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# How development sculpts hippocampal circuits and function

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38 Abstract

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

55

56 Graphical abstract

57

58 CLINICAL HIGHLIGHTS

59

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

62

63 • Internal dynamics are important for hippocampal function and partly preconfigured,  
64 possibly during development.

65

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

69

70 • The emergence of recurrent connectivity is a critical step in the development of the  
71 hippocampal structure

72

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

76

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

79

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

82

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

85

86

## 87 Introduction

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

97 Hippocampal cognitive maps are produced by sequences of transient neuronal  
98 activation that keep track of and order spatial and non-spatial information (continuously  
99 varying) in an allocentric or egocentric reference frame (15, 92, 147, 208). They may unfold  
100 at various temporal scales, from several seconds, the timescale of behavior, to a few  
101 milliseconds, nested and compressed within the period of the theta rhythm (~8Hz) or within  
102 sharp-wave ripples (~200Hz) (43, 80). Interestingly, hippocampal sequences do not simply  
103 represent serially ordered external information, rather, they arise from the interaction  
104 between environmental inputs and internal dynamics supported by the intrinsic functional  
105 properties of the hippocampal network (43, 135). The internal functional organization of  
106 hippocampal circuits is indeed a major contributor to sequence generation. The sequential  
107 activation of hippocampal neurons can be disengaged from external signals at all timescales.  
108 Hence, hippocampal sequences unfolding at the behavioral timescale have been recorded in  
109 the absence of changing sensory or feedback cues, mainly during running behavior (79, 127,  
110 148, 208, 260). Similarly, still during exploration, but nested within the period of a theta  
111 cycle, sequences representing the ongoing trajectory in space at an accelerated rate that are  
112 involved in decision and planning also emerge from the integration of sensori-motor  
113 information into internal dynamics (80). Most notably, hippocampal sequences critically  
114 involved in memory encoding and consolidation are also observed offline during quiet rest or  
115 sleep, when body or environmental control over dynamics are minimal (156, 230, 266). In  
116 addition, hippocampal sequences are rooted within functional circuits that are remarkably  
117 rigid against transient perturbation (260, 278) and stable across days (109). It is possible

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

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

145

## 146 **Lasting traces of early development in adult hippocampal circuits**

147

148 The hippocampus is an elongated brain structure spanning three main anatomical axes  
149 (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 <sup>3</sup>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 than 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

182 stratum radiatum (Figure 1A). This gradient matches the quantitative differences in the  
183 passive and active electrophysiological properties of pyramidal neurons (PN) in the adult CA1.  
184 Indeed, adult CA1 PNs occupying regions where PNs are presumably born earlier display a  
185 smaller HCN-mediated h-current (I<sub>h</sub>) (176, 181), a lower membrane resistance (R<sub>m</sub>) (103,  
186 181)) as well as higher excitability (47, 189) and bursting propensity (see Table 1 and Figure  
187 1B). Interestingly, cells located in the *subiculum* or CA2, two subregions with an earlier  
188 temporal origin than CA1, also display a smaller I<sub>h</sub> (163) (but see (234)), a lower R<sub>m</sub> (129,  
189 163, 234), higher excitability (207), and burst propensity (69). It should be noted that CA2  
190 itself was recently shown to display significant heterogeneity along the proximo-distal axes  
191 (93), despite its overall earlier temporal origin compared to CA1 and CA3, possibly indicating  
192 the need for in depth examination of its embryonic developmental schedule. The diversity of  
193 intrinsic electrophysiological properties among CA3 PNs also distributes along the proximo-  
194 distal axis, revealing a similar trend for R<sub>m</sub> with the earlier born distal CA3 (CA3a) displaying a  
195 lower R<sub>m</sub> than proximal CA3 cells (234). Different trends for I<sub>h</sub> and excitability have been  
196 reported with earlier born regions (CA2, CA3a) displaying a larger I<sub>h</sub> and lower excitability, but  
197 higher burst propensity (20, 69, 234). We will see in the next section how these cellular  
198 properties follow a stereotyped schedule during development, serving as ideal proxies of  
199 neuronal maturation stage, as if the delays in maturation originating from different neuronal  
200 birthdates partly remained in the adult. As expected from the lack of clear developmental  
201 gradient in CA1 along the longitudinal axis, the dorso-ventral segregation of these properties  
202 is not as clear, while a continuous genetic gradient has been observed (47). That said, PNs  
203 located in the dorsal part of CA1 (possibly slightly older than the ventral region), display less  
204 I<sub>h</sub>, a lower R<sub>m</sub> and a lower action potential threshold (9, 12, 22, 73). The link between  
205 birthdate and integration into adult hippocampal circuits is particularly striking when  
206 considering connectivity. This was already evident in seminal early studies that noted how the  
207 order of neurogenesis in the entorhinal cortex, proceeding from lateral to medial, also strictly  
208 correlated with the order of its termination on CA1 PNs, with afferent fibers from older cells  
209 of origin (lateral entorhinal cortex) projecting to older CA1 pyramidal cells (CA1a), while  
210 afferent fibers from younger cells (medial entorhinal cortex) projected to younger CA1  
211 pyramidal cells (CA1b,c, (22)). This isochronic patterning of entorhinal projections has been  
212 recently further dissected at functional level across the transverse and radial CA1 axes (180)  
213 and also applies to the inputs from the early generated CA2 region, projecting onto deep

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

229 Maybe even more than for local excitatory glutamatergic circuits, the overall mesoscopic  
230 organization of adult GABAergic inhibitory circuits is particularly interesting to revisit from the  
231 perspective of developmental timing (Figure 1C). Indeed, both along the radial and transverse  
232 axes of development, it appears that late born PN (superficial) and subregions (CA3c) are  
233 more likely to drive CA1 interneurons, while early born regions (CA2, CA3a) and cells (deep)  
234 receive stronger inhibitory inputs (72, 158, 207, 234, 257). In addition, the fine temporal  
235 pairing rule of connectivity also seems to apply to GABAergic circuits, since early born PV cells  
236 target deep CA1 cells while late born PV cells target superficial CA1 cells (72). The equation  
237 between birthdate and laminar position also holds for hippocampal GABAergic neurons,  
238 where neurons born in the Medial Ganglionic Eminence (MGE), generated earlier, distribute  
239 in deep layers (*stratum oriens and pyramidale*), while cells born in the Caudal Ganglionic  
240 Eminence (CGE) mainly locate in superficial layers (*stratum lacunosum moleculare*) (245).  
241 This fine organization of inhibitory and excitatory circuits according to birth order may be  
242 predetermined at the earliest stages of development given that glutamatergic ensembles  
243 sharing a common clonal origin also share common presynaptic perisomatic GABAergic inputs  
244 (271).



245 The pre-existing differences in excitability or connectivity rooted in the different temporal  
246 origins of hippocampal neurons should result in functional differences (89). Interestingly,  
247 linked to the advent of large-scale approaches to record neuronal activity there has been a  
248 recent rise of interest in the analysis of the heterogeneity in place field properties among  
249 hippocampal neurons. These recent studies mostly use extracellular recordings and/or head-  
250 fixed preparations, which should be taken into account when interpreting the findings given  
251 the unprecise spatial resolution of the former and the difference in place cell properties  
252 reported in the latter (2, 49, 217). Regardless, when combining the information of many  
253 recent reports a clear picture emerges by which early born subregions and PNs (i.e. CA2,  
254 CA3a, CA1a,b, and deep CA1) are comprised of a higher fraction of place-modulated neurons  
255 (59, 189), however, their spatial coding specificity is poorer (59, 97, 113, 119, 207) as they  
256 are more likely to display multiple and/or wider and less stable place fields than their younger  
257 counterparts (CA1c, CA3c, superficial CA1, Figure 1D). The latter not only display highly  
258 selective and stable place fields, but are also better at discriminating transient tactile,  
259 olfactory or object information (97, 163). One interesting possibility could be that PNs  
260 located in the deep CA1 sublayer, although place-modulated, comprise cells representing  
261 contextual identity rather than a spatial map. Indeed it was recently established that  
262 “engram cells” (cells expressing cfos after presentation of a novel context), like many deep  
263 CA1 PNs (189) and unlike other place cells, exhibit higher firing rates, larger place fields with  
264 poorer information content, and higher modulation by entorhinal inputs (241). In other  
265 words, hippocampal function may be roughly divided into two functional categories according  
266 to birthdate, where regions and cells generated early would serve a generalizing function and  
267 later ones would assist content discrimination. This is a general rule that may even extend to  
268 the function of the late-generated dentate gyrus and CA3c (157, 178, 234). More  
269 particularly, in CA1, older PNs are presumably better tuned to receive external sensory inputs  
270 as their firing is more anchored to external landmarks while later born PNs, would be more  
271 likely to convey an internal “memory stream”, more likely to participate in SWRs, and more  
272 likely to convey self-referenced information, with slower if any remapping and more stable  
273 place maps (59, 97, 107, 145, 189). This hypothesis agrees with the earlier maturation of  
274 unstable landmark-based place cells (223, 265), the “overgeneralizing” infantile memory,  
275 and protracted emergence of episodic memory and idiothetic navigation (216).

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

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

313

## 314 **Emergence of the hippocampal structure**

315

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

324

### 325 *Hippocampal neurogenesis*

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

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

367

### 368 *Migration of hippocampal cells*

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

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

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

404

405 *Maturation of the cellular properties of hippocampal cells*

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

435 GABAergic synapses (7, 55) within Giant Depolarizing Potentials (GDPs, (24), Figures  
436 4C,7&8).

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

457

#### 458 *Developmental cell death*

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

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

492

#### 493 *Wiring of hippocampal circuits*

494 Local recurrent connectivity and long-range extrahippocampal inputs differ in their  
495 developmental profile, the former globally emerging later (postnatally, (99, 179)) than the  
496 latter (before birth, see below and Figure 5). Most sensory information is conveyed to the  
497 hippocampus through the entorhinal cortex. The LEC matures before MEC and projects onto  
498 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

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

537 While long-range inputs seem to settle before birth, the first postnatal week is the  
538 time when local recurrent connectivity emerges (Figure 5). Dendritic GABAergic innervation  
539 develops before the perisomatic GABAergic coverage (58, 179, 251), and most likely after  
540 long-range GABAergic connectivity (259) (Figure 5). In general, the intrinsic morpho-  
541 physiological properties of GABA neurons develop according to their birthdate, following a  
542 stereotyped sequence (8), with early born interneurons contributing to a significant fraction  
543 of local axonal coverage (211). Interestingly, the end of the first postnatal week marks an  
544 abrupt surge of recurrent connectivity with the emergence of perisomatic GABAergic  
545 innervation in the CA1 pyramidal layer and the exuberant branching of CA3 axon collaterals  
546 (99, 111, 179, 238). This is also the time when connectivity between CA3 and CA1 develops,  
547 starting from P2 (Figure 5) (84). A similar phenomenon has been reported in the neocortex,  
548 including recently through imaging of perisomatic GABAergic domains in the barrel cortex  
549 (195). Interestingly, in that region, transient targeting of deep layer somatostatin  
550 interneurons by early thalamic inputs contributes to the emergence of perisomatic inhibition  
551 (177, 249). Following that idea, one could speculate that hippocampal somatostatin  
552 interneurons, activated by extrahippocampal inputs, whether or not of thalamic origin, would  
553 directly support the development of perisomatic GABAergic synapses, as in the neocortex.  
554 We would thus like to propose a general scheme by which early bottom-up inputs, conveyed  
555 through canonical or non-canonical paths would foster the emergence of recurrent  
556 connectivity in an activity-dependent manner. Such recurrent connectivity, emerging at the  
557 end of the first postnatal week, before active exploration, gives birth to “smart networks”  
558 capable of learning and sustaining self-organized internal dynamics (204).

559

560 **Early hippocampal dynamics**

561

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

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

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

598 - in somatosensory circuits, in which sensory feedback from spontaneous myoclonic  
599 movements triggers activity, in a somatotopic fashion, in somatosensory regions of the spinal  
600 cord, thalamus and cortex, and most likely participates in the activity-dependent formation of  
601 cortical sensory maps during the critical period of thalamocortical plasticity (125, 143, 184,  
602 273).

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

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

621

#### 622 *Spontaneous uncorrelated activity*

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

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

632

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

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

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

660

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

662 Giant Depolarizing Potentials (GDPs) are historically the first population activity  
663 pattern described in hippocampal slices of neonatal rodents (24, 96, 111, 142) (Figure  
664 8A&B). GDPs can be observed in hippocampal slices and the intact hippocampal formation *in*  
665 *vitro* starting from the perinatal period and vanish at the end of the second postnatal week  
666 (Figures 6&8). GDPs are associated with population bursts and elevations of intracellular  
667 calcium lasting several hundreds of milliseconds and occurring at a frequency of ~10/min.  
668 Participation of neurons in GDPs decreases along with a reduced number of neurons excited  
669 by GABA during the second postnatal week (96, 142, 250). GDPs typically originate from the  
670 CA3 region of the hippocampus which operates as a GDP-generator because of: (i) a relatively  
671 high amount of recurrent excitatory glutamatergic connections between PNs, (ii) spontaneous  
672 bursting of many CA3 PNs supported by non-inactivating sodium conductance and low  
673 expression of potassium channels involved in  $I_m$  (185, 228, 229, 253) and (iii) the presence  
674 of highly connected GABAergic hub neurons (33). From CA3, GDPs typically propagate to CA1  
675 and to DG, but they may also originate in CA1 and backpropagate to CA3 (32, 185, 228, 253,  
676 263). Backpropagation of GDPs may be supported by CA1 GABAergic hub cells with  
677 extended axonal morphology (30). In the preparation of interconnected hippocampi *in vitro*  
678 (136), GDPs propagate to the contralateral hippocampus via the ventral hippocampal  
679 commissure and medial septum and EC (138, 160). Interestingly, in EC-hippocampal slices,  
680 spontaneous bursts of activity in EC fail to propagate to the hippocampus (62, 201). In the  
681 longitudinal axis, GDPs typically originate in the septal (dorsal) part of the hippocampus and  
682 propagate relatively slowly (7-10 mm/min) towards the ventral hippocampus (160). This may  
683 reflect the earlier birthdate of dorsal CA3 neurons than ventral ones.

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

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

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

721 their functional network integration, nicely parallel the developmental emergence of GDPs  
722 (259).

723 The age of non-hub cells also influences their participation in GDPs. As discussed above, the  
724 date of transition from an SPA to GDP network depends on the age of the cell (8, 175). This is  
725 also supported by clear correlation between the emergence of synaptic currents (that marks  
726 a transition from SPAs to GDPs) and the level of morphological differentiation of PNs and INs  
727 (118, 251), also seen in fetal macaque hippocampal slices (141). It is equally possible that  
728 the developmental excitatory to inhibitory switch in the action of GABA is set by birthdate as  
729 shown for early-born GABA cells (259). Thus, the dates of both entry to and exit from GDP-  
730 circuits could be individually determined for each neuron according to its age.

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

744

#### 745 *Early Sharp Waves and tails in vivo*

746 Early sharp waves (eSPWs) frequently followed by afterdischarges (so-called “tails”) are the  
747 earliest coordinated activity pattern reported *in vivo*, starting from P1 in the rodent CA1  
748 (Figures 6&9). Based on their developmental timeline and their significant association with  
749 polysynaptic GABAergic events, eSPWs were initially described as the *in vivo* counterpart of  
750 GDPs (161). However, this equation may need to be slightly revised according to recent  
751 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

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

841 One last major subtype of hippocampal network activity patterns are theta oscillations, which  
842 in the adult rodent are observed during episodes of locomotion, active engagement, or REM  
843 sleep and provide an internal clock distributing CA1 dynamics into spike sequences (80, 262).  
844 It should be noted that theta oscillations do not necessarily generalize across species. Indeed,  
845 LFP fluctuations in humans, non-human primates, and bats tend to be either non-rhythmic, or  
846 concentrated in short oscillatory bouts as well as being task and cognitive state-dependent  
847 (40, 41, 86, 101, 128). However, the absence of a continuous theta rhythm, as reported in

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

852 In the adult rodent, CA1 theta oscillations are supported by the interplay between  
853 inputs from the septum, MEC, and CA3 with local and long-range GABAergic neurons and  
854 resonant intrinsic firing properties. The development of theta oscillations in the hippocampus  
855 was first described by LeBlanc and Bland in the form of intermittent bursts of activity within  
856 the theta frequency range occurring in CA1 and DG from P8-9 during movement and starting  
857 from P10 during RUN/REM-states or following cholinergic-agonist application (154). Starting  
858 from P8-10, theta-coherent activities synchronize the hippocampus, red nucleus, LEC,  
859 prefrontal cortex and ventromedial thalamus (3, 36, 65, 112). Notably, pharmacological  
860 inactivation of the medial septum blocks hippocampal theta oscillations at P12 (3, 36, 65,  
861 112). From P10 to P23-28, theta oscillations increase in amplitude and frequency from 4 to 7  
862 Hz. This developmental profile for theta oscillations has been confirmed by several studies  
863 (65, 161, 191), with a few reports suggesting an earlier emergence at P1-2 in the form of  
864 short bouts at 7-8 Hz frequency (36, 131). These events in younger animals may well result  
865 from the passive propagation of cortical spindle-bursts to the hippocampus (132). The exact  
866 network mechanisms underlying emergence and developmental changes in hippocampal  
867 theta oscillations, which likely involve maturation of theta-generative properties in CA3 and  
868 EC networks, local, notably inhibitory CA1 circuits, as well as cholinergic and  
869 noradrenalinergic control remain an open question for future investigations.

870

#### 871 *Role of GABAergic circuits in coordinating early hippocampal dynamics*

872 While previous research has clearly identified instrumental roles of GABAergic neurons in the  
873 generation of GDPs *in vitro*, data on how interneurons shape network activity in the neonatal  
874 hippocampus *in vivo* remain sparse. On the one hand, barrages of synaptic GABAergic  
875 currents have been recorded during eSPWs and tails in CA1 PNs at P3-6 (161). Yet,  
876 manipulating interneuron activity did not provide consistent results (153). Lowering the  
877 excitability of hippocampal INs decreased the amplitude and frequency of eSPWs, while  
878 enhancing IN excitability did not affect eSPWs at P3 (Figure 10). At P7, manipulating  
879 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

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

917

## 918 Emergence of hippocampal sequences

919

920 The second postnatal week is the time when bottom-up driven eSPW and HNOs are  
921 progressively replaced by endogenous events in the form of SW-associated ripples and theta  
922 nesting gamma oscillations. As reviewed above, the emergence of these patterns is most  
923 likely supported anatomically by the appearance of recurrent networks comprising  
924 perisomatic inhibition and Schaffer Collateral CA3 inputs. At this stage, CA1 circuits switch  
925 from being mainly bottom-up driven by spontaneous activity originating from the sensory  
926 organs to displaying spontaneously recurring internal dynamics supported by  
927 intrahippocampal circuits, as revealed by the observation of recurring network bursts in the  
928 form of GDPs in preparations disconnected from external inputs such as slices. During this  
929 period, active exploration of the environment is limited, these spontaneous activities are  
930 therefore probably limited in their informational content and rather serve local network  
931 calibration purposes. The second postnatal week to a large extent remains a black box of  
932 hippocampal development that ends with the emergence of landmark-modulated place cells  
933 and stationary sequences (Figures 11&12). The early appearance of place cells bound to  
934 external cues together with reactivation of stationary places (91, 197) suggests an earlier  
935 development of allothetic (i.e. cue-based) representation in CA1 (Figure 12). Accordingly,  
936 CA1PNs coding for cue-enriched environments in the adult were preferentially found in the  
937 deep part of the CA1 *stratum pyramidale*, where older cells should eventually locate (92,  
938 225).

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

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

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

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

984 In conclusion, experience-dependent sequences would be the latest hippocampal  
985 pattern to mature during development (Figures 11&12). Whether internal preconfigured  
986 sequences emerge before remains a debated issue. That sequences reactivating non-spatial  
987 contents of experience appear earlier is also an open possibility. Indeed, the observation of  
988 place cells requires the animal to move in an environment, which is delayed compared with  
989 the development of other senses such as olfaction. It is now well established that the  
990 hippocampus also encodes non-spatial features (eg. time, odors, sound frequencies,  
991 conspecifics) (15, 148, 168) and ripples may therefore reactivate content other than spatial  
992 information (18).

993

## 994 Development of hippocampus-dependent cognitive functions

995

996 This section does not aim to provide a comprehensive review of the ontogeny of  
997 spatial cognition and episodic memory, the two cardinal hippocampal functions, since many  
998 excellent recent reviews are dedicated to this very matter (see for example (71, 123, 136,  
999 152, 216, 226, 240)). Instead, our objective is to interpret the emergence of these functions  
1000 in the light of the developmental origin of hippocampal diversity. One particularly appealing  
1001 concept towards this goal is the idea that navigation across autobiographical events (episodic  
1002 memory) and in the real world (spatial navigation) relies on two mechanisms of hippocampal  
1003 representation, one that is map or schema-based and depends on external multisensory  
1004 landmarks (allocentric) and the other that is self-referenced and often requires body  
1005 movement (egocentric) (42). In the adult, both representations work together but one may  
1006 dominate according to the availability of external cues (for example in the dark, egocentric  
1007 navigation dominates). Besides, these representations differentially contribute to a given



1008 cognitive function. Hence, it has been proposed (42) that map-based navigation would  
1009 support allothetic navigation and semantic memory (i.e. generalization of knowledge  
1010 independent from context) while self-referenced information would be central to path-  
1011 integration and episodic memory (i.e. ‘mental travel’ in time and space in reference to self).  
1012 Given that earlier born CA1 pyramids are better tuned to cue-based representation and  
1013 generalization while those born later encode self-referenced information (see section  
1014 “Lasting traces of early development in adult hippocampal circuits”), episodic memory would  
1015 be expected to develop later than allothetic navigation and semantic memory.

1016         The development of episodic memory has been the focus of many cognitive studies in  
1017 humans. Infants both lack knowledge of the self as an independent entity (121) and are  
1018 unable to form or store memories for recall later in life, a phenomenon termed *infantile*  
1019 *amnesia* until roughly two years of age (71, 216). Neither is spatial memory mature in infants  
1020 before 20 months of age (203). In rodents, the onset of hippocampus-dependent spatial  
1021 memory is delayed with respect to the emergence of place cells as assessed using different  
1022 behavioral tasks that include the Morris Water Maze (5, 219), spatial alternation (104),  
1023 Barnes maze, (182) or object location (56). It likely relies on environmental cues (5, 219),  
1024 the same way place cells from young animals are stabilized by boundary information (196). In  
1025 addition, grid cells, critical elements for path integration mature later than hippocampal place  
1026 cells (150), which display distance coding based on self-motion (27). In addition, episodic  
1027 aversive events elicited in rodents at the beginning of the third postnatal week create a latent  
1028 trace in the hippocampus (108, 243).

1029         While the emergence of complex forms of episodic memory and self-based navigation  
1030 may be protracted, some aspects of hippocampus-dependent learning and memory are  
1031 present early in life in infants. Besides its classic role in episodic memory, the hippocampus  
1032 was recently proposed, based on human data, to be involved in statistical learning, i.e. the  
1033 ability to extract regularities from the sensory environment and therefore segment a  
1034 continuous sensory flow into sequences of cognitive units (117, 226). Statistical learning  
1035 develops much earlier than episodic memory, as early as at 8 months in infants (220).  
1036 Therefore, one appealing possibility would be that the first hippocampus-dependent cognitive  
1037 function is statistical learning. This would culminate, once rodents or infants are able to  
1038 travel in space, in the formation of place fields (150, 265), i.e. the chunking of a space  
1039 continuum into segmented units. Statistical learning should inform predictive models and

1040 allow more abstract, generalized and semantic knowledge. In this respect, infantile  
1041 generalization (136, 216, 218) may be envisaged as a consequence of the early dedication  
1042 to statistical learning of the hippocampus.

1043         Recent modelling work suggested that the hippocampus supports the computations of  
1044 both episodic memory and statistical learning via two pathways, the trisynaptic pathway  
1045 (EC>DG>CA3>CA1) supporting episodic memory with the temporoammonic pathway enabling  
1046 statistical learning (222). Experimental work in rodents indicates that early network dynamics  
1047 in CA1 are mainly driven by direct EC inputs(255), while anatomical evidence in macaques  
1048 (152) and rodents suggests protracted development of CA3, DG and consequently of the  
1049 trisynaptic pathway (see section above). Both findings therefore give functional and  
1050 anatomical support to the early development of the temporoammonic pathway (before the  
1051 trisynaptic circuit) and the possible early commitment of the hippocampus to statistical  
1052 learning. Given the correspondence of the developmental timelines between rodents and  
1053 humans, this would start during the third trimester of gestation and certainly extend  
1054 postnatally. A consequence of statistical learning is predictive abilities. It was also proposed  
1055 that, in the adult, the predictive ability of the hippocampus and its role in retrieving memories  
1056 are embedded in separate output pathways (21). Interestingly, in that framework, long-range  
1057 hippocampal GABAergic neurons could function as an anatomical support to broadcast a  
1058 predictive error signal (21). These cells are among the earliest to be generated (see previous  
1059 section), again supporting the idea of an early wiring of intra and extra-hippocampal circuits  
1060 for learning regularities and predictive coding.

1061

1062         In summary, we would like to propose that the hippocampus performs generalization  
1063 based on statistical learning from the sensory world before being able to support egocentric  
1064 episodic memory. This sequence in cognitive abilities nicely mirrors developmental schedules  
1065 both at cellular and circuit level, with earlier born cells displaying a generalizing function, and  
1066 the monosynaptic pathway maturing before the trisynaptic circuit. Future work in rodents is  
1067 needed to confirm the possible implication of the hippocampus in statistical learning and its  
1068 circuit basis, and in particular, to compare the developmental timelines for cue-based vs.  
1069 internal hippocampal sequences.

1070

1071 **Summary and conclusion**

1072  
1073 Hippocampal circuits emerge through a long developmental journey with several  
1074 episodes and milestones. The first phase is neurogenesis and migration. Indeed, despite its  
1075 fundamental role in learning and memory, the functional organization of the adult  
1076 hippocampus is not only formed through experience-dependent plasticity, but is partly  
1077 hardwired at the earliest stages of development, including embryonic neurogenesis. This is  
1078 reflected in the dynamics of the adult CA1, which operates through a combination of plastic  
1079 and rigid cells, bound together within segregated functional assemblies that support stable  
1080 internal dynamics (107, 170). The propensity of individual cells to keep track of experience  
1081 through intrinsic or synaptic plasticity may be rooted in their temporal origin, as indicated in  
1082 several recent studies, with early born neurons serving a generalizing function and later born  
1083 neurons assisting content discrimination. Future studies combining fate-mapping and *in vivo*  
1084 physiology are needed to bridge the gap between neurogenesis and adult hippocampal  
1085 function. Whether the final contour of hippocampal assemblies is set early in ontogenesis and  
1086 stabilized through activity-dependent processes (eg. SPA), as described for cortical columns,  
1087 remains an open question. Addressing this major issue should contribute to unraveling the  
1088 topological logic of hippocampal functional maps.

1089 Following neurogenesis and migration, the second phase starts at birth, when  
1090 hippocampal circuits integrate into a large-scale bottom-up network that processes  
1091 somatosensory feedback triggered by neonatal movements (Figure 12). This period is  
1092 dominated by recurring network bursts, in the form of early sharp-waves and/or beta-gamma  
1093 oscillations. While the exact circuit mechanisms and spatial organization of these bursts  
1094 remain partly unknown, they certainly mirror the fact that extra-hippocampal inputs develop  
1095 before intrahippocampal connectivity schemes, including feedforward inhibition. Future work  
1096 is needed to reconcile the descriptions of early hippocampal dynamics *in vitro* and *in vivo* and  
1097 in particular to probe the early synaptic function of GABAergic transmission. At present some  
1098 *in vitro* patterns like SPAs lack an *in vivo* counterpart. Work is also necessary to describe the  
1099 calcium dynamics associated with early electrophysiological activity patterns. Regardless, we  
1100 propose that this period, which corresponds roughly to the third trimester of gestation in  
1101 humans (53, 270), ends with the first postnatal week in rodents followed by a transition  
1102 period with an emergence of adult activity patterns (theta and gamma oscillations, adult  
1103 SPWs and ripples) during the second postnatal week. This is a critical period of structural

1104 plasticity that terminates with the emergence of hippocampal recurrent connectivity,  
1105 including feedback inhibition supporting the segregation of hippocampal assemblies, possibly  
1106 along the radial axis (Figure 12). This is likely an activity-dependent but experience-  
1107 independent process through which hippocampal “receptive fields” and local circuits calibrate  
1108 local inhibition to the statistics of the external world. In other words, this second episode is  
1109 likely the period when hippocampal circuits start building an internal model based on  
1110 spontaneous and content-free activity from sensory organs and sensory feedback from  
1111 myoclonic movements (Figure 12). This would fit the hypothesis that the hippocampus would  
1112 initially support statistical learning. Future experiments are needed to test this hypothesis,  
1113 either in rodents performing novel tasks aiming at probing statistical learning or in human  
1114 babies for example using MEG (117). Addressing this critical question would enable the gap  
1115 between species to be bridged. However, it requires a closer collaboration between cognitive  
1116 and systems developmental neuroscience.

1117         Towards the end of that period, both an “internalization” and a “sparsification” of  
1118 activity are observed, most likely reflecting the emergence of a powerful inhibitory landscape  
1119 and the consolidation of CA3 inputs. This period of structural plasticity is then followed by a  
1120 period of internal spontaneous activity within the hippocampal formation supporting the  
1121 emergence of circuits capable of comparing CA3 and EC inputs prior to active exploration.  
1122 This period of functional plasticity ends with the emergence of place fields, first unstable  
1123 (223) and landmark-based (265), followed by sequences integrating internal dynamics and  
1124 external environmental cues. There are still many open questions, including those regarding  
1125 the role of early network oscillations in the maturation of specific circuits and their link with  
1126 adult network patterns or the role and function of specific GABAergic circuits. Nevertheless,  
1127 we believe that the study of hippocampal development in the context of circuit physiology  
1128 will pave the way for understanding memory circuits in the brain by watching the assembly of  
1129 its building blocks.

1130

1131 **Figure Legends**

1132

1133 **Figure 1: Possible link between the timing of neurogenesis and the diversity within CA1**  
1134 **pyramidal cells in the adult hippocampus as reflected by their anatomical distribution.**

1135 **A:** schematic cartoon illustrates the distribution of CA1 pyramidal neurons (PN) along the  
1136 transverse and radial (inset) axes according to their presumed birthdate (from E12.5 to  
1137 E18.5). Early born PNs (ebPNs) are represented in pink and later-born PNs (lbPNs) in green. **B-**  
1138 **D:** Physiology (**B**), Connectivity (**C**), and Function (**D**) segregate along these two axes matching  
1139 the timing of neurogenesis as illustrated below. **B:** Input resistance ( $R_{in}$ ) is smaller in deep or  
1140 distal CA1PNs (pink) than in superficial or proximal ones (green). **C:** Integration within  
1141 perisomatic GABAergic inputs (red circles) also differentiates between eb and lbPNs, with  
1142 lbPNs (located superficially or proximally) preferentially connecting onto interneurons and  
1143 ebPNs preferentially contacted by perisomatic GABAergic inputs. **D:** Distal and deep PNs are  
1144 more likely to display multiple place fields than proximal or superficial ones. *B* from Ref. (129),  
1145 with permission from *Journal of Comparative Neurology*; *C* from Ref. (207), with permission  
1146 from *Hippocampus*; Ref. (158), with permission from *Journal of Neuroscience*; *D* from Ref  
1147 (119), with permission from *Neuron* and Ref. (97), with permission from *Nature*  
1148 *Communications*.

1149

1150 **Figure 2. Early born GABAergic neurons (ebGABA) display characteristic physiology,**  
1151 **connectivity, and function in the adult CA1. A:** Fate-mapping experiments demonstrated that  
1152 ebGABAs (born at E9.5) adapt their firing in response to long current injections (**B**), receive  
1153 less local GABAergic inputs (lower putative PV contacts) (**C**), and display high functional  
1154 connectivity (**D**). *B-D* from Ref. (30), with permission from *Nature Communications*.

1155

1156 **Figure 3. Developmental timeline of the neurogenesis and migration of CA1 neurons.**

1157 CA1 pyramidal neurons (PNs) and GABAergic Interneurons (INs) are born and migrate into  
1158 their final positions from E10 until postnatal day 5 (P5) with different schedules for early-born  
1159 (eb, red) versus late-born (lb, green) cells. The timing of neurogenesis is indicated for a few  
1160 subtypes of INs. SOM: somatostatin, PV: parvalbumin; nNOS: Nitric Oxide, Chand.: chandelier,  
1161 CR: Calretinin.

1162

1163 **Figure 4: Developmental sequences for the maturation of morpho-physiological properties of**  
1164 **CA1 neurons. A:** Schematic description of postnatal changes in the morpho-functional  
1165 properties of CA1 neurons. **B:** Input resistance and I<sub>h</sub> decrease as postnatal age increases. **C:**  
1166 Spontaneous activity shifts from gap-junction mediated Synchronous Plateau Assemblies  
1167 (SPA, red) to synapse-driven Giant Depolarizing Potentials (GDP, blue) while the  
1168 morphophysiological properties of GABAergic cells change from displaying filopodia, adaptive  
1169 firing, and large miniature events to smooth cell bodies, firing diversity and small amplitude  
1170 minis. **D.** The expression of KCC2 at the membrane is also developmentally regulated  
1171 according to age with ebINs displaying membrane KCC2 as early as P3. *B* from Ref. (76), with  
1172 permission from *Hippocampus*; *C* from Ref. (8), with permission from *Journal of Neuroscience*;  
1173 *D* from Ref. (259), with permission from *Journal of Comparative Neurology*

1174

1175 **Figure 5: Developmental timeline describing the wiring of CA1 hippocampal circuits.** Long-range  
1176 glutamatergic (top) inputs from the entorhinal cortex and septum as well as long-range  
1177 GABAergic inputs reach CA1 first as early as the late embryonic stages. In turn, CA1  
1178 interneurons with a long-range projection to the septum mature before dendritic inhibition  
1179 while somatic GABAergic inputs develop towards the end of the first postnatal week.

1180

1181 **Figure 6: Global timeline for the development of hippocampal network activity patterns.**

1182 *A, in vivo* and *B, in hippocampal slices and intact hippocampus preparation in vitro.* Green  
1183 indicates transient immature patterns, orange indicates emerging adult patterns. eSPW, early  
1184 Sharp Waves; SPW, adult sharp waves; SPA, Synchronous Plateau Assemblies; GDP, Giant  
1185 Depolarizing Potentials.

1186

1187 **Figure 7: Emergence of correlated neuronal activity in the developing hippocampus *in vitro.* A:**  
1188 Developmental timeline of expression of hippocampal network activity patterns *in vitro.* **B:**  
1189 Uncorrelated calcium spikes (black) are observed until birth when they are replaced by gap-  
1190 junction mediated Synchronous Plateau Assemblies (SPA, red). In turn, SPAs are progressively  
1191 replaced by Giant Depolarizing Potentials (GDP, blue) as illustrated by the histogram plotting  
1192 the fraction of cells involved in either pattern as a function of time. These three patterns are  
1193 associated with characteristic calcium fluorescence transients. **C:** GDPs actively shut down  
1194 SPAs as shown by the example of a GDP terminating a calcium plateau and the associated

1195 membrane potential oscillations measured in current-clamp mode. **D**: Neurons involved in  
1196 SPAs are connected by electrical synapses as revealed by the spikelets recorded in current  
1197 clamp (bottom right trace) and by multiple neuron labelling with neurobiotin. *B and D* from  
1198 Ref. (55), with permission from Neuron; *C* from Ref. (8), with permission from *Journal of*  
1199 *Neuroscience*.

1200

1201 **Figure 8: Giant depolarizing potentials in hippocampal slices in vitro.** **A**: Timeline of GDPs. **B**:  
1202 Example traces of gramicidin perforated patch recordings from a CA3 pyramidal cell, multiple  
1203 unit activity (MUA) and local field potential (LFP) recordings from the CA3 pyramidal cell layer  
1204 in a P6 rat hippocampal slice. **C**: Dynamic changes in GABAergic and glutamatergic currents in  
1205 P5-6 CA3 pyramidal cells during GDPs. Note that GABAergic currents transiently switch their  
1206 direction from depolarizing to hyperpolarizing at the peak of GDPs. **D**: GDP network model.  
1207 GDPs are initiated in CA3 recurrent network (1) with support of GABAergic INs (2), and further  
1208 conveyed to CA1 via Schaffer collaterals and GABAergic projections (3), and to dentate gyrus  
1209 via GABAergic projections. **E**: Top, neuroLucida reconstruction of the hub-IN (axon, red and  
1210 dendrites, black) on a schematic drawing of the hippocampus. Left, Current-clamp recordings  
1211 from the stimulated (grey box) hub-IN for six consecutive stimulations (gray). Four out of six  
1212 trials triggered GDPs. Right, fraction of cells active as a function of time after repetitive hub-  
1213 INs stimulation and corresponding peristimulus time histogram. **F**: Top, histogram displaying  
1214 the percentage of active cells (black) during stimulation of an early born IN (ebGABA) that was  
1215 patched and stimulated by injecting suprathreshold depolarizing current steps (green trace).  
1216 Bottom, box plots of “Inter GDP intervals” of a representative ebGABA cell (left) **G**: Arch-  
1217 mediated optogenetic inhibition of MGE-derived INs with a 10 s light stimulus (green)  
1218 suppresses spontaneous GDPs and generates rebound GDPs in CA1. Left, Recording  
1219 configuration with focus of yellowgreen light stimulus in CA1 to inhibit MGE-derived  
1220 interneurons. Right, Example of simultaneous recordings in an MGE-derived IN (gray) and a  
1221 neighboring PN (black). Activation of the Arch-current greatly reduced the frequency of  
1222 spontaneous GDPs in both cells, which returned once the light was turned off. *B and C* from  
1223 Ref. (140), with permission from *Journal of Neuroscience*; *E* from Ref. (33), with permission  
1224 from *Science*; *F* from Ref. (30), with permission from *Nature Communications*; *G* from Ref.  
1225 (263), with permission from *Journal of Neuroscience*.

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1227 **Figure 9. Comparison of early sharp waves (eSPWs) with adult sharp waves (SPWs).** **A:** Timeline  
1228 of eSPWs and SPW/ripples. **B:** Left, Example traces of the forelimb twitch (green circle),  
1229 population burst in MEC-L3 (blue circle) and eSPWs (red triangle) recorded from the CA1  
1230 pyramidal cell layer (pcl), stratum radiatum (sr) and stratum lacunosum-moleculare (slm) in a  
1231 P5 rat pup. Vertical color bars above traces indicate single unit activity. Middle,  
1232 corresponding current-source density of eSPWs with the most prominent sinks in *sr* and  
1233 around the hippocampal fissure. Right, eSPW network model. Note that sequential activation  
1234 of various structures in this scheme follows the bottom-up information transfer from the  
1235 spinal cord to hippocampus. **C:** Left, Example traces of adult SPW/ripple in CA1 pcl and sr.  
1236 Middle, current-source density of SPWs with the most prominent sink in CA1 *sr*. Right, SPW  
1237 network model. Note that SPWs are internally generated in the hippocampus and support  
1238 top-down information transfer from the hippocampus to the extrahippocampal targets. **D:**  
1239 Left, eSPWs are preceded by activation of MEC-L3 units in neonatal rat pups, whereas adult  
1240 SPWs are associated with activation of neurons only in the hippocampal output deep EC  
1241 layers. *B* from Ref. (254), with permission from Cerebral Cortex; *C* from Ref. (44), with  
1242 permission from *Hippocampus* and Ref. (233), with permission from *Journal of Neuroscience*;  
1243 *D* from Ref. (254), with permission from Cerebral Cortex and Ref. (52), with permission from  
1244 *Journal of Neuroscience*.

1245

1246 **Figure 10: Pharmacogenetic silencing of interneurons inhibits hippocampal activity in P3 mice.**  
1247 **A:** Representative recording for P3 reduction of GABAergic neuron excitability. MUA of  
1248 spontaneous activity in CA1 hippocampus, along with associated *sr* LFP and thoracic  
1249 movement detection and electromyography. Activity is dominated by eSPW whose spike  
1250 density is reduced following subcutaneous SalB (KORD agonist) injection. **B:** Quantification of  
1251 KORD-induced suppression of GABAergic neuron excitability and control conditions. *A* and *B*  
1252 from Ref. (200), with permission from *Science Advances*.

1253

1254 **Figure 11. Developmental timeline for the emergence of cognitive sequences in the CA1 region**  
1255 **of the hippocampus (A).** **B:** Sharp-Wave-associated Ripples (SPW-Ripples) start being observed  
1256 at P12 and their power progressively increases until the end of the third postnatal week. **C:**  
1257 At P15, the first internal representations are observed in CA1 in the form of unstable place  
1258 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.

1290 This period ends with the emergence of internal sequences (stage 4) integrating experience  
1291 into internal dynamics.  
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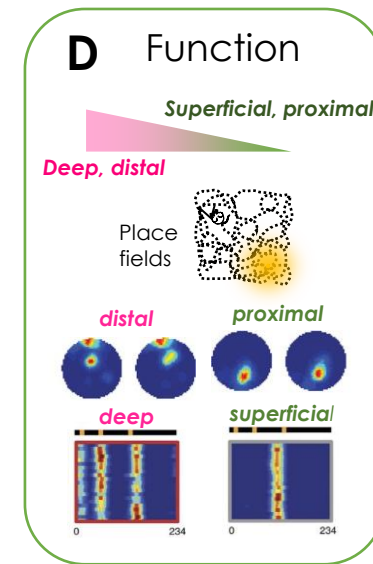
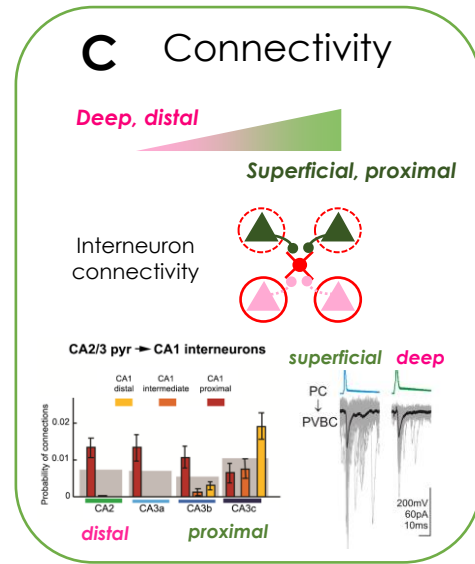
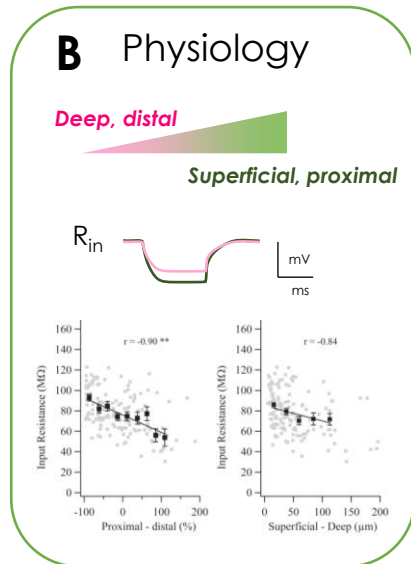
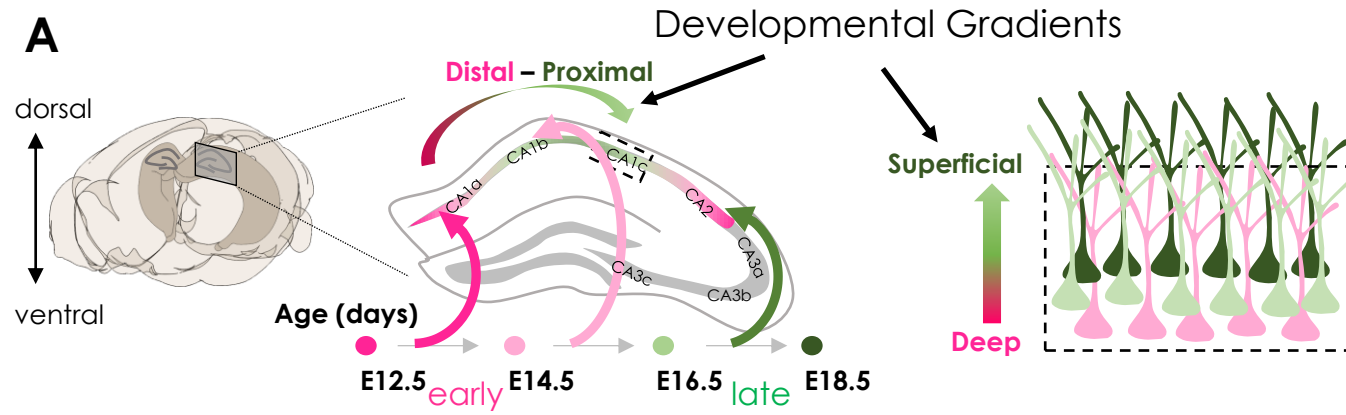
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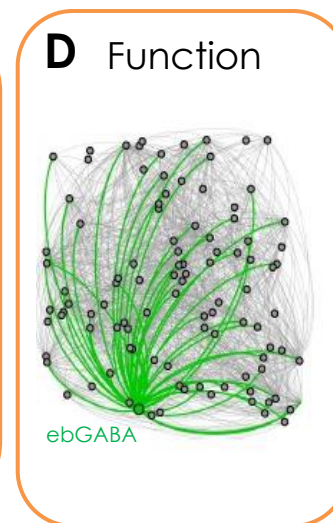
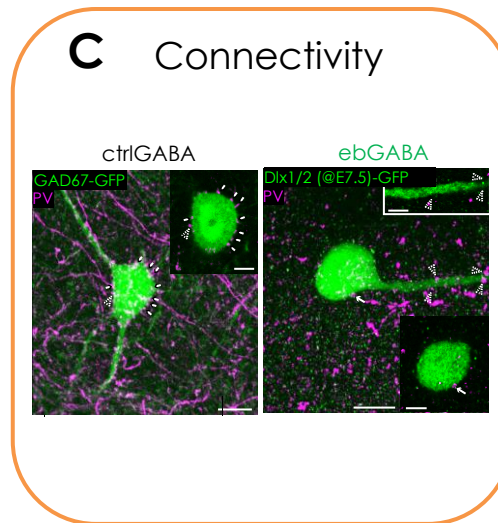
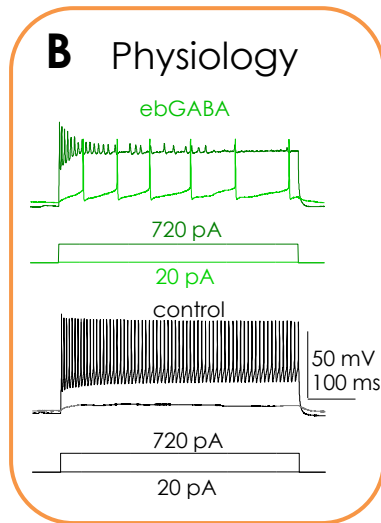
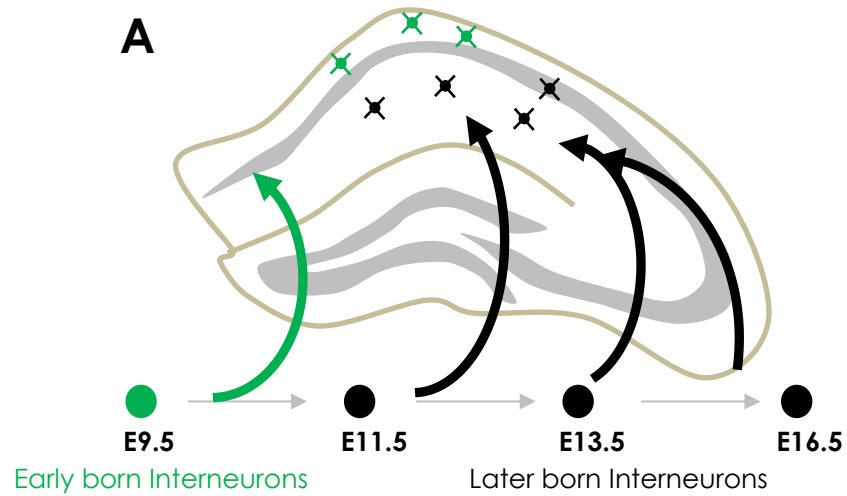
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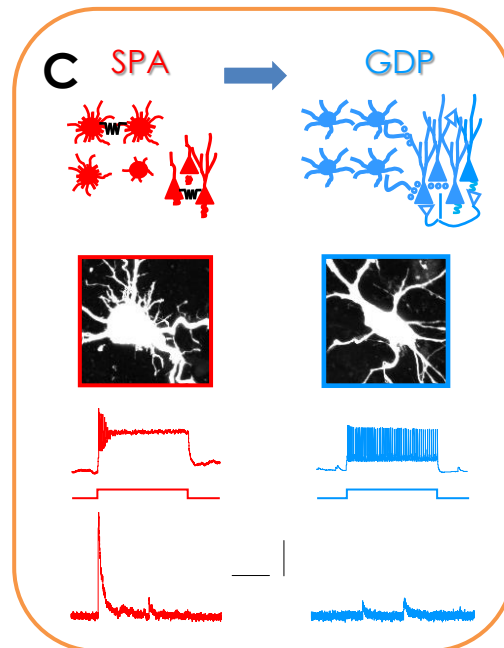
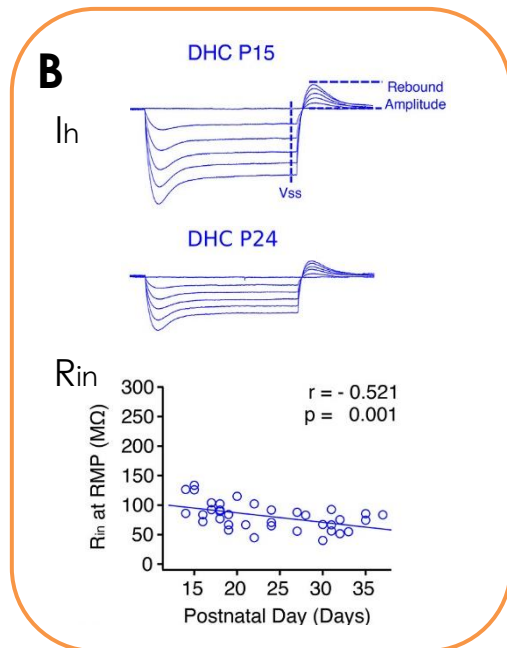
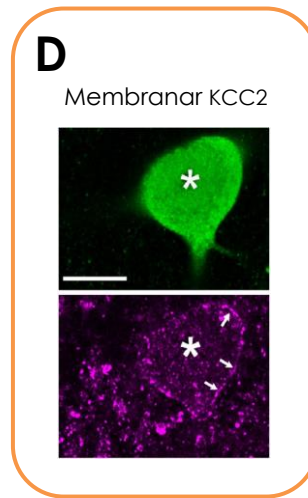
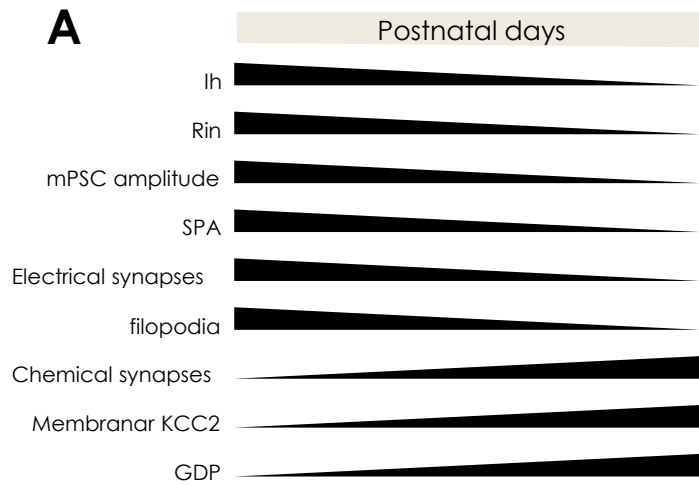


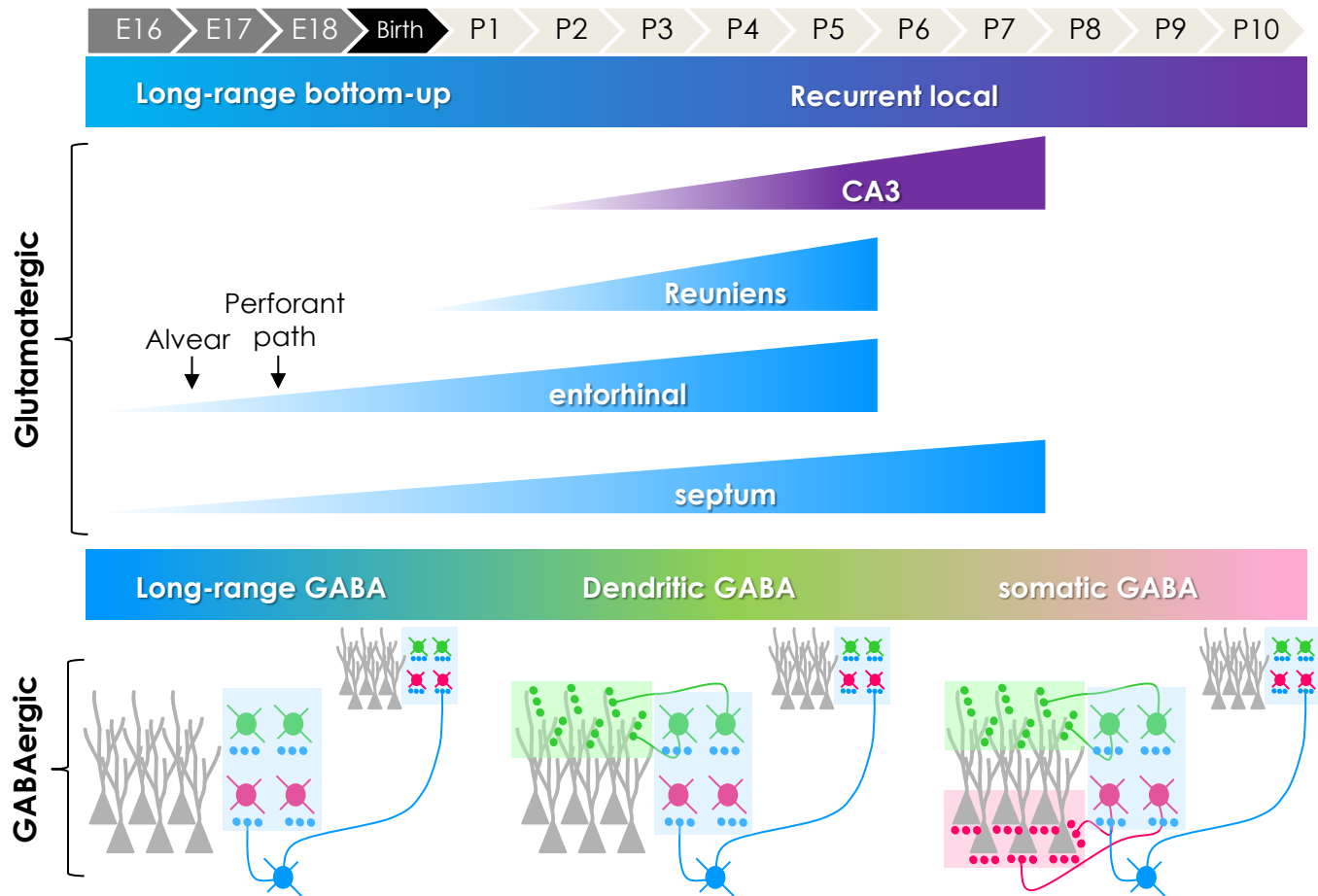
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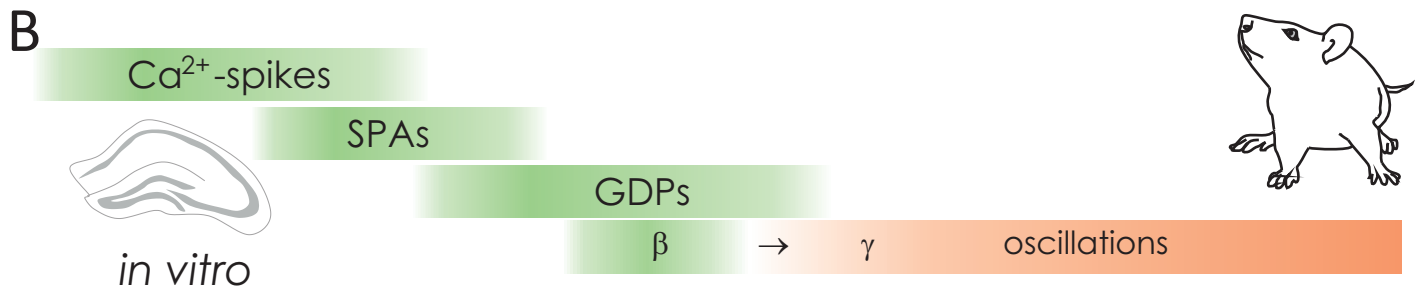
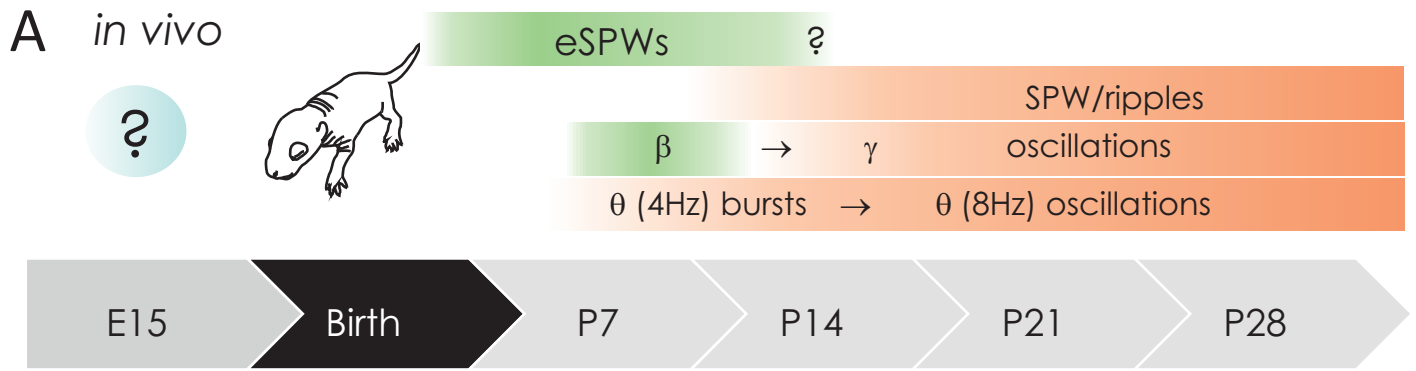










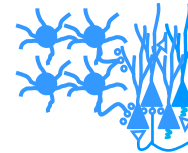
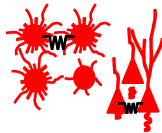
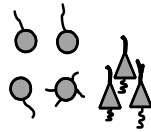


**A** E16 E17 E18 Birth P1 P2 P3 P4 P5 P6 P7 P8 P9 P10

Ca<sup>2+</sup> spikes

SPA

GDP

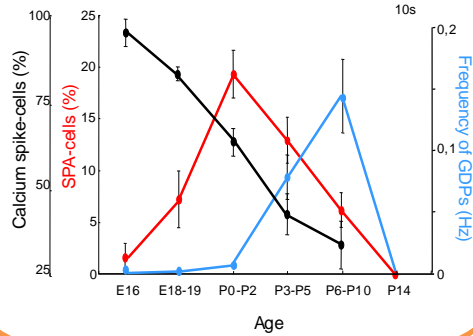
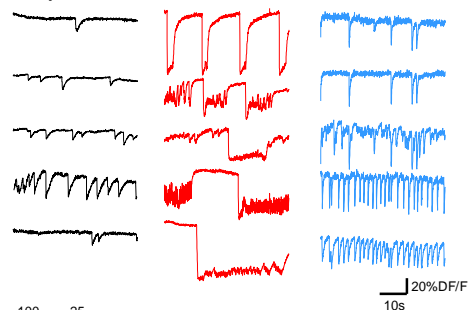


**B**

Calcium spike

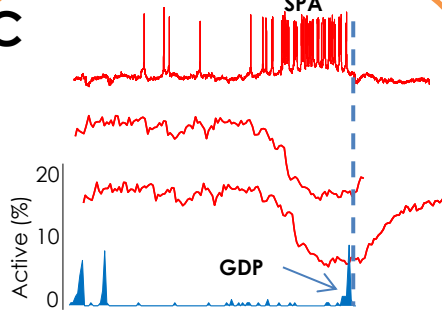
SPA

GDP



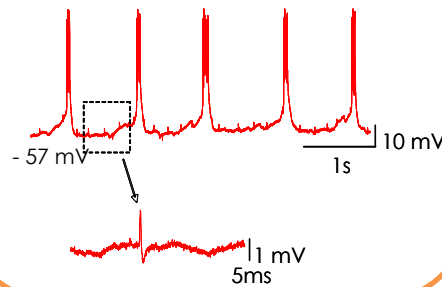
**C**

SPA

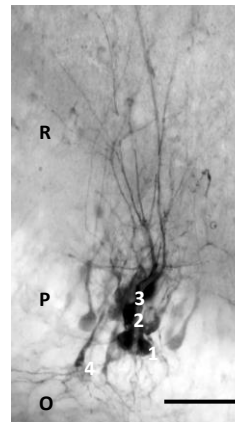
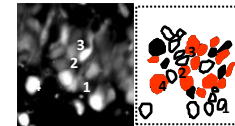


Active (%)

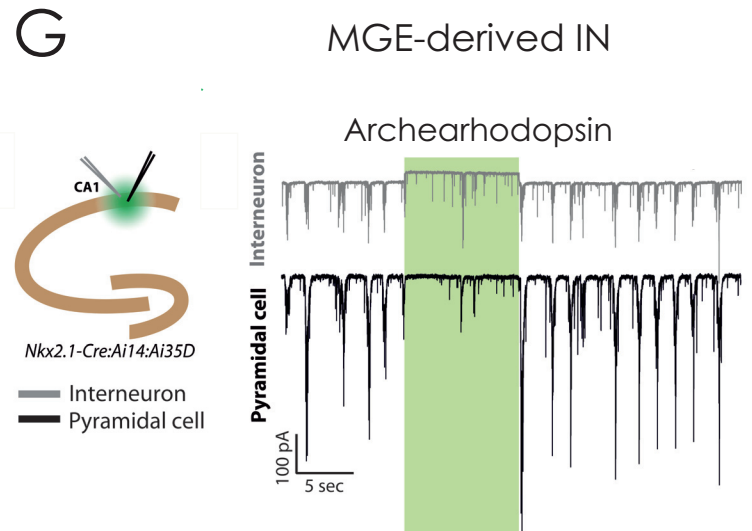
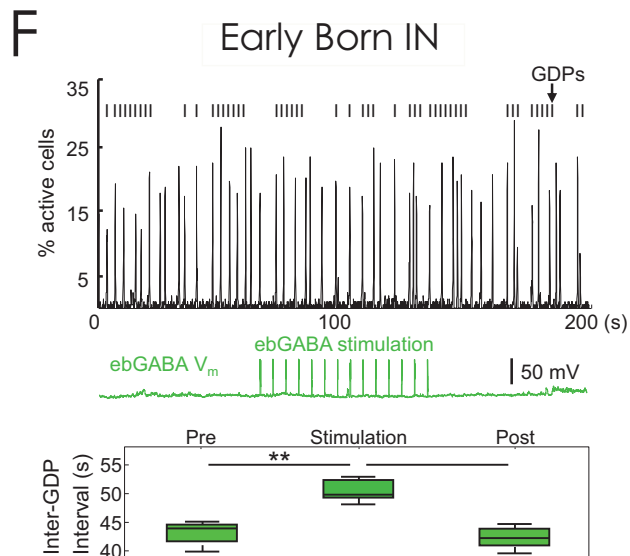
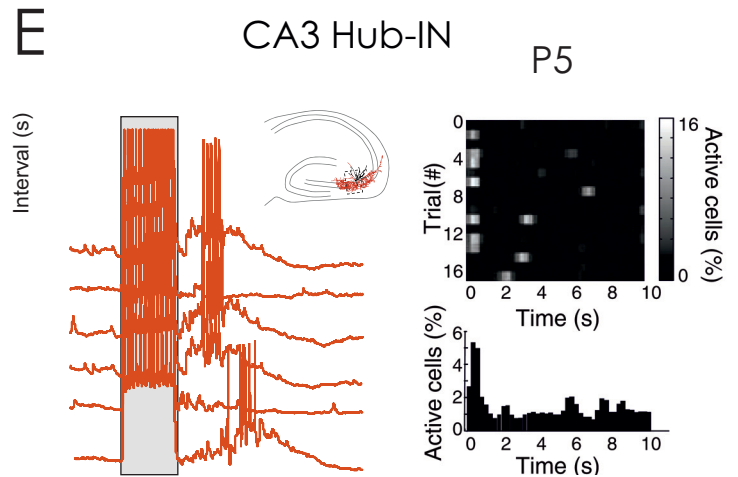
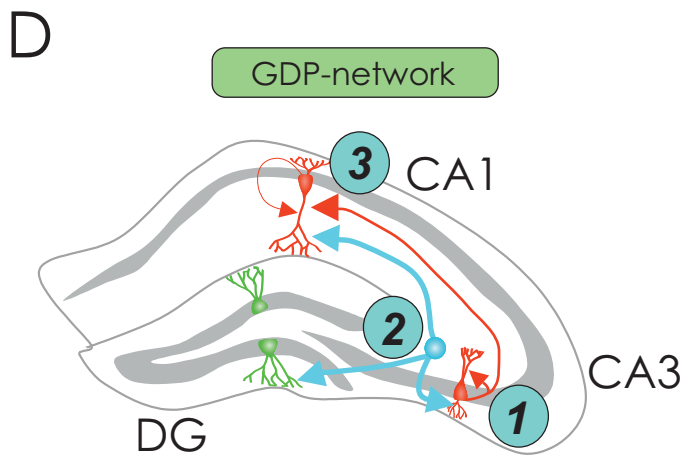
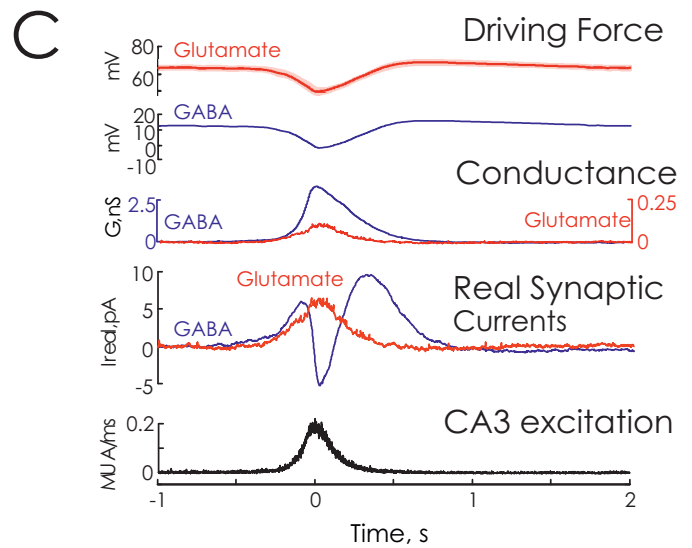
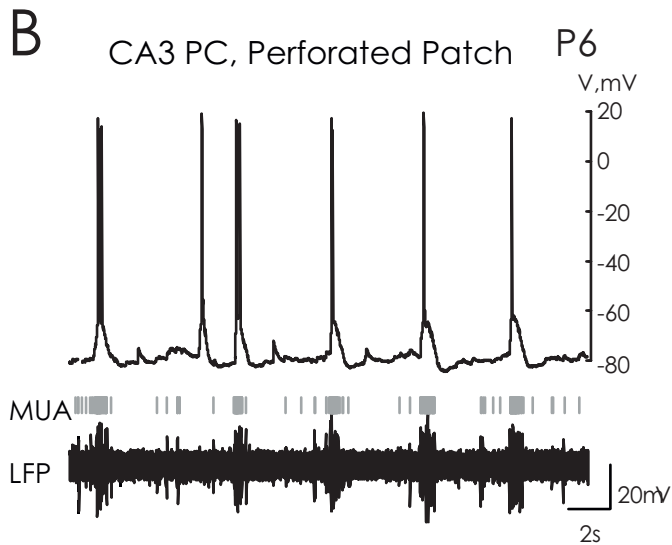
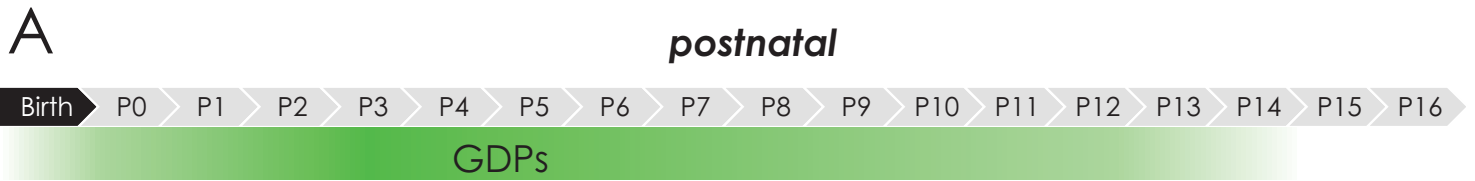
GDP

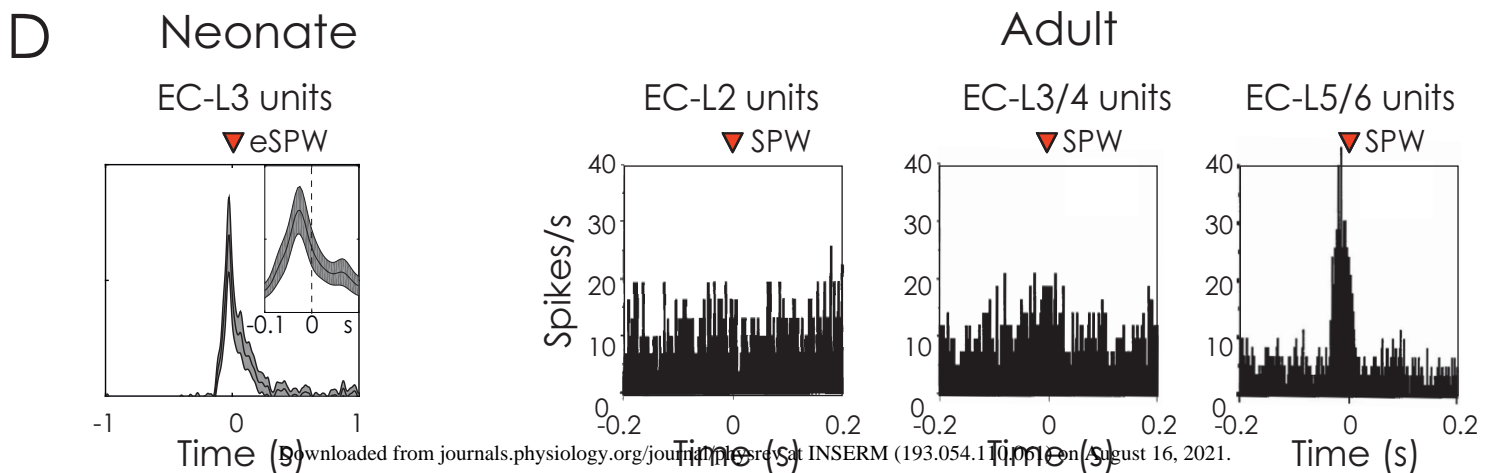
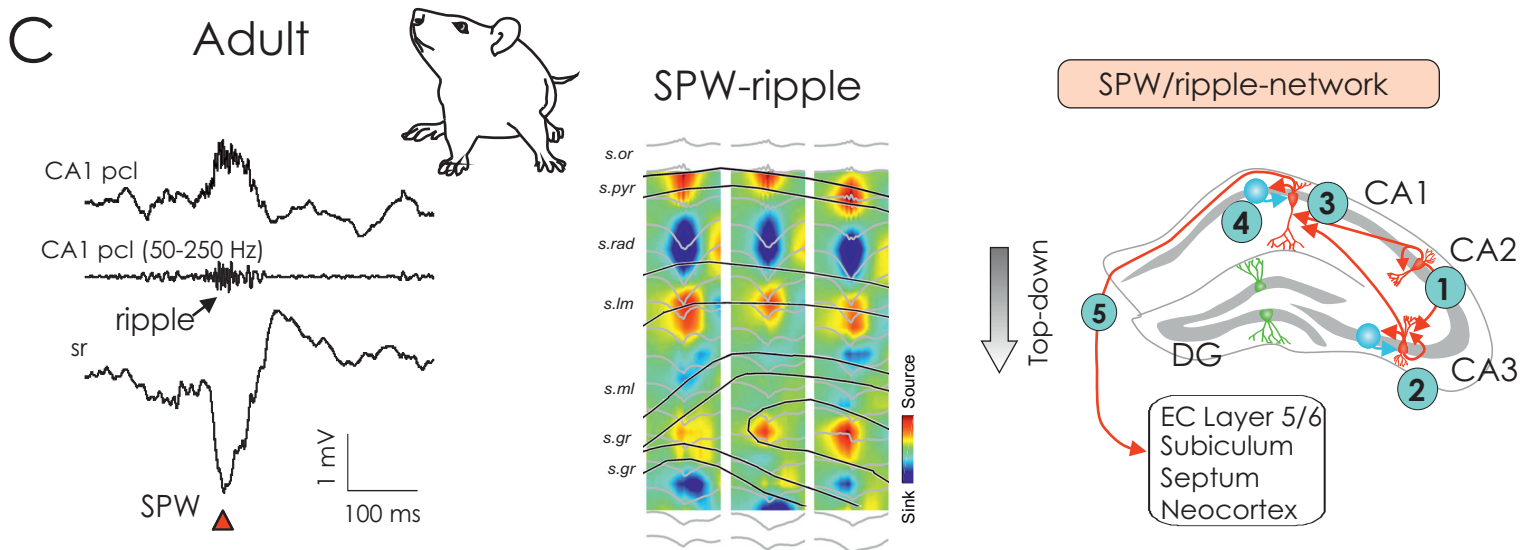
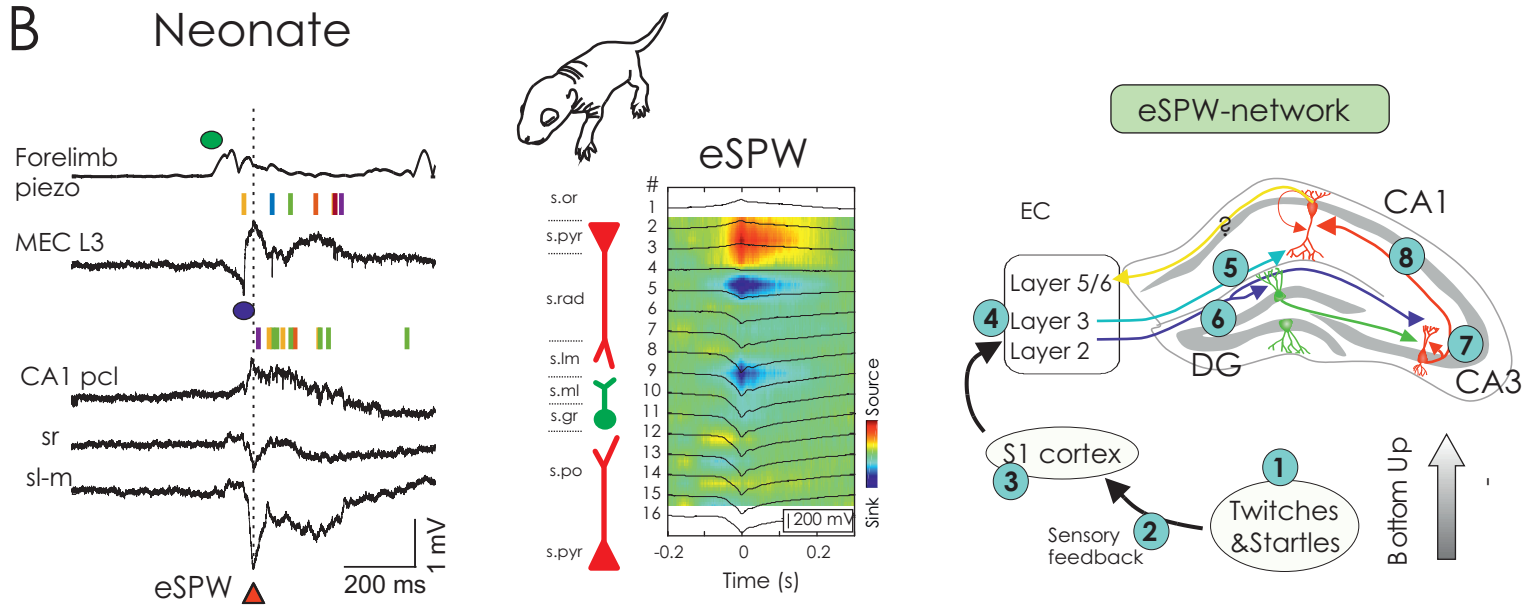
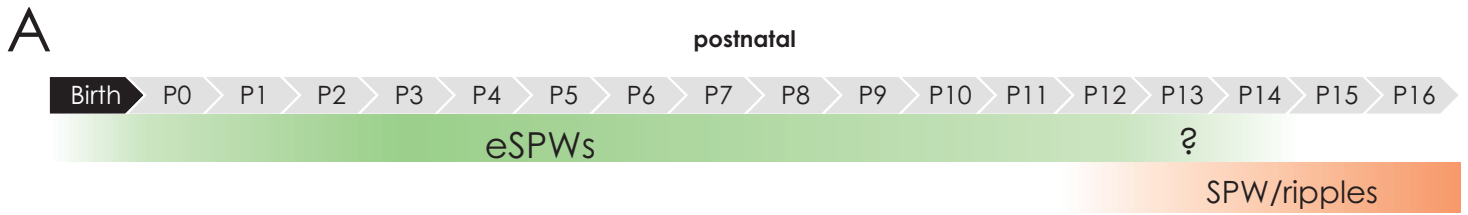


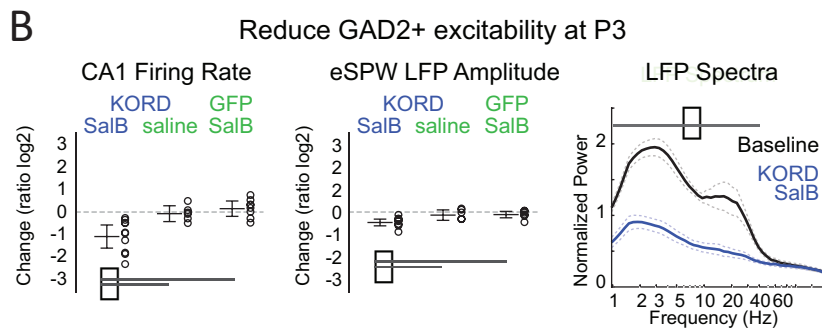
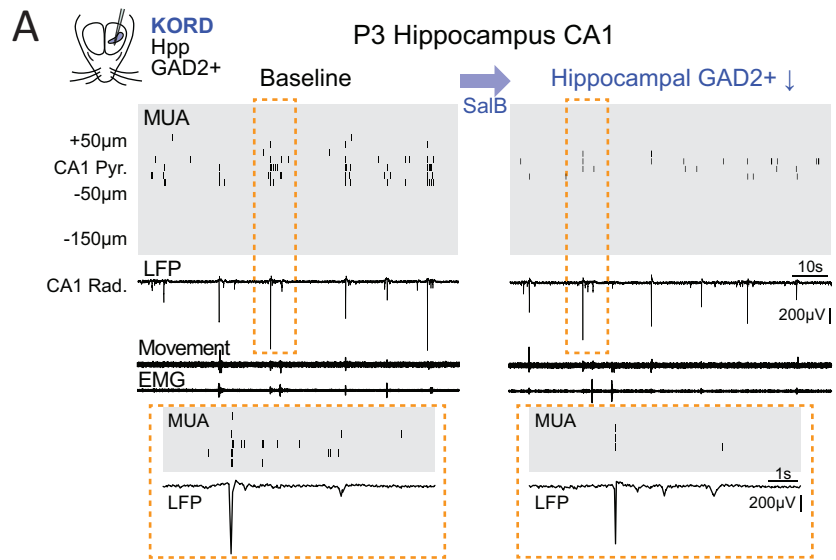
**D**

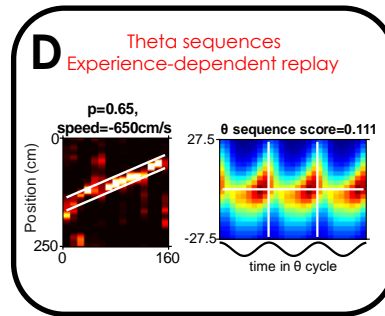
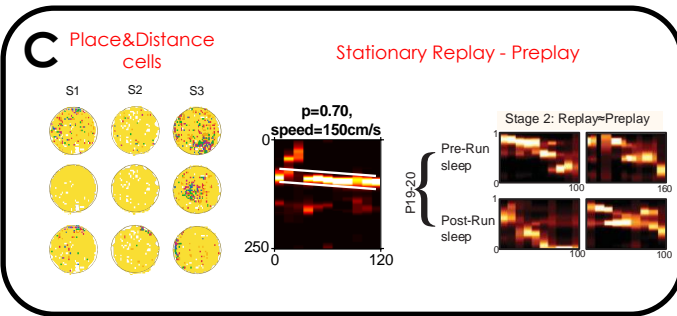
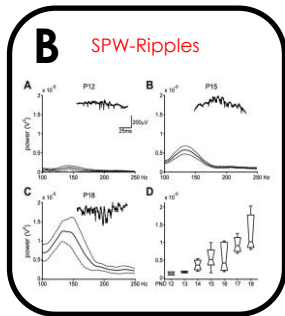
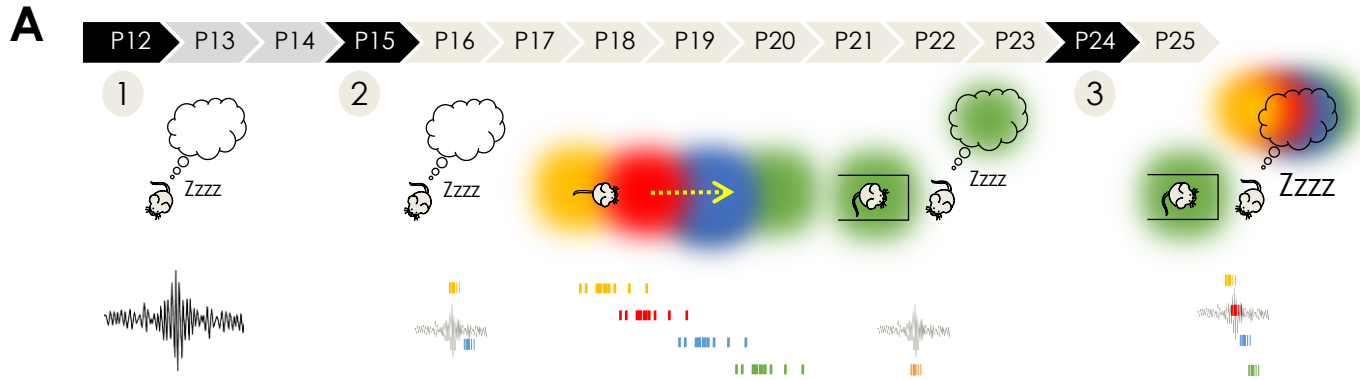


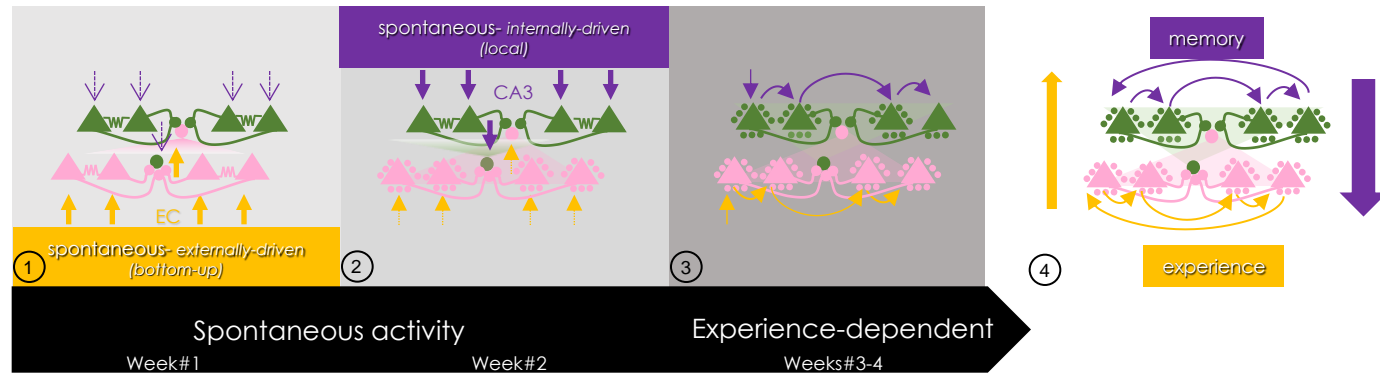












		early	late	References
Physiology	Rm			Masurkar et al. (181), Graves (103), Jarsky et al. (129), Sun et al. (234)
	lh			Masurkar et al. (181), Maroso et al. (176), Li et al. (164)
	I/O			Cembrowski et al. (47), Mizuseki et al. (189), Oliva et al. (207)
	burstiness			Misuzeki et al. (189)
Connectivity	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,  $I_h$ : 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	<i>In vivo</i>	<i>In vitro</i>
Calcium spikes	E16-P6	Uncorrelated neuronal activation in absence of electrical and chemical connections	Not reported	Crepel et al. (55) <i>Neocortex:</i> 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) <i>Neocortex:</i> Allene et al. (7), Dupont et al. (82) <i>Striatum:</i> 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) <u>Synonyms:</u> <i>Unison-firing pattern</i> Harris & Teyler (111) <i>Synchronous calcium oscillations</i> Leinekugel et al. (162) <i>Early network oscillations</i> 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) Mohs & 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***

