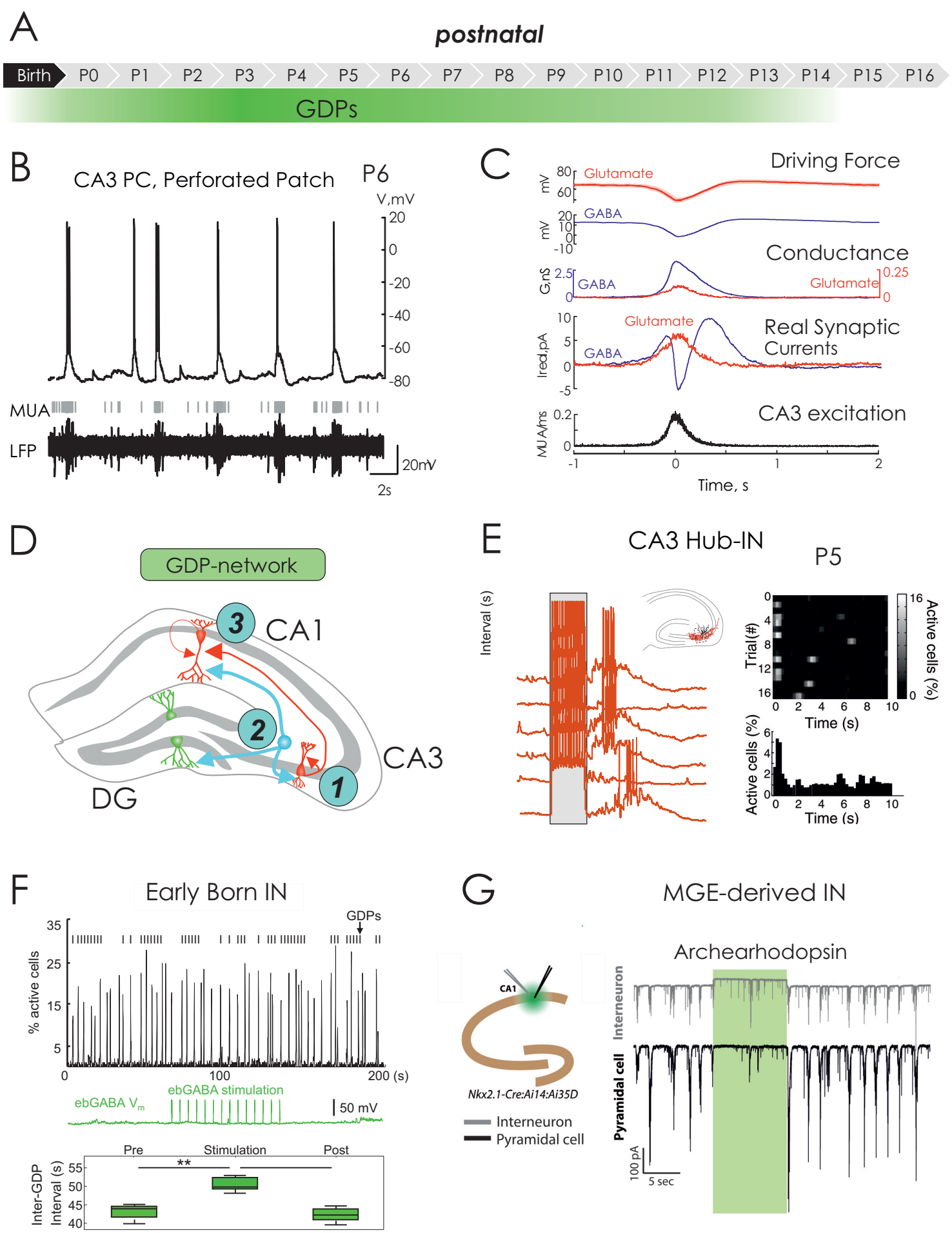

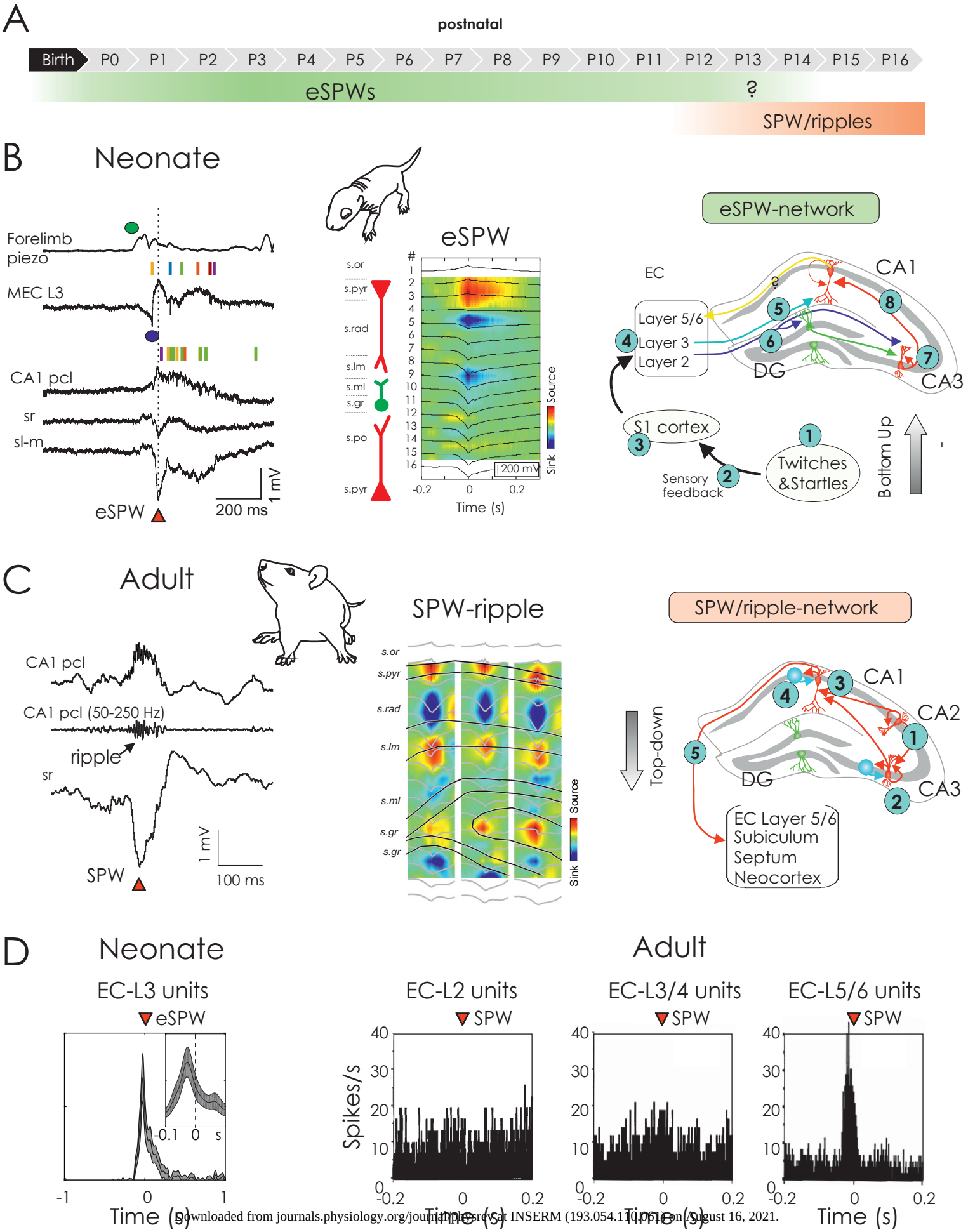

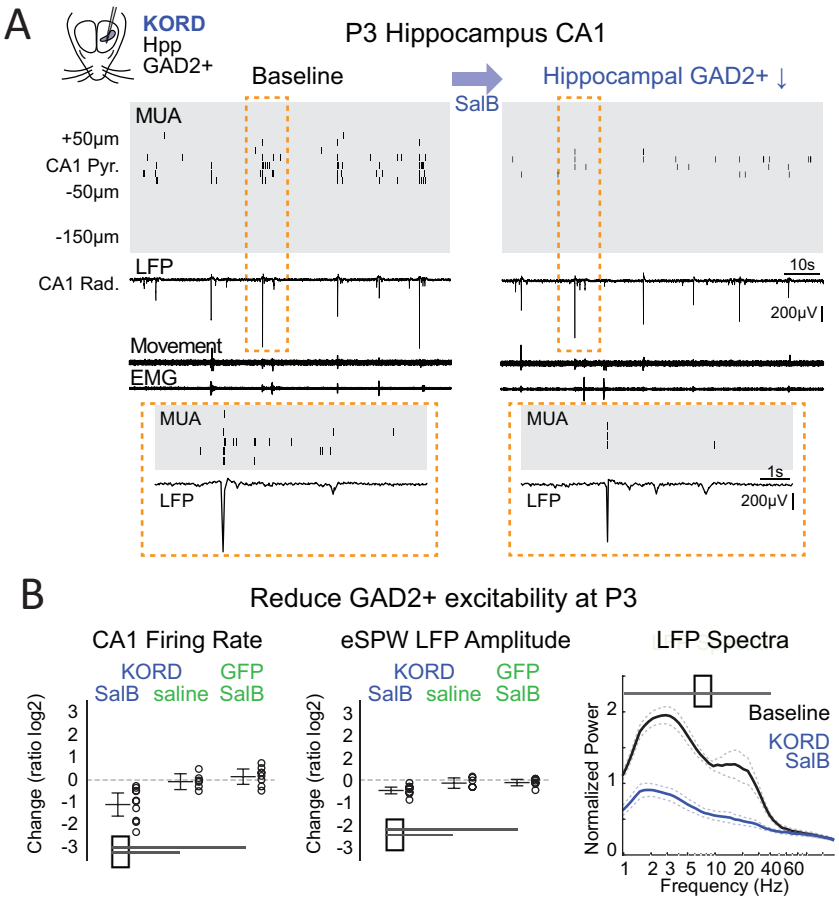

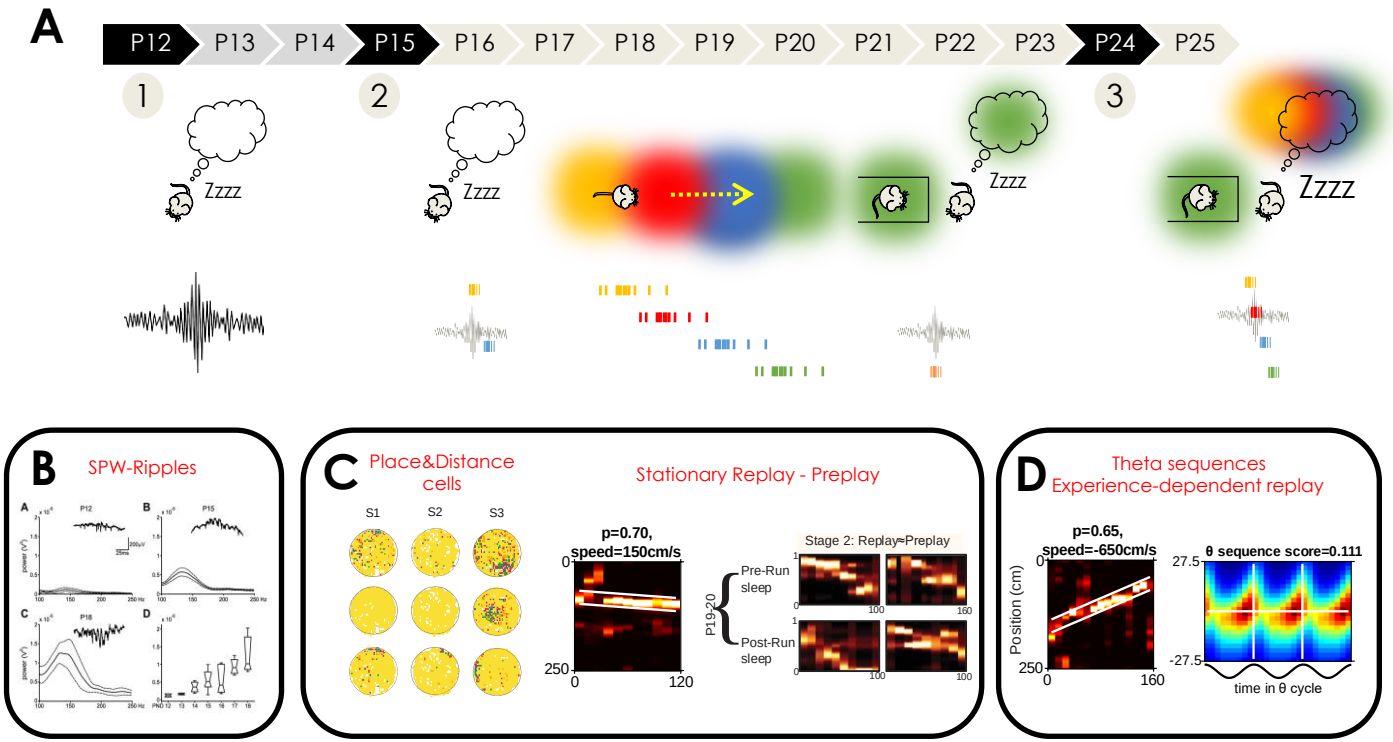

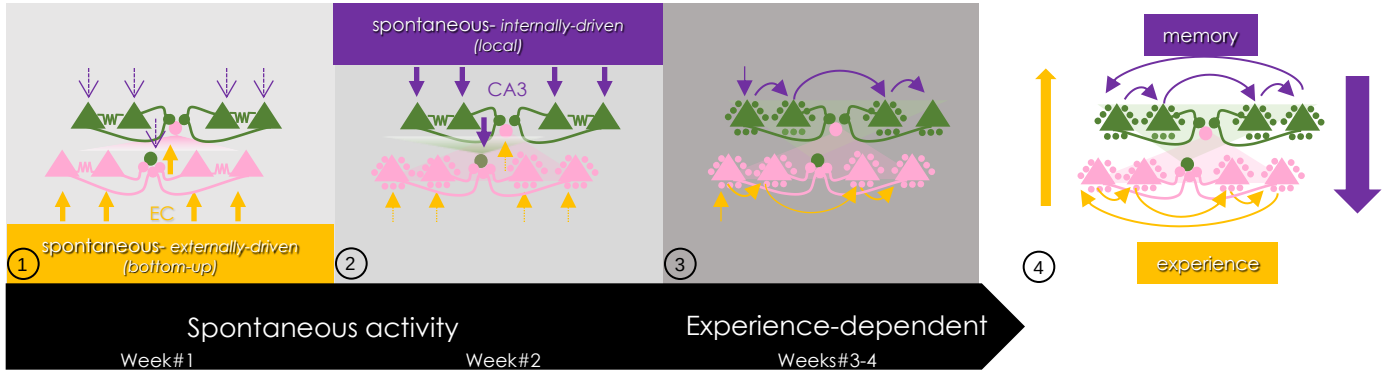

		early	late	References
Physiology	Rm			Masurkar et al. (181), Graves (103), Jarsky et al. (129), Sun et al. (234)
	Ih			Masurkar et al. (181), Maroso et al. (176), Li et al. (164)
	I/O			Cembrowski et al. (47), Mizuseki et al. (189), Oliva et al. (207)
	burstiness			Misuzeki et al. (189)
Connectivity	Early born afferents (eg. LEC, CA2)			Bayer (22), Masurkar et al. (180), Kohara et al. (145), Valero et al. (257), Nasrallah et al. (202), Sun et al. (234).
	Early born targets			Altman and Bayer (10), Deguchi et al. (63)
	Perisomatic inhibitory input			Lee et al. (158), Donato et al. (73), English et al. (87), Valero et al. (257), Oliva et al. (207), Sun et al. (234).
	Output on inhibitory cells			Lee et al. (158), Donato et al., English et al., Valero et al. (257), Oliva et al. (207)
Function	Fraction of place cells			Misuzeki et al. (189), Danielson et al. (59), Sharif et al. (225), Fattahi et al. (92)
	Idiothetic coding			Fattahi et al. (92), Sharif et al. (225)
	Spatial coding specificity			Henriksen et al. (119), Hartzell et al. (113), Danielson et al. (59), Oliva et al. (207)
	Place field stability			Grosmark et al. (107), Kohara et al. (145), Danielson et al. (59), Misuzeki et al. (189), Geiller et al. (97)
	SWR recruitment			Valero et al. (257), English et al. (87), Böhm et al. (31)
	Content discrimination			Geiller et al. (97), Li et al. (164), Marrone et al. (178), Lee et al. (157)

Table 1. Diversity in physiology, connectivity and function among principal cells in the adult hippocampus reflects developmental origin. Different parameters characterizing the diversity of hippocampal principal cells in physiology, connectivity, and function were analyzed and compared. The table summarizes data from several studies (listed in the references column). Measurements were classified as depicting putatively early- versus late- born neurons depending on the soma position within the main anatomical axes of the hippocampus. Boxes were filled in light or dark gray if the parameter mentioned on the left column was found significantly lower or higher, respectively. Rm: membrane

resistance, Ih: h-current, I/O: Input/output relationship between injected current (input) and evoked action-potential firing (output); burstiness: probability to produce bursts of spikes. LEC: Lateral Entorhinal Cortex, SWR: Sharp Wave- associated Ripple.

Pattern	Age	Presumable Mechanism	*In vivo*	*In vitro*
Calcium spikes	E16-P6	Uncorrelated neuronal activation in absence of electrical and chemical connections	Not reported	Crepel et al. (55) *Neocortex:* Komuro & Rakic (146), Allene et al. (7), Bortone & Polleux (34)
SPA (Spontaneous Plateau Assemblies)	E18-P6	Spontaneous plateau depolarizations in sparse groups of neurons synchronized via gap-junctions	Not reported	Crepel et al. (55), Allene et al. 2012 (8) *Neocortex:* Allene et al. (7), Dupont et al. (82)) *Striatum:* Dehorter et al. (64)
GDPs (Giant Depolarizing Potentials)	P0-P13	Population CA3 bursts synchronized by synergistic excitation of principal neurons and interneurons via glutamatergic and depolarizing GABAergic synapses, conveyed to CA1 via Schaffer collaterals	Not reported in isolated form. CA3 activation is reflected in Schaffer collateral – mediated Sink 1 of eSPWs in stratum radiatum Marguet et al. (174), Valeeva et al. (254, 255, 256)	Ben-Ari et al. (24), Leinekugel et al. (160), Khazipov et al. (142), Crepel et al. (55), Khalilov et al. (140) Synonyms: *Unison-firing pattern* Harris & Teyler (111) *Synchronous calcium oscillations* Leinekugel et al. (162) *Early network oscillations* Garaschuk et al. (96)
eSPWs (Early Sharp Waves)	P1-P10?	Externally driven L2/3 EC population bursts conducted to hippocampus via temporoammonic and perforant pathways, and	Leinekugel et al. (161), Karlsson et al. (132), Marguet et al. (174), Ahlbeck et al. (3), Valeeva et al. (254, 255, 256), Murata & Colonnese (200), Graf et al.	Not reported in neonatal hippocampal slices; L2/3 EC population bursts are present in vitro but they do not propagate to hippocampus

		supported by CA3 network	(102)	Sheroziya et al. (227), Unichenko et al. (252), Namiki et al. (201), Dawitz et al. (62)
Adult SPW-Ripples	Onset at P12	Internally generated CA2/3 population bursts, conveyed to CA1 via Schaffer collaterals and associated with high-frequency ripple oscillations	Leinekugel et al. (161) Buhl & Buzsaki (38)	Maier et al. (**169**), Behrens et al. (**23**), Hajos et al. (**115**), Holderith et al. (**120**), Aivar et al. (**4**) See Table 2 in Buzsaki (44) for the full bibliographic coverage
Hippocampal network oscillations (theta-bursts, beta/gamma oscillations)	P7-P14	CA3 - L2/3 EC driven and shaped by inhibition oscillations, likely precursors of adult theta/gamma oscillations	LeBlanc & Bland (154) Lahtinen et al. (149) Mohns & Blumberg (191)(192) Brockmann et al. (36) Marguet et al. (174) Ahlbeck et al. (3) Del Rio-Bermudez et al. (65); (66)	Hajos et al. (115) Holderith et al. (120) Tsintsadze et al. (248)

Table 2. Early activity patterns in the developing rodent hippocampus *in vivo* and *in vitro*