Hippocampal Neurophysiology Across Species

16

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Abstract

Comparative research in neuroscience can contribute to the understanding of general principles underlying brain function; it can also provide testable hypotheses that direct future research. This chapter provides a comparative review of the neurophysiology of the hippocampal formation across mammals. Over the last 40 years, the vast majority of findings on hippocampal electrophysiology were based on research from a single animal model—the rat. Yet, while rat hippocampal studies provided one of the richest datasets in systems neuroscience, the paradigms generated based on rat data were, until recently, largely untested in other mammals—and at least some of the ideas have been questioned by the few studies that were conducted in other species. Here we will summarize the data available from different mammalian species regarding hippocampal neurophysiology, focusing on similarities and differences across species—including functional implications. We will limit our discussion to two aspects: spatial cell types in the hippocampal formation and hippocampal oscillations. We will conclude by highlighting some of the major gaps in the available comparative data and by raising a "call to arms" to conduct further comparative research on the hippocampal formation.

16.1 Introduction

Different animal species have very different lifestyles, behaviors, and phylogenetic histories, and hence we may expect some differences in brain function. Yet, those brain functions that are core to all mammals should be conserved. Therefore, comparative studies could help identify the core properties of a given brain system. While sensory systems are indeed typically studied in many species, this is not the

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case in hippocampal research. Why is it that neurophysiological data on the hippocampus, collected over the last 40 years, were recorded almost exclusively in rats? In the 1960s, this was not the case: at that time, many species were used as animal models for hippocampal studies—including rabbits, dogs, cats, rats, and monkeys (Green and Arduini 1954; Winson 1972; O'Keefe and Nadel 1978; Robinson 1980). The shift to rats as the one central model occurred in the 1970s and 1980s, following the major finding of place cells by O'Keefe and Dostrovsky (1971)—and henceforth, most hippocampal research in animals focused on spatial cognition and spatial memory in the rat (O'Keefe 2007). Only in the 1990s, when the power of transgenic mice became available, some researchers started using the mouse. As we will review below, these studies demonstrated major similarities between rats and mice, but also some differences. Concurrently, research of hippocampal neurophysiology in monkeys has gradually increased in volume, including studies of place cells and additional types of cells such as "spatial-view cells" (Georges-François et al. 1999), which are not found in rats—indicating the need for further comparative research. In 2007, we introduced a new mammalian species to hippocampal research, the bat, which revealed many similarities but also substantial differences to the rat (Ulanovsky and Moss 2007)—leading to new functional insights, as we will argue below. Additional interspecies comparisons are needed, in order to help identify hippocampal functional properties that generalize across species, versus those that do not. Here we will compare hippocampal-formation neurophysiology across different mammalian species, including rats, mice, bats, and primates. We will concentrate on two aspects: the spatial cell types of the hippocampal formation (place cells, head-direction cells, grid cells, and border cells) and hippocampal oscillations (focusing on high-frequency ripples and on theta oscillations). Finally, we will suggest some future experiments to enhance our understanding of hippocampal function across species.

16.2 Functional Properties of Spatial Neurons in the Hippocampal Formation

16.2.1 Place Cells

Place cells, neurons that are activated when the animal passes through a specific region of the environment, were first discovered in the rat hippocampus by O'Keefe and Dostrovsky in 1971 (see example in Fig. 16.1a). Place cells were found in other species only >20 years later: in 1993 in monkeys (Ono et al. 1993—although this is controversial: see below), then in 1996 in mice (McHugh et al. 1996), in 2003 in humans (Ekstrom et al. 2003), in 2007 in bats (Ulanovsky and Moss 2007), and in 2009 in another rodent species—chinchillas (Muir et al. 2009; basic properties of place cells in chinchillas seem quite similar to rats, so we will not discuss them further below). There was also a preliminary report of place cells in rabbits (O'Keefe 1979), but this awaits further confirmation.

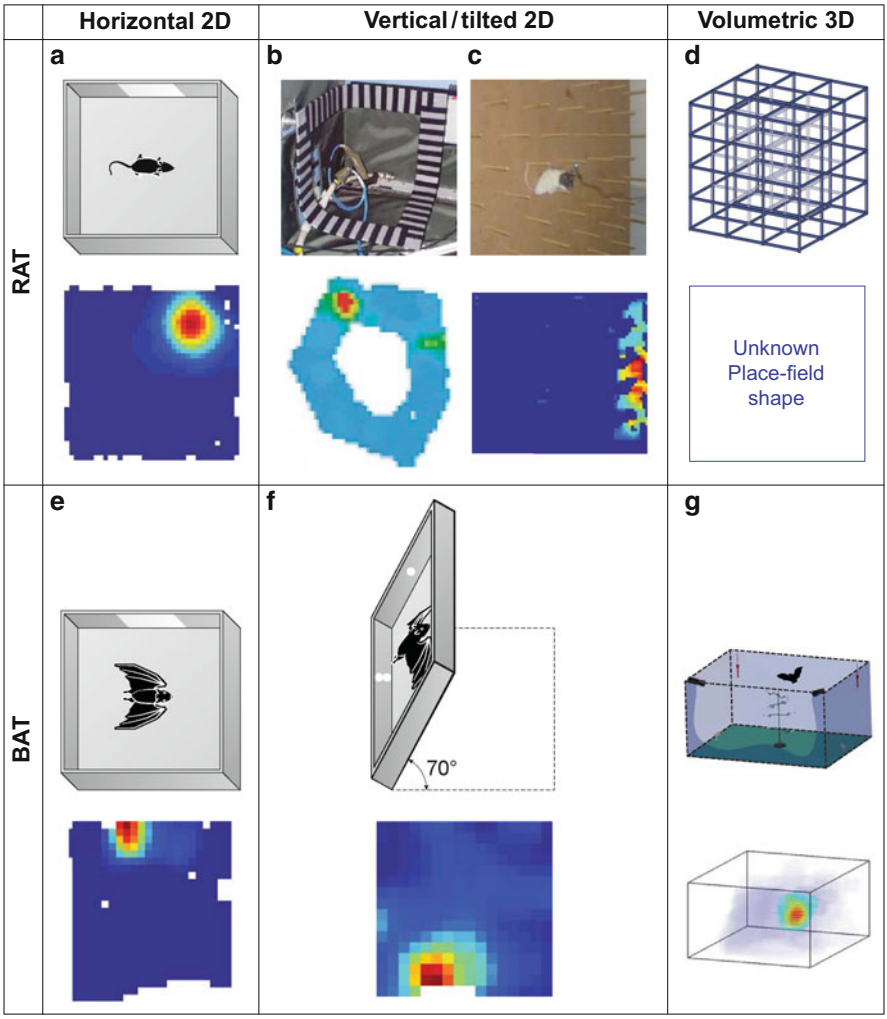

Fig. 16.1 Hippocampal place cells in rats and bats in 2D and 3D. (**a**–**d**) Rats. (**e**–**g**) Bats. In each case, the *top panel* shows the behavioral setup, and the *bottom panel* the place fields. (**a**) Rat running in a horizontal 2D arena [adapted with permission from Whitlock et al. (2008)]. (**b**, **c**) Rats climbing on vertical surfaces aboard a NASA space shuttle (**b**) or on a 90°-tilted pegboard platform (**c**) [adapted with permission from Knierim et al. (2000), and Hayman et al. (2011), respectively]. (**d**) Volumetric 3D place fields were not measured to date in rats (shape of 3D place fields in rats is unknown). (**e**) Bat crawling on a horizontal arena [from Yartsev et al. (2011)]. (**f**) Bat crawling on a nearly vertical arena, which was tilted by 70° [from Ulanovsky and Moss (2007)]. Note the isotropic shape of the place field. (**g**) Volumetric 3D place field from a freely flying bat, showing a nearly isotropic (spherical) place field [from Yartsev and Ulanovsky (2013)]. Peak firing rates in panels **a**, **b**, **c**, **e**, **f**, and **g** were 40, 2, 3.7, 4.7, 1.8, and 15 Hz, respectively

We will start by listing the similarities and will then discuss some of the major differences in place-cell properties across species. Table 16.1 compares the basic characteristics of place cells (as well as of other spatial cell types: see below) in the

Table 16.1 Functional properties of spatial cells in the hippocampal formation: cross-species comparison

Cell type	Property	Rats	Mice	Bats	Primates
Place cells	Existence	Yes[1]	Yes[2]	Yes[3]	Yes[4, 5] (but see text for controversy regarding place cells versus spatial-view cells)
					We will separate below three types of setups: • Place cells in freely moving monkeys • Place cells in humans and monkeys in virtual reality (VR) • Spatial-view cells in monkeys
	Brain areas where these cells were found to date	Hippocampus (CA1, CA3, DG, Subiculum)[6]	Hippocampus (CA1, CA3, DG, Subiculum)[2, 7–9]	Hippocampus (CA1, Subiculum)[3, 10–12]	Hippocampal formation[4, 5, 13]
	Complex-spike/regular firing	Complex-spike[1, 14]	Complex-spike[2, 15]	Complex-spike[3, 10, 11]	Complex-spike[13, 16]
	Fraction from all recorded complex-spike cells (CA1)	30–45 %[17]	~50 %[2]	30–40 %[3, 10, 11]	Place cells in free movement: ~33 %[4, 13]
					Place cells in VR: 32 % in monkeys[18] and 24 % in humans[5]
					Spatial-view cells: ~10 % in both monkeys[19, 20] and humans[5]

Peak firing rates	Range 0.2–35 Hz[21–23]	Range ~1–30 Hz[2, 24–26]	Crawling bats: range 0.2–16 Hz[3, 10, 11]	Place cells in free movement: range ~1.5–43 Hz[13]
			Flying bats: range 0.3–28 Hz[11]	Place cells in VR: *unclear*
				Spatial-view cells: ~3–44 Hz[19, 20]
Increase of firing rate with velocity	Yes[27]	*Unknown*	Yes[11]	*Unknown*
Typical number of fields for each neuron in 2D (open field ~1 m^2 arenas)	1–2[17, 21]	1–2[2, 25]	1–2[3, 10, 28]	Place cells in free movement: 1–3[4, 13, 29]
				Place cells in VR: *unclear*
				Spatial-view cells: 1–2[20]
Increase of place-field size and of the number of fields in larger 2D environments	Yes [30–32]	*Unknown*	Yes[11]	*Unknown*
Directionality of firing in 1D	Yes[27]	Yes[2]	Yes[12]	Place cells in free movement: *unknown*
				Place cells in VR: yes (Humans in VR[33])
				Spatial-view cells: *unknown*
Stability (correlation of firing-rate map across sessions, during open-field random foraging)	Range: $r = 0.6$–0.8[21–23, 34]	Range: $r = 0.1$–0.35 [25, 35, 36]	Average: $r = 0.74$ (big brown bat)[3]	*Unknown*
3D tuning	Some studies show elongated fields in the vertical z-dimension[37], while others seem to show more circular fields on a vertical wall[38]	*Unknown*	Nearly isotropic (spherical) 3D place fields in flying bats[11]; isotropic (circular) tuning on a tilted surface[3]	Variety of place-field shapes on vertical wall[13]: generally *not* elongated in the vertical dimension

(continued)

Table 16.1 (continued)

Cell type	Property	Rats	Mice	Bats	Primates
Head-direction cells	Existence	Yes[39]	Yes[40, 41]	Yes[10, 42]	Yes[43]
	Brain areas where these cells were found to date	Presubiculum[44–46]	Medial entorhinal cortex[40, 41]	Presubiculum[42]	Presubiculum[43]
		Medial entorhinal cortex[47]	Anterodorsal thalamus[52]	Medial entorhinal cortex[10]	
		Lateral mammillary nucleus[48]			
		Retrosplenial cortex[49]			
		Anterodorsal thalamus[50]			
		Lateral dorsal thalamus[51]			
		Additional areas[39]			
	Fraction from all recorded cells that exhibit directional firing	Presubiculum: 25–50 %[45, 53]	MEC: ~10 %[41]	Presubiculum: 30 %[42]	Presubiculum: 33 %[43]
		MEC: ~50 %[47, 53]		MEC: 10 %[10]	
	Peak firing rates	Presubiculum: peak rates are typically < 20 Hz[45, 53], though a few cells go up to ~100 Hz[45]	*Unclear*	Presubiculum: peak rates in crawling bat are < 12 Hz[42]	Presubiculum: range of peak rates: ~2–30 Hz[43]
		MEC: peak rates are typically < 20 Hz[47, 53, 54], though a few cells go up to ~45 Hz[53]			
	Tuning width in the horizontal plane (width at half-height)	Presubiculum: ~55–60°[45, 53]	*Unknown*	Presubiculum: 79.0° ± 3.9°[42]	Presubiculum: ~75°[43]
		MEC: ~65–70°[53]			
	3D tuning	Tuning to azimuth, and possibly weak selectivity to elevation[48]. Roll was never tested	*Unknown*	Tuning to all 3 Euler angles of head direction: azimuth, elevation, and roll[42]	*Unknown*

Grid cells	Existences	Yes[55]	Yes[40]	Yes[10]	Yes • Grid cells in VR in Humans[56] • "Spatial-view grid cells" in Monkeys[57]
	Brain areas where these cells were found to date	MEC[55] Presubiculum[53] Parasubiculum[53] Subiculum[58]	MEC[40]	MEC[10]	Posterior EC[57]
	Complex-spike/regular firing	MEC principal cells (not necessarily grid cells) are mostly regular firing[59]	*Unclear*	Bat grid cells are mostly regular firing (ref. 10, their Supplementary Fig. 2)	*Unclear*
	Fraction from all recorded cells in MEC	20–80 % (depending on layer and on size of arena)[53, 55]	~50 % (in layers II and III)[40]	36 % (average across all layers)[10]	12 % (average across all layers)[57]
	Peak firing rates	Range of peak rates: ~1–50 Hz[22, 23, 47, 55]	Range of peak rates: ~1–40 Hz[40, 41]	In crawling: less than 2 Hz[10] In flight: *unknown*	Range of peak rates: ~1–20 Hz[57]
	Increase of firing rate with velocity	Yes[47]	Yes[40]	Yes[10]	*Unknown*
	Stability across sessions	Mean: r = ~0.4–0.75[22, 23, 47, 55, 60]	Mean: $r = 0.7$[40]	*Unknown* (just one session was recorded)	*Unknown* (just one session was recorded; stability between first and second half of the session was very low, median $r = 0.24$[57])
	Co-localized grid cells in superficial layers share similar orientation and spacing but have different phases	Yes[55]	Yes[40]	Yes[10]	*Unknown*
	Grid spacing increases along the dorsoventral axis of MEC	Yes[55, 61]	Yes[40, 41]	Yes[10]	Yes[57]
	Conjunctive grid × head-direction cells	Yes (only in layers III–VI, not in layer II[47, 53])	Yes (in all layers[40, 41])	Yes[10]	*Unknown*

(continued)

Table 16.1 (continued)

Cell type	Property	Rats	Mice	Bats	Primates
Border cells	Existence	Yes Border cells in free movement [54, 62, 63]	Probably (not tested with insertion of a new border)[41]	Probably (not tested with insertion of a new border)[10]	Probably (not tested with insertion of new border[57]). These were not measured in free movement, but are "spatial-view border cells"[57]
	Brain areas where these cells were found to date	MEC[54, 63] Subiculum[62]	MEC[41]	MEC[10]	Posterior EC[57]
	Fraction from all cells in MEC	~10 %[54]	~8 %[41]	< 10 %[10]	~9 %[57]

This table focuses on data from freely moving animals and does not discuss in detail results obtained in virtual-reality (VR, e.g., refs. [64–66]) setups—except VR in primates (both humans and monkeys), where free-movement versus virtual-reality setups are mentioned separately

When listing properties of place cells, we focus on data from hippocampal area CA1—for which there are the most extensive datasets to compare across species

When listing properties of head-direction (HD) cells, we focus mostly on data from presubiculum and medial entorhinal cortex (MEC)—where the most extensive datasets exist across species

1. O'Keefe and Dostrovsky (1971), 2. McHugh et al. (1996), 3. Ulanovsky and Moss (2007), 4. Ono et al. (1993), 5. Ekstrom et al. (2003), 6. Andersen et al. (2007), 7. Hussaini et al. (2011), 8. Lee et al. (2009), 9. Chang and Huerta (2012), 10. Yartsev et al. (2011), 11. Yartsev and Ulanovsky (2013), 12. Geva-Sagiv et al. (2013), 13. Ludvig et al. (2004), 14. Fox and Ranck (1981), 15. Muller (1996), 16. Skaggs et al. (2007), 17. Wilson and McNaughton (1993), 18. Hori et al. (2005), 19. Rolls et al. (1997), 20. Georges-François et al. (1999), 21. Fyhn et al. (2004), 22. Wills et al. (2010), 23. Langston et al. (2010), 24. Rotenberg et al. (2000), 25. Muzzio et al. (2009b), 26. Rotenberg et al. (1996), 27. McNaughton et al. (1983), 28. Ulanovsky and Moss (2011), 29. Matsumura et al. (1999), 30. O'Keefe and Burgess (1996), 31. Kjelstrup et al. (2008), 32. Fenton et al. (2008), 33. Jacobs et al. (2010), 34. Van Cauter et al. (2008), 35. Kentros et al. (2004), 36. Muzzio et al. (2009a), 37. Hayman et al. (2011), 38. Knierim et al. (2000), 39. Taube (2007), 40. Fyhn et al. (2008), 41. Giocomo et al. (2011), 42. Finkelstein et al. (2012), 43. Robertson et al. (1999), 44. Ranck (1985), 45. Taube et al. (1990a), 46. Taube et al. (1990b), 47. Sargolini et al. (2006), 48. Stackman and Taube (1998), 49. Cho and Sharp (2001), 50. Taube (1995), 51. Mizumori and Williams (1993), 52. Yoder and Taube (2009), 53. Boccara et al. (2010), 54. Solstad et al. (2008), 55. Hafting et al. (2005), 56. Jacobs et al. (2013), 57. Killian et al. (2012), 58. Lever (2013), 59. Frank et al. (2001), 60. Derdikman et al. (2009), 61. Stensola et al. (2012), 62. Lever et al. (2009), 63. Savelli et al. (2008), 64. Harvey et al. (2009), 65. Domnisoru et al. (2013), 66. Schmidt-Hieber and Häusser (2013)

rat, mouse, bat, and primate. Note that there is relatively little comparative information even for the very basic properties of place cells (e.g., firing rate, place-field size, stability, directionality, and other properties; see Table 16.1). This problem is most noticeable in monkeys, where detailed characterization is mostly lacking, but also in mice, where most studies focused on molecular or genetic manipulations, rather than on basic characterization of place cells. That said, many properties of place cells seem similar in all these species (Table 16.1). In rats, place cells have been found in multiple hippocampal areas: CA1, CA3, subiculum, and dentate gyrus. In the other species, the hippocampus was not studied nearly as intensively as in rats, and place cells were mainly studied in CA1 (Table 16.1). We will therefore restrict our functional comparisons to the CA1 area only. In all animal models, the firing patterns of place cells are characterized by prevalence of complex-spike bursts, suggesting that these are pyramidal cells (Harvey et al. 2009; Epsztein et al. 2010). In all species and in all tested environments, between 30 and 50 % of the pyramidal cells in CA1 were found to be active during exploratory behavior; the majority of those are place cells. Further, in all species, the peak firing rates of place cells were found to range from <1 to 20–30 Hz. In rats and bats, the peak firing rates were found to be correlated with movement velocity (McNaughton et al. 1983; Yartsev and Ulanovsky 2013; see Table 16.1); such correlation awaits to be tested in mice and primates. In bats, place cells tend to exhibit low firing rates during crawling, when the movement speed is on average 3 or 4 cm/s (peak firing rates 0.2–16 Hz; Table 16.1)—but the firing rates go up dramatically during flight, when movement speed can reach 3 m/s and peak firing rates go up to 28 Hz (Table 16.1; Yartsev and Ulanovsky 2013).

Additional properties of place cells that are similar across rats and bats include the increase in place-field size and number of place fields in larger environments (this was demonstrated in rats and bats but awaits testing in mice and primates) and the directionality of place cell firing in one-dimensional (1D) tracks (Table 16.1).

One domain where there seems to be a real difference between rats and bats on the one hand, and mice on the other hand, is place-field stability. As originally reported in rats, the spatial representation of a familiar environment is stable: when place cells are recorded over several hours in the same environment, the fields occur at the same location, as quantified by correlating the firing-rate maps between consecutive recording sessions (Muller and Kubie 1987). The same is true for bats (Table 16.1; Ulanovsky and Moss 2007; Yartsev and Ulanovsky 2013): in both rats and bats, place fields are stable with a correlation of $r \sim 0.6$–0.8 between sessions (Table 16.1). In contrast, place fields in mice are unstable, with correlation coefficients of $r \sim 0.1$–0.35 (Table 16.1; Kentros et al. 2004; Muzzio et al. 2009b). What factors could explain the low stability in mice? The answer to this question is still unclear. In the original study that showed place-field instability in mice (Kentros et al. 2004) and in subsequent studies (Muzzio et al. 2009b), place fields were stabilized by increased attentional demands. However, even under the highest attentional load, mouse place fields exhibit a stability of $r \sim 0.3$–0.45—much less stable than in rats or bats. We speculate that a possible explanation for this discrepancy may be the effect of other senses besides vision. Olfactory cues, in

particular, may play a key role in place-field formation. In rats, when lights are turned off and olfactory cues are wiped from the floor, place fields become unstable (Save et al. 2000); yet, if olfactory cues are maintained when turning off the lights, place cells fire stably (Quirk et al. 1990; Save et al. 2000). Further support for the role of olfaction in controlling place fields was provided by a recent experiment in rats, where the rotation of a set of stable olfactory cues (odor ports) led to a corresponding rotation of place fields (Ozdogan and Morris 2012; see also Goodridge et al. 1998). While olfactory cues are likely to play an important role in rats and in bats, we hypothesize that they should be of particular importance for mice. Indeed, laboratory mice have poorer visual acuity than hooded laboratory rats or Egyptian fruit bats (Pettigrew et al. 1988; Heffner et al. 1999; Prusky et al. 2000) but have a very developed olfactory sense. Further, various pheromone effects are found strongly in mice but weakly in rats (such as the Bruce effect—see Cheal and Sprott 1971; Marashi and Rulicke 2012). Likewise, a number of studies demonstrated that olfactory bulbectomy is devastating to mouse species-typical behaviors, but much less so for rats: sexual, aggressive, maternal, and other pheromone-related behaviors are all strongly reduced in bulbectomized mice but are less affected in bulbectomized rats (Schultz and Tapp 1973). If we assume that hippocampal maps are formed according to a sensory hierarchy—namely, the most dominant senses in each species (which may be task-specific) will control the place fields—then this may have implications for place cells. Some notable cross-species sensory differences are in visual acuity, which is better in rats than it is in mice (Prusky et al. 2000) and in olfaction, which is more dominant in mice than in rats (see above); further, Egyptian fruit bats have highly developed senses of vision and echolocation (Heffner et al. 1999; Holland et al. 2005; Yovel et al. 2010). Consequently, according to our hypothesis, rats are expected to develop more visually based maps (even in the presence of olfactory cues); Egyptian fruit bats would develop maps based on a combination of vision + echolocation; whereas mice would develop a more olfactory-based map. This could have implications for place-field stability, because open-field arenas used in place-cell experiments are not controlled for olfactory cues—and because self-deposited odors are continuously formed by the animal when it runs across the arena and are therefore unstable across time, the place fields in mice will be less stable—because according to our hypothesis, mice pay particular attention to the (unstable) olfactory cues. To test this hypothesis, one would need to manipulate the different sensory cues in the different species. For example, stable visual cues should be used while cleaning carefully all odors; or conversely, stable olfactory cues (odor ports) should be used in the dark. Consistent with this hypothesis is the observation that place-field stability in mice increases when the mouse attention is directed primarily to visual cues (in experiments where reward was visually guided: Muzzio et al. 2009b). The effects of these and similar sensory manipulations should be carefully tested in mice, rats, and bats.

Another domain in which there might be possible differences between place cells across species is the representation of three-dimensional (3D) space. There were a few attempts to characterize the tuning of place cells in a variety of 3D environments, in several species: rats, bats, and monkeys. Notably, in all rat studies

that employed tilted or vertical platforms, the animals were in fact constrained to move on a particular 1D or 2D surface that was embedded in 3D space (Fig. 16.1b, c); thus the rats were not navigating in a *volumetric* 3D space (Knierim et al. 2000; Knierim and McNaughton 2001; Jeffery et al. 2006; Hayman et al. 2011). On tilted surfaces, place fields in rats are generally circular (Jeffery et al. 2006)—similar to place fields in horizontal 2D arenas (Wilson and McNaughton 1993; Henriksen et al. 2010). For vertical 2D surfaces, the few studies that were published were not always consistent with each other. One study in rats moving on a 3D surface aboard a NASA space shuttle has found a variety of place-field shapes, with fields in the 3D corners being rather isotropic (circular), while fields on linear portions of the track were somewhat elongated along the running direction—similarly to place fields on standard 1D horizontal tracks (McNaughton et al. 1983); importantly, there was no systematic elongation in any one absolute direction in space (Fig. 16.1b; Knierim et al. 2000). Another study, using a vertically oriented pegboard, reported a somewhat different result, with place fields being systematically elongated (non-isotropic) along the vertical z-dimension (Fig. 16.1c; Hayman et al. 2011; Jeffery et al. 2013). Discussion of the underlying sources of difference between these two studies in rats is beyond the scope of the current chapter; a detailed discussion can be found in Ulanovsky (2011) and Taube and Shinder (2013). In monkeys climbing on vertical walls, a variety of place-field shapes were found (Ludvig et al. 2004), generally being rather isotropic and not elongated in the vertical dimension. In bats, isotropic fields were found in 2D horizontal arenas (Fig. 16.1e; Yartsev et al. 2011) and on 2D surfaces tilted by 70° (Fig. 16.1f; Ulanovsky and Moss 2007, 2011)—as well as in a recent study of 3D place fields in flying bats, where >90 % of the 3D place fields were statistically not different from a sphere (Fig. 16.1g; Yartsev and Ulanovsky 2013). In summary, in most studies in rats, monkeys, and bats, in both 2D and 3D environments, hippocampal place fields tended to have a rather isotropic shape: mostly circular fields in 2D and spherical fields in 3D (with the exception of one study in rats that reported a systematic vertical elongation of place fields on vertical apparatus: Hayman et al. 2011). It would be interesting to test rats or monkeys in a truly volumetric 3D apparatus (e.g., the one depicted in Fig. 16.1d, top)—such an experiment was not conducted so far—and to see if isotropic volumetric 3D place fields will be found in these species, or not.

Finally, there have been several reports of spatial responses that are very different from classical rodent-like place cells; these reports came from pigeons, as well as from monkeys and humans. In pigeon hippocampus, only neurons with multi-peaked and unstable firing-fields were found so far (Bingman et al. 2003; Hough and Bingman 2004; Kahn et al. 2008)—very different than the well-circumscribed place fields in rodents or bats (Fig. 16.1). This difference could indicate that the "correct" regions of the pigeon hippocampus were not yet recorded from—which calls for additional experiments in pigeons. Alternatively, it could be that birds truly do not have mammalian-like place cells, perhaps due to their different evolutionary history, or to the different anatomical structure of their hippocampus. For further discussion of possible functional differences and similarities between the hippocampus of mammals, birds and reptiles, see Treves et al. (2008).

In monkeys, some studies have demonstrated the existence of "spatial-view cells," neurons that respond when the monkey looks at a certain point in the room (a "spatial-view" field), regardless of the animal's location (Rolls and O'Mara 1995; Georges-François et al. 1999; Rolls 1999, 2002). It was even suggested that monkey hippocampus might contain only spatial-view cells, and that the reported place cells in monkeys are in fact spatial-view cells that exhibit an apparent spatial selectivity (Georges-François et al. 1999). According to this explanation, the monkey exhibits behavioral correlations such that it tends to look at a certain spatial view more often when it is located within a certain region of the environment—which will result in an observed place field, which is not real (Georges-François et al. 1999). There has been a fair amount of controversy over this suggestion, and it remains unclear how many of the reported place cells in monkey hippocampus are true place cells and how many are spatial-view cells. The reason why it has been difficult to dissociate these possibilities is that this requires recording neural activity while measuring the position and eye direction (gaze) of freely moving monkeys, a difficult task. Experiments so far were done either without measuring eye-gaze (Ludvig et al. 2004), or in monkeys that were not totally free to move (Rolls and O'Mara 1995; Georges-François et al. 1999), or both (Ono et al. 1993; Nishijo et al. 1997; Matsumura et al. 1999). The need to resolve this conundrum is yet another reason why it would be crucial to measure neural activity, position, and eye-gaze in monkeys that are freely moving in 2D environments or in 3D environments such as the one depicted in Fig. 16.1d.

In humans, there are only a handful of reports on single-cell neuronal activity related to navigation. Place cells in the human medial temporal lobe were first reported by Ekstrom et al. (2003) (see Table 16.1) and then by Jacobs et al. (2010) and Miller et al. (2012). In addition, Ekstrom et al. (2003) reported the presence of cells responding to views of landmarks; however, unlike spatial-view cells in monkeys, not all of the reported view cells in humans were location-independent. Additionally, unlike in the monkey experiments, where the animals faced a variety of directions, in these experiments in humans the subjects could only turn at 90-degrees angles; this 90° angular resolution in Ekstrom et al. (2003) made it difficult to verify that these were true spatial-view cells. Recently there were also reports of "path cells," neurons that encode the current direction of traveling: these were found both in a circular virtual environment (Jacobs et al. 2010) and in more complicated virtual environments (Miller et al. 2012); see Table 16.1. Further studies are needed to corroborate the finding of view cells and path cells in humans and their relation to place cells—and to assess the relative contribution of these cell types to navigation.

16.2.2 Head-Direction Cells

Head-direction (HD) cells are neurons that are activated when the animal's head is oriented towards a specific absolute direction. Unlike place cells, the activity of HD cells is largely independent of the animal's position and can be elicited even if the

animal is being moved passively (Taube 2007). In addition, while place fields seem to "mature" along the rat's ontogeny, adultlike HD cells were found in very young rat pups, as early as 16 days old (Langston et al. 2010; Wills et al. 2010). HD cells were first discovered in the dorsal presubiculum of rats in 1983 by James Ranck (Ranck 1985), and their basic properties were described in 1990 (Taube et al. 1990a, b). Later on they were found in other species: in 1999 in monkeys (Robertson et al. 1999), then in 2008 in mice (Fyhn et al. 2008), and in 2011 in bats (Yartsev et al. 2011) (see also Winter and Taube 2014).

Similar to place cells, HD cells were mainly studied in rats, where they were identified in multiple subcortical areas, including the lateral mammillary nucleus, the striatum and some thalamic nuclei (lateral dorsal and anterodorsal nucleus), and several other areas (reviewed in Taube 2007). HD cells were also found in several cortical structures, including the retrosplenial cortex and medial entorhinal cortex (MEC), in addition to the cortical area where they were first found, the dorsal presubiculum (also called postsubiculum; Taube 2007). In other species, HD cells were studied mainly in the cortical structures: in mice, HD cells were studied to date only in MEC (Fyhn et al. 2008; Giocomo et al. 2011); in bats, HD cells were found both in presubiculum and in MEC (Yartsev et al. 2011; Finkelstein et al. 2012); and in monkeys, they were found so far only in the presubiculum (Robertson et al. 1999). Accordingly, we will limit our cross-species comparison of HD cells to presubiculum and MEC.

In rats, bats, and monkeys, the fraction of HD cells out of all cells in presubiculum is rather similar—between 25 and 50 % (there are no presubicular recordings in mice, so far); in contrast, the fraction of HD cells in MEC seems to be more variable, ranging from 10 % in mice and bats to 50 % in rats (Table 16.1). These differences in reported fraction of HD cells in MEC could reflect a true species difference, or it could be due to differences in data-sampling across MEC layers. Peak firing rates are $<$20 Hz in most HD cells in rat presubiculum and MEC (Table 16.1; Taube et al. 1990a; Sargolini et al. 2006; Boccara et al. 2010), with a few cells going up to 100 Hz (Taube et al. 1990a). Similar firing rates are found in monkeys. We note that the available information on HD cells in monkeys is based on a very small cell sample (Robertson et al. 1999), so the fraction of HD cells and their firing rates should be taken with caution.

Tuning widths of HD cells are quite similar between rats, bats, and monkeys (Table 16.1; no quantification is available for mice): in all three species, the width of the tuning curve at half of the peak firing rate is typically between 55° and 80° (Table 16.1). This width refers to the HD curve in the horizontal plane (tuning to the azimuthal angle, or yaw). Indeed, the large majority of HD cell studies were done in the horizontal plane, while HD cell representation in the other two planes was much less studied. In rats, the neuronal representation for elevation appears to be less prominent than for azimuth, while the neuronal representation for roll was never tested systematically (Stackman and Taube 1998; Calton and Taube 2005). In bats, in contrast, we recently found a substantial neuronal representation also for elevation and roll, in the presubiculum (Finkelstein et al. 2012). This interesting difference between HD cells in rats and bats could result from differences in

experimental methodology or in recorded areas (no experiments to date have tried to measure 3D HD tuning in the presubiculum of rats), or it could reflect true species differences in tuning of 3D HD, perhaps arising from differences in 3D locomotion or in 3D sensory inputs during ontogeny.

Finally, we note that, overall, very little comparative work has been done on HD cells—even less than on place cells. For example, while the contribution of visual and vestibular inputs for controlling HD tuning was studied extensively in the rat (Taube 2007), virtually nothing is known about sensory determinants of HD cells in the mouse, bat, or primate. Likewise, we do not know whether, in species other than the rat, HD cells show remapping, in the sense that they rotate their preferred direction between different environments. If they do, then an important question would be whether, similarly to rats, this remapping (rotation) is coherent across neurons (Taube 2007). These and many other questions await experimental testing.

16.2.3 Grid Cells

Grid cells—neurons showing spatially periodic selectivity, firing at the vertices of a hexagonal (or triangular) grid spanning the entire environment—were first discovered in MEC of rats in 2004/2005 by Moser, Moser and colleagues (Fyhn et al. 2004; Hafting et al. 2005). Each grid is characterized by a particular combination of spacing (distance between fields), orientation (angle relative to an external reference axis), and phase (displacement of the grid relative to an external reference point) (see also Derdikman and Moser 2014).

Since their discovery in rats, grid cells were also found in the MEC of freely moving mice (Fyhn et al. 2008) and bats (Yartsev et al. 2011), and very recently also in humans navigating in virtual reality (Jacobs et al. 2013). A study in head-fixed, stationary monkeys engaged in a visual-search task has reported grid-like neurons in the monkey MEC, which fired in relation to the gaze of the monkey within the reference frame of the vertical screen (Killian et al. 2012). These neurons in monkey MEC could be thought of as "spatial-view grid cells," because—just like the spatial-view cells in the monkey hippocampus (Georges-François et al. 1999; and see above) – they are tied to where the animal is looking at, rather than to its physical position in space. However, because the properties of these "spatial-view grid cells" in monkeys are in many ways similar to standard grid cells in rats, mice, and bats, we will discuss them all together.

In rats, mice, and bats, grid vertices were shown to be separated by ~60° angles, on average (Hafting et al. 2005; Fyhn et al. 2008; Yartsev et al. 2011—though we note that grid cells can be also quite elongated and deviate from 60°: see Brandon et al. 2011; Yartsev et al. 2011; Stensola et al. 2012). Grid cells in rats, mice, bats, and monkeys are organized in functional columns, in the sense that co-localized grid cells share similar spacing and orientation (Hafting et al. 2005; Fyhn et al. 2008; Yartsev et al. 2011; Killian et al. 2012). Further, in all these species, grid cells exhibit a large-scale functional organization, forming a gradient of the grid spacing along the dorsoventral axis of MEC (whereby cells in dorsal

MEC, close to the postrhinal border, show smaller spacing than cells located more ventrally; Table 16.1). In contrast to grid spacing and orientation, the grid phases of co-localized neurons are randomly shifted, spanning all possible phases (this was shown only in mice, rats, and bats). Recently, grid cells in rats were shown to be organized in discrete, steplike modules, rather than in a smooth gradient along the dorsoventral axis (Barry et al. 2007; Stensola et al. 2012); this arrangement awaits testing in other animal species. Almost none of the above properties of grid cells were tested in humans (Jacobs et al. 2013).

Another characteristic that is similar across rats, mice, and bats is the positive correlation between movement velocity and the firing rate of grid cells (Table 16.1). As in the case of place cells, this correlation might explain the low firing rates of MEC neurons in crawling bats, because they crawl rather slowly (Yartsev et al. 2011). Accordingly, the peak firing rate of grid cells is expected to be much higher in flying bats, similar to the case for 3D place cells (see above); this prediction remains to be tested.

Grid cells in rats and mice were found to be relatively stable across sessions, with correlations r ranging between 0.5 and 0.7. In monkeys and bats this stability was not tested, because just a single session was recorded (the within-session stability of grid cells in monkeys, when comparing the first and second half of the session, was reported to be very low: median $r \sim 0.24$; see Killian et al. 2012).

The MEC of rats, mice, and bats includes a set of diverse spatial cell types, including pure grid cells, HD cells, conjunctive grid × HD cells, and border cells (the latter will be described in the next section)—which seem to have similar properties across species (Table 16.1; bats—Yartsev et al. 2011; mice—Fyhn et al. 2008; Giocomo et al. 2011). Yet the laminar arrangement of these cell types is slightly different in mice as compared to rats and bats: whereas MEC layer II of rats and bats contains mainly pure grid cells, layer II in mice contains a mixture of a high fraction of HD cells and conjunctive grid × HD cells, in addition to pure grid cells (Fyhn et al. 2008; Yartsev et al. 2011); though we note that a larger cell sample needs to be collected in bats to verify this. This difference may be related to the diffuse anatomical border between the superficial layers in mouse dorsal MEC (Fyhn et al. 2008)—and it is unknown whether this species difference has any functional significance. In monkeys, HD cells and conjunctive grid × HD cells still need to be found in MEC.

A major difference between grid cells in rats and mice, on one hand, and bats and monkeys, on the other hand, is that rodent grid cells exhibit very pronounced theta oscillations, while in bats and monkeys theta oscillations seem to be very weak and appear in intermittent bouts (Yartsev et al. 2011; Killian et al. 2012). This difference has major implications for models of grid cells and will be discussed further in the section on theta oscillations, below.

16.2.4 Border Cells

Border cells (or boundary cells) are neurons that are activated along one or several borders of the environment. They were first described in rats (Savelli et al. 2008;

Solstad et al. 2008; Lever et al. 2009) and later reported in mice (Giocomo et al. 2011) and bats (Yartsev et al. 2011) in an open-field environment. Recently, "spatial-view border cells" were found in monkeys that visually scanned a computer screen (Killian et al. 2012). In all species, border cells comprise a small percentage of the MEC population—about 10 %—and are intermingled with grid cells and HD cells. We note though that there is an important caveat in the demonstration of border cells in mice, bats, and monkeys. In rats, it was demonstrated that, after introducing a new parallel wall, the border cells started to fire also along the new, similarly oriented border (Solstad et al. 2008; Lever et al. 2009). These tests, however, were not conducted to date in mice, bats, or monkeys. Moreover, almost none of the basic properties of border cells were studied outside of the rat. Therefore, the definitive demonstration of border cells in mice, bats, or monkeys—as well as their detailed characterization in these species—awaits further experiments.

16.3 Oscillations in the Hippocampal Formation

Neural oscillations in the hippocampus were studied in detail as early as 1954 (Green and Arduini 1954; and in a preliminary study already in 1938: Jung and Kornmüller 1938), in a variety of species—including rabbits, cats, dogs, rodents, bats, and monkeys (Vanderwolf 1969; Winson 1972; Robinson 1980; Buzsáki 2006; Ulanovsky and Moss 2007; see also Lever et al. 2014). The most prominent oscillations found in hippocampal LFP are delta (1–4 Hz), theta (4–10 Hz), beta (12–25 Hz), gamma (30–100 Hz), and high-frequency ripple oscillations (100–250 Hz). We will focus below on ripples and theta oscillations, for which cross-species comparative data exist; much less is known across species about the other frequency bands, such as gamma. We note that although much of the research on theta oscillation until the early 1980s was done in non-rodent species (reviewed in detail in Winson 1972; Robinson 1980)—and in fact, the original discovery of hippocampal theta was done in rabbits and cats (Green and Arduini 1954)—we chose to focus below, for coherence purposes, mostly on the same model species which we discussed above when reviewing spatial cells, namely rats, mice, bats, and primates.

16.3.1 High-Frequency Ripples

Ripples are hippocampally generated high-frequency oscillations that are most prominent during slow-wave sleep or during quiet wakefulness (epochs of relative inactivity during the awake state). Ripples have short duration, lasting typically between 40 and 100 ms, and are accompanied by intense synchronous firing of a substantial fraction of the hippocampal neuronal population ("population burst"). These ripple events are thought to send information to neocortex for long-term memory storage (Siapas and Wilson 1998; Sirota et al. 2003; Battaglia et al. 2004)

and thus to be crucial for hippocampal-neocortical communication and memory consolidation (Buzsáki 2006; Jadhav et al. 2012).

The basic properties of ripple oscillations in CA1 are very similar between rats, mice, bats, and primates—see Table 16.2 (Chrobak and Buzsáki 1996; Buzsáki et al. 2003; Skaggs et al. 2007; Ulanovsky and Moss 2007; Yartsev et al. 2011). In all species, ripples are most prevalent during slow-wave sleep and calmness (see Fig. 16.2a, f for examples of ripples from rats and bats). In all species, high-frequency ripples have their maximal amplitude in the CA1 pyramidal layer (see for mice and bats: Fig. 16.2b, g) and are riding on top of sharpwaves that reverse their polarity in the CA1 pyramidal layer (Buzsáki et al. 2003; Ulanovsky and Moss 2007): see Table 16.2. Similar to rats and mice, CA1 neurons in bats increase their firing rate during sharpwave-ripple events (Fig. 16.2a, f), and their firing is phase locked to the ripple oscillation, with peak firing rate occurring at the trough of the ripple (Fig. 16.2c, h) (Ulanovsky and Moss 2007); thus, ripples in bats, rats, and mice are not only qualitatively similar but in fact quantitatively have the exact same numerical value for the phase of best locking (Csicsvari et al. 1999; Buzsáki et al. 2003; Ulanovsky and Moss 2007; Yartsev et al. 2011). In all species, ripples in CA1 often occur in doublets, i.e., there is a relatively higher prevalence of short inter-ripple intervals <200-ms, as compared to longer intervals (see distributions of inter-ripple intervals from mice and bats: Fig. 16.2d, i) (Buzsáki et al. 2003; Ulanovsky and Moss 2007). While the durations of ripples in CA1 are quite similar across species (Table 16.2), ripple frequencies seem to slightly differ between species, with typical frequencies of 120–200 Hz in rats, 120–170 Hz in mice, 120–160 Hz in bats, and 100–120 Hz in monkeys and humans (Fig. 16.2e, j and Table 16.2).

Ripples in MEC were studied to date only in rats and bats (Chrobak and Buzsáki 1996; Yartsev et al. 2011). As in CA1, properties of ripples in MEC appear to be very similar between rats and bats. In both species, MEC ripples often occur in doublets and are accompanied by an increase in neuronal firing rate that is phase locked to the ripples' oscillatory cycles (Chrobak and Buzsáki 1996; Yartsev et al. 2011). Ripples in MEC, in both rats and bats, have a similar frequency to ripples in CA1 (120–200 Hz in rats, 120–160 Hz in bats: Chrobak and Buzsáki 1996; Yartsev et al. 2011). Duration of ripples in MEC is similar between rats and bats (Yartsev et al. 2011), but in both rats and bats, this duration is shorter than that of CA1 ripples, and generally the MEC ripples tend to be more variable than CA1 ripples. We thus conclude that high-frequency ripples, in both CA1 and MEC, are very similar across species, including rats and bats.

While the basic properties of ripple oscillations are highly similar across species—which may suggest that they serve similar functions across mammals—there has been in fact very little comparative work on the functional significance of ripples. Thus, while in rats there is evidence for hippocampal-neocortical interactions via ripples (Siapas and Wilson 1998; Sirota et al. 2003; Battaglia et al. 2004), and a demonstrated role for ripples in spatial working memory (Jadhav et al. 2012), such experiments were not done so far in other species—with the exception of one study in monkeys which showed that around the time of ripples,

Table 16.2 Hippocampal oscillations: cross-species comparison

Oscillation	Property	Rats	Mice	Bats	Primates
Ripples	Frequency	120–200 Hz[1–3]	120–170 Hz[2, 4]	120–160 Hz[5, 6] (see also our Fig. 16.2j)	Monkey CA1: 100–120 Hz[7, 8] Human CA1: 80–160 Hz[9]
	Duration	Typically ~50 ms[3]	Mean ~65 ms[4]	Mean ~45–50 ms[5, 6]	Monkey CA1: ~40–50 ms[7, 8] Human CA1: ~50 ms[9]
	Tendency of ripples to occur in doublets, spaced ~100–200 ms	Yes	Yes[2]	Yes[5] (see also our Fig. 16.2i)	Monkeys: occasionally[7]
	Ripple amplitude is maximal in the CA1 pyramidal cell layer	Yes[10, 11]	Yes[2, 12]	Yes[5] (see also our Fig. 16.2g)	Monkeys: yes[7]
	Ripples in CA1 associated with sharpwaves; sharpwave polarity reverses in the CA1 pyramidal cell layer	Yes[10, 11]	Yes[2]	Yes[5, 6]	Monkeys: yes[7]
	Increase of neuronal firing-rate in CA1 during a sharpwave-ripple complex	Yes[10, 11]	Yes[2]	Yes[5, 6] (see also our Fig. 16.2f)	Monkeys: yes[7]
	Phase locking of CA1 neurons onto ripple phase	Yes. Spikes locked to ripple trough[10, 11]	Yes. Spikes locked to ripple trough[2]	Yes. Spikes locked to ripple trough[5, 6] (see also our Fig. 16.2h)	*Unclear*
Theta	Frequency	5–10 Hz[13]	5–10 Hz[2]	4–8 Hz[5, 6]	3–8 Hz[14, 15]
	Behavioral correlate	Exploration and locomotion[13]	Exploration and locomotion[2]	Active sensing: echolocation; no dependence on locomotion[5]	Active sensing: visual search using saccades
	Continuity	Continuous (during exploration and locomotion, and REM sleep)[13]	Continuous (during exploration and locomotion, and REM sleep)[2]	Intermittent bouts[5, 6]. Bout duration 1–2 s; bouts occur every 20–40 s	Intermittent bouts in monkeys[7, 16] and in humans[14]

(continued)

Table 16.2 (continued)

Oscillation	Property	Rats	Mice	Bats	Primates
	Locking of CA1 place-cell spikes onto theta phase (when theta is present)	Yes	Yes	Yes	Probably
		Peak discharge at ~30° after the trough of locally recorded theta[17]	Double-peak locking: first peak at ~30° after the trough of theta[2]	Place cells have their peak discharge at ~30° after the trough of theta, in both big brown bat and Egyptian fruit bat[5, 6]	Hippocampal neurons in humans do show phase locking to theta during theta bouts[15], but the neurons in that study were not necessarily place cells[15]
	Theta amplitude increases in size below the CA1 pyramidal cell layer, towards the hippocampal fissure	Yes[11]	Yes[2]	Yes[5]	*Unknown*

Note: because most of the available cross-species comparative information comes from studies of hippocampal area CA1, we limited this table to CA1 data (see main text for some additional comparisons, e.g., ripples in MEC versus CA1)

1. Chrobak and Buzsáki (1996), 2. Buzsáki et al. (2003), 3. Nguyen et al. (2009), 4. Maier et al. (2011), 5. Ulanovsky and Moss (2007), 6 Yartsev et al. (2011), 7. Skaggs et al. (2007), 8. Logothetis et al. (2012), 9. Bragin et al. (1999), 10. Buzsáki et al. (1992), 11. Ylinen et al. (1995), 12. Gordon et al. (2005), 13. Buzsáki (2002), 14. Ekstrom et al. (2005), 15. Rutishauser et al. (2010), 16. Stewart and Fox (1991), 17. Csicsvari et al. (1999)

the neocortex is excited while most subcortical regions are inhibited (Logothetis et al. 2012). Similarly, while a large literature exists on replay and preplay of place sequences by the population bursts that accompany the ripples (see Jadhav and Frank 2014), there were only two studies that showed ripple-associated replay in mice (Dragoi and Tonegawa 2011, 2013), and no such studies were done to date in bats or primates (one study in monkeys did show replay in neocortex (Hoffman and McNaughton 2002), but did not examine hippocampal data, nor the relation to ripples). Thus, it is crucial to conduct much more comparative work on ripples, in order to, first, establish if there are any differences between species and, second, can such differences teach us anything interesting about hippocampal processing. For example, if one would record from populations of spatial-view cells in the hippocampus of monkeys trained on a visual-search task, would there be replay of ripple-associated sequences of spatial views by these hippocampal ensembles? Would this depend on whether the monkey performs a random-search visual task, in which the eyes are saccading quite randomly, as opposed to visual smooth

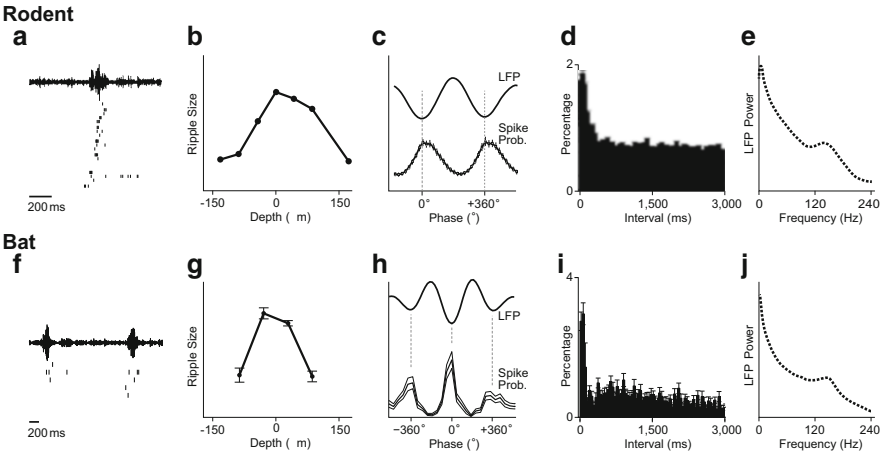

Fig. 16.2 High-frequency ripples oscillations are very similar in rodents and bats. (**a**–**e**) Rodents. (**f**–**j**) Bats. (**a**, **f**) Examples of high-frequency ripples (filtered in the ripple frequency range) and associated population burst across many neurons (raster), in rat (**a**) and big brown bat (**f**). (**b**, **g**) Ripple amplitude is maximal at the CA1 pyramidal cell layer; shown is ripple amplitude (y-axis) versus depth, with $x = 0$ indicating the layer, in mice (**b**) and big brown bats (**g**). (**c**, **h**) Very similar phase locking of spikes from CA1 pyramidal cells onto the phase of CA1 ripples; shown is the phase locking in mice (**c**) and big brown bats (**h**). (**d**, **i**) Ripples tend to occur often in doublets with <200-ms intervals; shown are examples of inter-ripple interval distributions in mice (**d**) and big brown bats (**i**). (**e**, **j**) Similar ripple frequencies for bats and mice; shown are power spectra of hippocampal LFP in CA1 during slow-wave sleep, in mice (**e**) and Egyptian fruit bats (**j**). Big brown bat data in (**f**–**i**) were replotted from Ulanovsky and Moss (2007); Egyptian fruit bat data in (**j**) replotted from Yartsev et al. (2011). Data in (**a**) reproduced with permission from Foster and Wilson (2006); data in (**b**) remeasured from Gordon et al. (2005); data in (**c**, **d**) reproduced with permission from Buzsáki et al. (2003); data in (**e**) remeasured from Gordon et al. (2005)

pursuit, where the eyes are moving smoothly through a sequence of views? Or, in bats, would one find replay of sequences that are associated with sonar behaviors? Would such replay correlate with subsequent memory performance? Any such findings will shed light on the function of ripples and the ripple-associated replay phenomenon, in hippocampal processing across species.

16.3.2 Theta Oscillations

Hippocampal theta oscillations have been studied extensively for 60 years, starting with the pioneering work of Green and Arduini (1954), and this massive neuroscientific effort has produced a staggering amount of experimental data and a plethora of theories (reviewed in Buzsáki 2006; Andersen et al. 2007). One of the most striking features that emerged over these 60 years or research is the cross-species *differences* in theta oscillations (Winson 1972; Robinson 1980). In rodents (rats and mice), the main behavioral correlate of theta is exploration and locomotion (Vanderwolf 1969), whereby theta is observed continuously while the animal is

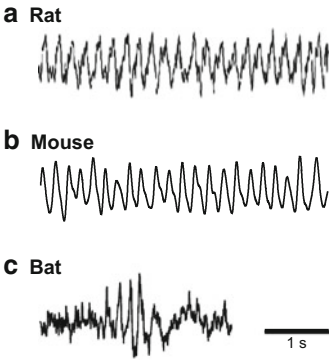

Fig. 16.3 Theta oscillations are continuous in rodents but occur in short intermittent bouts in bats. (**a**, **b**) Examples of continuous theta oscillation recorded in hippocampal dorsal CA1 area of rodents: Recordings from a rat (**a**) [reproduced with permission from Hollup et al. (2001)] and a mouse (**b**) [reproduced with permission from Wulff et al. (2009)]. (**c**) Example of a short, intermittent bout of theta recorded in hippocampal dorsal CA1 area of an Egyptian fruit bat [from Yartsev et al. (2011)]. LFP was filtered between 1 and 117 Hz in (**a**), 1–20 Hz in (**b**), and 1–475 Hz in (**c**)

running in the environment (Fig. 16.3a–b) (see also Lever et al. 2014). In cats, by contrast, theta is observed most strongly when the animal is in fact stationary and is visually tracking prey or other moving items with its eyes (Winson 1972; Robinson 1980). In rabbits, theta is observed most prominently upon presentation of a sensory stimulus, unrelated to the movement state of the animal (Winson 1972; Robinson 1980). In monkeys and humans it has been very difficult to observe hippocampal theta oscillations, and those few studies that did find them, during behavior, sleep, or anesthesia, reported that theta is weak and occurs in short intermittent bouts (Stewart and Fox 1991; Cantero et al. 2003; Ekstrom et al. 2005). A recent study in monkeys performing a visual-search task found theta bouts that were related to eye-saccading behaviors (Jutras and Buffalo 2009; Jutras et al. 2013). In bats, our own studies showed similar results to those from humans and monkeys: theta oscillations were difficult to detect in the bat and occurred in short intermittent bouts that lasted ~1 s and occurred every ~30 s on average (Fig. 16.3c; Ulanovsky and Moss 2007; Yartsev et al. 2011). In big brown bats, we found that theta bouts were more prominent in time-epochs when the bat explored the arena using echolocation (Ulanovsky and Moss 2007). Thus, the phenomenology of theta oscillations differs substantially across species—which is in striking contrast to the case of the other hippocampal oscillation discussed above, the high-frequency ripples, which seem to be very similar across species, including between rats and bats (see previous section and Table 16.2).

We note that one feature which may be common to all of these occurrences of theta, across species, is the relation to sensory inputs (Table 16.2). If we consider the hypothesis that theta is important for the processing of stimuli across time and in learning of temporal sequences (Skaggs et al. 1996; Wallenstein and Hasselmo

1997; Jensen and Lisman 2005), then maximal theta may be expected when sensory information arrives at high rates or changes rapidly. In rats, which rely mostly on their well-developed proximal senses, new olfactory and somatosensory information arrives most rapidly when the animal runs at high velocities, and hence we would expect theta amplitude to increase with running velocity, as is indeed the case. In bats, which rely on echolocation, we would expect theta amplitude to increase with the rate of echolocation calls, as we indeed found (Ulanovsky and Moss 2007). In monkeys performing a visual-search task, in which they rely on eye saccades, we would expect theta to be related to the occurrence of saccades, as was indeed reported (Jutras and Buffalo 2009; Jutras et al. 2013). In fact, what is common to olfaction and whisking in rats, echolocation in bats, and eye saccades in monkeys is that these are all active-sensing systems—in which the animal is engaged in actively scanning space and collecting sensory information from the environment (Nelson and MacIver 2006). Thus, it could be that the phenomenological differences in theta oscillations that were observed across species are in fact related to differences in active-sensing strategies—while the general principle still holds that hippocampal oscillations are related to processing of active-sensing inputs, across all species (see further discussion of this prediction in our paper: Ulanovsky and Moss 2007).

Theta rhythmicity of spike trains is another key characteristic of hippocampal and entorhinal neurons in rodents. Neurons in the rodent hippocampus and MEC exhibit robust and strong locking of single-unit and multiunit spikes onto the theta oscillation (Csicsvari et al. 1999; Buzsáki et al. 2003). In contrast, place cells and grid cells in bats show very weak locking to theta, and this weak locking is observed only during the short intermittent theta bouts (Ulanovsky and Moss 2007; Yartsev et al. 2011; Yartsev and Ulanovsky 2013). This has important implications for theories of hippocampal and entorhinal function, because a major class of models of grid formation—the "oscillatory interference models"—relies critically on the existence of continuous theta rhythmicity in the spike patterns of grid cells (Burgess and O'Keefe 2011). Our finding of grid cells without theta oscillations in the MEC of bats (Yartsev et al. 2011) argues strongly against these theta-based models of grid formation [although it was proposed that interference-based mechanisms might operate at non-theta frequencies in bats (Heys et al. 2013); for additional views and a detailed description of these models, see Lever et al. (2014), Navratilova and McNaughton (2014)].

Several additional recent studies, in mice and bats, have provided further evidence against the theta-based models. First, two recent studies have examined suprathreshold and subthreshold dynamics of MEC grid cells in mice navigating in virtual-reality environments (Domnisoru et al. 2013; Schmidt-Hieber and Häusser 2013). These studies found that when the mouse enters the grid field, the subthreshold membrane potential exhibits ramp depolarizations—which is consistent with predictions of continuous attractor network models; moreover, there is relatively little increase in theta power within the grid field, and sometimes theta is even decreased—which argues against the oscillatory interference theta-based models of grid formation (Domnisoru et al. 2013; Schmidt-Hieber and Häusser 2013).

Second, while MEC layer II stellate cells in rodents show prominent subthreshold theta oscillations and theta-frequency resonance (Giocomo et al. 2007), a recent slice study in bats depicted a different picture (Heys et al. 2013). This study reported the lack of theta-frequency subthreshold membrane potential oscillations and no theta-band intrinsic resonance in layer II stellate cells of bat MEC—in neither big brown bats nor Egyptian fruit bats (Heys et al. 2013). Some stellate cells in bats lacked any resonance whatsoever, in any frequency, while other neurons showed resonance at extremely low frequencies of ~1 or 1.5 Hz—although this resonance was very weak (Heys et al. 2013). This is reminiscent of the weak subthreshold oscillations found in MEC layer II of monkeys (Buckmaster et al. 2004). Thus, it seems that the biophysical resonance properties of MEC neurons in bats and monkeys do not support theta oscillations—which, again, argues against the oscillatory interference models of grid formation (at least not at the theta frequency range) but is consistent with continuous attractor network models of grid cells (Fuhs and Touretzky 2006; McNaughton et al. 2006; Burak and Fiete 2009; Couey et al. 2013), as well as with adaptation-based models (Kropff and Treves 2008).

We suggest that much more work needs to be done on theta oscillations across rodents, bats, primates, and additional species, in order to study in more detail the interplay between cellular and network mechanisms in the hippocampal formation, across mammals—and also to elucidate whether the interspecies differences in theta oscillations are indeed related to differences in active-sensing behaviors between the different species, as we proposed (Ulanovsky and Moss 2007).

Concluding Remarks: The Need for Further Comparative Studies

While much progress has been made in describing basic properties of spatial cell types and hippocampal oscillations across species, a lot more work needs to be done. There are clearly differences between species, even within rodents—such as the marked differences in place-field stability between rats and mice. The differences between rodents, bats, and primates are even more substantial—as illustrated by the example of the theta oscillations—but we note that in many other ways there are also striking similarities across mammalian species, such as in the properties of high-frequency ripple oscillations and in functional properties of place cells and grid cells. We propose that by contrasting and comparing hippocampal processing across species, we would unravel the *invariant* properties of hippocampal function—which are crucial for truly understanding hippocampal processing across mammals.

Moreover, there are many "known unknowns": hippocampal properties that were investigated to date only in rats and for which it is simply unknown whether and how they manifest in other species. For example, can we find remapping in non-rodent species? Which kinds of remapping? How do they depend on different sensory inputs or on the behavioral context?

Second, as we noted above, there were hardly any large-scale ensemble recordings of hippocampal populations in non-rodent species. Will one find evidence for prospective and retrospective coding in neural ensembles recorded from non-rodent species, as was found in rats? Or—if one would record from

populations of spatial-view cells in the hippocampus of monkeys trained at a visual-search task, would they exhibit replay of sequences of spatial views? And what about replay of sequences of remembered items in monkey hippocampus? Or sequences of auditory sonar targets in bat hippocampus? What would this teach us about hippocampus, space, time, and memory?

Third, over 40 years of hippocampal research have produced an amazing set of findings on the spatial cell types of the hippocampal formation, in laboratory-sized environments. But what if we could record place cells or grid cells in animals locomoting over kilometer-sized environments—would we find kilometer-sized place fields and huge grids? Or perhaps, as suggested by some theoretical studies, a radically different picture would emerge, for example, based on combinatorial grid coding (Sreenivasan and Fiete 2011; Mathis et al. 2012a, b). Similarly, would place cells exhibit a single well-circumscribed field, as in laboratory-sized arenas – or perhaps each cell will have dozens of fields in a kilometer-sized environment? It is crucial to answer these questions, if we are to understand hippocampal spatial representations and the neural basis of navigation under truly ethologically-relevant conditions.

And of course, there are many "unknown unknowns" that await us down the comparative road. The lack of theta oscillations in the hippocampus of bats was one such unexpected finding. The discovery of spatial-view cells and "spatial-view grid cells" in the hippocampal formation of monkeys was another. Many more surprises surely lie ahead. We are just starting to scratch the interesting facets of hippocampal neurophysiology across species.

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