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The development of spatial and memory circuits in the rat.

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Review

Introduction

The hippocampus, along with other brain regions in the parahippocampal formation that together make up the temporal lobe, has long been recognized as a brain structure that supports multiple forms of memory¹⁻⁵. In humans, the hippocampal network is necessary for episodic memory, and in rodents, particularly relevant to spatial memory^{6,7}. The psychological representation of allocentric (world-centered) space – a ‘cognitive map’⁸ - is stored in the hippocampal formation in the rodent, within which can be found a network of neurons whose firing is modulated by the animal’s position and orientation in space.

Four main classes of spatial neurons have been discovered so far in the rodent. Place cells, recorded from regions CA1 and CA3 in the hippocampus proper, fire to the unique location of the animal within an environment⁹. Head direction cells, recorded in a wide network of structures including the midbrain, hypothalamus, thalamus and the hippocampal formation, respond when the animal points its head in a particular compass direction, and their directional preference is invariant to location^{10,11}. Grid cells can be recorded from parahippocampal cortices and fire in a repeating hexagonal mosaic of locations that span the whole environment, and the periodicity in their firing patterns is relatively robust to environmental change¹² (but see Stensola et al 2015¹³, Krupic et al 2015¹⁴). Boundary responsive cells, described in the medial entorhinal cortex (mEC) and dorsal subiculum, are active along environmental borders that constitute barriers to movement, such as walls or drop edges¹⁵⁻¹⁷. In addition, other types of cells with spatial responses that are a combination of two or more of these four main categories have also been identified^{18,19}. Place, head direction and grid cells, or signals akin to these have also been described across several animal species besides rodents (for example, in fish²⁰, fruit bats²¹⁻²³, macaque monkeys²⁴⁻²⁷, and humans²⁸⁻³⁰), suggesting that spatially tuned neurons are a fundamental component of vertebrate spatial memory and behavior.

The contribution of each spatial cell type to the synthesis of a consistent allocentric representation has been investigated extensively in the adult rat, but it is only through studying development that the organizational chronology of the network can be specified. Developmental studies conducted in the last few years have provided some insight into the timeline of emergence of the different spatial components of the hippocampal spatial neural network. This review will highlight the key findings of the extant literature on the development of hippocampal spatial circuits in the rodent, with a focus on the emergence of the four main spatial cell types (place, head direction, grid and boundary responsive cells). We will start with a succinct review of the sensorimotor (Section 1A) and behavioral (Section 1B) development of the rat (for a more in depth review of these topics please refer to Wills et al 2013³¹ and Dumas et al 2005³²), which will provide the background against which to interpret the timeline of emergence of the neural spatial responses in the hippocampal formation and beyond (Sections 2 and 3).

1. Review of main sensorimotor and behavioral milestones in the rat

A. Sensorimotor development: From helpless to active and independent in three weeks

The first 2-3 weeks of a rat’s life are restricted to the confines of the nest and the litter huddle, with the pup fully dependent on its dam for sustenance and survival. Born blind, deaf and barely mobile, rats begin experiencing the external world through rudimentary

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3 olfactory, tactile and vestibular senses^{33,34}. Sensorimotor capacities undergo growth and
4 functional organization, but remain immature. For example, the visual system undergoes
5 extensive internal organization both peripherally and centrally, but remains unresponsive to
6 external stimulation up to a week after birth³⁵⁻³⁹. The first adult-like sensory response to
7 emerge is that of first order vestibular neurons at P6^{40,41}.
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10 A rapid expansion of the rat's sensorimotor repertoire takes place in the second postnatal
11 week (Figure 1) to enable active sampling of environmental cues. Beginning from P7/8, rat
12 pups gain the motor ability to pivot about the abdomen, and are able to crawl with their
13 abdomens off the ground and supported on four limbs from P12-13. Full quadrupedal
14 walking, as well as rearing and grooming behaviors, emerge by the end of the second week³³.
15 The olfactory system becomes adult-like by P9-12, allowing the pup to perform the highly
16 complex task of discriminating odors belonging to their own nest from odors of another
17 litter⁴². The tactile sense, in the form of whisking (repeated cycles of retraction and
18 protraction of the whiskers), also appears in an adult-like form between P11-13⁴³. In
19 contrast, the auditory and visual systems are slow to develop. The ear canals of the rat
20 become unsealed only at around P12-13, and rats begin to show responses to auditory
21 stimulation from P13, but are not yet able to use auditory stimuli as orienting cues⁴⁴⁻⁴⁶. The
22 visual system starts to become weakly responsive to visual stimulation, but the eyelids
23 remain fused until the end of the second postnatal week.
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27 The third postnatal week marks the assembly of the full complement of functional
28 sensorimotor capacities in the rat pup. At around P15, the eyelids of the rats come
29 unfused^{47,48}, allowing processing of patterned visual stimuli for the first time. One study
30 reported that visual evoked responses develop rather slowly in the rat, and do not reach
31 maturity until P23³⁷, while another study showed stable and adult-like responses in the
32 primary visual cortex (V1) to drifting sinusoidal gratings by P16³⁸. Regardless of the
33 maturity of responses, both studies concur that a certain level of activity can already be
34 evoked in the visual cortex at eye opening. The last step towards independence, weaning off
35 of the dam's milk, is generally achieved around the end of the third postnatal week in the
36 laboratory rat, whilst there is evidence that in the wild, weaning takes place significantly
37 later^{49,50}.
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40 B. Development of spatial behavior: allocentric spatial navigation emerges at around 41 P20 42

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44 Within hours of birth, rat pups are able to use olfactory cues to seek out and attach
45 themselves to the nipples of the dam. From the moment rat pups are able to pivot on their
46 abdomens (P8), they show an ability to orient themselves towards the nest after they have
47 been separated and placed outside of the nest³³. These forms of rudimentary orienting
48 behaviors are not necessarily hippocampus-dependent⁵¹, but may simply reflect beacon-
49 based homing behavior.
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52 From the beginning of the third postnatal week, all sensorimotor capacities have become
53 available, and exploratory behavior begins to take shape. When the entire litter is removed
54 from its nest and placed in a novel environment, rat pups make tentative forays away from
55 their littermates beginning from P16-18, with the outgoing segments becoming
56 progressively longer over the course of the next week, and the homeward component
57 remaining rather rapid and direct⁵². Left undisturbed in the nest, pups only begin to
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3 spontaneously exit the home cage from P15. At that age, the amount of time spent outside
4 the nest is very limited, increasing sharply only from P18⁵³. Interestingly, for individual
5 pups, the onset of significant active exploration when left in an open field occurs abruptly,
6 which for most pups is overnight from P20-21⁵⁴.
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9 True hippocampus-dependent spatial navigation emerges at around the same time as
10 spontaneous active exploration, at the end of the third postnatal week. The onset of learning
11 in the Morris Water Maze, as indicated by a reduction in time needed to find the hidden
12 platform and increased search in the correct quadrant, takes place from around P20^{55,56}.
13 Pups display successful 8-arm radial maze navigation from P21⁵⁷, the same age at which
14 spontaneous alternation on a T-maze can be observed⁵⁸. However, although the onset of
15 hippocampus-dependent spatial cognition can be seen at approximately P20, the maturation
16 of spatial behavior continues well into the second month of life^{55,58-61}.
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18 2. Tracing the emergence of allocentric spatial signaling in the brain

19 A. Head direction cells: The first of the spatial signals to emerge and mature

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21 Two pioneering studies on the development of the spatial cell types reported that an adult-
22 like head direction signal can already be detected from the dorsal presubiculum (dPrS) and
23 medial entorhinal cortex (mEC) of rat pups at P15-16^{62,63}. This is interesting because it
24 precedes spontaneous experience of large-scale space in rats. What is even more surprising
25 is that this early head direction signal is as finely graded and accurate as in the adult. At P16,
26 the proportions of head direction cells are comparable to those found in the adult, and so are
27 the amount of directional information that the cells carry and their directional specificity
28 (i.e. tightness of the directional tuning curve). The stability of the head direction signal
29 within and across exposures to the same environment is also adult-like as early as P16.
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33 Two more recent studies extended the search for the origins of the head direction signal and
34 found that head direction cells can be detected as early as P11-12 in the rat dPrS, ADN⁶⁴, and
35 mEC⁶⁵, 3-4 days before the eyes of rats are open (Figure 2A). However, head direction cells
36 are fewer in number at P12 than at P16, and lack maturity in the directional information
37 they carry. In addition, although these early head direction cells have a clear and stable
38 preferred firing direction within a 5-minute exploration session, they are unable to maintain
39 the same directional preference during a subsequent visit to the same environment⁶⁴.
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43 Immature though the head direction signal may be at P12, it is interesting that these early
44 head direction cells exist before the eyelids of the rats come unfused. In the adult rat, visual
45 landmark cues are especially salient in influencing the preferred firing directions (PFDs) of
46 head direction cells, and are able to do so within 80 ms of exposure⁶⁶. In contrast, the
47 emergence of head direction cells before the rat has access to patterned visual input, in the
48 form of visual landmarks or optic flow, suggests that vision is not necessary for the
49 organization of the head direction network.
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53 Furthermore, not only are head direction cells present before eye opening, there is evidence
54 to suggest that the underlying network connectivity may already be well established. The
55 head direction network has been modeled using continuous attractor dynamics that
56 postulate a ring attractor with a 'hill' of activity that is moved around the ring by a
57 combination of angular velocity and visual inputs⁶⁷⁻⁷³. A prediction that emerges from
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3 attractor dynamics is that PFDs of different head direction cells should always display fixed
4 angular differences from one another. Within the mature head direction network, the PFDs
5 of head direction cells may gradually drift across time in complete darkness, or may be
6 shifted by some amount in response to a change in the visual array or environment, but all
7 head direction cells recorded in the same rat will rotate their PFDs by the same amount,
8 maintaining global coherence in the angular difference between cells^{74,75}, and the internal
9 organization of the head direction system appears intact even during sleep⁷⁶. In pre-
10 weanling rats that display less stable head direction signals than in the adult rat even under
11 normal lighting conditions, this phenomenon of angular coherence can still be seen as early
12 as P16⁶², and even before eye opening⁶⁵, indicating that the underlying synaptic connectivity
13 that is organized prior to visual input is able to support attractor dynamics.
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17 Although unnecessary for organizing the head direction network, vision is clearly important
18 for anchoring the emerging network to the external frame of reference. Prior to eye opening,
19 the head direction signal lacks stability between repeated samplings of the same
20 environment, but once patterned vision becomes available, the head direction signal
21 becomes significantly more able to maintain a fixed representation with respect to the
22 environment. Vision is also important for the maturation of the nascent head direction
23 signal. The stability of the head direction signal within a session, as well as the amount of
24 directional information carried, improves significantly with access to patterned vision. The
25 improvement in reliability and quality of the head direction signal coincident with eye
26 opening appears to be the only maturational spurt in the developmental timeline of head
27 direction cells. In addition, a prominent and distal visual landmark can gain influence over
28 the PFDs of head direction cells within 24 hours of eye opening⁶⁴ (Figure 2B-C). In order to
29 test conclusively if patterned vision indeed drives, or is simply coincident with, the
30 maturation of the head direction signal, further experiments that manipulate the timeline of
31 natural eye opening would be necessary.
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35 The early emergence of the head direction signal ahead of other spatial cell types, without
36 the need for vision or the experience of large-scale space, suggest that the head direction
37 signal may be a primary spatial signal that is organized independently of other spatial cell
38 types. Indeed, the head direction signal remains intact in adult animals after lesions of the
39 hippocampus⁷⁷. Rather, the generators of the head direction signal appear to reside outside
40 of the hippocampal formation in the LMN/DTN circuit^{78,79}, and there is evidence that
41 vestibular function is necessary for the maintenance of the head direction signal⁸⁰⁻⁸². In turn,
42 the early emergence of the head direction signal may contribute to the formation or
43 maturation of other spatial cell types. For example, it is likely that the grid signal in the mEC
44 relies on the pre-existence of a stable directional input in order to emerge, as grid cells of the
45 mEC and parasubiculum (PaS) lose their spatial periodicity when the head direction signal is
46 silenced in the adult rat⁸³.
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50 There are only a handful of theoretical models so far that address the development of the
51 head direction system. All of these models include a distal visual landmark which entrains
52 the nascent network; the advantages of a distal visual landmark cue is its locational
53 invariance with respect to the rat's movements^{84,85}. However, with experimental data that
54 excludes patterned vision as a prerequisite for setting up the nascent head direction
55 network^{64,65}, new models of the development of the head direction circuit are needed. One
56 such possibility is a head direction network that can be entrained using local non-visual
57 sensory cues. The olfactory system and the tactile system are two senses that are functional
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3 and adult-like by P11/12. Olfactory cues are particularly important for the survival of the rat
4 pup⁸⁶, and even if olfactory cues may be less effective than visual cues at anchoring the PFDs
5 of adult head direction cells⁸⁷, this does not eliminate the possibility that during early
6 postnatal life, olfactory cues may be critical in providing a sense of orientation to the
7 developing rat pup. Tactile cues may also provide spatial cues in the form of boundary or
8 geometric information. Integration of boundary information as the animal moves around the
9 environment, may act to stabilize the internally generated head direction signal without the
10 need for a distal visual cue.
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13 Another possibility is that the head direction network can be set up in the absence of
14 external sensory inputs, instead relying purely on internal cues such as vestibular input,
15 which is robust very early on, to organize the network⁸⁸. Experimental evidence that probes
16 the angular coherence between the PFDs of head direction cells when the head direction
17 signal is unanchored from all external sensory inputs will be necessary to unambiguously
18 test the hypothesis that the head direction circuit does not inherit its structure from the
19 external world, but rather, develops in an experience-independent manner.
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22 B. Place cells: a tale of gradual development, from the boundaries inwards

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24 Place localized firing can be observed as early as P14 in the rat, before the emergence of
25 spatial behavior. The numbers of place cells in pre-weanling rats are low, and in general,
26 these early place cells have immature spatial properties; they have lower spatial information
27 and coherence within a trial, and less stability across multiple experiences in the same
28 environment, compared to place cells in adult rats^{62,63} (Figure 3A). However, even at P16,
29 there are instances of adult-like place cell activity that remain stable across multiple visits to
30 the same environment (Figure 3B). A recent study extended these findings to show that
31 place cells in rats are functional even earlier, from P14, before the first spontaneous
32 exploration of large-scale space in the rat⁸⁹. Unlike head direction cells that display a
33 maturational spurt coincident with eye opening, place cells mature gradually over a much
34 longer time period⁹⁰. By the end of the fourth postnatal week, place cells appear adult-like in
35 numbers, while their spatial information, coherence and stability continue to mature well
36 into the second month of life^{90,91}.
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40 Following the discovery of grid cells, several theoretical models proposed the linear
41 summation of grid cell activity as a possible mechanism of place field formation^{92,93}.
42 However, in the adult rat, place cell spatial firing has been shown to be independent of grid
43 cell periodicity, evidenced by a study in which grid cell spatial tuning was abolished through
44 septal inactivation, but hippocampal place fields were spared⁹⁴. Moreover, during postnatal
45 development, place cells are already functional almost a week before grid cells can be first
46 detected, suggesting that grid cells cannot be driving the organization of the place cell
47 network⁶².
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50 An earlier model describes place cell activity as resulting from the thresholded sum of the
51 activity of cells that encode allocentric boundary information⁹⁵ (Figure 3E). Interestingly,
52 recent evidence supports the view that this model may be particularly relevant to the early
53 development of place cells. Muessig et al⁸⁹ demonstrated that in pre-weanling rats, the place
54 cell representation of space is denser, more stable and more accurate in locations close to
55 environmental boundaries (Figure 3C), suggesting that boundary information may
56 contribute to stabilizing the place signal in young animals.
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4 Although grid cells may not serve to support the emergence of place cell representations,
5 grid cell activity may still be important for their subsequent function and maturation.
6 Indeed, Muessig et al⁸⁹ observed an abrupt transition for place maps which become equally
7 accurate and stable throughout the environment around weaning (P21 in laboratory rats;
8 Figure 3D). Remarkably, this coincides with the appearance of periodic and stable grid cell
9 firing, and suggests that the role of grid cells may be to provide an accurate map of space in
10 locations where landmarks are sparse/noisy. Further evidence for the role of grid cells in
11 supporting place cell representations is the finding that although bilateral mEC lesions in the
12 adult rat do not completely abolish place cell activity, they significantly decrease the
13 precision and stability of place cell signaling^{96,97}.

16 C. Border cells: Adult-like from P17

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18 Compared to head direction cells, much less is known about the ontogeny of boundary
19 responsive cells. Since their discovery in 2008¹⁵⁻¹⁷, only one study has been published about
20 boundary responsive cells in development. As early as P17, boundary responsive cells can be
21 found in the rat mEC that are essentially adult-like, comparable to those in the adult rat in
22 numbers, firing rate, border score, and stability within and across exposures to the same
23 environment. Some measure of maturation of the boundary signal continues into adulthood,
24 specifically the spatial information and coherence of boundary firing fields⁹⁸. Preliminary
25 reports suggest that adult-like boundary responsive neurons can also be recorded from the
26 dorsal subiculum in pre-weanling rats⁹⁹.

29 D. Grid cells: The last spatial signal to emerge

30
31 Grid cells are the last of the four main spatial cells to emerge in the rat. The earliest time
32 point at which adult-like stable and periodic grid firing can be observed is P20⁶² (Figure 4),
33 and prior to that, no significant number of grid cells can be detected. One study⁶³ reported
34 that grid cells can be detected from as early as P16 (albeit with very low within-trial stability
35 and periodicity – gridness - scores), while a subsequent study from the same laboratory
36 confirmed the absence of adult-like grid cells in rats before P20⁹⁸.

37
38 Although grid cells emerge later than head direction cells, the grid signal attains near-adult
39 levels of maturity within 48 hours in numbers, stability and gridness scores⁶² (Figure 4B). In
40 fact, for individual mEC grid cells, grid properties appear to emerge overnight¹⁰⁰. This
41 suggests that like the head direction network, a connectivity framework may already be well
42 established at the time of emergence of the grid signal.

43
44 Grid cell firing patterns can be characterized by scale and orientation, describing the
45 distance between maxima of activity, and the alignment of neighboring maxima to a
46 reference line, respectively. In the adult rat, grid cells from one animal can be grouped into
47 discrete modules of spatial scale and orientation¹⁰¹. Within the same animal, co-recorded
48 grid cells have the same scale and orientation⁶², and similar to the fixed angular coherence
49 seen in the young pre-eye opening head direction network, the earliest co-recorded grid
50 cells (P22) in the same rat rotate in register with one another in response to a perturbation
51 of the environment, suggesting that the intrinsic connectivity in the grid network is in place
52 as soon as the grid signal emerges functionally^{63,100}. Some lines of anatomical evidence
53 suggest that intrinsic connectivity may be present much earlier: recent work by Ray and
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3 Brecht¹⁰² confirms that the hexagonal arrangement of calbindin-positive pyramidal cells in
4 layer II of the mEC is already in place at birth in the rat. They also suggest a dorso-ventral
5 gradient in the timing of maturation of the medial entorhinal circuit, with the maturation of
6 the ventral mEC occurring around the onset of exploratory behavior.
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9 One theory regarding the development of grid cells suggests that grid patterns may be self-
10 organized through a learning process, driven by band-like inputs, which themselves may be
11 a result of the integration of self-motion information along certain directions¹⁰³. However,
12 whether band-like cells akin to those described in the adult rat¹⁰⁴ (but see Navratilova et al
13 2016¹⁰⁵) exist early in development remains to be proven.
14

15 An alternative model of grid cell development¹⁰⁶ instead suggests that an experience-
16 dependent process relying on velocity information and spike time-dependent plasticity
17 could create the network connections necessary for grid cell firing. Critically, this model
18 requires that an animal explore an environment whilst stable angular velocity and place
19 signals are present as inputs to the developing network. The early maturing head direction
20 network may provide the angular velocity information, while border cells or early place cells
21 may provide the locational information for the setting up of the grid network. Indeed,
22 excitatory input from place cells is necessary for grid periodicity in adult rats¹⁰⁷, and
23 preliminary work that raised rats in spherical environments without sharp boundaries
24 suggest that boundary information may be important in organizing the periodic firing of grid
25 cells¹⁰⁸. The model also predicts an abrupt maturation of spatial tuning in grid cells that
26 happens after a period of exploration, and is consistent with the reported rapid maturation
27 of the grid network from P20 to P21⁶².
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31 3. A coda on memory development: how does spatial neuron development enable the 32 emergence of spatial memory? 33

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35 Each of the different spatial cell types has their unique time course of emergence and
36 maturation in the rat (Figure 1). Interestingly, three of the four spatial cell types – head
37 direction, boundary responsive, and place cells - emerge days before the onset of true
38 allocentric navigation (which occurs around weaning in the rat). What, if any, are the links
39 between the emergence of spatial circuits and that of spatial memory and navigation?
40

41 On a synaptic level, functional maturation of excitatory transmission in the hippocampus
42 parallels the emergence of spatial memory. In pre-weanling rats, postsynaptic excitability in
43 CA1 is lower than in adults, while the threshold for initiation of activity-dependent synaptic
44 potentiation is higher, suggesting that the CA1 network acquires its adult-like plasticity
45 progressively during development. Importantly, increasing the excitability at the SC-CA1
46 synapse by prolonging glutamatergic responses through the delivery of a pharmacological
47 modulator of AMPA receptors results in the accelerated maturation of hippocampus-
48 dependent spontaneous alternation on the Y-maze^{109,110}. These results suggest that the
49 emergence of spatial memory is in part delayed by the slow maturation of CA1 postsynaptic
50 responses.
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54 Interestingly, a recent study from our laboratory¹¹¹, demonstrates that although immature in
55 terms of spatial information and stability, place cells in pre-weaning rats exhibit key
56 properties of associative networks: they generate new representations upon exposure to a
57 novel context, and can re-activate familiar representations on the basis of an incomplete set
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3 of sensory cues (Figure 5). Thus, as early as exploratory behaviors emerge in the rat (around
4 P16), and despite the absence of adult-like stable grid signals, the hippocampus can process
5 incoming sensory information in an associative fashion. These results highlight an
6 interesting, yet puzzling disconnect between basic associative processing, already available
7 at P16 to the developing hippocampus and the emergence of allocentric navigational skills,
8 which has not been described earlier than P20-22 in the rat.
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11 The emergence of grid cells at around P20 may be an important watershed for the
12 emergence of spatial memory. The regular periodicity of grid cells has been speculated to
13 serve as a metric for distance¹¹². True allocentric spatial behavior requiring the knowledge
14 and use of location, direction, and distance information may not be possible without the full
15 complement of spatial cell types. In addition, the sharp improvements in both stability and
16 accuracy of place cell firing away from environmental boundaries from P22, coincident with
17 the rapid maturation of grid cells, suggest a developmental switch in hippocampal spatial
18 processing resulting from an increase in the accuracy of path integration in environmental
19 locations away from prominent environmental landmarks.
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22 On a network level, the emergence of spatial memory may also be supported by the
23 maturation of network oscillations in the hippocampal formation. Theta-band (7-12 Hz)
24 oscillatory LFP is strongly associated with spatial behavior such as movement and
25 exploration¹¹³, and can be detected in the rat pup from P8^{114,115}. Gamma-band (30-100 Hz)
26 oscillations, which are thought to function as an organizer of the theta rhythm, begin to
27 emerge in the rat from P2 and show a sharp growth in power coincident with the emergence
28 of theta oscillations¹¹⁵. Large slow deflections seen in the hippocampus from P2, and
29 complementary fast 'ripples' (140-200 Hz) seen from P7 during sleep, may also serve to
30 coordinate network connectivity in the developing hippocampal formation^{115,116}. Together,
31 these early oscillatory LFPs, much like the propagation of retinal waves setting up
32 retinotopic maps in the visual cortex³⁶, may serve to set up functional connectivity first
33 within, then across networks of spatial cell types. Spatial memory may emerge once the
34 modulation of spatial cells by oscillatory LFP is mature. This hypothesis is partially
35 supported by evidence that the percentages of theta-modulated cells in the CA1 and
36 entorhinal cortex reach adult-like levels by P22⁶².
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41 The continued slow maturation of hippocampus-dependent memory may be in part due to
42 the protracted maturation in the stability and accuracy of place cells, well into the second
43 postnatal month^{62,63,90}. The slow maturation of network oscillations may also restrict the
44 maturation of spatial learning. In particular, theta oscillations continue to mature in
45 amplitude and frequency past weaning^{114,115,117}. A third possibility accounting for the late
46 emergence of spatial navigation is related to the presence of high levels of neurogenesis in
47 the dentate gyrus in the early postnatal period. The rat hippocampus goes through a period
48 of explosive growth and refinement in the first few postnatal weeks, with a high rate of
49 neurogenesis in the subgranular zone of the dentate gyrus that drops to half of the initial
50 rate only after the second postnatal month¹¹⁸. The large numbers of new cells which are
51 generated and functionally integrated into hippocampal circuits have been shown to
52 interfere with the consolidation of long term memory, leading to instability in memory
53 retention in young animals. Thus, it is tempting to speculate that the high levels of
54 neurogenesis in the dentate gyrus might also contribute to the slow trajectory of maturation
55 of spatial learning in rats^{119,120}.
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Conclusions

The study of spatial networks in development has afforded greater insights into how different spatial cell types mature, and how they may contribute to each other's function both during development and in adulthood. The research reviewed so far shows that different spatial cell types emerge at different time points, and mature along different temporal trajectories. This suggests that different sensory inputs may be necessary for the organization of each spatial cell network, for example, vision may be necessary for grid network organization, but not for the head direction network. New theoretical models that move away from reliance on visual organization of the head direction network, as well as integrate the sequential emergence of different spatial cell types into a single model, will be necessary.

The emergence of spatial memory and behavior may be a result of a multi-level orchestration of molecular, cellular and network level changes that converge at around the time of weaning, when the exploration of large-scale space becomes a necessity for survival outside the nest. The dissociation between spatial behavior and spatial cell development will be an interesting area of investigation for future work.

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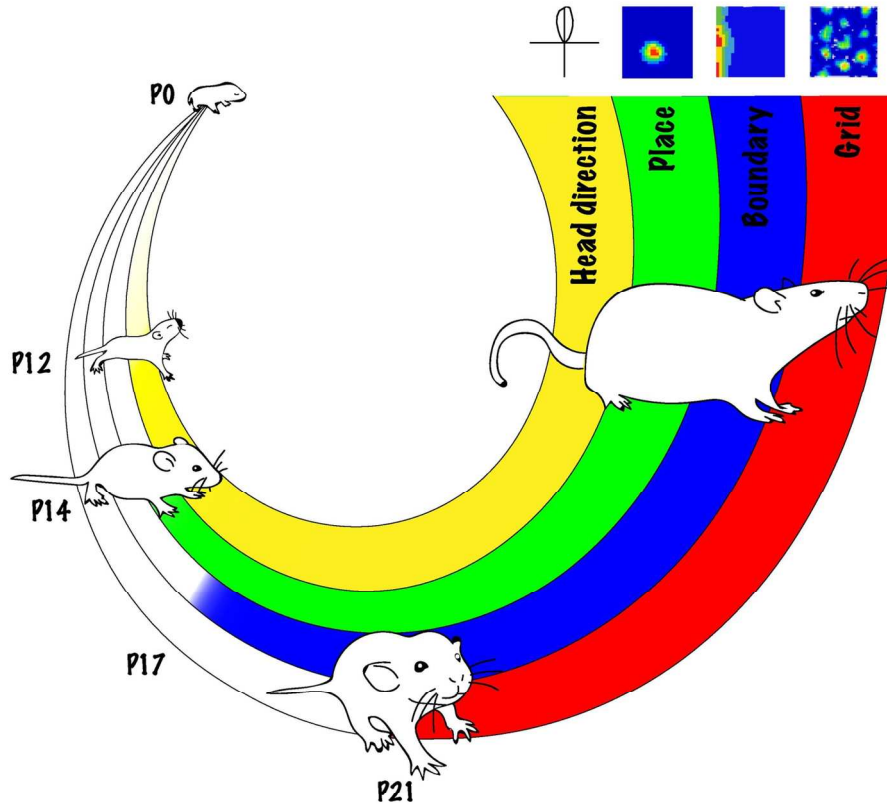
5 **Figure 1. Postnatal developmental timeline of sensorimotor capacities, spatial behavior, and**
6 **spatial cell activity in the rat.** Each colored bar delineates the time course of emergence
7 (unshaded) and maturation (slant-shaded) for each modality, behavior, or cell type. Red dots mark
8 the emergence of a particular phenomenon.
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11 **Figure 2. Head direction cells are present before eye opening and mature rapidly with vision**
12 **onset** (adapted from⁶⁴). (A) Polar plots of head direction cells recorded from rat pups at postnatal
13 days (P) 12, 15, 20, and in the adult rat (Ad). Days relative to eye opening day (E) are shown in
14 parentheses (E0 is eye opening day). Two 5 minute long trials are shown (Trials 1 and 2),
15 separated by five minutes during which the rat rested in a separate holding platform. Insets show
16 polar plots for first and second half of Trial 1. For each polar plot, peak firing rate (in Hz) is
17 shown in the top left corner, and Rayleigh vector score (a measure of directional tuning) is shown
18 in the top right corner. (B-C) Head direction cells are anchored to a prominent visual cue within
19 24 hours of eye opening. (B) Diagram of the experimental set up showing rotation of the
20 prominent visual cue (in yellow) by 180° from Trial A (Baseline) to Trial B (Rotated). (C) Polar
21 plots for one head direction cell from the same animal responding to the rotation of the visual cue
22 across two consecutive days, the day of eye opening (E0) and one day after eye opening (E1).
23 Numbers in top left corner of polar plots are peak firing rate (in Hz), top right corner are Rayleigh
24 vector scores.
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28 **Figure 3. Place cells mature slowly in the rat and are more stable near environmental**
29 **boundaries before weaning** (adapted from⁸⁹). (A) Place cells in young pups carry less spatial
30 information and are less stable across trials than in the adult rat. Firing rate maps of place cells
31 recorded from rat pups at postnatal days (P) 16, 22, and in the adult rat (Ad). Two 10 minute long
32 trials are shown (Trial 1 and 2) separated by 10 minutes during which the rat rested in a separate
33 holding platform. Numbers in top left corners of firing rate maps are peak firing rates (in Hz). (B)
34 A sub-set of place cells displaying adult-like inter trial stability and spatial information scores can
35 be recorded in rat pups as early as P14. Firing rate maps of place cells recorded from rat pups at
36 P14, P15 and P16. Two 10 minute long trials are shown (Trial 1 and 2) separated by 10 minutes
37 during which the rat rested in a separate holding platform. (C-D) Stability of the place signal away
38 from environmental boundaries improves significantly after weaning. (C) Mean across-trial
39 stability (\pm SEM) of place cells with firing fields in the edge (Ed) and center (Cn) zones of the
40 recording environment before weaning (Pre), post weaning (Post) and in the adult rat (Ad).
41 Weaning occurs at P21 in the lab. (D) Scatter plots of across-trial stability versus distance of the
42 firing field from the wall, before weaning (P16-17), after weaning (P22-23) and in the adult rat
43 (Ad). Lines of best fit that are significant to the $p < 0.05$ level are shown as solid black lines, and
44 the r^2 and p for regression are indicated above each plot. (E) Pictorial representation of the
45 contribution of boundary responsive and grid cells to the accuracy of the place signal close to and
46 away from environmental boundaries. The emergence of grid cells at P21 coincides with the
47 stabilization of place fields away from the edges of the environment.
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51 **Figure 4. Grid cells emerge abruptly from P20-21.** (A) Firing rate maps and spatial auto-
52 correlograms are shown for individual cells recorded across two trials (Trial 1 and 2) from the
53 mEC from P16 to P20-21, as well as in the adult rat. Numbers in top left corner of firing rate maps
54 are peak firing rate (in Hz), top right corner are gridness scores. (B) The percentage of mEC cells
55 that qualify as grid cells in pre-weanling rats (P16-21, in red), post-weanling rats (P22-30, in
56 green) and adult rats (Ad, in blue). Dashed line indicates the 95% confidence level that more grid
57 cells are found than those expected in spatially random firing.
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4 **Figure 5. Place cells in pre-weanling rats are already capable of associative processing of**
5 **sensory information, before the emergence of allocentric spatial navigation** (adapted from¹¹¹).
6 (A) Place cells display remapping when animals are introduced into a novel environment at P18.
7 Firing rate maps for three example place cells recorded at P18 are shown as pups explored a
8 familiar (left) and a novel (right) environment, demonstrating remapping. Pictorial depictions
9 show bird's eye views of experimental environments. In the novel environment, all intra-maze
10 cues change, and extra-maze cues are obscured by a black curtain. Each row shows one place cell,
11 and peak firing rates (in Hz) are shown in the top left corner of each rate map. (B) Mean (\pm SEM)
12 across-trial stability between two exposures to the familiar environment (Fam vs Fam), and
13 between a familiar and novel environment (Fam vs Novel) for pre-weanling place cells (weaning
14 takes place at P21 in the lab), demonstrating a near-zero correlation of place cell firing fields
15 across the two environments. (C) Place cells are already capable of pattern completion and
16 separation by P16. Firing rate maps for example pre-weanling place cells recorded while the rat
17 pup was exposed to a familiar environment, and three manipulations using visually identical
18 replicas of portions of the recording environment: replica walls ('Change Walls'), replica floor
19 ('Change Floor') and replica walls and floor ('Change Floor + Walls'). The first two conditions
20 produce no change to place cell maps, whereas changing both walls and floor leads to remapping.
21 Each row shows one place cell, and peak firing rates (in Hz) are shown in the top left corner of
22 each rate map. Example place cells were recorded at P17 ('Change Walls', 'Change Floor') and
23 P16 ('Change Walls + Floor'). (D) Place field stability in different environmental manipulations
24 described in (C), relative to a familiar environment (Fam) measured by average spatial correlation
25 (\pm SEM) for pre-weanling pups. A non-linear pattern of change is observed, whereby replica
26 'Walls' or 'Floor' produces no reduction in stability relative to a familiar baseline (pattern
27 completion), whereas replica 'Walls + Floor' produces a strong remapping (pattern separation).
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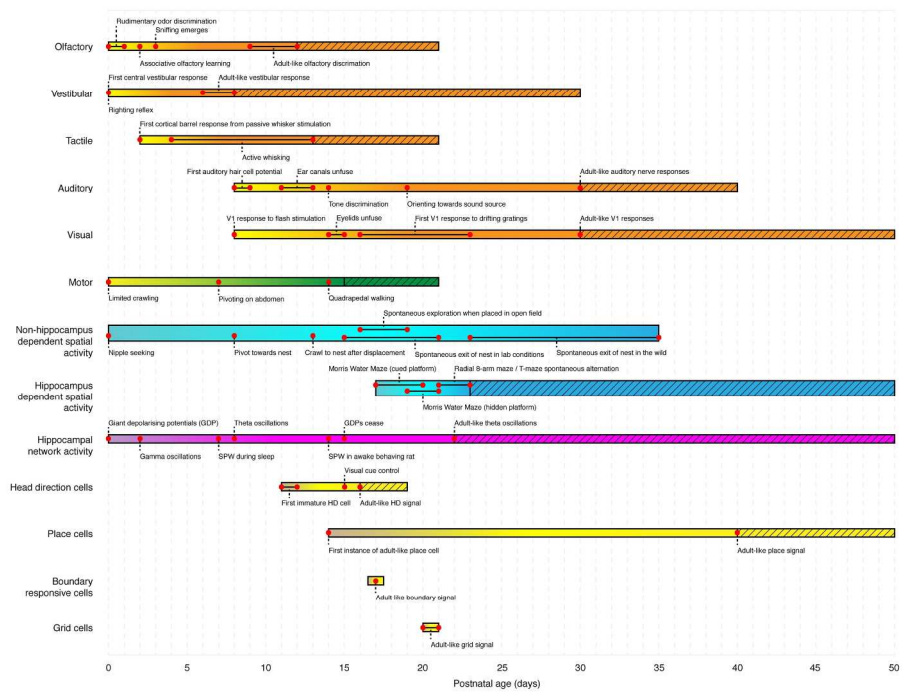


Figure 1. Postnatal developmental timeline of sensorimotor capacities, spatial behavior, and spatial cell activity in the rat. Each colored bar delineates the time course of emergence (unshaded) and maturation (slant-shaded) for each modality, behavior, or cell type. Red dots mark the emergence of a particular phenomenon.

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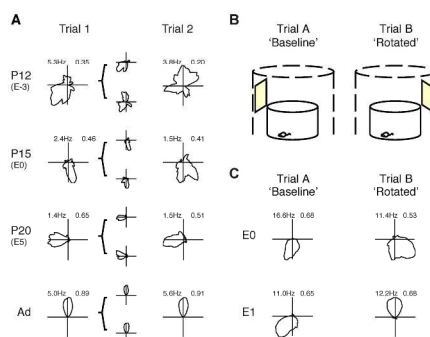


Figure 2. Head direction cells are present before eye opening and mature rapidly with vision onset (adapted from 64). (A) Polar plots of head direction cells recorded from rat pups at postnatal days (P) 12, 15, 20, and in the adult rat (Ad). Days relative to eye opening day (E) are shown in parentheses (E0 is eye opening day). Two 5 minute long trials are shown (Trials 1 and 2), separated by five minutes during which the rat rested in a separate holding platform. Insets show polar plots for first and second half of Trial 1. For each polar plot, peak firing rate (in Hz) is shown in the top left corner, and Rayleigh vector score (a measure of directional tuning) is shown in the top right corner. (B-C) Head direction cells are anchored to a prominent visual cue within 24 hours of eye opening. (B) Diagram of the experimental set up showing rotation of the prominent visual cue (in yellow) by 180° from Trial A (Baseline) to Trial B (Rotated). (C) Polar plots for one head direction cell from the same animal responding to the rotation of the visual cue across two consecutive days, the day of eye opening (E0) and one day after eye opening (E1). Numbers in top left corner of polar plots are peak firing rate (in Hz), top right corner are Rayleigh vector scores.

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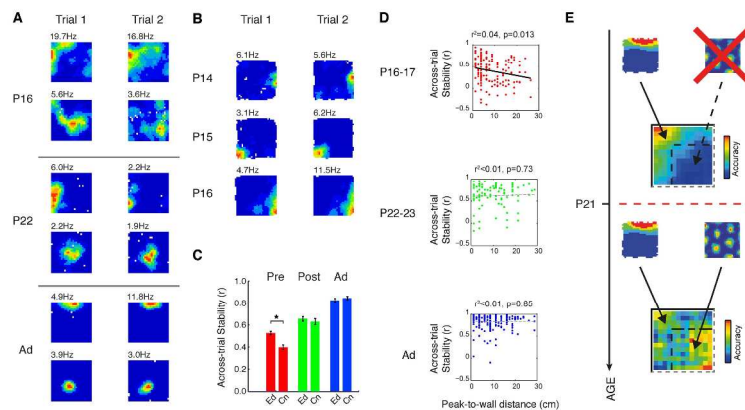


Figure 3. Place cells mature slowly in the rat and are more stable near environmental boundaries before weaning (adapted from89). (A) Place cells in young pups carry less spatial information and are less stable across trials than in the adult rat. Firing rate maps of place cells recorded from rat pups at postnatal days (P) 16, 22, and in the adult rat (Ad). Two 10 minute long trials are shown (Trial 1 and 2) separated by 10 minutes during which the rat rested in a separate holding platform. Numbers in top left corners of firing rate maps are peak firing rates (in Hz). (B) A sub-set of place cells displaying adult-like inter trial stability and spatial information scores can be recorded in rat pups as early as P14. Firing rate maps of place cells recorded from rat pups at P14, P15 and P16. Two 10 minute long trials are shown (Trial 1 and 2) separated by 10 minutes during which the rat rested in a separate holding platform. (C-D) Stability of the place signal away from environmental boundaries improves significantly after weaning. (C) Mean across-trial stability (\pm SEM) of place cells with firing fields in the edge (Ed) and center (Cn) zones of the recording environment before weaning (Pre), post weaning (Post) and in the adult rat (Ad). Weaning occurs at P21 in the lab. (D) Scatter plots of across-trial stability versus distance of the firing field from the wall, before weaning (P16-

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3 17), after weaning (P22-23) and in the adult rat (Ad). Lines of best fit that are significant to the $p < 0.05$
4 level are shown as solid black lines, and the r^2 and p for regression are indicated above each plot. (E)
5 Pictorial representation of the contribution of boundary responsive and grid cells to the accuracy of the place
6 signal close to and away from environmental boundaries. The emergence of grid cells at P21 coincides with
7 the stabilization of place fields away from the edges of the environment.
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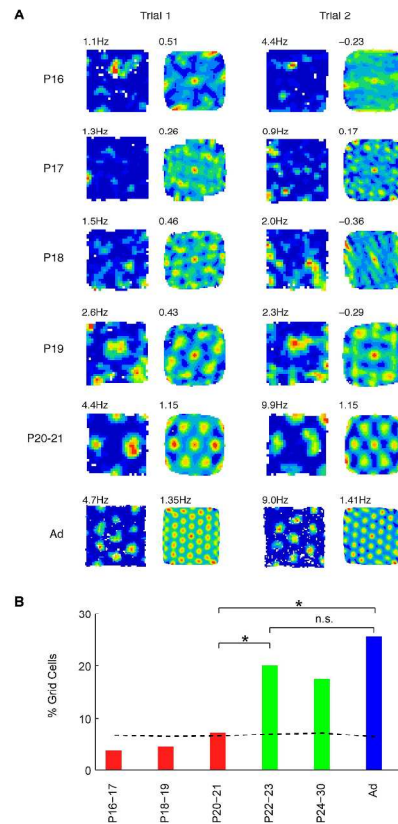


Figure 4. Grid cells emerge abruptly from P20-21. (A) Firing rate maps and spatial auto-correlograms are shown for individual cells recorded across two trials (Trial 1 and 2) from the mEC from P16 to P20-21, as well as in the adult rat. Numbers in top left corner of firing rate maps are peak firing rate (in Hz), top right corner are gridness scores. (B) The percentage of mEC cells that qualify as grid cells in pre-weanling rats (P16-21, in red), post-weanling rats (P22-30, in green) and adult rats (Ad, in blue). Dashed line indicates the 95% confidence level that more grid cells are found than those expected in spatially random firing. 297x420mm (300 x 300 DPI)

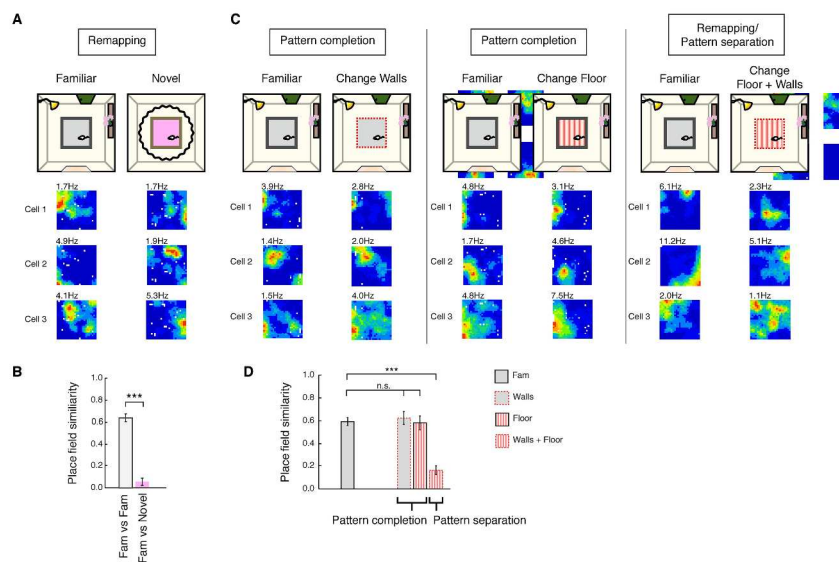


Figure 5. Place cells in pre-weanling rats are already capable of associative processing of sensory information, before the emergence of allocentric spatial navigation (adapted from 111). (A) Place cells display remapping when animals are introduced into a novel environment at P18. Firing rate maps for three example place cells recorded at P18 are shown as pups explored a familiar (left) and a novel (right) environment, demonstrating remapping. Pictorial depictions show bird's eye views of experimental environments. In the novel environment, all intra-maze cues change, and extra-maze cues are obscured by a black curtain. Each row shows one place cell, and peak firing rates (in Hz) are shown in the top left corner of each rate map. (B) Mean (\pm SEM) across-trial stability between two exposures to the familiar environment (Fam vs Fam), and between a familiar and novel environment (Fam vs Novel) for pre-weanling place cells (weaning takes place at P21 in the lab), demonstrating a near-zero correlation of place cell firing fields across the two environments. (C) Place cells are already capable of pattern completion and separation by P16. Firing rate maps for example pre-weanling place cells recorded while the rat pup was exposed to a

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3 familiar environment, and three manipulations using visually identical replicas of portions of the recording
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