

Theta Rhythm of Navigation: Link Between Path Integration and Landmark Navigation, Episodic and Semantic Memory

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ABSTRACT: Five key topics have been reverberating in hippocampal-entorhinal cortex (EC) research over the past five decades: episodic and semantic memory, path integration (“dead reckoning”) and landmark (“map”) navigation, and theta oscillation. We suggest that the systematic relations between single cell discharge and the activity of neuronal ensembles reflected in local field theta oscillations provide a useful insight into the relationship among these terms. In rats trained to run in direction-guided (1-dimensional) tasks, hippocampal cell assemblies discharge sequentially, with different assemblies active on opposite runs, i.e., place cells are unidirectional. Such tasks do not require map representation and are formally identical with learning sequentially occurring items in an episode. Hebbian plasticity, acting within the temporal window of the theta cycle, converts the travel distances into synaptic strengths between the sequentially activated and unidirectionally connected assemblies. In contrast, place representations by hippocampal neurons in 2-dimensional environments are typically omnidirectional, characteristic of a map. Generation of a map requires exploration, essentially a dead reckoning behavior. We suggest that omnidirectional navigation through the same places (junctions) during exploration gives rise to omnidirectional place cells and, consequently, maps free of temporal context. Analogously, multiple crossings of common junction(s) of episodes convert the common junction(s) into context-free or semantic memory. Theta oscillation can hence be conceived as the navigation rhythm through both physical and mnemonic space, facilitating the formation of maps and episodic/semantic memories. © 2005 Wiley-Liss, Inc.

KEY WORDS: place cells; hippocampus; oscillations

THE SHORT SAGA OF THETA OSCILLATIONS AND BEHAVIOR: A LESSON FOR THE FUTURE?

The story of theta oscillations is an edifying chapter in the history of behavioral-cognitive neuroscience. The controversy regarding the exact behavioral correlate(s) of theta oscillation has raged for decades, generating over 1,500 published experiments and occasional strong feelings among the contestants. It is much like the tale about the elephant and the wise blind men of Hindustan. Virtually every conceivable overt and covert behavior has been associated with hippocampal theta activity (Fig. 1). I just list a few examples below to illustrate the flavor of the various ideas. The first hypothesis about theta's role was arousal, on the basis of the observation that in the anesthetized rabbit noxious stimuli induced cortical desynchronization and hippocampal theta oscillation

(Jung and Kornmüller, 1938; Green and Arduini, 1954; Coleman and Lindsley, 1977). The first experiments in behaving animals were carried out by Grastyán et al. (1959). According to Grastyán's pioneering work in the cat, theta reflected an “orienting reflex, searching for stimuli with significance to the subject” (see also Vinogradova, 2001; Vinogradova and Dudeva, 1972; Buzsáki et al., 1979, 1981). “Attention to the conditional stimulus” (Adey et al., 1960; Holmes and Adey, 1960) was next on the list, followed by “information processing” (Adey, 1967), “visual search” (Brown, 1968), and “arousal, decision-making, memory consolidation” (Bennett and Gottfried, 1970; Bennett, 1973; Bennett et al., 1973; Bennett and French, 1977). All these studies shared the view that hippocampal theta is associated with high level processing of environmental stimuli. A somewhat different idea was put forward by Pickenhain and Klingberg (1967), suggesting that theta could be used for “comparing sensory activity with previously stored information.” This “comparator” idea has been repeatedly emphasized by others as well (Sokolov, 1963; Vinogradova and Dudaeva, 1972; Hasselmo, 1999; Lörincz and Buzsáki, 2000; Lisman and Otmakhova, 2001; Vinogradova, 2001). “Memory consolidation” (Destrade 1982), “learning and extinction” (Gray, 1970, 1972), “learning and retention” (Bennett, 1973), “classical conditioning” (Teitelbaum et al., 1977; West et al., 1981; Berry et al., 1978), “positive emotions and motivation” (Grastyán et al., 1966), “phase (time)-shifted encoding and retrieval” (Wallenstein et al., 1998; Koene, 2003), and “short-term memory buffer” (Lisman and Idiart, 1995) were added to the growing list of hypotheses. These ideas, along with “information processing not necessarily involving movement” (Winson, 1974), and “habituation” (Irmis, 1974; McLardy, 1981) can also be roughly placed into the framework of processing the “input” by the brain. In contrast, a number of hypotheses argued in favor of the “output” or motor control role of hippocampal theta. The most influential of these hypotheses has been the “voluntary movement” hypothesis of Vanderwolf (1969, 1988; see also Lopes da Silva and Kamp, 1969; Lopes da Silva et al., 1974; Arnolds et al., 1979). Vanderwolf suggested that theta occurs only during intentional or voluntary movement (a term introduced by J.H. Jackson; see Taylor, 1958), as opposed to immobility and “involuntary,” i.e., stereotypic activity. The stereotyped “rhythmical exploratory sniffing behavior”

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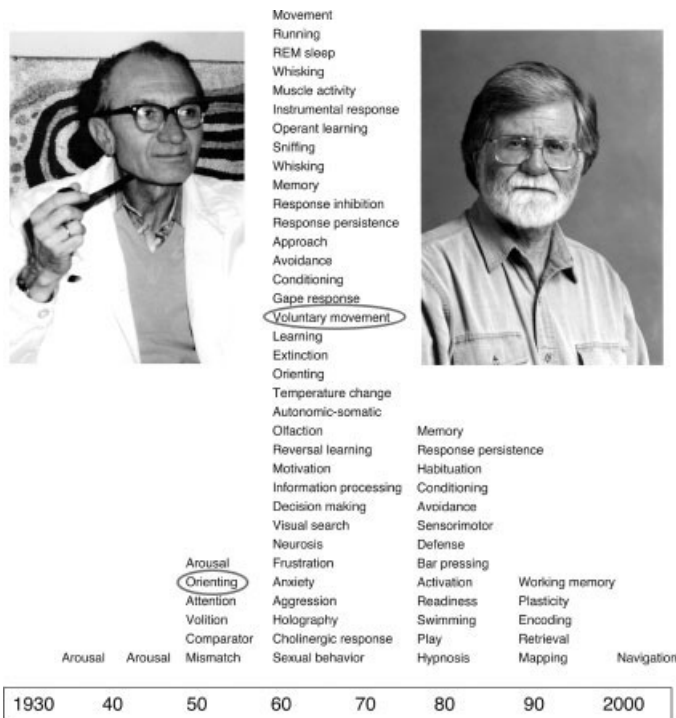


FIGURE 1. Time line of hypothesized behavioral correlates of hippocampal theta oscillations. Most correlates can be lumped as “sensory-attention” (input function) or motor output function. Andre Grastyán’s (left) “orienting response” hypothesis was the first, which was derived from observations in behaving animals (cat). The most influential hypothesis in the rat has remained the “voluntary movement” correlate by Cornelius (Case) H. Vanderwolf (right). Note the large variety of the hypotheses and their culmination in the 1970s. The behavior (independent variable)–brain mechanism (dependent correlate) approach failed to produce a consensus on the behavioral significance of theta oscillations.

(Komisaruk, 1970) and “sniffing” (Macrides, 1975), accompanied by theta rhythm, were taken as exceptions to this rule. “General readiness, preparation to make adaptive responses to biologically significant stimuli” (Klemm, 1972), “operant behavior” (Lopes da Silva and Kamp, 1969), “skeletal movement” (Black et al., 1970; McFarland et al., 1975), “swimming but not shivering” (Whishaw and Vanderwolf, 1971), “activation of central neural structures which program or generate movement” (Nadel et al., 1975), “timing of bar pressing” (Buño and Velluti, 1977; Semba and Komisaruk, 1978), “response inhibition” (Douglas, 1969; Altman et al., 1973; Sainsbury, 1998), and “response persistence” (Glazer, 1974a,b) are further examples of the view that theta oscillations exert some sort of control on the motor output of the brain. The proposal of a “sensorimotor” correlate of theta was a sly compromise (Bland, 1986). REM sleep (Grastyán and Karmos, 1961; Lissák et al., 1962; Jouvet, 1967; Radil-Weiss, 1974) and some further interesting ideas, including “animal hypnosis” (Klemm, 1982), “autonomic-somatic interaction” (Powell and Joseph, 1974), cutaneous temperature change” (Horowitz et al., 1974), “anxiety” (Gray et al., 1970, 1972; Lucas et al., 1974), “sexual behavior” (Kurtz, 1975) or more specifically “mounting and pelvic thrusting” (Sainsbury,

1970), and “copulatory behavior with the exception of ejaculation” (Kurtz and Adler, 1973) can be added to the list. For an exhaustive list of works on the behavioral correlates of theta oscillations, see Miller (1991) and Lengyel et al. (2005) for computational models. Despite seven decades of hard work on rabbits, rats, mice, gerbils, guinea pigs, sheep, cats, dogs, old world monkeys, chimpanzees, and humans by outstanding colleagues, to date, there is no widely agreed term that would unequivocally describe behavioral correlate(s) of this prominent brain rhythm. By exclusion, the only firm message that can be safely concluded from this brief summary is that in an immobile animal no theta is present, provided that no changes occur in the environment (and the animal is not “thinking”). Pointing out species differences in the behavioral correlates of theta is informative (Winson, 1972) but such comfortable compromise does not tell us whether it is the hippocampus or the rest of the brain, which is different. Furthermore, even if we keep the list of conjectured behavioral correlates of theta oscillations only in a single species, we are still far from a potential consensus, warranting alternative approaches of research.

From Behavior to Brain vs. From Brain to Behavior Strategies

Processing environmental inputs requires “attention,” as does intentional movement. With the introduction of the term “voluntary,” theta oscillation research unintentionally entered the territory of “intentionality,” a label that refers to the “substance” of all subjective mental activity (Dennett, 1987). Thus, an inescapable deduction from the behavior–brain correlation approach is that the “will” plays a critical role in theta generation. An alternative, and perhaps more sober, conclusion is that our behavioral-cognitive terms are simply working hypothetical constructs that do not necessarily correspond to any given brain mechanism. Although the true goal of neuroscience research is to reveal how the brain generates behavior and how particular mechanisms, such as theta oscillations, can categorize and define behaviors, most behavioral-cognitive research, to date, seems to work in the opposite direction. We take a man-created word or concept, such as one of those in the above list, and search for brain mechanisms that may be responsible for the generation of the conceived behavior. Despite the best intentions, such approach has limitations. For example, Vanderwolf used sophisticated “ethological,” fine-grain analysis of behavior (cf. Vanderwolf, 1988). Ironically, it is through his work that theta became linked with free will. Grastyán objected passionately to the term “voluntary,” yet he could not avoid its connotations. He dedicated the last decade of his life to understanding the neurophysiological substrates of play behavior and concluded that theta is an invariant correlate of play in kittens and cats (personal communication). According to Huizinga (1955), one of Grastyán’s favorite philosophers, play is “a voluntary activity or occupation executed within certain limits of time and place.” To avoid the association with “voluntary” or “attentional,” I have used the term “exploratory” in my description

of theta behaviors, although the term has never been approved by either Grastyán or Vanderwolf. A valid objection is that it is arguable to call walking the same alley the hundredth time “exploration.” Are we in need of yet another term?

An alternative strategy to understand the role of theta oscillations in behavioral organization is to reveal its content. By content I mean the synaptic and cellular mechanisms that give rise to a population “order parameter” (Haken, 1987) measured by the mean field of theta waves. It is through this process that we gain insight into the temporal organization of population activity of single neurons. It is the time metric of theta that determines the synaptic interactions within and among cell assemblies, which in turn are responsible for transforming inputs to the entorhinal–hippocampal system into output patterns modifying neocortical circuits and behavior (cf. Miller, 1991; Buzsáki, 1996).

Hypothesized Functions of the Hippocampal–Entorhinal System

The behavior–brain correlate strategy of cognitive neuroscience may be also responsible for the prevailing paradoxes of hippocampal function(s) at a more general level. As was the case with theta oscillations research, multiple, hard-to-relate terms have been associated with hippocampal function in general, including attention, voluntary movement, dead reckoning (Wegintegration or path integration) navigation, map-based (cognitive) navigation, episodic and semantic memories. Are all these behaviors, in humans and other animals, generated by the cell assemblies of the entorhinal–hippocampal system? Are they using the same or different anatomical substrates and exploiting physiological rules?

Starting with patient H.M. (Scoville and Milner, 1957), a consensus emerged that the hippocampus and associated structures are responsible for declarative (episodic and semantic) memories (Squire, 1992; Cohen and Eichenbaum, 1993; Milner et al., 1998; Eichenbaum, 2002). In its intended definition, episodic memory is claimed to be uniquely human, which endows the individual with the capacity to reference personal experiences in the context of both time and space (Tulving, 1987, 2002). It is these life-long experiences, representing unique events through space–time that give rise to the feeling of the self and are the source of individuality. Singular episodes can reemerge through the process of free recall. These features place strong constraints on studying the brain mechanisms of episodic memory in animals. Semantic knowledge, on the other hand, is a largely context-free form of information. It is the explicit “meaning” of things (Tulving, 1972; Squire, 1992). Against this background, how are we expected to work out physiological mechanisms of declarative memories in animals simpler than humans?

Not surprisingly, hippocampal research on animals gave rise to different perspectives. Among these, the discovery of “place cells” provided the most important insights into hippocampal function (O’Keefe and Dostrovsky, 1971). In their comprehensive book on the hippocampus, O’Keefe and Nadel (1978) have considered several interpretations for the coding values

of place cells, including dead reckoning or route navigation (Mittelstaedt and Mittelstaedt, 1980; Pickering, 1996) and landmark or map-based navigation. For numerous reasons, compelling from the available evidence at that time, they settled on allocentric map-based navigation. Subsequent work has described multiple, interconnected maps in the dentate, CA3 and CA1 regions, and the EC (Quirk et al., 1992; Jung and McNaughton, 1993; cf. Muller, 1996; Frank et al., 2000; Fyhn et al., 2004; Lee et al., 2004; Leutgeb et al., 2004). Allocentric, map-based navigation is essentially a geometric triangulation process, which depends primarily on the perceptual (input) properties of the brain (Burgess and O’Keefe, 1996; O’Keefe and Burgess, 1996). The cognitive map theory, however, does not explain how the spatial metric, necessary for distance and angle estimates, is created in the first place. A spatial metric in sensory systems cannot arise without movement of the body (Thompson and Varela, 2001; Khazipov et al., 2004), which is an essential part of dead reckoning navigation.

The discovery of head direction cells (Ranck, 1985; Muller et al., 1996a), speed modulation of place cell firing, and other findings at odds with the cognitive map theory lead McNaughton et al. (1996; Samsonovich and McNaughton, 1997) to reconsider dead reckoning (path integration; see also Touretzky and Redish, 1996; Redish and Touretzky, 1997) as an alternative explanation for the overall observations of hippocampal unit activity and hippocampal damage. As opposed to allocentric or map-based navigation, dead reckoning exploration uses self-motion-generated (also called idiothetic) cues only. By time integration of vestibular, somatosensory and other self-derived information, travel distance can be calculated (Mittelstaedt and Mittelstaedt, 1980; cf. Gaffan, 1998; Mittelstaedt, 2000). According to McNaughton et al. (1996), the necessary temporal metric for path integration arises from the rhythmic steps of self-motion.

Even the path integration-associated dramatic shift in thinking about the hippocampus failed to connect either single unit or theta oscillation functions to episodic or semantic memories. Furthermore, confidence in the involvement of the hippocampus in dead reckoning navigation has decreased recently (Alyan and McNaughton, 1999; Moser et al., 2005). Although the original formulation of the cognitive map theory (O’Keefe and Nadel, 1978) implied that “addition of a temporal component to the basic spatial map in the human provides the basis for an episodic memory system” or even language (O’Keefe, 1999), the relationship between the essentially egocentric episodic memory and allocentric landmark navigation has remained a controversial issue. For illustration, here is a recent explicit opinion: “I reiterate the basic tenet of the cognitive map theory that the processing and storage of spatial information is the primary and perhaps exclusive role of the hippocampus in the rat, and that the data that appear to contradict this have been misinterpreted” (O’Keefe, 1999). Again, a convenient but disputable way to settle the issue would be to declare that there exist species-specific differences in entorhinal–hippocampal computation.

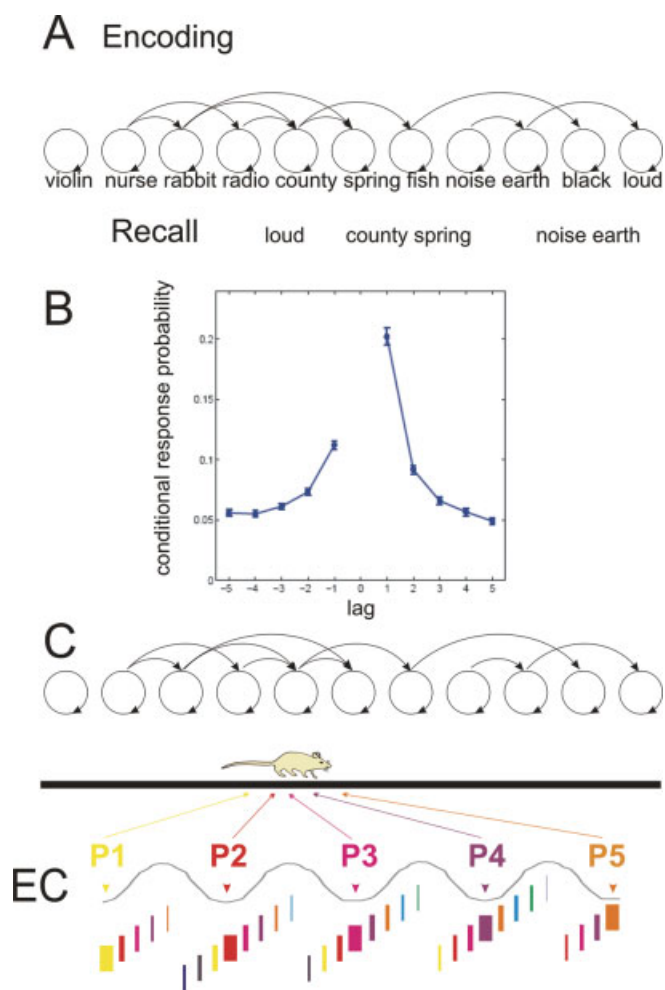


FIGURE 2. Analogy between episodic learning and 1-dimensional navigation. **A:** Learning and free recall of an episode. Arrows indicate first and higher order relationships, which facilitate recall of items with nearby positions (e.g., county spring, noise earth). **B:** Conditional response probability of recall as a function of positional lag. Note advantage for recalls to nearby serial positions and an asymmetry favoring forward recall. **C:** Schematic illustration of the within-theta cycle sequential activation of hippocampal cell assemblies. The width of the bars indicates firing intensity of the assemblies. The assembly at the trough of theta corresponds to the current location (places P1 to P5). Rows of ticks correspond to eight different assemblies. Note that the sequentially activated assemblies are replayed repeatedly within single theta cycles, with the same assembly occupying different phases of the cycle. EC, input from the EC (arrowheads) provides updated information about the external environment. In the absence of external or idiothetic cues (i.e., free recall), assemblies are advanced by the previous cycles (e.g., P1 recalls P2). The graph in (B) is reprinted with permission from Howard and Kahana (1999).

Coming from the tradition of human psychology, Eichenbaum (Eichenbaum et al., 1999; Eichenbaum, 2000) suggested that spatial mapping is simply a byproduct of a “relational memory” system. The hippocampus may not be only about place, even in simple animals (see e.g., Gluck and Meyer, 1993; Hampson et al., 1996). For example, Eichenbaum’s experiments demonstrated that when odor representation requirements are

confronted with spatial information, subsets of stimuli respond selectively to the quality of the odorant, irrespective of the rat’s position in the environment (Wood et al., 1999). Bunsey and Eichenbaum (1996) designed behavioral experiments, in which the rat had to memorize the relations between spatial or non-spatial stimuli and found that animals with hippocampal damage were consistently inferior in solving such tasks. According to the relational hypothesis (Wallenstein et al., 1998; Eichenbaum et al., 1999), one group of hippocampal neurons code for spatial cues, others for distances between them, and yet other groups for overlapping combinations of cues, etc (see also Hampson et al., 1999). A spatial map is then nothing else but a large collection of cue conjunctions that overlap, with the conjunctions providing a framework for moving among the cues. In its conceptualization, Eichenbaum’s relational theory is similar to O’Keefe and Nadel’s mapping idea, but extended to include nonspatial domains. However, neither theory provides an adequate explanation for the relationship between episodic learning and maps; geographical or abstract. In contrast to the experimental detail-rich cognitive mapping theory, the relational framework suggests that the re-interpretation of place cell observations in rats can fit the requirement of episodes. Relational theory does emphasize the temporal requirement of episodic memory but remains mute on the origin of the temporal metric. It simply assumes that subsequent items in a chain of events are somehow connected in time. The chaining hypothesis, however, can account only for first order (immediate neighbor) relations, without being able to explain the documented higher order connections of episodic memories (Fig. 2; Howard and Kahana, 1999). Later, we will discuss that hippocampal theta oscillations are indispensable for the emergence of both first and higher order linkages. A further issue that remains to be explained is the relationship between episodic and semantic memories, especially whether they share the same or different neuronal substrate(s) as the one used in place navigation (Eichenbaum et al., 1999).

The Theta Link

For long decades, hippocampal memory research in human subjects coexisted with animal work on theta oscillations, but the two lines of research did not connect until recently (Klimesch, 2000; Kahana et al., 2001). Similarly, studies on place cells and hippocampal theta oscillations peacefully coexisted but for long did not profit from each other. Although several laboratories found a quantitative and reliable relationship between cell firing and theta phase in long recording epochs, these studies did not explicitly deal with place cells (Buzsáki et al., 1983; Bland, 1986; Fox et al., 1986; for recent studies, see Csicsvari et al., 1999; Klausberger et al., 2003). Furthermore, pharmacological studies by Vanderwolf suggested that there might be different forms of hippocampal theta oscillations. He introduced the atropine-sensitive and atropine-resistant dichotomy (Kramis et al., 1975; cf. Vanderwolf et al., 1988), which we relate today to the cholinergic CA3 theta generator (Bland et al., 1988) and the NMDA receptor-dependent entorhinal

input (cf. Buzsáki, 2002). At a meeting honoring Endre Grastyán's work in 1984, O'Keefe made a seemingly trivial but seminal comment: he suggested that perhaps we should "speculate about the possibility that in fact there are various phase relationships that can occur between these two EEG patterns and that may be part of the function of the EEG is to create interference patterns as a function of the different phase of these two theta waves. This might be a beginning to examine the function of these theta waves" (see General Discussion in: Buzsáki and Vanderwolf, 1985). His implicit insight was that the interference of two oscillators beating at slightly different frequencies but acting on the same neuron(s) can systematically affect spike timing. Eight years later, he and Recce (1993) verified the hypothesis experimentally by showing that the spikes of a place cell shift systematically relative to the phase of the ongoing theta oscillation. They called the phenomenon "phase precession," a unique and systematic relationship between the timing of spikes and the theta phase.¹ As the rat enters the field, spikes occur on the peak of theta recorded at the CA1 pyramidal layer and may retard a full cycle as the entire receptive field of the cell is traversed. The phase-precession demonstration was the first experimental evidence for the long-suspected temporal "code" (see also Skaggs et al., 1996; Harris et al., 2003; Mehta et al., 2002). The possibility of a causal relationship between the timing of spikes and overt behavior spawned dozens of computer modeling papers exploring possible mechanisms (cf. Zugaro et al., 2005).

With the discovery of phase precession, time re-entered the field of place cell research through theta oscillations, offering a potential link between single neuron research and episodic memory. Interestingly, the phase precession phenomenon was taken as further evidence in support of the map-based navigation theory of the hippocampus, even though no landmarks are needed to successfully run back and forth on a linear track, an apparatus used to demonstrate the robust phenomenon. As opposed to the firing rate, which waxes and wanes as the rat moves in and out of the place field and varies as a function of the running velocity of the rat (McNaughton et al., 1983; Czurkó et al., 1999), the phase of spikes relative to the theta clock progresses monotonically as the rat traverses the field (O'Keefe and Recce, 1993; Skaggs et al., 1996). Recently, Huxter et al. (2003) suggested that firing rate is of secondary importance for place coding and that the liberated rate dimension is available for coding something else. According to their suggestion, the hippocampus serves a dual role in spatial mapping and episodic memory, assisted by phase and

rate coding, respectively (Huxter et al., 2003). It is not clear though how such hypothesized division of labor relates to a previous dichotomy, suggesting that in humans map-based navigation is predominately mediated by the right medial temporal lobe, whereas the context-dependent episodic memory is more dependent on the left medial temporal lobe (O'Keefe et al., 1998; Spiers et al., 2001). Furthermore, in light of the known mechanisms of theta field generation by cell assemblies, it is hard to envision how rate and phase could be independently manipulated (Harris et al., 2003; Mehta et al., 2002; Buzsáki and Draguhn, 2004). If rate changed completely independent of the phase, it would be difficult to explain the relationship between membrane polarization, spiking and the generation of the extracellular mean field (cf. Buzsáki 2002). Paradoxically, in the proposed scheme of Huxter et al. (2003) time (phase) is assigned to map-based navigation, which does not need it, whereas time is taken away from episodic memories, which do.

These caveats notwithstanding, the discovery of phase precession (O'Keefe and Recce, 1993) and its extended analysis (Skaggs et al., 1996) provided a novel temporal organizing mechanism for bringing cell assemblies together in the time frame critical for neuronal plasticity, which we will discuss later. With it, a macroscopic order parameter (theta oscillation) that has been associated with a large class of behaviors previously (Fig. 1) became linked to place cell research as well. From this new vantage point we can re-examine the relationship between single cells, cell assemblies, and behavior.

A Proposal

What is the relationship, if any, between dead reckoning and landmark navigation, episodic and semantic memory, and theta oscillations—these seemingly disparate functions attributed to the hippocampus and associated structures by various approaches? How can we synthesize experiments and views on humans and animals into a coherent picture, or at least, into a productive framework? The proposal below specifies some key areas for future research. The central strategy in this brain-based approach is to relate the organizational rules of recall in human memory to the "coding"- and retrieval-associated neuronal assembly patterns in animals, according to the following hypotheses:

1. Learning of sequentially presented or inspected random items in an episodic task is formally identical to the coding of sequential places in a linear (1-dimensional) route. Hebbian plasticity converts the first and higher order travel distances and episodically linked items into synaptic strengths.
2. Formation of episodes and neuronal representations of 1-dimensional routes require a temporal metric that we identify with the theta period. Navigation in 1-dimensional routes gives rise to unidirectional place cells, so that different assembly sequences are activated on the opposite journeys.
3. Time-independent, cognitive (2-dimensional) maps are formed from overlapping multiple traverses (junctions) of dif-

¹Not known to the authors, an analogous phenomenon, error precession, has been described earlier. Dunlap (1910) reported that when subjects had to syncopate in synchrony with a metronome, the timing errors tended to occur in advance of the next beat. The errors grew systematically until a correction occurred. Dunlap attributed the error precession to a frequency mismatch between stimulus and response, not unlike the 2-oscillator interference model of O'Keefe and Recce (1993). More recent experiments by Chen et al. (2001) demonstrate that timing errors are characterized by a $1/f^2$ type power law dynamics.

ferent routes explored by dead reckoning. Exploration gives rise to omnidirectional (explicit) place cells, representing junctions.

4. Analogously, semantic memories are gradually formed from multiple overlapping episodes with common items (junctions) among the episodes, through which process the temporal context attenuates or disappears.

5. Because creation of maps and semantic memories require interleaving routes and episodes with common junctions, which depends on cross-over rather than elapsed time, consolidation of such knowledge does not have a characteristic time constant.

6. Both semantic information and the analogous maps are eventually transferred from the hippocampal system to the neocortex. This transfer takes place mostly during sleep.

Provided that the above hypotheses are verified, the fundamental conclusion then is that the operations in the hippocampal networks of simple and complex brains are not qualitatively different.

Support for the Proposal

There are two key threads in the above hypotheses. First, maps and semantic memories evolve from dead reckoning exploration and episodes, respectively. Second, the neuronal bases of 1-dimensional travel and map-based navigation are the same or at least strongly related to episodic and semantic memories, respectively. Some of these ideas and the links between them have been expressed implicitly or embedded in specific frameworks previously (Rawlins and Tsaltas, 1983; Kanerva, 1988; Alvarez and Squire, 1994; McClelland et al., 1995; Levy, 1996; McNaughton et al., 1996; Muller et al., 1996b; Rolls, 1996; Solomon and Groccia-Ellison, 1996; Shiffrin and Steyvers, 1997; Wallenstein et al., 1998; Eichenbaum et al., 1999; Lisman, 1999; Samsonovich and Ascoli, 2005).

One-dimensional navigation and episodes

We distinguish between travel along a noncrossing, 1-dimensional line and exploration in 2-dimensional space with travel path junctions (Fig. 3) for two reasons. First, such a distinction appears important to the brain, because cell assembly representation of 1-dimensional travel and 2-dimensional map construction are fundamentally different in the hippocampus, as reflected by the directional firing property of place cells. Second, only navigation with junctional crossings provides graphs and maps of the environment (Muller et al., 1996b).

The simplest form of navigation is moving along a straight line, for example running back and forth on a linear track for a reward. In principle, the same applies for traveling along a spiral or any random route as long as the travel path does not cross previously visited locations. Even in the absence of visible or otherwise sensed landmarks, entorhinal-hippocampal networks can calculate travel distance from the product of the temporal metric of theta oscillation and velocity-correlated changes of firing rate of place cells (McNaughton et al., 1983;

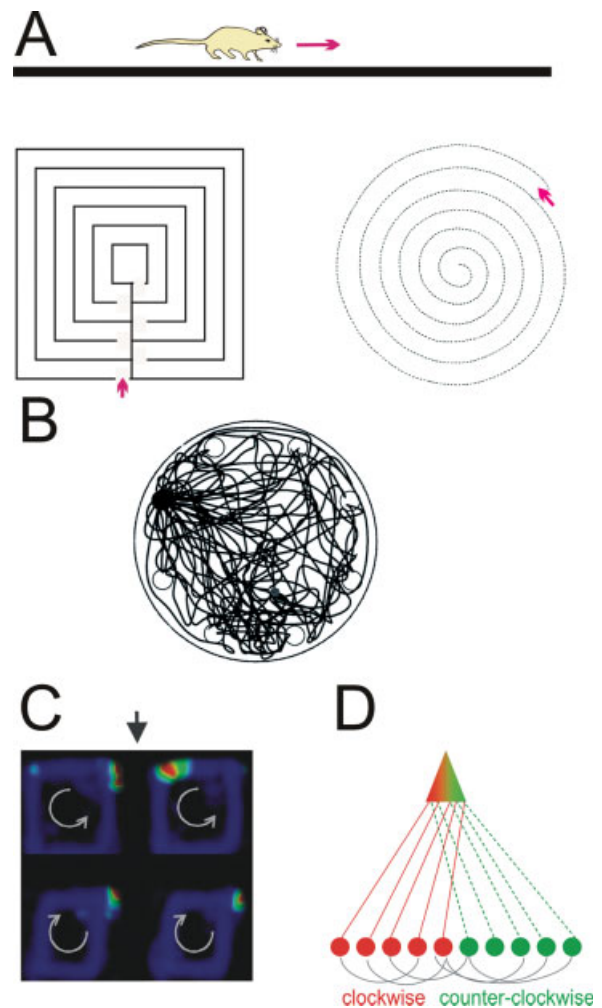


FIGURE 3. Exploration with path crossings (junctions) gives rise to omnidirectional place cells and maps. **A:** Unidirectional (nonjunctional) travel on a linear track, complex maze or spiral maze without visible distant landmarks does not establish junctional landmarks. **B:** During dead reckoning navigation (random walk) multiple path junctions generate landmarks and path-independent map. **C:** Junction cells are under the control of multiple cell assemblies. Example shows a bidirectional place cell in the corner of a rectangular platform (food area), independent of the direction of travel. Long-term potentiation (LTP) of the intrahippocampal connections (arrow) converted the bidirectional place cell (left panels) into a unidirectional cell (right panels). **D:** Hypothetical mechanism of bi- and omnidirectionality. The place cell (triangle) is bidirectional because it is under the control of multiple assemblies. After changing the synaptic weights within the CA3–CA1 matrix, by LTP one set of assemblies (representing counter-clockwise travel) was weakened and became unidirectional. Part B is reproduced from Whishaw and Brooks (1999), Part C reprinted from Dragoi et al. (2003) with permission from Elsevier.

Samsonovich and McNaughton, 1997; Czurkó et al., 1999). The rate modulation is not speed (scalar)- but velocity (vector)-dependent because rate changes in place cell activity during wheel running are direction-dependent (Czurkó et al., 1999). The metric provided by path integration, in turn, can be used to calculate distances among the ordered locations of perceived objects. Longer routes are difficult to encode with self-motion

cues only, because no error correction is available in true dead reckoning navigation (McNaughton et al., 1996). The same applies to the perceived objects. For example, driving to a destination in a new city on a foggy day, given only directions, allows you to trace your way back but does not provide enough information to solve detour problems, find shortcuts or allow you to return to the same destination from another position (O'Keefe and Nadel, 1978; Muller et al., 1996a).

We assume that internal and external cues, when available, are used interchangeably or cooperatively in the brain. Coding of sequential places in a linear (1-dimensional) route is formally analogous to learning sequentially presented or inspected random items in an episodic memory task. To address this hypothesis, below we examine how hippocampal neuronal assembly coding in a 1-dimensional task relates to the internal organization of episodes.

In linearly organized tasks (such as 1-dimensional tracks), hippocampal cell assemblies discharge sequentially, with different assemblies used in runs in the opposite direction: place cells are unidirectional (McNaughton et al., 1983; Muller et al., 1994; Markus et al., 1995; Brunel and Trullier, 1998). The current position of the rat is determined by the most intensely firing cell assembly. In case of CA1 pyramidal neurons, this assembly is anchored to the trough of CA1 pyramidal layer theta, which serves as an attractor for CA1 unit firing (Harris et al., 2002, 2003; Mehta et al., 2002; Buzsáki and Draguhn, 2004). This fluctuating rate–phase relationship is the cause of periodic renewal of activity at theta frequency. If rate changed independent of phase, population (mean) activity would be stationary and no oscillation could be measured in the extracellular field. Given the 10–25 ms life time of hippocampal cell assemblies (Harris et al., 2002), 6 to 9 assemblies can be active in a single theta cycle (Fig. 2). These assemblies represent past, present and future locations. Each assembly is evolving and dissolving over 6 to 9 theta cycles, as reflected by the increasing and decreasing probability of discharge of the assembly members on successive theta cycles and the heavy tails of the place fields. Thus, each assembly is repeated several times while the animal traverses approximately 30–40 cm of distance, which is the size of an average place field (Skaggs et al., 1996; Samsonovich and McNaughton, 1997). Since the rat moves forward about 5 to 6 cm in each theta cycle, parts of each place field are re-represented 6 to 9 times. By this mechanism the maximum firing assemblies at successive theta troughs are activated repeatedly in single cycles with assemblies representing successive positions on the track, thereby “compressing” assemblies in time (Skaggs et al., 1996; Dragoi et al., 2003 SFN Abstract) so that they fire 10–25 ms of one another (Harris et al., 2003). Because of the rules of spike timing-dependent plasticity (Magee and Johnston, 1997; Markram et al., 1997), current and future locations can be bound together in a forward direction in the recurrent CA3 and CA3 to CA1 synapses (Mehta et al., 1997; Dragoi et al., 2003 SFN Abstract).

Distances between successive place fields are believed to be stored by the synaptic strengths between cell assemblies (Muller et al., 1996a; Tsodyks et al., 1996; Jensen and Lisman, 2005).

Although there is no direct proof of this assumption, the time differences between successive assemblies within the theta cycle support this hypothesis (Dragoi et al., 2003 SFN Abstract). The time differences, as assessed by the slope of the phase precession, increase with the size of the field (i.e., with distance between peaks) but are independent of the running speed of the animal or the firing rate of the neurons (Huxter et al., 2003). When the size of the field increases within a single session, the slope of phase precession is commensurately decreased (Ekstrom et al., 2001). These findings are best explained by assuming that time-differences between assemblies at the temporal scale of the theta period correspond to synaptic strengths between cell assemblies, representing sequences of places. Because place representations are brought together into the cycle time of theta, not only directly adjacent, but multiple places, can be linked together by synaptic plasticity. This can occur because the probability of anatomical connections between any two hippocampal cell assemblies in the CA3 recursive system and in the CA3–CA1 connection matrix is similar irrespective of their physical location (Li et al., 1994) and it is the timing rule of synaptic plasticity that functionally connects assembly A more strongly to assembly B than to assembly C in the sequence. In short, the theta “compression” mechanism (Skaggs et al., 1996) and the temporally sensitive plasticity rule allow the formation of not only first order (direct neighbor) but also higher order representations. As a result, the current position is sandwiched in the context of past and future locations in each theta cycle. Thus, in contrast to a simple sequence “chain” (Eichenbaum et al., 1999), the hippocampus forms multiple-level connections, made possible by the large random “synaptic space” of the hippocampus.

To date, it is not clear how time differences, i.e., the hypothesized synaptic strengths between the assemblies, are brought about in the first place. One possibility is that they are formed during hippocampal sharp waves, associated with immobility and drinking/eating at the end of the track, when several-fold larger number of assemblies fire together than during theta (Buzsáki, 1989; Buzsáki et al., 1992; Ylinen et al., 1995; Csicsvari et al., 2000; Samsonovich and Ascoli, 2005).

The above physiological experiments in the rat can be related to observations in humans. Two important principles of episodic free recall are (a) contiguity and (b) temporal asymmetry, referring to the consistent observation that subsequent recall of an item is facilitated by the presentation or recall of another item that occurred close in time to the item just recalled, and that forward associations are stronger than backward associations. These items are not necessarily positionally adjacent (Fig. 2; Kahana, 1996; Howard and Kahana, 1999; Howard et al., 2005). Similar to place sequences on a linear track, sequences of arbitrary items in an episodic task, are essentially unidimensional, so that distant relations correlate with temporal relations (Fig. 2). The difference between rats and humans therefore may lie in the nature of the inputs rather than in the nature of hippocampal computation.

An ideal structure for episode coding and recall is an auto-associator, since free recall is essentially a pattern completion

problem (Marr, 1971; McNaughton and Morris, 1987; Kanerva, 1988; Treves and Rolls, 1994). The asymmetric nature of the strongly recursive CA3–CA3 and CA3–CA1 connections (Li et al., 1994), combined with temporal ordering of cell assemblies and spike timing-dependent plasticity, favor temporally forward associations. Similar to the distance coding on the linear track in the rat, the distance between the items on the list of an episode can be coded by the synaptic strengths among the cell assemblies corresponding to the items (Howard and Kahana, 1999). Since a run on a 1-dimensional track can be conceived as an episode, we may generalize the hypothesis by suggesting that in episodic tasks theta period provides the temporal context, and the theta-compression mechanism supports higher order associations. Theta time compression can also explain how items separated by seconds or longer intervals from each other can be bound together by synaptic plasticity, a problem left unanswered by the chaining hypothesis of episode learning (Eichenbaum et al., 1999). Excitation (“information”) in an autoassociator can move in various directions, albeit not with the same probabilities (Kanerva, 1988). As discussed above, the timing rule of synaptic plasticity functionally connects item A more strongly to item B than to item C in the sequence. Nevertheless, if for some reason item B cannot be recalled, the excitation in the hippocampal autoassociator spreads towards the next best-connected representation, which is C.

In free recall, human subjects repeat items in a later session without explicit cues. For free recall it is the context that serves as a cue. In contrast, rats on a linear track are tested repeatedly while the environmental and idiothetic cues are available. It is primarily these cues that call up the assemblies. Nevertheless, when several cues are removed from the environment, the sequence can remain stable (O’Keefe and Conway, 1978; Muller and Kubie, 1987), due to pattern completion by the hippocampal autoassociator (Samsonovich and McNaughton, 1997), similar to an episodic recall. With environmental cues present, the cues will supervise and affect the direction of activity sequences by initiating a new search in the autoassociator at each theta cycle (Tsodyks et al., 1996; Jensen and Lisman, 2005; Zugaro et al., 2005), similar to cue-guided changes in the story-telling of episodes. Spontaneous or free recall requires that the cell assembly sequences of successive theta cycles are advanced by the content of the previous cycle rather than by external cues. In support of such mechanism in animals, we observed spontaneous changes in firing rate and associated phase precession of place neurons while the rat was running in a wheel with its head staying stationary (Harris et al., 2003). Because environmental and self-motion cues were kept constant, such internally generated sequences can be potentially regarded as neuronal correlates of episodic recall. Finally, as is the case in error-accumulating dead reckoning navigation, episodes with longer sequences are more difficult to encode and recall (Howard and Kahana, 1999). In summary, we surmise that hippocampal networks give rise to cell assembly patterns that are responsible for the behaviorally observed features of episodic memory.

Spatial maps and semantic memory

Place cells in directed (1-dimensional) navigation have unidirectional place fields, determined primarily by the place sequences passed. The unidirectional nature of place fields does not change or increase with extensive exposure of the animal to linear tracks or other 1-dimensional paths. In contrast, place cells may become omnidirectional minutes after the animal is introduced into a 2-dimensional environment and they remain omnidirectional (O’Keefe and Nadel, 1978; Muller and Kubie, 1987; Wilson and McNaughton, 1993; Muller et al., 1994; Markus et al., 1995; Frank et al., 2005). What is the cause of such a striking difference? Below, we consider that omnidirectional cells emerge from unidirectional cells (for similar arguments, see Kanerva, 1988; Brunel and Trullier, 1998; Eichenbaum et al., 1999) as a result of 2-dimensional exploration. Dead reckoning exploration is essentially a random walk-type of navigation with frequent stops (Mittelstaedt and Mittelstaedt, 1980; Golani et al., 1993), during which the paths of navigation often cross. Exploration is a primary drive in animals even when positional cues provide immediate shortcut solutions (Whishaw and Brooks, 1999). As a result, these road intersections and the associated place cells will be tied to multiple routes or episodes. The landmark junctions are critical for correcting the positional errors, which accumulate during 1-dimensional navigation and are essential for the construction of a map (Muller et al., 1996b; Samsonovich and McNaughton, 1997; Mittelstaedt, 2000). Previous computational modeling suggested that omnidirectionality of place cells is created at these navigational junctions (Sharp, 1991; Brunel and Trullier, 1998; see also Eichenbaum et al., 1999). The establishment of such junctions and corresponding neuronal connections may therefore indicate the emergence of a map. The junctions and associated bi-, multiple- or omnidirectional place cells serve as an error-correction or calibration mechanism, updating the animal’s position. To generate a *full* map and a corresponding neuronal graph type representation of an environment (Muller et al., 1996b; Samsonovich and McNaughton, 1997), each place should be visited by dead reckoning exploration (with vision available, eye movement “visits” to explore places may be sufficient), so that sufficiently large numbers of navigational junctions and corresponding omnidirectional cells are generated. Possession of a map presupposes that you (or someone else) have already visited all locations shown on the map. After exploration, the map becomes an embodiment of the spatial relations among objects. It allows for the computation of positions, distances, and angles among landmarks and assists effective navigation even without locomotion. Once a map is generated, navigation becomes a simple trigonometric problem, without the requirement of a temporal context (O’Keefe and Nadel, 1978; Burgess and O’Keefe, 1996; Burgess et al., 2002). In short, dead reckoning exploration is a prerequisite for map-based navigation (Whishaw and Brooks, 1999), which in turn allows for the creation of omnidirectional, temporal context-free place cells in the entorhinal–hippocampal networks. It follows that 1-dimensional and 2-dimensional (map-based) navigations

are interchangeable only *after* a map has been established because map-based navigation *evolves* from 1-dimensional crossing routes. These two forms of navigation may represent a continuum rather than exclusive mechanisms. Without omnidirectional place cells, the default navigation strategy is dead reckoning. Although direct experimental evidence is still lacking to fully support the above scenario, the examples below are compatible with the hypothesis.

In the radial arm maze and plus maze neurons are typically unidirectional in the arms (McNaughton et al., 1983; Muller et al., 1994). When rats are trained to run on a rectangular path, bidirectional place cells are occasionally observed at the corners with food locations (Fig. 3; Markus et al., 1995; Dragoi et al., 2003), perhaps because the rat spends more time at these locations and changes directions more often. Moreover, consummatory behaviors are associated with sharp wave bursts that may facilitate omnidirectional binding. On linear tracks, bidirectional cells are rare but they can emerge if objects block the path (Battaglia et al., 2004), thus initiating exploration and sideways movements. These findings suggest that directionality of place cell firing is not simply due to current environmental and idiothetic cues but depends on the historical relationship between such factors and the animal. Nevertheless, further experiments are required to clarify the relationship between unidirectional and omnidirectional place cells and their representations. At the network level, omnidirectionality is an indication that the neuron is part of multiple place cell assemblies (Fig. 3) and serves as a “hub” in the network, which can be accessed by multiple specific routes. Similar mechanisms may be exploited elsewhere in the brain. For example, dead reckoning navigation-induced omnidirectionality of hippocampal place cells is analogous to the high incidence of scanning eye movements at “significant” aspects of the visual scene and cells in the pinwheel centers of the primary visual cortex (Bonhoeffer and Grinvald, 1991; Sharma et al., 2003).

What is the relation between 2-dimensional map-based navigation and semantic knowledge? We suggest that the link is the creation of omnidirectional neurons (graph junctions or hubs) in the hippocampus and EC. The omnipotentiality of a place cell can be taken as evidence that the rat approached its place field from multiple directions. The omnipotentiality is also an indication that the cell is a part of a multitude of specific assemblies and its activation no longer depends on a unique temporal sequence of cell assemblies. In other words, omnidirectional place cells no longer require a temporal context. Applying the same idea to humans, multiple episodes with common junctional items can free the common item from its context(s) (e.g., Shiffrin and Steyvers, 1997). For example, meeting someone with an unusual name, such as György, for the first time, is an episode. However, after learning about individuals with the same name (e.g., György Ligeti, György Konrád, György Kepes, György Lukács, György Kurtág, György Ránki), the six-letter item loses its episodic connections and assumes a semantic meaning: a name.

Such “one memory, two retrieval mechanism” view on the episodic–semantic distinction is a long-debated issue in human psychology (cf. Nadel and Moscovitch, 1997; Buzsáki et al.,

1997; Meeter and Mutte, 2004). Computer models of categorization that learn via changes of connections work essentially in the same manner (McClelland et al., 1995). Neurons of an omnidirectional or “explicit” assembly collectively define or symbolize the “meaning” of an item. Such explicit, higher order representation is invariant to the conditions that created it. This framework is therefore different from the relational theory (Wallenstein et al., 1998; Eichenbaum et al., 1999), since the emphasis is not on first-order temporal, spatial, or other relations per se, but on the explicit nature of the representation. More importantly, the parallel is between map-based navigation and semantic memory rather than between cognitive mapping and episodic memory.

Exploration of a small enclosure (i.e., visits to every part with multiple crossings) may require only a few minutes, leading to the rapid establishment of omnidirectional place cells and a map (Wilson and McNaughton, 1993). Driving through the same landmarks of a city from different directions, on the other hand, may occur at arbitrary intervals, which can be days or years, depending on how often you visit the city. Similarly, the time interval between interleaving episodes may be a minute or decades, and the transition between episodic and semantic information by way of omnidirectional cells can ensue only if the previous episode(s) has been retained and recalled in the entorhinal–hippocampal system at the time of the new episode(s). From this perspective, consolidation of semantic information does not have a universal, characteristic temporal gradient (Squire, 1992; Squire et al., 1993). Maturation of semantic knowledge requires simultaneous (re)presentation of old and new episodes, a process that may be facilitated by systematic exploration (e.g., targeted reading or experimentation) or by chance. The crucial requirement for the conversion of semantic knowledge from overlapping episodes is not elapsed time or some slow molecular biological process but the occurrence of sufficient numbers of episodes with a common junction. Episodes and semantic memories are therefore sequential, although interleaving, rather than parallel (Nadel and Moscovitch, 1997). Semantic memories do not suddenly emerge but evolve in steps, depending on the availability of new episodes with common junctions.

Once formed, storage of landmark-guided maps and explicit semantic information may not require the large combinatorial associational network provided by the hippocampus. Furthermore, while 1-dimensional navigation and episodic memory fully relies on the metric of theta oscillation and its time-compression mechanism, linking episodes together and making the links stronger may occur either in the waking state or during the “off-line” (nontheta) states of entorhinal–hippocampal networks (Buzsáki, 1989). In the absence of theta-associated behaviors, a truly self-organized pattern, called sharp wave burst, emerges in the recursive networks of the CA3 region and sweeps through the entire hippocampal–entorhinal system at irregular intervals (Buzsáki et al., 1983; Buzsáki et al., 1992; Chrobak and Buzsáki, 1994; Ylinen et al., 1995). The main physiological difference between theta oscillations and sharp wave bursts is the content of the two patterns. During a theta

cycle < 1% of pyramidal cells discharge, whereas up to 16% of the pyramidal cells in the CA3–CA1–subicular complex–EC axis may participate in sharp wave bursts (Chrobak and Buzsáki, 1994, 1996; Csicsvari et al., 2000). Importantly, some of the same neurons and neuron sequences are replayed during sharp wave bursts as during the previously rehearsed episode(s). However, many more episodes are compressed into the 150 ms sharp wave event than in several seconds of theta (Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996; Kudrimoti et al., 1999; Nádasdy et al., 1999; Lee and Wilson, 2002), creating opportunities for crossing episodes at the time-scale of synaptic plasticity. The synchronous sharp wave bursts may also serve to transfer solidified maps and semantic information from the hippocampus to the neocortex (Buzsáki, 1989; Wilson and McNaughton, 1994; McClelland et al., 1995; Lörincz and Buzsáki, 2000). For these physiological reasons, the nontheta states of the hippocampus are believed to be critical for consolidation of declarative memories (Maquet, 2001; Hobson and Pace-Schott, 2002). Sharp wave events may link together episodes not available simultaneously in the waking brain, and thereby facilitate creative knowledge (Gais and Born, 2004; Wagner et al., 2004).

A prediction of the presented framework is that episodic memory relies on the intact entorhinal–hippocampal system (Nadel and Moscovitch, 1997; Nadel et al., 2000; Tulving, 2002) generating theta oscillations. Because maps and semantic memories depend on dead reckoning exploration and episode encoding mechanisms, respectively, impairment of hippocampal functions inevitably interferes with the emergence of such new knowledge (Bayley and Squire, 2005). On the other hand, once maps and semantic information are solidified and transferred to perirhinal and hitherto undisclosed neocortical destinations, part of that knowledge base can be retained even in the absence of theta oscillations or the hippocampus (Nadel and Moscovitch, 1997; Teng and Squire, 1999; Corkin, 2002; Manns et al., 2003; Frankland and Bontempi, 2005; Winocur et al., 2005). However, novel links among items stored in disparate neocortical regions and new ones will not be possible without the large combinatorial space of the hippocampus and its theta-compressing mechanism. It is acknowledged though that, to date, empirical support for the conjectured relationship between episodic and semantic memories and the contribution of hippocampal and parahippocampal regions is not particularly strong and require further exploration (Vargha-Khadem et al., 1997; cf. Bachevalier and Vargha-Khadem, 2005).

Theta Rhythm of Navigation

Now we are in a position to define theta oscillations from the brain's point of view. Experiments with single cells and cell assemblies have revealed that the quantal theta periods are necessary for chunking events and places together in time so that the participating neuronal assemblies can be tied together in a proper temporal and spatial context. The temporal compression of cell assemblies in combination with the rules of synaptic plasticity allows for activity to jump from one assembly

sequence to the next. Thus, from the perspective of the brain, the theta oscillation is an essential temporal organizer, a metric that relates synaptic strengths to the changes in the outside world. Theta is the temporal means of navigation in both neuronal space during episodic memory and real space during self-motion. Given its basic physiological role in hippocampal function, perhaps it is not surprising why it has been associated with so many different overt and covert behaviors (Fig. 1).

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