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Analysis and Modeling of Coordinated Multi-neuronal Activity

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Preface

A study of dynamics of neural assemblies and spike sequences is crucially important in understanding brain functions. For example, memory is an important brain function for both humans and animals. Our everyday activities are entirely dependent upon memory. The ability to maintain good memory also becomes increasingly important because our life expectancy is getting longer. Understanding how memory is encoded and maintained in the brain is therefore an important issue in the field of neuroscience.

Since the discovery of amnesia in the patient H.M., the representation and consolidation mechanisms of hippocampus-dependent memory have been studied extensively. The investigation has benefitted not only from human studies but also from animal studies. In animal studies, multielectrode recordings have become an increasingly widespread tool in electrophysiology, enabling the recording of spiking activity from tens to hundreds of neurons simultaneously. Since information in the brain is processed by the exchange of spikes among neurons, a study of such group dynamics is extremely important in understanding hippocampus-dependent memory.

The spike patterns and local field potentials (LFPs) have been analyzed by various statistical methods. These studies have led to important findings of memory information processing. For example, reactivation of behaviorally induced neural activity has been suggested to play an important role in memory consolidation. It has also been suggested that coordinated interaction between hippocampal and cortical activity may facilitate the consolidation of hippocampus-dependent memory. The first goal of this book was to provide a state-of-the-art finding of memory information processing through the analysis of multi-neuronal data.

Understanding an underlying mathematical principle of information processing by coordinated neural activity can be further facilitated by computational modeling. In other words, an entire picture of the hippocampus-dependent memory system would be elucidated through close collaboration among experiments, data analysis, and computational modeling. Not only does computational modeling benefit the data analysis of multielectrode recordings, but it also provides useful insight for future experiments and analyses. The second goal of this book was to provide a state-of-the-art review of the computational modeling of hippocampus-dependent memory.

The book was aimed at providing comprehensive introduction regarding this very attractive and rapidly progressing field of research. The intention was not to provide a definite textbook, but rather, to provide the state-of-the-art review of the progress over the last two decades. We aimed to provide readers with a comprehensive introduction on what aspects of sequential phenomena are understood, what aspects have yet to be understood, and what questions and approaches are necessary to answer questions that remain unresolved on this topic.

The book is composed of five sections: (1) method of multielectrode recording, (2) coordinated neural activity in rodent hippocampus and associated areas, (3) cortical neural activity and interaction with the hippocampus, (4) memory reactivation in humans, and (5) computational modeling of coordinated neural activity. Chapters were ordered in a coordinated fashion. At the same time, each chapter was intended to be self-contained so that it would allow readers to access the contents without consulting other chapters.

I would like to thank Ann Avouris, the former Springer Senior Editor of Neuroscience, for providing us this wonderful opportunity. I would also like to thank Diane Lamsback, the Springer Developmental Editor, for her enormous assistance and support in making this book happen. In addition, I would like to thank Simina Calin, the present Springer Senior Editor of Neuroscience, and Michael Koy, the Springer Project Coordinator, for their continued encouragement. Finally, I would like to thank all the authors who have contributed their outstanding chapters to the book.

Lethbridge, AB, Canada Masami Tatsuno, PhD

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Part I
Method of Multi-Electrode Recording

Chapter 1
Techniques for Large-Scale Multiunit Recording

Hendrik W. Steenland and Bruce L. McNaughton

Abstract Single and multineuron extracellular electrophysiology has proven to be one of the most effective techniques to explore the behavior of neurons in freely behaving animals since the 1950s. Electrode technology has evolved over the past 60+ years, with improvements in electrode profiles, configurations, biocompatibility, and driving mechanisms leading to substantial gains in the isolation of single neuron activity and increases in the possible number of simultaneously recorded neurons. Moreover, combining electrode recording and nanotechnology with pharmacological and optogenetic manipulations are expected to bring about a new age for precise recording and manipulation of neurons. In this chapter we review the technical developments of extracellular electrophysiology in freely behaving animals, with special emphasis on the development of microelectrode technology.

Keywords Microelectrode • Hyperdrive • Electrophysiology • Extracellular • Freely behaving

Extracellular Recording

Deriving the Extracellular Action Potential

The extracellular action potential is derived from currents flowing across the resistive extracellular medium between charged locations on the cell surface. The voltage drop between these locations is a consequence of ion conductance, most notably voltage-sensitive sodium and potassium channels. The primary advantage of extracellular recording is that neural activity can be recorded without puncturing the cell membrane, thus making recordings more stable over long time periods. Also, multiple neurons can be often detected on the same extracellular probe, capturing more accurately the population dynamics. One disadvantage is that the extracellular

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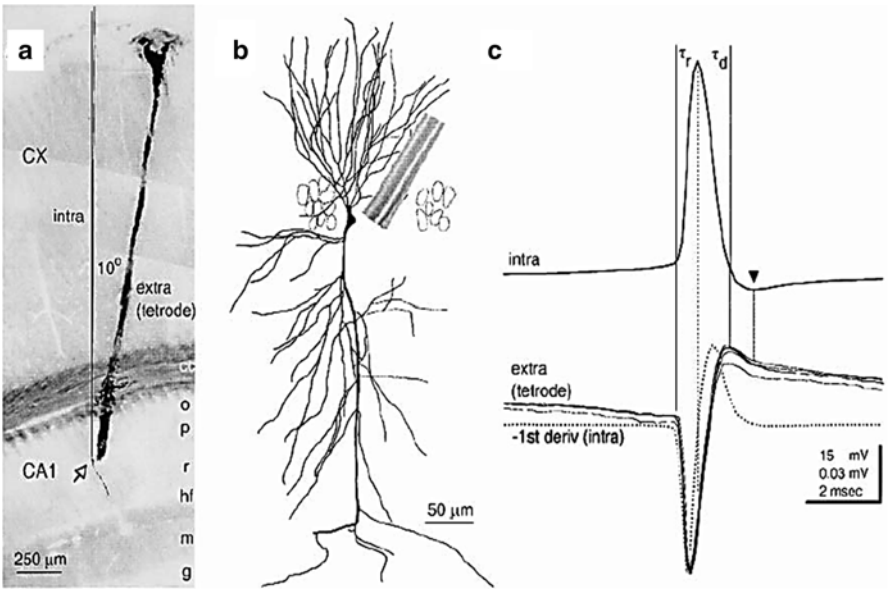

Fig. 1.1 Deriving the extracellular spike waveform. (**a**) Histological representation of an intracellular electrode and an angled extracellular tetrode recording (marked by angled blood stain) from the same cell in the CA1 pyramidal layer (*open triangle*) of an anesthetized rat. Intracellular electrode is drawn on the figure as a *vertical line*. (**b**) Camera lucida reconstruction of the intracellular recorded neuron under study. Tetrode is drawn adjacent to neuron soma. (**c**) Comparison of intracellular (*top*) and extracellular waveforms (*bottom dark line*). Note taking the negative first derivative of the intracellular waveform approximates the early components of the extracellular waveform. (**a**, **b**, and **c**) Reprinted with permission from Henze DA, Borhegyi Z, Csicsvari J, Mamiya A, Harris KD, Buzsaki G. Intracellular features predicted by extracellular recordings in the hippocampus in vivo. J Neurophysiol. 2000;84(1):390–400

potentials tend to be in the range of ~100 µV, two orders of magnitude less than transmembrane potentials. This poses challenges due to both intrinsic noise of the recording system, typically in the low microvolt range [1], and "far-field" noise due to signals from other neurons. The latter can be partially overcome with specialized methods to isolate the signals from individual neurons including careful positioning of fine-tipped electrodes close to individual cells, "triangulation" of neuron signals by recording simultaneously at several nearby points in space [2], and application of algorithms and statistics to separate neurons based on their waveform features [3, 4].

The relationship of the extracellular potential waveform to transmembrane potentials (i.e., membrane currents) has practical implications for sorting multiunit activity and identifying neuronal classes (e.g., bursting cells). To this end, pioneering electrophysiologists carried out simultaneous intracellular and extracellular recording from the same cell [5]. More recently, Henze et al. [6] conducted simultaneous intra- and extracellular recording of hippocampal CA1 neurons in an anesthetized rat preparation. Figure 1.1a, b illustrates a sharp glass electrode penetrating a pyramidal CA1 cell for intracellular recording with an adjacent tetrode [7–9] to

record the extracellular spike discharge. As indicated in earlier studies [10, 11], it was found that the negative first derivative of the intracellular signal closely approximates the detected extracellular waveform (Fig. 1.1c). Note that the negative going phase of the extracellular signal is a consequence of inward current near the soma due to altered gNa^+ (sodium conductance). It can also be appreciated that the time course of the first negative peak of the extracellular waveform closely matched the negative first derivative of the intracellular signal corresponding to depolarization. In addition, it was shown that changes in action potential amplitudes due to cell bursting could be observed at the extracellular level.

Equivalent Electrical Circuit for Recording Extracellular Potentials

We can use electrical circuits ("equivalent circuits") (Fig. 1.2) to represent the extracellular recording configuration. The first consideration is the recording configuration. Typical high-quality in vivo electrophysiology requires a minimum of three connections to the animal body. The first connection is the ground lead which is used as a return line for the headstage power. Additionally, when the final termination point of this ground is connected to a Faraday cage, which encapsulates a preparation, 60 Hz line noise can be dramatically reduced. The remaining two electrodes are the recording and the reference electrodes. The recording electrode can be positioned near cells of interest to monitor changes in extracellular potential. The reference electrode is often placed in a region of low cell density such as a fiber bundle, minimizing signals from other neurons but hopefully recording the same "far-field" noise as the active electrode. This noise can include 60 Hz mains external noise or internally generated noise such as heartbeats or masseter chewing artifacts. In conjunction with a differential amplifier, the reference electrode is used to subtract common mode signals (i.e., noise) from the signals of interest (i.e., local action potentials). Accordingly, an ideal reference electrode would record the same undesired signals as the active electrode [12, 13].

To record from neurons in freely behaving animals, signals are usually buffered with a unity gain (1×) headstage to increase the electrical current while maintaining the signal voltage (hence, 1× gain). This increase in signal current reduces the impact of interfering currents generated in the tether leads. These interfering currents are generated as a consequence of electromagnetic fields (e.g., from AC power sources) and cable flexion, while the signal current is carried from the headstage to the amplifier. In addition, the headstage requires very high input impedance (Z value) to prevent it from dramatically influencing the signal being sampled [14] and should be located as close to the signal source as possible. Since electrodes are not protected on the input side of the headstage from noise pickup, they should be protected from mechanical vibration.

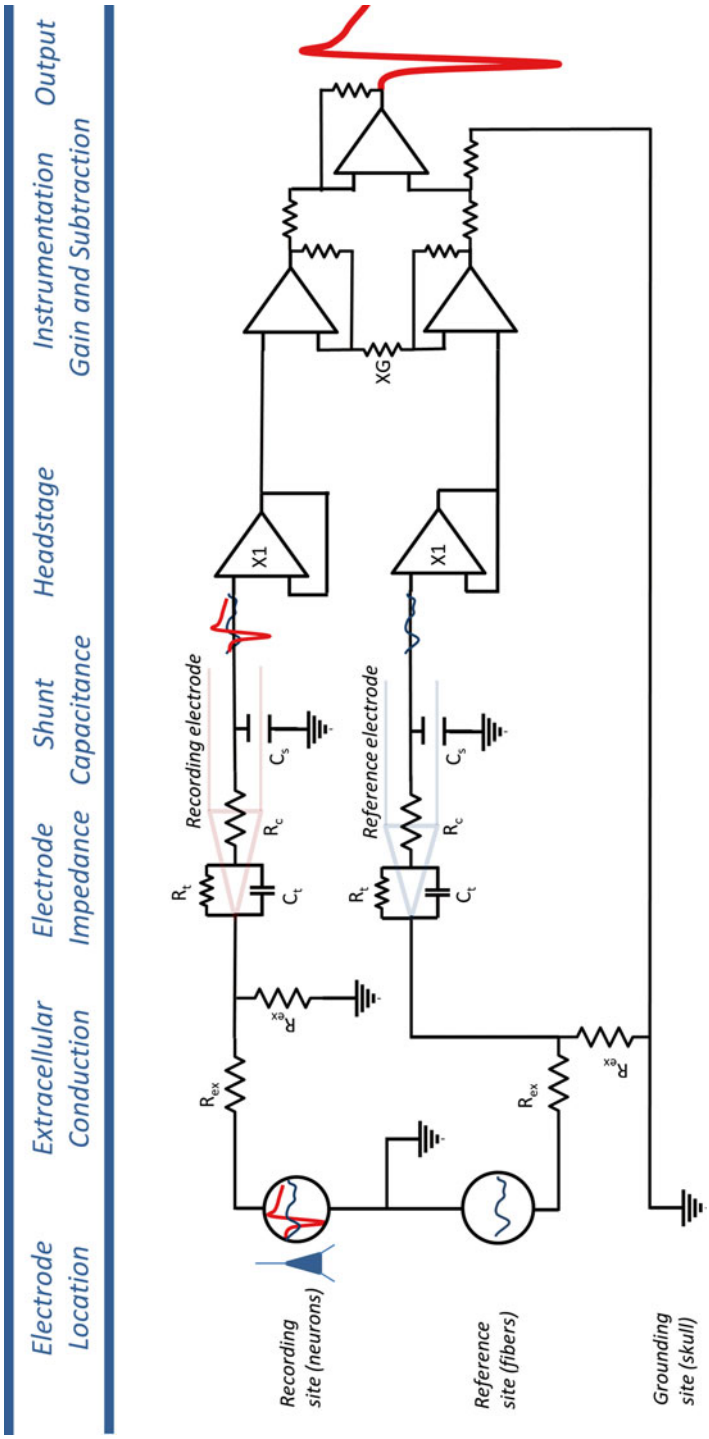

Fig. 1.2 Equivalent circuit for extracellular spike recording. Generally, a minimum of three contacts are made to the subject, including a recording, reference, and ground electrodes. Changes in extracellular ion concentrations are transmitted across the resistance (R_{ex}) of the extracellular space to the recording and reference electrode tips. This signal must interface with the electrode tip through its impedance (resistance of tip R_t and capacitance of tip C_t). Once the charge has passed the electrode tip, some of the signal is lost due to dissipation across the capacitance of the electrode insulation. The resistance of the electrode material is denoted by "Rc". The signal travels to the headstage, where the voltage is held constant (X1) but the current is amplified and therefore protected (or buffered) from environmental interference. The signal is then sent to a differential (instrumentation) amplifier that subtracts out the common components between the two signals (presumably background noise) to purify the signal of interest. This amplifier also adds a degree of gain (XG) so that the signal range can match that of the analog to digital conversion (not shown)

The Extracellular Recording Volume

Extracellular currents are generated whenever there are voltage differences between two points on a neuron, such as when there is a spike generated at the soma or when excitatory synapses are activated on a dendrite. These points of different potential are commonly referred to as current sources (local positivity) and sinks (local negativity). Because the extracellular fluids are a passive, resistive medium, these currents result in extracellular potential fields relative to a remote neutral (ground) point. For elongated, asymmetric cells, like typical neurons, these potential fields resemble (approximately) a simple dipole field, because the currents flow in loops around the cell (Fig. 1.3a). Thus, the sign of the potential at a particular point in time at a given point along the neuron depends on whether current has depolarized the cell at that spatial location, leaving a net negative charge outside the cell. Moreover, the magnitude of the dipole at a particular point depends on the voltage associated with the local current density relative to a reference point. The current decreases proportionately to the inverse square of the distance from the dipole [15, 16], and in general, the greater the distance between the points of different potential (dipole separation), the further the current spreads. Thus, at a given distance, larger fields tend to be generated by cells with longer dendrites. For further discussion on the field potentials and current source density, see Leung [17].

How much does the extracellular signal decrease with distance from its source? Rosenthal [18] estimated the extracellular voltage-distance relationship to be represented by the decay function 100 mV/(x)μm, where x is the distance from the neuron. At 250 μm distance from a cell body, one would expect a 400 μV signal. By contrast, voltage estimates based on data from the hippocampus, while following the same decay trend, are much lower. For example, Henze et al. [6] found that recordings from CA1 pyramidal cells, within a 100 μm radius, tended to be 60 μV or less with tetrodes, much less than that estimated by Rosenthal. Suffice it to say that there is a strong decline in extracellular amplitudes as the recording electrode is moved away from the neuron or source.

How many neurons can an extracellular electrode detect? The potential number of neurons in a specific volume of tissue can be compared to the actual number of neurons recorded. Henze et al. [6] argued that since the density of neurons in CA1 hippocampus is 300,000 cells/mm^3 [5], if the recording volume was a cylinder of 50 μm radius and height of 60 μm, then potentially 141 neurons should be recorded on one electrode (Fig. 1.4). For the motor cortex, assuming a density of 30,000/mm^3 [19] for the cortical cells, one would expect a comparable volume of 14 recordable neurons. Henze et al. [6] argued that their discrepancy with the actual number of neurons might be due to the fact that a large percentage of cells may not have sufficiently high spontaneous activity. Another possibility is that damage to tissue could reduce the viable recording population either by killing some neurons or by changing the pathways of current flow. Finally the possibility exists that a tortuous (non-isotropic) path taken by the extracellular signal to reach the electrode impacts the number of recordable cells.

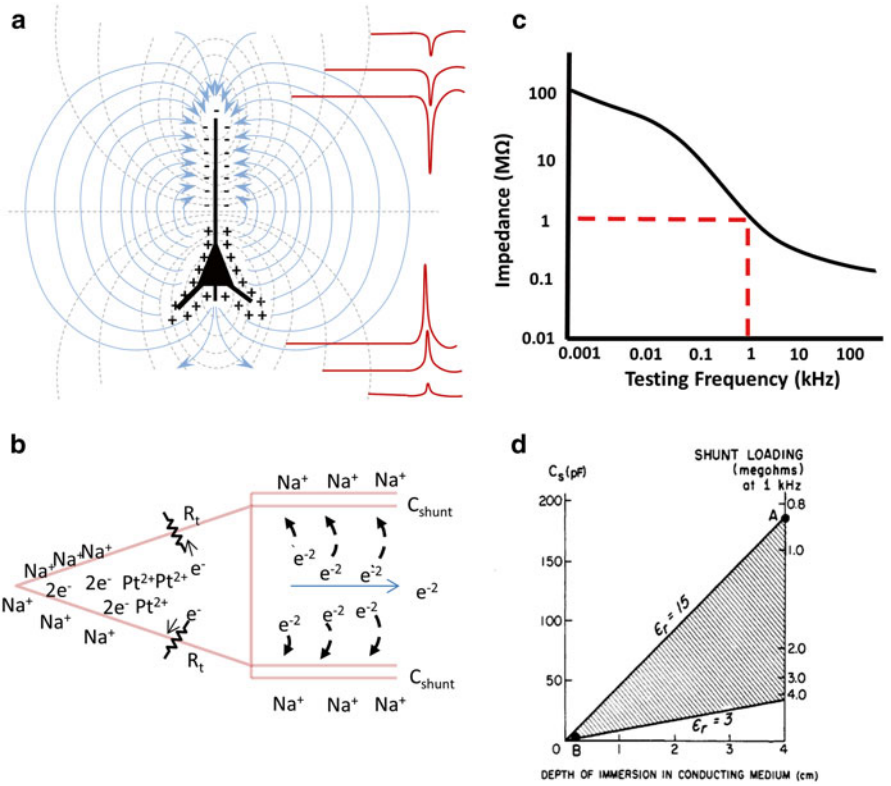

Fig. 1.3 Electrode-electrolyte interface. (**a**) Dipole representation of pyramidal neuron. Current is represented by *solid lines* traveling from source (+) to sink (−) in the extracellular space. Equipotential regions are represented by *dashed lines. Red lines* represent theoretical action potentials recorded at different distances from the source or sink. Signal strength decays with distance from the source and sink regions. (**b**) Theoretical illustration of the electrode-electrolyte interface. When the electrode is interfaced with the extracellular medium a bilayer forms between the electrode (e^- electrons) and electrolyte (Na^+). This forms the capacitive component of the electrode impedance and is responsible for the charge transfer in polarizable electrodes (note, other electrolytes have been excluded for simplicity). The resistive (R_t) component of the electrode impedance can also permit charge transfer. Shunt capacitance (C_{shunt}) acts to dissipate the charge transfer to the recording equipment if the insulation is insufficient. (**c**) Electrode impedance of a metal electrode as a function of frequency. Note high-impedance electrodes (>100 k**Ω** at 1 kHz) are optimized for high-frequency signal detection. *Red dotted lines* indicate typical impedances of the electrode before electroplating measured with a BAK impedance meter at 1 kHz. With kind permission from Springer Science + Business Media: Medical and Biological Engineering, Glass-coated platinum-plated tungsten microelectrodes, 1972, 662–72, Merrill EG, Ainsworth A. (**d**) Estimated shunt capacitance (C_{shunt}) for two different electrode insulations (varnish, dielectric $\epsilon_r = 3$, and solder glass, dielectric $\epsilon_r = 15$) in two different solutions (saline and mineral oil respectively) at different emersion depths in their respective mediums. The right-hand ordinate is a plot of the shunt impedance to ground or the impedance to signal loss. Electrode with a low dielectric insulation and insulated by mineral oil has the least signal loss. Thus according to this plot, shunt capacitance may only become a problem if the immersion depth in the brain is deep (e.g., >4 cm) and insulation is not optimized. © 1968 IEEE. Reprinted, with permission, from Robinson DA. Electrical Properties of Metal Microelectrodes. Proceedings of the Institute of Electrical and Electronics Engineers. 1968;56(6):1065–71

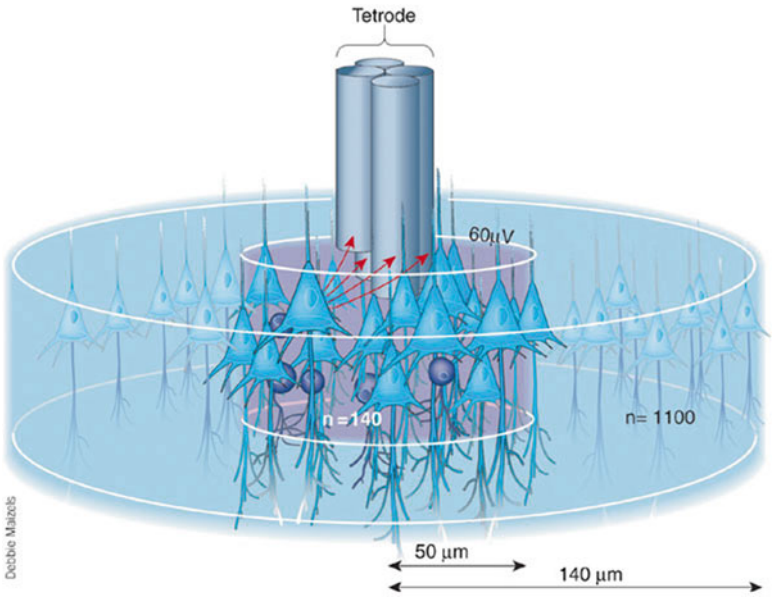

Fig. 1.4 Extracellular recording volume. Estimated number of potentially recordable CA1 neurons in the vicinity of a tetrode. One hundred and forty neurons of greater than 60 **μ**V should potentially be recorded within a 50 **μ**m radius (*purple volume*) of the tetrode. Reprinted with permission from Macmillan Publishers Ltd: Nature Neuroscience, Buzsaki G, Large-scale recording of neuronal ensembles, 7(5):446–51, copyright 2004 [98]

The extracellular field is composed of contributions from "dipoles" from numerous neurons, depending on local neural density and firing rates. This creates the complication that many neurons may be of the same type and may therefore generate similar action potential waveforms. An additional complication arises when spikes from two or more nearby neurons overlap in time; their extracellular potential waveforms summate, making the isolation of individual waveforms essentially impossible. Therefore, the traditional basis for extracellular "single" unit recording has been to select neurons by placing a fine-tipped electrode close enough to a particular neuron in a field of neurons. Because of this proximity the individual voltage contribution of that particular neuron will be greater than those in the far field (a benefit of the dipole inverse square function); however, such selectivity is difficult and renders the signal much more sensitive to slight movements of the electrode relative to the neuron (a negative consequence of the inverse square function, since the rate of change of signal with distance is larger closer to the origin).

Electrode-Electrolyte Bilayer

When electrodes are inserted into electrolyte or extracellular solution, cations and anions are thought to form an electrode-electrolyte interface termed a bilayer [20, 21] (Fig. 1.3b). Electronically this bilayer can be modeled as a combination of

resistance and capacitance components, which is collectively known as impedance (inductive component of impedance is not discussed). Impedance is a measure of the opposition to an alternating current (AC) flow. This concept is especially important, as the electrical currents in and around cells can also be considered alternating currents changing over timescales of about a millisecond. If this bilayer is formed, how then does current pass into the electrode to be picked up by the headstage? As we will see, whether or not an electrode is easily oxidized will determine whether neurons are recorded via capacitive discharge or direct conductance through the resistive surface of the electrode tip.

Polarized Versus Nonpolarized Electrodes

Theoretically two types of electrodes exist, those that are polarizable and those that resist polarization [20]. Ideally a perfectly polarizable electrode displaces current through loading and unloading the electrode interface capacitance [20]. The platinum electrode is a good example of polarizable electrode. By contrast, nonpolarizable electrodes pass current directly through the electrode-electrolyte interface [20] via oxidation-reduction reactions. The Ag/AgCl electrode is a good example of a nonpolarizable electrode. Accordingly charge displacement (for polarizable electrodes) or true charge transfer (for nonpolarizable electrodes) would occur when an electrode is placed near a source or sink of a dipole generated by a neuron or set of neurons during electrochemical changes associated with action potential generation (i.e., conductance of K^+ and Na^+).

The recorded electrode tip impedance varies with the AC frequency used to test the electrode [20, 22] (Fig. 1.3c), with high frequencies experiencing less impedance and low frequencies experiencing more opposition to current flow. This is particularly important since high-impedance electrodes are used to measure high-frequency action potentials. However, this feature may make these electrodes less suitable for recording local field potentials, particularly because of the high-pass filtering properties of the electrodes. Low frequencies tend to load and saturate the electrode tip capacitance and restrict further charge transfer to the headstage. However, this may only affect signal amplitude when microelectrodes are used in combination with low-input-impedance headstages (in the <40 MΩ range) [13]. By contrast, nonpolarizable electrodes tend to be good at recording low-frequency potentials since charge is transferred directly to the recording equipment. An additional property of electrodes is that as they are dipped deeper and deeper into electrolyte or the brain, the impedance appears to drop [12] (Fig. 1.3d). This phenomenon is actually a consequence of shunt capacitance C_s along the shaft of the electrode [12]. Indeed, there is actually charge dissipation between the metals of the electrode across the electrode insulation to the extracellular space and to the ground. An obvious method to counteract this is to increase the quality of insulation with a low dielectric (low permittivity).

Chronology of Metal Microelectrode Development

Single and Multiconductor Electrodes

Glass microelectrodes filled with electrolytic solution preceded the invention of the metal microelectrodes for recording from single neurons and probably influenced the use of glass as an insulating material early in the development of wire microelectrodes. Metal electrodes appeared superior for long-term in vivo recording because they were strong and their conductor was metal rather than an ionic solution. The parameters which early physiologists were trying to optimize were as follows: low electrical impedance to minimize noise pickup, a small tip diameter to isolate single neurons, and sufficient rigidity to prevent breakage during the insertion into the nervous system [23]. Today, we would expand this list to include biocompatibility and stability of signal over long periods of time. Moreover, the ability to separate one neuron from a background of neurons was of essential interest for early electrophysiologists, since algorithms to sort neurons had yet to be invented. Figure 1.5 shows a chronology of the major microelectrode developments which will subsequently be discussed.

In 1951, Weale [23] heated a glass capillary tube and pulled, drawing out an insulation for an electrode. He then fed a fine silver wire down the tube to produce a tip at the end of the electrode. A similar method was used by Svaetichin [24] who pulled molten silver solder into a glass capillary to produce the electrode tip. Subsequently, Dowben and Rose [25] developed a low-impedance electrode by a similar method composed of a finely drawn capillary tube with a 50 % tin/50 % indium core. Electrodes were able to record deep thalamic neurons with amplitudes as high as 1.2 mV in a cat model. In 1959, Gesteland et al. [26] reported their methodology for constructing the Wood's metal electrode. Wood's metal is composed of bismuth, lead, tin, and cadmium and has a very low melting temperature (~70 °C). Gesteland et al. [26] pulled a glass capillary to a fine tip and forced a piece of Wood's metal wire down the center of the capillary. When the shank of the pipette tip was heated with a hot plate, the Wood's metal wire melted at one end, and it could be pushed from the back, along the capillary to the end, to form the tip of the electrode.

Probably, one of the most famous early microelectrodes is the lacquer-coated tungsten microelectrode used by Hubel [27]. Hubel's electrode was designed for the specific purpose of recording chronically from minimally restrained cats. The tungsten electrode was mainly selected for its durability. This durability permitted Hubel to produce sharp-tipped tungsten electrodes through electrolytic sharpening and also permitted passage of the electrode through the dura mater. With these electrodes, units were isolated ranging from 0.5 to 10 mV for extracellular recording and could be recorded for up to an hour in minimally restrained cats. Subsequently, Green [28] developed a stainless steel electrode which had the advantage of lower noise when compared to tungsten electrodes and could be used to mark the electrode site with deposits of iron, followed by histological verification with a Prussian blue reaction. Similar to those of Hubel, these electrodes could sometimes record

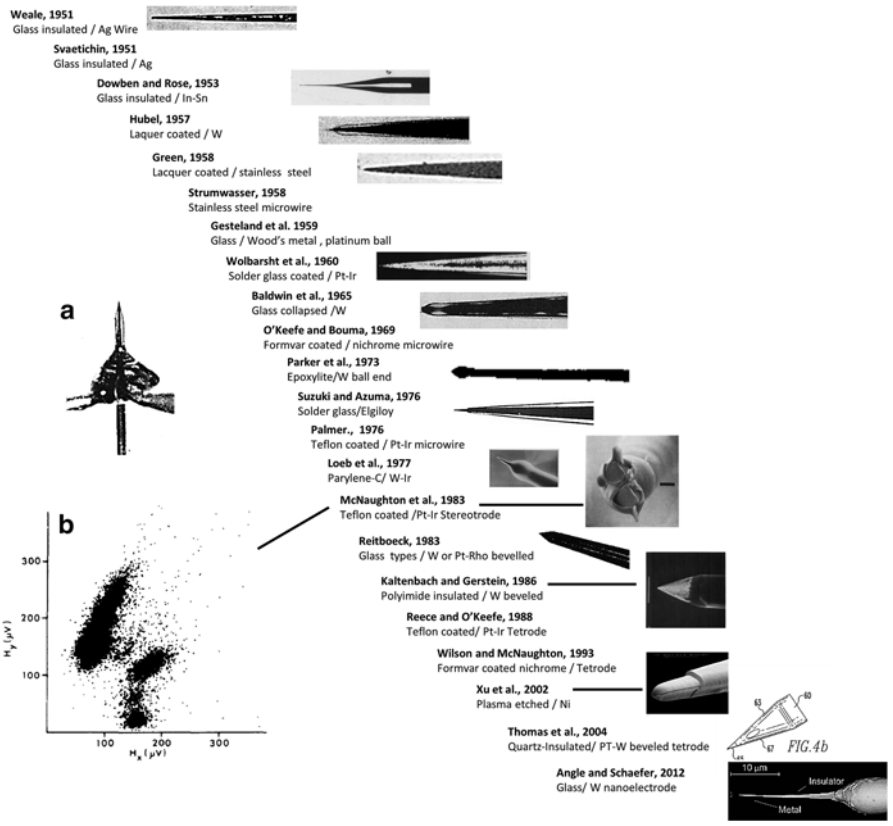

Fig. 1.5 Chronology of important microelectrode developments. The chronological development of metal microelectrode tips and their insulation from 1951 to 2012. Where possible, a photo is included of the actual electrode developed by the scientist. Under each reference is the insulation type and the conductor used (e.g., insulation/conductor). Reprinted with permission from Macmillan Publishers Ltd: Nature, Weale RA, A new micro-electrode for electrophysiological work, 167(4248), 529–30, copyright 1951. From Dowben RM, Rose JE. A metal-filled microelectrode. Science. 1953;118(3053):22–4. Reprinted with permission from AAAS. From Hubel DH. Tungsten Microelectrode for Recording from Single Units. Science 1957; 125(3247). Reprinted with permission from AAAS. Reprinted with permission from Macmillan Publishers Ltd: Nature, Green JD, A simple microelectrode for recording from the central nervous system, 182(4640), 962, copyright 1958. From Wolbarsht ML, Macnichol EF, Jr., Wagner HG. Glass Insulated Platinum Microelectrode. Science. 1960;132(3436):1309–10. Reprinted with permission from AAAS. From Baldwin HA, Frenk S, Lettvin. Glass-Coated Tungsten Microelectrodes. Science 1965; 148(3676). Reprinted with permission from AAAS. Reprinted from Electroencephalography and Clinical Neurophysiology, 35(6), Parker TD, Strachan DD, Welker WI, Tungsten ball microelectrode for extracellular single-unit recording, 647–51, Copyright 1973, with permission from Elsevier. Reprinted from Electroencephalography and Clinical Neurophysiology, 41(1), Suzuki H, Azuma M, A glass-insulated "Elgiloy" microelectrode for recording unit activity in chronic monkey experiments, 93–5, Copyright 1976, with permission from Elsevier. © 1977 IEEE. Reprinted, with permission, from Loeb GE, Bak MJ, Salcman M, Schmidt EM. Parylene as a chronically stable, reproducible microelectrode insulator. IEEE Trans Biomed Eng. 1977;24(2):121–8. Reprinted from Journal of Neuroscience Methods, 8(4),

10 mV extracellular spikes. Also notable was that in 1958, the first long-term (>1 day) neural recordings from an unrestrained animal conducted with a ground squirrel [29] using an 80 μm stainless steel microwires.

From this point, the evolution of the single fiber electrode took various twists and turns with modifications to tip geometry, insulations, and conductive materials. The first sharp-tipped platinum (70 %) and iridium (30 %) microelectrode was introduced by Wolbarsht et al. [30]. The electrodes were coated with molten solder glass using a heated loop (Fig. 1.5a). The next technical innovation came when Baldwin et al. [31] attempted to collapse a Pyrex glass capillary onto a fire-etched tungsten filament [31]. Finally O'Keefe and Bouma introduced the use of formvar-coated nichrome wires (25 μm core) for recording from the cat amygdala, which would later become a standard use in tetrodes [32].

In 1973, Parker et al. introduced a varnish (Epoxylite)-insulated tungsten ball electrode, which consisted of an electrode with a small ball 5–15 μm in diameter at the tip of the electrode [33]. The modification was thought to improve stability of the electrode in the brain and reduce damage from the otherwise sharp electrodes. Thereafter, this electrode did not become popular; however the necessity to solve the electrode stability problem persists today. The Elgiloy electrode was introduced by Suzuki and Azuma [34] and was composed of a nickel-cobalt alloy with about 15 % iron. These electrodes were insulated with solder glass and found to penetrate the monkey dura mater and record cells from microvolts well into the millivolts range. Concurrently, Palmer [35] was the first to publish the use of Teflon-coated 37 μm platinum-iridium microwires (90 % Pt/10 % Ir) to record cerebellar neurons in freely behaving animals. Importantly, the recorded cells could be held for up to a

Fig. 1.5 (continued) McNaughton BL, O'Keefe J, Barnes CA, The stereotrode: a new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records, 391–7, Copyright 1983, with permission from Elsevier. Reprinted from Journal of Neuroscience Methods, 8(3), Reitboeck HJ, Fiber microelectrodes for electrophysiological recordings, 249–62, Copyright 1983, with permission from Elsevier. Reprinted from Journal of Neuroscience Methods, 16(4), Kaltenbach JA, Gerstein GL, A rapid method for production of sharp tips on preinsulated microwires, 283–8, Copyright 1986, with permission from Elsevier. Reprinted from Sensors and Actuators A: Physical, 96(1), Xu CY, Lemon W, Liu C, Design and fabrication of a high-density metal microelectrode array for neural recording, 78–85, Copyright 202, with permission from Elsevier. Courtesy of Thomas RECORDING in Giessen, Germany. Reproduced with permission from Angle MR, Schaefer AT. Neuronal recordings with solid-conductor intracellular nanoelectrodes (SCINEs). PLoS One. 2012;7(8):e43194. (**a**) The process of solder glass insulation, whereby a wire was repeatedly dipped into a bead of molten solder glass [30, 99]. With kind permission from Springer Science + Business Media: Medical and Biological Engineering, A Glass-Covered Platinum Microelectrode, 2, 1964, 317–27, Guld C. (**b**) Multiunit separation using a stereotrode. By comparing the amplitude of the units recorded simultaneously on wires X and Y of a stereotrode, a 2D projection can be made to separate neuron from neurons. Five obvious clusters (individual neurons) can be seen. Reprinted from Journal of Neuroscience Methods, 8(4), McNaughton BL, O'Keefe J, Barnes CA, The stereotrode: a new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records, 391–7, Copyright 1983, with permission from Elsevier

week. Finally, in 1977, parylene C was introduced as an insulating material for tungsten and iridium electrodes. This process enabled precise tip exposures, and the material appeared to be very biocompatible, enabling scientists to isolate neurons from the monkey motor cortex for up to 100 days [36].

Until the 1980s the glass-coated sharp electrode held the spotlight for high-amplitude spike recordings, being able to pick up spikes from microvolts to millivolts. However, these electrodes weren't well equipped to sort multiunit activity. Indeed, multiunit activity was often considered a nuisance because of this difficulty. The sharp electrode was also not well noted for holding cells from day to day, especially in animals larger than a rat, where pulsation of the brain could influence electrode position. Finally, sharp electrodes suffered from an inability to discriminate cells in densely packed regions such as the hippocampus. Microwires, while not being able to penetrate the dura, had already shown evidence for stability in long-term recording [29]; however, microwires tend to detect small voltage signals (50–300 μV) and pick up an abundance of multiunit activity. Moreover their composition was such that they were difficult to implant, unless they were bundled together or reinforced. In spite of these apparent disadvantages, in 1983, McNaughton et al. [2] exploited some of these features as a primary advantage through the invention of the stereotrode. The stereotrode consisted of two Teflon-insulated 20 μm (75 % Pt/25 % Ir) wires twisted together and cut transversely with a pair of sharp scissors. The electrodes were simple and cost-effective, and the multiple conductors increased the strength of the electrode such that it could be implanted through the pial surface. The most important feature of the stereotrode was that the two wires of the stereotrode were spaced just microns apart so that each microwire could pick up signals from cells within and overlapping proximity. Thus, the same spike could be detected on both wires, but their spike sizes would not be the same. Accordingly, the spike amplitude for each covarying spike could be plotted with one spike represented on the *Y* axis and another spike on the *X* axis. This plot naturally forms clusters of neural data which can be grouped as statistically discrete spikes (Fig. 1.5b). While the conceptual advantage of the tetrode owes its inception to McNaughton et al., who suggested that a tetrahedral array would be optimal, the addition of the two extra microwires to the stereotrode to produce a tetrode owes credit to O'Keefe and Reece [37]. However, the most commonly used modern tetrode is the formvar nichrome (nickel and chrome) (40 μm total OD of the four wires) tetrode, introduced for large-scale hippocampus recording with multiple tetrodes [9].

In 1983 a quartz-coated platinum/rhodium electrode was produced which was beveled to a sharp point on a diamond grit grinding wheel [38]. The method for the platinum/rhodium electrodes was based on the Taylor wire method [39] for producing glass-coated wire and represented a substantial improvement in the reliable production of coated electrodes (often referred to as the Reitboeck electrode). Importantly, like the glass electrodes that preceded it, this electrode could penetrate the dura and drive straight through the brain tissue with minimal deviation. Quartz also has a lower dielectric constant than standard glass, so it acted as a better insulator. Finally, these electrodes were reported to have micro-striations or grooves on their

metal contacts which lowered electrode impedance. The German company, Thomas Recording later became known for the production and distribution of Thomas electrodes including a quartz-coated tetrode (see below).

The simple use of the grinding wheel to sharpen glass quartz-coated electrodes was also used by Kaltenbach and Gerstein [40] who sharpened polyimide-insulated tungsten microwire (25 μm). Thus, pre-insulated microwire technology began to cross-pollinate with that of the sharpened electrode technology.

In 2004 Thomas et al. [41] patented a 4-core quartz-insulated platinum (95 %) and tungsten (5 %) tetrode. This ~80 μm (OD) tetrode is beveled on a diamond grinding wheel and can be pulled thinner with the aid of a heating element. This electrode combines the best features of glass-coated electrodes with that of the pre-insulated microwire tetrode, effectively synthesizing the two most well-used historical techniques. Recently, a solid-conductor intracellular nanoelectrode (SCINES) has been constructed with a tungsten core conductor [42] and glass insulation. These electrodes were designed with the primary concern of puncturing the plasma membrane of neurons without producing leakage of current from the membrane. Puncturing or perforating membranes is nothing new for metal electrodes, dating back to Hubel's reports of sharpened tungsten electrodes. However, fluid-filled glass pipette electrodes have been the primary choice for intracellular recording, while extracellular recording is primarily done with metal electrodes. The SCINES electrode tip is milled microscopically with a focused ion beam to <300 nm. Shunt capacitance is reduced with special insulating procedures, and tips are coated with a hydrophobic compound "silane" to facilitate penetration into cells. These electrodes could pick up intracellular signals of a few millivolts including subthreshold neuronal potentials.

Microwire Electrode Arrays

As our understanding of electrochemistry and tip geometry of electrodes progressed so did the desire for large-scale neuronal recording. With increased numbers of neurons, we could examine neuronal activity simultaneously to study neuron-neuron communication and patterns of activity within the neural network. Early scientists used bundle electrodes to increase their potential neuron yield [32, 35, 43, 44] (Fig. 1.6a). However, simply offsetting the position of the individual wires in a bundle could produce a linear array of electrode contacts for which neurons could be detected across cortical layers and in different brain regions simultaneously.

One of the first notable designs of a linear array electrode was developed by Barna et al. [45]. This electrode array was constructed from a 30 gauge stainless steel hypodermic needle with a portion of the tube machined to half its width. Sixteen stainless steel microwires (25 μm) were passed through the tube, bent by 90°, and fixed to the side of the machined region (in the *Z* axis), with an interelectrode spacing of 400 μm (Fig. 1.6b).

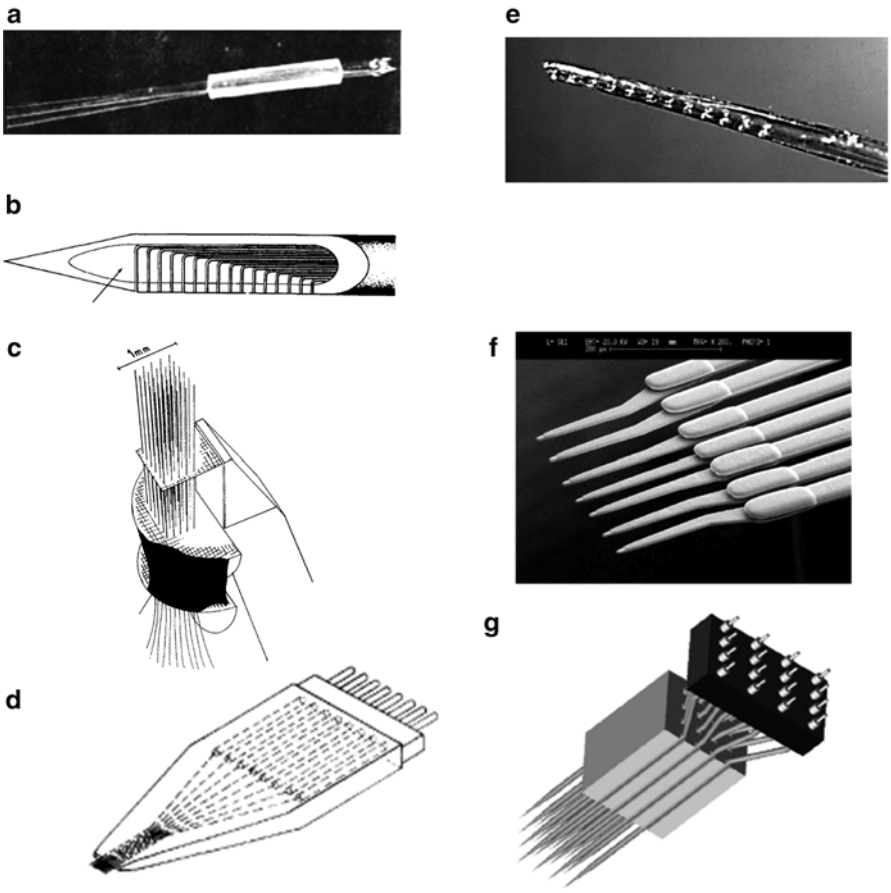

Fig. 1.6 Development of microelectrode arrays. (**a**) The bundled electrode preceded the array. This particular bundle was composed of sharpened tungsten electrodes and was implanted in humans [43]. Reprinted from Electroencephalography and Clinical Neurophysiology, 23(3), Marg E, Adams JE, Indwelling multiple micro-electrodes in the brain, 277–80, Copyright 1967, with permission from Elsevier. (**b**) Needle electrode linear array, electrodes are bent at 90° and clipped along the side of the 30G needle [45]. Reprinted from Electroencephalography and Clinical Neurophysiology, 52(5), Barna JS, Arezzo JC, Vaughan HG, Jr., A new multielectrode array for the simultaneous recording of field potentials and unit activity, 494–6, Copyright 1981, with permission from Elsevier. (**c**) Shows the three grids used to construct the 5×6 matrix of quartz-coated microelectrodes, and the bottom two grids are epoxied together to produce a substrate to hold the electrodes in parallel [46]. With kind permission from Springer Science+Business Media: Experimental brain research, Simultaneous recording with 30 microelectrodes in monkey visual, 41(2), 1981, 191–4, Kruger J, Bach M. (**d**) Parallel linear electrode array using metal microwires [47]. Reprinted from Journal of Neuroscience Methods, 11(3), Verloop AJ, Holsheimer J, A simple method for the construction of electrode arrays, 173–8, Copyright 1984, with permission from Elsevier. (**e**) Bundle array with 12 nichrome wire contacts [48]. Reprinted from Journal of Neuroscience Methods, 40(2, 3), Jellema T, Weijnen JA, A slim needle-shaped multiwire microelectrode for intracerebral recording, 203–9, Copyright 1991, with permission from Elsevier.

The first notable two-dimensional electrode array consisted of a 5×6 matrix of quartz-glass microelectrodes with platinum-iridium cores beveled to a fine tip and spaced at 160 μm [46] (Fig. 1.6c). Neurons were detected on at least 50 % of the implanted electrodes. Shortly thereafter, a parallel linear array was developed which consisted of eight 33 μm Karma wires spaced at 100 μm. This electrode array was primarily intended to record hippocampal field potentials [47] (Fig. 1.6d).

Jellema and Weijnen [48] developed a method for constructing a bundle array, consisting of 12 formvar-coated nichrome microwires (25 μm) embedded in Epoxylite resin with a 150 μm interelectrode spacing (Fig. 1.6e). This electrode array closely resembled styles of silicon probes at the time; however, as expressed by the authors, the silicon probe was financially prohibitive. The details of silicon probe techniques will be described in Chap. 2.

Eventually molding processes were used to enhance the feasibility of rapidly constructing electrode arrays [49]. However, with commercial metal electrode fabrication, the experimenter could focus on the experiment rather than on electrode and electrode array fabrication [50].

Xu et al. [51] combined fabrication techniques used in silicon chip production to produce a high-density metal microelectrode array (Fig. 1.6f). The basic concept was to electroplate the entire metal portion with nickel or permalloy (nickel-iron alloy). The second step was to remove silicon substrate to free the metal shanks of the electrode. The third phase was to add parylene C as an insulator for the electrodes. The tips of the electrodes were then exposed with photolithography followed by plasma etching, procedures commonly used in silicon chip manufacture.

Floating Wire Microelectrode

When recording from the neurons it would be best if we could track the life and experience of those neurons from days to years. This is seldom the case because there are pulsations of the brain, due to vascular supply and respiration, which change the position of the brain relative to the electrode. While this tends to be most prominent in larger vertebrates such as cats and primates, there is also the problem of bone growth which can gradually lift the secure electrode from its position in the brain. Indeed, it would only take a movement of 5 μm or less to significantly influence the amplitude of a recorded brain cell. This section focuses on floating

Fig. 1.6 (continued) (**f**) Electroplated parallel metal electrode array with silicon base [51]. Reprinted from Sensors and Actuators A: Physical, 96(1), Xu CY, Lemon W, Liu C, Design and fabrication of a high-density metal microelectrode array for neural recording, 78–85, Copyright 2002, with permission from Elsevier. (**g**) Shows a 4×4 matrix tungsten electrode array spaced by custom molds [49]. ©2005 IEEE. Reprinted, with permission, from Takahashi H, Suzurikawa J, Nakao M, Mase F, Kaga K. Easy-to-prepare assembly array of Tungsten microelectrodes. IEEE Trans Biomed Eng. 2005;52(5):952–6

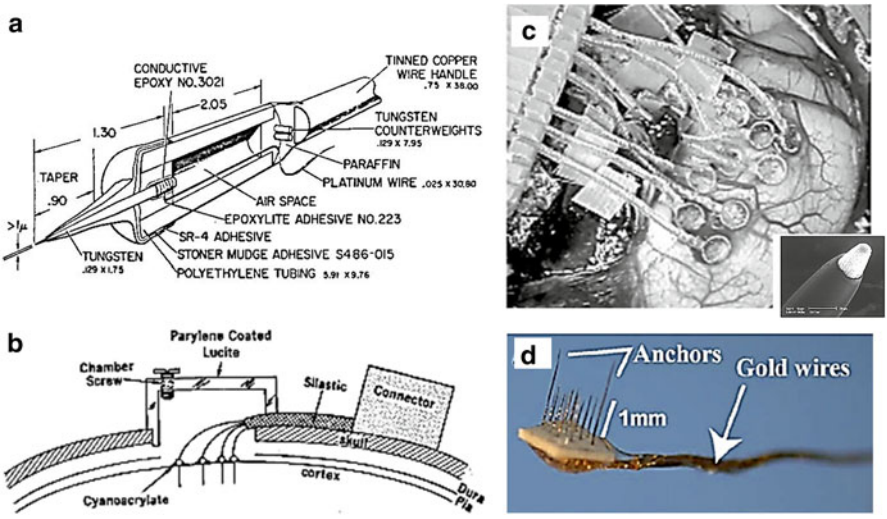

Fig. 1.7 Floating microelectrode technology. (**a**) First floating microelectrode device to record the frog vestibular system in outer space. Notice the air space, fine platinum wire, and counter weights, all used to minimize movements of the electrode relative to the body in which it was implanted. Reprinted from Electroencephalography and Clinical Neurophysiology, 25(1), Gualtierotti T, Bailey P, A neutral buoyancy micro-electrode for prolonged recording from single nerve units, 77–81, Copyright 1968, with permission from Elsevier. (**b**) Floating microwire electrodes free to move with pulsations of the brain and a chamber used to maintain cranial pressure and electrolytic interface. With kind permission from Springer Science + Business Media: Medical and Biological Engineering, A new chronic recording intracortical microelectrode, 14(1), 1976, 42–50, Salcman M, Bak MJ. (**c**) Pneumatically implanted sets of microelectrode arrays (circular pads) in the primate brain. Note the flexible leads to the left. The *bottom right inset* shows a scanning electron micrograph of the electrode tip. Reproduced with permission from Bradley DC, Troyk PR, Berg JA, Bak M, Cogan S, Erickson R, et al. Visuotopic mapping through a multichannel stimulating implant in primate V1. J Neurophysiol. 2005;93(3):1659–70. (**d**) Floating microelectrode array with anchor spikes. Reprinted from Journal of Neuroscience Methods, 160(1), Musallam S, Bak MJ, Troyk PR, Andersen RA, A floating metal microelectrode array for chronic implantation, 122–7, Copyright 2007, with permission from Elsevier

microelectrode devices which have been used in an attempt to match movements of the brain with that of the electrodes.

The first floating electrode was called a buoyancy microelectrode and owes its inception to Gualtierotti and Baily [52, 53]. This represented the first rational development of an electrode device which would move with nervous tissue (Fig. 1.7a). The tungsten electrode (Hubel design) used in this device was made buoyant because of an air pocket in the device for which it was attached. The device was additionally counterweighted, so the geometrical center of gravity was focused on the electrode. Finally, the electrode electrical connection was made with a small and flexible lead wire, so there would be minimal strain on the electrode when it was interfaced with the recording device. Electrical signals from the frog vestibular

nerve could be recorded from 2 to 5 days and during parabolic flights in a jet plane. These same floating electrodes were later used to study the vestibular system of the frog in outer space. It should be noted that 10 years earlier, Strumwasser [29] and Burns [54] demonstrated neuron stability from days to weeks using pre-insulated microwires.

Burns et al. [54] suggested that the movement of the electrode with time is dependent on the age and growth of the animal. Based on their estimates, a cat weighing 2.5 kg with an electrode at a depth of 3 mm would move 1.4 μm/day. By contrast, for a cat weighing 4.25 kg, the electrode would be expected to move 0.14 μm/day, as its growth rate will have slowed down. Collectively, it is likely that rigid electrodes such as those used by Hubel and the entire history of glass-coated electrodes, while having better ability to isolate single units, cannot hold these cells for prolonged periods of time because of their rigidity. Rigid electrodes do however have a significant advantage in that they are able to puncture dura. However, an intact dura should reduce brain pulsation and therefore prevent swelling and displacement of the electrode relative to the cell of interest.

Salcman and Bak [55] were the first to consider the consequence of craniotomy on electrode stability. They implanted a sharpened, floating, parylene C-insulated, 25 μm iridium microwire through the pia mater. The wires were glued to the pial surface with cyanoacrylate glue (Fig. 1.7b). The contact end of the electrode was secured to an ultra-flexible lead wire so the microwire could float with movements of the brain. Even more interesting was that the electrode leads were suspended in a fluid-filled chamber to reestablish the integrity of the cranial vault.

It was only a matter of time before the microelectrode array found an application in floating electrode technology. Bradley et al. implanted arrays of iridium microelectrodes into the monkey visual cortex [56] (Fig. 1.7c). The arrays of electrodes had a flexible lead so they could float on top of the pia. Thus the floating microelectrode technology had moved from a single electrode recording in the vestibular nerve of a frog to high-density electrophysiology in a primate. Musallam et al. [57] modified the floating microelectrode design not only to be more cost-effective but also to have anchor spikes which stabilized the array so that superficial cells could be recorded (Fig. 1.7d). It was found that neurons could be recorded in a rat up to 3 months after implantation.

Electrode Conditioning

Electrode impedance can be a major nuisance when recording with microelectrodes. The high impedances are a result of the small tip exposure of the microelectrodes. However, these small tips also make the electrode susceptible to picking up noise from the environment (e.g., 60 Hz hum).

Electroplating the electrode tip induces the growth of crystals on the electrode which has the effect of maintaining tip geometry while increasing tip surface area (e.g., Fig. 1.8a, b). The increased surface area reduces the tip impedance, resulting

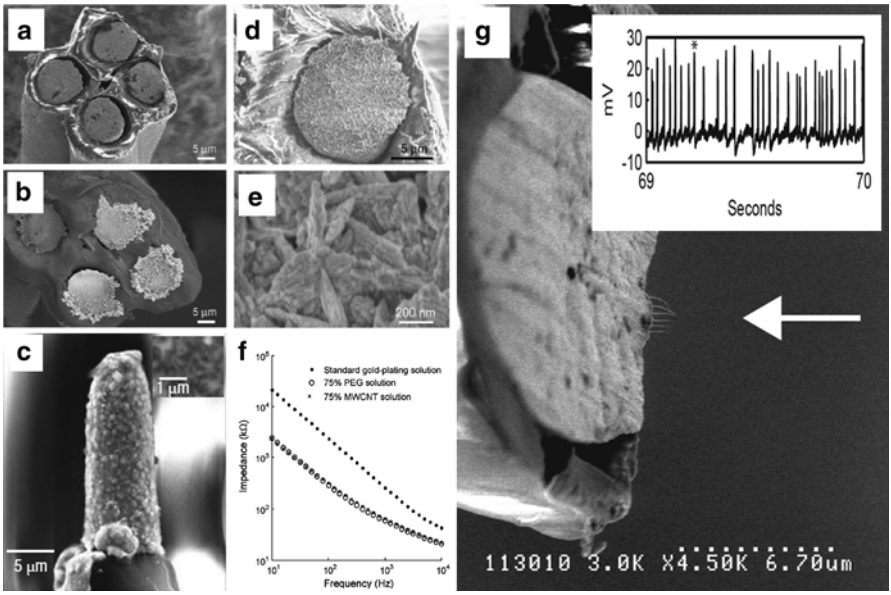

Fig. 1.8 Electrode conditioning. (**a**) Scanning electron micrograph of a tetrode before gold electroplating [62]. (**b**) Scanning electron micrograph of a tetrode after gold electroplating to 250 k**Ω** [62]. (**c**) Carbon nanotubes/gold attached to a tungsten microelectrode. Reprinted with permission from Macmillan Publishers Ltd: Nature Nanotechnology, Keefer EW, Botterman BR, Romero MI, Rossi AF, Gross GW, Carbon nanotube coating improves neuronal recordings, 3(7), 434–9, copyright 2008. (**d**) Tetrode tip plating has a "rice-like" appearance after electroplating with multiwalled carbon nanotubes [62]. (**e**) Magnified region of (**c**) showing "rice-like" coating is actually composed of bladed crystallites [62]. (**f**) Shows further decrease in impedance with electroplating with either of two additives, polyethylene glycol (PEG) or multiwalled carbon nanotubes (MWCNT) [62]. (**g**) Electron beam deposition of nanowires on the end of a single wire of a platinum-iridium electrode. *Inset* is intracellular recording from an intact T-cell neuron of a leech. Reproduced from Ferguson JE, Boldt C, Puhl JG, Stigen TW, Jackson JC, Crisp KM, et al. Nanowires precisely grown on the ends of microwire electrodes permit the recording of intracellular action potentials within deeper neural structures. Nanomedicine (Lond). 2012;7(6):847–53, with permission from Future Medicine Ltd. (**a**, **b**, **d**, **e**, and **f**) reprinted from Sensors and Actuators A: Physical, 156(2), Ferguson JE, Boldt C, Redish AD, Creating low-impedance tetrodes by electroplating with additives, 388–93, Copyright 2009, with permission from Elsevier

in less noise pickup from the environment. Electroplating is accomplished by the application of a current between an electrode and a plating solution (e.g., gold). A microampere DC current is passed through the microelectrode to attract the charged metal ion to the surface of the electrode. A reference electrode is also used to complete the circuit and to supply the solution with ions as they move from the solution to the plated microelectrode.

Svaetichin [24] has reported the use of platinum black to plate their silver microelectrodes. Dowben and Rose [25] later found that pre-plating their indium electrodes with gold could produce a base for which platinum black could be plated. Tungsten microelectrodes tend to be quite noisy, but plating with platinum followed

by gold reduces tip impedances [31, 58]. The gold pre-plating helps prevent platinum black from flaking off as the electrode penetrates through pia mater [59]. Robinson [59] noted that if an electrode is plated, the impedance will drop, but as time goes by, the impedance will gradually rise and experimenters often have to re-plate the electrodes just prior to use. The early introduction of the stereotrode consisted of a platinum-iridium wires that were plated with platinum to lower their impedance [2]. Soon thereafter, with the introduction of the nichrome tetrode, gold plating was used to reduce impedance [8]. Gold plating can reduce tetrode impedances from 1–2 MΩ down to 200 kΩ; however, if electrodes are over-plated, it has a tendency to short adjacent contacts within the tetrode tip. If reference and recording electrode impedances are precisely matched, most of the environmental noise is subtracted out with the differential amplifier. This can pose a problem for chronic recordings where the impedance of these electrodes may not remain stable with time.

One of the most successful methods of improving electrode impedance has been to electroplate electrodes in the presence of gold and carbon nanotubes using electrochemical techniques [60]. Carbon nanotubes have a high surface area and conductance, so they presumably make an ideal means of optimizing electrode tip impedance [61]. The mixture of carbon nanotubes in a gold solution could successfully coat stainless steel, tungsten single fiber electrodes (Fig. 1.8c), and tungsten stereotrodes. This coating appeared as a "rice-like" structure and significantly increased the ability to record neurons while decreasing the susceptibility to electrical noise. Subsequently, Ferguson [62] found that electroplating with the same additives as Keefer et al. [60] resulted in a "rice-like" shaped coating (Fig. 1.8d, e) and argued that the findings from Keefer were most likely to be a result of the carbon nanotubes absorbing into the electrode and acting as an inhibitor to gold plating. The result would be to limit the areas where the gold could plate the electrode, favoring the growth of new crystallites as opposed to the elaboration of previously plated crystals. Fergusson also used polyethylene glycol as a plating additive with gold and was able to produce the same rice-like structure while reducing electrode impedance (Fig. 1.8f). Finally, a combination of polyethylene glycol and carbon nanotubes with the gold solution produced a remarkably low-impedance electrode (30–70 kΩ). Although this may improve noise levels during recording it will only increase the resolution of far-field neurons.

Gesteland et al. [26] also noticed the benefit of additives for platinum microelectrode plating. They reported that the addition of gelatin to a platinum black solution produced a more adherent plating of platinum black on their Wood's metal electrode. With the invention of the quartz-insulated platinum/tungsten electrode, it was argued that the beveling procedure actually produces microgrooves [38] which reduce the impedance of the electrodes. As such they do not need to be plated prior to use; however some investigators do report gold plating to control their impedance [63]. Similar to tetrodes, single fiber tungsten, and stainless steel electrodes, effort has been made to coat Thomas electrode tips with carbon nanotubes to improve the signal-to-noise ratio. However, rather than use a mixture with gold, Baranauskas et al. [64] used a polypyrrole carbon nanotube composite. Similar to other composites, impedances were reduced between 1 and 10,000 Hz, with a dramatic increase in

signal-to-noise ratio in the 150–1,500 Hz range, which corresponds to the unit recording frequency band. Interestingly, consistent with Ferguson et al. [62], carbon nanotubes also appeared to increase the spike amplitude (from an average of 0.5 to 0.7 mV).

While lowering impedance of electrodes may reduce noise contamination, we need improvements in the opposite direction, toward stable high-density recording of high-amplitude spikes. We need clean signals from all the cells in a neural volume if we want to decode or predict the brain. Some interesting developments are starting to be seen in the field of nanotechnology. For example, what if nanowires could be grown on the tips of the electrode? Indeed, this concept is already being explored through the use of electron-beam-induced deposition to extend nanowires (microns long at 10–30 nm diameter) from the end of platinum-iridium electrodes [65] (Fig. 1.8g). Aluminum oxide was next laid down as an insulator, using an atomic layer deposition technique. Finally, a focused ion beam was used to mill the ends of the wires so as to expose their tips by removing the insulation and thereby producing impedances of around 1 MΩ. Remarkably, 15 mV potentials could be recorded from hippocampal slice preparations and 20 mV spikes from a leech preparation. We expect that approaches like this will pave the way for the future of metal microelectrode technology.

Chronology of Hyperdrive Development

The history of methods utilized to implant electrodes is one of diversity and innovation. The harpoon method was a common method to implant microwires, while the development of the hyperdrive in the 1970s came to be among the most common to independently move electrodes within the brain and can be used for either fine wire electrodes (e.g., tetrodes) or with single conductor electrodes.

Harpoons and Bundles

O'Keefe and Bouma [32] implanted their nichrome electrodes, fixed to a harpoon/probe with Carbowax (or polyethylene glycol). When the wax dissolved in the brain, the probe could be removed, leaving the electrodes in the surrounding tissue to detect neurons. Similarly, Burns et al. [54] inserted 30 μm platinum microwires through the dura by attaching the electrodes to a sharpened tungsten needle with sucrose. Westby and Wang's [66] approach was to use an array of microelectrodes attached with sucrose to a glass capillary. Remarkably, the investigators found that 81 % of their 252 implanted wires obtained neural recordings, many of which were still recording neurons 5 weeks later. As new methods for isolating neurons have been developed (below), the harpoon method for electrode insertion is rarely used.

Manual Microdrives

The microdrive was invented so that electrodes could be lowered into the brain in order to isolate new neurons. Early on, the term "microdrive" referred to the entire assembly of drive units [67]; it would later acquire the meaning of individual drive unit, while the term "hyperdrive" would refer to a set of microdrives. Because of these semantic issues, we will use the more modern terminology. A summary of many important hyperdrives and their schematics is shown in Fig. 1.9, the details for which we will discuss subsequently.

Blum and Feldman [67] invented a hyperdrive with independent movement of four electrodes for the study of the motor cortex of an anesthetized cat. The hyperdrive could be secured to a stereotaxic apparatus and consisted of four microdrives that could be independently driven by a micrometer. Soon after, Humphrey [68] invented a hyperdrive that closely approximates what we use today. This hyperdrive consisted of five microdrives, each driven by a mini setscrew which could advance the microdrive 277 μm/revolution against the force of a spring. The setscrews drove a piston that was attached to a tungsten electrode. The hyperdrive was intended for use with monkeys and cats and most remarkably was reported to be reloadable. Ainsworth and O'Keefe [69] had a similar design in which four drivescrews constituted the microdrive mechanism; however, instead of the drivescrews moving up and down, a drive nut would move up and down. The drive nut, tethered to the electrode, would move with the turn of the drivescrew (350 μm/revolution). Importantly, the drive was only 3 g, so it could be used for implantation in rats.

Other single microdrive units were introduced in the 1970s and appear to be adaptations of the design by Rank [70], the mechanism for which consisted of a screw which moved up and down inside a base [71]. The center of the screw was hollowed out, and the electrode was inserted through this hole [70]. The primary benefit of these drives was that they were small and could be used easily with rodents while awake or during sleep. However, the design features meant that electrodes turned with the drivescrew, which caused damage to the brain tissue and loss of neuron recording stability. There were various modifications made to this design, but only a few features are worth noting. Correction for rotation of the electrodes was explored by Deadwyler et al. [72] and Bland et al. [73], and the ability to replace electrodes was explored by Winson [71]. Finally, a design similar to Rank's drive was used to lower pre-insulated nichrome microwires into the brain for the first time in the hope of combining the best features of a floating electrode with those of a drivable electrode [74].

Another milestone was the development of the first purely actuated microdrive. This drive consisted of a screw that, when turned, drove a gear which was coupled to a geared linear post. Thus, rotational force was converted directly to linear actuation. This actuator was coupled to a glass-coated tungsten electrode which advanced 500 μm/revolution. It was capable of picking up stable units averaging 300–500 μV.

One of the most well-used microdrives was invented by Kubie et al. [44] and is still used today. The design consisted of ten 25 μm nichrome microwires which

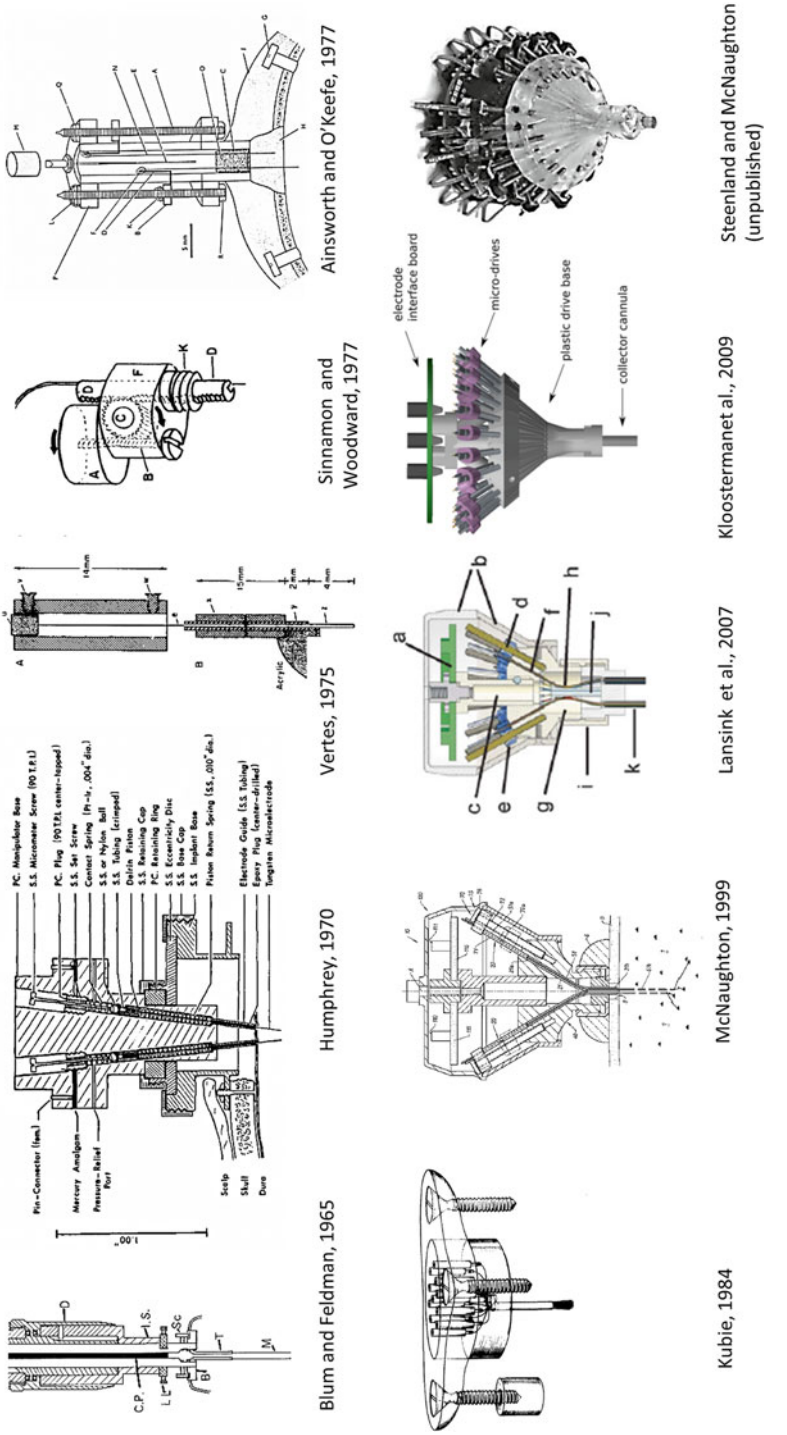
Blum and Feldman, 1965
Humphrey, 1970
Vertes, 1975
Sinnamon and Woodward, 1977
Ainsworth and O'Keefe, 1977
Kubie, 1984
McNaughton, 1999
Lansink et al., 2007
Kloostermanet al., 2009
Steenland and McNaughton (unpublished)
electrode interface board
micro-drives
plastic drive base
collector cannula

Fig. 1.9 Chronology of important manual hyperdrive developments. The manually driven hyperdrive evolved out of the combination of sets of microdrives. The microdrive mechanism commonly consisted of turning a thread which was coupled to the actuation of the electrode through a gear, nut, or shuttle. © 1965 IEEE. Reprinted, with permission, from Blum B, Feldman B. A microdrive for the independent manipulation of four microelectrodes. IEEE Trans Biomed Eng. 1965;12(2):121–2. Reprinted from Electroencephalography and Clinical Neurophysiology, 29(6), Humphrey DR, A chronically implantable multiple microelectrode system with independent control of electrode positions, 616–20, Copyright 1970, with permission from Elsevier. Reprinted from Electroencephalography and Clinical Neurophysiology, 38(1), Vertes RP, A device for recording single unit activity in freely-moving rats by a movable fine-wire microelectrode, 90–2, Copyright 1975, with permission from Elsevier. Reprinted from Physiology & Behavior, 19(3), Sinnamon HM, Woodward DJ, Microdrive and method for single unit recording in the active rat, 451–3 [100], Copyright 1977, with permission from Elsevier. Reproduced with permission from Ainsworth A, O'Keefe J. A lightweight microdrive for the simultaneous recording of several units in the awake, freely moving rat. J Physiol. 1977;269(1):8P–10P. Courtesy of John Wiley & Sons. Reprinted from Physiology & Behavior, 32(1), Kubie JL, A driveable bundle of microwires for collecting single-unit data from freely-moving rats, 115–8, Copyright 1984, with permission from Elsevier. McNaughton B, inventor; Implantable multi-electrode microdrive array. USA patent 5928143. 1999. Copyright Arizona Board of Regents for the University of Arizona. Reprinted from Journal of Neuroscience Methods, 162(1, 2), Lansink CS, Bakker M, Buster W, Lankelma J, van der Blom R, Westdorp R, et al., A split microdrive for simultaneous multi-electrode recordings from two brain areas in awake small animals, 129–38, Copyright 2007, with permission from Elsevier. Reproduced with permission from Kloosterman F, Davidson TJ, Gomperts SN, Layton SP, Hale G, Nguyen DP, et al. Micro-drive array for chronic in vivo recording: drive fabrication. J Vis Exp. 2009 [26]

were each bundled together in a stainless steel tube. The drive mechanism consisted of three independently drivable screws attached to a platform. Similar to Gualtierotti and Baily [52, 53], who invented the buoyancy electrode to study the vestibular system in outer space, Knierim et al. [75] explored the neuronal activity of the hippocampus, in zero gravity on a NASA flight, with a new hyperdrive design originally based on earlier designs from the same lab [9, 76]. The particular hyperdrive used for the NASA mission was constructed by Kopf instruments and later patented by Bruce McNaughton [7]. The major innovations in this drive are listed in its patent and include a circular array of 14 tetrodes that run parallel to one another and are orientated outwardly via guide tubes. Additionally, the microdrives consisted of tripods with a central nut connected to a threaded rod (fixed to the hyperdrive base). When the nut was turned, the microdrive moved, guided linearly by the two legs and the threaded rod. Thus, electrodes fixed in these drives could be moved forward with a turn of the nut and be guided into the brain by the array of guide tubing. This drive was later redesigned to include an additional electrode bundle so that two brain regions could be simultaneously targeted [77].

Kloosterman et al. [78] published a fabrication protocol for a hyperdrive which was designed with SolidWorks software and could be made from plastic, using 3D stereolithography printing process. The flexibility of the design software in combination with the printing process will permit easy customization of hyperdrives at a reasonable cost in years to come. The Kloosterman drive shares many features with the Kopf drive; however, the microdrive mechanism is a di-pod rather than a tripod. Moreover, the threaded screw which moves the microdrive downward actually moves via tapped threads arrayed around the drive. A more recent development in our laboratory (unpublished) using the Kloosterman drive involves the use of flexible connections between each microdrive and a specialized hyperdrive electrode interface board. This flexible connection permits us to reload standard tetrodes or Thomas quartz-insulated electrodes into rats, should the older electrodes begin to fail. Such flexibility is expected to increase neuron yield and long-term use of the subject under study.

While most of the drive styles listed above were designed for rats or larger animals, there remained a major problem with recording from smaller animals such as birds and mice. Given the enthusiasm for genetic work in mice, the design of drives to suit these ends were also required. Korshunov developed a 120 mg mini-microdrive module to be used with sharp microelectrodes in freely behaving mice and baby chicks. The microdrive mechanism consisted of a module for which linear movement (250 μm revolution) of the electrode occurred through turning a threaded drive tube. With similar technology, Korshunov also developed the first waterproof microdrive system so animals could be tested in the Morris water maze [79], even while submerged underwater. Many microdrives for mice and rats are also available from neuroscience vendors. However, with an increasing focus on the study of distributed networks and the integration of optogenetic and pharmacological technologies, the need for flexible, in-house design is again growing, supported by modern modeling software (e.g., SolidWorks) and fabrication processes (e.g., stereolithography).

Rotary Motorized Hyperdrives

Many hyperdrives use rods or threaded screws as the means to move parts of the microdrive up and down. However, all of the hyperdrives reviewed thus far require the experimenter to manually turn the microdrive mechanism. Some investigators have taken the approach of motorizing the microdrive mechanism. The advantage is that the animal under study doesn't need to be restrained in order to move the electrodes. Furthermore, the precision of actuation and the isolation of neurons would be improved. The downside is the cost and the weight of the device to be carried on the animal's head. A summary of the important rotary motorized hyperdrives and their schematics is shown in Fig. 1.10, the details of which we will discuss subsequently.

Findlay [80] devised an early DC motorized microdrive for freely behaving cats and rabbits. The motor terminated in a worm and pinion gear to actuate the electrode up and down in a linear fashion. The motor could be controlled remotely and could advance the electrode by a mere 1.25 μm. Subsequently, Barmack et al. [81] developed a microdrive that was driven directly by a stepper motor and was intended for primate work. The advantage of stepper motor drives over DC style drives is that each step is very precise. Fee and Leonardo [82] set out to miniaturize the motorized microdrive for small animals such as mice and small song birds which can lift about 2–5 g of weight on their skulls. Their finished product weighed around 3 g and consisted of three independently drivable DC mini-motors. Each of the three motors could be independently controlled, and the motor was directly coupled to a threaded rod which drove a shuttle. The shuttle moved up and down linearly as the threaded rod turned (~160 μm/turn) and drove the electrode (fine sharp tungsten) into the brain. The examples of unit isolation reported by Fee and Leonardo [82] were between 1 and 4 mV reaching up to 10 mV, orders of magnitude higher than pre-insulated fine wire electrodes. Just as remarkable was that if the amplitude of the cell recording drifted, the electrodes could be readjusted without touching the animal under study.

Yamamoto and Wilson [83] substantially expanded upon the mini-motorized microdrive technology that Fee and Leonardo [82] had introduced. The authors introduced three new major features. First, they found a way to multiplex the signals that drive the motors, which cut down on weight and cabling to the animals head when the drive was implanted. The second feature was to increase the number of motors for the mouse style hyperdrive (4.8 g) to 7 while the rat microdrive (29 g) had 21. Third, the microdrive base was constructed using a stereolithography technique which meant that the device could be constructed from strong lightweight material. The drive could move a tetrode in steps as small 0.6 μm. The largest spikes reported were approximately 2.35 mV, which is 4.25× lower than those reported by Fee and Leonardo, possibly owing to the use of a blunt tetrode rather than a sharp electrode.

While motorized hyperdrives have come a long way from their original inception, the cost of production for these devices is high, and the parts involved are

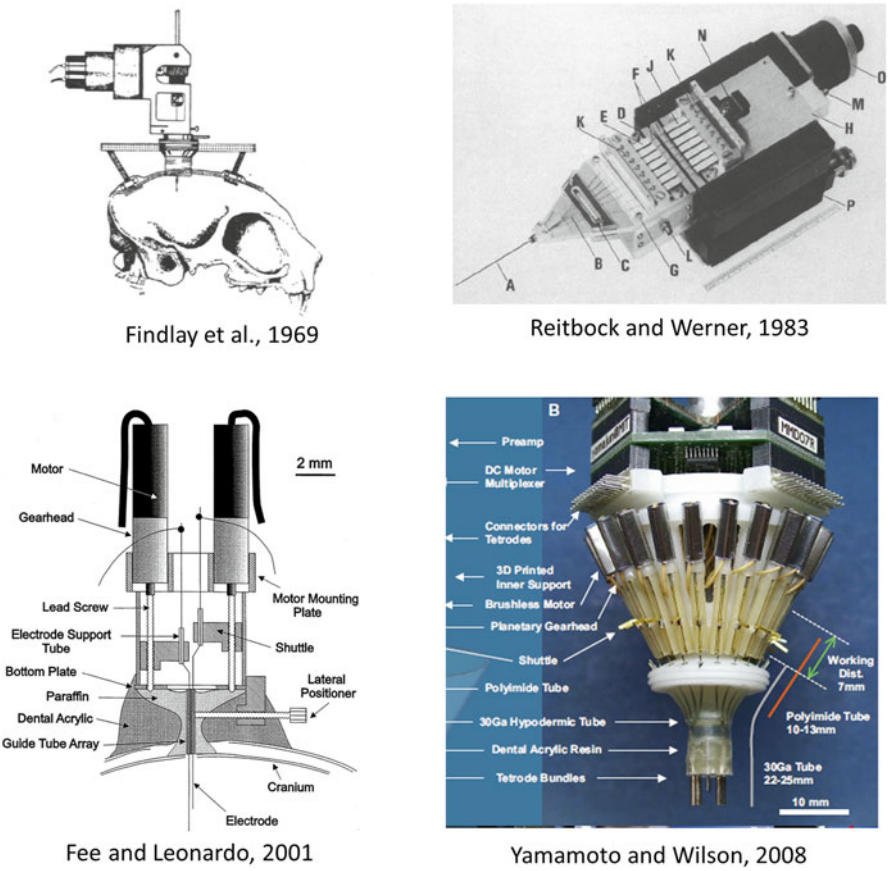

Fig. 1.10 Rotary motorized hyperdrives. Developments of motorized drives to increase the precision of neuron isolation. Such drives also permit the experimenter to manipulate electrode depth without directly interacting with the animal. Reproduced with permission from Findlay AL, Horn G, Stechler G. An electrically operated micro-electrode drive for use on unanaesthetized animals. J Physiol. 1969;204(1):4P–6P. Courtesy of John Wiley & Sons. With kind permission from Springer Science + Business Media: Experientia, Multi-Electrode Recording-System for the Study of Spatio-Temporal Activity Patterns of Neurons in the Central Nervous-System, 39(3), 1983, 339–41 [101], Reitbock HJ, Werner G. Reprinted from Journal of Neuroscience Methods, 112(2), Fee MS, Leonardo A, Miniature motorized microdrive and commutator system for chronic neural recording in small animals, 83–94, Copyright 2001, with permission from Elsevier. Reproduced with permission from Yamamoto J, Wilson MA. Large-scale chronically implantable precision motorized microdrive array for freely behaving animals. J Neurophysiol. 2008;100(4):2430–40

delicate (e.g., motors). They also add substantially to the weight of the hyperdrive. Should hyperdrives become more useful for doing intracellular recording with nanowires or juxtacellular recording, it should be expected that the motorized hyperdrives will be essential for precision control. However, unless DC or stepper motors can be made smaller and of lighter weight while retaining their torque, it may be of interest to look toward piezoelectric motors.

Piezomotor Hyperdrives

Piezoelectric motors are now becoming incredibly popular, probably in part due to their involvement in focusing lenses for the smartphone industry. The piezocrystal shape becomes distorted when a voltage is dropped across it. This distortion can be harnessed to create motion. Linear motion peizomotors eliminate the need for using threaded screws and gears to couple rotation to linear actuation in the microdrive. Moreover, peizomotor motion or steps can be incredibly small with nanometer resolution. This section will discuss some of the recent advances in piezomotor hyperdrive development.

Cham et al. [84] used a linear actuating piezomotor hyperdrive for semi-chronic use in primates with sharp platinum-iridium electrodes (Fig. 1.11a). In addition, the authors integrated an autonomous control algorithm so that a computer could isolate the neurons through driving the piezoelectric motor and checking the resulting spike signals (Fig. 1.11b). The only drawback with these motors, as with any motors, is the electrical noise they produce on the recording electrode when actuating. Park et al. [85] improvised a single piezoelectric microdrive (5 g) for mice and found it helpful for the micro-positioning of their electrodes. The idea was later improved by Yang et al. [86, 87] by using a more practical piezoelectric motor, reducing the weight to 1.82 g, and integrating a position feedback system (Fig. 1.11c). Yang et al. [86] found that micro-positioning of the tetrodes (<5 μm) was sufficient to increase the number of clustered units within the tetrode recording (Fig. 1.11d). In addition, the minimum step of the piezoelectric motor was 1 μm, and the electrical noise generated by actuation was negligible for recording purposes. However, this drive was still only able to position a bundle of tetrodes without the independent manipulation of the tetrodes. In the future this style of drive can be extended to produce a hyperdrive for remote control of electrode positions in high-density electrophysiology.

High-Density Electrophysiology and Stimulation

In vivo multiunit electrophysiology has been combined with behavioral manipulations for the past 60 years. In contrast, in vitro experiments involve local manipulations but do not consider the context of the behaving animal. Neither of these methods can completely reverse engineer the brain. An effective engineering approach relies on the local ability to manipulate parts of a system and see both local and global effects of the system. The following section will examine attempts to systematically manipulate local regions of the brain while simultaneously monitoring neuron responses in vivo.

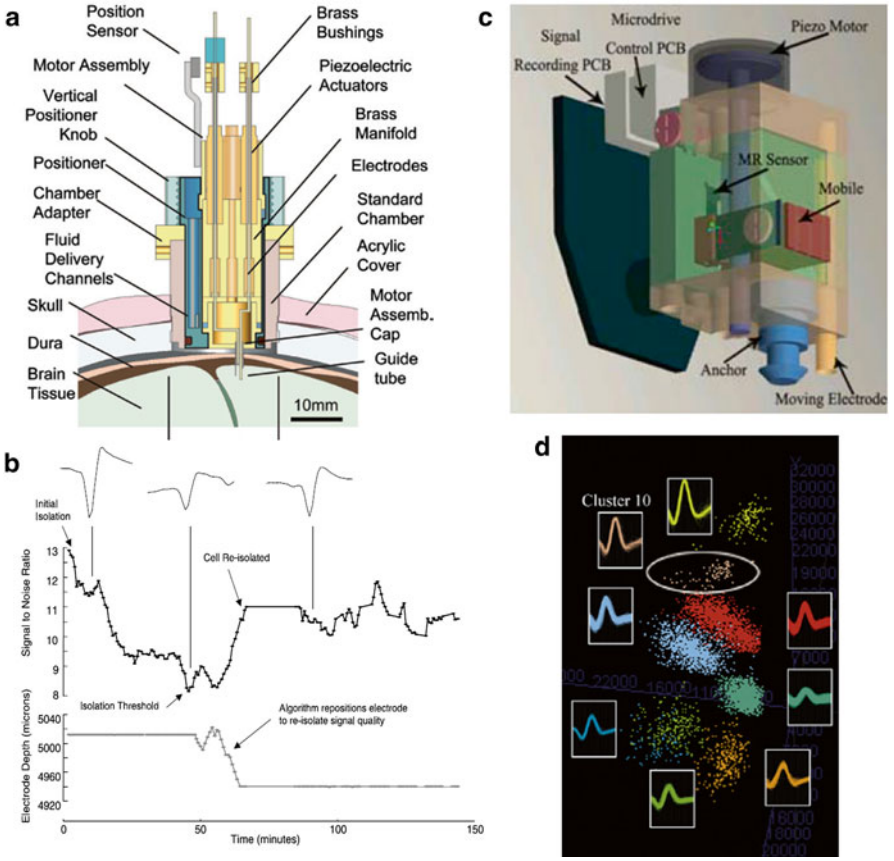

Fig. 1.11 Piezomotor hyperdrives. (**a**) Cross section through a piezomotor hyperdrive with independent motion of four motors, a sensor is used to calculate the position that the electrodes have actuated. Note there are no gears or threaded rods, just a piezomotor coupled to an electrode. Reproduced with permission from Cham JG, Branchaud EA, Nenadic Z, Greger B, Andersen RA, Burdick JW. Semi-chronic motorized microdrive and control algorithm for autonomously isolating and maintaining optimal extracellular action potentials. J Neurophysiol. 2005;93(1):570–9. (**b**) Results of an autonomous algorithm, used to control the positioning of the electrode depth to optimize the signal-to-noise ratio of particular spikes. Algorithm was used to control the hyperdrive in (**a**). Reproduced with permission from Cham JG, Branchaud EA, Nenadic Z, Greger B, Andersen RA, Burdick JW. Semi-chronic motorized microdrive and control algorithm for autonomously isolating and maintaining optimal extracellular action potentials. J Neurophysiol. 2005;93(1):570–9. (**c**) Example of a piezoelectric microdrive for moving a single electrode bundle in mice. © 2008 IEEE. Reprinted, with permission, from Yang S, Lee S, Park K, Jeon H, Huh Y, Cho J, et al. Piezo motor based microdrive for neural signal recording. Conf Proc IEEE Eng Med Biol Soc. 2008;2008:3364–7. (**d**) Tetrode recording with a piezoelectric microdrive in mice. The *circle* around the clustered cell represents a new cluster which was isolated with actuation of the piezomotor by just 4 **μ**m. Reprinted from Journal of Neuroscience Methods, Vol/edition number, Yang Y, Cho J, Lee S, Park K, Kim J, Huh Y, Yoon E-S, et al., Feedback controlled piezo-motor microdrive for accurate electrode positioning in chronic single unit recording in behaving mice, 117–127, Copyright 2011, with permission from Elsevier

Drug Delivery and Spike Recording

Pharmacology is among the most well-used methods employed to manipulate local brain regions while simultaneously monitoring behavior. However, in spite of this advantage, there is a paucity of literature combining pharmacology with high-density electrophysiology. This is in part due to the lack of effective drug delivery strategies that do not also produce pressure artifacts on neuron recording (e.g., microinjection). In addition, local manipulation does not always influence behavior, since the drug may not spread far enough. Finally, the specificity of drug manipulations depends on the quality of the pharmacological agents. A method which has been rather underused is that of reverse microdialysis. A microdialysis probe consists of a fluid inlet and outlet and a semipermeable membrane probe tip interposed between the inlet and outlet (Fig. 1.12a). With this method, drugs can be delivered without increasing local pressure around the tip of the probe.

Early attempts to combine microdialysis with electrophysiology revolved around local field potential and seizure manipulations [88]. However, designs began to incorporate bundles of microwires implanted adjacently to the microdialysis probes. For example, Ludvig et al. used a Kubie drive to position microwires and a dialysis probe in the hippocampus [89] (Fig. 1.12b, c). This electrode-microdialysis configuration could record up to 3 days in freely behaving animals. Once the electrode and probe were lowered into the hippocampus, the investigators found that they could both activate and deactivate neurons when the perfusion solution was switched to either high potassium or lidocaine, respectively (Fig. 1.12d, e). Moreover, in some cases, all eight electrodes could record neural activity, while perfusion solutions were switched. Subsequently, a Kubie style microdialysis multiunit drive was developed for use in primates [90], and recent advances have combined the Gothard-McNaughton style hyperdrive [76] with microdialysis for studies in rats [91].

By far, one of the major limitations to microdialysis is lag time for the drug to reach the probe tip. When a solution is switched from artificial cerebral spinal fluid (control) to a drug, the drug must be pumped through tubing from that switch to the microdialysis probe; this can take between 5 and 10 min. In 2002, Ludvig et al. [92] invented a device for rapid switching of perfusion solutions. The basic concept is to have both the perfusion solution and the drug pumped through separate channels to a switch located on the animal's head. Under these conditions, drugs could be delivered rapidly (within 1 min) of switching to the solution of interest.

Optical Stimulation and Spike Recording

The excitement for the optogenetic approach has become widespread. Optogenetics involves using light to activate light-sensitive channels (e.g., channelrhodopsin-2) which have been expressed in specific neurons [93]. Activating these channels permits specific manipulations of the neurons at on the millisecond timescale [94].

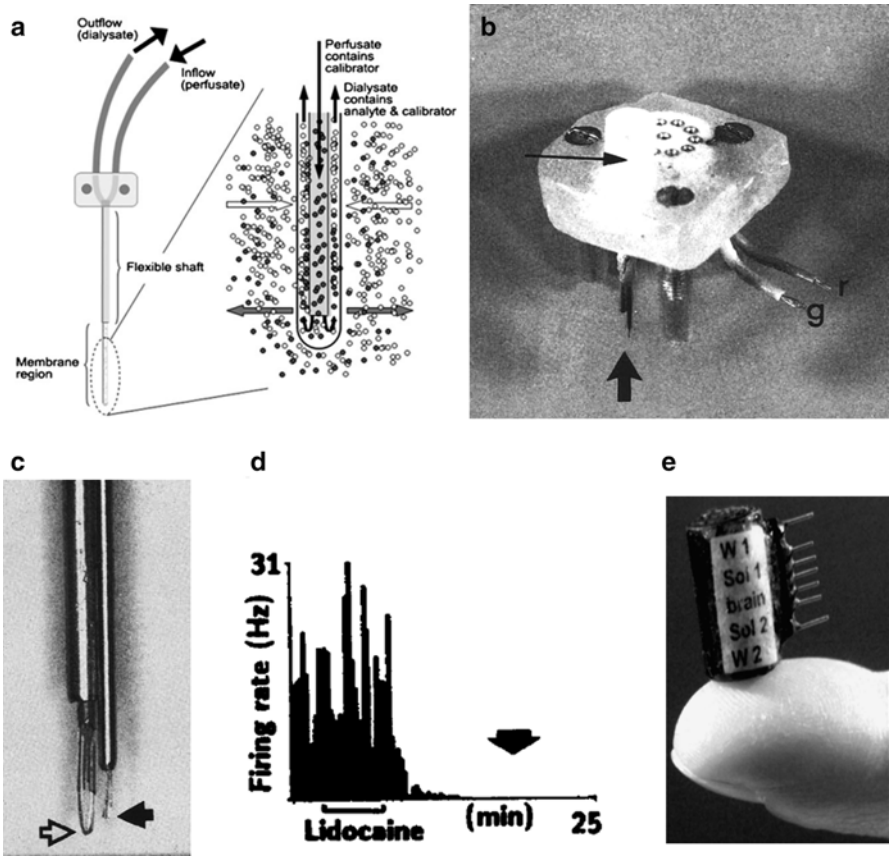

Fig. 1.12 Combined microdialysis and spike recording. (**a**) Example of a microdialysis probe. The inlet feeds to a semipermeable membrane which permits higher concentration compounds to pass into the brain. The outlet relieves pressure. With kind permission from Springer Science + Business Media: Pharmaceutical Research, AAPS-FDA workshop white paper: microdialysis principles, application and regulatory perspectives, 24(5), 2007, 1014–25 [102], Chaurasia CS, Muller M, Bashaw ED, Benfeldt E, Bolinder J, Bullock R, et al. (**b**) Combination of Kubie microdrive with microdialysis probe. The three screws around the perimeter are used to actuate the wires and microdialysis probe into the brain [89]. (**c**) Close-up of the microwire bundle and the dialysis probe tip (spaced 500 **μ**m apart) [89]. (**d**) Neural response to dialysis of lidocaine in the vicinity of the microwire electrodes. Washout with ACSF did lead to full recovery of neural responses [89]. (**e**) Rapid fluid switches which can be attached to the skull of freely behaving animals. Outermost tubes are air valves for opening and closing connection to the "brain." Two tubes are used as return lines to wash (W) drug out. Two tubes are used to preload solutions (Sol) (e.g., ACSF and drug [92]). Reprinted from Brain Research Protocols, 9(1), Ludvig N, Kovacs L, Kando L, Medveczky G, Tang HM, Eberle LP, et al., The use of a remote-controlled minivalve, carried by freely moving animals on their head, to achieve instant pharmacological effects in intracerebral drug-perfusion studies, 23–31, Copyright 2002, with permission from Elsevier. (**b–d)** Reprinted from Journal of Neuroscience Methods, 55(1), Ludvig N, Potter PE, Fox SE, Simultaneous single-cell recording and microdialysis within the same brain site in freely behaving rats: a novel neurobiological method, 31–40, Copyright 1994, with permission from Elsevier

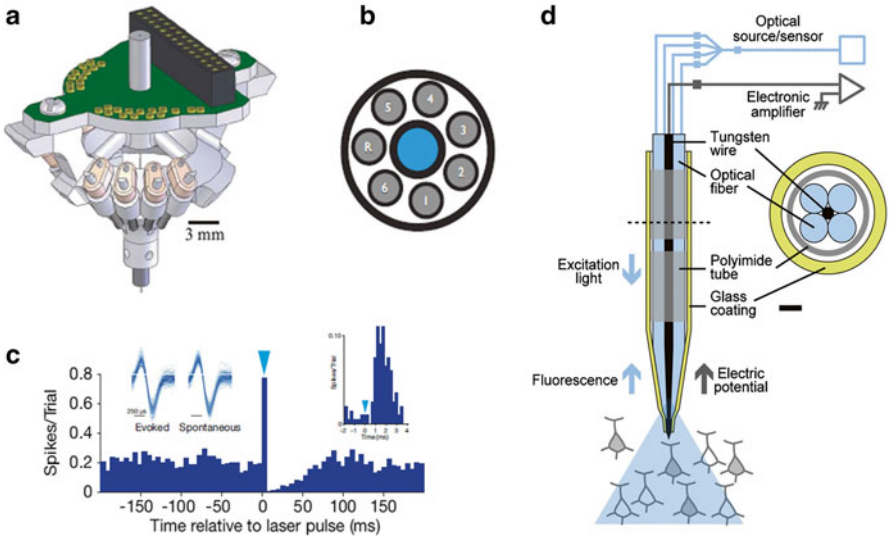

Fig. 1.13 Combined optogenetics and spike recording. (**a**) Example of an optogenetic hyperdrive with six tetrode recording channels and one reference electrode. Fiber optic is driven through the center of the hyperdrive [95]. (**b**) Cross-section through the drive bundle showing orientation or electrode positions and that of the optical fiber [95]. (**c**) Stimulation of inhibitory neurons expressing channelrhodopsin-2 inhibits firing of locally recorded neurons [95]. (**a**–**c**) © 2011 IEEE. Reprinted, with permission, from Siegle JH, Carlen M, Meletis K, Tsai LH, Moore CI, Ritt J. Chronically implanted hyperdrive for cortical recording and optogenetic control in behaving mice. Conf Proc IEEE Eng Med Biol Soc. 2011;2011:7529–32. (**d**) Glass-coated electrode composite of four optical fibers and one central sharp tungsten electrode. This electrode was capable of exciting channelrhodopsin while detecting fluorescent emission spectra (from EYFP). Emission was used to determine the proximity to channelrhodopsin-2 expressing regions in the primate thalamus. Reprinted from Journal of Neuroscience Methods, 211(1), Tamura K, Ohashi Y, Tsubota T, Takeuchi D, Hirabayashi T, Yaguchi M, et al., A glass-coated tungsten microelectrode enclosing optical fibers for optogenetic exploration in primate deep brain structures, 49–57, Copyright 2012, with permission from Elsevier

Siegle et al. [95] were the first to develop a hyperdrive capable of simultaneous optogenetic stimulation and high-density electrophysiology in mice (Fig. 1.13a). The drive was constructed with stereolithography, and an optical fiber was positioned in the middle of the hyperdrive with six recordings and one reference electrode concentrically placed around it (Fig. 1.13b). The optical fiber was set to shine into the brain from the cortical surface, and specific interneurons were engineered to carry the channelrhodopsin-2 protein. Importantly, light stimulation was found to inhibit recorded neurons, presumably through activation of these inhibitory neurons (Fig. 1.13c).

The hyperdrive described above is an excellent start for using optogenetics in high-density electrophysiology; however the spatial selectivity of the fiber optic is rather lacking, because it relies only on particular neurons that express the channelrhodopsin. Additional spatial selectivity might be added by designing recording

microelectrodes with an integrated fiber optic. Tamura et al. [96] designed a glass-coated, four-channel fiber optic and one-channel tungsten microelectrode, so that stimulation and recording could be conducted with the same electrode. The construction of this electrode borrowed the 1970s techniques for collapsing glass capillary over the tungsten electrode [58, 97] using an electrode puller. Figure 1.13d shows an example of the final construction, with the sharpened tungsten electrode core oriented at the center and four optical fibers orientated around it. Not only could this electrode activate cells expressing channelrhodopsin in primates, it could also detect emission spectra from fluorescent YFP tagged neurons when the laser light was shone on them. Using this emission, the authors could dial their electrode down to the approximate location for which neurons expressed both the channelrhodopsin and fluorescent protein. This electrode design has incredible potential for large-scale electrophysiology. If this electrode composite could be miniaturized and made flexible, it might be suitable for loading into a hyperdrive. Moreover, the ability to excite silent cells in the vicinity of the electrode may help solve the problem of why so few cells get recorded when there are such dense populations surrounding the electrode. Finally, there is a need to invent a fiber-optic tetrode, which may permit the dissection of local circuit connectivity.

Summary

This review serves as a substrate to understand the history and synthesis of technical developments for metal microelectrode over the past 60+ years. Many theoretical issues have advanced, including our understanding of the electrode-electrolyte interface and how best to condition electrodes. After 60 years of exploration, both the pre-insulated microwire and the glass-coated electrode still persist, and new outlets in optogenetics and developments in nanotechnology are being discovered. Hyperdrives have been revised numerously, and in some inceptions incorporate motors and piezoelectric actuators for precision movement of electrodes. Moreover, hyperdrive construction has been made entirely flexible through the use of stereolithography. We are encountering a new age of large-scale electrophysiology, in which simultaneous manipulation and recording of intracellular and extracellular neurons in vivo will combine seamlessly with pharmacology and optogenetics.

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Chapter 2
Silicon Probe Techniques for Large-Scale Multiunit Recording

Hendrik W. Steenland and Bruce L. McNaughton

Abstract Chapter 1 laid the groundwork for extracellular electrophysiology and the history of microelectrode and microdrive development. However, one of the most technically advanced areas of electrode fabrication is found in the microprobe (e.g., silicon probes) industry where nanoscale fabrication techniques are used to increase recorded neuron yield. To date, these probes have the highest number of contacts per probe and can be combined with integrated circuits, optogenetic control, and drug delivery. This chapter will review a history of development in this field, emphasizing technical advances and what it means for the investigation of neurons.

Keywords Silicon probes • High-density electrophysiology • Integrated circuits

Introduction

If one were to reverse engineer any piece of foreign electronics by blindly picking through each piece of hardware for which there was no part number, this task would be nearly impossible. The same situation exists when trying to understand the hardware of the brain. Given the incredible number of cells in the brain, in combination with the enormous number of synapses which change their connection weights, it becomes clear that the goal of reverse engineering even 1 mm^3 of brain tissue is a daunting task. Microelectrode technology can record multiple neurons simultaneously and extract general themes or patterns of brain function, but it is a far cry from reverse engineering. Moreover, the shaft of a standard microelectrode does not have any contacts for which to pick up neural activity; rather neural activity is only detected at the tip. Silicon microprobes represent one attempt to increase the detection of the number of neurons, without compromising the size of the probe. This chapter will focus on the development of varieties of silicon microprobes and their use in neuroscience.

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The Passive Silicon Probe

In the 1970s, Wise et al. [1] united the silicon chip industry with neuroscience through the production of the first in vivo silicon probe. Figure 2.1a, b shows an illustration of their silicon probe. This microprobe was considered a passive probe since it did not contain any powered electronic circuitry for amplifying or filtering collected data. Many years have passed since this time, and microprobes have advanced considerably. A more recent passive probe designed by Kindlundh et al. [2] is depicted in Fig. 2.1c. In this case however, the electrode contacts can be seen as many small, recessed windows, populating the shaft of the probe.

Before the advantages of silicon probes are discussed, the basic process of silicon probe production will be outlined. The fabrication process typically consists of four steps: substrate preparation, metallization, insulation, and finishing. Substrate preparation often includes applying a photoresist, to protect regions of the silicon which will define the shape of the electrode. The silicon can then be etched around this protected region forming a mesa (raised region). The metallization step consists of plating a metal (e.g., gold) onto silicon substrate. The insulation step in the case of Wise [1] consisted of the deposition of silicon dioxide (glass) over the metal contact; however, many different types of insulation may be used. Electrical contacts can be exposed by selective removal of insulation from regions of the probe using a photoresist in combination with etching. The finishing procedure consists of removing the probe from the rest of the silicon wafer using an etchant process and connecting the probe to output wires. These processes are constantly under refinement, and the reader is referred to a more extensive review [3].

It can readily be appreciated that there are several fundamental advantages that the silicon microprobes have over classical microelectrodes. (1) For example, there is a high degree of reproducibility of these microprobes and their construction can be efficient if the appropriate process hurdles have been overcome. (2) The packing density of electrode contacts per given volume is well above that of traditional microelectrodes. (3) The microprobes have reproducible recording impedances compared to microelectrodes. This means that rejecting common mode signals, via referencing to one of the channels in the probe, is advantageous for the removal of biological, mechanical, and stimulus artifacts [4]. (4) The geometry of the circuit is known, and so it is easy to decipher where the electrode contact is in the brain, relative to the other contacts. (5) The use of silicon substrates makes it possible to incorporate integrated circuits for amplification, filtering and multiplexing into the microprobe (known as an active microprobe, see below). (6) The precision of the spacing of a microprobe offers the advantage of recording across different layers of the cortex, which can provide insights into the origin and propagation of seizure and brain waves [5]. (7) The silicon substrate can act as a ground plane when it is placed in the brain to reduce crosstalk between adjacent channels [1]. (8) So little metal is used in microprobe fabrication techniques, so shunt capacitance is small relative to a standard microelectrode [1]. (9) The ability to detect many neurons increases the probability that one can detect monosynaptic connections between neurons

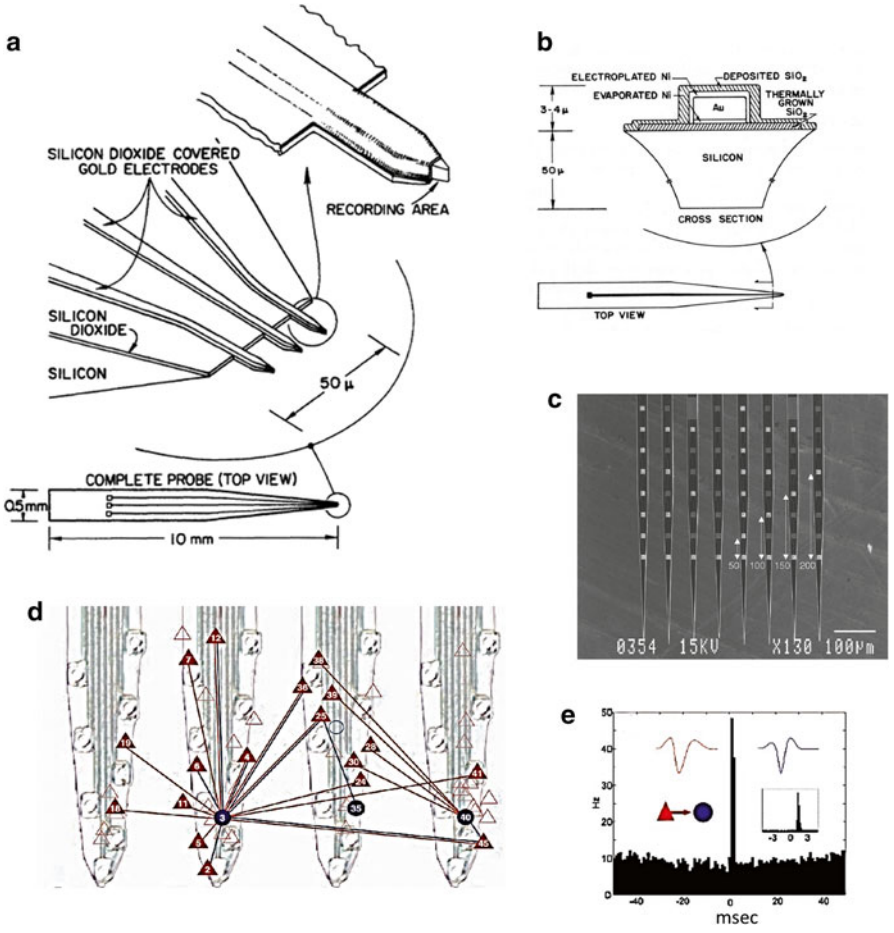

Fig. 2.1 The first passive silicon probe for in vivo spike recording. (**a**) A silicon multielectrode with three recording contacts and insulated with silicon dioxide. The exposed recording area/tip can be seen peeking out from under the silicon dioxide. © 1970 IEEE. Reprinted, with permission, from Wise KD, Angell JB, Starr A. An integrated-circuit approach to extracellular microelectrodes. IEEE Transactions on Bio-Medical Engineering. 1970;17(3):238–47. (**b**) Cross section through silicon probe, depicting the various layers including: nickel (Ni), silicon dioxide (SiO_2), gold (Au), and silicon. © 1970 IEEE. Reprinted, with permission, from Wise KD, Angell JB, Starr A. An integrated-circuit approach to extracellular microelectrodes. IEEE Transactions on Bio-Medical Engineering. 1970;17(3):238–47. (**c**) Scanning electron micrograph of a 64-site probe where selected windows have been open to make contacts (*bright squares*). Reprinted from Sensors and Actuators, 102(1), Kindlundh M, Peter N, Hofmann UG, A neural probe process enabling variable electrode configurations, 51–8, Copyright 2004, with permission from Elsevier. (**d**) Detecting functional connections with silicon probes. *Filled red triangles* are pyramidal neurons, and *filled blue circles* are inhibitory neurons. *Red lines* indicate monosynaptic excitation, and *blue lines* represent monosynaptic inhibitions. Connections were detected by cross-correlation analysis (not shown). Reproduced with permission from Bartho P, Hirase H, Monconduit L, Zugaro M, Harris KD, Buzsaki G. Characterization of neocortical principal cells and interneurons by network interactions and extracellular features. Journal of Neurophysiology. 2004;92(1):600–8. (**e**) Example of monosynaptic excitatory connection as calculated with cross-correlation analysis. *Red triangle* represents a putative pyramidal cell, while the *blue circle* represents a putative interneuron. Reproduced with permission from Bartho P, Hirase H, Monconduit L, Zugaro M, Harris KD, Buzsaki G. Characterization of neocortical principal cells and interneurons by network interactions and extracellular features. Journal of Neurophysiology. 2004;92(1):600–8

(Fig. 2.1d, e) [6]. (10) Finally, the extracellular potential conduction can be recorded along a neuron from the dendritic tree to the axon hillock, because of the precise spatial distribution of the electrode sites.

One of the major problems with the passive electrode is attaching a sufficient number of leads so that all the recording channels can be sampled. In addition, as the number of leads increases so will the difficulty of having such probes float in the brain. Multiplexing is an excellent means to reduce the number of data lines connected to an active microprobe (see below). A few other requirements should be mentioned for the design of an ideal microprobe. Firstly, tissue displacement from an electrode array must be small enough to avoid disrupting the physiological system under study [7]. In addition, the height of the probe shank above the cortex needs to be kept to a minimum (<1 mm, in primates) so that it can float with the brain tissue [7]. Finally, given the small size of neurons, the minimal placement of electrode contacts on a silicon probe should be between 50 and 100 μm.

The Active Silicon Probe

Passive microprobes are probes that are similar to microelectrodes in that they simply act as channels to take information from the brain and relay it to integrated circuits. By contrast, active microprobes include dedicated integrated circuits for processing information as it is detected from the brain [8]. To explain how this is possible, we will take a step back and explain what makes silicon substrates special.

Silicon is a semiconductor, meaning that under particular conditions, electrical conduction through this material can be increased. This is the fundamental property that makes the modern transistor possible. When the atomic lattice of a silicon wafer is bombarded with ions such as boron, the electrical conductivity of the chip can be biased, changing the composition of the silicon wafer into a semiconductor. By applying voltage to semiconducting silicon, one can change the flow of current, sort of like controlling the flow of water by altering the size of a bottleneck. Largely, this is what the transistor does, with the exception that electrical current is controlled. Connections between these transistors can then be laid down in combination with resistive and capacitive components to make an integrated circuit on the silicon wafer. The fundamental benefit to silicon probe manufacture is that buffering, amplification, filtering, multiplexing, and wireless transmission can all be carried out on the probe using these components. An example of this active silicon technology including many of these components can be seen in Fig. 2.2.

Two major issues tend to influence the active silicon probe. The first is providing sufficient encapsulation for the integrated circuit, so that it is protected from fluid. The second issue is the amount of heat dissipated from the microprobe to the surrounding tissue. Temperature must be kept to a minimum so that it does not lesion surrounding areas [8]. Powering active probes can cause heat dissipation, and according to Wise [7], this power dissipation must be lower than 20–30 mW.

If the final goal is to turn a passive probe into an active probe, scientists are then constrained in their techniques for the production of silicon probes. For example, deep boron diffusion is used to direct the shape of the silicon probes, but the area where integrated circuits are included need to be masked off from this doping process [9]. In addition, the substrate which supports the recording region of the probe needs to contain silicon, so that semiconductor properties can be exploited. The process must also be efficient to produce many probes in a cost-effective way (e.g., Peckerar et al. [10]). Finally, an ideal neural implant would be wireless; however, wireless devices would require a method for powering the device, possibly through inductive battery charging. Moreover, the high quantity of data collected with high-density probes would require sufficient bandwidth. Indeed, there has been effort and progress made toward integrating these features with silicon probes [11].

Active and passive probes have often been produced by circumscribed groups of researchers operating out of a particular institute. The most well known have been the Michigan and Utah groups, so their work will be discussed next according to the particular development group.

Worldwide Silicon Microprobe Developments

Michigan Probes

In its infancy, microprobe construction was relatively slow and required difficult fabrication sequences [9]. In 1985, Najafi and Wise developed a 10-channel, gold-contact microprobe which measured up to 3 mm in length and was about 50 μm wide by 15 μm thick using a single-sided wafer fabrication process [9]. Recordings were made from the cerebellar cortex, detecting action potentials as large as 200 μV.

Drake et al. [12] described the recording capabilities of a 15 μm thick by 90 μm wide microprobe built on a silicon substrate using photolithographic techniques. The probe was inserted through the pia matter into the cortex of an anesthetized rat. Interestingly, the authors report that electrode contacts on the face of the probe tended to have better amplitude recordings (up to 675 μV) than along the edge of the probe. Significantly, when adjacent recording sites were spaced at 100 μm or less, the same cell could be picked up on both recording sites. Consistent with the methods used in tetrode recording [13], this can be useful to discern the identity of individual neurons among a field of action potentials.

Najafi and Wise [14, 15] also produced the first active microprobes for in vivo investigation. These probes contained integrated chip CMOS (complementary metal–oxide–semiconductor) circuitry for signal amplification, multiplexing, and self-testing. In addition, realizing that not every site of the probe would have a good quality signal, the probe could be multiplexed between 32 analog channels from which to collect the best neural data. Later versions of probes developed by this group included electrical stimulation technology (see section “Silicon Probes and

Electrical Stimulation"). Moreover, an 8×16 3D array (inter-shank spacing 200–400 μm) of such microprobes was created with an astonishing 1,024 recording sites [16]. Since the attachment of wires to each of the recording channels would add forces which would disrupt the ability of the probe to float in the brain, multiplexing technology was required to reduce the data transmission lines. In addition, similar to the Utah probe (see section "Utah Array"), a special device was needed to insert the array through the arachnoid and pia matter and into the brain. In contrast to the Utah method, this device was spring loaded, and the array was held in place by a vacuum. The authors report that cortical units had amplitudes as high as 500 μV (peak to peak).

Kipke et al. [17] tested the utility of a floating Michigan probe in both the auditory and somatosensory cortices of chronically instrumented rats. The amplitude of recorded spike activity ranged from 50 to 800 μV peak to peak. The authors found that signal could be recorded for up to 6–28 weeks with 80 % of the recording contacts detecting neural spike activity. Michigan probes with active components, including unity gain, preamplification, and multiplexing, needed to be put to the test. One of the main limitations in developing and implementing such a device was due to low-frequency/DC drift of the preamplifier [18]. Olsson attempted to solve this problem through the addition of a high-pass filter which included a subthreshold-biased MOS transistor [18]. In this case, the MOS transistor acted as a resistor, forcing the output offset voltage to be equal to the input offset voltage. This same component also permitted the tuning of the high-pass filter right on the silicon probe. Olsson [18] also demonstrated the feasibility of multiplexing silicon probe data acquisition in vivo at 5 kHz.

The small size, reliable manufacture and high-density of recording sites make silicon microprobes potentially ideal for neuro-prosthetic applications. However, a useful implantable device would be preferred to float with the brain and would require a low profile. Yao et al. [19] developed a low-profile three-dimensional active silicon probe array (256 recording sites) (Fig. 2.2b, c). What was unique about this design is that the integrated circuits for stimulating and recording could be folded over to reduce the height of the device. Remarkably, the probe assembly only required seven leads for control and to acquire data.

An interesting offshoot for silicon probes has been to use them for detecting monoamine concentrations in the extracellular space [20, 21]. In such developments, the contacts of the silicon probe are sputter coated with carbon and coated with Nafion (for voltammetry recording). Some probes can detect both neural activity and changes in monoamine concentration from different sites within the same probe. Currently, the Michigan probe can be purchased from the company NeuroNexus.

Utah Array

Interest in the Utah array was initiated with the hope of restoring sensory function with visual cortex prosthesis [22]. This Utah array consisted of a 4.2×4.2×0.12 mm thick substrate from which 100 conductive silicon needles project (Fig. 2.3a. b).

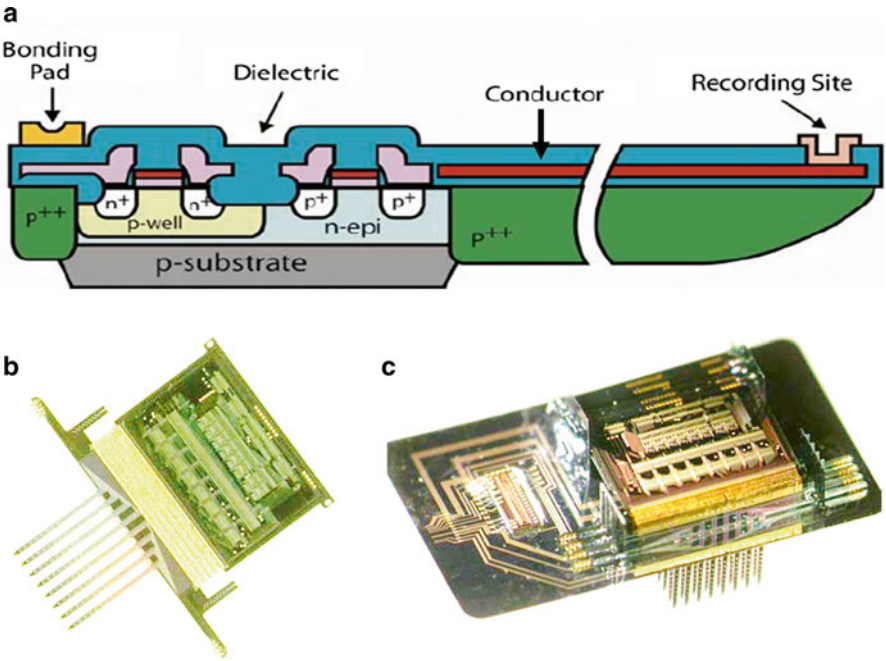

Fig. 2.2 Active silicon probe. (**a**) Cross section of a silicon probe with different layers of insulation (*blue* dielectric), conducting signals (*red* conductor), recording site (peach), etchant stop layer (p^{++}silicon), transistor gate (*small red* regions), and oxide layer (*small pink* regions) interposed between doped p+(sources) and p+(drains) and n+(sources) and n+(drains). p-well and n-epi are doped regions controlled by their respective base regions. The combination of these complimentary npn and pnp MOSFETs forms a CMOS transistor and can be exploited for active electronic functions of the silicon probe [45]. © 2004 IEEE. Reprinted, with permission, from Wise K, Anderson DJ, Hetke J, Kipke DR, Najafi A. Wireless Implantable Microsystems: High-Density Electronic Interfaces to the Nervous System. Proceedings of the IEEE. 2004;92(1):76–97. (**b**) Active stimulating and recording probe. Probe has active CMOS circuitry including on-chip digital-to-analog conversion for stimulation and preamplifiers to record spikes [19]. © 2005 IEEE. Reprinted, with permission, from Yao Y, Gulari MN, Ghimire S, Hetke JF, Wise KD. A low-profile three-dimensional silicon/parylene stimulating electrode array for neural prosthesis applications. Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference. 2005;2:1293–6. (**c**) The recording probe in (**b**) can be assembled in to an array. The probes had a flexible region which permitted the active circuitry to fold over, limiting the profile of the device [19]. © 2005 IEEE. Reprinted, with permission, from Yao Y, Gulari MN, Ghimire S, Hetke JF, Wise KD. A low-profile three-dimensional silicon/parylene stimulating electrode array for neural prosthesis applications. Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference. 2005;2:1293–6

The needles are 1.5 mm long and 90 μm at their base with polyimide as an insulator. The sharpened ends of the needles were coated with platinum to facilitate charge transfer with the interfacing tissue. However, several modifications had to be made before this final version. What is most innovative about the original manufacture of these probes is that the scientists doped specific regions of the silicon with

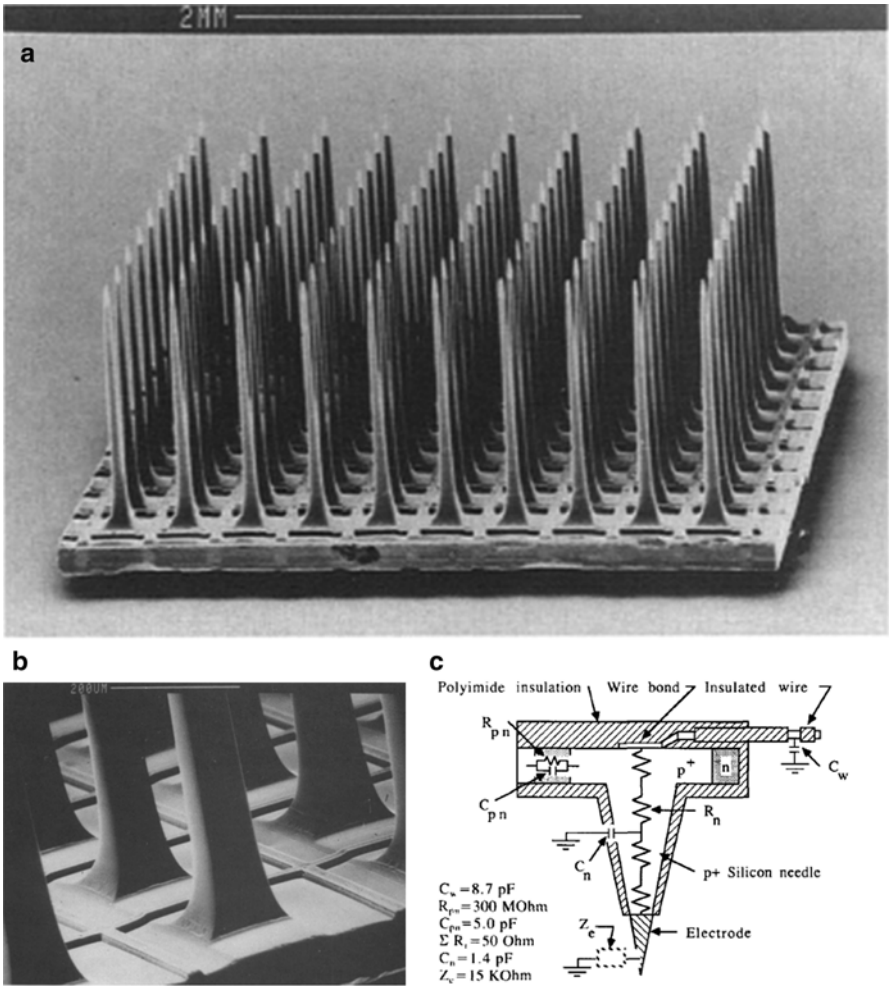

Fig. 2.3 The Utah array. (**a**) Scanning electron micrograph of a revised Utah electrode array. Reprinted from Brain Research, 726(1–2), Nordhausen CT, Maynard EM, Normann RA, Single unit recording capabilities of a 100 microelectrode array, 129–140, Copyright 1996, with permission from Elsevier. (**b**) Scanning electron micrograph showing the glass insulating regions as raised bumps between the columns. With kind permission from Springer Science+Business Media: Annals of Biomedical Engineering, A glass/silicon composite intracortical electrode array, 20(4), 1992, 423–37, Jones KE, Campbell PK, Normann RA. (**c**) The original equivalent circuit schematic of the thermo-migrated Utah array probe. The circuit shows wire capacitances (C_w), pn junction capacitance (C_{pn}) and resistance (R_{pn}), silicon needle resistance (R_n) and insulation capacitance (C_n), and the electrode contact impedances (Z_e). Polyimide was used as insulation, and the electrode tip was plated with platinum. The p and n refer to doped regions of the probe which as a consequence of their spatial arrangement reduce current leakage to adjacent probes (not shown). © 1991 IEEE. Reprinted, with permission, from Campbell PK, Jones KE, Huber RJ, Horch KW, Normann RA. A silicon-based, three-dimensional neural interface: manufacturing processes for an intracortical electrode array. IEEE Transactions on Bio-Medical Engineering. 1991;38(8):758–68

aluminum through a process of thermo-migration. The result is 100 columns of p+-doped semiconducting material. (An equivalent circuit can be seen in Fig. 2.3c.) Since the columns were realized in a solid block of material, the investigators used a computer-controlled, dicing saw to produce a 10×10 array of rectangular columns and thus separate the p+-doped silicon. The final shape of the needle was created by chemically etching the 100 columns of silicon to a point. Notably, this was the first array to be constructed vertically, while all other probes had been constructed on their flank. Subsequent alteration to this array included a glass dielectric to provide insulation between individual electrode needles in the array [23] (Fig. 2.3b). In this design, the thermo-migration procedure was not used to dope the silicon; rather a pre-doped p-type silicon substrate was used, and was sawn into an array. This method was found to improve interelectrode impedance and capacitance.

In theory, a two-dimensional array of electrodes should produce a bed-of-nails effect when inserted into the brain. To circumvent this problem, and implant the Utah array, Rousche and Normann [24] designed a pneumatically actuated impact insertion system. To implant the Utah array through the meninges, a minimum speed of 8.3 m/s was required, with the resultant electrode depth at 1.5 mm. With the electrical properties refined and the insertion method standardized, the recording quality of the Utah probe was tested in cat striate cortex [25]. 58.6 % of the electrodes in the array detected evoked neural responses as large as 200 μV. In these recordings, signals were not yet multiplexed, so all 100 wires were connected between the array and a 100-channel printed circuit board. Currently, the Utah probe is commercially available from Blackrock Microsystems in Salt Lake City, Utah.

MIT Probe

Kuperstein and Whittington [26] designed a 24-contact microprobe with 85 μm contract spacing (Fig. 2.4a, b) at the Massachusetts Institute of Technology. Contacts were arranged along the edge of the probe, rather than the face, to increase the contact with the brain. With this design, neural signals were recorded from the cat visual cortex [26] and the olfactory and hippocampal cortices of the rat, with signal to noise similar to conventional microelectrodes [27]. Molybdenum was used as a substrate to increase the strength of the probe; however, the use of this substance as a substitute for silicon practically excludes the possibility for silicon-based integrated circuitry.

Hopkins Probe

Like the MIT probe, the Hopkins probe contains a strong and flexible molybdenum substrate with polyimide insulation (Fig. 2.4c) [4]. This probe was developed at Johns Hopkins University by Blum et al. [4]. The probe was 19 μm thick with up to

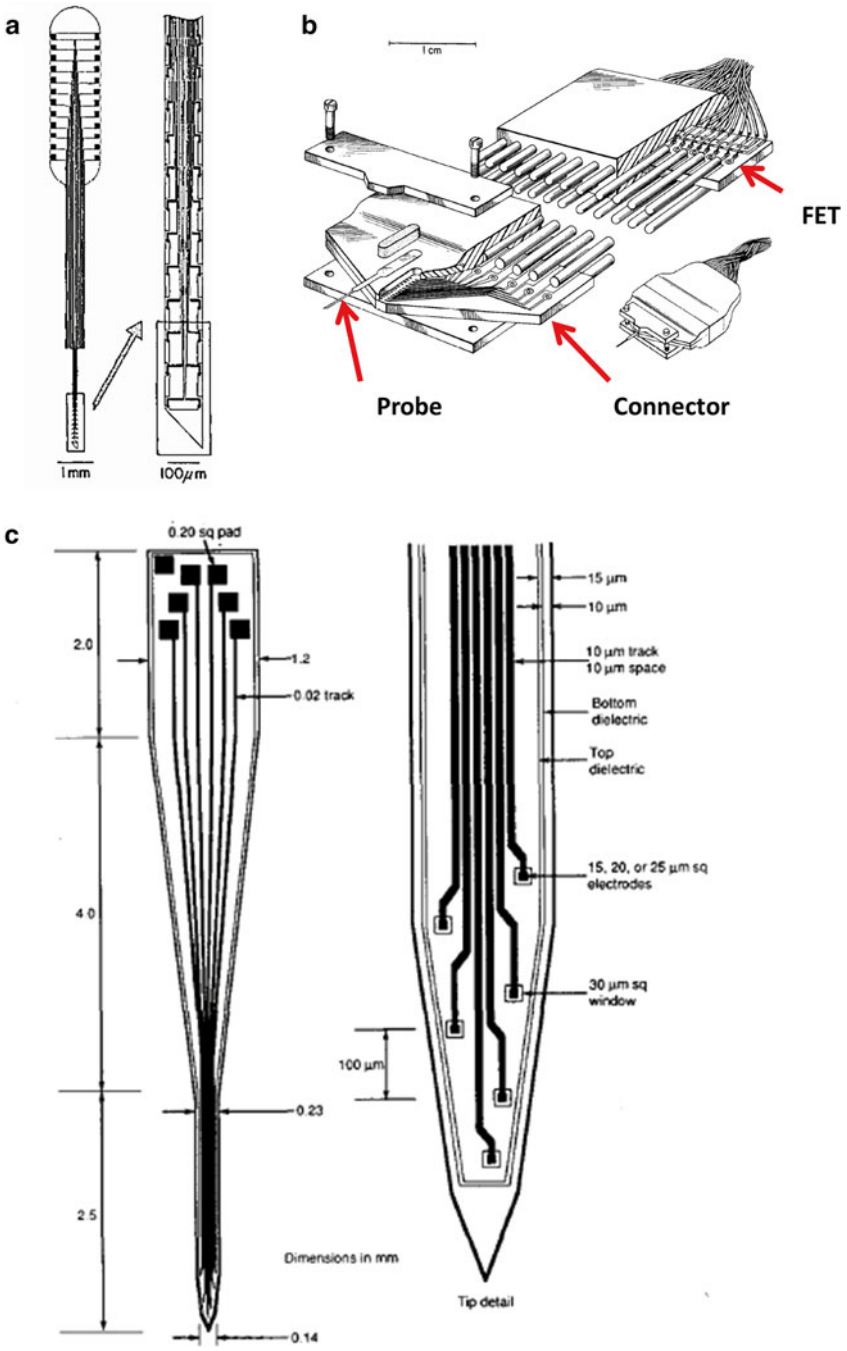

Fig. 2.4 The MIT and Hopkins probes. (**a**) MIT probe with contacts located around the perimeter. Reprinted from Neuroscience, 15(3), Kuperstein M, Eichenbaum H, Unit activity, evoked potentials and slow waves in the rat hippocampus and olfactory bulb recorded with a 24-channel

eight gold recording channels [4]. The advantage of this probe is that it did not require advanced semiconductor processing technology. Since molybdenum is conductive, it needed to be separated from the electrical recording contacts; therefore, the electrodes were constructed on top of a thin layer of polyimide which adhered to the substrate. A final layer of polyimide is placed over channels and small holes in the polyimide permit the electrical contact with the extracellular recording environment. This probe was reported to record action potentials greater than 100 μV from the rat spinal cord.

Caltech Probes

Silicon microprobes typically have one side with recording contacts, because of constraints on the manufacturing process. However, if electrical contacts could be etched on both sides of the probe, neuron recording yield could be increased. At Caltech University, Du et al. [28] developed a dual-sided microprobe on a silicon substrate with 16 individually addressable recording sites on each shank. Moreover, two silicon substrates were stacked parallel to one another to make a 3D array. As a consequence, the neuronal source could be triangulated much like a tetrode. Recordings from the locust nervous system with this microprobe yielded spikes as high as 800 μV.

Du et al. [29] also developed a silicon microprobe with nanofabricated high-density recording leads using an electron-beam lithography technique. This technique does not require the use of a mask and can produce submicron features. This microprobe was manufactured with signal amplification, band-pass filtering, and 32:1 multiplexing, impedance testing, and required a mere 6 lines to control power and data acquisition. The small electrical routing sizes (<300 nm) permitted an increase in the number of recording channels on this probe (up to 64) and the spread of recording contacts across the face of the probe (Fig.2.5a–c). The maximum spike amplitude recorded in the thalamus was on average 150 μV. With a mere 40 μm spacing of electrodes, adjacent channels could be used to look at local circuit connections using cross-correlation.

Fig. 2.4 (continued) microelectrode, 703–12, Copyright 1985, with permission from Elsevier. (**b**) Specialized connector and MIT probe (*left*) with a preamplifier (*right*). The FETs of the preamplifier are represented by the small pads located between the pins and the jumper wires (which connect to the output leads). *Bottom right* is the assembled probe, connector, and amplifier. Reprinted from Neuroscience, 15(3), Kuperstein M, Eichenbaum H, Unit activity, evoked potentials and slow waves in the rat hippocampus and olfactory bulb recorded with a 24-channel microelectrode, 703–12, Copyright 1985, with permission from Elsevier. (**c**) Depiction of the spatial arrangement on the Hopkins probe. © 1991 IEEE. Reprinted, with permission, from Blum NA, Carkhuff BG, Charles HK, Jr., Edwards RL, Meyer RA. Multisite microprobes for neural recordings. IEEE transactions on bio-medical engineering. 1991;38(1):68–74

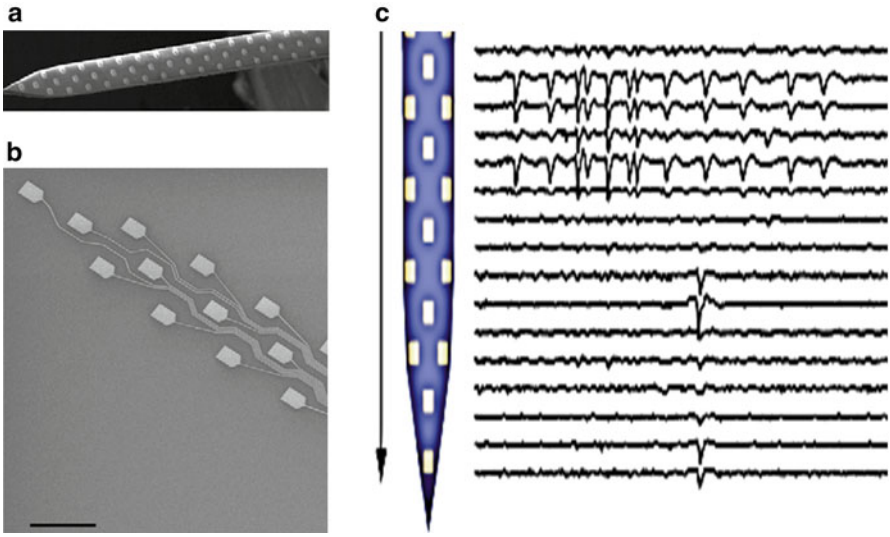

Fig. 2.5 Caltech probe. (**a**) High-density microprobe configuration with scale bar is 200 μm. (**b**) Gold recording sites composed (*rectangles*) and leads (290–1,000 nm). Scale bar is 50 μm. (**c**) Parallel recording from all leads of the microprobe after data was multiplexed. Recordings were made from the mouse thalamus. Figures reproduced with permission from Du J, Blanche TJ, Harrison RR, Lester HA, Masmanidis SC. Multiplexed, high density electrophysiology with nanofabricated neural probes. PloS one. 2011;6(10):e26204

Silicon Probes and Actuation

Microprobes typically have enough contacts to span many cortical layers; accordingly there is little need to adjust the depth of the electrode while it is in the cortex at its final destination. However, there have been some attempts to permit adjustment of the silicon probe even after implantation in the brain. One option is to design micromechanical structures to directly interface with the silicon probe. This concept was made apparent with a review by Wise in 1991 [3], which showcased development of micromachined gears and other micromechanical components.

The closest approximation to what was envisioned by Wise appears to be the recent actuating devices developed by Muthuswamy et al. [30]. This device microactuated a 3-channel polysilicon microelectrode array (Fig. 2.6). The probes are moved with thermal actuators with a step resolution of 8.8 μm and a total range of 5 mm. The actuators can heat up to several hundred degrees, but because the actuators are so small, the heat is not appreciably transferred to the recording probe. The actuators are coupled to a ratcheting system that drives a shuttle up and down. The device was able to sample neural activity of the somatosensory cortex of chronically implanted adult rats in the range of 400–900 μV. Subsequently, Muthuswamy et al. [30] developed an electrostatic driving mechanism for actuating polysilicon

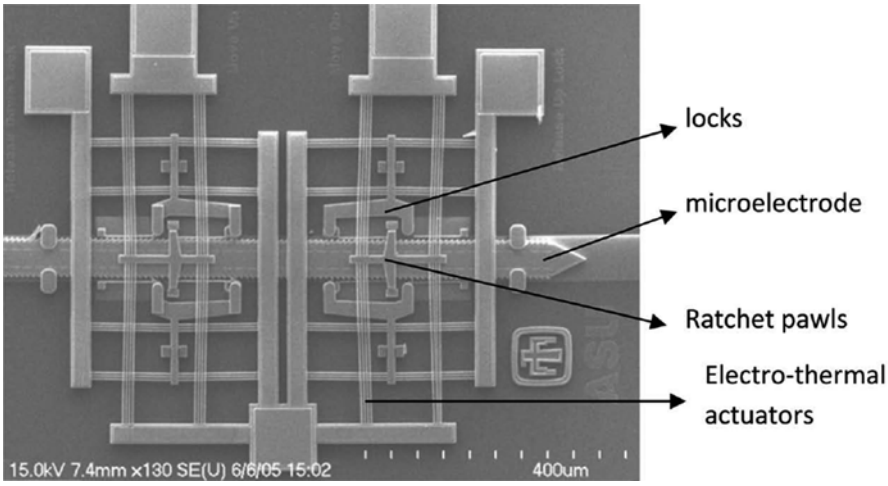

Fig. 2.6 Actuating probes. An electron micrograph of an electrothermal microactuator. The microelectrode is a mere 50 μm wide. Reproduced with permission from Muthuswamy J, Anand S, Sridharan A. Adaptive movable neural interfaces for monitoring single neurons in the brain. Frontiers in Neuroscience. 2011;5:94 [46]

microelectrodes with gears down to 1 μm precision. Electrodes can be moved a total distance of 5 mm. Recordings were obtained chronically from the somatosensory cortex of rats yielding units of amplitudes ranging from 100 to 500 μV.

In Chap. 1, the use of hyperdrives was discussed for actuating microelectrodes in the brain. Recently, a similar use has been appropriated for silicon probes. Vandecasteele et al. [31] describe a method to implant a 4-shank, 32-site silicon probes using a movable microdrive. In this example, connecting the silicon probe to the headstage required a mini-flexible polyimide cable.

Silicon Probes and Electrical Stimulation

A microprobe that has the potential to both record and respond to neural activity has practical application in neural prosthesis. Based on this practical possibility, neuroscientists have tried to build microprobes with combinations or recording and stimulation. This first stimulating microprobe consisted of 8–16 silicon contacts that could not only detect neural activity but also have the capacity to respond and influence neural activity through the application of electrical stimulation [32]. Subsequently, Kim et al. [33] developed a 64-recording-site probe which was also capable of stimulation (Fig. 2.7a, b). The probe would use a serial bit stream to supply the probe with an address and the magnitude of the current (+127 to −127 μA). On-chip integrated circuits were used for analog data amplification and filtering. Among the many interesting circuit features, this probe also had on-chip impedance

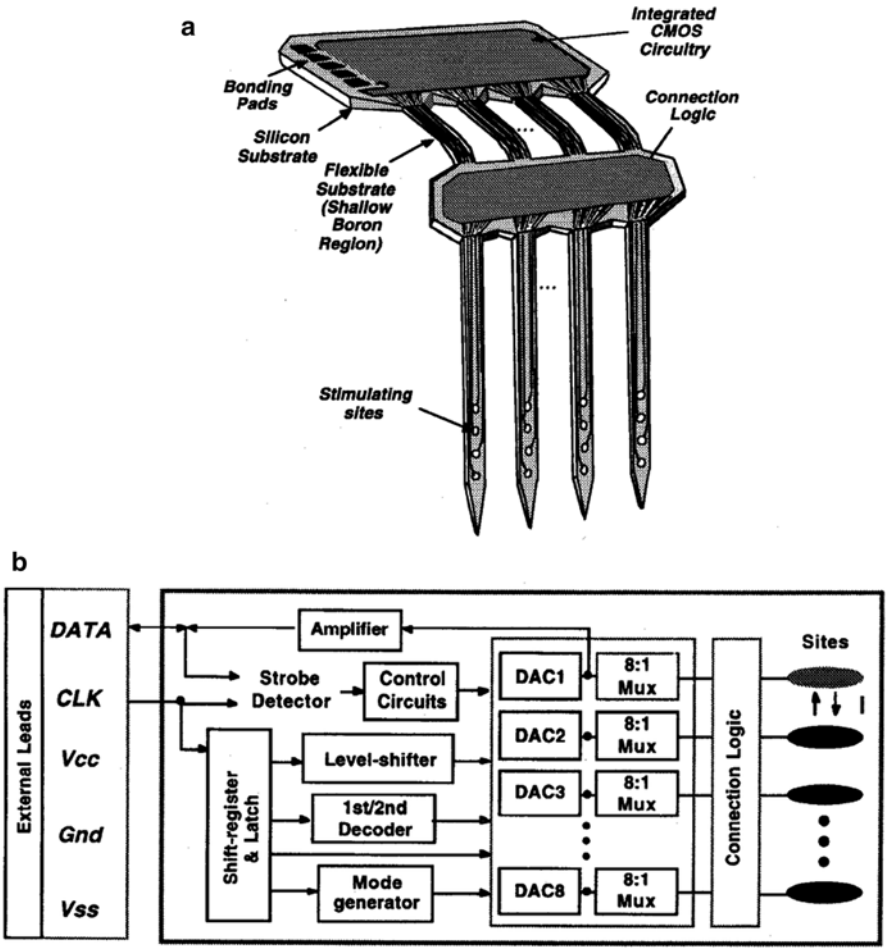

Fig. 2.7 Electrical stimulation microprobe. (**a**) Basic structure of a multiplexed neural probe. The contacts on the shanks can act as both stimulating and recording electrodes controlled with onboard circuits. A flexible substrate permits the probe to fold [34]. (**b**) Block diagram of on-chip circuit. The data line carries 8:1 multiplexed input. The on-chip DAC or digital-to-analog converters are used to send electrical stimulation to the recording sites. Bidirectional data flow permits control signals to be sent for stimulation and acquire signals to be sent for data acquisition [34]. © 1997 IEEE. Figures reprinted, with permission, from Kim C, Wise K. Low-Voltage Electronics for the Stimulation of Biological Neural Networks Using Fully Complementary BiCMOS Circuits. IEEE Journal of Solid-State Circuits. 1997;32(10):1483–90

testing for all channels of the probe. Subsequently, Kim et al. [34] developed a chronic stimulation and recording Michigan probe with BiCMOS technology. This permitted the advantages of CMOS for digital circuitry but reduced the power consumption with integrated bipolar transistor technology. In 2005 [18] Michigan probe technology, combined with multisite stimulation, was tested in an in vivo preparation. One hundred microsecond pulses were found to evoke spikes in nearby recorded neurons with currents as low as 4–8 μA.

Silicon Probes and Drug Delivery

Given the silicon probe's utility in acquiring high-density neural data, it became desirable to modulate neural activity with more selectivity than what electrical stimulation offers. Chen et al. [35] designed a silicon probe capable of delivering pharmacological agents as well as simultaneously recording from neurons. The silicon substrate possessed multiple flow channels (10 μm) and orifices near the electrode recording sites (Fig. 2.8a–c). At the back end of the probe, the channels are fitted with polyimide tube, so that pharmacological agents could be perfused. The authors found that they could inhibit local neuron activity with the perfusion of gamma-aminobutyric acid. Cheung et al. [36] introduced a silicon probe fabrication method based on SOI (silicon on insulator) technology to produce a silicon probe with a sprinkler-style fluidic channel. The holes for this sprinkler (3×3 μm) were spaced 50 μm apart along a 6 mm length of the probe.

One of the most complex drug delivery probes to date was developed by Spieth et al. [37]. This probe consisted of a 3D array of 4×4 probes, which has a form that is similar to that of the Utah array. Each probe was significantly longer (8 mm) than the Utah array (1.3 mm) and had multiple recording contacts (Fig. 2.9a–d). Microchannels were incorporated into the probes for drug delivery and a special elastic microfluidic cable was developed so that fluid could be delivered to the probe while

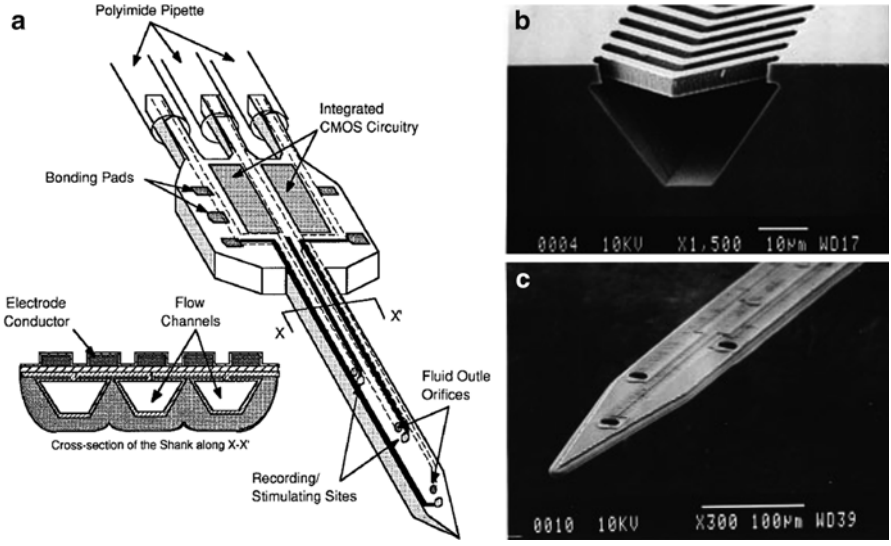

Fig. 2.8 Drug delivery microprobe. (**a**) Micromachined probe which has three channels for drug delivery in addition to recording and stimulation sites. Note the integrated CMOS and the polyimide contact sites. (**b**) Electron micrograph cross section of the etched micro-channel. The chevron pattern will later be sealed for the finished product. (**c**) Electron micrograph of a probe containing three drug delivery orifices. © 1997 IEEE. Figures reprinted, with permission, from Chen J, Wise KD, Hetke JF, Bledsoe SC, Jr. A multichannel neural probe for selective chemical delivery at the cellular level. IEEE transactions on bio-medical engineering. 1997;44(8):760–9

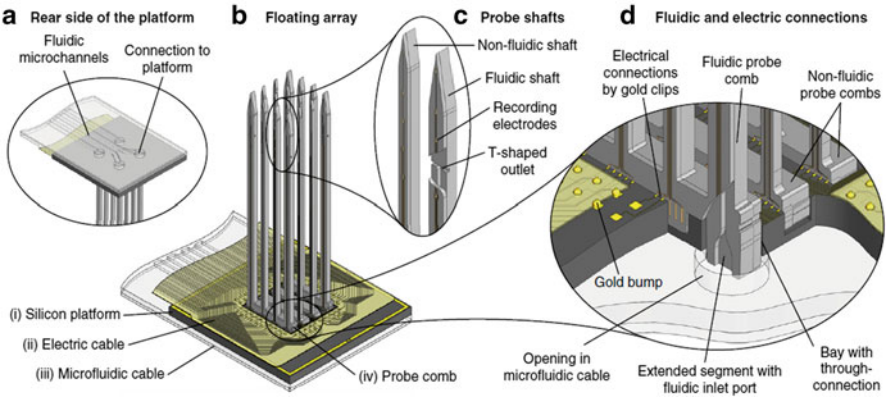

Fig. 2.9 Drug delivery microprobe array. (**a**) Floating 3D array for recording and drug delivery. (**b**) Underside of the probe assembly with flexible cable for liquid delivery. (**c**) Combined fluidic and non-fluidic probes in the same shaft. (**d**) Fluidic and electronic connections. Figures reproduced with permission from Spieth S, Brett O, Seidl K, Aarts AA, Erismis M, Herwik S, et al. A floating 3D silicon microprobe array for neural drug delivery compatible with electrical recording. Journal of Micromechanics and Microengineering. 2011;21:1–16. © IOP Publishing. Reproduced by permission of IOP Publishing. All rights reserved

the probe floats in the brain. The infusion rate of the probe could range from 1 to 5 μL/min. Future developments will likely see refinements in design, integrated circuits, and possibly glutamate biosensors.

Silicon Probes and Optogenetics

As discussed in Chap. 1, optogenetics is a very powerful tool for neuroscientists, permitting the possibility of turning on and off neurons using light. Integrating optics and silicon probes will permit the ability to specifically stimulate local neurons while monitoring neural responses.

Rather than design a new silicon probe, the most expeditious way to combine fiber optics with high-density electrophysiology is simply to glue a fiber optic assembly to a microprobe. Stark et al. [38] constructed a fiber optic stimulator probe by attaching a diode to an optical fiber. The end of the fiber optic probe was etched to a fine tip and was attached to the silicon probe, above the level of the recording contacts. Since the light source was a diode, it was feasible to drive each fiberoptic probe independently and with varying levels of stimulation, controlled by regulating current to the diode. Probes that were implanted into the hippocampus were found to reliably evoke neural activity in both rats (expressing exogenous opsins) and transgenic mice (expressing ChR2 (channelrhodopsin 2) under the control of a CaMKII or PV promoter).

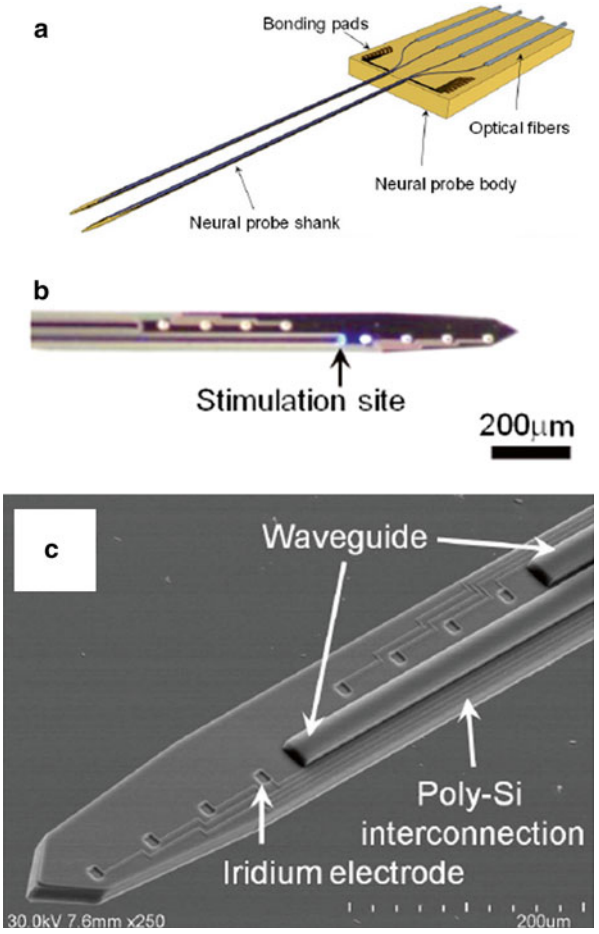

Fig. 2.10 Combined optogenetic silicon probe. (**a**) Drawing of a dual-shank neural probe with waveguides for conducting light to the brain for optogenetic control. (**b**) Light transmission through a waveguide. (**c**) Single shank showing the waveguide and the iridium electrode contact. © 2011 IEEE. Figures reprinted, with permission, from Im M, Cho IJ, Wu F, Wise KD, Yoon E. A dual-shank neural probe integrated with double waveguides on each shank for optogenetic applications. Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference. 2011;2011:5480–3

Im et al. [39] developed a combination silicon and optogenetic probe. The process of making this probe involved the use of a photo-definable polymer to pattern dual 15 μm waveguides on an 8-channel recording shank of the probe (Fig. 2.10a–c). In addition, optical fiber grooves were etched into the back of the probe so that optical lines could be attached to the probe. A variation of this design, with a single waveguide composed of oxynitride was used to test the feasibility of optogenetic activation of recorded neurons [40]. The probe functioned well, being able to entrain neural activity in the rat hippocampus to 25 Hz sinusoidal light stimulation in ChR2 expressing rats.

Schwaerzle et al. [41] designed an optical stimulation microprobe by using onboard bare laser diode chips. The probe shanks measured 8 mm long, carrying four electrodes and a waveguide that interfaced with the laser diodes. The addition

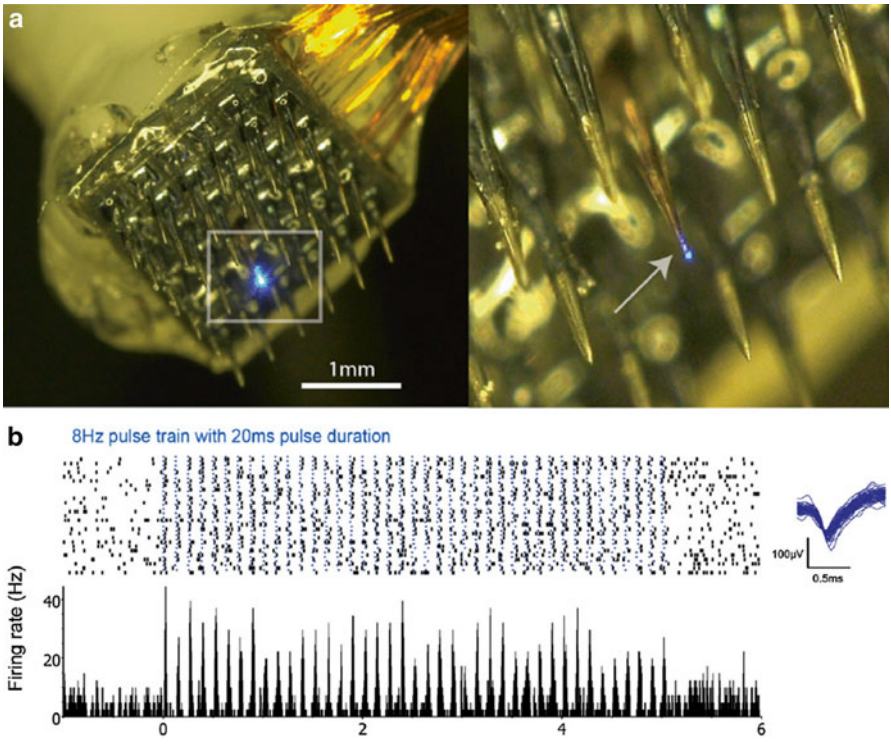

Fig. 2.11 Utah-optogenetic probe. (**a**) 6×6 multielectrode array with one of the elements replaced by a sharpened optrode. Electrode shank length is 1 mm, and spacing between electrodes is 400 **μ**m. A *blue* laser light can be seen emitting from the optrode tip. (**b**) Peristimulus time histogram of a neuron that is entrained to optogenetic stimulation at 8 Hz. Figures reproduced with permission from Wang J, Wagner F, Borton DA, Zhang J, Ozden I, Burwell RD, et al. Integrated device for combined optical neuromodulation and electrical recording for chronic in vivo applications. Journal of neural engineering. 2012;9(1):016001 © IOP Publishing. Reproduced by permission of IOP Publishing. All rights reserved

of these laser diodes was an important advance as it reduced the necessity for contact with fiberoptic cabling and obviates the need for a hybrid optical–electrical commutator.

Not only have the 2D style microprobes been outfitted for optogenetics, but a 6×6 Utah array has also been fit with optogenetic capabilities [42, 43]. In this realization, a sharpened optical probe was swapped with one of the original recording shanks in the Utah array (Fig. 2.11a). Thus, light could be delivered to neurons surrounding that shank, and the response of neurons in other shanks could be recorded. When the array was implanted into ChR2 expressing rats, pulses of light were found to entrain both local field potentials and neurons (Fig. 2.11b).

Summary

Silicon microprobes have evolved dramatically since their inception including the number of recordable channels, the repeatability of their manufacture, and superior integration with a variety of stimulation methods, including optogenetic, electrical, and pharmacological methods. Moreover, microprobes offer the possibility of a fully integrated silicon recording device. One of the big hurdles which remain is a standardized technology to broadcast neuronal signals from these microprobes with a transmitter. Moreover, there may still be a need to increase signal quality of microprobes, as sharp microelectrodes tend to record signals of higher magnitude than silicon probes (compare Chap. 1) and therefore may lend to better spike sorting. Alternatively, tetrode-configured silicon probes are improving upon our ability to isolate neurons. Altogether, the future of high-density microprobes appears to be requisite for the extraction of both the fine details and functional engineering principles of the brain.

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Part II
Coordinated Neural Activity in Rodent Hippocampus and Associated Areas

Chapter 3
Overview of Neural Activity in the Awake and Sleeping Hippocampus

Michael Eckert and Masami Tatsuno

Abstract Since the early 1950s, the hippocampus has been known to play a crucial role in some forms of memory. Recent advancements in multielectrode recording technology (see Chaps. 1 and 2) have made it possible to record the simultaneous activity of large numbers of cells, and this has increased our understanding of how the hippocampus functions both during behavior and at rest. In this chapter, we provide an overview of hippocampal anatomy and electrophysiology that will serve as an introduction to the upcoming chapters. Following a brief description of its anatomical structure, we review neural activity during awake and sleeping hippocampus separately. Topics covered include place cells, theta phase precession, and memory-trace replay during rest, slow-wave sleep, and REM sleep.

Keywords Hippocampus • Place field • Memory • Sleep • Replay

Introduction

The first evidence that the hippocampus was important for higher cognitive function came from the neurosurgical patient Henry Molaison (patient H.M.). H.M. underwent bilateral surgical resection of the medial temporal lobes in an attempt to alleviate severe epilepsy. While the surgery was successful in reducing the severity and frequency of his seizures, H.M. now exhibited a profound memory deficit. He seemed unable to form new autobiographical memories and also exhibited a partial loss of memory for events prior to the surgery, although his memory for more distant events seemed intact [1, 2]. Since then, many studies in different species have demonstrated that the hippocampus plays a crucial role in memory formation and maintenance [3]. Indeed, H.M.'s amnesia, which began following his operation at the age of 29, persisted until his death at the age of 82.

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Following this discovery, substantial research has been devoted to the anatomy and electrophysiology of the hippocampus in an attempt to understand how it functions, particularly with respect to memory processes. At the input stage of the hippocampus, the dentate gyrus appears to function as a pattern separator, whereby small changes in input patterns result in distinct patterns of cellular activation, which may ensure that memory representations do not interfere with one another [4–6]. Upstream from the dentate gyrus, the recurrent collaterals of the CA3 subregion of the hippocampus suggest that it can function as an autoassociative memory network by performing pattern and reconstruct stored representations from degraded inputs [7, 8]. The connectivity pattern between the hippocampus and the rest of the brain, in particular the neocortex, also suggests an important role in memory. The hippocampus sits at the top of a processing chain, receiving highly processed input from multiple neocortical association areas and in turn sends projections back out to most of the neocortex.

The electrophysiological evidence gathered over the years also points to an important role for the hippocampus in cognitive function and memory in particular. Donald Hebb [9] had posited early on that information storage in the brain occurred via activity-dependent changes in synaptic strength. Bliss and Lomo [10] found experimental evidence of this in the hippocampus when they showed that patterned electrical stimulation applied to the inputs of the hippocampus resulted in a lasting enhancement of synaptic strength within the hippocampus. The ability to undergo synaptic modification is necessary of a structure involved in memory storage and a wealth of experiments since Bliss and Lomo have shown that all subregions of the hippocampus are capable of this rapid yet relatively persistent synaptic modification.

These anatomical and electrophysiological findings suggested a fundamental role for the hippocampus in memory processing. As more sophisticated recording technology developed, allowing the recording of multiple individual cells, a more detailed view of hippocampal activity during behavior became possible. In this chapter, we will review how the activity of cells in the hippocampus behave during waking and sleep after a review of the basic anatomy of the hippocampus.

Anatomy

The hippocampus is a part of the hippocampal formation, a group of brain areas in the limbic system that also consists of the subiculum, presubiculum, parasubiculum, and entorhinal cortex (Fig. 3.1). The hippocampus proper is divided into the dentate gyrus and Ammon's horn (CA1, CA2, and CA3). Compared to other brain areas, the hippocampal formation has a unique architecture and connection pathways that have been studied extensively, especially in the rat. The hippocampal circuit is characterized by its unidirectional tri-synaptic excitatory pathway. Input from a wide range of neocortical association areas converges on the superficial layers (layers II and III) of the entorhinal cortex. Axons from the superficial layers of the entorhinal

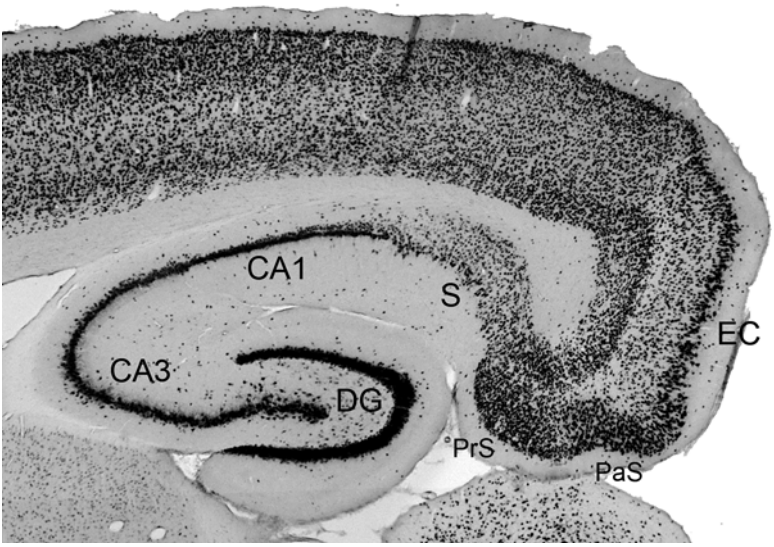

Fig. 3.1 Nissl-stained horizontal section of a rat brain showing the hippocampus and surrounding cortex. *EC* entorhinal cortex, *DG* dentate gyrus, *CA Cornu Ammonis*, *S* subiculum, *PrS* presubiculum, *PaS* parasubiculum

cortex project to the dentate gyrus as well as the CA fields of the hippocampus, forming the major hippocampal input pathway called the perforant path. The synapses formed on the dentate gyrus granule cells form the first stage of the tri-synaptic pathway. The dentate gyrus then projects to CA3 via axons called mossy fibers, forming the second stage of the tri-synaptic circuit. The neurons in CA3, in turn, project to CA1 via axons called Schaffer collaterals, forming the final stage of the tri-synaptic circuit. The neurons in CA1 further project to the subiculum and layer V of the entorhinal cortex. Finally, the neurons in the subiculum project predominantly to the layer V of the entorhinal cortex and also to the presubiculum and the parasubiculum. Neurons in the layer V of the entorhinal cortex project back to many neocortical areas.

The brief description provided above is based on the anatomy of the rat hippocampal formation. One important question is whether the hippocampal formation in the rat, monkey, and humans is similar or not. The volume of the hippocampus is indeed greatly different (10 times larger in the monkey than in the rat and 100 times larger in humans than in the rat) and the entorhinal cortex is more complex for monkey and humans. However, the basic hippocampal structure is similar among these species. This observation provides the basis for an assumption that the findings made in rats are comparable, to a certain extent, to studies in monkeys and humans.

In this chapter, we will review the literature of rat hippocampus because of the large amount of research that exists compared to monkeys and humans. For more detailed and complete review of hippocampal anatomy, see Andersen et al. [11] and Shepherd [12].

Sequential Activity in Awake Hippocampus (Place Cell and Theta Phase Precession)

When fine electrodes are inserted into the brain, two types of electrophysiological activity can be recorded. The first is local field potentials (LFP), which reflects the average activity of large numbers of neurons, possibly including contributions from action potentials, excitatory and inhibitory synaptic potentials, and dendritic and glial slow potentials. The other is single unit activity, which reflects action potentials (spikes) emitted by a single neuron.

In the mid-1960s, Vanderwolf [13] recorded the hippocampal LFP from freely behaving rats and identified three states: the theta state, the large irregular amplitude activity (LIA) state, and the small irregular amplitude activity (SIA) state. The theta state is a regular oscillation between 6 and 10 Hz that is observed during waking and REM sleep. The septum and brain stem provide the neuromodulatory inputs to hippocampal pyramidal cells and drive them into the theta state. The theta state can be further classified into two types based on pharmacology. During arousal/attention theta is sensitive to anticholinergic drugs such as atropine and scopolamine. During translational movement theta can be modulated by serotonergic and glutamatergic modulators. LIA is a state characterized by irregular large amplitude waves with strong power in 1–4 Hz frequency range. It is observed mainly during behaviors that do not involve movement through the environment such as quiet sitting, eating, drinking, and grooming. SIA is a state with very low-amplitude, desynchronized LFP waves. During SIA only a small subset of hippocampal neurons are active while the rest remain almost silent [14]. It is observed during behavioral transitions such as when a rat stops running abruptly. Among these three states, the theta state is the most relevant for the awake animal; therefore, we will focus on hippocampal neural activity that occurs in the theta state in this section. Neural activity in LIA and SIA will be discussed in the next section.

Based on recordings from rat CA1 and CA3, Ranck [15] originally identified two classes of cells: theta cells and complex cells. It is now accepted that theta cells consist of one or more types of interneurons and that the complex cells are pyramidal cells. Theta cells have high average firing rates (10–100 Hz) that are strongly modulated by theta, with some cells increasing their firing during theta (theta-on cells) and others decreasing their firing rate during theta (theta-off cells). Nitz and McNaughton [16] suggested that one possible function of theta cells in CA1 is to identify familiar and novel environments and control the processes of learning in CA1.

Compared to theta cells, complex cells have lower average firing rates that are strongly modulated by the animal's position in space. O'Keefe and Dostrovsky [17] first showed that complex cells fire rhythmically during the theta state when the rat moves around and enters a particular location within the environment. These cells are called place cells and the spatial locations that they fire in are called place fields (Fig. 3.2). Discovery of these place cells leads to the development of the cognitive map theory [18]. Although most place cell recordings are performed in CA1 and

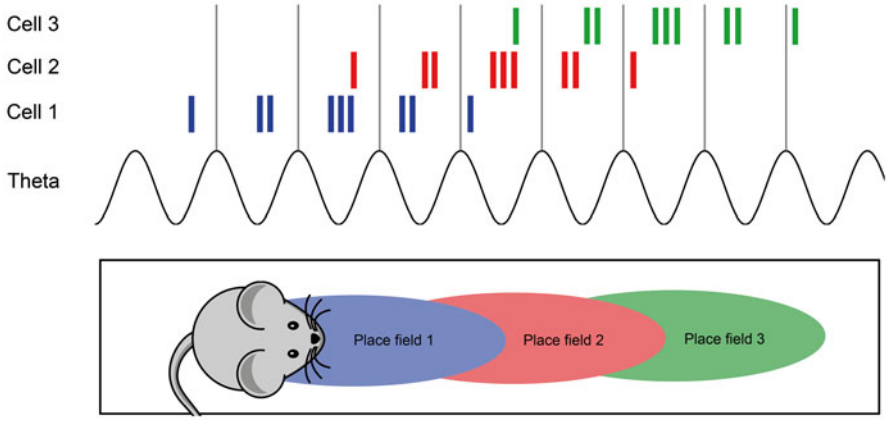

Fig. 3.2 Place cell firing and theta phase precession. As the rat runs down the track moving through successive place fields, the respective place cells fire bursts of action potentials. Spike activity is generally maximized near the center of place field. Spiking occurs initially at a specific phase of the theta oscillation and then occurs progressively earlier in the theta cycle as the rat moves through the place field

CA3, place cells have also been recorded from the subiculum, presubiculum, parasubiculum, and entorhinal cortex. In addition to rats, place cells have been reported in monkeys and humans. For instance, Ono and his colleagues [19] reported placed-coded cells in monkey hippocampal formation while the monkey moved about in a cart. Additional studies from the same group further confirmed place-like cells in monkeys [20, 21]. In humans, unit activity has been recorded from epilepsy patients with implanted electrodes and place responsive cells were reported in the hippocampus during virtual locomotion [22].

Using multielectrode technology, simultaneous recordings of multiple place cells have demonstrated the sequential activation of cells with different place fields. For example, Lee and Wilson [23] recorded place cells in CA1 and demonstrated beautiful sequences of place cell activity as the rat ran back and forth on a track (Fig. 3.3a, b). The pattern of recorded activity showed that the animal's location in an environment is not given by the activity of a single place cell; instead, it is given by the pattern of firing across a large number of cells. It is therefore expected that the spatial location of a rat can be reconstructed from the activity of many simultaneously recorded neurons. This idea was first examined by Wilson and McNaughton [24]; they demonstrated that the spatial trajectory of the rat can be estimated from the population firing rate vectors. This line of research has been developed by many researchers, contributing to the development of more accurate decoding algorithms [25–27].

In addition to the modulation of firing rate by location, the firing of complex cells with respect to theta also changes. As the rat moves through a place field, a place cell will fire bursts of action potentials at successively earlier phases of the theta cycle, a phenomenon termed theta phase precession [28] (Fig. 3.2; see Chap. 12 for

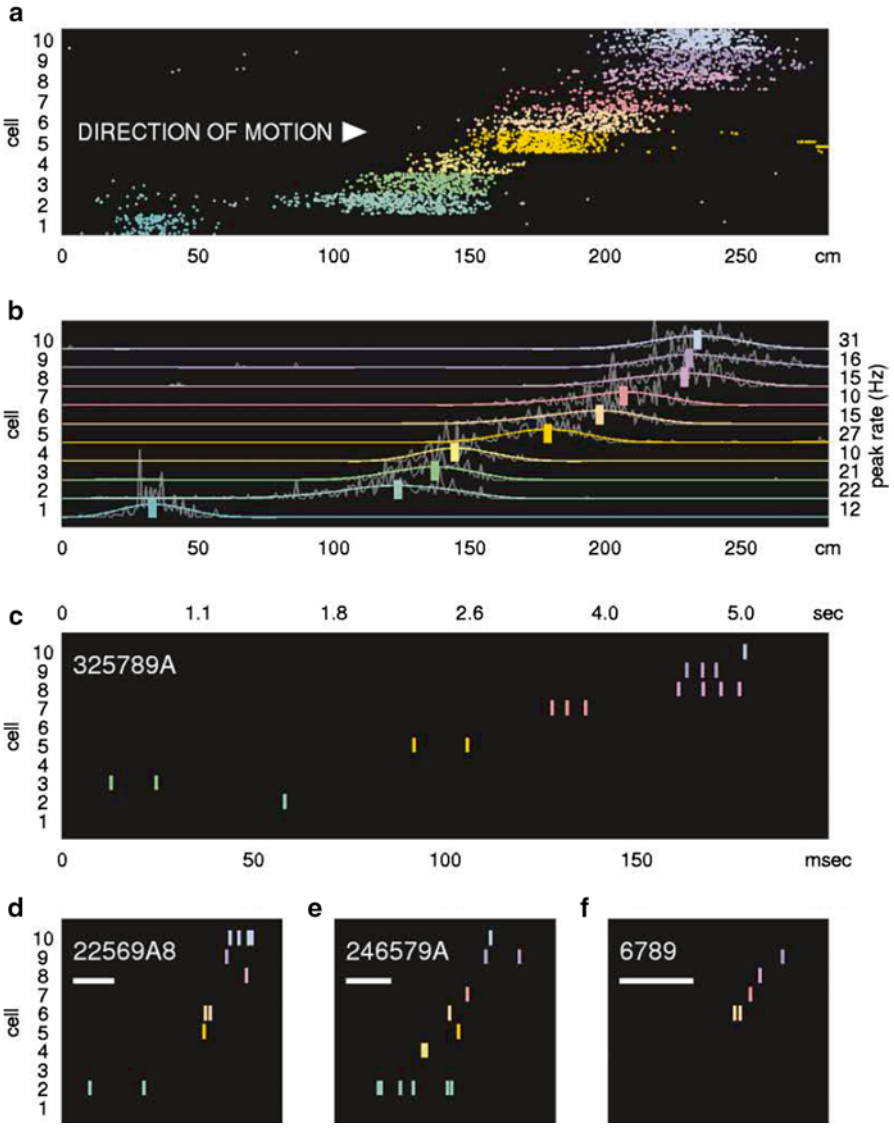

Fig. 3.3 Sequential activation of place cells during behavior and sleep. (**a**) Rasters of ten simultaneously recorded CA1 neurons plotted as a function of position on a linear track. (**b**) Place fields constructed the firing of the cells in **a**, with the peak firing rate marked as a *vertical line*. (**c**) During sleep, a subset of the cells fire in the same sequence as they did during behavior but on a compressed timescale (note difference in timescale between **b** and **c**). (**d**–**f**) Three other examples of sequential reactivation of place cells during sleep. Reprinted from Neuron, 36(6), Lee AK, Wilson MA, Memory of sequential experience in the hippocampus during slow-wave sleep, 1183–94, copyright 2002, with permission from Elsevier

possible mechanisms of theta phase precession). Jensen and Lisman [29] explored the possibility that the neuron's spiking phase contained additional spatial information and found that the accuracy of the rat's estimated location was increased by more than 40 % if the phase relationship was taken into account. However, Harris et al. showed that phase precession also occurred for nonspatial behaviors as well, suggesting that phase precession may not be tied to spatial computations only [30]. Indeed, they also demonstrated that a cell's spike timing could be more accurately predicted by taking into account population activity beyond that predicted by firing rate and phase precession suggesting that intrinsic network activity is also an important determinant of spiking [31].

Various properties of place cells have been investigated extensively in the last three decades. For example, the majority of place cells have a single place field in a single typical testing environment [24]. The average size of the place field varies with location along the long axis of the hippocampus, with fields expanding from dorsal to ventral [32]. In open fields, the place cells fire irrespective of the direction in which the animal is facing [24]. In restricted fields such as a straight track, the firing of the place cell becomes directionally tuned, firing more when the animal passes through the field in one direction compared to the opposite direction [33]. Both external sensory cues and internal proprioceptive/vestibular cues influence place field structure, location, size, and shape [34–36]. That is, place cells are not simply responding to a particular configuration of distal or proximal cues; rather, they signal something more abstract. Furthermore, as we will see in the upcoming chapters (Chaps. 4–6, and 14), the firing of place cells is also related to reward- and goal-related information.

The spatial tuning of complex cells develops during the first 1–1.5 months of the rat's life. Martin and Berthoz [37] recorded pyramidal neurons from rats at ages between P27 and adult. They found that the place fields of younger animals were larger and more diffused than those of adults. The size of the place fields became smaller with age, finally reaching adult values at P52. In more recent studies, researchers placed electrodes in the hippocampus of freely moving 14-day-old rats [38, 39]. They showed that place cells were already present at day 16, 2 days after the eyes have opened. Taken together, behavioral and electrophysiological studies suggest that the tuning of rat hippocampal neurons develops over the first month of life and reaches adult levels around 40–50 days after birth.

Two other major classes of spatially tuned cells in the hippocampal formation are head direction (HD) cells [40] and grid cells [41]. HD cells are sensitive to the orientation of the rat's head with respect to the environmental frame and will fire at any location within an environment as long as the rat is oriented in the preferred direction. They have been found in several brain areas, including the anterodorsal thalamus, the entorhinal cortex, and the para- and postsubiculum [42–44]. The firing of grid cells, like place cells, depends on the animal's position in the environment. However, whereas place cells generally exhibit a single firing field in an environment, grid cells fire at multiple locations in an environment and these fields form a regular grid pattern [41]. Grid cells have been mainly studied in the superficial

layers of the medial entorhinal cortex, but they are also found in the deep layers [44]. Because the superficial layers of the MEC form the major input to the hippocampus, it has been suggested that the grid cell input provides the hippocampus with its spatial metric that gives rise to place cells [45]. However, it has recently been shown that the reverse is also true, that the grid-like firing field of MEC cells depends on input from the hippocampus [46].

In summary, when an animal is awake, hippocampal neurons fire rhythmically with a strong correlation to the LFP theta oscillation. As the animal moves around in an environment, sequential patterns of place cells are activated, giving rise to a population code that is rich in spatial information. In the next section, we will discuss how hippocampal neural activity is organized in relationship to LIA and SIA and how it can be related to a neural activity during waking.

Sequential Activity of Sleeping Hippocampus (Memory Replay, Awake Resting, Non-REM Sleep, and REM Sleep)

Sleep in mammals is broadly divided into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. In humans, NREM sleep is further divided into three stages by neurophysiological features [47]. In rodents, NREM sleep is not divided further and is also called slow-wave sleep (SWS). The stages of rodent sleep are characterized by their predominant LFP rhythms in the hippocampus. SWS is dominated by LIA which exhibits strong power in the delta frequency range (1–4 Hz) whereas REM sleep is dominated by theta oscillations (6–10 Hz). A third state, termed SIA, is characterized by a lack of synchronized EEG activity and occurs frequently at the end of REM periods. In this section we will review how sequential single unit activity differs between these states.

LIA is characterized by the presence of sharp waves. Buzsaki and colleagues have suggested that sharp waves originate as a large, synchronous discharge of CA3 neurons which in turn leads to a strong depolarization at the CA1 Schaffer collateral synapses [48–50]. Sharp waves last approximately 100 ms and occur randomly with an average interval of 1 s. Sharp waves are most often observed during slow-wave sleep and quiet sitting and less often observed during behaviors such as eating, drinking, and grooming. Sharp waves are associated with ripple oscillations of 100–200 Hz. Cell firing during LIA is low on average [14], but during ripple oscillations, there are synchronous bursts in almost all theta interneurons and in a much smaller number of complex-spike pyramidal cells.

One possible function of LIA is to strengthen synaptic modifications during slow-wave sleep [51]. It has been suggested that consolidation of memories takes place in part during sleep, in particular during slow-wave sleep [52], and experiments have demonstrated that neuronal firing patterns that occur during waking are reactivated during subsequent sleep. This phenomenon is called memory-trace reactivation or memory-trace replay. The first electrophysiological evidence of reactivation came from an experiment by Pavlides and Winson [53]. They recorded pairs of

place cells in rats during sleep sessions following exposure to a radial arm maze during which the rat was allowed to visit only one of the cell's place fields. They distinguished three sleeping states: slow-wave sleep, REM sleep, and pre-REM sleep. Relative to REM sleep, pre-REM sleep was characterized by more LFP synchrony, heavier breathing, and apparent whisker movement. Note also that they did not distinguish between LIA and SIA in this study. During all stages of sleep, there was a selective increase in the firing rate of the cell that had been allowed to be active in its place field prior to sleep. This finding was an important demonstration that the activity of a single neuron can be maintained during subsequent sleep.

Considering Hebb's postulate for synaptic plasticity ("neurons that fire together wire together"), it is important to ask whether correlations between cells established during waking are maintained during subsequent sleep. Supporting evidence came from an experiment by Wilson and McNaughton [54]. Using a cross-correlation function, they showed that task experience resulted in increased correlations between pairs of neurons with overlapping place fields and that these correlations were maintained during subsequent slow-wave sleep. Further studies showed that these correlations were more pronounced during sharp-wave ripple wave events and they decayed to a statistically undetectable level in about 30 min [55, 56] (Fig. 3.4a).

Skaggs and McNaughton [57] were the first to provide evidence that the sequential pattern of cell firing during waking is preserved during sleep. They found that the temporal ordering of firing between pairs of cells was preserved during slow-wave sleep, albeit in a compressed form (Fig. 3.4b). Wilson's group [23] then showed that activity sequences of multiple place cells replayed during sleep and that this replay was compressed in time, occurring 10–20 times faster compared to waking (see Fig. 3.3c, d).

Sequential reactivation events have also been detected during waking, when there are pauses in the rat's behavior. Foster and Wilson [58] first showed that the sequence of place cells that was activated as a rat ran along a track was reactivated in the reverse order when the rat was at rest after reaching the end of the track. It was soon shown that forward sequence reactivation also occurs during waking and it is more likely to occur at the beginning of a track run [59] (Fig. 3.5). Like reactivation during sleep, forward and reverse reactivation during waking occurs on a compressed timescale and is associated with sharp waves. Interestingly, the forward reactivation that occurs at the beginning of a track run occurs not only for familiar tracks but also occurs for a completely novel track. Dragoi and Tonegawa [60] showed that when an animal reaches the end of a track, in addition to the reverse reactivation of the recently experienced sequence of place cells, there is a forward reactivation of place cell sequences for a novel track that the animal has not yet experienced. Once the rat is allowed to run down the novel track, the preplayed sequence of place cells is activated. Thus the hippocampus appears to use pauses in behavior to review recent experiences and preview future experiences.

In summary, there is increasing evidence supporting hippocampal memory-trace reactivation during LIA. These findings suggest that LIA plays an important role in consolidation of hippocampal memories. It has been also suggested that LIA can be

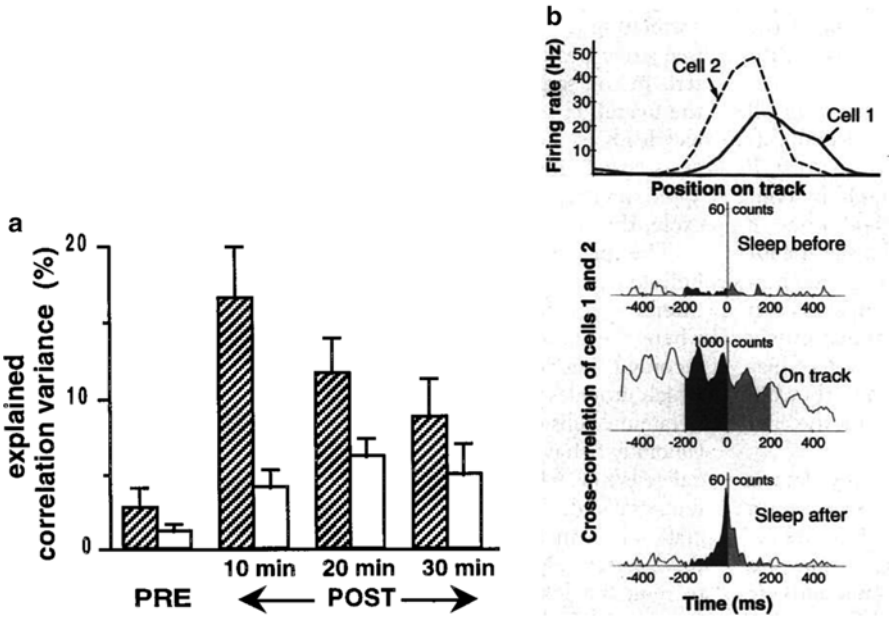

Fig. 3.4 Memory-trace reactivation during sleep. (**a**) Significant reactivation (explained variance measure) is observed early during post-task sleep and is observed more in sharp wave-ripple events (*hatched bars*) compared to inter-SPW events (*open bars*). The amount of reactivation decays during the first 30 min of sleep. Reproduced with permission from Kudrimoti HS, Barnes CA, McNaughton BL. Reactivation of Hippocampal Cell Assemblies: Effects of Behavioral State, Experience, and EEG Dynamics. The Journal of Neuroscience. 1999;19(10):4090–101. (**b**) Example cross-correlation of two cells from pre-task sleep, task, and post-task sleep shows that the temporal order of task-induced firing correlations is preserved during sleep. From Skaggs WE, McNaughton BL. Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science (New York, NY). 1996;271(5257):1870–3. Reprinted with permission from AAAS

a period involving transfer of information from hippocampus to neocortex [51, 61]. The next important step is to show whether elimination of memory-trace reactivation indeed impairs memory consolidation. In fact, disruption of both awake [62] and sleeping [63, 64] sharp wave ripples in LIA impairs spatial memory processes (see Chaps. 5 and 7 for more discussion).

It has been also suggested that consolidation of memories takes place during REM sleep [65, 66]. (For an alternative perspective, see [67].) However, there is little evidence supporting memory-trace reactivation during REM sleep. To the best of the author's knowledge, the only report came from an experiment by Louie and Wilson [68]. They recorded CA1 pyramidal neurons during spatial experience and investigated reactivation during REM sleep using a template matching method. Unlike the temporally compressed replay that occurs during slow-wave sleep, replay during REM sleep occurred at the same timescale and even slower compared with waking. They also found that the replay was significantly delayed, occurring

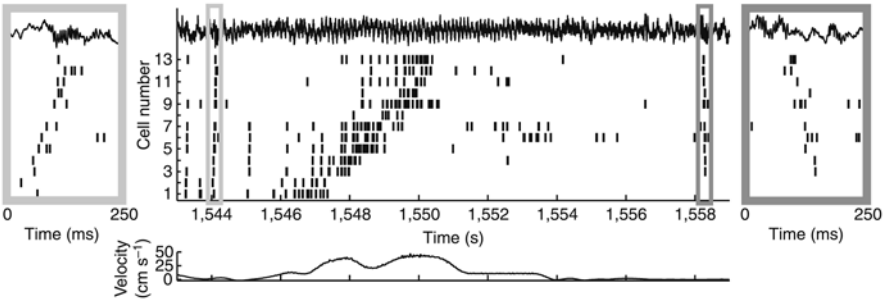

Fig. 3.5 Forward and reverse sequence reactivation during waking. The *middle panel* shows raster plots of simultaneously recorded CA1 neurons from a run down a familiar track. A clear sequence of activated place cells is visible along the length of the track. The *left panel* shows this sequence is reactivated on a compressed timescale in the forward direction during a pause in behavior prior to the run. The LFP trace above shows that the reactivation is associated with a sharp wave-ripple event. The *right panel* shows the reverse activation of the sequence during a pause at the end of the run. Adapted by permission from Macmillan Publishers Ltd.: Nature Neuroscience, Diba K, Buzsaki G. Forward and reverse hippocampal place-cell sequences during ripples, 10(10), 1241–2, copyright 2007

almost 24 h later (before the next recording session), but not immediately after the experience. These findings suggest that if reactivation occurs during REM sleep, its function could be different from the replay during slow-wave sleep. Another interesting study came from experiment by Poe et al. [69], though they did not directly investigate reactivation during REM sleep. By investigating the phase relationship of place cell activity and theta oscillations in CA1, they found that firing of place cells during REM sleep was more likely to occur at the peak of theta oscillation following a novel experience but shifted to the trough of theta oscillation following a familiar experience. Since synaptic strengthening is facilitated at the peak of the theta cycle and synaptic depression is facilitated during the troughs [70], the authors speculated that hippocampal circuits may be restructured during REM sleep by selectively strengthening recent memories and weakening older ones. This is consistent with a hypothesis that the hippocampus serves as a short-term memory storage and that REM sleep may strengthen recent memories and help keep them in hippocampus for a short period of time and erase older memories, making room for new ones [71].

Unlike LIA and REM sleep, SIA's function is not well understood. During SIA, the LFP flattens and becomes desynchronized, typically for a relatively brief period (~2 s). SIA can occur during LIA, but it occurs most frequently at the termination of a REM episode [14, 72]. Unit activity during SIA is very different from LIA and theta as most of the cells stop firing completely. A small fraction of cells, however, remain active and fire at a high constant rate for the duration of the SIA epoch. The active fraction of cells often have place fields around the sleeping location; thus, it is possible that SIA reflects a state when the animal wakes and becomes aware of his environment but is not actively engaged with it yet [14].

Conclusion

H.M.'s amnesia following resection of his temporal lobes provided the first clue that the hippocampus was crucial for memory and higher cognitive function. Evidence supporting this view has accumulated over the years, in particular as a result of increasingly sophisticated electrophysiological techniques. Recordings from rodents have demonstrated that when the animal is awake and engaged in its environment, the cells of the hippocampus and entorhinal cortex provide information about the animal's position and orientation in the environment. During pauses in behavior, reactivated sequences of place cells describe trajectories that the animal has just traversed as well as upcoming trajectories that the animal will travel through next. Then, during sleep, sequences of activity that occurred during waking are replayed, primarily during sharp wave events that occur during slow-wave sleep. Taken together this experimental evidence suggests that replay of sequential activity allows for repeated, coordinated activation of ensembles of cells that drives synaptic strengthening according to Hebb's postulate ("neurons fire together wire together"), allowing stable memory traces to form. From anatomical evidence, and more recently electrophysiological studies, it is also clear that the hippocampus interacts extensively with the neocortex, the proposed repository for long-term memory. The memory-trace reactivation that occurs during sleep likely involves an interaction between the hippocampus and neocortex and serves to consolidate memories of recent experience.

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Chapter 4
Associative Reactivation of Place–Reward Information in the Hippocampal–Ventral Striatal Circuitry

Carien S. Lansink and Cyriel M.A. Pennartz

Abstract Thinking back to an exciting event often includes the scene in which the event took place. Associations between spatial locations and emotional events, such as obtaining rewards, are important for surviving in a changing environment and depend critically on communication between the hippocampus and ventral striatum. The potential contribution of subcortical brain areas such as the ventral striatum to memory consolidation has remained underexposed as the focus of consolidation research has been on the hippocampal–neocortical dialogue in declarative memory. This chapter highlights the cross-structural reactivation of place–reward information in the hippocampal–ventral striatal circuitry during sleep, an "off-line" process that is thought to contribute to memory consolidation by strengthening synapses between neurons activated in a preceding behavior. The reactivation process is temporally organized such that place information in the hippocampus is preferentially activated in advance of ventral striatal motivational information. This is consistent with the orchestrating role of the hippocampus predicted by consolidation theories. Neural representations are replayed on a compressed timescale, meaning that firing patterns of several seconds of real-time experience are reinstated in a time window of several hundreds of milliseconds. On this temporal scale, the reactivation of place–reward information may contribute to long-lasting changes in synaptic efficacy such as spike-timing dependent plasticity in hippocampal–ventral striatal connections. Cross-structural reactivation of place–reward information in the hippocampal–ventral striatal circuitry demonstrates the distributed way the brain processes, links, and retrieves different aspects of the memory.

Keywords Nucleus accumbens • Reactivation • Learning • Memory consolidation • Reinforcer • Motivation • Tetrode • Spatial • Context

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Introduction

The consolidation of memories is a complex cascade of processes that continues during periods of rest and sleep after the initial acquisition of information [1]. Spontaneous reactivation of neuronal activity patterns representing aspects of a scene or event during these "off-line" periods is thought to strengthen synaptic connections activated during the preceding behavior [2–5]. Reactivation has been primarily studied in the hippocampus [6–10] and neocortex [11–15]. This emphasis is in line with current concepts on declarative memory consolidation stressing that the "fast-learning" hippocampus may store an initial representation of an experience based on sensory cortical information, whereas over time the memory trace would be transmitted back to the neocortex where it is anchored for long-term storage [3, 4]. Consistent with these ideas, reactivation theories have proposed that the recurrence of memory traces in the hippocampus may initiate and coordinate a process of reactivation in associated neocortical ensembles leading to strengthen and refine the neocortical memory trace [2, 5]. For instance, the hippocampus has been proposed to encode a code or "pointer" for an organism's environmental context, and the reactivation of this code may enable neocortical elements associated with the same context to be bound and stored together [16, 17]. This hippocampal–neocortical focus, however, leaves unattended the possibility that reactivation may be a widespread phenomenon in which subcortical brain areas also contribute to memory consolidation, whether memory traces are declarative, procedural, or of a yet different nature.

This chapter aims to highlight the importance of a subcortical structure—the ventral striatum—in the process of off-line reactivation, specifically in relation to the hippocampus. The hippocampal–ventral striatal circuitry is critically involved in the formation of place–reward associations [18], which are essential, for example, during foraging, when animals need to maintain a representation of a multitude of reward properties such as the location at which the reward can be found. Here, we review and discuss results showing that temporally ordered, cross-structural reactivation between the hippocampus and the ventral striatum is a plausible mechanism contributing to the consolidation of place–reward associations and propose a testable hypothesis on the dynamics and implications of reactivation in the hippocampal–ventral striatal circuitry.

The Ventral Striatum Is Implicated in Post-experiential Processing of Information

One of the main target areas of hippocampal and subicular projections is the ventral striatum [19–21], which mostly consists of the nucleus accumbens. Besides being innervated by the hippocampal formation, the ventral striatum receives extensive input from various cortico-limbic structures such as the prefrontal cortex,

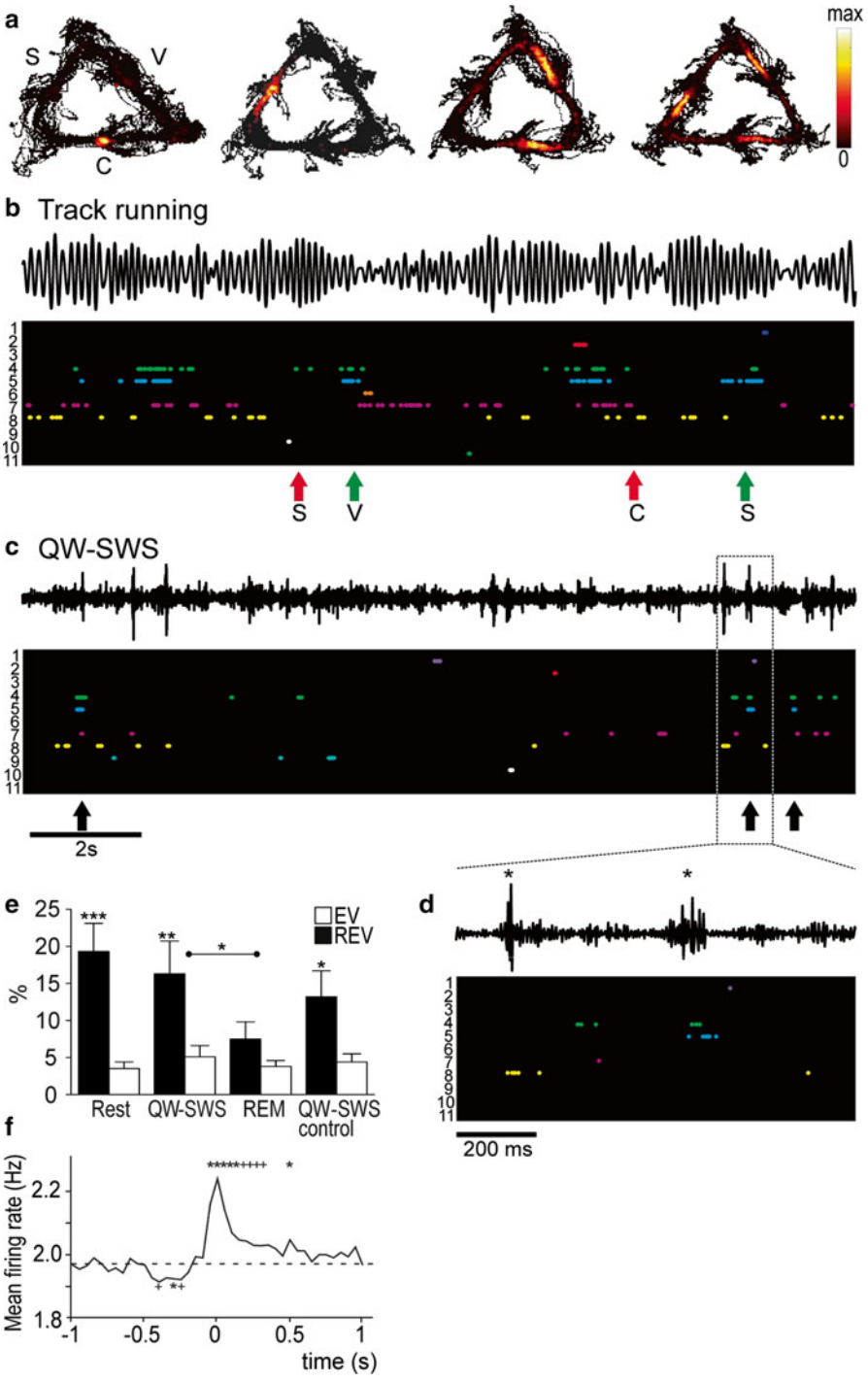
amygdaloid complex, and the midline thalamic nuclei [22–25]. Output projections from the ventral striatum reach brain areas related to motor behavior and motivation such as the ventral pallidum, the substantia nigra pars reticulata, the ventral tegmental area (VTA), and the lateral hypothalamus [26].

The current view on ventral striatal functioning can be summarized as driving or invigorating behavior on the basis of the motivational value of environmental cues and contexts [27–30]. Central to this view is that the ventral striatum integrates spatio-contextual information from the hippocampus and information on discrete cues from the basolateral amygdala and prioritizes action patterns to obtain or avoid reinforcers. This notion is supported by lesion studies indicating ventral striatal involvement in hippocampus-dependent behavioral paradigms requiring the use of spatial environmental knowledge to reach a goal, such as contextual conditioning and the Morris water maze [18, 31–33]. Ventral striatal lesions also deteriorate performance in amygdala-dependent behavioral paradigms such as appetitive and aversive conditioning to discrete cues and tasks in which Pavlovian cues gain motivational control over instrumental behavior (i.e., Pavlovian to instrumental transfer) [18, 34–38].

The role of the ventral striatum in reward-related processing is further emphasized by chronic recordings of single-unit activity in the rodent ventral striatum and primate striatum. Single units have been shown to signal reinforcers and cues that predict outcome by increments and decrements in firing rate (for increments see Fig. 4.1a). Their firing responses are time-locked to the receipt of primary reinforcers of both positive and negative valence and to the onset of salient environmental cues that are associated to specific future outcomes (i.e., outcome-predictive cues), respectively [39–44]. Primate neurons fire differentially in relation to the availability of a reward [45] and to the type [46], magnitude [47], and temporal proximity [48, 49] of predicted outcome. Functional MRI studies using human subjects have shown predictive activations of the ventral striatum during appetitive learning for juice and money rewards, as well as during learning with aversive stimuli such as pain [50–53].

Accumulating evidence also underscores the significance of the ventral striatum in the consolidation of memories. Several studies have shown that interference with protein synthesis, glutamate, and/or dopamine receptor function in the ventral striatum shortly following training on spatial [54, 55], Pavlovian approach [56], and instrumental [57] learning tasks impaired performance on the next day. The acquisition and consolidation of task-related information may depend on long-term changes in the efficacy of synapses formed by glutamatergic afferents onto the principal cells of the ventral striatum, i.e., medium-sized spiny neurons [58, 59]. This hypothesis is corroborated by the finding that post-task interference in the receptor- and signal-transduction cascade underlying long-term potentiation (LTP) induction in the nucleus accumbens impairs consolidation of an instrumental learning task [60].

Spontaneous reactivation of ventral striatal ensemble firing patterns during periods of sleep immediately following a behavioral experience would confirm the participation of this area in post-training information processing. It also would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QW-SWS
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provide a potential neurophysiological mechanism for striatal involvement in the consolidation of cue–reward and place–reward associations. We began testing this hypothesis in two separate experiments by recording spike trains and local field potentials from the ventral striatum of rats when they performed a reward-searching task on a T- or triangle-shaped track flanked by two periods of rest [61, 62]. Reactivation was quantified with an analysis that, based on partial regression methods, represents the similarities in firing pattern correlations for all pairs of simultaneously recorded cells [63]. The *explained variance* (*EV*) reflects the extent to which the variance in the distribution of cell pair firing-rate correlations during rest and sleep following track running can be accounted for statistically by the pattern of correlations induced during reward searching on the track. In addition, the analysis controlled for the distribution of correlations that was present in the rest and sleep periods before track running (i.e., the baseline period; before the activation of neurons in the behavioral task, executed on the same day). A within-control measure, i.e., *reverse explained variance* (REV) [62, 64], was derived by exchanging the pre-track and post-track rest periods in the abovementioned procedure. Because this

Fig. 4.1 Reactivation of reward-related information in the ventral striatum. (**a**) Ventral striatal units showing reward-related firing patterns. Rats ran along a triangular track to obtain three types of reward, each available at the center of one side (S: sucrose solution, V: vanilla cream, C: chocolate mousse). Each lap one of the three reward locations was baited, whereas the other two were left empty. Each panel shows the color-coded spatial firing distribution of a single ventral striatal unit superimposed on the rat's trajectory on the track (*black*). According to the color scale on the right, *dark red colors* indicate low local firing rates whereas increasingly higher firing rates are represented by *yellow* and *white*. Neurons increase their firing rate during the approach and arrival at one, two, or all three reward sites. (**b**) Example of the firing patterns of a ventral striatal ensemble of 11 neurons plotted in parallel with the filtered local field potential recorded near the hippocampal fissure (6–10 Hz). When the rat ran along the track, oscillations in the theta frequency dominated hippocampal local field potentials. In a period of 15 s, the rat visited four times a reward site, two of which were baited (indicated with *green arrows*) and two were not (indicated with *red arrows*). Each row in the black field represents a single unit, its spikes being marked by *colored dots*. Note the concurrent firing patterns of the "*green*" (4) and the "*blue*" (5) units. (**c**) The filtered hippocampal local field potential recorded in the CA1 pyramidal layer during quiet wakefulness and slow-wave sleep (QW-SWS) is characterized by the occurrence of ripples (100–300 Hz). "*Green*" (4) and "blue" (5) units are repeatedly simultaneously active, indicated by *black arrows*. (**d**) Enlargement of a segment of **c**. Spikes of the "*green*" (4) and "*blue*" (5) as well as *yellow* (8) units are aligned to ripples in the hippocampal local field potential (marked with *asterisks*). (**e**) Ventral striatal ensembles show reactivation indicated by a significant difference between the EV and REV (in %) across sessions. Significant reactivation occurred during QW-SWS but not during REM sleep. EV values for QW-SWS were significantly higher than for REM sleep. Reactivation was found when periods of QW-SWS were taken into account that matched the length and timing of REM sleep periods in the sleep cycle, indicating that the lack of REM sleep reactivation could not be explained by the relatively late occurrence of REM sleep periods after sleep onset or by the relatively short duration of REM sleep compared to SWS (QW-SWS control). Statistics: Wilcoxon's matched-pairs signed-rank test $***P<0.001$; $**P<0.02$; $P<0.05$. (**f**) Peri-ripple time histogram showing the mean firing rates of a population of ventral striatal neurons ($n=340$) aligned to the onset of hippocampal ripples ($t=0$; bin size: 50 ms) occurring in the post-behavioral rest period. Statistics: one way ANOVA test, $+P<0.005$; $*P<0.001$. Adapted from [61, 62]

measure disrupts the temporal order of episodes that reactivation of neuronal patterns assumes, REV values should be lower than EV values if significant reactivation occurs.

In both the T- and triangle-track experiments, the ventral striatum showed reactivation of firing patterns (Fig. 4.1b–e). Reactivation appeared to be limited to periods of slow-wave sleep (SWS), which is in line with most of the hippocampal literature [7, 63]. In periods of rapid eye movement (REM) sleep, EV values were not significantly different from REV values [61]. The lack of reactivation in REM sleep could not be explained by the relatively late occurrence of REM sleep periods after sleep onset or by the relatively short duration of REM sleep compared to SWS (Fig. 4.1e).

Human sleep deprivation studies, however, have ascribed a prominent role to REM sleep in procedural and emotional memory consolidation [65–68]. This is not necessarily in conflict with the reactivation results stressing the importance of SWS, because REM sleep, which is characterized by strong oscillations in theta frequency (6–12 Hz) and an associated high cholinergic tone, might contribute in a different way to memory consolidation. For instance, selective memory traces may be strengthened at the expense of others due to shifting of phase relationships between firing patterns and the theta cycle and concomitant shifts in LTP/long-term depression (LTD) induction [69]. Also, during REM sleep molecular cascades may be activated that are not demonstrable by electrophysiological screening. In support of this, REM sleep has been proposed to mediate gene-expression-dependent synaptic plasticity by activation of molecular signaling pathways [70] involving muscarinic receptors (see [64] for a more detailed review of the possible contributions of REM sleep to memory consolidation).

Despite these similarities, ventral striatal reactivation appears to differ from hippocampal reactivation. Whereas hippocampal reactivation was reported to generally decay in ~30 min after the onset of post-task rest [63, 71], the ventral striatum did not show a decline of reactivation across a period of 40 min of post-experiential rest. This difference could not be plausibly attributed to a difference in behavioral tasks used.

Thus, not only is the ventral striatum involved in the integration of various streams of cortical and limbic information to invigorate appropriate behavioral patterns, it also contributes to memory consolidation processes guiding motivated behaviors. Reactivation may contribute an important step to these.

The Ventral Striatum Contributes Motivational Value to Reactivation of Memorized Information

A key finding on ventral striatal reactivation was that this area specifically and preferentially reactivates reward-related information (see Fig. 4.1b–d). This was demonstrated by the stronger reactivation of neurons that expressed a transient change in firing rate related to the rat's arrival at reward sites located in the centers of the

sides of the triangle track compared to neurons that did not show such a response pattern [61]. This strong reactivation was accounted for by spike trains that were emitted in close temporal relation to reward site visits. These were more strongly reactivated than spike trains occurring at other locations on the track such as its corners. This evidence indicates that the ventral striatum contributes a motivational value component to the reactivated memory trace. Here, we defined motivational value as the net payoff expected in the future when a stimulus or situation associated with the value occurs or an associated action pattern is pushed.

The preferential reactivation of reward-related information in the ventral striatum indicates that this structure reprocesses a different type of information than the dorsal hippocampus. As hippocampal reactivation has been studied in populations of dorsal CA1 neurons showing location-specific firing (i.e., "place fields" [72, 73]), it is reasonable to assume that this process pertains primarily to spatial and contextual information [7, 8, 63, 74]. The combined findings point to an important organizational principle of the reactivation process: multiple brain areas are participating in the reactivation of a single event, and each area contributes a distinct aspect to the reactivated trace. Reactivation therefore may be conceived as a distributed process in which some structures reactivate information about the physical–sensory properties of an object (e.g., sensory neocortex) [14] and others about its spatiotemporal context (hippocampus) and motivational value (ventral striatum).

The ventral striatum participates in a larger network of cooperating brain structures that are involved in processing reward-related information and together control motivated behavior [28–30]. A prominent structure in this network, the medial prefrontal cortex, also shows reactivation during periods of SWS following a behavioral episode [13, 15, 71]. Although the nature of the replayed information was not directly addressed in these studies, Euston et al. showed that in a spatial task neurons fired differentially in anticipation of and during receipt of medial forebrain stimulation rewards [75]. A study by Peyrache and colleagues, on the other hand, showed reactivation of neuronal patterns related to response selection at a decision point in a behavioral task where rats had to apply one of several rules to successfully navigate to the reward location [15].

Thus, in addition to the ventral striatum, other brain areas might reactivate yet other aspects of emotional and motivational information, although to date it is unclear what the specific contribution of each area is and how the areas interact. Based on anatomical evidence the most straightforward hypothesis would be that first the ventral striatum receives information on delivery of reinforcers and their associated cues and contexts through projections from the prefrontal cortex, amygdala and hippocampus. Subsequently, reward-related information processed by striatal neurons may reenter the cortico-limbic system via a route through the ventral pallidum and mediodorsal nucleus of the thalamus, projecting back to the prefrontal cortex [76, 77], or via dopamine release in mesolimbic and mesocortical areas triggered by VTA activity that is regulated by striatal output [78].

Hippocampus Leads Ventral Striatum in Cross-structural Reactivation of Place–Reward Information

Reactivation across multiple brain structures such as the hippocampus and ventral striatum suggests the existence of a mechanism facilitating the coherent reprocessing of pieces of information belonging to the same event. At the same time, such a mechanism prevents the formation of erroneous associations with other events. Concurrent cross-structural reactivation, which was observed to occur in the hippocampal–neocortical circuit [11, 14], may subserve such a function. Joint reactivation was also found between the hippocampus and ventral striatum (Figs. 4.2 and 4.3), and the reactivation strength was positively correlated with two characteristics of hippocampal–ventral striatal pairwise firing. First, the co-expression of a hippocampal place field and a reward-related correlate in the ventral striatum and, second, a firing order during track running in which the hippocampal cell fired before the striatal cell (Fig. 4.3a) [79].

As regards the first characteristic, cell pairs co-expressing a hippocampal place field and a reward-related correlate in the ventral striatum reactivated more strongly than pairs of which only one or none of the neurons showed such a response (Fig. 4.3a, left panel). This indicates that it was the specific combination of spatial/contextual and reward-related information that was reinstated in the rest period following food searching behavior. Joint reactivation of hippocampal and ventral striatal ensembles may provide an opportunity to integrate neuronal representations of contextual and motivational information to enable the acquisition of place–reward associations. Such associations support the ability to predict and localize desired foods and liquids while foraging and are known to be dependent on the hippocampal–ventral striatal circuitry. Indeed, Ito and colleagues [18] showed with disconnection lesions that communication between the hippocampus and the shell region of the ventral striatum is essential for context-dependent memory retrieval and place learning. This is consistent with most previous work on ventral striatal involvement in spatio-contextual learning tasks [31–33]. Some previous studies, however, showed serial transmission between hippocampal area CA1 or subiculum and the ventral striatum to be essential only in novel spatial situations and not in tasks requiring previously acquired information about reward locations [80, 81]. These results seemingly contradict Ito et al. [18], but discrete cues may have been available to the rat to help solve the task.

The second factor indicative of strong reactivation was the cell pair's firing order during track running (Fig. 4.3a, right panel). Cell pairs of which the firing of the hippocampal cell preceded that of the ventral striatal cell during track running reactivated more strongly than pairs showing the opposite pattern or pairs not showing a clear firing order. During track running, many pairs of which the ventral striatal cell fired in advance of the hippocampal cell were available, but apparently these pairs contributed less or not to reactivation.

Each row of cross-correlograms in Fig. 4.2d shows that the firing order in a pair consisting of a hippocampal unit (HC1–3, target) and a ventral striatal unit (VS1,

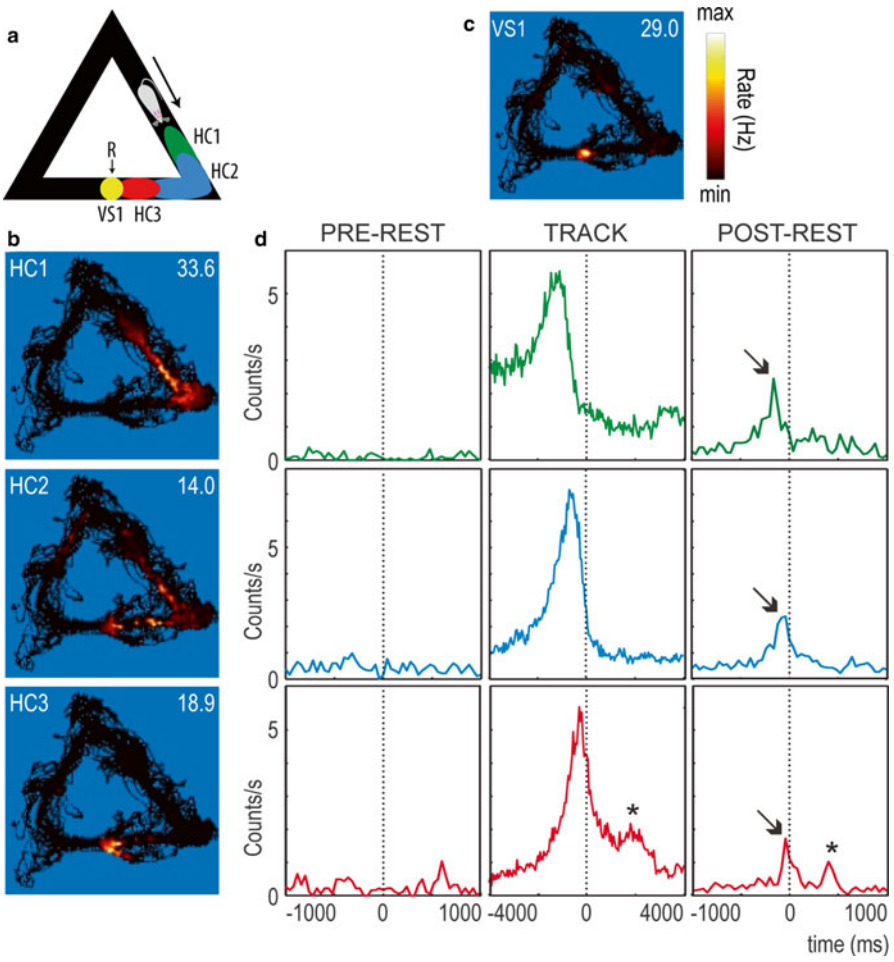

Fig. 4.2 Firing order is preserved in time-compressed cross-structural reactivation. (**d**) Each row of cross-correlograms shows the temporal relation of firing of neuron pairs consisting of one VS neuron (VS1; reference; panel **c**) and one of three HC neurons (HC1–3; target; panel **b**) during pre-behavioral rest (PRE-REST), track running (TRACK), and post-behavioral rest (POST-REST). (**b** and **c**) The *blue squares* show the color-coded spatial firing distribution of three hippocampal (HC1–3) and one ventral striatal neuron (VS1), which were recorded simultaneously (rate maps are plotted as in Fig. 4.1a). The maximal firing rates are noted in the *top right corners*. The schematic at the *top left* (**a**) indicates the alignment of the place fields of the hippocampal cells (panel **b**) and the reward-related cell of the ventral striatum (panel **c**) and therefore the order in which the different cells activate when the rat runs in a clockwise direction. (**d**) Hippocampal activity is synchronized on ventral striatal firing (time = 0, bin size 20 ms). The colors used in the cross-correlograms correspond to the colors of the HC place fields in panel **a**. During track running hippocampal place cells and ventral striatal reward-related cells show correlated firing with peaks at different offsets relative to time zero, in line with the spatial distance between the firing fields. This correlated firing was absent in pre-behavioral rest but reinstated during post-behavioral rest. In the *bottom example* a secondary peak during track running is recurring in post-behavioral rest (*asterisks*). Reactivation of firing activity was compressed in time, but the relative time lag of firing within and between pairs was preserved. The *top example* shows that the firing fields do not have to overlap spatially or temporally in order to show correlated firing during behavior and subsequent rest. Adapted from [79]

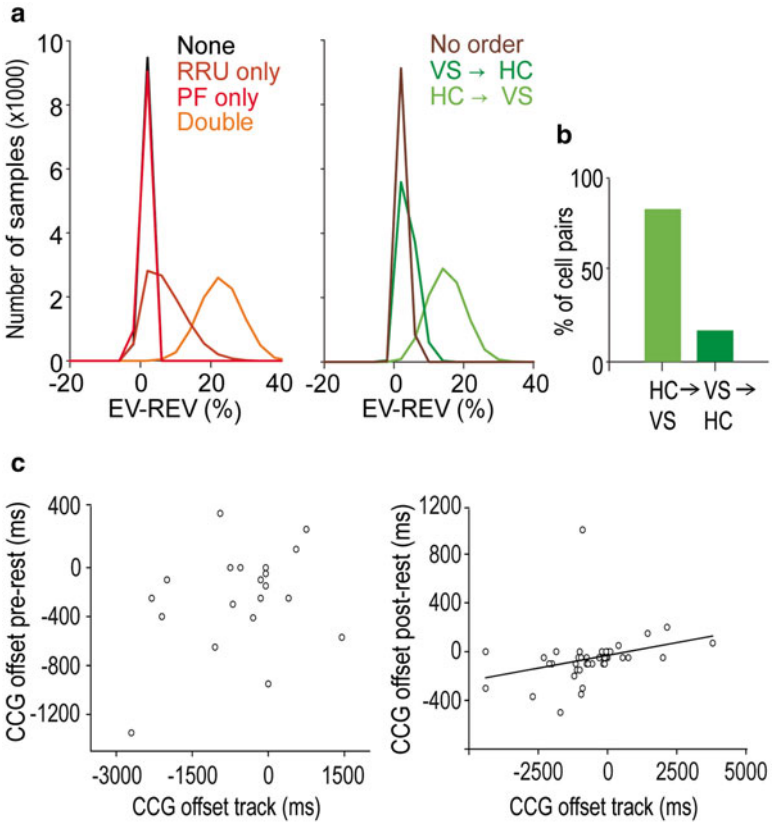

Fig. 4.3 Hippocampus leads ventral striatum in reactivation of place–reward information. Illustration of the three main characteristics of cross-structural reactivation. (**a**, *left panel*) *Content*: reactivation for subgroups of cell pairs exhibiting specific characteristics such as behavioral correlates was assessed by computing EV and REV values with a bootstrap procedure (1,000×) in which all pairs of the same kind were pooled across sessions. Graphs show EV-REV values to indicate differences between groups. Cell pairs expressing a double correlate (double) showed significant reactivation in contrast to pairs that only showed one correlate (place field (PF) only or reward-related correlate (RRU) only) and pairs that did not show any correlate (None). (**a**, *right panel*) *Order*: cell pairs of which the hippocampal cell fired before the ventral striatal cell during track running (HC → VS) showed stronger reactivation than pairs of which the ventral striatal cell fired before the hippocampal cell (VS → HC) or pairs that did not fire consistently in a specific order (No order). (**b**) Reactivation occurred in a forward direction, meaning that the firing order within cell pairs was maintained from behavior to subsequent sleep. In the majority of the "double correlate" reactivating cell pairs, the hippocampal cell fired before the ventral striatal cell in both periods. (**c**) *Temporal compression*: the relative time offsets of peaks in cross-correlograms were preserved from track running to post-behavioral rest. This is shown by a positive correlation between the peak offsets during track running and post-behavioral sleep (*right*; $R^2 = 0.09$, $P < 0.05$), whereas peak offsets during track running and pre-behavioral sleep were not correlated (*left*). The peak offsets during post-behavioral rest were significantly reduced compared to track running, indicating that reactivation occurred on a compressed timescale compared to behavior (~factor 10, also visible in Fig. 4.2). Adapted from [79]

reference) is preserved from the behavioral period (TRACK) to the post-rest phase (POST-REST). Spatial firing-rate distributions of the units used in the cross-correlograms are shown in the blue-background squares (hippocampus: Fig. 4.2b; ventral striatum: Fig. 4.2c), and Fig. 4.2a schematically shows the alignment of the firing fields of these different units. The colors of the hippocampal place fields correspond to the colors used in the cross-correlograms (Fig. 4.2d). During TRACK each of the pairs shows correlated firing patterns with firing peaks at different latencies relative to time zero, corresponding to the spatial distance between the firing fields. During POST-REST, but not PRE-REST, this correlated firing activity was also present. The timescale on which concurrent firing is taking place is compressed during POST-REST compared to TRACK, but note that the relative latency between the firing of the HC and the VS neuron is preserved.

Analysis of the temporal relation between hippocampal and ventral striatal firing showed that in pairs expressing a double correlate (i.e., place field in the hippocampus and reward-related correlate in the ventral striatum) generally the firing order on the track was preserved in the subsequent rest period. This occurred in 89 % of the pairs exhibiting a double correlate, indicating *forward* reactivation (Fig. 4.2d). In the large majority of pairs showing forward reactivation, the hippocampal cell fired preferentially before the ventral striatum during both periods (this occurred in 84 % of the reactivating pairs showing forward reactivation; Fig. 4.3b). This is consistent with the hippocampus operating in advance of the ventral striatum in the reactivation of place–reward information. This is currently the most direct evidence supporting a temporally leading role of the hippocampus in reactivation together with any other brain structure. This organization of firing order obeys the direction of the anatomical hippocampal–striatal projection [19, 20] and complies with a central tenet of consolidation theory, proposing the hippocampus to initiate reactivation in its target structures [2–5].

Hippocampal Ripples as a Mechanism Orchestrating Ventral Striatal Reactivation

The hippocampus is proposed to initiate and orchestrate joint reactivation in its target structures when excitability and reactivation within the hippocampus are strongest, i.e., during sharp wave–ripples events that occur in CA1 local field potentials during periods of quiet rest and SWS, awake immobility, and consummatory behaviors [63, 82, 83]. Selective suppression of hippocampal sharp wave-ripples during wakefulness or post-behavioral sleep impaired the performance of rats on a spatial memory task [84–86]. Several indications of sharp wave-ripples associated reactivation in the ventral striatum support the role of these events as a mechanism for brain regions to interact intensively. First, ventral striatal reactivation was primarily mediated by cells that change their firing rates (i.e., increments, decrements, or a combination) upon the emission of hippocampal sharp wave-ripples in

post-behavioral rest (Fig. 4.1f) [62]. Second, reactivation in the ventral striatum appeared particularly strong during ~200 ms following the emission of sharp wave-ripples [61]. Lastly, reward-related spike patterns of cells exhibiting a behavioral correlate became temporally more aligned with sharp wave–ripples episodes during post-behavioral rest relative to pre-behavioral rest. These results are in line with evidence from another hippocampal target, the medial prefrontal cortex, where reactivation was about 70 % stronger during hippocampal sharp wave-ripples compared to baseline and peaked about 40 ms after the onset of a sharp wave-ripples [15]. Also, during SWS and specifically within hippocampal sharp wave-ripples, firing in the hippocampus was shown to advance firing in the medial prefrontal cortex by 40 ms, although reactivation was not specifically addressed in this study [87].

Thus, reactivation in both ventral striatum and medial prefrontal cortex is associated with hippocampal sharp wave-ripples, and the temporal order in which the hippocampus fires first is critical to replay in the ventral striatum [79]. This order of spike generation and reactivation supports a scenario in which the initiation of cross-structural reactivation is under control of the hippocampus, although it cannot be excluded that reactivation in the ventral striatum is driven by other sources, e.g., the medial prefrontal cortex and/or amygdala.

As mentioned before, selective suppression of ripples during a behavioral task was shown to impair subsequent performance on the task, indicating that consolidation already starts during ongoing behavior [86]. Reactivation of neuronal patterns was demonstrated to occur also in ripple epochs during a track-running task when rats were pausing at reward sites and, on some occasions, were consuming the available reward [9, 10, 74, 83]. Thus, reactivation and memory consolidation may indeed be specifically associated with the occurrence of ripples rather than being dependent on sleep per se. Whether striatal and joint hippocampal–striatal reactivation also occur during awake states is yet unknown.

Cross-Structural Reactivation Is Compressed in Time

As hippocampal reactivation occurs predominantly during ripples, the relatively short duration of these events (~100–200 ms) poses a time limitation on the extent to which information can be replayed on each occasion. A similar time constraint on reactivation may be effective in the ventral striatum and other hippocampal target structures, such as the medial prefrontal cortex, provided that reactivation occurs during periods of enhanced neuronal activity in association with hippocampal ripples. Reactivation may assume several modes of operation. First, stretches of neural activity representing the behavioral experience may be replayed in “real time” and become truncated at the moment the sharp wave–ripples event has ended. In this case, only very short time periods of the experience can be replayed. Alternatively, as the sleeping brain is not constrained by behavioral demands, reactivation may occur at the speed determined by the brain’s cellular and transmission dynamics (cf. [13]). In this case, neural activity patterns would be time-compressed

during reactivation compared to the behavioral experience. This implies that a period in the range of seconds of the maze experience can be replayed during a time window of a few hundreds of milliseconds during sleep. As a consequence, time lags between neural firing are shortened considerably, which is likely beneficial for spike-timing dependent plasticity [88–91].

Results on hippocampal–ventral striatal reactivation support the latter hypothesis because the cross-correlograms showed the time lags between the firing of neurons to be about 10× shorter for post-behavioral rest than for track running (Figs. 4.2d and 4.3c right panel) [79]. Also, the peaks in the cross-correlograms of post-behavioral rest were significantly narrower than those of track running (Fig. 4.2d). Even hippocampal–striatal pairs that exhibited nonoverlapping firing fields on the track showed near-synchronous firing during sleep, and the overall shape of the cross-correlograms was preserved despite the compression. The compression factor we found is comparable to the factor ~7 reported for the medial prefrontal cortex [13] but considerably lower than the factor 20 found for the hippocampus [8], but see [92].

Hippocampal spike sequences may, however, already get time-compressed as they occur during behavior instead of—or in addition to—the post-behavioral rest period through theta phase precession [13, 93, 94]. As a consequence of the tendency of hippocampal cells to fire at earlier phases of the theta cycle as the rat progresses through a place field, spikes representing adjacent place fields occur in rapid succession within the theta cycle. In this way, temporal alignment of activity patterns takes place on a condensed timescale already during behavior. It was proposed that spike pattern timing may be composed of different mechanisms depending on the brain area, i.e., phase precession during behavior in the hippocampus and compression during sleep in the medial prefrontal cortex and other structures such as the ventral striatum [13]. These mechanisms, however, are not mutually exclusive and may act in concert. A phase precession on hippocampal theta oscillations has been demonstrated in the ventral striatum [95], which suggests that in this structure theta phase precession may exist in addition to compression. Assuming that theta phase precession accounts for a factor 20 compression in the hippocampus, it could explain the compression in the ventral striatum which is less strong than in the hippocampus (factor 10). But an important aspect of the theta phase precession hypothesis on time-compressed reactivation is that it assumes that only cell pairs that are active in the same theta cycle (~100–125 ms) reactivate. The limited time frame of a theta cycle implies that reactivating cell pairs show overlapping or adjacent place fields at least in their tails. Hippocampal–ventral striatal cross-correlograms revealed also cell pairs that exhibited nonoverlapping firing fields on the track and were concurrently active during subsequent sleep (Fig. 4.2). As these firing patterns during behavior are temporally separated in the order of seconds, they do not occur in the same theta cycle and need to be compressed in order to reactivate together. Thus, at least within the ventral striatum, spike pattern condensation by theta phase precession may occur in shorter segments of an experience (~100–2,000 ms), and compression during SWS may take place across longer behavioral periods (several seconds). Inspection of local field potential spike records suggests that prolonged

segments can be reactivated across multiple ripples (cf. [96]). Taken together, we hypothesize that strengthening of synaptic connections activated during a behavior occurs in two modes. First, spike patterns may be condensed through theta phase precession. The high cholinergic tone associated with theta activity may aid initial storage of the memory trace through concurrent muscarinic receptor activation and G-protein-modulated expression of zif-268 [64, 70]. Second, compression of the memory trace brings several seconds of "real-time" behavioral experience together in a time frame of hundreds of milliseconds. Repeated reactivation of sequential place and reward information on such timescale may potentiate spike-timing-dependent plasticity in the associated hippocampal–ventral striatal synapses [88–91]. Through such repeated, compressed reactivation of several seconds of a behavioral episode in which a series of place fields is followed by a reward-related correlate, value information is not only paired with locations and cues nearby but also with more remote locations and cues on the path leading to the reward site.

Cross-Structural Reactivation Decays Slowly in the First Hour of Post-behavioral Rest

As mentioned above, there is a difference between the decay times of hippocampal and ventral striatal reactivation. Reactivation in the ventral striatum was found to be of equal strength across the first 40 min following the behavioral task [61, 62], whereas hippocampal reactivation generally decays to undetectable levels in ~30–40 min [63, 71] (Lansink et al., unpublished observations). Interestingly, joint hippocampal–ventral striatal reactivation was detected across the first hour of concatenated periods of sleep, but its strength gradually declined in this period [79]. This result supports the notion that the hippocampus may influence reactivation in the ventral striatum across a considerable time period, but also indicates that at some point the ventral striatum can sustain reactivation independently of the hippocampus. Generally, reactivation studies detect the phenomenon only during rather short periods following an experience (~up to 1 h). But if reactivation would present a correlate of memory consolidation in a sustained manner, it is predicted to occur during the entire consolidation process, i.e., during periods of days, weeks, or even years. Although there is currently no clear consensus about whether reactivation is sustained on the longer term (hours to days; [cf. [71, 97]]), it was shown that during awake behavior and SWS, behavioral experiences of the non-immediate past were replayed [9, 10]. Neural spike sequences belonging to a behavioral experience *A* were found to be reinstated minutes to hours after the experience when rats were engaged in a different behavioral task *B* or were resting following behavior *B*.

Over time, the strength of reactivation decays in the hippocampus but less in the ventral striatum and may in both structures eventually become indistinguishable from neuronal "noise." This, however, does not necessarily imply that the process has terminated but it may become undetectable with the current recording and analysis

methodologies. Further research is required to understand why different decay dynamics exist across areas and how the ventral striatum sustains reactivation without hippocampal support.

Reactivation and Plasticity in Hippocampal–Ventral Striatal Circuits: A Hypothesis

Integrating insights on hippocampal–ventral striatal reactivation with current knowledge in the field leads to a clear and testable hypothesis on the dynamics and implications of the reactivation process within and between these structures.

Because of the auto-associative and ripple-generating properties of hippocampal area CA3 [82, 98, 99], we assume that spontaneous burst firing and reactivation arise here, perhaps as a result of decreased neocortical input [100] and activity changes in pontine nuclei [101]. Propagation of sharp wave-ripples to the CA1 area is most likely to excite those assemblies that were activated in a previous experience as these neurons have a higher probability to spike than others [6]. Thus, a neural representation of the spatial/contextual aspects of a preceding scene or event is reinstated in the hippocampal network [7, 102].

Via the subicular complex or hippocampal CA1 area directly, massive excitatory drive associated with sharp wave-ripples reaches target sites of the hippocampal formation such as the entorhinal and prefrontal cortex and, via the fimbria–fornix, ventral striatum (Fig. 4.4a). Repetitive electrical stimulation of the fimbria–fornix in anesthetized rats was shown to induce postsynaptic potentials and short- and long-term potentiation in the ventral striatum and prefrontal cortex [103–105]. Likewise, bursts of hippocampal activity may excite neurons in both areas and initiate reactivation in multiple targets at the same time. In the ventral striatum, synchronized activity of hippocampal cells representing the animal's location in a particular scene may induce a transition to a more excitable state of the neuronal ensemble [e.g., [106, 107]]. Through the association between neural representations of contextual information and reward, or a predictive cue as proxy, represented at least by subsets of ventral striatal neurons, the context will become predictive of an emotionally relevant outcome and thereby gains motivational value.

Once in a highly excitable state, converging hippocampal, amygdaloid, thalamic, and prefrontal glutamatergic afferents on ventral striatal neurons may activate a distributed ensemble, capturing relevant aspects of the foregoing behavior (Fig. 4.4a) [61, 108]. The contrast between the active ensemble and others may be enhanced by intra-striatal feed forward [109–111] and feedback mechanisms [112–115] involving fast-spiking interneurons and medium-sized spiny neurons. Moreover, firing patterns across structures (e.g., the hippocampus, prefrontal cortex, amygdala, and ventral striatum) may at this stage be synchronized and collectively represent behaviorally significant aspects of the preceding scene or event.

As a result of time-compressed reactivation during SWS, firing patterns of hippocampal and ventral striatal ensembles are confined to time windows comprising

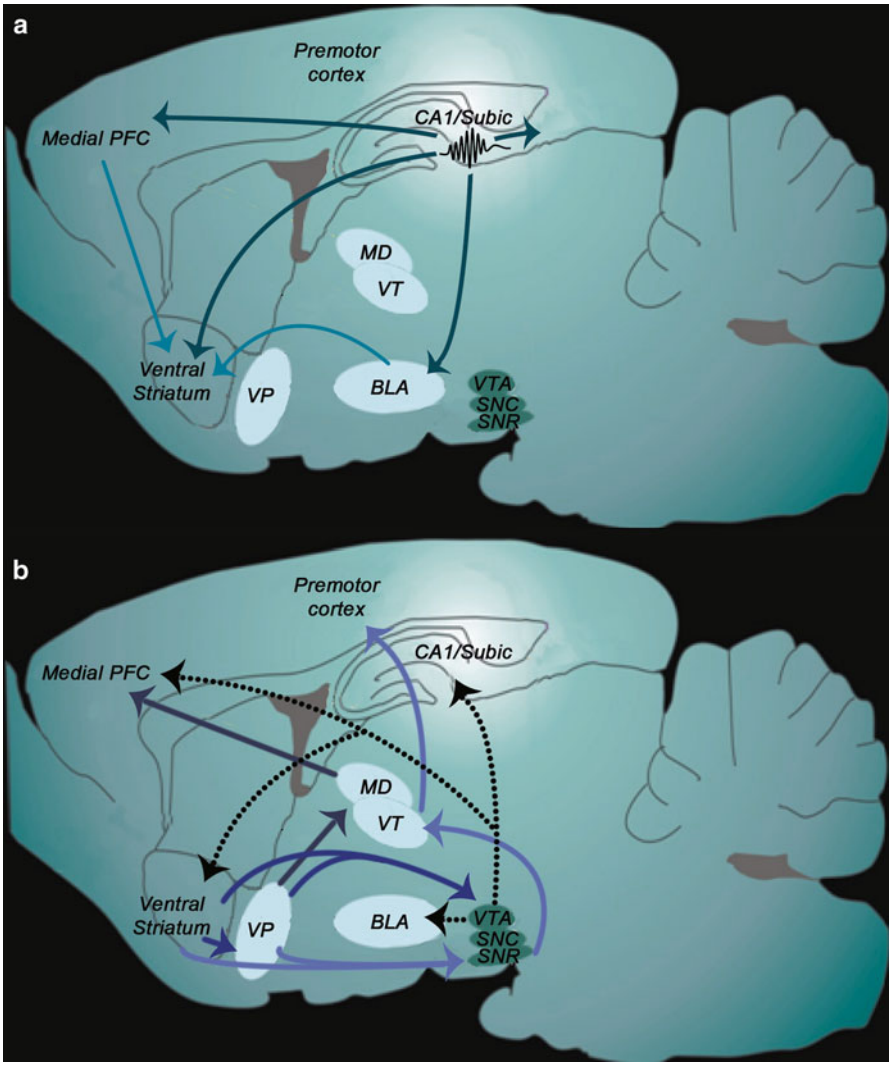

Fig. 4.4 Schematic representation of the flow of information through the hippocampal–ventral striatal circuitry and beyond during reactivation. (**a**) Sharp waves that originate in hippocampal area CA3 are transmitted to CA1. Via the subicular complex or hippocampal CA1 area directly, excitatory drive associated with sharp wave ripples reaches target sites of the hippocampal formation such as the ventral striatum but also entorhinal (Ent Cx) and prefrontal cortices (medial PFC) and basolateral amygdala (BLA). All in *dark green arrows*. In the ventral striatum, synchronized activity of hippocampal cells representing a spatial location or episode may induce a transition to a more excitable state of the neuronal ensemble that was activated by reward and motivated behaviors associated with that scene during behavior preceding the reactivation. Once in an excitable state, converging hippocampal, amygdaloid (*blue arrow*), thalamic, and prefrontal (*blue arrow*) glutamatergic afferents of ventral striatal neurons may activate a distributed ensemble, capturing relevant aspects of the foregoing behavior. Firing patterns across these structures may at this stage be synchronized and collectively capture a detailed representation of the preceding scene or event.

tens to hundreds of milliseconds, which is a condition required for the induction of spike-timing dependent plasticity [88–91]. Consistent with the unidirectional projection from the hippocampus to the ventral striatum [19, 20] and the prerequisite for associative long-term potentiation that the presynaptic cell has to fire shortly in advance of the postsynaptic cell, those cell pairs of which the hippocampal cell fired closely before the striatal cell reactivate and others hardly do [79]. In this way, ripples may not only transmit reactivated information to hippocampal target structures, but may also facilitate lasting changes in glutamatergic inputs to the ventral striatum [58]. These lasting modifications are proposed to make ventral striatal neurons responsive to contexts and other environmental cues predictive of reward so that these cells effectively become spatially driven predictors of reward [116]. Periods of reactivation in ventral striatal ensembles may last as long as the duration of increased excitability following ripple onset (~200–500 ms) [62] and may therefore outlast those in the hippocampus as the duration of sharp wave-ripples is shorter than of these periods. Moreover, reactivating sequences may span multiple ripples in succession [96].

Ventral striatal output reaches the ventral pallidum, ventral tegmental area (VTA), lateral hypothalamus, and substantia nigra pars compacta and reticulata [26, 117] and may, via these relay stations, convey reward-related information to downstream systems. First, output to the subthalamic nucleus and the substantia nigra pars reticulata may reach the premotor cortex through the ventral thalamus [76]. By these routes motivational information about cues and contexts could contribute to selection of an appropriate behavioral pattern, depending on the activity patterns in cortico-limbic structures (Fig. 4.4b).

Second, the ventral striatum and ventral pallidum project to the VTA [26, 118, 119] where they can influence the activity of dopamine neurons and thereby regulate mesolimbic and mesocortical dopamine release (Fig. 4.4b). The VTA has recurrent dopaminergic projections to the ventral striatum but also projects to the hippocampus, amygdala, dorsal striatum, and medial prefrontal cortex [120–122]. The ripple-associated "off-line" retrieval of value information in the ventral striatum [61] may induce dopamine cells to generate a feedback or an error-in-reward-prediction signal which potentially reaches each of the respective projection areas [78, 123, 124]. Such signals might underlie dopamine-associated maintenance of long-term potentiation and memory consolidation in the hippocampus [125–130] and ventral striatum [54, 56, 123, 131], but see [58] and the medial prefrontal cortex [132–134].

Fig. 4.4 (continued) (**b**) Ventral striatal reactivation may affect several downstream systems. (1) *Light purple arrows*: ventral striatal output may reach the premotor cortex through the substantia nigra pars reticulata (SNR), the subthalamic nucleus (not shown), and the ventral thalamus (VT). (2) *Middle purple arrows*: the ventral striatum and the ventral pallidum (VP) project to the ventral tegmental area (VTA) where they can influence activity of dopamine neurons and thereby regulate mesocortical and mesolimbic dopamine transmission (*dashed arrows*). The VTA has recurrent dopaminergic projections to the ventral striatum but also projects to the hippocampus, amygdala, and medial prefrontal cortex. (3) *Dark purple arrows*: ventral striatal output may reach the medial prefrontal cortex through projections to the VP and mediodorsal thalamic nucleus (MD). *SNC* substantia nigra pars compacta

Third, via projections mainly from the ventral pallidum to the mediodorsal thalamic nucleus, ventral striatal output may affect the medial prefrontal cortex [76] and thus regulate a network of structures involved in the consolidation of reward-dependent learning rules, task sets, and contexts (Fig. 4.4b) [135].

Concluding Remarks

Concepts on declarative memory consolidation have directed the focus of reactivation research to the hippocampus and neocortex. As reviewed in this chapter, however, the engagement of the ventral striatum indicates that reactivation should be considered a highly distributed process in which also subcortical structures contribute to the composition and strengthening of memory traces comprising various attributes of a single experience. Coherent, cross-structural reactivation, such as demonstrated between the hippocampus and the ventral striatum, may serve to integrate information processed in different parts of the brain and prevent formation of erroneous associations with other events. In this process, the hippocampus is proposed to initiate and coordinate reactivation in connected areas. This notion is now supported by evidence demonstrating that joint hippocampal–ventral striatal reactivation is organized such that the neural code for place information in the hippocampus is activated slightly in advance of reward-related information in the ventral striatum. These findings are expected to inspire novel research investigating how memory traces are encoded, stored, and retrieved in brain-wide neuronal networks.

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Chapter 5
Hippocampal Sequences and the Cognitive Map

Andrew M. Wikenheiser and A. David Redish

Abstract Ensemble activity in the hippocampus is often arranged in temporal sequences of spiking. Early theoretical and experimental work strongly suggested that hippocampal sequences functioned as a neural mechanism for memory consolidation, and recent experiments suggest a causal link between sequences during sleep and mnemonic processing. However, in addition to sleep, the hippocampus expresses sequences during active behavior and moments of waking rest; recent data suggest that sequences outside of sleep might fulfill functions other than memory consolidation. These findings suggest a model in which sequence function varies depending on the neurophysiological and behavioral context in which they occur. In this chapter, we argue that hippocampal sequences are well suited to play roles in the formation, augmentation, and maintenance of a cognitive map. Specifically, we consider three postulated cognitive map functions (memory, construction of representations, and planning) and review data implicating hippocampal sequences in these processes. We conclude with a discussion of unanswered questions related to sequences and cognitive map function and highlight directions for future research.

Keywords Sequence • Cognitive map • Replay • Theta • Hippocampus

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A Taxonomy of Hippocampal Firing Sequences

What Are Sequences?

In this chapter, we discuss the possible functions of temporally coordinated, sequential, firing patterns in hippocampal neurons. First, however, it behooves us to articulate more precisely how we define firing sequences. In our view, sequences are fast, discrete bursts of temporally structured spiking involving numerous hippocampal neurons. Critical to our definition, the temporal structure within the fast timescale sequence reflects or recapitulates important aspects of ensemble firing properties over longer epochs (Fig. 5.1). Spatial tuning is the most obvious slow timescale correlate of many hippocampal pyramidal neurons [1, 2]; consequently, many firing sequences are time-compressed representations of paths through the environment [3–5]. However, sequences should not be thought of as strictly spatial phenomena; neurons with nonspatial firing patterns could also participate in structured sequential representations.

The temporal organization of spiking in sequences exceeds the precision necessary to achieve the canonical tuning properties of hippocampal neurons; place cells could show identical spatial tuning without expressing fast timescale sequences. Sequences thus comprise an additional layer of temporal organization beyond cells' primary tuning properties. Understanding how sequential organization arises, whether it is modulated by behavior, and what functions (if any) it serves is important for better understanding neural representations in the hippocampal network.[1]

Readers may note that we use the term "firing sequence" in place of other descriptors (like "reactivation" or "replay") commonly used to label these events. The term "sequence" captures the unifying property shared by all of these events (temporal organization) while remaining agnostic as to function. This is important, as current understanding of sequence function is incomplete, albeit developing rapidly. Furthermore, as seemingly similar representations might be involved in multiple unique functions during different behavioral or physiological states, a term specifying one particular function seems inappropriately limiting.

Hippocampal Network States

Local field potential (LFP) activity, the low-frequency voltage signal derived from summed electrical activity in the region of tissue surrounding the electrode tip, has a long history of study in the hippocampus [1, 7–10]. Consequently, the behavioral

[1] The hippocampus is divided into multiple anatomical subfields [6], with the majority of place cell recordings deriving from the CA1 and CA3 regions. These regions exhibit interesting differences in both efferent and afferent connectivity [1]. In this chapter, we do not focus on these differences, but instead consider sequences recorded in both regions.

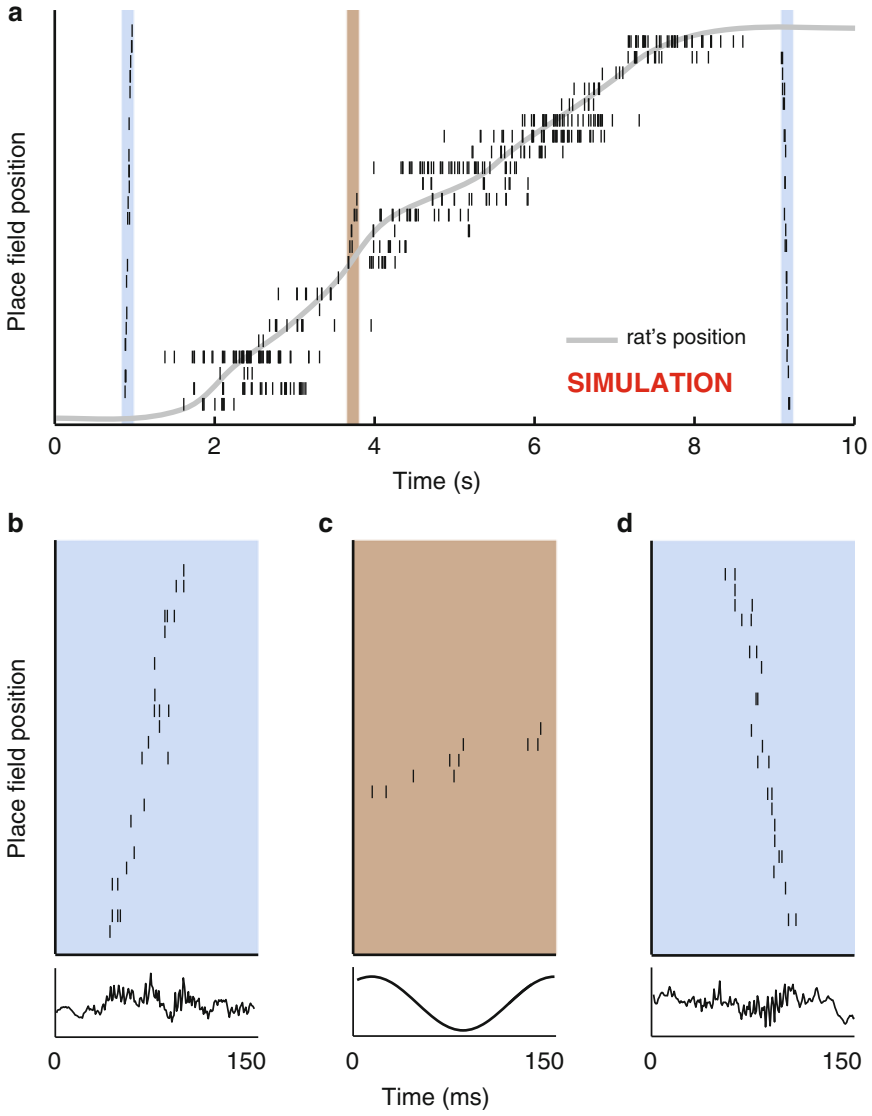

Fig. 5.1 Simulated activity in an ensemble of place cells is plotted as a rat runs through an environment (**a**). Each row represents the activity of a single neuron, and cells are sorted based on where their fields occurred in space. Sequences are reproduced (with the accompanying LFP activity) on an expanded timescale in the lower portion of the figure. Sequences before and after the animal's trajectory (during the LIA network state), occur with both forward (**b**) and backward (**d**) ordering. During active behavior, when the hippocampus is in the theta network state, place cells spiking is organized into sequences bounded by theta oscillations (**c**)

correlates and underlying single-cell activity associated with different hippocampal LFP patterns are well established. Because hippocampal firing sequences often co-occur with characteristic LFP signatures [11, 12], LFP recordings provide both a useful readout of hippocampal network state and a convenient means of detecting candidate firing sequences.

Theta State

Hippocampal LFP patterns are typically divided into theta and non-theta states. During the theta state, the LFP is dominated by strong, theta frequency (5–12 Hz) oscillations [1, 8, 9, 13]. Two distinct forms of theta oscillation (type I and type II) have been described. Type I theta occurs during "voluntary," primarily movement-related behaviors and occupies the upper portion (7–12 Hz) of the theta frequency band. Type II theta occurs when animals are stationary, but in some way alert or attending to their surroundings (e.g., during presentation of conditioned stimuli, preparation of a motor response, fearful freezing). The frequency of type II theta tends toward the lower regions (5–7 Hz) of the theta band. In addition to differences in behavioral correlates and dominant frequencies, types I and II theta are further distinguishable by pharmacology and the brain structures responsible for generating each [14]. The theta network state is also prominent during rapid eye movement (REM) sleep [1].

Theta Sequences

The discovery of phase precession in hippocampal place cells [15] demonstrated that spike timing could carry information along with the cell's firing rate. As noted by Skaggs and colleagues [16], phase precession implies that the relative timing of different place cells' spikes within a theta cycle should reflect the order in which the cells' place fields are arranged in space, giving rise to orderly sequences of place cell spiking. It is now well established that such sequences do exist [12, 17, 18]. Subsequent work suggests that theta sequences occur during both type I and type II theta states and can include both spatial and nonspatial information [18–22].

Large, Irregular Activity (LIA) State

During non-theta states, the hippocampal LFP exhibits broad-spectrum voltage fluctuations, often referred to as large, irregular activity (LIA; [1, 8]). Behavioral correlates of the LIA network state include inattentive wakefulness, consummatory behaviors, and grooming. Slow-wave sleep is also accompanied by LIA [1, 8, 23, 24].

The disorganized voltage fluctuations characteristic of LIA are punctuated by transient, population bursts of spiking that engage large numbers of neurons in the hippocampus. These short bursts of heightened synchrony are called sharp wave-ripple (SWR) complexes because of the distinctive LFP oscillation associated with them [1, 9, 24].

LIA Sequences

Evidence for sequential firing patterns in the hippocampus was first observed during SWRs in slow-wave sleep. Early work showed that correlations between pairs of place cells coactive during behavior were enhanced during post-behavior sleep [25]. It has since been established that place cell spiking in and around SWRs during sleep represents extended, temporally precise spatial trajectories through previously visited environments [11, 26–28]. Additionally, similar sequence representations occur within SWRs during awake LIA [29–32].

Cognitive Maps and the Hippocampus

Tolman proposed the idea of a cognitive map based on behavioral studies of rats, envisioning a proactive, predictive learning system that could flexibly manipulate and retrieve information to guide surprisingly complex behaviors [33–36]. Tolman's conception of the cognitive map was an internal representation of the environment, constructed by animals in the absence of explicit reward or punishment, and used to generate expectancies or predictions about the cause and effect structure of the world [37, 38]. The cognitive map theory ascribed unprecedented mental abilities to rats; needless to say, these ideas were not without controversy [39–41]. Nevertheless, subsequent work has many of Tolman's conjectures, and his cognitive map framework is increasingly accepted. O'Keefe and Nadel [1], based on behavioral and neurophysiological studies in rats, presciently postulated the hippocampus as the neural instantiation of the cognitive map. Recent research on hippocampal function in both humans [42, 43] and increasingly nonhuman species [44, 45] has converged on a theory of hippocampal computation close to Tolman's cognitive map, including prospective processes like mental time travel [46, 47], prediction [48, 49], and imagination [50–53]. There is now growing consensus that the hippocampus is essential for these sorts of future-oriented, synthetic, cognitive processes.

In this chapter, we argue that spiking sequences in the hippocampus play an important role in the development, maintenance, and modification of a Tolmanian cognitive map that learns to predict reliable environmental features and can aid decision-making by allowing subjects to project themselves in both time and space. Functional roles previously attributed to the hippocampus mesh well with the cognitive map theory. We review three processes associated with the hippocampus

(memory, construction of novel representations, and planning), discuss their place within the cognitive map framework, and consider evidence that computations involving hippocampal sequences could underlie these forms of information processing.

Memory: Storing Environmental Features to Develop Expectancies

The hippocampus has long been connected with mnemonic processes due to a consilience of neuropsychological, behavioral, and electrophysiological data [1, 2, 54]. It is not surprising then that many models of hippocampal function link sequences with memory-related computations [1, 3, 4, 24, 54–59]. Memory processes have a place in Tolman's cognitive map framework; he theorized that behavior such as "searching for the stimulus," in which animals actively investigate their surroundings, apparently in search of stimuli that caused noteworthy outcomes, is important for learning about the consequences of behavior [37]. Memory representations could function in linking the current state of the environment with the past, aiding the development of predictive associations and allowing animals to learn the "causal texture" of their surroundings [37, 38].

Sequences During Sleep LIA

A popular idea, dating back at least to theoretical work by Marr [55], is that memories are initially encoded in the hippocampus, but are eventually transferred to neocortical sites for long-term storage in a process known as consolidation [3, 60]. Related theories [24] have suggested consolidation entails an intrahippocampal transfer of information (between, e.g., CA3 and CA1 regions). Identifying the brain locus of a particular type of memory's final resting place remains an area of active research [54, 61]; nevertheless, models of consolidation generally require some mechanism for inducing long-term changes in synapse function to store memories.

In many ways, LIA-associated hippocampal sequences are well suited to mediating memory consolidation in neural systems. Sequences were first documented during sleep [25, 26], long known to be important for learning and memory improvement, when the reduction of incoming sensory signals allows internal brain dynamics to dominate information processing. Because sequence representations are temporally compressed, spiking occurs on a timescale fast enough to induce long-lasting changes in synaptic strength, and patterns of spiking experienced during behavior are repeated multiple times during LIA sequences, further increasing the odds of activating plasticity mechanisms [3, 4, 62, 63].

The content of sleep LIA sequences reflects previous behavioral experience, consistent with a role for LIA sequences in memory consolidation. Cells active during behavior fire at a higher rate during sleep [64], and correlations between pairs of place cells coactive during exploration are enhanced during post-behavior sleep [25]. The enhancement of post-behavior correlation strength reflects the order in which cells were activated during behavior [26], suggesting ensemble-level coordination of place cell "reactivation" during sleep. In aged animals, the temporal patterning of LIA sequences is altered, and the extent of sequence alteration predicts spatial memory impairment [65].

In addition to this large body of correlational evidence, recent experiments have causally linked SWR events during sleep and memory consolidation. Real-time detection of SWRs allows researchers to deliver precisely timed electrical stimulation to the hippocampus, disrupting spiking sequences often present during SWRs, but otherwise sparing normal ensemble activity. Using this technique, two groups have found that stimulation contingent on SWRs during post-behavior sleep impairs learning, providing strong evidence in favor of a causal role for SWRs in consolidation [66, 67]. It is important to note that because the electrical stimulation used in these experiments is a fairly nonspecific manipulation that has the potential to simultaneously affect multiple processes in the hippocampus (e.g., spiking, LFP activity, synaptic plasticity), SWR disruption does not uniquely identify a single process that is critical for memory consolidation. Additionally, as discussed above, sequences are less tightly correlated with SWR occurrence than previously thought, raising the possibility that some non-sequence process disrupted by stimulation causes the memory impairment. Nevertheless, these experiments provide some of the strongest evidence to date that a SWR-associated hippocampal process plays an important role in memory consolidation during sleep.

Construction: Building a Cognitive Map with Hippocampal Sequences

A key point of the cognitive map theory is that learning is an active process, which can disassemble and rebuild stored information to generate de novo representations [37, 38]. A classic illustration of such behavior is latent learning, the discovery that animals can extract and integrate information about an environment in the absence of reinforcement or motivated information seeking. Latent learning implies that animals build structured representations of their surroundings without any obvious need to do so and that this might occur without any measurable change in behavior.

Hippocampal sequences (during both LIA and theta states) could participate in the construction of flexible, behaviorally relevant representations of the world. We propose that the hippocampus initially parses experience (potentially both spatial and nonspatial aspects, as discussed below) in theta sequences, enhancing connections between sequence items close to each other in representational space,

creating representational "chunks." During LIA-associated sequences (in both online and off-line states), the hippocampus strings together information acquired in theta sequences, forming integrative representations that capture relationships between distant portions of the environment. By recombining information in configurations that differ from actual experience (e.g., backward sequences), the hippocampus can generate representations of never-experienced paths, which can then be integrated with the rest of the cognitive map, providing animals access to representations necessary for planning flexible behavior.

From Phase Precession to Theta Sequences

As discussed earlier, it was initially proposed that the phase precession [15] of individual place cells might be a mechanism for preserving the correct ordering of place cell spiking within each theta cycle [12, 16, 17, 68, 69], resulting in the formation of theta sequences. However, recent findings suggest instead that theta sequences are the primary organizing principle of spiking within theta cycles and that phase precession is an epiphenomenon resulting from sequence readout as rats move forward [48, 69]. For instance, spike time correlations between pairs of place cells are more reliable than the correlation between spike phase and position that results from phase precession [17]. Similarly, theta sequences are more precisely patterned than would be expected if phase precession alone organized place cell spike timing [12].

When estimated across many cycles, the average theta sequence representation begins slightly behind the rat's current location and extends forward in the direction of motion [12, 16, 70]. Closer examination of theta sequences has revealed greater variability than was previously appreciated. Gupta and colleagues [18] examined theta sequence representations on a cycle-by-cycle basis as rats performed a spatial decision-making task. They found that while theta sequences generally represented a region of space around the rat, the beginning and ending points of these representations varied considerably. Some sequences began behind the rat and ended at its current location, other representations were centered around the rat, and still others began near the rat and swept forward to varying extents. The expression of these different types of theta sequences was modulated in a manner consistent with a role in actively parsing the environment; as rats approached turns, food delivery sites, and other areas of the maze that might plausibly have gained motivational or informational salience, theta sequences shifted from starting near the rat and projecting forward to starting behind the rat and projecting up to its actual position. Thus, as a rat approached a prominent landmark, the hippocampal representation coursing over the rat's location in each theta cycle shifted from predictive and forward-directed to more retrospective or backward-looking (Fig. 5.2). This shift in sequence content around landmarks imposed a distinctive organization on the hippocampal representation of space, in which semi-discrete, landmark-bounded "chunks" of the environment emerged [18]. A recent study of rats performing a linear track task reported a similar result, with CA1 place cell activity appearing more

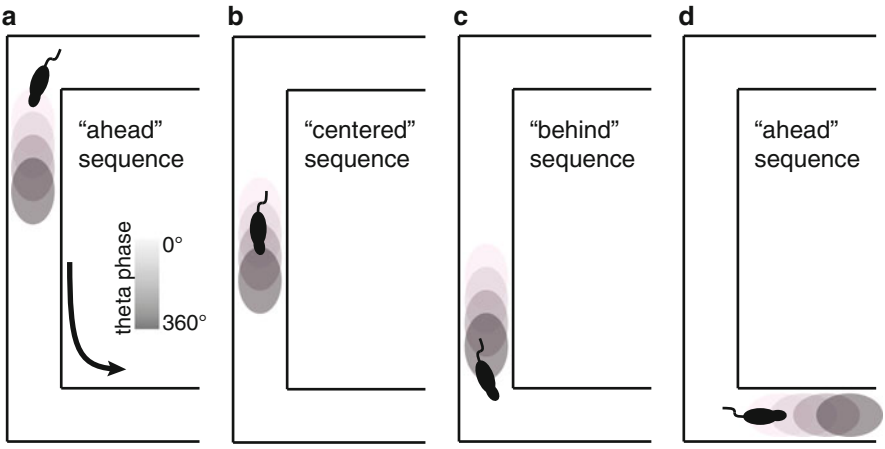

Fig. 5.2 The content of theta sequences is modulated by salient features of the environment in a manner that gives rise to a distinctive "chunked" representation of space [18]. In this example, the landmarks are two turns on a maze. Immediately after rounding the first corner (**a**), sequences begin at the rat's current location and extend asymmetrically, such that a greater portion of space in front of the rat is represented. Midway between turns (**b**), sequences tend to be more centered on the rat (although still forward shifted). As the rat nears the second turn (**c**), sequences shift backward, beginning some distance behind the rat and extending up to its current position. Finally, once past the final turn (**d**), representations are again largely ahead of the animal. Note that this leads to an increased density of representations covering the regions between landmarks and well-defined boundary regions near landmarks that representations tend not to cross

forward-directed as subjects left feeder sites at the ends of the track and more backward-looking on approach to feeders [71]. Interestingly, forward representations were associated with greater LFP power in the low gamma frequency (25–55 Hz) range, suggesting coupling between CA1 and CA3. In contrast, backward-lagging spikes occurred when fast frequency gamma (60–100 Hz) was prominent, suggesting strong entorhinal cortex drive [72].

These results suggest that, rather than passively coding features of the environment as they exist, representations within theta cycles can actively segment space, effectively performing a sort of information compression that could be useful behaviorally.

Awake LIA Sequences Construct Adaptive Representations

In addition to LIA sequences during sleep, sequences also occur during LIA, when animals are quiescent but awake [29, 31, 32, 73]. In contrast to sleep LIA sequences, which possess many properties suggestive of a memory consolidation function, the content and ordering of representations within awake LIA sequences are consistent

with a role in manipulating portions of previous experience to construct novel, i.e., never-experienced, representations.

The content of awake sequences and actual behavior can diverge substantially, both on a moment-by-moment basis and when considered over longer timescales. For instance, sequence representations do not necessarily begin near the animal, nor are they bound to cross through the position the rat currently occupies [74–76]. In fact, sequences representing previously experienced environments (which recruit place cells that are not active in the current location) have been described, intermingled with "local" sequences representing paths through the animal's current surroundings [31, 74]. Neither does cumulative behavioral experience have a strong influence on the frequency with which portions of the environment are included in sequences. For instance, in rats performing a multiple-T decision-making task, the probability of a location being included within awake LIA sequences was sometimes inversely related to how often that area was visited [76]. In a session where only left-side laps were rewarded (and rats consequently made few visits to the right loop of the maze), sequence representations to the unrewarded side were actually more frequent than those representing the path the rat traveled more often that day [76].

Cognitive factors seem to have a strong influence over the content of awake LIA sequences. When animals encounter new environments for the first time, awake LIA sequence content is biased toward representing recently explored portions of space [77]. This suggests that novel experience might be prioritized for incorporation into existing representations via expression in awake LIA sequences. Similarly, reinforcement seems to sculpt awake LIA sequence content. Sequences are more likely to occur during quiescence following reward delivery, and the resulting representations preferentially include regions of space associated with reward delivery [78]. The enhanced sequence representation of rewarded locations follows the time course of task learning, suggesting that LIA sequences construct an adaptive representation used to guide behavior [78]. These results are all consistent with the idea that new experience is integrated with previous learned cognitive components of the cognitive map by coordinated representation during awake LIA sequences.

Sequences during awake LIA can occur in the opposite order of experience (backward sequences; [29, 32, 75, 76]). From a consolidation perspective, this seems problematic, as it could lead to the storage of a memory with the wrong serial ordering. Because awake LIA sequences occur both forward and backward, consolidation during awake LIA would be vulnerable to memory interference, as forward and reverse trajectories represent equally plausible experiences, but the rat may have traveled in only one direction.[2] On the other hand, from a construction perspective, backward sequences could be a key building block for assembling never-experienced trajectories.

[2] Recent evidence [73] suggests that backward LIA-associated sequences are present during sleep as well (albeit to a lesser extent than forward-ordered representations), suggesting that in some cases a similar problem with directional ambiguity could occur during off-line consolidation. Alternatively, this might suggest that both consolidation and constructive processes coexist during slow-wave sleep [79, 80].

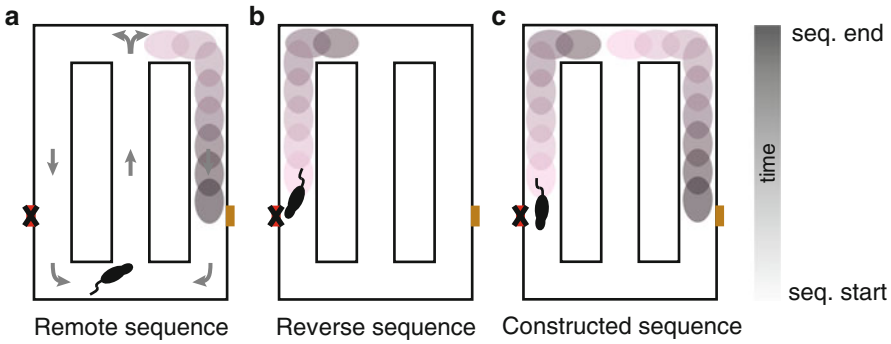

Fig. 5.3 Combinatorial expression of sequences can generate trajectory representations never directly experienced by the subject. In this example (modeled after the results in [76]), a rat is performing a T-maze decision-making task. Food delivery sites are marked with *rectangles*; in this example, only the right-side feeder is rewarded. *Arrows* in (**a**) indicate the possible directions the rat is allowed to travel at each location on the maze. A forward sequence spanning the region between the choice point and the right feeder (**a**), preceded by a backward sequence originating at the left feeder and ending at the choice point, could be used to represent the unexperienced trajectory from left-side feeder to right-side feeder (**c**), a shortcut between potential reinforcers. Gupta and colleagues [76] observed constructive sequences like this more frequently than would be expected due solely to chance, sequential expression of the sequences in (**a**) and (**b**)

Gupta and colleagues [76] observed novel trajectories represented within awake LIA sequences. During the performance of a spatial decision-making task, the authors discovered sequences connecting spatially contiguous portions of the maze that the rat had never traversed. Forward- and backward-ordered sequences occurred in equal proportion during the performance of this task; never-experienced trajectories were constructed via linking backward and forward representations of neighboring maze segments (Fig. 5.3). Representations that synthesize novel trajectories by linking chunks of previous experience are an important idea within Tolman's cognitive map theory [36] and could subserve shortcut behavior or other cognitive processes requiring extrapolation beyond actual, physical experience [50, 76, 81].

Together, the findings reviewed here suggest online LIA sequences, in conjunction with theta sequences, are involved in synthesizing representations of the world by assembling bits of previous experience and connecting them together in a novel fashion. It is interesting to note that the data discussed here concerning construction within awake LIA sequences [76] and chunking within theta sequences [18] derive from the same set of neural recordings. While theta sequences show clear evidence of spatial segmentation [18], awake LIA sequences were not constrained in this respect, representing trajectories that crossed landmarks in a way that theta sequences did not [76]. This is further suggestive of a more integrative function for awake LIA sequences in linking information, in contrast to the parsing and compression function evidenced by theta sequences.

Planning Function in Hippocampal Sequences

Tolman suggested that an important function of the cognitive map was to allow animals to mentally explore the outcomes of possible courses of action before committing to one [37]. Behaviors like "vicarious trial and error" (VTE), in which animals pause before making difficult decisions and alternately orient toward possible options, support this proposal [34, 35, 37]. In more modern parlance, we might call Tolman's VTE concept mental time travel [47], episodic future thinking [82], or imagination [53], all of which seem to involve hippocampal function in humans. Representations that could be used to perform mental simulations over possible actions coupled with valuation signals that balanced the costs and benefits associated with each would be powerful tools in a decision-making arsenal [83, 84].

Sequence representations in the hippocampus could play an important role in computing predictions about future states of the world. As discussed previously, theta sequences often contain a predictive component near the end of each theta cycle [48]. Maurer and colleagues [70] demonstrated that the look-ahead representation late in the theta cycle is modulated by behavior in a manner consistent with predictive function. By carefully examining average ensemble representations across the theta cycle, they found that the extent of space represented within a cycle scaled with running speed. This scaling resulted in representations that extended farther forward as animals moved more quickly and were arguably in greater need of predictive representations extending farther along their immediate future path [70].

Similar theta sequence representations could play a role in planning as animals pause before making a difficult choice. Johnson and Redish [85] analyzed ensembles of CA3 hippocampal neurons recorded as rats performed a multiple-T decision-making task. While pondering high-cost decisions, rats paused at the choice point and engaged in VTE, one of Tolman's cognitive map hallmarks [34, 35, 37]. Coincident with VTE, decoded hippocampal representations became nonlocal, projecting forward along the maze ahead of the rat's current location, tracing out trajectories along possible future paths (Fig. 5.4). Analysis of the LFP recorded during these nonlocal events revealed clear theta oscillation and the absence of LIA-associated LFP signatures, suggesting that theta sequences underpinned the decoded representations [85] (also see Chap. 14). Evidence in support of this idea can also be seen in Gupta and colleagues' [18] explicit analysis of theta sequences, which revealed two populations of events—one during active locomotion and another during periods of immobility. These results suggest a model in which sequences during type I theta represent an information gathering and processing stage, while sequences during type II theta are a planning process [56, 57]. The timing of types I and II theta sequences is consistent with this idea (type I sequences during active exploration and type II sequences during pauses, when animals might be planning future actions).

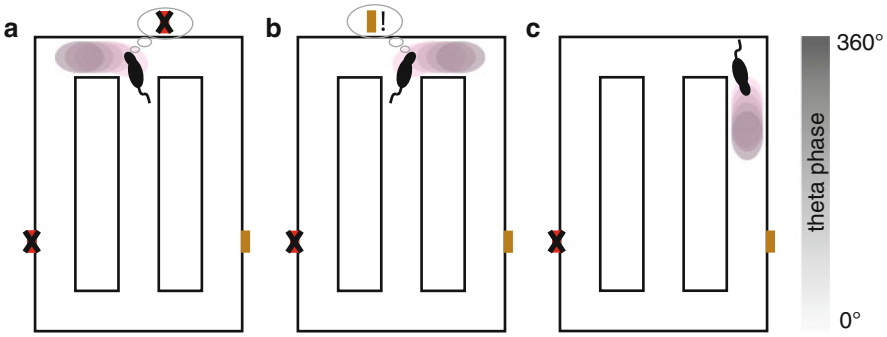

Fig. 5.4 Forward-shifted theta sequences could be a means of mentally investigating potential future options. In rats performing a T-maze decision-making task, Johnson and Redish [85] found that CA3 hippocampal representations projected ahead of animals as they paused at the choice point. These forward-directed, decoded representations typically traversed both the left (**a**) and right (**b**) paths of the maze. Representations like these could be useful for calling up value information associated with each option to adaptively guide behavior (**c**), perhaps via interactions with other brain regions such as the prefrontal cortex [132, 133] or the ventral striatum [134]

Nonspatial Information in Theta Sequences

An important feature of the cognitive map is that nonspatial information can be embedded within the primary spatial tuning of hippocampal neurons, where it could be used in coordinating future behaviors along with spatial representations. Just as spatial phase precession could result from spatial sequence readout during forward movement, phase precession during nonspatial behaviors might be thought of as nonspatial theta sequences expressed during an imagined, mental progression through the representational dimension of the sequence [48]. Representations like these are consistent with processes like mental time travel [46, 47] and imagination [53] and could be useful for mentally exploring the consequences of future actions.

Previous experiments suggest (but do not show explicitly) that nonspatial information represented by the hippocampus is also organized into sequences within theta cycles. Early work established that phase precession can occur even when rats are not actively moving through space [19]. Pastalkova and colleagues [20] furthered this work, providing tantalizing evidence for the existence of theta sequence-like representations of nonspatial information. In their experiments, rats performed a hippocampus-dependent delayed spatial alternation task. During the delay periods punctuating alternation trials, rats were trained to run on a stationary running wheel, which induced strong theta oscillation in the hippocampus. During alternation trials, hippocampal neurons showed typical spatial tuning. However, during wheel-running epochs, hippocampal cells showed strong, reliable tuning to time spent in the running wheel, consistent with previous theoretical work [86]. Different subsets of time-encoding neurons were activated during delays that preceded leftward or rightward alternation trials, and much like place cells, these temporally tuned cells showed clear phase precession [20]. Hippocampal neurons with temporal tuning

have since been found in rats performing other behavioral tasks that require planning [87–89]. Together, these findings are strongly suggestive of coordinated, sequential representations within theta cycles, in this case encoding a temporal, rather than spatial, sequence.

Takahashi et al. [22] recorded hippocampal pyramidal neurons in rats performing a nosepoke-based alternation task. Subjects initiated a trial by maintaining a nosepoke in a central well until the fixation period expired and then alternated nosepokes in wells to the left or right of the fixation port. During fixation, pyramidal neurons showed theta-modulated spiking spanning portions of the delay period. Reminiscent of Pastalkova and colleagues' [20] findings, unique ensembles of neurons were recruited prior to leftward or rightward alternation trials [22]. Fixation period spiking phase precessed relative to LFP theta, consistent with coordinated theta sequences (in preparation).

Lenck-Santini and colleagues [21] recorded hippocampal neurons as rats performed a shock avoidance task. At the beginning of trials, subjects were dropped on to the metal floor of the test arena. The rats then had to jump out of the arena within a particular time window (>2 s but <15 s from trial start) to avoid electric shock. Hippocampal pyramidal neurons discharged around both the beginnings of trials and the self-initiated escape jumps, and these spikes precessed over subsequent theta cycles, suggesting that ensembles of hippocampal neurons may have encoded the temporal intervals around important task-related events. Although executing the jump to safety was, of course, a voluntary movement, jump-responsive neurons began phase precession seconds before the actual jump. Administration of moderate doses of the cholinergic antagonist scopolamine interfered with the reliable generation of type II theta oscillation, and the extent to which normal theta patterns were disrupted was predictive of behavioral errors on a trial-by-trial basis. These findings suggest a behaviorally relevant role for phase precession of nonspatial information during type II theta [21].

A Causal Role for Theta Sequences in Planning

Studies reviewed in this section provide evidence that both spatial and nonspatial features of the environment are encoded within theta sequences, that cells encoding nonspatial information phase precess, and that the behavioral task subjects are performing can influence the content of theta sequences. These data are consistent with a role for theta sequences in planning, but establishing a causal link has proven difficult.

Cannabinoid agonists offer a surprisingly specific manipulation of the precise timing of place cell spikes [90, 91]. Robbe and colleagues [91] administered a cannabinoid agonist to rats trained to perform a delayed spatial alternation task. The drug had a strong behavioral effect, reversibly reducing task performance to chance. Surprisingly, when the authors analyzed recordings of CA1 pyramidal neurons,

normal spatial firing patterns were mostly unaffected by the drug. Temporal coordination between cells, however, was disrupted. Theta phase precession was greatly attenuated following drug administration, and the correlation between place field separation and theta-scale cross-correlogram lag weakened substantially. Thus, a manipulation that disrupted temporal organization (while mostly sparing other place cell properties) had drastic effects on behavior in a hippocampus-dependent task.

Because cannabinoid receptor activation impaired performance of an already-learned task [91], these data support the idea that theta sequences play an important role in online planning processes. Close inspection of position tracking data before and after drug administration ([91]; their Fig. 1) suggests that cannabinoid activation altered behavioral dynamics in an interesting way. When the drug was active, the subject displayed much more pausing on the central stem of the maze and at the choice point. Additionally, the rat appears to have spent more time peering over the edge of the maze and generally scanning his surroundings [91]. This is suggestive of an increase in VTE, a behavior Tolman [34, 35] and others [83, 85, 92] have associated with deliberative decision-making. Usually, however, VTE is a much more transient event [85, 92]. A fascinating possibility is that with dysfunctional sequence expression in the hippocampus, rats remain deliberative and indecisive for much longer periods, lacking sequences for planning a suitable course of action. Because cannabinoid agonism also caused notable motor side effects [91], this hypothesis, although intriguing, remains speculative.

LIA Sequences and Planning

Is online planning function in the hippocampus the exclusive domain of theta sequences? Emerging results suggest that LIA sequences might be involved as well. The recent report of "pre-play," LIA sequences that represent trajectories through regions of an environment that subjects can view but not physically enter [93], suggests that the hippocampus is equipped to plan trajectories over regions of space it has not yet encountered. Alternatively, pre-play could be interpreted as a constructive process, involved in allocating representations to nearby, but novel, regions of space. Interestingly, while observation alone is not sufficient for the development of stable place cells covering unvisited portions of the environment [94], the dorsal hippocampus has been implicated in processing visible but inaccessible objects [95]. It is possible, as suggested by Rowland and colleagues [94], that pre-play serves to establish a rough, approximate spatial representation that is subsequently refined and bound to prominent environmental features upon direct physical experience. Although the behavioral implications of pre-play are not yet clear, this sort of representation could be useful in both the planning and constructive cognitive map functions outlined in this chapter.

In rats trained to shuttle back and forth between food delivery sites placed at both ends of a linear track, awake LIA sequences expressed before and after completion of trials contained representations consistent with both planning and memory-like functions [32]. While paused at a feeder site, before initiating a new trial, forward-ordered sequences beginning at the rat's current location and extending to the opposite feeder were detected. Interestingly, after arriving at a feeder, sequences retracing the recently completed journey in reverse were recorded [32]. The sequences preceding trial start might play a role in planning upcoming trajectories. Reverse-ordered sequences occurring after the completion of a trial may have some memory role, perhaps in associating past behavior with reward, in a process reminiscent of Tolman's [37] "searching for the stimulus" or the credit assignment problem of reinforcement learning [29, 96, 97]. Interestingly, forward-ordered sequences occurred more frequently than backward sequences in this study [32], suggesting that whatever function differently ordered sequences may have fulfilled, forward sequences were in greater demand than backward sequences.

The results of a study by Jadhav and colleagues [98] support a causal role for awake LIA sequences in online planning. The authors probed the function of awake SWRs in rats learning to perform a hippocampus-dependent decision-making task [99]. In these experiments [98], electrical stimulation disrupted spiking during SWRs, following the same paradigm used to probe the function of SWR sequences during sleep [66, 67]. In the behavioral task, rats were required to visit the arms of a W-shaped maze in a particular order. Inbound trials required rats to run from an outer arm to the central stem. In contrast, on outbound laps, rats departed the central stem and headed to the outer arm opposite that they had visited most recently. Interestingly, although hippocampal lesions slow the learning of both inbound and outbound trials, real-time disruption of awake SWRs specifically impeded acquisition of outbound trials. Further, in animals pretrained to proficiency on the task, SWR disruption resulted in mildly degraded performance on outbound choices [98]. Although subject to the same caveats discussed above in reference to sleep SWR disruption [66, 67], these data provide strong evidence that awake SWRs play some role in coordinating behavior in real time, in addition to whatever learning function they might fulfill. Consistent with this idea, recent work by Pfeiffer and Foster [100] showed that sequences recorded while rats performed a goal-directed navigation task were biased to end in the spatial location that the rat would next travel to.

Unanswered Questions and Ways Forward

In this chapter, we have described hippocampal firing sequences and reviewed theories relating to the function they might subserve. Although a great deal of progress has been made in this direction, many knowledge gaps remain. Here, we identify pressing unanswered questions concerning sequence function and discuss possible experimental strategies that could be used to approach them.

How Does the Ventral Hippocampus Contribute to the Cognitive Map?

The vast majority of data relating to hippocampal sequences comes from recordings made in the dorsal region of the hippocampus. More ventral regions of the hippocampus receive unique anatomical inputs [101] and exhibit different patterns of gene expression [102]. Additionally, lesions of the dorsal and ventral hippocampus cause distinct changes in behavior [103–108]. This has led to the suggestion that the dorsal and ventral hippocampal regions are distinct functional modules, with the dorsal hippocampus involved in more cognitive operations and the ventral hippocampus playing a greater role in affective processes [109–111]. Although we have focused on the cognitive functions of hippocampal sequences in this chapter, affective information bound to the cognitive map could also aid animals in adaptively selecting behavior.

Only a handful of electrophysiological studies have recorded neural activity in ventral regions of the hippocampus [112–115]. In general, differences between dorsal and ventral hippocampal neural representations seem to be more quantitative than qualitative. The spatial tuning of neurons in the ventral hippocampus tends to be broader and perhaps less organized, with place fields often covering large swaths of a given environment. In addition, ventral hippocampal neurons seem more likely to encode nonspatial aspects of the world (e.g., closed vs. open arms on a radial maze; [115]). Theta modulation (of both the LFP and single-unit spiking) is greatly attenuated in the ventral hippocampus. However, the existence of some phase precessing ventral hippocampal neurons argues that dorsal and ventral hippocampal regions may share at least some information-processing mechanisms [114–116].

Ventral hippocampal representations could provide useful input to many of the cognitive map functions described in this chapter. For instance, the larger field size in ventral neurons would produce an even greater predictive look-ahead component if spiking is indeed organized into theta sequences [116]. However, little is currently known about sequence representations in the ventral hippocampus; establishing whether or not theta and LIA sequences exist in the ventral hippocampus and examining how they differ from sequences in more dorsal regions could reveal how ventral and dorsal hippocampal activity is coordinated. Understanding whether and how ventral hippocampal neurons contribute to cognitive map-like representations might require the development of new behavioral tasks. For instance, if the ventral hippocampus is more involved in affective processes, a task requiring animals to escape from an anxiety-provoking stimulus (e.g., [117, 118]) might reveal how cognitive and affective information are combined to guide behavior.

Why Are Sequences Rare?

Hippocampal sequences are striking because they possess structure and informational content that clearly distinguishes them from “spontaneous” (i.e., apparently random) activity in other structures. Nevertheless, many SWRs are accompanied by

spiking that lacks any detectable sequence content. Similarly, in Gupta and colleagues' [18] study of theta sequences, only a fraction of theta cycles were found to contain significant structure. There are several possible explanations for these findings.

One possibility is that methodological or technical issues sometimes prevented the detection of sequences represented by the hippocampus. For instance, ensemble size could profoundly limit sequence detectability. Similarly, the distribution of place fields an ensemble of neurons expresses could limit the number of theta sequences observed. Advances in recording technology and techniques increasingly render these concerns moot, however. As the number of simultaneously recordable neurons increases, it will be possible to examine quantitatively how this variable impacts sequence detection.

Spiking that appears to be nonsequential might simply reflect our ignorance of what the cells are encoding. Detecting sequence activity depends on our ability to compute place fields for hippocampal neurons during active behavior. Using the wrong set of tuning curves to decipher spike sequences might explain why bursts of ensemble spiking sometimes do not seem to form an interpretable representation. For instance, it is known that LIA sequences can represent an entirely different environment than the one a rat currently occupies [31, 74]. Although the typical laboratory rat presumably does not physically explore more than a handful of environments thoroughly enough to establish strong place cell maps, it remains possible that some apparent non-sequences are simply representations of distal locations for which experimenters have no knowledge of the cells' tuning.

Nonspatial tuning could also thwart detection of sequences. Of course, if clear nonspatial firing correlates can be identified, nonspatial sequences could be measured as easily as spatial sequences. An important unanswered question is whether hippocampal neurons with nonspatial tuning are incorporated into sequence representations (during either LIA or theta network states) in the same manner as spatially tuned hippocampal cells.

It is also possible that some ensemble bursts of spiking are simply not self-consistent sequence representations. Random bursts of spiking might be adaptive in some cases, perhaps enabling some sort of homeostatic downscaling of synaptic weights [119]. Another possibility (not mutually exclusive) is that SWRs and theta cycles are times at which the hippocampal network is primed for plasticity [120] and that these network events are essentially "containers" that can be filled with sequence content (or not) depending on the behavioral and cognitive demands faced by the subject at the moment. Consistent with this idea, rabbits being trained on an associative learning task acquire the task more quickly when training trials are initiated contingent on awake hippocampal SWRs [121]. Similarly, electrophysiological evidence shows that presenting behaviorally relevant tone cues to rats during post-behavior sleep biases LIA sequence content toward representing the regions of space that were associated with the tone during behavior [122]. These findings suggest that LIA sequence content can be influenced in real time, even by incidental external stimuli, which effectively hijack whatever representation may have otherwise occurred. This suggests that sequence content ought to reflect the cognitive

demands an animal is faced with during behavior. Relatively simple behaviors would be expected to induce a greater proportion of incoherent bursts of spiking in and around SWRs, as the hippocampus has little need to construct, consolidate, or otherwise operate on experience when behavior does not demand it. More complex tasks might be expected to induce more complicated sequence representations. Although these ideas are speculative, they are testable with today's recording technologies and cleverly designed, well-controlled behavioral tasks.

How and When Do Hippocampal Sequences Interact with Other Brain Regions?

In this chapter, we have argued that hippocampal sequences sharing many similarities actually have unique functional roles, depending on when they occur, what information they represent, the behavioral state of the animal, and the network state of the hippocampus. If this is the case, it seems likely that sequences with different functions would interact with distinct subsets of other brain regions. This raises the question of how information flow out of the hippocampus is routed to the appropriate structure.

One possible mechanism for coordinating information transfer between brain regions is oscillatory interactions. Changes in cross-structural synchrony or other properties of the LFP could transiently link hippocampal activity to certain brain regions while simultaneously disconnecting hippocampal output from other parts of the brain [10, 123–128]. Such a scheme allows rapid reorganization of functional interactions across the brain. If cross-structural coordination were actually achieved in this way, hippocampal sequences involved with particular functions might have unique and consistent LFP correlates that would distinguish them from sequences performing other roles. If such signals could be identified and detected online, SWR disruption techniques and other experimental manipulations could be applied to particular functional classes of hippocampal sequences. Experiments like these could shed light on both the behavioral impact of hippocampal sequences and the neural mechanisms by which sequences achieve their effects. It is already known that hippocampal SWRs during off-line states influence the firing rate of neurons in the ventral striatum [129] and the prefrontal cortex [125] and that neurons in these structures encoding task-relevant rule [125] or reward [130, 131] information are preferentially modulated. Likewise, during active behavior, hippocampal theta oscillations influence the timing of spikes in the prefrontal cortex [132, 133] and ventral striatum [134]; future work aimed at further characterizing the LFP signatures of functional interactions between brain regions seems a promising approach to better understanding sequence function.

A related question is whether and how the brain measures sequence quality. Sequences expressed in the hippocampus range from high-fidelity representations of behavioral patterns to seemingly random bursts of spiking activity. Intuitively, it

seems as though only high-quality representations would be useful for broadcasting to other structures. Carr and colleagues [135] have suggested that slow gamma oscillations in the hippocampal LFP clock activity within LIA sequences. They found that gamma synchrony between CA1 and CA3 hippocampal subregions is predictive of high-quality LIA sequence representations. A signal indicating the self-consistency of a sequence representation could be useful for many of the potential sequence functions described in this chapter. Such a signal (especially one involving changes in network properties) could also play a role in determining where and how the sequence representation is routed to and the extent to which structures downstream of the hippocampus are affected.

Interactions between the hippocampus and other brain regions should also be considered in the opposite direction, that is, rather than being influenced by hippocampal output, other brain areas might influence the content that is included in sequences. As discussed above, sensory input (even during sleep) can affect sequence content [122]; it seems likely that neural input to the hippocampus has a similar effect. Accordingly, examining how inactivation of extra-hippocampal brain regions affects sequence content could elucidate how information processing outside the hippocampus sculpts hippocampal representations.

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Chapter 6
Reorganization of Hippocampal Place-Selective Patterns During Goal-Directed Learning and Their Reactivation During Sleep

David Dupret and Jozsef Csicsvari

Abstract Firing patterns of hippocampal principal cells are thought to participate in the formation of mnemonic representations of place, which ultimately can be used to guide the behavior of animals in space. Past studies have suggested that place-selective activity in the hippocampus can emphasize the representation of discrete locations associated with a strong behavioral salience. In the first part of this book chapter, we review work that has described how that hippocampal neuronal activity patterns reorganize during spatial learning. These studies revealed that new hippocampal maps emerge during spatial learning to represent the location of goal locations and demonstrated that, during recall, the reinstatement of these maps predicts successful memory performance. In the second part of this chapter, we discuss the role of sleep in memory consolidation in the context of goal-oriented spatial learning. We summarize work that has demonstrated the replay of goal-oriented neuronal assembly patterns that predict subsequent memory recall. Moreover, we argue that the initial strengthening of new maps may in fact take place during learning, triggered by waking sharp-wave/ripple patterns occurring at goal locations. These reviewed studies highlight that the reorganization and replay of place cell firing patterns might constitute a circuit signature for the expression of newly acquired hippocampal engrams.

Keywords Hippocampus • Place cells • Remapping • Sharp wave/ripple • Reactivation • Goal-directed learning

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Decades of research have lead to the widely accepted view that the hippocampus provides the brain with an allocentric representation of space, which is used to guide animals in their daily behavior. Numerous lesion studies have established that an intact hippocampus is required for learning the location of discrete places in reference to surrounding, external spatial cues. This was best documented by large body of experimental work on navigation in the Morris water maze [1–3]. Importantly, it has also been established that hippocampal principal neurons code for the location of the animal. These "place" cells selectively increase their activity when the animal moves through the cell's place field [4, 5]. Recording studies during exploration of open-field environments have shown that, once established, new place maps tend to be stable over time as the environment becomes familiar [6, 7]. This suggests that hippocampal place fields constitute the buildings blocks of spatial engrams and that their stability might signal the presence of memory patterns. In this regard, one needs to determine the extent to which the variability in place cell discharge relates to the ongoing changes/fluctuations of the real world in order to understand how hippocampal maps adapt to behavioral experience. Such adaptation of spatial maps has indeed been revealed; for example, it was shown that place cells can alter their firing patterns in response to changes in the layout of the environment [8, 9]. Moreover, their firing is influenced in an otherwise unchanged environment by additional factors such as speed, direction of movement, path stereotypy, and even behavioral task demands (e.g., [10–15]). In these conditions, a global (complete) remapping of place fields can be observed. That is, entirely new place fields appear and already existing place fields disappear or move to different locations. Alternatively, maps may reorganize through rate remapping during which the location of the place field is unchanged; however in-field firing rate of the cell is altered [9, 15–18].

Hippocampal remapping was traditionally studied in relation to the spatial exploration of different environments or when changes took place in the same environment. In these experiments, animals explored familiar or novel environments or a previously experienced environment in which some features such as shape or color were changed, while other features were kept constant. In these conditions, most place cells undergo the same type of remapping, suggesting that each environment is represented by a unique combination of place cell activity. However, in some instances, only a subset of place cells remaps their place fields in response to changes in certain environmental features or changes in behavioral task contingencies [19, 20]. This partial remapping could be due to the fact that different subsets of place cells anchor their place fields to different environmental features and hence use different reference frames. One possible reason for the coexistence of multiple maps associated with the same environment has been suggested to be the demand for the animal to keep track of different reference frames to solve spatial problems, particularly during reward-associated behavioral tasks [21]. Indeed, early studies have shown that the change of reward locations can trigger remapping. Here, place field remapping can be observed when animal's task is shifted from a foraging task in which the food is scattered randomly to a task in which they have to retrieve rewards from fixed locations [14]. Further support came from experiments in which

reward locations marked by cylindrical landmarks are moved across navigation trials [22]. In this task, the position of two landmarks moved from trial to trial with respect to fixed distal cues, while their relative positions were fixed. Moreover, the animal had to reach the rewards from a start box, the location of which was also moved across trials. In this condition, a subpopulation of place cells bound their place fields to goal location-related reference frames, while other place cells either fired in reference to the animal's physical position in the arena or relative to the start box.

Goal-oriented remapping is not exclusively anchored at appetitive reward locations [23–28], which suggests that hippocampal maps can represent the behavioral relevance of locations. When rats were trained to escape from water by finding a hidden fixed platform in an annular water maze, place fields tended to accumulate near the goal location of the escape platform [26]. This goal-oriented clustering of place fields has been observed after learning, in probe session in which the platform was however no longer present [26]. Importantly, no such preferred representation of the goal location was observed when the rats were instead trained to find variable goal locations in the same maze. Moreover, in the same spatial memory task, many place cells begun to increase their activity at a new goal location when the escape platform had been moved from a previously learned location to a new one [25]. A goal-related firing activity has also been observed in rats trained to a place preference task where the visit of an unmarked goal location triggered the release of a food pellet at a random location; in these experiments, many place cells selectively increased their activity at the goal location and, at the same time, maintained a place field outside the goal location [27].

Maps anchored to different reference frames can switch quickly, and different maps can even alternate rapidly when the behavior of the animal demands it. For example, such dynamic flickering of maps is seen in a two-frame place avoidance task in which animals have to keep track of two zones to avoid an electrical shock [29]. These experiments take place in a rotating arena, while animals foraging for food must keep away from the two zones, a stationary shock-zone and a zone rotating with the table. In this task, one map representation is linked to the external cues, while another one rotates with the arena, and because the animal has to keep track simultaneously of both reference frames, the maps flicker from one to the other rapidly.

As we summarized above, studies on place field remapping have emphasized the contribution of the hippocampus in the formation of brain representations of space. They also highlighted that multiple reference frames can exist, which enable behaviorally relevant locations to be represented by a subpopulation of place cells. Such goal-related maps could provide a more accurate code for salient locations to improve behavioral performance. It has been suggested that the formation of goal-related maps may highlight learning processes enabling the reliable association of a reward with a discrete location in space. Ultimately they can also serve as a code for spatial memory traces. However, an alternative explanation of these studies is also possible. One cannot exclude that the goal-oriented remapping is not caused by learning per se, but the findings may be better explained by associated changes in

behavioral patterns. That is, goal-related remapping might have been triggered by changes in the path stereotypy or related changes in the motor behavior. Excluding these possibilities requires systematic investigations using specially designed spatial learning paradigms.

Reorganization of Hippocampal Place Cells During Goal-Directed Spatial Learning

In order to test whether network activity in the hippocampus can code for a memory trace, one needs to track neuronal responses during the entire memory formation process including encoding, consolidation, and recall. In the context of spatial memory traces, one would expect that some place cells remap their place field during the acquisition of new spatial memories to represent the information that has to be learned and later remembered in relation to the task demand. During goal-directed learning, such reorganization of place cell activity should be, to some extent, oriented toward the learned goal locations to enable their mnemonic coding. If this is the case, one would need to show that such goal-oriented remapping is a consequence of learning and has not been merely triggered by alterations of motor behavior or locomotion path as seen when animals develop efficient navigation during the learning phase. Importantly, when such new memories are assessed later, the successful recall, as measured by good memory performance during recall, should correlate with the reinstatement of the newly acquired firing patterns such as the new goal-oriented maps acquired during learning. One would also expect that such learning-related neuronal patterns may also recur during the consolidation stage to facilitate the stabilization of memories, as we discuss later.

There have been several behavioral tasks developed as dry maze equivalents of the Morris water maze to assess place learning, including the Barnes maze or auditory avoidance task [30, 31]. We have chosen a task using the cheeseboard apparatus [32], which is a circular arena that contains many food wells in which food can be hidden in order to demonstrate the mnemonic contribution of hippocampal place cells [33]. Each day, rats have to learn a new set of three goal locations where food rewards were hidden and retrieve these rewards before returning to the start box to collect an additional reward (Fig. 6.1a). During this learning period, typically consisting of at least 40 trials, the task performance of the animals improves rapidly, reaching a nearly optimal performance within the first 5 trials (Fig. 6.1b). This shows that rats can rapidly encode reward locations and remember them across the remaining trials.

Work examining the stability of newly formed maps in novel environments suggested that NMDA-dependent plasticity is required for the stabilization of new maps when these maps are tested over longer periods [7]. This work also showed that such plasticity-associated map stabilization was needed even when the delay was as short as 2 h. Therefore, as we wanted to minimize the overall duration of our experiments to ensure stable neuronal recordings, we assessed the memory for the

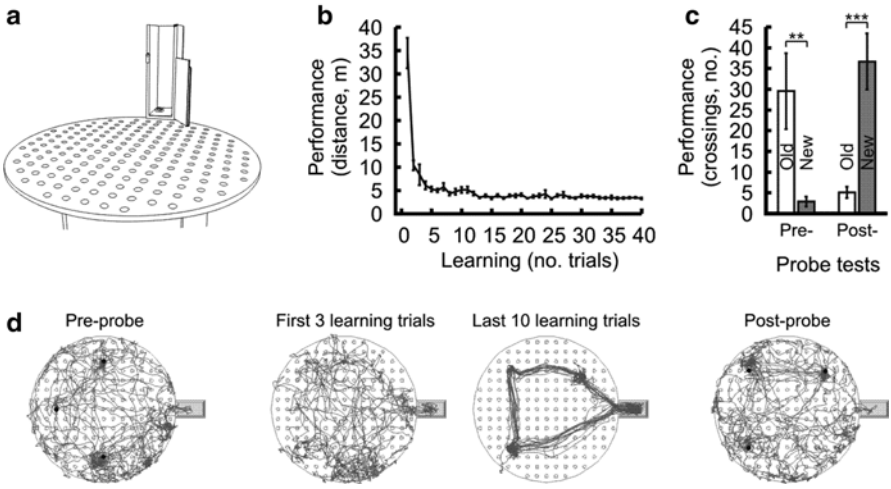

Fig. 6.1 Goal-directed learning paradigm on the cheeseboard maze. Rats were trained in a matching-to-multiple-places task to locate a new set of three hidden food rewards every day on a cheeseboard maze (**a**). Learning performance was estimated by the distance traveled to find all rewards per trial (**b**; means ± s.e.m). Memory performance (**c**, means ± s.e.m) was measured by the number of crossings at the goal locations learned the day before ("old") and the current day ("new"). Representative examples of animal's path (**d**); for clarity, only the first 10 min of each probe session are depicted (*black dots*: learned goal locations). Adapted from [33]

newly learned locations approximately 2 h after learning in subsequent probe trials. During the probe trials, food was no longer available, and recall performance was assessed by the number of crossings through the goal areas. As in the Morris water maze task where rats frequently cross the location of the removed escape platform, the previously learned reward locations were also crossed frequently by the rats trained on the cheeseboard maze (Fig. 6.1c, d). We also performed experiments under NMDA blockade (systemic administration of CPP). In these experiments, animals were able to learn goal locations under NMDA blockade, but they were no longer able to recall these goal locations after the 2 h delay. This confirmed that the newly learned spatial memories are needed to undergo some degree of NMDA-dependent stabilization for successful recall.

To reveal how spatial memories of new goal locations were represented in the hippocampus during our task, we recorded the activity of multiple place cells and oscillatory field potential patterns using multichannel extracellular techniques. As we mentioned above, previous work suggested that place cells can fire in reference to reward and associated goal locations [14, 22–24, 27, 28, 34, 35]. As with previous work, many place cells fire at the newly learned reward locations on the cheeseboard maze in our task as well (Fig. 6.2). However, in our case, we found that remapping was region specific. Here, goal-related remapping took place in the CA1 region of the hippocampus only, while CA3 place cells did not alter their spatial selectivity. Importantly, the reorganized CA1 place maps were reinstated in the

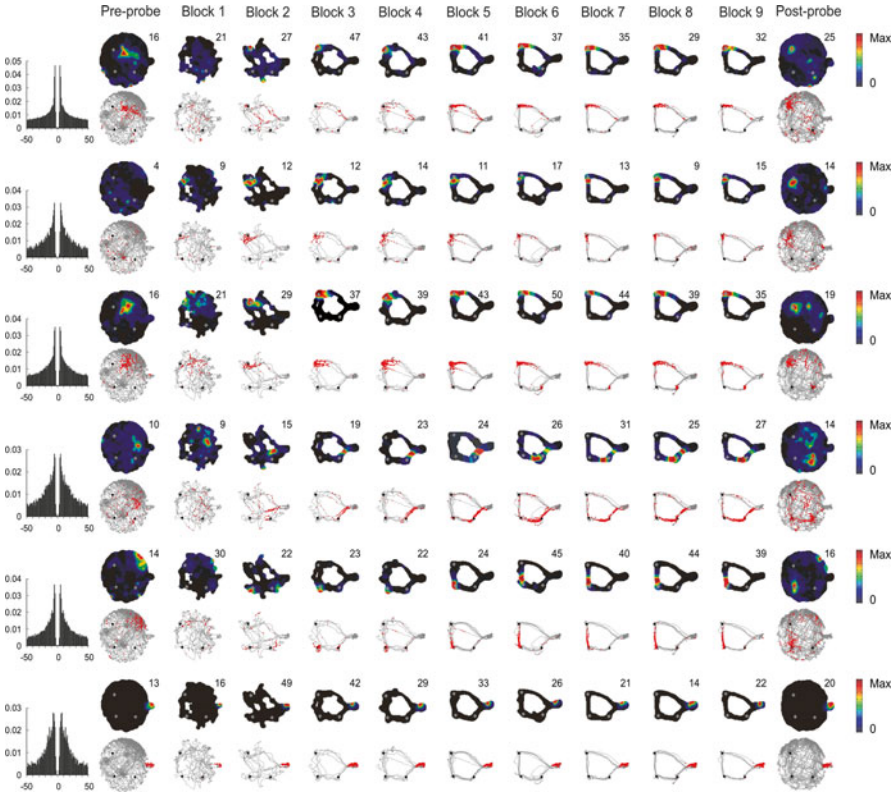

Fig. 6.2 Examples showing the activity of CA1 hippocampal place cells on the cheeseboard maze. Simultaneously recorded CA1 place cells are shown on alternating rows with their auto-correlogram, color-coded place rate maps, and individual spike locations superimposed on the animal's path. Both rate maps and raw spike data are depicted for each probe session ("pre-probe," "post-probe") and across successive learning trial blocks. The color code in the rate maps is from *blue* (low firing rate) to *red* (peak firing rate), with the maximum firing rate (Hz) of the color scale indicated on the *top right* of each map. High firing rate regions marked by warm colors indicate the "place field" of the cell and *gray dots* mark the goal locations. In the figures showing the movement path of the animal (*gray traces*), *red dots* mark action potential locations and black dots indicate the goal locations. Adapted from [33]

subsequent memory probe session where these new goal locations were recalled successfully. Moreover in the NMDA blockade experiments, while goal-oriented maps were formed during learning, these were not reinstated in the subsequent probe trials, mirroring the behavioral impairment of the animal.

Next we examined whether the alteration of motor patterns could cause the remapping of the CA1 cells in our task. To control for the effect of path stereotypy, we used a version of the task in which food locations were marked by visual intra-maze guide posts. In this paradigm, the animal did not need to use allocentric learning strategies to associate the food reward with discrete locations in space.

Consequently, we did not detect learning-related reorganization of hippocampal maps in this cued version of the task; the bait locations were no longer represented preferentially by CA1 place cells. Despite this, during this cued version of the task animals followed virtually identical stereotyped paths at similar speed as in the allocentric version of the task. Therefore, this control experiment excludes the possibility that alterations of motor behavior patterns underlie the remapping of place cells during the allocentric learning of goal locations. Further support for the notion that goal-oriented remapping relates to behavior during memory recall comes from the observation that the strength of hippocampal remapping established at the end of learning predicted recall performance. Specifically, the proportion of place cells that encoded a goal location correlated with the frequency at which animals returned to this location during the probe session. This suggests that the hippocampal maps may play a role in the recall of goal locations.

Our work on the cheeseboard maze provided additional support for the role of place maps in the representation of spatial memory traces. Yet, many questions are still unresolved and will require future work. The findings established on the cheeseboard maze need to be confirmed in other behavioral paradigms to test whether place cell remapping to newly learned goal locations always takes place during goal-directed behavior and especially to determine whether such remapping always takes place in the CA1 region only. Similarly it remains to be determined to which extent goal-related remapping occurs along the septo-temporal axis of the hippocampus. Further work is also needed to investigate how long this representation of a newly learned location is maintained, specifically whether such representations remain when familiarity increases. Ultimately, the role of hippocampal remapping during the learning process itself remains to be determined. To seek an answer to this question, we recently examined whether map formation dynamics during learning matches that of learning speed.

Dynamics of Hippocampal Place-Related Assembly Patterns During Spatial Learning

As a first level of investigation, we find that map formation dynamics lag behind learning speed in our cheeseboard task. Although the improvement in the behavioral performance we observed during learning reached asymptotic levels within few trials, the reorganization of hippocampal maps continued to evolve thereafter. To quantify the reorganization of hippocampal maps during the course of learning, in our earlier work we compared hippocampal maps that were calculated across successive trials during learning to those observed in the probe sessions before and after [33]. This type of analysis suggested a gradual reorganization of maps from the old to the new ones. These calculations, however, only examined the average temporal expression of the hippocampal maps over longer time windows consisting of entire trials. As we mentioned above, cell assembly firing patterns can flicker rapidly between the expression of distinct maps [21, 29, 36]. In our earlier work, we

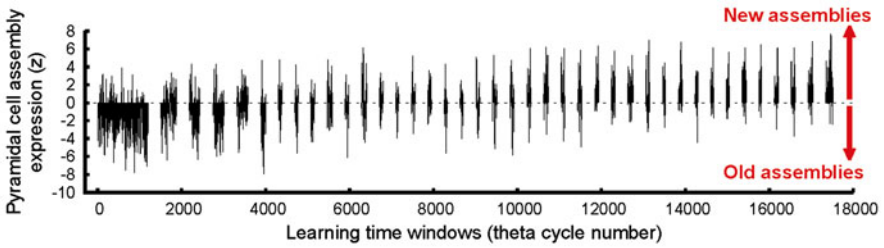

Fig. 6.3 Theta-paced flickering of hippocampal cell assemblies during spatial learning on the cheeseboard maze. In this analysis, the dynamic expression of pyramidal assemblies was quantified in theta cycles of each learning trials using a Fisher *z*-test. Positive *z* values indicate times when pyramidal firing patterns preferentially expressed the new cell assemblies ("new assemblies") while negative values indicate the expression of the old ones ("old assemblies"). Each block represents a learning trial spaced by intertrial intervals. Note the flickering between the old and the new assemblies in each trial. Adapted from [39]

may have missed such rapid switching between different maps; the rapid flickering of old and new maps may potentially explain why the neural dynamics related to map expression appears to occur at a slower time scale than learning speed. Accordingly, one possible explanation for this discrepancy could be that the new maps emerge early during learning, but they are initially competing against old maps. In this case, the old maps associated with previous learning episodes would still be temporarily expressed because in the initial phases of the task, the animal retains the old maps as well. However, as learning progresses, the new maps may undergo some additional refinement as they gain dominance over the old maps. Previous theoretical studies have indeed suggested that competitive network dynamics are an integral part of learning and cognitive processes (e.g., [37, 38]).

To test whether map switching can explain the discrepancy between the time course of both remapping and learning, we examined the temporal dynamics of map expression at short timescales during the course of learning [39]. We examined the possibility that flickering takes place between old and newly formed representations during goal-directed learning on the cheeseboard task. As in a recent study [36], we used theta oscillatory cycles during learning as time windows to evaluate whether the ongoing population activity was more similar to the assembly patterns representing the old maps (i.e., expressed before learning) or the new ones (i.e., recalled after learning). We found that, in the first learning trials, both the old and the new assemblies were expressed in nonoverlapping theta cycles, while later trials were dominated by the new maps (Fig. 6.3). Hence assemblies associated with new maps emerged early during the learning period, at the same time as the behavioral performance increased rapidly. However, initially new maps flickered with the old maps across nonoverlapping theta oscillatory periods.

These results could potentially be explained if map competition takes place during learning. As animals reliably locate rewards at new locations, newly formed maps gain influence because these can successfully predict the current goal locations

needed for the animal to solve the task. Animals may initially retain the old maps as it is uncertain whether the change of reward locations is transient or lasting. Our results also confirmed that the emergence of the new maps is correlated to the rapid improvement of behavioral performance. The mechanisms by which such a selection of the new maps over the old ones is achieved remain to be identified. One possibility lies in the involvement of the inhibitory circuit and its fine interplay with the activity of pyramidal cell assemblies [39]. Such a mechanism of map selection might then allow for the further refinement of new maps to aid efficient behavioral performance, provided that the newly acquired maps undergo a process of stabilization.

Sharp-Wave/Ripple Responses During Learning and Sleep

The memory for newly learned goal locations was stable following the completion of learning, suggesting that the newly acquired patterns might have undergone a process of consolidation. It is known that newly formed memories are labile and prone to interference with competing old memory traces. A consolidation process ensures the stability of the new memory traces allowing them to be reinstated to support later memory-related behavior [40–42]. Indeed, the role of the resting state, and particularly sleep, in memory consolidation has been demonstrated by several studies [43, 44]. Typically subjects do better in learning tasks if learning takes place in the evening and recall in the subsequent morning as compared to those in which learning took place in the morning and recall in the end of the day [45]. Moreover, memory recall could be facilitated by interventions during sleep. For example, reintroducing task-related sensory cues (i.e., odor, sound) during sleep that has been part of the context in which learning occurred has been shown to improve the subsequent memory recall [46, 47]. Certain stages of sleep are dominated by slow oscillatory patterns [48]. These slow-wave sleep periods are important for the consolidation of hippocampus-dependent declarative memories. Indeed, strengthening the power of slow oscillations by transcranial current stimulation improves the recall of declarative memories [49].

During slow-wave sleep, in the hippocampus, the most dominant oscillatory patterns are the intermittent sharp-wave/ripple events (SWRs, 150–250 Hz) [50–53]. During these events that are linked with 200 Hz ripple oscillations in the CA1 pyramidal layer and negative sharp waves in the stratum radiatum, a large number of CA3 and CA1 pyramidal cells fire action potentials together. These SWRs have been postulated to have a role in memory consolidation [42]. In support of this hypothesis, it was shown that hippocampal waking firing patterns are replayed during sleep SWRs, that is, SWR-related firing patterns resemble those observed in the previous active waking periods [54–56]. It has been suggested that SWRs might promote memory consolidation by promoting neuronal plasticity [57] and, through this, they could strengthen previously stored mnemonic patterns. It has been also proposed that SWRs may take part in systems-level memory consolidation by transmitting reactivated engrams to extra-hippocampal circuits [42].

In relation to place maps, SWRs and the associated reactivation of waking place cell patterns could represent a mechanism by which new hippocampal maps are stabilized [58]. As a consequence SWRs could facilitate the stabilization of new maps to promote the consolidation of related spatial memories. Indeed there is experimental support linking SWRs to spatial learning: the electrical stimulation-induced disruption of SWRs in sleep periods is associated with spatial learning impairments in mazes [59, 60]. These studies however could not link reactivation itself to spatial memory consolidation. Therefore, we set out to determine whether neuronal patterns during SWRs in sleep represent patterns that are related to learning and tested whether the reactivation of learning-related patterns can predict memory performance.

In the context of goal-directed learning on the cheeseboard maze, we hypothesized that goal location-related patterns will be emphasized during the following sleep period, reflecting what is subsequently remembered by the animal [33]. Therefore, in examining whether learning-related firing patterns are preferentially reactivated, we found that firing patterns observed at newly learned goal locations were reactivated stronger than patterns expressed by cells representing the start box (Fig. 6.4a). This result is in line with the finding that reward-related hippocampal waking patterns are enhanced during SWR events [61]. Importantly we went further by identifying the firing content of individual SWR in order to establish which location was best represented on the cheeseboard by each of the SWRs. We computed reactivation maps from each sleep SWR by measuring how similar the firing pattern of a SWR was to the waking patterns expected at the different location on the cheeseboard during waking periods (Fig. 6.4b). This analysis led to two results. Firstly, we observed that in many of the reactivation maps, only one location was preferentially represented which corresponded with one of the goal locations (Fig. 6.4c). This result suggests that places with a strong behavioral valence such as those predicting the presence of reward can be emphasized during sleep reactivation. Secondly, the occurrence frequency at which a given goal location was reactivated during SWRs predicted how well that particular location was remembered in the following probe session (Fig. 6.4d). This finding establishes a predictive value

Fig. 6.4 (continued) Place field similarity was calculated using place fields established at the end of learning while SWR cofiring was calculated in sleep periods before ("pre-") and after ("post-") learning. Correlation coefficients represent the partial correlations of place field similarity with the cofiring strength of one sleep session, each controlled by the cofiring strength of the other sleep session. (**b**) Illustration of the population vector-based procedure to compute SWR reactivation maps. For each map, the pixel color represents the correlation coefficient between assembly firing patterns that occurred during a single SWR and those representing that *x*–*y* location on the maze during the waking period. (**c**) Examples of individual sleep SWR reactivation maps (*black dots*: learned goal locations). Note that correlation coefficients are highest at one of the bait locations (color scale: correlation coefficient). (**d**) Scatter plot depicting post-probe memory performance (number of crossings at a given goal location) as a function of the proportion of SWRs in which assembly patterns represented the same goal location (in *gray*: regression line). Adapted from [33]

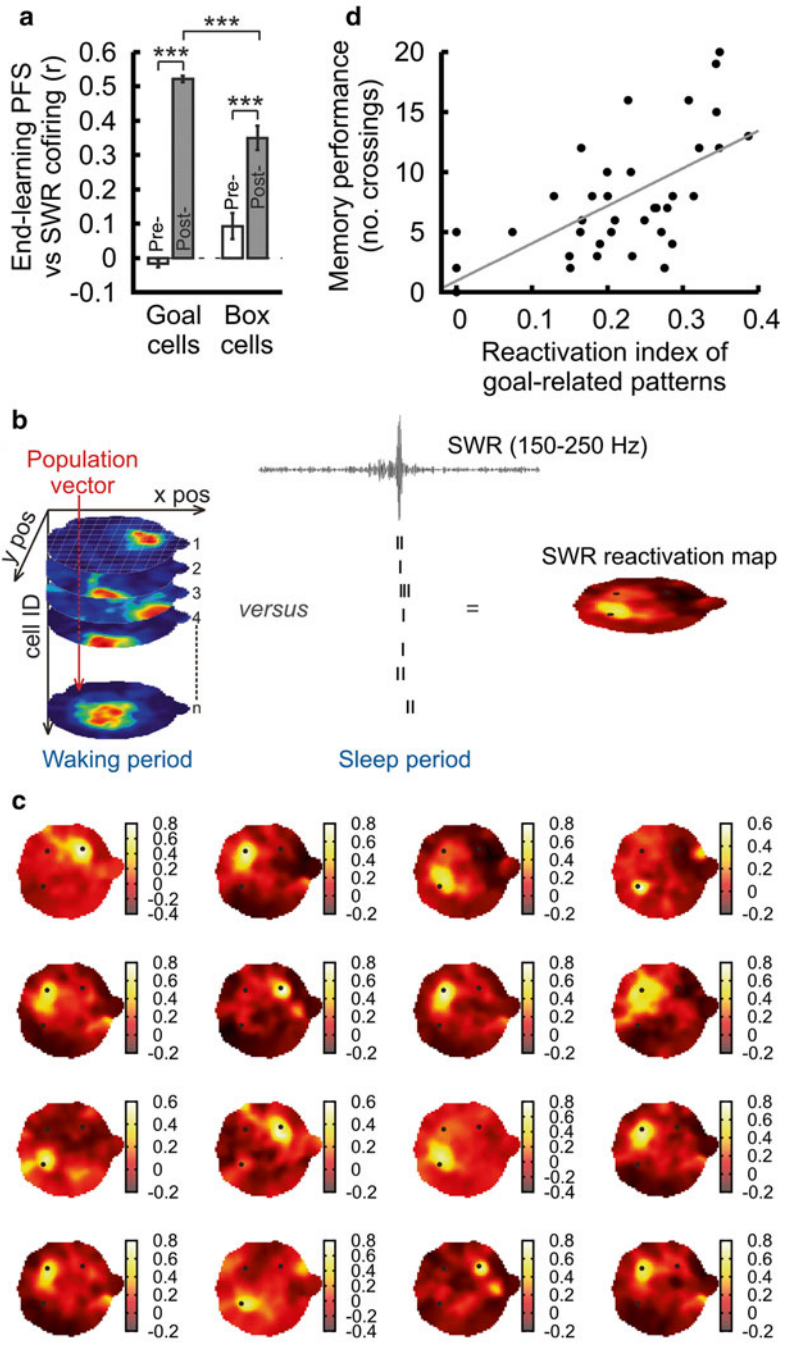

Fig. 6.4 Reactivation of CA1 place-related assembly patterns following goal-directed learning on the cheeseboard maze. (**a**) Correlation between place field similarity ("PFS") and sleep SWR cofiring strength calculated between pairs of "goal-centric" and "start-box" cells (means ± s.e.m).

for sleep reactivation in estimating memory performance and therefore highlights that it can represent a network mechanism for memory consolidation.

SWR-related activity is not only present during slow-wave sleep and in long periods of waking immobility but also during behavioral sessions in which animals are active. Waking neuronal patterns during SWRs occurring in these active waking periods have also been examined. This work revealed the reactivation of place cell firing patterns during these SWR as well and that these patterns could even represent entire movement sequences which may or may not have originated at the location where the SWR occurred [58, 62–69]. These waking SWRs have been suggested to play a role in the stabilization of new maps [62, 68] and to provide further time windows for memory consolidation during online periods. An interesting idea that has been put forward suggests that they may have a role in memory recall particularly in working memory tasks. As a confirmation for this latter hypothesis, spatial working memory deficits were detected when waking sharp waves were disrupted by electrical stimulation [70]. This study used a spatial alternation task on a W-maze that contained both working and reference memory components at different stages of the run. The on-the-fly electrical disruption of awake SWR resulted in deficits in the working memory component of the trials without affecting the spatial reference memory. As these animals were extensively trained beforehand to perform the task, the stability of the equally well-established maps was not expected to be affected by the electrical stimulation. Whether waking SWRs participate in the stabilization of new hippocampal maps and/or are incorporated into preexisting ones therefore remains to be tested.

Importantly, all waking SWRs are not identical as it is possible to differentiate two forms of them. Exploratory-related SWR (eSWR) events occur during brief (~2 s) pauses in locomotor activity, while other waking patterns (iSWR) can be detected during longer waking immobility [62]. iSWRs are similar to sleep SWRs in the sense that assembly patterns representing any locations of the animal's environment can be reactivated. In contrast, eSWRs are strongly influenced by the current location of the animal and mainly place cells with place fields that overlap with the location of the eSWR are active here. Nevertheless, place cells coding for the current location of the animal synchronize their activity during eSWRs much stronger than expected outside the SWRs during theta oscillations [62]. Such eSWR-related synchronization of place cell firing responses favors conditions for neuronal plasticity [57], specifically amongst cells representing the same location. This can help map stabilization and the initial strengthening of cell assemblies beyond their reactivation during sleep, therefore representing an online network mechanism to incorporate and stabilize new hippocampal maps.

We have specifically examined the expression of goal-associated patterns during eSWRs during learning on the cheeseboard maze. We have been able to detect both eSWR and iSWRs. Surprisingly the number of detected eSWRs at a particular goal location predicted the memory performance of that location, while iSWR numbers were not able to. This result highlights that one would need to differentiate eSWRs and iSWRs patterns in order to test for their behavioral role. Moreover we also

noticed that network synchronization was much stronger during eSWRs that occurred at the newly learned goal locations than in the start box. Such enhanced network synchronization of eSWRs is similar to those observed during the exploration of novel environments [68] and in relation to reward outcomes [61]. Hence, eSWRs tend to enhance the synchronization within those assemblies of cells that encoded newly learned goal locations. Furthermore, eSWR-related firing synchrony measured at different goal locations during learning also predicted the subsequent memory performance of the animal. Finally, the enhanced synchrony at goal locations during eSWRs could not be detected under NMDA blockade suggesting that the eSWRs may not have a role during the learning per se, but in the subsequent recall of these patterns, which was impaired under NMDA blockade. These findings point to a role of eSWRs in the stabilization of newly formed maps and in the concomitant stabilization of new spatial memory traces. Yet, establishing a causal evidence for the role of eSWRs in the stabilization of newly formed representations of discrete places and the related plasticity mechanism for their incorporation into preexisting maps is still lacking.

Conclusion

Here we have highlighted work supporting the notion that the reorganization and reactivation of hippocampal place cell firing patterns can contribute to goal-directed spatial learning. The data we reviewed demonstrated that spatial behavior involving learning a new set of goal locations is associated with the remapping of a subpopulation of place cells such that these cells encode the novel association between a discrete location and the reward. Such remapping cannot merely be explained by noncognitive factors such as changes in the motor behavior of the animal as such changes were observed only in conditions where allocentric learning of goal locations was required. Moreover, current data suggest a dual role in the CA3 and CA1 in these processes in which CA1 assemblies may be involved in the representation of particular discrete locations, while CA3 maps may hold a representation of the entire environment in which navigation has to be performed. More work is required however to confirm this complementary role of CA1 and CA3 regions, notably in other behavioral tasks. Furthermore, it would be essential to provide a causal link between hippocampal remapping and goal-directed learning.

Here we also reviewed a possible physiological mechanism for the stabilization of new maps and the resulting stabilization of memory traces coding goal locations. We highlighted the role of reactivated patterns that take place during SWRs. We also described that excitatory activity related to waking SWRs may play novel or complementary roles to those observed during sleep. Pinpointing the precise role of waking and sleep SWRs in learning and in the stabilization of memory traces will require systematic future work that could provide further insights to the inner working of the brain during memory formation.

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Chapter 7
Causal Relationship Between SPWRs and Spatial Learning and Memory

Gabrielle Girardeau and Michaël Zugaro

Abstract Consolidation is the process by which recently acquired memories are gradually strengthened and reorganized for long-term storage, potentially involving a transfer from the hippocampus to cortical areas. Hippocampal sharp-wave ripples (SPWRs) are transient fast oscillations (200 Hz) occurring during slow-wave sleep, rest, and short immobility periods. Because place cells are sequentially reactivated during SPWRs, and because their frequency would be propitious to induce long-term potentiation, SPWRs have been considered a likely candidate mechanism for spatial learning and memory consolidation. Establishing a causal link between the two requires closed-loop interventional experiments where SPWRs are detected *online* and suppressed in a spatiotemporally selective manner. This was achieved in three studies where SPWRs were suppressed either during sleep and rest following training on a spatial task or during training on the spatial task. The resulting impairments in performance in all three studies established for the first time a causal link between sleep and rest SPWRs and memory consolidation on the one hand, and awake SPWRs and working spatial memory on the other hand. These studies also raised the question of a differential role for awake and sleep/rest ripples that will require further investigation. Similarly, conclusive evidence for a role of SPWRs in hippocampo-cortical information transfer remains elusive.

Keywords Hippocampus • Sharp wave-ripples • Memory consolidation • Spatial memory • Causal neuroscience • Neuronal replay • Closed-loop stimulation

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Introduction

Some of the earliest studies that uncovered causal relationships between the activity of specific brain areas and cognitive functions such as memory were carried out on human patients suffering from cerebral injuries or surgical resections. Perhaps the most influential case is the study of patient HM, who had undergone bilateral ablation of the hippocampus, entorhinal cortex, and amygdala in order to cure a severe, drug-resistant epilepsy [1]. This work was instrumental in establishing the critical role of the hippocampal formation in certain forms of declarative and spatial memory. Further, because HM's amnesia was temporally graded—new memories could not be formed, but older memories were mostly spared—this contributed to the development of the main theories of memory consolidation [2, 3]. Memory consolidation is the process by which initially labile memories are gradually stabilized to form long-term memory traces. This process, known as "systems consolidation", typically takes place over the course of several days, months, or even years. It involves the gradual strengthening and reorganization of memories with time and is believed to involve some form of hippocampo-cortical transfer of information. At the cellular and molecular level, "synaptic" consolidation refers to faster processes that occur in the minutes and hours following learning and that are responsible for the formation of long-term memory, including structural and functional changes in existing synapses, as well as synapse formation and pruning.

General Theories of Systems Memory Consolidation

The numerous and consistent reports of graded retrograde amnesia led to the formulation of the standard memory consolidation theory (SMC, [2]). In this model, the hippocampal formation plays a time-limited role in declarative memory storage and recall. Memories are gradually transferred to extra-hippocampal areas via the consolidation process and eventually become independent of the hippocampus. This model received strong support from a series of studies that provided evidence for a differential involvement of hippocampal and cortical areas depending on the remoteness of the tested memory [4, 5]. For instance, Bontempi et al. [6] trained rats to find three food rewards at fixed locations in an eight-arm radial maze and imaged (^{14}C)2-deoxyglucose uptake as a marker of neuronal activity to compare the brain areas activated by recall of the task after a retention delay of either 5 or 25 days. When recall occurred 5 days after training, the dorsal and ventral hippocampus, subiculum, entorhinal, and posterior cingulate cortices were strongly activated. After 25 days, however, the level of activation in these structures was low, whereas activity was increased in frontal, temporal, and anterior cingulate cortices (ACC), consistent with a transfer of memory traces from hippocampal to cortical areas. However, based on novel experimental results and detailed reexamination of the literature, this theory has been challenged and alternative models have been proposed. In particular, the multiple trace theory [3] posits that the hippocampus remains involved in certain

forms (e.g., episodic) or aspects (e.g., detailed) of long-term memory. This theory has been supported by numerous experimental data, including the recent study of Goshen et al. [7] who tested the role of the hippocampus in reactivating remote contextual fear memories in mice. Using fast optogenetical tools, the authors were able to selectively inactivate the hippocampus during recall and showed that this abolished fear expression even weeks after learning. Such results indicate that the hippocampus can remain involved in certain forms of remote memory and question a sequential recruitment of the hippocampus and neocortex. Conversely, the neocortex may also be critically involved in early stages of memory formation. Lesburguères et al. [8] trained rats in a social transmission of food preference task, where the animals learn that certain novel foods are safe by sampling their odor on the breath of littermates. The authors showed that inactivation of the orbitofrontal cortex during sampling impaired the subsequent expression of long-term food preference. While these results provide fundamental insights into the respective roles of the hippocampus and neocortex in long-term memory, a common feature of all major theories of memory formation remains that memory traces are progressively reorganized for long-term stabilization and that this process involves a complex dialogue between the hippocampus and neocortex.

The "Two-Step" Model of Memory Consolidation

Mechanistic theories of memory consolidation [9, 10] proposed that memory formation follows a two-step process sequentially involving online and offline (e.g., sleep) processes with different physiological signatures. Rapid encoding would take place in the hippocampus during awake states, sustained by plastic changes resulting from neuronal activity orchestrated by theta (~8 Hz) oscillations. Indeed, in the superficial layers of the entorhinal cortex (EC), which are the main cortical projection to the hippocampus, principal cells are strongly modulated by the ongoing theta oscillation [11], suggesting that during exploratory behavior, the flow of information is directed from cortical areas to the hippocampus. Moreover, encoding could be favored by the higher levels of acetylcholine observed during theta, which enhance feed-forward functional connectivity [11, 12]. During subsequent sleep, lower levels of acetylcholine would give way to preponderant recurrent effective connectivity, favoring endogenous activity. Previously encoded information could thus be reactivated, strengthened, and potentially transferred to neocortical areas for long-term storage. Consistent with this idea, the consolidation of a declarative task is impaired in humans when acetylcholine levels are maintained high during slow-wave sleep (SWS) by blocking acetylcholine degradation [13]. Besides, the deep layers of the entorhinal cortex, which constitute a major output of the hippocampal formation, are selectively activated during sharp wave-ripple (SPWR) events characteristic of hippocampal activity during SWS [11], possibly underlying the propagation of information toward extra-hippocampal areas. Indeed, hippocampal ripples are transient fast oscillations during which neuronal populations discharge at ~200 Hz,

similar to the frequency used to experimentally elicit long-term potentiation (LTP), the main candidate cellular and molecular mechanism for memory. SPWRs were therefore proposed as a candidate mechanism for offline memory consolidation [9].

Evidence for a Link Between Sleep Ripples and Memory Consolidation

Experimental evidence supporting this theoretical prediction has since accumulated. High-frequency stimulation of the hippocampal commissural pathway not only efficiently triggers LTP of population postsynaptic potentials (PSPs) and population spikes but also increases the amplitude and occurrence rate of SPWR events, suggesting a link between SPWRs and LTP-induced alteration of hippocampal cell excitability [14]. Consistent with this result, learning has been shown to induce LTP [15] and to increase the incidence of SPWRs during sleep following training on a spatial memory task [16] and in an odor-reward association task [17]. In the first study, rats were either trained on an eight-arm radial maze where the same three arms were baited every day or pseudo-trained on the same maze with all arms baited. During the first 4 days, ripple incidence in sleep following training was similar in both the trained and pseudo-trained groups and greater than in control rats that remained in their home cages. More importantly, a supplementary increase was observed in the trained group concomitant with a significant improvement in performance at the sixth day of training. Further, we have recently shown that learning, but not mere spatial experience, increases the "drive" for SPWRs during subsequent sleep: perturbing ripples then results in compensatory increases in SPWR incidence—and this effect depends on the activation during behavior of NMDA receptors, which are known to be critical for LTP [18]. The link between LTP induction and SPWRs was confirmed in an in vitro study [19]. Using hippocampal slices that did not exhibit spontaneous SPWRs, the authors applied classical high-frequency stimulation (100 Hz) to hippocampal area CA1 stratum radiatum and showed that this induced spontaneous, in vivo-like SPWRs in CA1 and CA3, triggered by CA3. Taken together, these results suggest that hippocampal SPWRs are influenced by synaptic plasticity occurring during wake periods. Place-selective firing and sequence encoding are believed to selectively potentiate subsets of CA3 cells, the increased excitability of which favors them as SPWR-initiator cells during subsequent sleep [20]. Indeed, during SWS following a spatial experience, the place-cell activity elicited during exploration is reinstated in hippocampal circuits: sequences of place cells coding for entire spatial trajectories are replayed in the same order as during spatial exploration ([21–23], see also Chaps. 3–6). However, whether SPWRs can conversely trigger LTP in the hippocampus and target areas remains unclear. One study showed a possible involvement of SPWRs in hebbian processes [24]. In this study, the authors mimicked the classical in vivo LTP induction protocol pairing postsynaptic depolarization of a cell with massive stimulation of its afferent pathway, using endogenous SPWRs as the afferent stimulation. Coupling experimentally

induced depolarization of a CA1 cell with SPWRs induced LTP, as indicated by the subsequent increase in the responsiveness of the cell to SPWRs. Together with the demonstration that experimental induction of LTP in the hippocampus can artificially impose a new configuration of place fields in space [25], this is consistent with the idea that under physiological conditions, SPWR-induced plasticity could stabilize newly formed place maps (see also [26]). Taken together, sleep replay of awake neuronal activity, reciprocal interactions between SPWRs and LTP, and experience-dependent ripple and replay incidence all provide strong correlational links between SPWRs and memory consolidation.

Using genetically engineered mice in which CA3 output could be selectively and inducibly suppressed, Nakashiba et al. [27] showed that functionally disconnecting CA3 and CA1 reduces the incidence of both ripples and reactivations and impairs contextual fear memory. However, the same mouse line had previously been shown to be capable of learning the watermaze task [28], a standard spatial memory test where animals must swim to a hidden platform that can be located using the spatial configuration of stable distant visual cues [29]. Because of the limited temporal specificity of the genetically induced CA3–CA1 disconnection, it is conceivable that this more broadly affected hippocampal function, in particular initial sequence encoding during theta oscillations, making the impaired replay more delicate to interpret. To date, direct genetic alteration of brain circuits does not achieve the precise temporal resolution required to selectively alter discrete short duration neuronal events such as ripples.

The Causal Role of Sleep and Rest Ripples in Memory Consolidation

Selective suppression of SPWRs requires closed-loop systems where neural activity is monitored and manipulated depending on ongoing signals. A direct method to demonstrate a causal relationship between ripples and memory is to show the impairing effect of such targeted perturbations on memory consolidation. This was performed in two studies [30, 31] where ripples were detected online and automatically suppressed by brief single-pulse stimulation of the ventral hippocampal commissure (VHC), a pathway containing the fibers that reciprocally connect the hippocampi of the two hemispheres (Fig. 7.1). This stimulation blocks hippocampal discharges for 50–250 ms (depending on the intensity), presumably via massive recruitment of interneurons and network disfacilitation. Because ripples result from an interplay between principal cell and interneuron discharges, this also interrupts the ongoing local field potential oscillation. Ripples were detected by band-pass filtering the signal recorded in the CA1 pyramidal cell layer and then thresholding the amplitude of the filtered, rectified signal. Threshold crossing automatically triggered VHC stimulation. The effect of ripple suppression on memory consolidation was assessed by measuring changes in performance on spatial memory tasks. In the first study [30], we suppressed ripples during the first hour of sleep and rest following

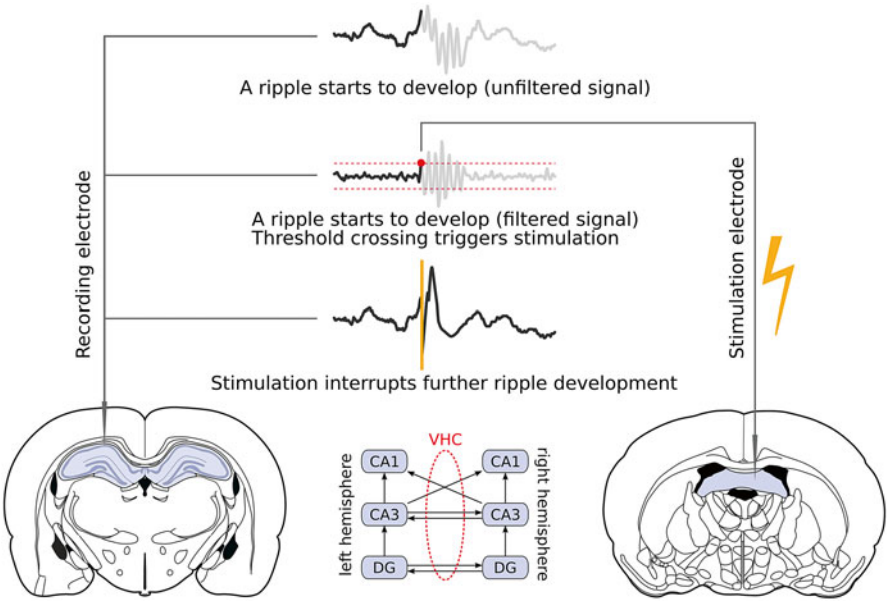

Fig. 7.1 A closed-loop real-time circuit for causal neuroscience: online ripple suppression. The signal recorded in the pyramidal cell layer of dorsal CA1 is band-pass filtered in the ripple band (100–250 Hz) and thresholded. Threshold crossing automatically triggers a brief, single-pulse stimulation of the ventral hippocampal commissure, targetting both hippocampi simultaneously. This stimulation transiently suppresses neural activity for 50–250 ms and prevents further development of the ripple

daily training on an eight-arm radial maze (Fig. 7.2a). To solve the task, the rats needed to remember from trial to trial (3/day) and day to day the fixed locations of the three baited arms. Because this information remained relevant over the course of the entire training period (15 days), the task is referred to as a "reference" memory task, which requires memory consolidation. While visiting a non-rewarded arm is thus considered a reference memory error, returning to an already visited arm is considered a "working" memory error—one which reveals an incapacity to remember information that remains useful for only a limited period of time, until a specific action is performed. In this task, working memory is only useful during a given trial: it does not benefit from memory consolidation and is thus not expected to be affected by ripple suppression. We compared the performance of test animals in which ripples were suppressed to two control groups: a naive unimplanted group and a group in which ripple detection triggered delayed stimulation, leaving ripples intact. The latter group thus received the same number of stimulations than the test group but had

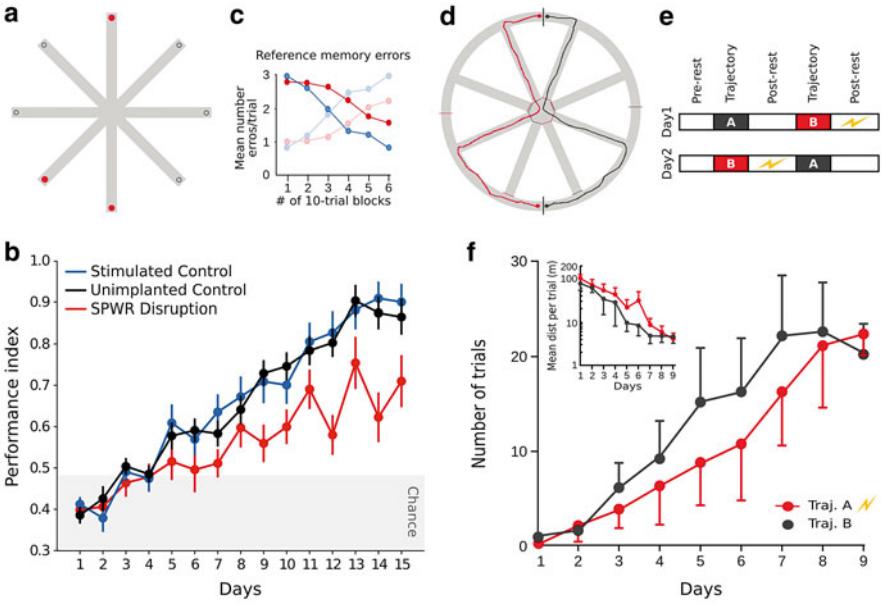

Fig. 7.2 Causal role of sleep and rest ripples in spatial memory. (**a**–**c**) SPWR disruption or hippocampal lesion impairs performance on a radial maze. (**a**) Animals were trained daily on an eight-arm radial maze (3 trials/day) where three arms were baited (*red dots*). These remained fixed in space during the 15 training days. (**b**) Performance was impaired in animals in which the stimulation disrupted ripples (*red*) compared to control animals (stimulations leaving ripples intact, *blue*; no stimulation, *black*) (reproduced from [30]). (**c**) The impairment induced by SPWR disruption was similar to that observed after complete hippocampal lesion (*red*) (adapted from [32]). The two curves were flipped to facilitate the comparison with (**b**). (**d**–**f**) SPWR disruption impairs learning of a spatial trajectory. (**d**) Animals were trained to learn two different trajectories on the same maze. (**e**) SPWRs were suppressed after training on one of the trajectories only. The order of training on the two trajectories was randomized over days. (**f**) Performance, measured as the number of trials and the distance traveled, was selectively impaired on the trajectory after which ripples were suppressed (*red*) compared to the control trajectory (*black*) (adapted from [31])

normal, unperturbed ripples. The results showed that the control animals which received delayed stimulation performed as well as the unimplanted animals, ruling out potential uncontrolled effects of hippocampal stimulation on performance. Conversely, test animals in which ripples were suppressed were significantly impaired on the radial maze task, indicative of their inability to consolidate spatial information over the training days (Fig. 7.2b). Importantly, the number of working memory errors was comparable in the three groups, indicating that working memory was not affected by ripple suppression.

In the study by Ego-Stengel and Wilson [31], the protocol was designed so that each animal would be its own non-stimulated control. Each rat was thus trained daily to learn two different trajectories on the two sides of a wheel-shaped maze (Fig. 7.2d). Ripples were suppressed following training on the first trajectory, but not following training on the second trajectory. The order of trajectories was balanced between days and animals (Fig. 7.2e). The results showed that learning was selectively impaired on the trajectory after which ripples were suppressed (Fig. 7.2f).

Note that in both studies, learning was incompletely abolished. Several factors could account for this. First, the residual performance improvement observed in our study [30] was comparable to that reported for hippocampus-lesioned rats trained on the same task ([32], Fig. 7.2c) which probably develop alternative, hippocampus-independent strategies (see, e.g., [33]). Incidentally, this underscores that selective ripple suppression powerfully affects memory: indeed, this targeted perturbation did not affect hippocampal activity outside ripples nor cortical activity, yet turned out to induce impairments as dramatic as complete hippocampal lesions. A similar argument can be made about the study of Ego-Stengel and Wilson [31], although comparable data from hippocampus-lesioned rats is not available. A second factor possibly accounting for residual performance in both studies is that ripples were only suppressed during a limited amount of sleep and rest time (1 h) after training. While this protocol was warranted by the finding that the incidence of replay events embedded in SPWRs rapidly decreases during the first hour after training [34], a few studies suggest that neural activity during training can still influence online activity 24 h later [35, 36], although this remains debated [37]. Still, the animals were allowed to sleep normally in the >20 h periods between successive recording sessions, which allowed for a substantial number of unperturbed ripples. This might have been sufficient to sustain residual learning. Similarly, the short bouts of neural activity occurring at the very start of the ripple, before it was detected (ranging from one cycle to one-third of the ripple), could have also played a role. Lastly, ripples of smallest amplitude were probably not detected and were therefore unaffected by the simulation. Such ripples would be triggered when CA3 synchrony is weaker [38] but may still have an influence, albeit reduced, on downstream targets.

In conclusion, the studies of Girardeau et al. [30] and Ego-Stengel and Wilson [31] provided the first direct experimental evidence for a causal link between sleep and rest ripples and memory consolidation, confirming theoretical predictions formulated 20 years earlier [9]. At this point, however, several questions remain unanswered. While there is now ample evidence that ripples support memory consolidation during sleep and rest, this does not rule out other potential, complementary roles for sleep SPWRs. Consistent with the synaptic downscaling theory of sleep [39], some authors have suggested that ripples could contribute to resetting synaptic connectivity [40] to prepare the hippocampal network for subsequent learning. However, more recent evidence suggests that SWS promotes synaptic plasticity, while synaptic downscaling may actually occur during REM sleep [41, 42]. Importantly, whether SPWRs actually underlie a transfer to the neocortex, as suggested by theoretical considerations and correlational experimental evidence (e.g., [43, 44]), remains to be demonstrated.

Evidence for a Link Between Awake Ripples and Learning and Memory Processes

Although SPWRs occur more frequently during slow-wave sleep and rest, they are also observed during awake states such as brief pauses during exploration, grooming, eating, or drinking. In particular, SPWRs are a prominent pattern when the animal pauses at reward sites during spatial tasks. In 1989, Buzsáki predicted that during such SPWR episodes, place cells should endogenously reactivate, starting from the most excitable cells. Activity would propagate from the most to the least recently excited cells: replay would thus start from place cells with firing fields near the reward site, continue with cells with fields located a little before the reward site, then more distant ones, etc. As a result, trajectories would be replayed in reverse order. This prediction was confirmed by Foster and Wilson [45] who found that a substantial proportion of place cells active on a linear track subsequently fired during SPWRs in reverse order. Moreover, the proportion of reverse replay was greater during exploration of a novel rather than a familiar environment (but see [46]). This result was confirmed and extended by Diba and Buzsáki [47] who documented forward and reverse replay, as well as forward and reverse "preplay," i.e., sequences reflecting the future trajectory. This supported the idea that awake SPWRs and replay might have a different physiological function than sleep SPWRs and replay. In particular, the fact that reverse replay occurred at a reward site suggested that this might contribute to an evaluation of the outcome of the trial and to its potential online memorization. Indeed, the presence or absence of a reward was shown to modulate reactivations during SPWRs: Singer and Frank [48] reported that the proportion of active cells during SPWRs and their coactivation probability were significantly enhanced during pauses after a rewarded trial compared to an unrewarded one. During the experiment, the rewarded arm sequence was changed and the rats had to adapt their strategy. This further enhanced the reward modulation of replay, suggesting that awake reward-related reactivations were involved in task acquisition. This was recently supported by the additional finding that, during the initial learning period on an alternation task, reactivation is enhanced during SPWRs preceding a correct trial compared to those preceding an incorrect one [49]. Awake SPWRs may thus play a role in evaluating and selecting future trajectories. Another notable difference between sleep and awake SPWRs is that during awake ripples, sequential activity can correlate with previous behavior [46, 50, 51] but can also represent trajectories that have never actually been experienced ("short-cuts", [52]). This potentially extends the role of neuronal replay to building the hippocampal cognitive map.

The Causal Role of Awake Ripples in Learning and Memory

The causal role of awake ripples in learning processes was first investigated by Nokia et al. [53, 54], who performed a series of closed-loop experiments in rabbits. In these studies, rabbits underwent trace eyeblink conditioning, a classical conditioning

procedure where a sound is paired to a mild air puff eliciting eyeblink. A stimulus-free ("trace") delay between the sound and air puff ensures that successful conditioning requires the hippocampus. In the first study, conditioning trials were timed 200 ms after ripple occurrence. On the first day of training, rabbits performed better than yoked control rabbits where conditioning trials took place regardless of the oscillatory state of the hippocampal network. The difference between the two groups eventually vanished with repeated training. These results suggest that neuronal activity during and immediately following awake ripples may contribute to learning. However, during extinction periods where the conditioned stimulus (CS) was presented without the air puff, time-locking the CS presentation to ripples actually slowed down the gradual suppression of conditioned eyeblink (extinction)—a puzzling result, given that extinction is considered a form of new learning. Interestingly, CS presentation triggered theta oscillations which were more synchronized with the CS if this was time locked to ripple oscillations, suggesting that the difference between the two groups may have at least partly resulted also from theta-related activity. In the second study, light stimulation was presented between conditioning trials, either upon ripple detection or regardless of the hippocampal oscillatory state. Although light did not disrupt ripples, it reliably triggered theta oscillations and reduced theta phase-locking after the subsequent CS. Light presentation slowed down acquisition in both groups, but the effect was more pronounced when the CS was ripple-locked. This further supported the idea that learning may involve an interplay between awake ripples and theta-related activity.

Evidence for a causal role of awake SPWRs in spatial memory was recently provided by Jadhav et al. [55]. In this study, the authors leveraged the online ripple suppression protocol described earlier to disrupt awake ripple activity in rats performing a continuous spatial alternation task in a W-shaped maze, which benefits from hippocampal processing (Fig. 7.3, [56]). Solving this task requires two complementary strategies. First, when the rats leave the central arm, in order to receive a reward, they must choose the arm that was not visited on the previous trial. Second, upon return from the side arm, they must choose the central arm to receive a reward. Thus, while the correct "inbound" (return) trajectory is invariant throughout the task, the correct "outbound" trajectory can only be selected if the animal remembers the previous trial, which requires working memory. The authors showed that awake ripple suppression impaired learning of the task over the course of the 8 training days: test animals whose ripples were suppressed learned more slowly and did not reach the performance level of control animals in which stimulation was delayed in order to leave ripples intact (Fig. 7.3). Interestingly, only the outbound component of the task was affected by ripple suppression. Because in control animals performing at asymptote levels, performance on outbound trials also declined when awake ripples were suppressed, this suggested a role for SPWRs in working memory. It is also noteworthy that place field stability was not affected by awake ripple suppression. Importantly, ripple rate during sleep following ripple suppression was not affected by awake ripple suppression, indicative of a lack of delayed compensatory rebound (see [30] for similar results on sleep ripples). The strength of reactivation following awake ripple suppression was not affected either, consistent with the idea that sleep and rest ripples and reactivations sustained learning of the inbound component of the task.

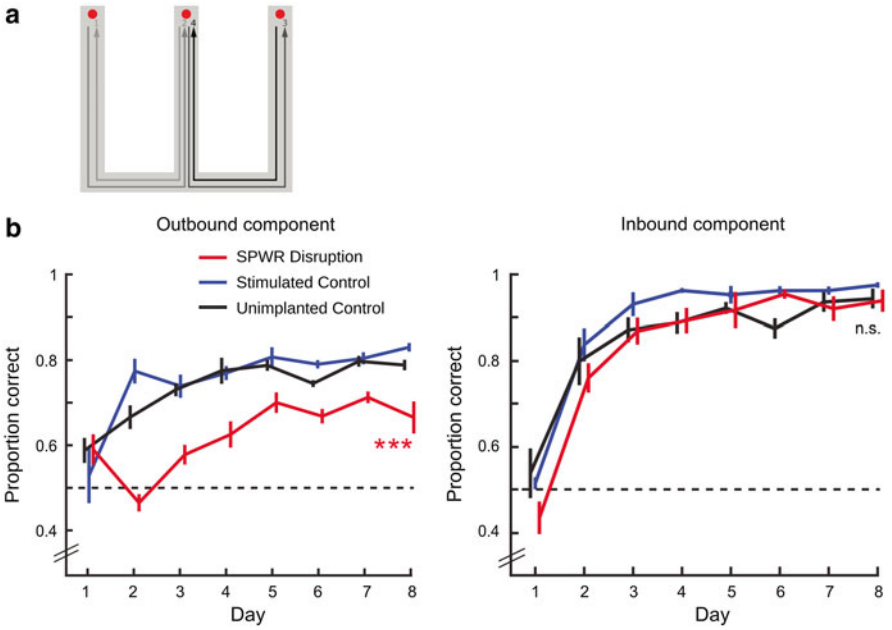

Fig. 7.3 Causal role of awake ripples in spatial memory. (**a**) Animals were trained on a spatial alternation task where they had to alternate between right and left outbound (1,3) trajectories. Following each choice, the rats returned to the center to initiate a new trial (inbound trajectory, 2,4). (**b**) Animals in which awake SPWRs were disrupted on the maze were impaired on the outbound trajectory (*left*) compared to stimulated controls with intact ripples (*blue*) and non-stimulated animals (*black*). However, all three groups performed normally on the inbound trajectory (*right*) (from [55]) (reprinted with permission from AAAS)

Conclusion

Numerous studies have now provided compelling evidence for a causal role of sleep and awake ripples in short- and long-term spatial memory. However, many questions remain to be elucidated. First, in closed-loop experiments, SPWRs were suppressed regardless of their "neuronal content", i.e., whether they were associated with relevant reactivations or not. It is thus currently unknown whether only those SPWRs associated with relevant reactivations play an effective role or if all SPWRs are crucial for spatial learning and memory. It is in fact conceivable that all ripple-associated activity is relevant to memory, but we are unable to decode or relate most of it to specific behaviors or internal representations. Similarly, differential roles for forward versus backward replay have not yet been established. While forward replay might subserve trajectory planning, backward replay could be involved in the evaluation of the preceding trajectory. Further insights would require the ability to detect and suppress specific place cell sequences in order to selectively disrupt trajectory replay (ideally discriminating between backward and forward replay) and

evaluate the consequences on learning and memory. Another crucial issue is whether ripple-mediated memory consolidation does involve the neocortex. While sleep ripples are coupled to cortical rhythms and reactivations and cortical slow oscillations have been causally linked to memory consolidation [57], direct evidence for a causal role of ripples in hippocampo-cortical transfer (as opposed to intra-hippocampal consolidation of memory traces) is still lacking. Closed-loop stimulation systems in rodents would allow to refine this finding by exploring more precisely the temporal relationships required between hippocampal and cortical activity for memory enhancement. A complementary option would be to selectively inactivate the cortical regions hypothesized to sustain long-term memories (such as the prefrontal and anterior cingulate cortices) during hippocampal ripples. These approaches will undoubtedly benefit from the recent development of optogenetic tools which allow increasingly precise spatiotemporal targetting of brain structures, cell types (e.g., [58]), or network properties (e.g., [59]).

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Part III
Cortical Neural Activity and Interaction with the Hippocampus

Chapter 8
Packets of Sequential Neural Activity in Sensory Cortex

Artur Luczak

Abstract Either spontaneously or in response to stimuli, neurons are active in a coordinated fashion. For example, an onset response to sensory stimuli usually evokes a 50–200 ms long burst of population activity. In this chapter, we summarize recent papers of the author showing that such bursts of neuronal activity are not randomly organized, but rather composed of stereotypical sequential spiking patterns. To underline this fine-scale internal organization of such population bursts, we will refer to them as "packets." It has been shown that packets are ubiquitous feature of spontaneous and stimulus-evoked network activity and are present across different brain states. Although these packets have a generally conserved sequential spiking structure, the exact timing and number of spikes fired by each neuron within a packet can be modified depending on the stimuli. In this chapter, we provide a detailed description of packets, and we discuss how the packet-like organization of neuronal activity may provide an explanation for multiple puzzling observations about neuronal coding. It is interesting to note that organizing population activity into packets resembles how engineers designed information transfer over Internet, where information is divided in small, formatted network packets to increase communication efficiency and reliability.

Keywords Auditory cortex • Somatosensory cortex • Population coding • Temporal coding • Upstate • Slow wave oscillation • Silicon microelectrodes • Brain state • Memory replay

Introduction

Progress in recording from a large number of neurons [1–3] allowed to advance our knowledge on how the activity of a single neuron is shaped by the action of other neurons [4, 5]. It has been found that even in the absence of external stimuli,

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population activity can exhibit complex self-organized patterns [6]. Its complex nature and general similarity with activity evoked by sensory input [7–10] suggests that spontaneous activity may play an important role in information processing [11, 12]. By studying spontaneous activity, a lot has been learned about the structure of cortical population spike patterns. During resting and sleep, cortical circuits (both in vitro and in vivo) spontaneously produce periods of activity known as "upstates" [13–17]. In vitro experiments have shown that neural activity within upstates has a sequential structure, with the order in which neurons fire largely conserved from one upstate to the next, reflecting the interaction of recurrent circuitry and intrinsic cellular dynamics [10, 18, 19]. Early evidence for sequentially structured spiking activity in vivo came from studies detecting the presence of precisely repeating spike motifs [20]. However, the statistical methods employed, as well as the long duration and high temporal precision of the detected motifs, have been controversial [21–23]. Recent analyses of in vivo population data have confirmed using straightforward statistical methods that population bursts such as upstates are indeed sequentially patterned for a period of the order of 100 ms, with temporal precision decaying as the upstate progresses [14].

Here we summarize a series of recent studies conducted by the author, describing the fine structure of sensory responses and spontaneous activity. By simultaneously recording from tens of neurons, it has been found that neuronal activity is composed of transient but coherent and structured bursts of population activity, which we termed "packets." Firstly, we will describe how packets contribute to the global structure of population activity. Next, we will analyze the sequential structure of packets and show how it is conserved across different brain states. We will then describe how sequential structure of packets encodes information about sensory stimuli. In the following sections, we will discuss possible mechanisms of packet formation and present a graphical summary of the main results. Lastly, we will describe how the concept of a packet can provide unifying model for neuronal coding, which binds together multiple seemingly contradictory observations about information processing.

Cortical Activity Is Composed of Population Activity Packets

The brain exhibits different patterns of activity depending on the behavioral state. On one extreme is a synchronized brain state which occurs during slow wave sleep or during deep anesthesia, where bursts of population activity called upstates are interspersed with periods of global neuronal silence (downstates) [17]. On the other extreme, when an animal is attentive to a task or stimuli, cortical activity is in desynchronized state, which is characterized by seemingly continuous population activity. This variability in cortical state can be also observed in quiescent waking animals [16, 24], which is illustrated in Fig. 8.1a. Note that even in a desynchronized state (Fig. 8.1a-bottom), population activity still exhibits coordinated 50–100 ms long

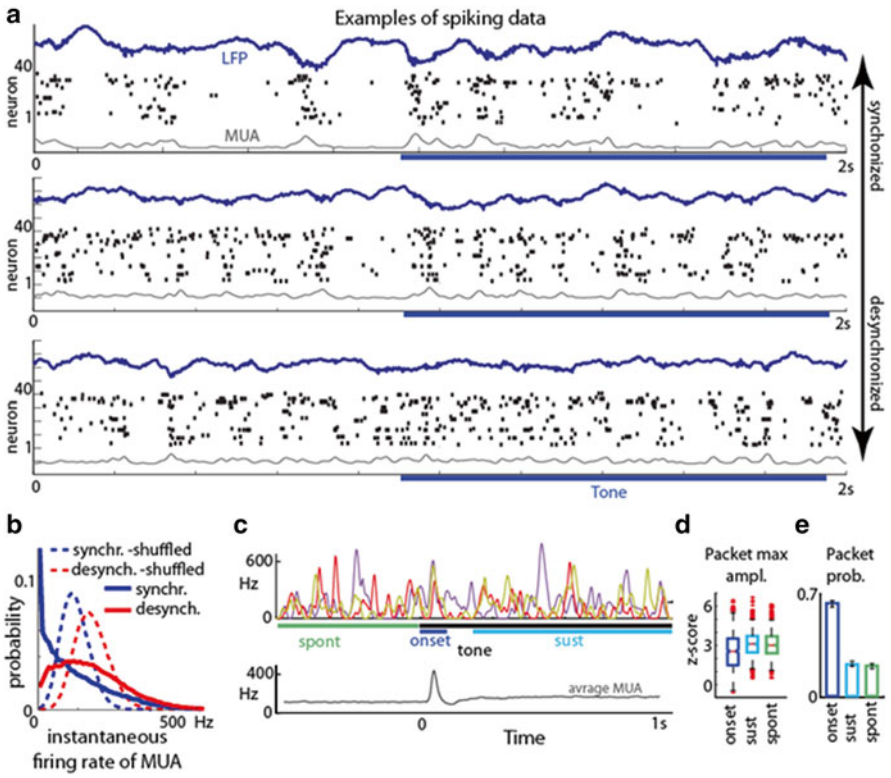

Fig. 8.1 Population activity in the auditory cortex shows coordinated bursts of activity (packets). (**a**) Examples of raster plots with periods of spontaneous activity followed by periods with tone presentation. Data recorded in auditory cortex in awake rat. Plots are sorted by cortical state. The raster shows spikes of simultaneously recorded neurons and the *blue trace* shows local field potential. At the *bottom* of the figure is the multiunit firing rate (MUA) computed as the smoothed summed activity of all neurons. Note that neurons tend to fire in transient bursts of 50–100 ms duration, with burst times including but not limited to tone onset. Activity during desynchronized states shows weaker global fluctuations but still exhibits complex fine structure. To visualize sequential activity within packets, neurons are sorted by latency in the same order in all three panels (see following section and Fig. 8.2f for more details). (**b**) Histogram of instantaneous MUA rates during sustained tone responses for desynchronized and synchronized trials. *Dotted lines* indicate the same analysis for trial-shuffled data. (**c**) *Top* of the panel shows examples of population rate on three single trials. Note that activity packets occur reliably at tone onset but sporadically during spontaneous and sustained periods. *Bottom* of the panel shows the trial-averaged population rate triggered at tone onset. (**d**) Box-and-whisker plots summarizing distributions of onset-evoked packets, and the distribution of amplitudes of the largest packets in the sustained and spontaneous periods. The central mark is the median, the edges of the box are the 25th and 75th percentiles. (**e**) Probability of occurrence of large activity packets (mean + 2 SD) during spontaneous, onset, and sustained periods. These analyses suggest that packets have similar amplitude for onset, sustained, and spontaneous periods but occur more reliably at stimulus onset. Figure reproduced from [24]

bursts which are also accompanied by a deflection of local field potential (LFP). These bursts are larger than expected from random fluctuation in firing rate, which is illustrated in Fig. 8.1b. This figure shows histograms of the distribution of population firing rate for the synchronized and desynchronized states (solid lines) as compared to trial-shuffled data (dashed lines) [24]. For synchronized data, the histogram (blue) shows a clear mode at 0, indicating the presence of prolonged down phases, and a "tail" corresponding to large bursts of activity. For desynchronized trials, the distribution of multiunit activity (MUA) was less skewed but still markedly different from the shuffled data, confirming the existence of smaller but still significant population bursts in the desynchronized state ($p < 0.001$ two-sample Kolmogorov-Smirnov test). We will call these population bursts "packets" to emphasize that each population burst has a fine-scale organization that carries stimulus-specific information, which we will describe in the following sections.

Activity Packets Occur More Reliably at Stimulus Onset but Are Not Larger than During Sustained or Spontaneous Periods

We will begin analyzing packets by looking at onset responses evoked by sensory stimulation. Figure 8.1c (top) plots the population rate in the auditory cortex for 3 trials with tone presentations. It suggests that the packets of activity accompanying tone onsets are not larger in amplitude than those occurring either within extended tone presentations or in silence. This might at first appear to contradict the fact that one sees clear onset responses when activity is averaged across multiple trials (Fig. 8.1c-bottom). The reason for this is that onset responses in averaged activity occur not because the activity packets triggered by tone onsets are larger than those occurring spontaneously or during sustained tone epochs but because activity packets are reliably evoked by tone onsets and occur at random times during sustained tone responses and spontaneous activity. To quantify this, we calculated, for each tone presentation, the height of the population rate peak after stimulus onset (0–100 ms), the height of the highest population rate peak in the preceding period of silence (−800–0 ms, to avoid offset responses from the previous tone), and the highest population rate peak in the sustained response period (200 ms–1 s after tone onset). Statistical test revealed that population rates at onset were significantly smaller than the highest peaks during 800 ms immediately before or after onset response at each trial (Fig. 8.1d; rates are expressed as z-scores to combine data from different experiments; $p_{\text{onset-sust}}$, $p_{\text{onset-spont}} < 0.0001$; $p_{\text{sust-spont}} = 0.2$, two-sample Kolmogorov-Smirnov test; [24]). This indicates that the population was typically more active at some moment during the sustained period or silence preceding each tone than at onset. However the probability of seeing an activity packet (measured as an instantaneous MUA rate larger than the mean + 2 SD) was significantly higher at onset as compared to any time point during spontaneous or sustained periods

(Fig. 8.1e). To verify that these results did not simply occur from occasional random spiking coincidences during the sustained and spontaneous periods (which are longer than the onset periods), we performed the same analyses on trial-shuffled data. This confirmed that the detected activity packets reflected true synchronous firing events [24]. Therefore, we concluded that the onset responses seen in activity averaged across trials reflect a stimulus-locked increase in the probability of activity packets, rather than an increase in their size.

Similarity of Sequential Spiking Activity of Stimulus-Evoked and Spontaneous Packets

So far we have only looked at population activity which reflects the sum of activity of all recorded neurons. Next, we will examine more closely the activity of individual neurons within packets and begin again by analyzing onset responses. Figure 8.2a–c shows raster plots and superimposed peri-event time histograms (PETHs) of three individual neurons in response to five different tones. Although the firing rate evoked in any given neuron varied with tone frequency, PETH shapes were largely conserved across tone frequencies. However, between neurons, PETH shapes differed considerably. To quantify the preservation of temporal structure across stimuli, we computed for each PETH a mean spike latency (MSL), defined as the mean spike time in the 100 ms after stimulus onset [9]. Figure 8.2d plots each neuron's MSL to its preferred tone frequency versus its average MSL to all other tones. For neurons with short latency (MSL below 40 ms for best frequency), the majority of points are below the diagonal, suggesting that for such neurons preferred stimuli often induce earlier firing ($p<0.001$, paired Wilcoxon signed rank test). Robust correlation between MSL for preferred and non-preferred tones (mean $R=0.72\pm0.24$; $p<0.001$) confirms that temporal profiles are diverse between neurons and largely conserved within the responses of each cell to different tones. Thus, if a neuron is driven to fire in response to a given tone, it will do so with a stereotyped cell-specific temporal profile but with precise timing and firing rate affected by stimuli.

Next, we asked whether spike patterns within spontaneously occurring packets are also temporally structured as packets evoked by sensory stimuli. Figure 8.2e (top) shows raster plots of two of the individual neurons' responses evoked by tone onset, and Fig. 8.2e (bottom) shows average activity of 30 simultaneously recorded neurons to tone stimuli. For comparison, Fig. 8.2f shows raster plots and PETHs of the same neurons as in Fig. 8.2e, triggered at the beginning of spontaneously occurring packets (upstates). Again, a similar sequential ordering was seen. To statistically confirm this similarity, a slightly different approach was used, as the beginnings of spontaneous packets are not experimentally controlled. To measure a cell's position in the firing sequence within a packet, we defined a measure μ_{cc}, the center of mass of its cross-correlogram with the summed activity of all other neurons within

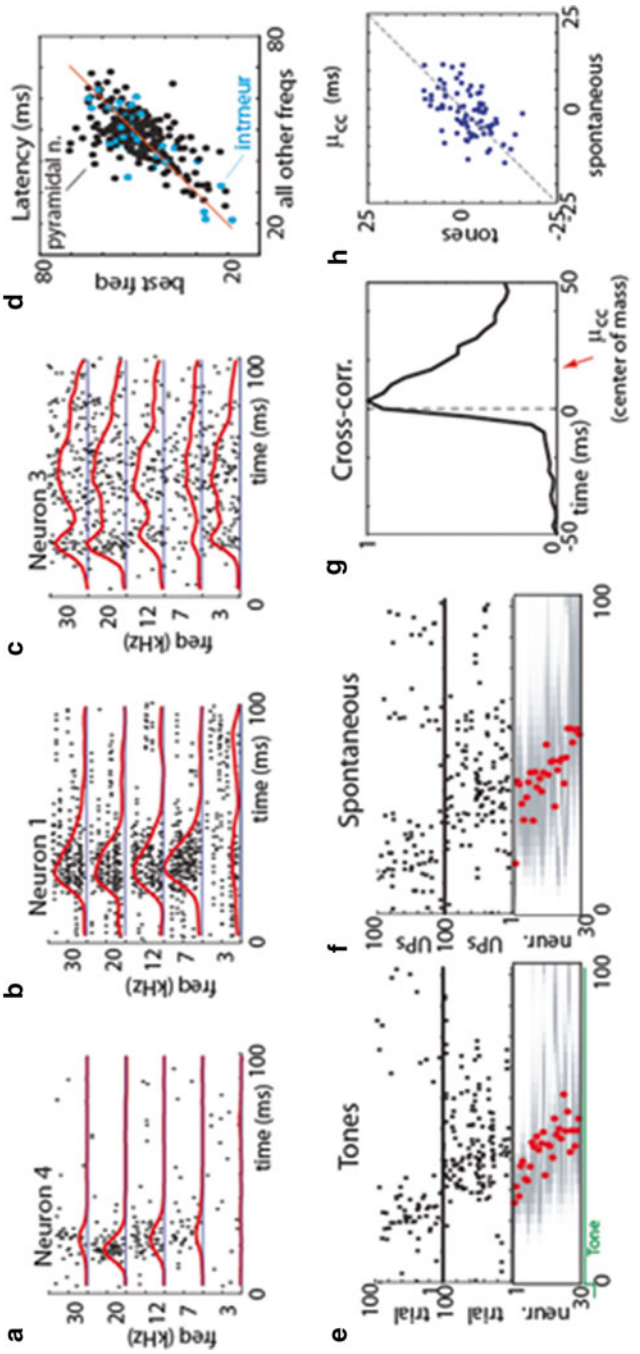
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Fig. 8.2 Similarity of stimulus-evoked and spontaneous packets of sequential spiking activity. (**a–c**) Raster plots showing responses of representative neurons to presentations of 5 pure tones (100 trials for each tone). *Red lines* represent peri-stimulus time histograms. It shows that individual neurons respond to different tones with stereotyped temporal profiles but varying firing rates. (**d**) Scatterplot showing each neuron's mean spike latency to its preferred tone frequency versus to all other tones. The *red line* corresponds to equal latencies. *Blue dots* represent putative interneurons as defined by spike width. While neurons typically show earlier firing to their preferred tone, this difference is an order of magnitude smaller than the differences between cells. (**e**-*top*) Raster plots showing spike times for two representative neurons to repeated presentations of a pure tone stimulus. (**e**-*bottom*) Average activity of 30 simultaneously recorded neurons to tone stimuli. *Gray bars* show pseudocolor representations of each neuron's peri-event time histogram (PETH); *red dots* denote each neuron's mean spike latency in the 100 ms after tone onset. Neurons are ordered vertically by the mean latency over all stimuli to illustrate sequential spread of activity. (**f**) Raster plots and average activity for the same neurons as in panel (**e**), triggered by upstate onsets. Note the similar temporal pattern to panel (**e**). (**g**) Normalized cross-correlograms of one neuron's spike times with the summed activity of all other cells. *Arrow* shows the center of mass (mean spike time) of correlograms (μ_{cc}). (**h**) Conservation of μ_{cc} across different stimuli and spontaneous events, indicating preservation of sequential order. Each point represents the values of μ_{cc} for a given cell in the conditions indicated on the axes. Reprinted from Neuron, 62(3), Luczak A, Barthó P, Harris KD, Spontaneous events outline the realm of possible sensory responses in neocortical populations, 413–425, copyright 2009, with permission from Elsevier

±50 ms (Fig. 8.2g; see Experimental Procedures in [9]). Values of μ_{cc} were correlated between spontaneous events and stimulus classes, demonstrating that firing order is consistent between stimulus-evoked packets and spontaneous packets (Fig. 8.2h; $R_{\text{unanesth: spont-ton}} = 0.53 \pm 0.17$; $p < 0.001$). Similar consistent temporal patterns were also observed in the somatosensory cortex [9] and in the visual cortex [25] indicating that the sequential structure of spontaneous and evoked packets is a general feature of cortical processing.

Sequential Packet Structure Is Robust with Respect to Different Brain States

Patterns of population activity can change substantially with brain state as illustrated in Fig. 8.1a (compare top and bottom rasters). Does this change in population pattern also affect the internal structure of packets? To investigate this question, we again employed cross-correlation analyses between a single neuron and MUA as illustrated in Fig. 8.2g, i. We found that cross-correlograms calculated separately during synchronized and desynchronized brain states had similar temporal profiles. Figure 8.3a, b shows the cross-correlograms for 45 neurons recorded simultaneously, with the order of neurons sorted by μ_{cc} measure in the synchronized state and the desynchronized state, respectively. μ_{cc} was strongly correlated between these states (Fig. 8.3c; $R = 0.67 \pm 0.23$ SD). This shows that packets in the synchronized and desynchronized states have largely preserved sequential spiking patterns. This also suggests that activity in both states is composed from the same type of packets, but in a desynchronized state, the time between consecutive packets decreases and creates an impression of continuous spiking patterns.

Relation to Local Field Potential (LFP)

The above analyses have indicated that a given neuron fires with largely stereotypical timing relative to the 50–100 ms long activity packets regardless of brain state. Because summed population activity is strongly correlated with the (negative) local field potential (as seen in raw data in Fig. 8.1a), we would expect that a neuron's timing with respect to these packets was related to its phase of firing with respect to the LFP. Figure 8.3d shows examples of the cross-correlogram of the same neuron with MUA (equivalent to spike-triggered MUA) and with LFP (Fig. 8.3e) in the synchronized and desynchronized states. It shows that this neuron fired after the majority of other neurons and after the maximum deflection in LFP in both states. The relationship between the μ_{cc} measure and LFP phase for simultaneously recorded neurons is presented in Fig. 8.3f; $R_{syn} = 0.73 + 0.17$ SD, $p_{syn} < 0.05$, circular-linear correlation [26]. It indicates that the importance of spike timing in relation to the LFP phase which was recently reported [27] could be the consequence of the sequential organization of activity packets.

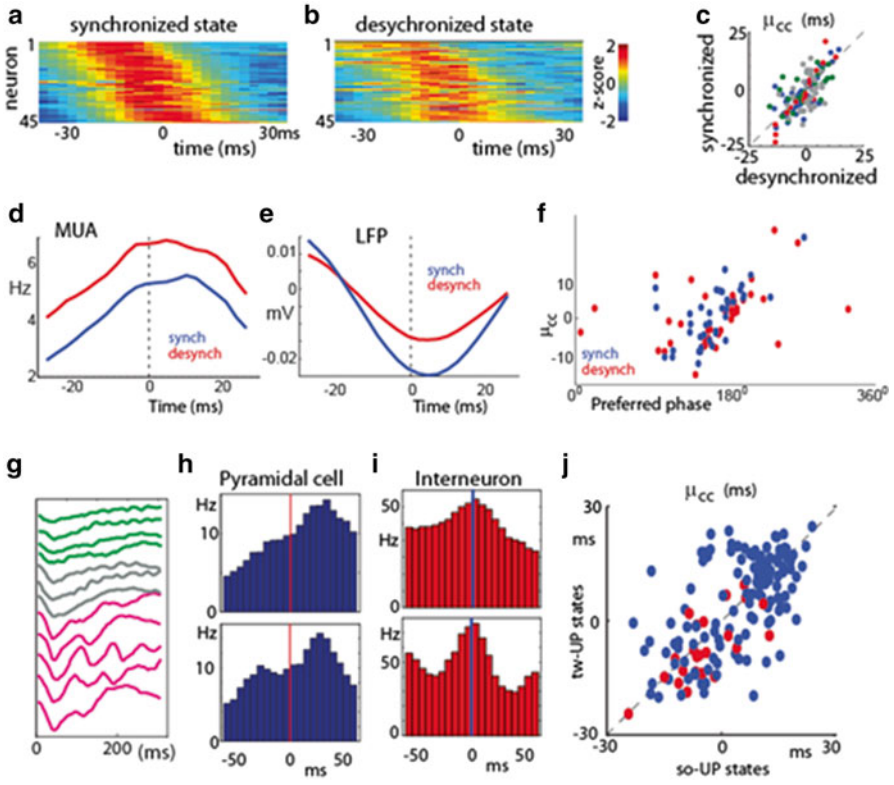

Fig. 8.3 Sequential spiking order within packets is preserved across different brain states. (**a**, **b**) Pseudocolor representation of CCGs for all neurons of a representative experiment, during synchronized (**a**) and desynchronized (**b**) periods. Each *horizontal line* of the pseudocolor matrix corresponds to the CCG of one neuron, vertically arranged in the same order for each plot, according to the value of μ_{cc} in the sustained period. For visualization, CCGs are normalized to mean 0 and unit variance. (**c**) μ_{cc} for each neuron calculated during sustained tone responses, in synchronized and desynchronized trials. Neurons from different animals are shown with different colors. The distribution of points along the *equality line* shows that each neuron's temporal relationship to the population is preserved across states. (**d**) Spike-triggered MUA histogram for an example neuron and (**e**) spike-triggered LFP for the same neuron during synchronized (*blue*) and desynchronized (*red*) brain state. Note that the (negative) peak of this curve occurs at a similar time to the peak of the spike-triggered MUA in panel d. LFP was band-pass filtered between 8 and 12 Hz. (**f**) Relation between μ_{cc} and mean LFP phase at 8–12 Hz. Each dot represents a single neuron. It shows that the phase relationship of spike timing to LFP mirrors the timing relationship to population activity. (**g**) Representative examples of upstate-triggered LFPs sorted by first peak amplitude from a single shank. (**h**) Cross-correlogram between a single neuron and multiunit activity during first 150 ms of upstates for putative pyramidal cells (activity of the analyzed cell is triggered at multiunit activity spikes). Note that each cell has a different timing relation to multiunit activity but that the timing relation is similar for upstates with and without 12 Hz modulation. (**i**) The same analysis for putative interneurons. As compared to putative pyramidal cells, putative interneurons show a less diverse timing in relation to multiunit activity. (**j**) Comparison of latencies calculated for upstates with and without 12 Hz modulation (latency is defined as the center of mass of the cross-correlogram; [28]). *Red* and *blue dots* denote putative interneurons and putative pyramidal cells, respectively. Distribution of points along the identity *line* (*dashed*) shows that regardless of upstate type, neurons have a consistent temporal relation to population activity. Figure reproduced from [24, 28]

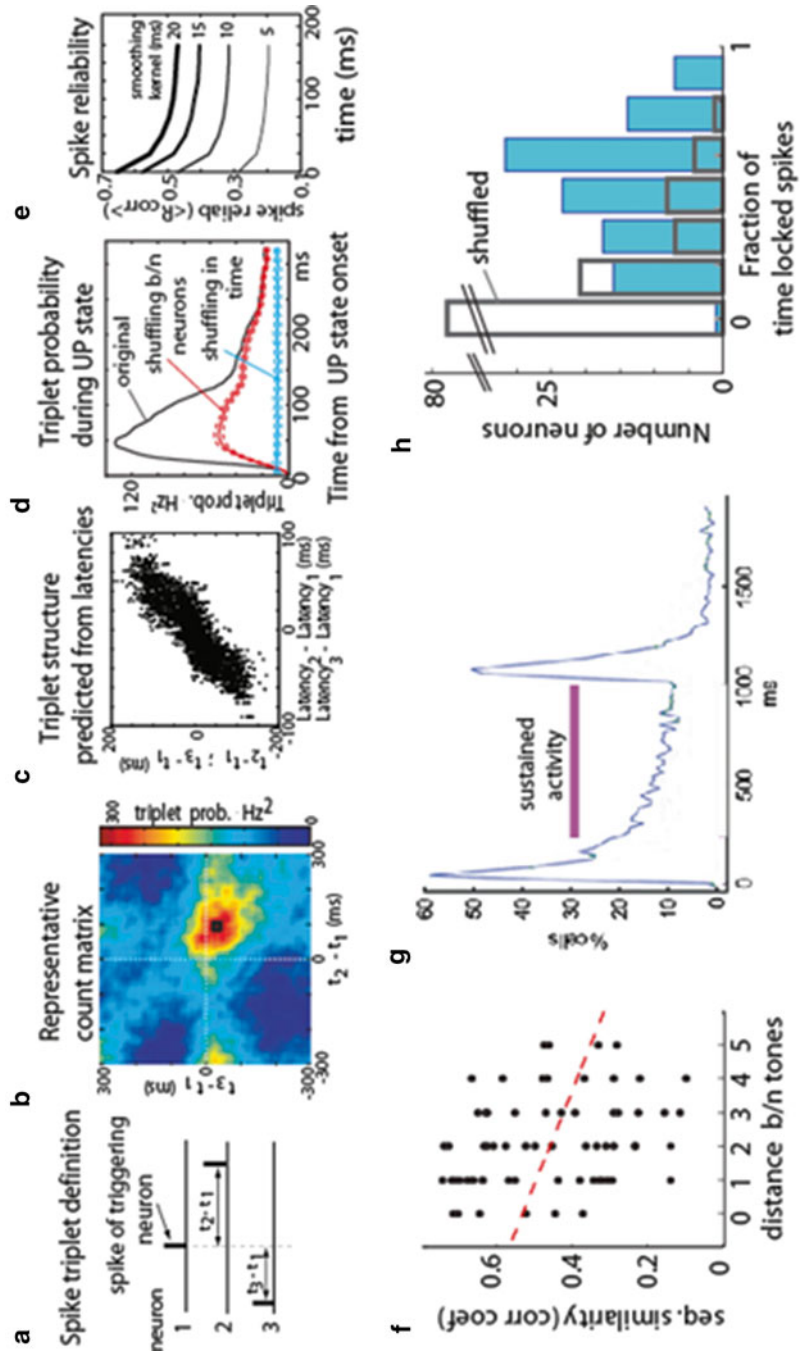
a
Spike triplet definition
spike of triggering neuron
neuron
1
2
3
t2-t1
t3-t1
b
Representative count matrix
triplet prob. Hz2
t3 - t1 (ms)
t2 - t1 (ms)
c
Triplet structure predicted from latencies
t2-t1 ; t3 - t1 (ms)
Latency2 - Latency1 (ms)
Latency3 - Latency1 (ms)
d
Triplet probability during UP state
original
shuffling b/n neurons
shuffling in time
Tripletprob. Hz2
Time from UP state onset
ms
e
Spike reliability
smoothing kernel (ms)
20
15
10
5
spike reliab (<Rcorr>)
time (ms)
f
seq. similarity (corr coef)
distance b/n tones
g
sustained activity
%cells
ms
h
shuffled
Number of neurons
Fraction of time locked spikes

Fig. 8.4 Spike precision and information coding within packets. (**a**) For every trio of neurons, a spike triplet is described by two inter-spike intervals (t_2–t_1 and t_3–t_1). (**b**) Count matrix for a representative triplet of neurons, indicating the probability of different ISI combinations. *Black square* denotes triplets occurring within ±10 ms of the mode. (**c**) Triplet structure reflects individual neural latencies. Each triplet is represented by two points: (latency of neuron 2–latency of neuron 1 and latency of neuron 3–latency of neuron 1). The strong correlation indicates that the structure of the triplets is predicted by the sequential structure of packets. (**d**) Occurrence of precisely repeating triplets peaks shortly after the start of UP states. *Blue* and *red curves* denote shuffled data for independent Poisson and common excitability models, respectively (the *dashed lines* indicate SD; [14]). (**e**) Spike timing reliability measure decays as a function of time after packet onset. Line width indicates the size of smoothing kernel. (**f**) Sequential structure of activity packets depends on tone frequency. Sequential similarity was measured as the correlation coefficient of μ_{cc} across the population for all pairs of tone frequencies. Note that the greatest similarity is seen between responses to different presentations of the same frequency (distance 0), whereas a smaller but nonzero similarity is seen for widely separated tone frequencies (distance 5). (**g**) Percentage of cells in the auditory cortex showing significant excitatory response to at least one tone stimulus, as a function of peri-stimulus time [54]. *Purple line* denotes sustained epochs. (**h**) Fraction of spikes, time-locked to population activity during sustained periods of tone presentations. Higher spike-locking values for the majority of neurons as compared to shuffled data (*gray line*) show that during sustained period neurons prefer to fire spike time-locked to packets [24]. Figure reproduced from [14, 24]

Relation to Spindle Activity

Another example of strongly preserved sequential packet structure can be found in somatosensory cortex of ketamine-anesthetized rats, where population activity patterns occurring at ~1 Hz can switch to faster ~12 Hz oscillatory patterns (spindles) [28]. Figure 8.3g illustrates representative examples of upstate-triggered LFPs during periods with and without 12 Hz oscillations (denoted by pink and green colors, respectively). To examine in more detail the temporal relationship between neurons' activity during different types of upstates, for each neuron, we calculated its cross-correlogram with MUA, as described in the previous section. Figure 8.3h, i shows such sample cross-correlograms for both periods, for representative pyramidal cell and for representative interneuron, respectively [29]. Cross-correlograms had similar skewness for upstates with and without 12 Hz modulation, which was also the case for the majority of recorded neurons (Fig. 8.3j; $R = 0.59$, $p < 0.01$). This shows that even with drastic changes in oscillatory brain activity, temporal relations between neurons with ± 50 ms window are remarkably stable, suggesting highly conserved sequential structure within packets.

Spike Precision and Information Coding

Precisely Repeating Spike Triplets

We have seen that neurons display consistent temporal relationships within packets, indicating that certain precise spike patterns should occur above chance level. Precisely repeated spike patterns have been reported in a number of cortical systems [10, 18, 19, 29–31], although the interpretation of these results has been controversial [21, 23]. We hypothesized that the consistent timing of individual neurons in relation to the onset of a packet could account for precisely repeating spike patterns seen at the population level. Confirmation of this hypothesis would provide both convincing evidence for the precise repetition of spike patterns and a simple explanation for it.

For computational tractability, we restricted our search to spike triplets occurring across three distinct cells [32] (Fig. 8.4a). For each cell trio, one cell was designated the trigger for calculation of the joint distribution of spike times of the other two [32]. Often, a clear mode was seen in these plots, suggesting that a particular sequence occurred preferentially (e.g., Fig. 8.4b). The location of the mode could be predicted from the neurons' individual latencies to packet onset (Fig. 8.4c). Note that spiking precession is not within 1 ms; therefore these results are not fully consistent with the concept of "synfire chains" which generally implies repeating patterns to have a millisecond-level precision [20]. Repeating triplets (defined as those whose inter-spike intervals (ISIs) were within ±10 ms of the mode, indicated by the black square in Fig. 8.4b) occurred preferentially shortly after UP state onset (Fig. 8.4d), with the highest precision of spikes at the beginning of the packets (see

Fig. 8.4e showing reliability of spiking over time; method adopted from [33]). This finding is consistent with [34] where the highest spiking precision was found shortly after stimulus onset and decreased thereafter. Therefore, we conclude that the timing and structure of repeating triplets is predicted by the relationship of individual neurons to packet onsets.

Temporal and Firing Rate Coding Within Packets

It is well documented that sensory stimuli can affect spike timing, especially for onset responses (see Fig. 8.2a or, e.g., [35]), but it is not clear if packets also show modification of temporal structure depending on stimulus. Thus, we next asked whether different tone stimuli caused variations around this common sequential structure. To test this idea statistically, we assessed the similarity of the sequential structure between the first and second half of the data set. Figure 8.4f shows the mean sequence similarity as a function of distance between frequencies, based on tonal order. Sequences become less correlated with increasing frequency difference between tones (Fig. 8.4f; $R = -0.22 \pm 0.08$ SD) which was not observed for shuffled data [24]. Thus, as observed with onset responses, even during sustained periods, the packets have a broadly conserved 50–100 ms sequential structure, but this structure exhibits further variations depending on tone frequency.

It is also well documented that information about external stimuli can be encoded by the firing rates of neurons. Closer examination of population activity revealed that in response to preferred stimuli, a neuron fires additional spikes but only when it is coordinated with the activity of other neurons. As an example, let's consider the population activity during sustained tone presentations which is composed of packets of activity as illustrated in Fig. 8.1. Theoretically, the extra spikes evoked by preferred stimuli could occur uniformly throughout the tone presentation, without regard to global network activity, or alternatively, extra spikes could occur specifically during packets of high network activity ("time-locked" to packets). To address this question, we estimated the fraction of spikes locked to packets during sustained tone presentation (Fig. 8.3g). For this, we used a measure-based MUA cross-correlogram with single neuron activity normalized by an autocorrelogram (for details, see [24]). Figure 8.3h shows values of the fraction of spikes time-locked to packets, which is significantly larger than would be expected for trial-shuffled data ($p < 0.001$). Thus, this analysis suggests that the additional spikes a neuron fires in response to its preferred tone are primarily occurring at neuron-specific timing within packet.

Possible Mechanisms of Packet Formation

Sequentially structured activity packets are seen in computational models of cortical circuits [36–38], in cortical slices [10, 19, 39], as well as in response to sensory stimuli in vivo [9]. We found that population responses to different stimuli are

subject to conserved spatiotemporal constraints, consistent with results in other modalities indicating conserved timing patterns in pairwise cross-correlograms [25]. One can imagine a number of ways in which the physical properties of a neural circuit could impose consistent constraints on the spike patterns it can generate. Firstly, cortical neurons have diverse intrinsic physiological properties [40–42] which may contribute to the consistent cellular timing which we and others observed [14, 43]. For example, cells with lowest threshold could be firing earliest in sequence [44]. Secondly, connectivity within cortical circuits is far from homogenous, for example, with strong reciprocal connectivity occurring more than expected by chance [45], suggesting that the stereotypical temporal structure of cortical activity packets may be also imposed by the connectivity of the cortical microcircuit. We suggest that these activity patterns are the functional manifestation of "default microcircuits"—local patterns of connectivity that impose similar spatiotemporal constraints on spontaneous and stimulus-evoked flow of activity, as illustrated in cartoon form in Fig. 8.5a [46].

Summary Illustration of Packets

Our main findings can be summarized by Fig. 8.5. Connectivity and cellular properties of neurons impose constraints on types of spiking patterns which can be produced by the local circuit (Fig. 8.5a). Thus, certain activity patterns will be more likely to emerge than other patterns (Fig. 8.5b-left). This can be illustrated as geometrical interpretation, where each population spiking pattern is represented as a single point (Fig. 8.5b-center). Experimentally observed spontaneous patterns are confined only to a small subregion of space of all possible patterns. Stimulus-evoked patterns are subject to the same circuit constraints and form subspace within spontaneous patterns [9]. Each type of stimuli results in a different firing rate of neurons, and to a smaller degree different timing, but with preservation of the overall structure within the activity packet (Fig. 8.5b—right).

In synchronized states, stimulus onsets usually evoke reliable activity packets with a duration of 50–100 ms, and similar packets occur irregularly during sustained tone responses and spontaneously (Fig. 8.5c). As described above, these packets have a broadly preserved sequential structure across stimuli and across onset, sustained, and spontaneous periods. However, both the firing rates and precise timing of the constituent neurons can vary with stimulus type (Fig. 8.5b-right). The additional spikes fired in response to preferred stimuli occur within packets rather than spread evenly throughout the stimulus duration. In desynchronized states, fluctuations in population rate are reduced, but timing relationships between neurons remain preserved (Fig. 8.5d). This suggests that population activity is built from discrete packets whose content conveys information about the stimulus, occurring reliably at onset and irregularly at other times, with desynchronized activity consisting of multiple overlapping packets rather than continuous, unstructured activity as previously assumed.

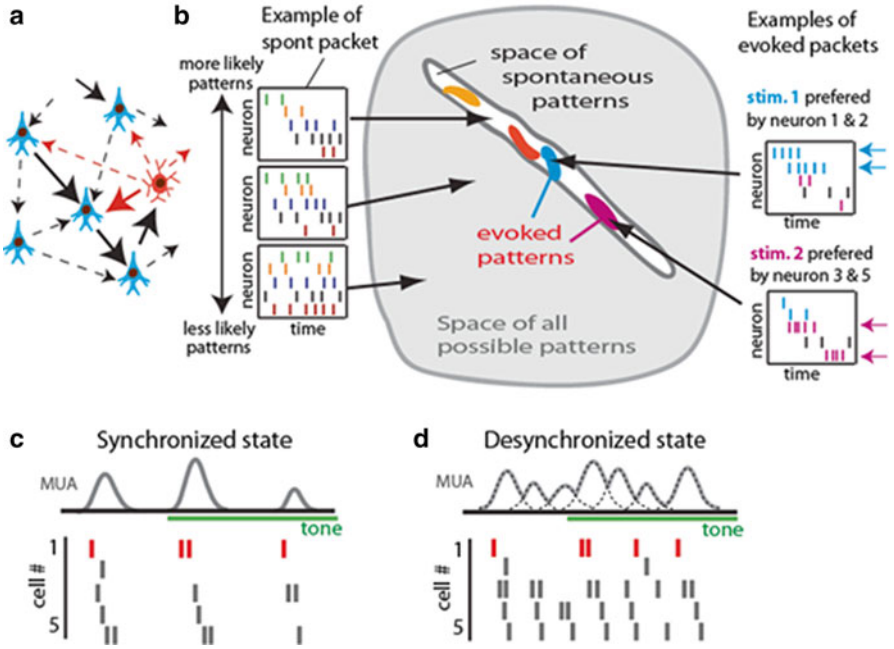

Fig. 8.5 Activity packets in graphical summary. (**a**) Cartoon illustration of the possible mechanism of packet formation. Due to constraints on connectivity, different inputs will result in similar spiking activity, which propagates preferentially through the strongest connections (*solid arrows*) embedded in a pool of weaker connections (*dashed arrows*). As a consequence of the connectivity pattern of the network, certain activity patterns are more likely to occur than others as illustrated in panel (**b**) (*left side*). (**b**-*center*) Cartoon illustrating the geometrical interpretation of our findings. The *gray* area illustrates the space of all spiking patterns theoretically possible for a packet. The *white area* represents the space of spontaneous packets; this is shown elongated and of small volume to illustrate strong constraints on patterns of activity imposed by a network. Packets evoked by different stimuli occupy smaller subsets within this (*colored blobs*). (**b**-*right side*) Illustration of stimulus-evoked packets. The overall structure of evoked packets is similar to the spontaneous packets; but the firing rate, and to a smaller degree, the spike timing of neurons, encodes information about stimulus identity. (**c**) Packets of population activity in a synchronized state are separated by periods of global silence. Tone onset reliably induces an activity packet, but packets also occur sporadically throughout the sustained and spontaneous periods. Within each packet, neurons fire with a stereotyped sequential pattern. Presentation of a neuron's preferred tone causes that neuron to fire at higher rates (*red*) but only during specific phase of activity packets. (**d**) In a desynchronized state, population activity does not show long periods of silence, but temporal relationships between neurons are similar to those in the synchronized state. This can be explained by a model in which many packets, individually similar to those seen in the synchronized state, are superimposed to produce a firing pattern that exhibits smaller fluctuations in global activity but retains a fine temporal structure. Figure reproduced from [24, 46]

Packet Structure May Explain Multiple Puzzling Observations About Neuronal Coding

Below we address the significance of packets. We list some of the most puzzling phenomena about neuronal coding, and we discuss how it could be understood in light of the sequential structure of packets. We argue that the "packet theory" presented here could provide a unifying concept on how information is processed in the brain.

- A packet structure provides time reference for temporal coding. It was shown that precise timing of spikes after stimulus onset can provide information about stimulus identity [35, 47]. Although an experimenter knows what the exact time of a stimulus onset is, it remains unclear how the brain could access this information to use spike timing in reference to onset. It was proposed that there could be neurons always firing with the same latency to any stimuli, thus providing reference for decoding information from spikes in which timing differs with stimuli [48]. Considering that many natural stimuli change gradually and do not have well-defined sharp onset, the above-described mechanism may not have general applicability. On the other hand, assuming that there exists a "typical" or "default" sequential activity pattern imposed by cortical microarchitecture, any variation in timing among neurons in this sequence can encode stimuli. Therefore, the "default" temporal structure of a packet can provide reference for the brain to interpret the timing of neurons.
- Packets show how temporal and firing rate coding coexists. As illustrated in Fig. 8.5b-right, in response to preferred stimuli, a neuron fires more spikes, but it is mostly restricted to the neuron-specific phase within a packet.
- Packets and cell assembly hypothesis. The idea introduced by Donald Hebb in the 1940s [49] proposes that neurons are active collectively in groups produced by Hebbian plasticity. Furthermore, Hebb postulates that different stimuli are represented by unique neuronal assemblies with completely different temporal patterns depending on task or stimulus. However, evidence for the conserved structure of packets necessitates a partial revision of Hebb's theory. Specifically, conserved activity patterns imply that *neuronal assemblies are like a variation on a one master theme rather than unique themes* for each stimulus or object. For example, auditory neurons in Fig. 8.5b (right) respond with similar temporal sequences to different tones, although each tone evokes a different variation of that pattern [9].
- Stereotypical activity within packets provides an explanation as to why precisely repeated spiking pattern can occur significantly more often than expected by chance [20, 29].
- Preplay. In behaving animals, task-induced patterns of neuronal activity are replayed during following rest which is believed to be a hallmark of memory formation [50]. Recent studies have shown that replayed patterns are also similar to spontaneous patterns that precede behavioral task. This phenomenon is termed

"preplay" and was elegantly shown in the hippocampus by [51]. Similarly, in ([52], Figure 1, 2007), the pre-task spiking patterns in the medial prefrontal cortex have an obvious similarity to patterns during the task and patterns replayed after the task. The data presented here is consistent with these results. Due to the connectivity constraints of local microcircuits, new experience does not create completely different patterns, but rather creates modification of existing patterns. Such task-induced gradual change of existing spiking patterns results that general structure of activity packets is preserved [53]. Also note that the timescale of preplayed and replayed patterns spanning up to a few hundred milliseconds is similar to the duration of packets. Thus, we hypothesize that memory replay could be the manifestation of described here packets carrying information about past experience.

Function of Packets

What could be the function of the sequential structure of packets? One perspective could be that it has no function as the system has to generate sequential patterns given the constraints imposed by network connectivity [46]. A different possibility from an engineering point of view could be that dividing neuronal activity in packets could serve similar function as Internet protocol (IP) packets, where splitting data in small chunks with a specific format improves communication efficiency and transmission reliability. Indeed, it was observed that in the brain constraining spiking activity to small temporal windows (e.g., only to a negative phase of underlying oscillatory activity) can improve information transfer between areas by synchronizing neuronal firing, and that mechanism is commonly used across the brain [11]. Moreover there are evidences that sequential organization of activity within packets may also have functional significance. For instance, broad tuning and highest spiking precision at the beginning of a packet may be designed to signal the beginning of a message with only general information about stimuli (roughly analogous to header of IP packets). Consequently, later activity within a packet may contain more precise information. Indeed, it was observed that activity that occurred later after stimulus onset is more stimulus specific, with finer tuning of neurons [54, 55], likely due to top-down modulation [56]. In result, our perception of continuous stimuli may be an illusion, as cortical activity may carry information not continuously, but rather in a form of discrete and structured packets.

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Chapter 9
Coordinated Sequence Replays Between the Visual Cortex and Hippocampus

Daniel Christopher Haggerty and Daoyun Ji

Abstract Based on our previously published study, in this chapter, we discuss the interaction between the hippocampus (CA1) and primary visual cortex (V1) in the acquisition and consolidation of memories with an emphasis upon how this study supports, and expands upon, contemporary memory theories. Both CA1 and V1 neurons were shown to contribute to the acquisition of hippocampal-dependent episodic memory and to the memory consolidation process during slow-wave sleep. V1 neurons also participate in hippocampal-*independent* remote memory function following consolidation. Thus, V1 neurons appear to be tuned to both external stimuli and internal memories. These data not only support key elements of contemporary memory theories but also provide fresh, new insights into the consolidation process. Our findings also raise important questions with regard to the distinctions between sensory and memory circuits.

Keywords Memory consolidation • Replay • Visual cortex • Hippocampus • Slow-wave sleep • Place cells

Introduction

The hippocampal formation is critically involved in episodic memory formation [1]. Damage to the hippocampus in humans, for example, in the well-known case of Henry Molaison (patient H.M.), can lead to profound memory deficits [2]. Patient H.M. underwent surgery to remove the foci of his intractable epilepsy, which resulted in the near complete bilateral lesion of his hippocampi. Although the surgery proved successful in alleviating his epileptic seizures, patient H.M. was left with two debilitating—yet revealing—symptoms. First, H.M. was left with anterograde amnesia, a condition that rendered him unable to remember any new information presented to him. Second, H.M. had lost most of his relatively *recent* memories

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for the last few years prior to the surgeries, a condition known as temporally graded retrograde amnesia [2, 3]. Interestingly, H.M. *was* able to remember *remote* memories from his distant past [2, 3]. The preservation of remote memory in patients such as H.M. leads to the conclusion that brain areas other than the hippocampus, presumably cortical regions, are also involved in memory function. H.M.'s revealing postsurgery pathology is indicative of a role for both hippocampal and cortical involvement in memory formation. As a result, several influential and interrelating theories of memory processing have emerged—based upon earlier theoretical works by David Marr on the proposed functions of the neocortex [4] and hippocampus [5]—including the complementary memory systems theory [6], the hippocampal indexing theory [7], and the two-stage memory processing model [8, 9]. In order to better understand hippocampal-cortical interactions that underlie memory function, we shall take a brief look at each of these models.

Complementary Learning Systems Theory

Complementary learning systems theory is based on the premise that both the hippocampus and the cortex are required for efficient memory formation and that the learning process is complicated by the fact that the two brain areas not only learn at different rates but that they are also functionally divergent [6]. Principal cell synapses in hippocampal region are highly plastic and, thus, more suited for the rapid acquisition of memories. Typical behavioral experiences, which take place rapidly and normally only once, necessitate the employment of a fast-learning brain area, such as the hippocampus, which can encode memories in an episodic spatiotemporal fashion. Complementary learning systems theory also posits that important knowledge previously acquired—i.e., that knowledge which is already stored within the cortex—needs to be relatively resistant to change. Therefore, the cortex displays a significant inertia toward synaptic modification, thereby preserving the fidelity of memories stored within the cortex from interference by the often-trivial goings-on in the external world. But the cortex *is* modifiable; rather, it requires a more repetitive reinstatement of experience for embedding memories. Because the cortex is already home to previously learned knowledge, this iterative process of memory encoding in the cortex takes place by interweaving new knowledge with the old [6, 10, 11]. New and salient "threads" of information selected for incorporation into an important conceptual framework integral for normal brain function need to be woven carefully into the preexisting cortical fabric of knowledge. This deliberate and conservative interweaving process—as part of the consolidation process—ensures that the new information is incorporated not only into the appropriate conceptual framework but also that the function of the relevant preexisting conceptual framework is improved, not degraded, by the integration of the new information.

In short, the complementary learning systems theory suggests that the hippocampus takes care of the moment-to-moment encoding of external information—whether salient or not—and the cortex provides the substrate for the integration of

salient information into preexisting conceptual frameworks. In this manner, the hippocampus acts as a "buffer to guard against inappropriate plasticity within the precious cortical processing system" [6]. However, this proposition does leave us with some explaining to do. First, how does the hippocampus "store" a memory of a cortically represented conscious experience? Second, by what mechanism does the locus of memory shift from hippocampus to cortex over time? Hippocampal indexing theory addresses the first question, which we shall discuss next.

Hippocampal Indexing Theory

Hippocampal indexing theory was developed in the mid-1980s [12, 13] and was proposed to describe the mechanism by which the hippocampus encodes widely distributed cortical representations of the external world in a reliable manner with considerable spatiotemporal efficacy (see reference [7] for a recent review). During a typical behavioral experience, the processing of multimodal sensory information is carried out by a distributed array of cortical modules (see Fig. 9.1). The moment-to-moment changes in the cortical arrays involved in carrying out sensory

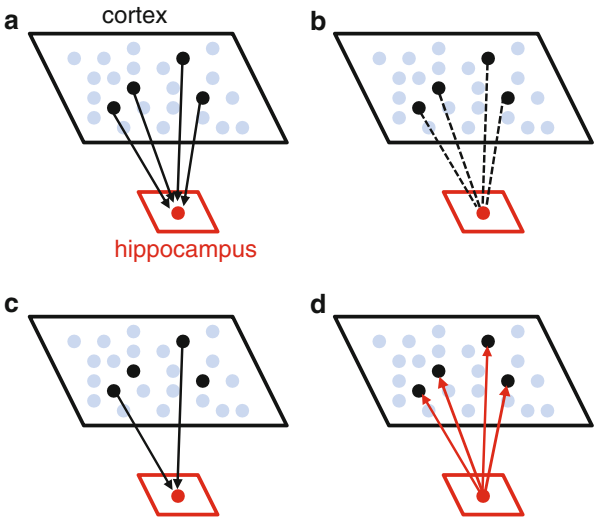

Fig. 9.1 The hippocampal and cortical interaction as proposed by hippocampal indexing theory. A broadly distributed cortical representation of the external world (**a**) is conveyed to the hippocampus via a reciprocal polysynaptic pathway. The memory for this cortical representation is encoded or indexed by the strengthening of hippocampal synapses (**b**). As a consequence, even a partial activation of the original cortical representation (**c**) can activate the hippocampal indexing ensemble and, as a result, reactivate the entire cortical ensemble of the original representation (**d**). Adapted with permission from Teyler TJ, Rudy JW. The hippocampal indexing theory and episodic memory: updating the index. Hippocampus. 2007;17:1158–69. Copyright 2007 Wiley-Liss, Inc

processing are responsible for the ever-changing phenomena of perception. In order to collate this broadly distributed activity into a single spatial and or temporal memory, the cortical activity is funneled through the entorhinal cortex—the gateway between the hippocampus and cortex—and into the hippocampus. At the terminus of the polysynaptic pathway from the cortex to hippocampus, a unique set of synapses are strengthened on the target hippocampal pyramidal cells. These few pyramidal cells now act as an *index* for that specific cortical representation [7]. These hippocampal pyramidal *indexing* neurons have a reciprocal relationship with the cortical cells that target them, with hippocampal afferents exiting via the entorhinal cortex and targeting the corresponding cells in the cortex. The indexing neuron itself—for example, a hippocampal CA1 pyramidal cell—often bears one or two attributes in that it may be either spatially (place) indexed [14, 15] and/or temporally (time) indexed [16, 17]. In this manner, cortical representations of current sensory perceptions and sensations can be captured and *indexed*, sequentially, as an animal moves through space and/or time. Furthermore, the entire pattern of the cortical representation of a perception or sensation can, in theory, be retrieved by only a partial input from the cortical array that was responsible for the initial experience (see Fig. 9.1c, d).

The requirement for the hippocampal indexing process and the meticulous integration of hippocampal memories into preexisting cortical conceptual frameworks has been described above. However, the mechanism by which a memory acquires hippocampal independence has not yet been fully elucidated. The two-stage learning theory does go some way to explaining this phenomenon [8, 9].

Two-Stage Memory Processing Theory

The state of the hippocampus can alternate between two modes "online" and "off-line." The online mode typically occurs, in rodents, during active running and exploratory behavior and is characterized by prominent theta/gamma oscillations, providing the necessary preconditions for rapid acquisition of information by the hippocampus (for a review, see reference [18]). This online mode reflects the first stage of the two-stage learning theory. The off-line mode occurs during less-active periods such as waking immobility and, most evidently, during slow-wave sleep. The off-line mode is analogous with the second stage of the two-stage learning theory. The original hypothesis suggested that in the off-line mode, conditions are such that intra-hippocampal *consolidation* of memory takes place [8]. This theory was extended to suggest that hippocampal-stored representations were also transferred to the cortex during the off-line period [9]. The current theory posits that the hippocampus triggers repeated replays or reinstatements of cortical representations from the previous online experiences, especially during slow-wave sleep [8, 9]. Thus, the memory can be transferred out of the hippocampus to the cortex via an off-line reiterative reinstatement process.

In summary of the above theories, we may suggest that for efficient memory function, the hippocampus must be able to rapidly index cortical representations

spatiotemporally, by virtue of its highly modifiable synapses, during online behavior and then during off-line behavior, by an iterative reinstatement process, the hippocampus incrementally transfers new information into preexisting cortical conceptual frameworks for remote memory storage. The question now remains: which areas of the cortex are reorganized for remote memory storage?

The Sensory Cortex in Memory Processing

There is compelling evidence that the prefrontal cortex (PFC) is involved in remote memory function [11, 19–22]. One interesting proposal suggests that the consolidation process gradually shifts indexing responsibilities from the hippocampus to the PFC [20]. However, a key question remains as to where in the cortex the sensory contents of an episodic memory trace are stored. Given that episodic memories can potentially be made of any combinations of all kinds of sensory information in various modalities, it is unlikely that one or a few cortical areas are dedicated to memory storage. Hippocampal indexing theory posits a more plausible scheme for cortical memory storage, suggesting that the sensory contents of an episodic memory trace are stored in the sensory cortices that originally process those contents. There is evidence that supports the involvement of the sensory cortex in this scheme of distributed memory storage. Lentiviral injections containing the regulator of G protein signaling-14 (*RGS-14*) into layer 6 of the secondary visual cortex—unlike injections into layers 2 to 3—prior to learning, enhanced normal object recognition memory in rats from ~45 min to several months, whereas selective elimination of layer 6 neurons in the secondary visual cortex prior to learning eradicated the capacity for object recognition [23]. In addition, task-related firing activities and firing sequences associated to visual cortical neurons can be reactivated later following the completion of the tasks [24, 25]. Finally, functional MRI studies in humans directly show that sensory-specific cortices are activated during vivid memory recall [26] and that the primary visual cortex can be activated during visual imagery [27]. Given the theoretical and experimental supports for a possible role of sensory cortex in memory storage, the rest of this chapter focuses our discussion on how the hippocampus and sensory cortex interact in relation to memory consolidation. Our purpose is to discuss the key findings of previously published work [28] within the context of the contemporary memory theories introduced earlier in this chapter.

Studying Hippocampal-Visual Cortical Interactions in Rodents

As in many other chapters in this book, we used the well-established paradigm of spatial navigation in rats as a model of episodic memories [29–31]. Hippocampal "place cells" fire at one or a few locations of a given space (place fields) [14,

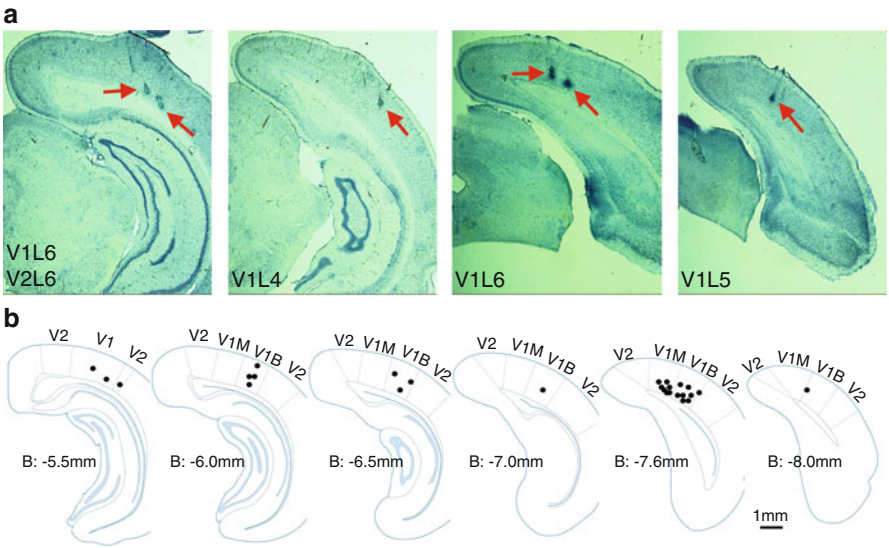

Fig. 9.2 Locations of recorded neurons in the visual cortex. (**a**) Coronal sections showing representative recording locations in V1. *Red arrows* indicate tetrode recording sites. (**b**) Summary of recording sites from all three rats overlaid onto figures of the appropriate stereotaxic coordinates from reference [77]. Most V1 neurons recorded in this study were from deep cortical layers

32–34]. It is surmised that the hippocampus indexes spatial memories using these place fields [29]. Episodic spatial memories are also endowed with various sensory properties constructed by cortical representations of the external world. It is the configuration of these sensory components that enables animals to make sense of space. A memory recall of a specific space inevitably also recovers those sensory components that define the space.

Decades of extensive studies have established that visual cues in an environment, especially the distal visual cues such as fixed landmarks, are the predominant sensory features that dictate the hippocampal place field locations [35–37].

It is reasonable to believe that when a place field is formed during learning, there is an array of visual cortical neurons that feed the visual information to the hippocampal place cells through a polysynaptic, multi-area pathway via the entorhinal cortex [38, 39]. We hypothesize that the visual cortical cells that feed into the hippocampal indexing system during the memory acquisition process may also represent the very fabric into which remote memories are interweaved during the consolidation process. In this view, the essence of systems memory consolidation, at least in part, is to gradually stabilize this cortical representation through off-line reactivations so that it can be retrieved independently of the hippocampus [40, 41]. Therefore, a key prediction of our hypothesis is that the same sets of hippocampal and visual cortical cells that are active during spatial navigation are also reactivated during sleep.

We tested this hypothesis by simultaneously recording from neurons at the pyramidal layer of the CA1 and from neurons in the visual cortex, mostly located in the deep layers [5, 6] of the primary visual cortex V1 (Fig. 9.2). Recordings were

performed when rats slept for 1–2 h (PRE sleep), followed by running a figure-8-shaped maze for about 30 min (RUN) and then a second sleep session for 1–2 h (POST sleep). During RUN, rats alternated between two well-learned trajectories on the maze for food rewards. Simple visual cues (stripes with different orientations and simple geometric shapes) were placed on the walls and floors of the maze.

Hippocampal and Visual Cortical Representations of Spatial Trajectories

As expected, as rats traveled along each of the trajectories, hippocampal CA1 neurons fired at specific locations (Fig. 9.3a) one after the other forming a sequence of activation (Fig. 9.3b), establishing, in effect, a series of hippocampal indexes.

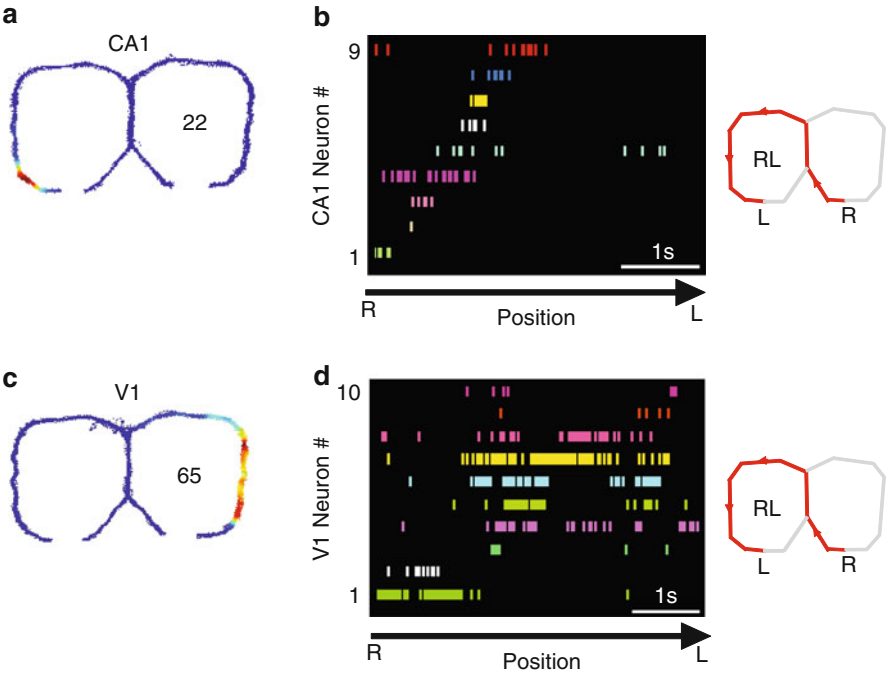

Fig. 9.3 Localized firing fields and sequences in the hippocampus and visual cortex. (**a**) A firing rate map for a CA1 place cell. *Blue track color* represents areas of no firing and *red-color track* represents area of peak firing. The *number* inside the track represents the peak firing rate of the cell. (**b**) Multiple CA1 cells are ordered according to their firing sequence based upon one lap of the R-L trajectory during RUN (*left panel*). The RUN trajectory (R-L) is displayed in the *right panel*. (**c**) A firing rate map for a V1 neuron similar to the CA1 neuron shown in (**a**). Like CA1 neurons, V1 cells also display location-specific firing characteristics. (**d**) Multiple V1 cells are ordered according to their firing sequence based upon the same lap in (**b**) of the R-L trajectory during RUN (*left panel*). The RUN trajectory (R-L) is displayed in the *right panel*

The pattern of sequential place cell firing is unique to specific trajectories and, therefore, gives rise to an episodic memory code for that trajectory.

Our hypothesis assumes that visual cortical neurons are involved in the formation of hippocampal place fields. Consistent with our proposal, a set of visual neurons also fired at specific locations on the maze (Fig. 9.3c). We then quantified the spatial information (a commonly used measure of location specificity, see ref [42]) of these firing fields. Using a threshold of spatial information > 0.5, we found that 49 % of our recorded neurons in the deep layers of visual cortex were location specific [28]. We also found that the location specificity of V1 neurons was much lower than that of CA1 neurons [28]. This was to be expected from our hypothesis that the visual cortical representation is only one of many components that comprise the largely multimodal sensory input to the hippocampus and that a significant amount of data compression—convergence—is likely to take place from V1 to the hippocampus. Although our hypothesis does not necessarily predict the existence of location-specific V1 cells, the fact that such cells do exist is appealing. It is likely that the percentage of the location-specific neurons found in our dataset does not necessarily reflect the real proportion of this type of cells in the visual cortex, since our samples were biased toward the low firing rate cells in deep layers. This subset of visual neurons also displayed a sequential firing pattern as the rats traveled along a particular trajectory (Fig. 9.3d). Such trajectory-specific firing patterns afford us a glimpse at the cortical code for spatial memories and permit us to view the reinstatement of memory traces in the visual cortex as in the hippocampus.

Reinstatement of Hippocampal-Visual Cortical Neuron Pairs During Slow-Wave Sleep

We demonstrate the existence of visual neurons with location-specific firing properties on the maze. Our hypothesis states that these visual neurons form part of the memory trace indexed by the hippocampal place cells active on the maze. Furthermore, we believe that visual cells that form part of the cortical representation being indexed by hippocampal cells should also be reactivated together when the memory trace is reinstated during sleep. We tested this hypothesis by examining whether pairs of hippocampal-visual neurons that were active together during RUN were also co-activated during sleep. We focused our investigation on periods of slow-wave (non-REM) sleep, when hippocampal ripple events (brief, ~100–250 Hz oscillations at the CA1 pyramidal cell layer) occur most frequently.

Neurons in the hippocampus and visual cortex often fire at overlapping locations on the figure-8 maze (Fig. 9.4a). As a result, their firing activities during RUN are highly correlated, as demonstrated by the prominent peak of their cross-correlation (Fig. 9.4b). As can be seen in Fig. 9.4b, CA1-V1 neuron pairs with high correlation during RUN were also highly correlated during POST slow-wave sleep, but not PRE. Remarkably, when the same two cells were examined on the following day using the same behavioral schedule, a similar finding was observed (Fig. 9.4c, d).

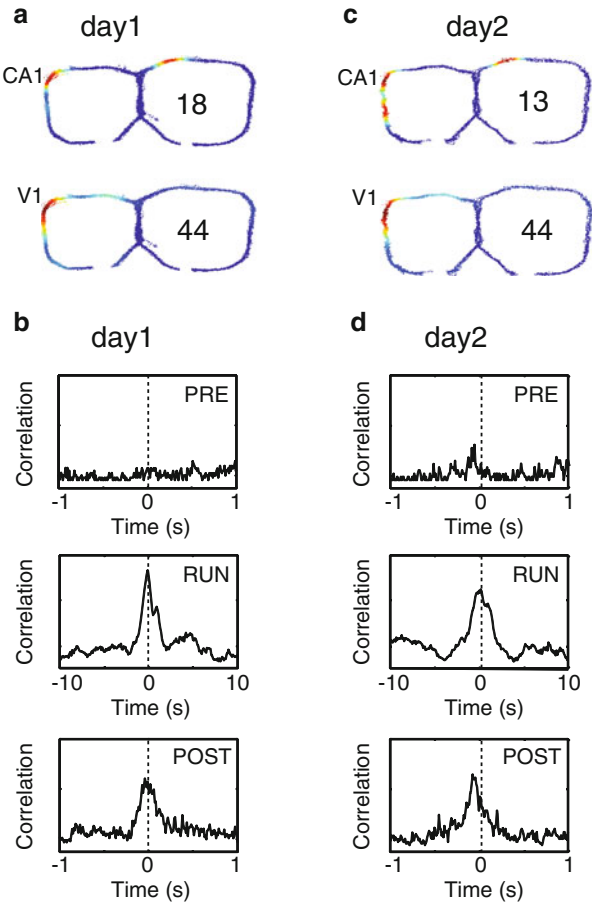

Fig. 9.4 Pair-wise cross-correlations between pairs of CA1 and V1 cells. (**a**) An example of a pair of CA1 and V1 cell rate maps that overlapped on Day 1 of a RUN session. (**b**) Cross-correlations of overlapping CA1-V1 cell pairs (such as described in **a**) in PRE, RUN, and POST. Overlapping CA1-V1 cells from RUN session did not co-fire during the PRE sleep session. In the POST sleep session following RUN, they were seen to maintain a high firing correlation. (**c**) The same CA1-V1 cell pair's rate maps from (**a**) in RUN session the following day. (**d**) Cross-correlations of the same CA1-V1 cell pairs had dropped to baseline level in PRE of day 2. This is indicative of an uncoupling of the CA1-V1 pair overnight. RUN increases the firing correlation of cell pairs in POST of day 2. Adapted from [28]

Specifically, the CA1-V1 correlation in POST of day 2 was increased from that in PRE, which was reduced to baseline level from the previous day's POST. This is consistent with many other studies showing that hippocampal reactivations after a task only last about 1–2 h [43, 44].

Next, all pairs of CA1-V1 neurons were divided into two groups: a "high-correlation" group, which had high correlation values during RUN, and a "low-correlation" group. We found that, for the high-correlation group, the mean correlation

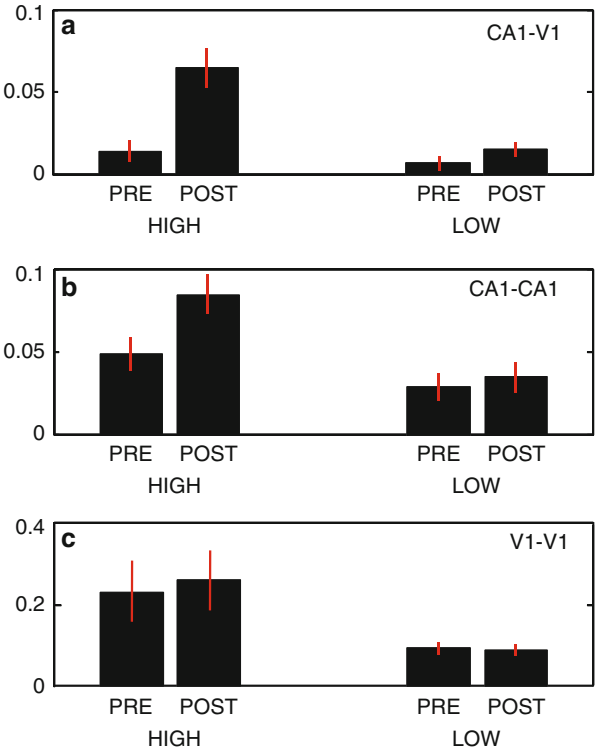

Fig. 9.5 Pair-wise cross-correlation analysis. (**a**) PRE and POST correlation values for CA1-V1 cell pairs. Cell pairs were assigned to a high- or low-correlation group based upon whether the pair showed a high or low correlation during RUN. Cell pairs with high RUN correlation showed a significant increase in correlation from PRE to POST unlike low-correlation pairs, indicating that CA1-V1 pairs that co-fired on the track during RUN maintained this co-firing in the POST session. (**b**) In a similar manner to CA1-V1 pairs described in (**a**), CA1-CA1 cell pairs with high correlation in RUN also showed a significant increase in co-firing from PRE to POST unlike low-correlation pairs. (**c**) V1-V1 cells pairs with either high or low correlation showed no increase between PRE and POST. This indicates that V1-V1 pairs that co-fired during RUN had no effect on co-firing during POST. (But, see main text)

value during POST was significantly higher than that of the PRE (Fig. 9.5a). This observation indicates that cells that fired together on the maze also fired together during POST. This increase in co-activation was specific to the high group and supports our hypothesis that the visual and hippocampal neurons participating in the same memory trace are reactivated concomitantly during sleep. Furthermore, according to our hypothesis, the same high correlation should be observed for both CA1-CA1 neuron pairs and V1-V1 neuron pairs. Consistent with previous results [43–46], we found that the hippocampal neuronal pairs with high correlations during RUN also showed high correlations during POST (Fig. 9.5b). However, the same analysis applied to the visual cortical neurons failed to find a significant

increase in correlation during POST for those pairs of visual neurons with high RUN correlation (Fig. 9.5c). Instead, we noticed the correlation values of these neurons were quite high during both PRE and POST. Thus, an already high correlation in PRE has little room for further correlation.

Fine Structures of Hippocampal and Cortical Activities During Slow-Wave Sleep

To better understand the high correlation of visual cortical neurons during PRE and POST, we examined how neuronal population activities of visual cortical neurons are organized during slow-wave sleep. In addition, we investigated intra-hippocampal neuronal population activity and the interregional interaction between population activities of the hippocampus and V1.

In our experiment, multiple recording tetrodes that simultaneously sampled firing activities at many sites within both the CA1 and V1 were used. When the multiunit activities across numerous sites in V1 were plotted, a striking structure emerged (Fig. 9.6a). The multiunit activity was highly synchronized and displayed epochs where the vast majority of neurons were active, followed by periods of total neuronal silence during slow-wave sleep. During these periods of cortical silence, phenomena such as K-complexes were seen in the local field potentials. K-complexes are an element of the slow and delta waves in non-REM sleep [28]. It is known that cortical neurons show distinct UP and DOWN states [47–53] and that and K-complexes are indicative of the DOWN state [51–53]. Therefore, the alternation between active and silent periods in our V1 multiunit activity indicates that cortical neurons switched between UP and DOWN states in a highly synchronized fashion during slow-wave sleep.

While cortical neurons clearly show UP and DOWN states in slow-wave sleep, membrane potentials of CA1 pyramidal neurons do not display UP and DOWN states [54–56]. Nevertheless, in our data, the multiunit activities across multiple CA1 sites were observed to alternate between active and silent periods (Fig. 9.6b), indicating a high degree of synchronized CA1 neuronal firing. Active periods in the hippocampus were also accompanied by ripple events in the CA1 local field potentials.

The synchronized UP/DOWN alternation means that cortical neurons fired together during UP states and shut down together during DOWN states, providing an explanation for the high correlation values between V1 neuron pairs in both PRE and POST. Unlike cortical neurons, CA1 neuron pairs did not show high PRE correlation [44]. We found that CA1 neurons fired very sparsely within UP states and, thus, the chance for any given pair of CA1 neurons to fire together was low.

For clarity and distinction in describing our results, the active periods of the multiunit activity are referred to as “frames” (see also reference [28]). Frames are comparable to the UP states described elsewhere [50, 51, 57–59] that are most commonly defined by the characteristics of the EEG or intracellular potentials. Frames of increased MUA in both the V1 and CA1 can last from 100 ms to several seconds.

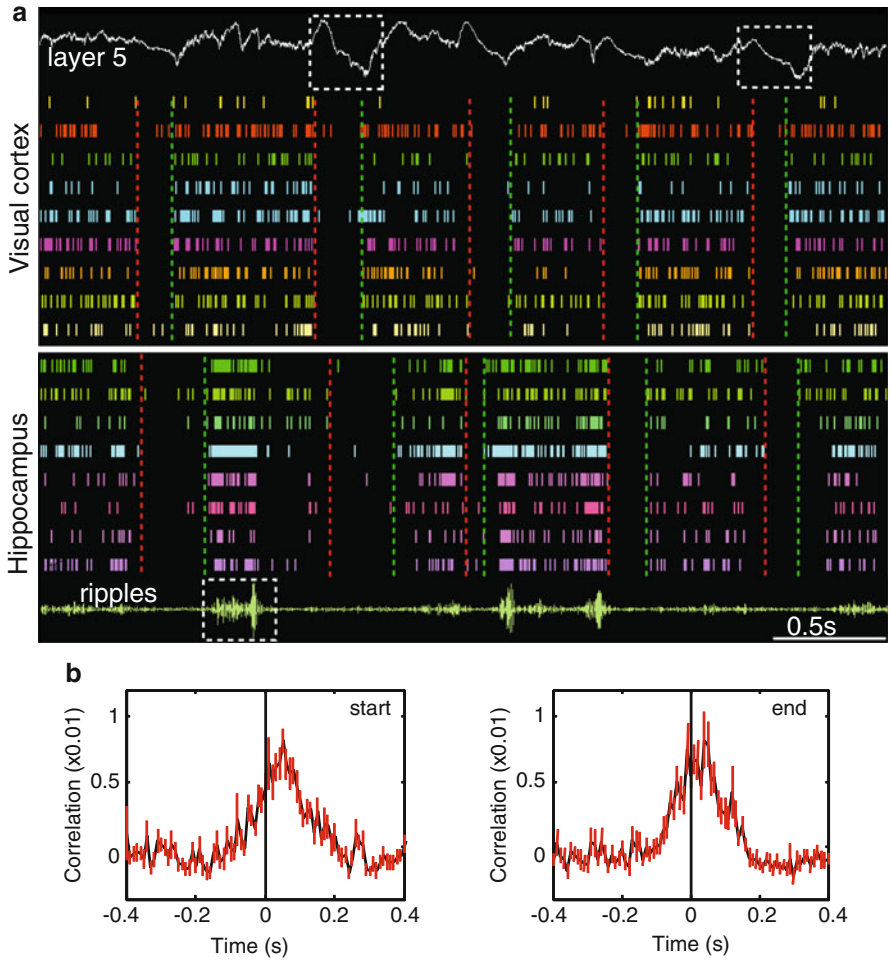

Fig. 9.6 Visual cortical and hippocampal frames and their interactions. (**a**) Visual cortical (*upper panel*) and hippocampal (*lower panel*) frames during an epoch of slow-wave sleep. *Green-* and *red-dashed lines* mark the beginning and end of a frame, respectively. An EEG trace from layer 5 of V1 with K-complexes (*dotted boxes*) is displayed in the *upper panel*. A hippocampal trace, filtered at 80–250 Hz to show ripples, is displayed in the *lower panel* and indicates that ripples (*dotted box*) occurred predominantly within hippocampal frames. (**b**) Average cross-correlogram (mean ± s.e.m., $n = 20$ sleep sessions) between cortical and hippocampal frame start and end times. The cortical frame was the reference and is shown to precede the hippocampal frame in both start and end time. Adapted from [28]

We detected the precise times at which frames were switched on and off and then computed the cross-correlation between the on/off times of visual cortical and CA1 frames. We found that cortical frames were turned on and off about 50 ms earlier than hippocampal frames (Fig. 9.6c). This time, delay is consistent with the ~5 synapses connecting V1 and CA1 [38, 39]. This result suggests a strong cortical input to the

CA1 region during slow-wave sleep. Because the classical memory consolidation model states that the hippocampus reactivates memory traces first and consequently feed the information to the cortex, our results appear to be unexpected. We would argue that this is not necessarily so. We suggest that it is the cortex that initiates the hippocampal-cortical dialogue and that this proposition does not, necessarily, preclude the hippocampus from initiating the memory reactivation first.

High-Order Sequence Replays in the Hippocampus and Visual Cortex

We have shown that the cells co-activated during RUN are also co-activated during POST slow-wave sleep. These observations provide evidence for the reactivation of behavior-related activities during sleep, but do not elucidate the specific neural patterns that encode particular memory traces. Since we have shown that spatial trajectories on the figure-8 maze were associated with specific firing sequences of multiple neurons in the hippocampus and visual cortex, it is important to examine whether these higher-order (more than four cells) firing sequences were replayed during sleep. Their replay would provide a significant piece of evidence supporting the existence of a sensory cortical representation of hippocampus-dependent memories.

Therefore, we constructed a template sequence of CA1 or visual cortical neurons that were active on a trajectory of the figure-8 maze during RUN. We then examined whether the sequence was replayed within individual frames of slow-wave sleep (see details in reference [28]). Sequences in the visual cortex and hippocampus were analyzed separately, because frames that occurred during slow-wave sleep in these areas did not appear precisely synchronized in time. As not all cells in a template sequence were active in a PRE or POST frame, only those frames containing at least four cells qualified as candidate frames for comparison with the RUN template. If the sequence within a candidate frame matched with the RUN template, we called it a "replay frame" (see Fig. 9.7a). For each RUN template, we defined a replaying ratio as the ratio between the number of replaying frames and the number of candidate frames. We found that the mean replaying ratio, averaged across all the templates, was significantly increased from PRE and POST in both the visual cortex and the hippocampus (Fig. 9.7b). Replaying events in both hippocampus and cortex were compressed in time by a factor of ~5–10 [28]. In addition, the replaying ratio in POST decayed back to the PRE level in approximately 1 h of sleep (Fig. 9.7c).

Spurious replaying frames could occur merely due to chance. How do we know the numbers of replaying frames found were significantly different from chance level? Fortunately, the distribution of the expected number of replaying frames out of a given number of candidate frames can be computed based on two simple assumptions: (1) cells are randomly ordered in each frame and (2) frames in a session were independent [28]. The independence assumption may not necessarily be true, especially for the visual candidate frames, many of which occurred next to each other in time. Therefore, we also randomly shuffled the cell identities and

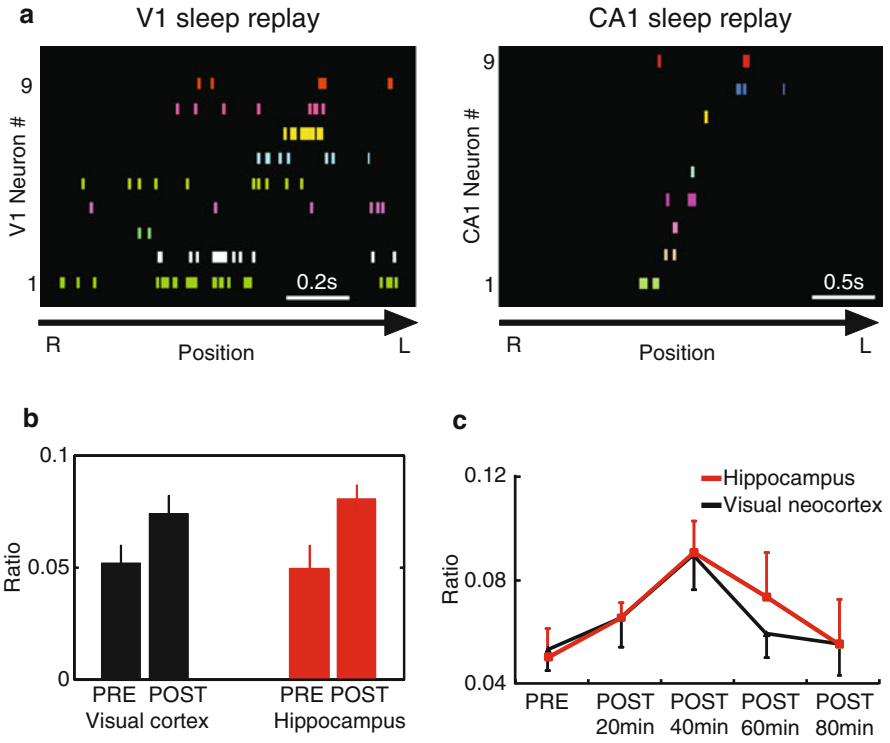

Fig. 9.7 High-order hippocampal and visual cortical replays during slow-wave sleep. (**a**) Visual cortical (*left*) and hippocampal (*right*) cells were ordered according to a RUN session trajectory (R-L in this case). The rastograms show replay events of specific trajectories in the visual cortical and hippocampal frames during slow-wave sleep. (**b**) The ratio of trajectory-specific replays increased in both hippocampus and visual cortex from PRE to POST presumably due to the effect of trajectory running during the intervening RUN session. (**c**) Both hippocampal and visual cortical trajectory-replay ratios peaked at ~40 min in POST sleep decayed to PRE level within 60–80 min

obtained the distribution of the chance-level number of replaying frames based on 1,000 copies of the shuffled data. Indeed, the computed and shuffle-generated distributions agreed quite well for hippocampal templates, but not so well for visual cortical templates (Fig. 9.8a, b). Nevertheless, according to both distributions, the numbers of replaying frames in POST were significantly greater than the chance in both the visual cortex and hippocampus. Interestingly, the number of replaying frames in PRE was also significantly above chance level in the visual cortex, but not in the hippocampus (Fig. 9.8a, b).

The results offer a much needed support for the current models of memory consolidation: a significant number of replay events during POST following an active maze-running task not only occur in the hippocampus but also in the visual cortex. More importantly, the fact that memory sequence replays exist in a sensory cortical area supports our hypothesis that sensory cortical neurons participate in memory consolidation and storage.

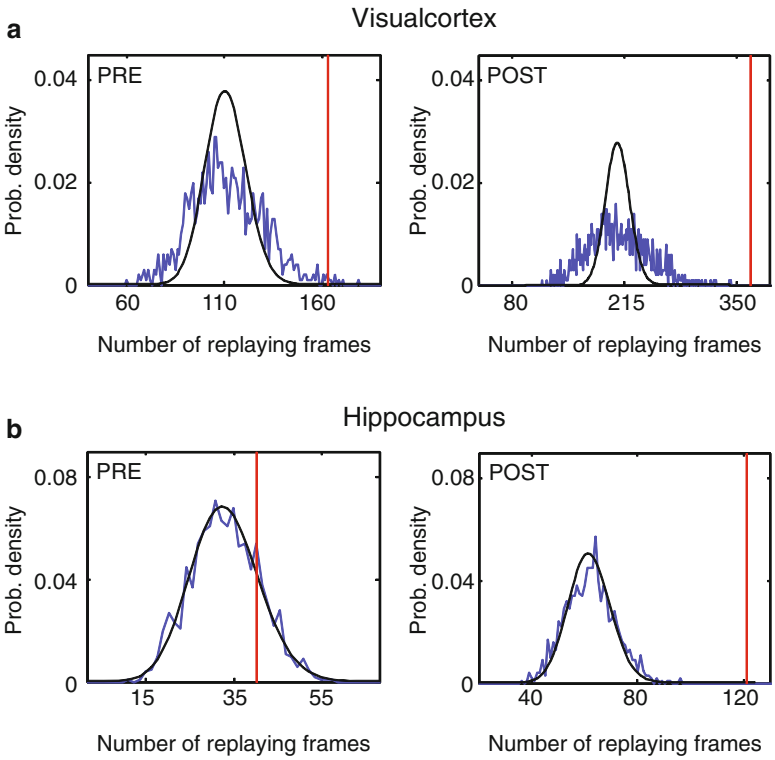

Fig. 9.8 The significance of hippocampal and visual cortical replays. (**a**) Actual number of observed number of replaying frames (*red line*). Chance (*black line*) and shuffle (*blue line*) distributions of the number of replaying frames that were randomly generated for visual cortex during PRE and POST. (**b**) Same as (**a**), but for the hippocampus. Adapted from [28]

Coordination of Hippocampal and Visual Cortical Sequence Replays

A key issue in the current memory consolidation theories proposes the existence of an active dialogue between the hippocampus and cortex during sleep for the purpose of memory consolidation. In essence, there should be times when the two areas "talk" to each other about the same memory traces. For such a conversation to take place, the replay events in both the hippocampus and cortex need to be coordinated. In our experiments, we asked, if one area was replaying a particular trajectory in a frame, what was the other area doing? Did it also replay the same trajectory?

Since the cortical and hippocampal frames were not necessarily synchronized in time, we answer the question by counting the pairs of cortical and hippocampal frames that replayed the same trajectory and overlapped in time. For comparison, we also counted the pairs that overlapped in time but replayed two different trajectories.

We identified 9 hippocampal-cortical frame pairs replaying the same trajectory in POST from 3 rats, but only 1 frame pair in PRE. We also identified 3 pairs replaying the different trajectories in POST and 0 in PRE. Because of the limited number of simultaneously recorded neurons from the two areas in freely moving animals, the number of replaying frames identified in the visual cortex and hippocampus was low (<0.2 %), relative to the total number of frames (replaying and non-replaying) available. Therefore, the chance-level number of overlapping replaying frames is small. We obtained the distribution of the chance-level number of replaying frame pairs by randomly shuffling the replaying frames among all available frames [28]. The shuffling analysis indicated that only POST replaying frame pairs were significantly greater than the chance level ($P=0.01$). This result suggests that the visual cortex and hippocampus tend to replay the same trajectory in POST but not PRE. To show that this is a robust result despite of the low numbers, we reanalyzed the data using a less rigorous definition of a replaying frame [28]. As a consequence, we found 25 overlapping pairs that replayed the same trajectory in POST ($P=0.004$) and only 3 in PRE ($P=0.91$). In contrast, we found 11 overlapping pairs that replayed the different trajectories in POST ($P=0.35$) and 5 in PRE ($P=0.24$). Therefore, we are confident that our data indicate a memory-specific communication between the hippocampus and visual cortex during slow-wave sleep.

In the paragraph above, we identified overlapping hippocampal replay frames and cortical replay frames. In this section, we ask a slightly different question about the coordination of cortical replays with hippocampal spiking activity. Here, we compare cortical replay frames with concomitant firing of individual hippocampal cells (Fig. 9.9a) and evaluate whether the spike timings of the hippocampal cells were consistent with the same trajectory being replayed in the cortex. This approach does not require that the hippocampal frames were replaying, or even candidate frames, therefore allowing the analysis of all available data points. First, a visual cell was paired with a hippocampal cell, and their average peak-firing time interval during running a trajectory in the RUN session was computed. Whenever a replaying frame was observed in the visual cortex during sleep, the peak-firing time interval of the same pair of cells was calculated (Fig. 9.9a). Then, for each template, the correlation between the RUN time intervals of all possible pairs in the template and those during sleep (replaying frames in PRE and POST were computed and combined in this analysis although most replaying frames were in POST; Fig. 9.9b). The significance of the correlation was evaluated by comparing it with the chance-level correlation, as determined by random shuffling of cell identities within their brain areas (Fig. 9.9c). We found a significant correlation between the RUN and sleep firing intervals for all the 11 cortical templates examined (not all templates generated enough replaying frames for this analysis). Similarly, we also analyzed the cortical-hippocampal firing intervals when hippocampal frames were replaying a trajectory. We found a significant correlation for nine out of ten hippocampal templates. These data indicate that when one brain area replays a trajectory, the activities of the cells in the other area are consistent with replaying the same trajectory. This result strengthens the notion that specific groups of cells in the visual cortex and hippocampus are engaged in active communications in slow-wave sleep to consolidate specific memory traces.

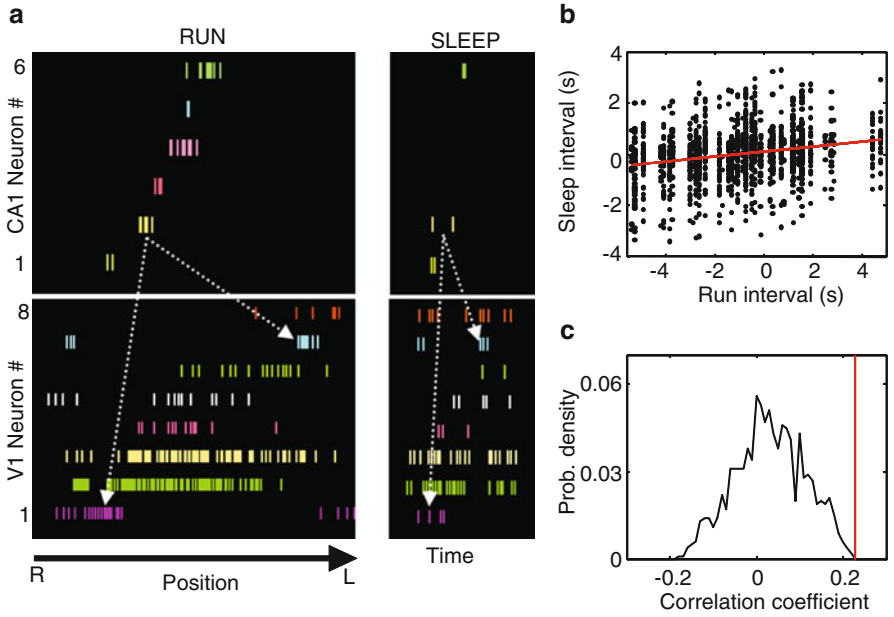

Fig. 9.9 Hippocampal activity during cortical replay frames. We computed the spike-timing relationships of CA1 and V1 neurons during RUN and sleep (PRE and POST were combined, see main text). (**a**) Multicell firing sequences from the hippocampus and visual cortex during a R-L trajectory running during a RUN session (*left panel*). The same cells are represented during a cortical replay frame (*right panel*). *Arrows* indicate the similar firing orders of a hippocampal neuron relative to two cortical neurons during RUN and during slow-wave sleep. (**b**) Time intervals between visual cortical and hippocampal cell pairs based on cortical replaying frames in sleep, compared with their corresponding RUN time intervals on a trajectory. *Solid line*, linear regression between the sleep and RUN intervals. CA1-V1 pairs maintain similar firing relationships during RUN and within cortical replay frames during sleep. (**c**) Distribution of shuffling-produced correlation. The *vertical red line* represents the actual observed correlation. Adapted from [28]

Discussion

The purpose of this chapter was to frame the results from our previous work [28] within the context of contemporary theories of memory. Our results not only support some key elements of the complementary learning systems theory [6], hippocampal indexing theory [7], and the two-stage memory processing theory [8, 9] but also offer fresh, new insights into the memory consolidation process.

Hippocampal-Cortical Memory Transfer

Our study indicates that replays in the hippocampus occur concomitantly with replays in the visual cortex in POST sleep. The coordinated replay across the cortex and hippocampus supports the two-stage memory processing theory. This theory, along with

other similar theories, suggests that following the acquisition of the initial memory during online waking behavior, the second stage of memory consolidation occurs off-line as the cortex and hippocampus interact during sleep [6–9, 19, 20, 40, 41]. One hypothesis is that the hippocampus reactivates the memory trace first and, as a consequence, initiates the hippocampal-cortical dialogue. In our study, due to the limited number of replaying events, we are unable to determine which area started the replay first [28]. Nevertheless, our data do suggest that the hippocampal-cortical interaction may not be necessarily unidirectional. We show that the cortical frames during slow-wave sleep both start and end earlier than the hippocampal frames. This suggests that even during sleep, hippocampal activity is energetically driven by the cortical input. More specifically, our data provides evidence that hippocampal frames could be initiated and terminated largely due to the cortical drive. The initial cortical drive may be the trigger for the firing of hippocampal neurons and, hence, hippocampal replay events, which may in turn trigger cortical replays. This cortical trigger may also be important in that hippocampal replay information sent to the cortex may only be properly consolidated at times of heightened receptivity in the cortex. From this point of view, the cortical trigger message to the hippocampus to initiate replay may be something along the lines of "I am labile *now*—modify me."

As stated earlier, our rats are well trained in running on the track and performing the behavioral task. Yet, even a month after training, hippocampal and cortical replays remain elevated in POST sleep, at least for the first hour. This short-lasting hippocampal memory trace is quite surprising, because behavioral studies indicate that spatial memories in rats are hippocampal-independent even a few weeks after learning [19, 20]. The observation that hippocampal-cortical replay routines drop to baseline within an hour may be indicative of that familiar waking experiences which were pre-consolidated. However, the two-stage memory system appears to be still performing consolidation functions in the first hour of POST session, suggesting that, by default, no matter how familiar the environment, the hippocampal-cortical dialogue in the early POST experience sleep reflects an episodic representation of that context—possibly even if an entire memory of that representation already exists in the cortex, independent of the hippocampus.

Memory Representations in the Sensory Cortex

Our findings that some cells in the visual cortex fire in a location-specific fashion and also participate in coordinated sequence replay are consistent with the distributed memory storage model that proposes that sensory details of spatial/episodic memories are stored in sensory cortices [7, 26, 60].

More interestingly, one of the key findings in this study is that trajectory-specific replay occurs in the visual cortex independently of hippocampal replays in the PRE sleep. The visual cortex appears to maintain a significant number of replaying events in PRE sleep session, despite the fact that the number of hippocampal-cortical replays decayed in the POST sleep session of the previous day. Here, we propose

that this baseline level of replaying events in spontaneous sensory cortical activities reflects the establishment of the permanent memory trace in the visual cortex.

The presence of preexisting sequences within the sensory cortex—but not hippocampus—during the PRE session supports the complementary learning system theory that the cortex is more rigid than the hippocampus [6]. This finding is also consistent with studies in the auditory cortex that reveal robust sequences, independent of sensory stimuli [61–63]. However, we also need to emphasize that the number of replay events in the visual cortex was still significantly increased from PRE to POST, although the increase was smaller than that in the hippocampus. This result suggests that the cortex *is* plastic and does participate in the consolidation process even after performance of a well-learned behavior.

Finally, our proposal that there are memory-related cells in the sensory cortex has far-reaching implications to our understanding of not only memory but also sensory processing/perception. Traditionally, the main function of the sensory cortical circuits is viewed as such that they should be optimally designed for representing and abstracting the relevant features from the external environment. For example, a majority of V1 cells are tuned to specific orientations of visual stimuli [64–66]. Recently, it has become apparent that visual cells, even those in V1, are modulated by internal information originating inside the brain, such as attention, task demands, and even rewards [67–71]. Thus, it would appear that visual processing is often not simply a passive response to outside stimuli but an interaction between the neuronal responses triggered by external stimuli and the context preserved within the internal state of the brain that is comprised of intention, attention, and importantly, *memories*! In this way, visual perception can be profoundly influenced by personal experience. The evolutionary benefit of having memory exerting influence on sensory neurons participating in the perceptive process is straightforward. The emergent property of the dynamic interplay between external stimuli and stored memories yields consciousnesses that are both reflexive *and* predictive. We believe that many neurons in the primary sensory cortex function to display representations of possible future conditions in the external world based upon previously acquired knowledge held within the hippocampus and, following consolidation, solely within the cortex itself. In this sense, the boundary between the memory and sensory circuitries is not as clear cut as previously thought.

Future Directions

Over the course of this study, we have made substantial progress in understanding hippocampal-sensory cortical interactions in the memory consolidation process. However, we have only scratched the surface of the mechanisms underlying systems memory consolidation. Here, we discuss a few unresolved questions concerning the interaction between the hippocampus and sensory cortices that we believe to be important and answerable in the near future.

The current study shows that some cells in the primary sensory cortices are involved in the hippocampal-dependent spatial memories. However, if the sensory cortices are involved in the long-term memory storage, what are the connections that support the interactions between the hippocampus and the sensory cortex? There is a well-defined pathway from V1 to the hippocampus, via a number of intermediate areas including the secondary visual cortex, temporal cortex, postrhinal/perirhinal cortex, and entorhinal cortex [38, 39, 72–76]. In a new spatial experience, external visual input activates specific groups of cells in visual cortical areas and, as a consequence, a group of place cells in the hippocampus. Presumably, hippocampal place cell ensembles represent an index for external space, whereas the cortical cells represent the sensory representation associated with that specific hippocampal ensemble. But, in terms of consolidation and memory retrieval, the hippocampal ensemble indexing a memory has the ability to reinstate a cortical representation of the original experience. How does the hippocampus *know* which *specific* cortical cells to target for reinstatement? It is known that at every stage of the pathway from the visual cortex to hippocampus, there exist "back projections" besides the forward projections that allow the bidirectional flow of information [38, 39, 72–76]. The function of back projections has long been proposed to be involved in memory retrieval and consolidation [74]. Therefore, it is not hard to imagine a general scheme for the flow of information from the hippocampus to the sensory cortex. Pursuing this hypothesis, the first step would be to prove that there are group of cells in the sensory cortex that can be back-activated by the hippocampus, ideally during the retrieval and consolidation of a specific memory trace. Second, we need to understand the circuit mechanisms of this back interaction by studying the anatomy and plasticity of back projections in the context of memory tasks.

Our study provides evidence that visual cortical neurons are involved in the representation of memories. Therefore, these neurons could be internally driven by stored memories. It is known that a majority of the cells in V1 are tuned to specific features of external visual stimuli [64–66]. Several questions do remain: what are those internally driven cells in V1? Are externally driven and internally driven V1 cells one and the same or separate classes of cell? Do they reside within different laminae of the sensory cortex? In addition, the ultimate purpose of these internally tuned neurons remains unclear. They may serve as a gateway for the hippocampus to reactivate a broad array of cells that amount to a full cortical representation, and perception, of a memory. It may be that their ultimate function, following consolidation, is to serve as elements of hippocampal-independent cortical memories.

The distributed memory storage model [7, 26, 60] proposes that the hippocampal place cells serve as indexes that bind sensory information from different modalities across multiple cortical areas. Eventually, we need to study not only the interaction between the hippocampus with a single sensory cortical but rather, the binding of multiple sensory modalities by the hippocampus. First, this line of research would establish that specific groups of cells in multiple sensory areas correlated with hippocampal place cells during memory formation can be reactivated during memory consolidation and retrieval. Second, it would demonstrate that the cortical cells

from different sensory modalities can be reactivated during memory retrieval, independently of the hippocampus, after the memory is well consolidated. Only then would the major elements of current memory processing theory have been tested. This kind of study requires the monitoring of a large number of cells simultaneously in the hippocampus and multiple distributed sensory cortical areas in behaving animals. Although it sounds technically difficult, it is not impossible. We are optimistic that rapid progress will be made in the near future.

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Chapter 10
Memory Consolidation, Replay, and Cortico-Hippocampal Interactions

Esther Holleman and Francesco P. Battaglia

Abstract Memory consolidation depends on the exchange of information between the hippocampus and the neocortex. The interaction between these two structures is based on dynamical processes such as oscillations, taking place during active behavior as well as sleep. Memory replay, that is, the reactivation, during sleep or other off-line periods, of the same configurations of neural activity that occurred during experience, is thought to be a key mechanism for memory consolidation. We review here the physiology of cortico-hippocampal interaction during sleep, as well as some results on cortical replay and its relationship with hippocampal activity.

Keywords Hippocampus • Cerebral cortex • Prefrontal cortex • Memory consolidation • Episodic memory • Semantic memory

Sleep is vital for the long-term consolidation of newly acquired information [1–3]. The exact mechanisms behind this consolidation are yet unknown and often debated. The two most accepted theories for a mechanistic role of sleep in memory consolidation are the synaptic homeostasis hypothesis [4] and the active systems consolidation hypothesis [5]. As the names suggest, these theories differ in their view of whether consolidation is a passive or an active process.

The synaptic homeostasis hypothesis claims that slow oscillations induce synaptic downscaling, which nullifies the weakly potentiated connections and thereby improves the signal-to-noise ratio for the more strongly potentiated synapses. This de-potentiation of synapses also "resets" (refreshes) the cells, facilitating the efficient processing of new information upon waking. At frequencies below 1 Hz, de-potentiation of synapses through long-term depression (LTD) does appear to take place [6]. Homeostasis may be very important for reducing the signal-to-noise ratio of existing memories, by "pruning" inessential connections [7], and may reestablish a convenient working point [8] for proper circuitry function and for the

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acquisition of new memories. Reinforcing this hypothesis, specific slow-wave sleep (SWS) deprivation in humans impairs subsequent encoding of new memories [9].

However, during these periods of slow oscillations, activity is characterized by hippocampal sharp wave-ripple complexes and cortical spindles. These high-frequency events are known to facilitate long-term potentiation [10–12], indicating that there is more to memory enhancement than de-potentiation alone. Sharp waves are fast depolarizations with a large amplitude (1–3 mV) that occur aperiodically in the stratum radiatum of the CA1 area of the hippocampus during SWS and appear to be generated in CA3, an area with abundant recurrent connectivity [13–15]. Fast field potentials of 100–300 Hz, known as ripples, are often found riding on the waves of this depolarization. These high-frequency oscillations are the result of extremely synchronous neuronal activity [16, 17]. In fact, these events are often referred to as the most synchronous activity observed in the brain [18].

Active systems consolidation theory proposes instead that stable memory representations are formed through the repeated reactivation during sleep of networks that were active during waking behavior in both the hippocampus and neocortex [19–21]. Here, the emphasis is not at the level of single synapses, rebalancing their weight, but at the level of brain-wide networks, in which information is reorganized. The hippocampus is thought to be the primary encoder for declarative memories, embedding them in *episodes*, spatiotemporally organized representations of all the components of life occurrences [22–24]. The hippocampus is also thought to initiate the consolidation process [25], by which the memorized information is gradually embedded in cortical networks. This is of great importance for the fate of memories, because, whether or not the hippocampus is ever completely freed from memory maintenance duties [26, 27], cortical networks are thought to have a greater storage capacity, and their slower learning rates prevent catastrophic interference, which could result in the destruction of all memory content [19]. Thus, systems consolidation seems crucial for the long-term maintenance of a large body of memories. According to the standard view of systems consolidation, the hippocampus supplies information at this reduced rate by "replaying" information about previous experience (see [5, 28] for reviews) in off-line periods when the memory is neither encoded nor retrieved. Because of the relative absence of sensory interference and the rich, peculiar patterns of spontaneous activity, sleep poses itself as the ideal state for the expression of replay. Collective activity events such as sharp wave/ripple (SWR) complexes in the hippocampus and slow oscillations and spindles in the cortex facilitate the transfer of information from the hippocampus to the neocortex. As we will see below, slow oscillations from the neocortex synchronize hippocampal SWRs. As a result, hippocampal replay and cortical spindle events are concentrated around the same time points, providing a temporal frame for the consolidation process.

It is to be noted that homeostasis and active consolidation do not need to be mutually exclusive, rather active processes may take place on a background of passive, noise-reducing rescaling, thereby avoiding synaptic saturation [7, 29].

In this chapter, we will briefly summarize recent findings on hippocampal and cortical replay, in the context of the neurophysiology of cortico-hippocampal interactions and the theory of systems consolidation.

The Neurophysiology of the Consolidation Processes

While the idea about the underlying computational processes goes back to the 1970s and 1980s [30–32], in 1989 Buzsaki [33] proposed a model for the physiological processes underlying the forming and consolidation of memory traces. This hypothesis consists of two distinct stages. The first stage describes the initial formation of the memory trace. This is then followed by a second stage in which the memory trace is consolidated. In the first stage, an unstable memory trace is formed during exploratory behavior, characterized by theta activity. Theta in rodents is a 6–10 Hz oscillation that dominates electrical activity in the hippocampus when subjects are moving around and attentive. During theta, select CA3 pyramidal cells are potentiated by input from granule cells in the dentate gyrus. This selectivity is determined by the response of the granule cells. Those granule cells that respond most to the environmental events will have a high firing rate; thereby, the CA3 pyramidal cells on which the mossy fibers of these active granule cells converge will be potentiated more relative to the surrounding pyramidal cells. This process ensures the specificity of information storage [34]. The second stage is characterized by the formation of a stable, more permanent form of the memory trace, which forms once the exploratory theta-dominated behavior subsides and slower oscillations surface, dominated by highly synchronized CA3 population bursts. This CA3 excitation converges onto a subset of CA1 cells and potentiates these, resulting in sharp wave-ripple complexes in the LFP signal. The potent depolarization resulting from this highly synchronous activity enhances the synaptic efficiency of both the activated CA3 and CA1 cells. This process allows the past state of the network to determine the exact combination of cells that fire during the bursts, ensuring that the most recent relevant information is strengthened.

Segmentation in to two physiological regimes, separating acquisition from consolidation, provides a way to acquire new information without jeopardizing the stability of older memory (the "stability-plasticity" dilemma described by [19] as well as earlier neural network literature—see [35]).

The switch between the two states is dictated by the neuromodulatory state: while during wakefulness a high cholinergic tone favors encoding [36], the most conducive condition for such replay is an idle or sleeping brain state [29]. When the brain is off-line, the normally continuous stream of external stimuli is absent, leaving room for the undisturbed reorganization and strengthening of recent memories. Furthermore, during SWS sleep, acetylcholine levels in the hippocampus decrease, facilitating endogenous activity through an increase in recurrent connectivity [36].

Buzsaki's model focused on the hippocampus; however, as mentioned previously, stable, long-term memory consolidation requires a dialogue between hippocampus and cerebral cortex. This latter structure also underlies significant dynamical changes between wakefulness and sleep; it may therefore be useful to define a "2-stage" model that includes the neocortex [37] and characterizes the functional and computational consequences of the intricate interplay that has been described in physiological studies.

Cortico-Hippocampal Interactions During Sleep

Sleep is characterized by the reoccurrence of two alternating phases: slow-wave sleep (SWS) and rapid eye movement (REM) sleep. During REM sleep, theta oscillations of 4–8 Hz are often observed (albeit not reliably in humans [38, 39]). During SWS a slow oscillation of 0.1–1 Hz dominates, interspersed by cortical spindles and hippocampal SWRs. SWS and REM sleep phases are discerned by clearly dissimilar neuromodulatory activity. The low cholinergic activity during SWS reduces tonic inhibition of incoming information in cortex, thereby facilitating communication with the hippocampus.

In contrast REM sleep is characterized by high cholinergic levels, as is the awake state. During REM sleep, the coupling between prefrontal and hippocampal area is greatly reduced [38–41], which could be used as an argument against its possible role in memory consolidation. The dominant activity pattern during SWS is a slow oscillation present throughout the neocortex and synchronizing large cortical areas [42, 43]. This oscillation is characterized by neural activity fluctuating from widespread depolarization to hyperpolarization, referred to as UP and DOWN states. The sudden transitions between these states can exercise a powerful influence on co-occurring oscillatory activity both within the cortex and other regions such as the hippocampus [44].

UP states are maintained by intrinsic intracortical excitatory feedback mediated by glutamatergic synapses [45]. They are therefore a quintessential cortical network phenomenon. DOWN states represent the termination of this excitatory feedback by inactivation of persistent Na^+ currents and the activation of Ca^{2+}-dependent K^+ currents [46–48] or by synaptic depression [49]. Importantly, this termination is not due to increased inhibitory activity. Rather, inhibitory interneurons oscillate in phase with principal cells, maintaining a balance between excitation and inhibition throughout the oscillation cycle [50]. As the circuit recovers from the influences that terminated the preceding UP state, a new UP state may be initiated, triggered by miniature EPSPs, or by T-type Ca^{2+} and persistent Na^+ current, and resuming activity in a pattern reflecting previously stored information [51] or intrinsic excitability properties of single neurons [52].

Slow oscillations can be observed in widespread cortical areas. It is possible that an area that appears to participate in this slow, synchronous activity actually acts as the pacemaker driving the other areas involved. Possible areas that could provide such a drive include the basal forebrain [53–55] and thalamus [45, 56]. However, the sparsity of thalamic projections to the entorhinal cortex, subiculum, and hippocampus [57] could limit the potential involvement of the thalamus in slow oscillations. Moreover, the fronto-caudal spread of the slow oscillations [43] and the time shifts between the neocortical and dentate gyrus oscillations [58] indicate that the dynamics underlying slow oscillations may be more intricate.

Slow oscillations and in particular the transitions between UP and DOWN states synchronize neural activity between distant cortical modules [59, 60]. This long range synchronization plays an important role in the realization of systems consolidation, which requires the establishment of connections across many modules [25].

Indeed, the presence of slow oscillations has been positively correlated with the strengthening of memory traces [61, 62]. In addition to intra-cortex coherence, slow oscillations also affect the activity of subcortical areas. Most remarkably, both the hippocampus and thalamus can be modulated in this manner through the slow oscillation [63]. The fast oscillatory events in these areas that relate to slow oscillations are sharp wave ripples (SWRs) in the hippocampus and spindles in the thalamus.

The influence of SWRs is not limited to the hippocampus. Ripples also appear to influence the specific spatiotemporal firing patterns of neocortical cells [41, 44, 64, 65]. Sharp wave ripples propagate to the cortex, resulting in the depolarization of prefrontal cells within 100 ms of hippocampal activity [41, 63–65]. In turn, although sharp waves are thought to be generated within the hippocampus, the timing of their occurrence appears to be modulated by the state of the neocortex, that is, whether it is in an UP or DOWN state. More specifically, even the exact timing of hippocampal activity and ripple events appears to be influenced by neocortical activity. Sirota [65] showed that cortical firing consistently preceded ripple events by 50–100 ms. Hippocampal activity [58] and membrane potentials of hippocampal cells [66, 67] are phase locked to hippocampal sharp waves, though interestingly with varying phase relationship depending the subfield: Isomura et al. [58] found that while activity in the dentate gyrus and CA1 peaks during cortical UP states, the activity in CA3 is larger during DOWN states. Inhibitory interneurons in CA1 have a more depolarized membrane potential during cortical UP states [66], most likely due to the influence of direct inputs from entorhinal cortex. For principal cells, the situation is more diverse: DG granule cells are depolarized during UP states, whereas CA1 pyramidal cells are hyperpolarized; meanwhile, cells in CA3 show diverse hyper- or depolarizing responses to UP states.

These results highlight the complexities of the hippocampal circuitry and of the interactions between cortex and hippocampus, which are yet to be completely clarified. Still there are some enticing speculations: as hypothesized by [33], hippocampal activity during the cortical UP states appears to facilitate consolidation. Select pyramidal neurons in CA3 fire while other cells in this area are suppressed through the activation of inhibitory cells, facilitating cell specificity in consolidation. These patterns of select activation and suppression appear to be mediated by the dentate gyrus. Granule cells transmit neocortical information at a gamma frequency to CA3 pyramidal cells through the potentiation of mossy fiber terminals [68]. Simultaneously these dentate cells also activate interneurons to achieve inhibition of the cells not directly activated [69]. The widespread inhibition observed in CA3 during the UP states is much less prominent in the DOWN state. As a result, activity is not limited to the rigid, predetermined patterns but instead allows for transient self-organized activity to emerge. The ripples that occur during DOWN states may serve to reorganize hippocampal information through the modification of intrahippocampal, subicular, and entorhinal connectivity without affecting neocortical targets. The nature of hippocampal activity in this case appears to depend on the state of the neocortex, which may regulate which patterns are replayed by the hippocampus depending on the current needs of cortical processing [37, 58, 70].

The other side of the loop, the flow of information from the hippocampus to the neocortex, is perhaps best supported by the coincidence of SWR events with transitions between DOWN and UP states in the cortex. [64] and [65] have shown that SWRs tend to coincide with the transition between DOWN and UP states, looking at diverse cortical areas. This is most likely due to the powerful excitatory input from hippocampal bursts helping to reenact activity in the recovering cortex during DOWN states. Vice versa, when looking at the medial prefrontal cortex, a neocortical area receiving direct afferents from CA1 and the subiculum [71], Peyrache et al. [63, 72] found that SWRs were also generated at an enhanced rate at the UP to DOWN transition. This may be understood by reminding the "bistable" nature of the slow oscillation process [49]. The same input can destabilize both the UP and the DOWN state, causing temporary settling in the other state. Indeed it has been observed [73] that other subcortical events, like stimulation of the ventral tegmental area, can trigger UP states or that K-complexes (a fast UP-DOWN-UP state alternation) may be generated by a brief sensory stimulus (e.g., auditory; [74]).

Closely associated to slow oscillations are *sleep spindles*, cortical LFP oscillations of roughly 7–17 Hz that tend to occur at the beginning of an UP state. These oscillations of thalamic origin appear to arise from the interaction between GABAergic neurons in the nucleus reticularis and glutamatergic thalamocortical projections. The former cells act as pacemakers, while the latter propagate the activity to cortical regions [29, 47, 75, 76]. The inhibitory and excitatory thalamic cell ensembles involved in the generation of spindles differ per spindle, as shown by Sirota et al. who observed remarkable variability in spindle power over spindle episodes [64].

In many studies, spindles have been associated with memory consolidation processes, as their occurrence is related to successive memory retention performance (see, e.g., [77–79]). Moreover, spindles tend to be phase locked to hippocampal [80] and parahippocampal [81] ripples. For those reasons, spindles have been speculated to be conducive to replay (or in any case, to active memory consolidation processes) in the cerebral cortex [29]. This point deserves further scrutiny: in the only study where this was specifically analyzed, replay in the prefrontal cortex peaked on average before spindle episodes, rather than simultaneously [72]. Moreover, while membrane potential of cortical neurons is strongly entrained by spindles (see, e.g., [82]), spiking activity in the somatosensory cortex [82] and prefrontal cortex [63] does not seem to be increased during spindle episodes. In contrast, a strong recruitment of inhibitory interneurons, in particular in superficial layers, was observed. Possibly for this reason, prefrontal responses to hippocampal SWRs were found to be damped [63] during spindles. Taken together, these observations seem to speak against a direct role of spindles in the hippocampo-cortical-directed replay phenomena. Rather, the data suggest a role of spindles in "deafferenting" the cortex not only from sensory stimuli as traditionally hypothesized (see, e.g., [83]), but also from subcortically generated inputs, for example, from the hippocampus, by means of strongly recruited feed-forward inhibition. Based on these considerations, an alternative view of the function of spindles is the tagging of networks to be consolidated. Inhibition-mediated deafferentation effectively isolates the cortex from other major inputs that could cause interference. This ensures that the cells activated during

the most recent sharp wave ripple remain the most predisposed to synaptic plasticity. Moreover, the selective enhancement of Ca^{2+} levels in cells during spindles [84] decreases the probability that extraneous information is consolidated.

Dynamics of Cortico-Hippocampal Replay

Memory replay has been thought to be generated by attractor-like dynamics [35]. In other words, replay occurs due to the effect of recurrent excitatory connections driving the activity state of a neural network to a "fixed point" dictated by the values encoded in the synaptic matrix and reflecting previous experience. Recurrent connectivity is especially strong in hippocampal subfield CA3, commonly taken as the first generator of replay processes [25]. However, it is also widespread in the cerebral cortex, lending credence to the role of attractor dynamics in spontaneous activity. Yet, in most simple models, local attractors are viewed as stable states of reverberating activity, the final states reached by a relaxation type of dynamics. That is, they coincide with the distribution of firing rates across neurons that the local network would tend to reach in the absence of new perturbing inputs. This is however not necessarily the case: other views of neural dynamics stress more the convergence to the attractor as the key phase in the process. Persistence of the attractor state may then be hampered by several dynamical factors, such as neural adaptation, synaptic depression [85], or by the changing inputs. Furthermore, interneurons may play a decisive role in the selection of which cell assembly is allowed to activate and in its successive disbanding. This would result in the transient emergence of attractor state, the sudden activation of a *cell assembly*, a tight integrated group of cells, which since the days of Donald Hebb [86] has been postulated to be the basic currency for information encoding. Cell assemblies were detected in the hippocampus with a targeted statistical analysis [87] as group of cells that were simultaneously activated within the time window of a gamma cycle (~30 ms). A similar dynamics was discerned in the medial prefrontal cortex, both during wakefulness and during sleep. In the studies of [88] and [72], rats performed a decision-making task on a Y-maze, while neural activities in the hippocampus and the prefrontal cortex were recorded. During task execution, these two structures oscillate coherently at theta frequency (6–10 Hz) in a behavior-dependent way: coherence is maximal at the "choice point" on the maze, and only after the task has been learned. Interestingly, the synchronization is accompanied by an increase in inhibitory efficacy of prefrontal interneurons. Because prefrontal interneurons, which receive direct afferents from the hippocampus [89], are fairly stably entrained by hippocampal theta [90], this increase in inhibitory synaptic efficacy may have the result of enforcing oscillatory coherence of pyramidal cells. Ultimately, interneurons may play a role in selecting which cells are "allowed" to fire at each gamma cycle and cause strictly timed co-firing of prefrontal cortex cells. Similar patterns of interneuronal activity resulted from prefrontal infusions of dopamine in anesthetized animals [88], which raises the possibility that neuromodulation has a handle on cell assembly

formation through interneurons. Neural ensemble synchronization and the emergence of assemblies were analyzed in these studies by relatively simple statistical techniques, based on principal component analysis (PCA) of the population vectors formed by the activity of tens of PFC neurons recorded simultaneously. Each principal component denotes a group of cells that is more likely than chance to coactivate within the window selected for binning. Specially tailored statistical methodologies were used to find out which of these coactivate groups were indeed significant [91].

With these methods, a time series could be produced measuring the instantaneous degree of coactivation of these ensembles, enabling correlation with behavioral state on one hand and electrophysiological events on the other. In fact, during behavior, assembly synchronization was most likely to occur at the choice point and after the task rule was learned [88], that is, with the same behavioral correlates as hippocampal-prefrontal coherence in theta oscillations. One may speculate that both long-range coherence (hippocampal-prefrontal) and local synchronization (across prefrontal neurons) are generated during behavior as the dopaminergic tone increases, for example, at the time of the last action selection before obtaining reward (i.e., at the Y-maze fork) as the animal becomes more confident of the upcoming reward. Also, the enhanced synchronization may have the effect of favoring spike-dependent synaptic plasticity. In fact, in the sleep following task performance [72], cell assemblies that were active at the choice point were the most likely to replay. It is therefore possible that cell assembly synchronization helps select the activity configurations based on their behavioral relevance and their usefulness towards reaching a reward (as signaled by dopamine). These selected configurations would be the ones that would engender the most plasticity and remain more strongly stored in memory. The statistical methods used in this series of studies were designed to describe the exact time course of replay during sleep. Several conclusions could be reached from this analysis. First, replay only occurs during electrophysiologically characterized slow-wave sleep, which was also shown in [92].

Replay is assessed by measuring the similarity between neural activity patterns recorded during active experience and in the ensuing sleep. Even in the absence of any memory-related phenomena, however, this similarity will not be zero, because of activity correlations that are induced by existing, stable connections. Because of this, it is necessary to compare the obtained similarity value with a baseline level, computed by comparing activity during active behavior with what observed in a sleep period prior to the task.

In the experiment of Peyrache et al., a replay value higher than baseline was only measured in periods when slow waves were present in the local field potential.

Second, replay in the prefrontal cortex peaks during hippocampal SWRs, demonstrating the importance of hippocampal input for initiating replay processes. Third, replay was correlated to cortical slow oscillations in a peculiar way: replay peaked before delta waves, the local field potential correlate of a DOWN state. This somewhat surprising result may be explained in two ways. Either the final part of an UP state, when the intrinsic cortical recurrent drive is subsiding, makes the cortex more amenable to follow the hippocampal drive and replay information under

hippocampal control, or the combination of a SWR and a replay event is strong enough to destabilize the UP state.

In fact, synchronizations both during behavior and during sleep [72, 88] are strong, *rare* events, characterized by power-law, fat-tail distributions of amplitudes and inter-event interval durations. With these probability distribution, there is a sizable chance to observe very large events, much more likely than with more customary distributions (e.g., Gaussian), where probability decays exponentially (or faster) with event size. These large events are the signatures of *avalanche*-like dynamics [93]: activity fluctuates randomly, until it finds a configuration that is uncommonly amplified by recurred feedback, up to the point where it can extend to large swaths of tissue. Thus, this peculiar behavior is another manifestation of attractor dynamics and of the convergence of dynamics towards one of a discrete set of states. A key question that will need to be addressed by further studies is the spread of these replay events. For system consolidation to occur, it is not enough that replay takes place in one cortical area. The prefrontal cortex is a critical structure for long-term memory and is thought to take on the "hub" role that is normally assigned to the hippocampus for recent memories. That is, the prefrontal cortex would contain the "index code" that connects representations spread out over the cortex, joining them into a unitary memory [21, 94]. However, for this to happen, it would be necessary for synchronization to spread from prefrontal cortex (and the hippocampus) to other cortical areas, in the sensory systems, as well as in the medial temporal lobe, which has to be tested in targeted experiments.

The study by Peyrache et al. [72] had a drawback in that it disregarded the temporal ordering aspect of neuronal activity. In fact, it has been known [95, 96] that hippocampal replay preserves not only the composition of synchronized cell groups but also the sequences in which these take place. This is important, as it may be an important drive for simulating and selecting among multiple possible sequences of action. In fact, this type of replay takes place also in wakefulness during small pauses in behavior [97–100], where it may play an important role in goal-directed behavior.

Replay of sequences has also been shown in prefrontal cortex [101] and the visual cortex [102]. A striking feature of these replay events is that they take place at a much compressed temporal rate (~7 times faster) with respect to the rate at which the same sequences are expressed during active experience.

Outlook: Cortico-Hippocampal Interactions as an "Engine" for Memory Reprocessing

The existence of a "dual memory system" with a fast learner for the initial encoding (the hippocampus) and a final, high-capacity store (the prefrontal cortex) is supported by a huge body of literature in the neurosciences of memory, which is not possible to review here in any detail. In the standard view, this dualism is needed to

overcome the difficulties of combining flexible storage of new information with the maintenance of a large body of memorized information [19].

Yet, increasingly in recent years, emphasis has been placed on the qualitative changes that memories undergo as they are placed into a more general framework of previous memories [103, 104]. This involves not simply passive repetition of memory traces but an active process that reorganizes the newly encoded memory traces in order to strategically position them into a relevant context. The reorganization of the memory trace is said to facilitate the extraction of features from the trace, allowing the forming of new associations that can lead to novel inferences and insights [105]. The framework for characterizing such processes has existed for a long time and has been recently revived by a series of studies in rats, showing that even lower mammals are capable of organizing knowledge into "schemas" [106, 107], which facilitate the learning of congruent information. In these experiments, schemas appeared as a result of memory consolidation. The instantiation of these schemas requires the presence of the hippocampus. Their final locus of storage is most likely neocortical and is likely to involve the interaction between multiple cortical areas, with an important role reserved for the medial prefrontal cortex [106]. Little is known about the computational processes behind the formation of schemas, but it seems plausible that replay plays an important role in this. If that is the case, then it is most likely that the concept of replay will have to be extended from a *verbatim* repetition of previous experience to a more complex process, which may support the search for the common underlying structure of several episodic memories [108]. The search for such processes has just started, in particular in experiments on human subjects [109]. But finding traces of these processes in neural ensemble activity will likely require new, more precisely targeted experiments, as well as analytical techniques beyond the current state of the art. This search will not only be relevant for the traditional field of memory studies, but also will also be applicable in the broader context of the neuroscience field. For instance, the organization of perceptual and decision-making processes poses similar requirements for storing and analyzing complex information, which may very efficiently be performed off-line, in a manner similar to memory consolidation processes [110].

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Part IV
Memory Reactivation in Humans

Chapter 11
Memory Reactivation in Humans (Imaging Studies)

Juliane Farthouat and Philippe Peigneux

Abstract Consistent evidence indicates that sleep participates in memory consolidation processes, possibly through the replay of learning-related neuronal activity. Besides animal data, noninvasive brain imaging studies in man (mostly using positron emission tomography [PET] and functional magnetic resonance imaging [fMRI]) have shown the spontaneous reactivation of cerebral activity in learning-related areas during sleep. Additionally, studies triggering reactivation using contextual cues during sleep have suggested a causal role for neuronal replay and reactivation in memory consolidation processes. Finally, several imaging studies support the hypothesis that post-learning sleep promotes a progressive transfer of information from hippocampus toward neocortical stores over time, as a possible consequence of the neuronal replay. Besides neuroimaging techniques, we argue that replay of neuronal activity may also be investigated and accessed at the behavioural level through the study of dreams and sleep disorders.

Keywords Sleep • Memory • Memory reactivation • Humans • Functional magnetic resonance imaging • Positron emission tomography • Consolidation • Brain plasticity • Neuronal replay • Slow wave sleep • Rapid eye movement sleep

Sleep is a multifunctional actor in our everyday (and night) life. Besides, for a few instances, energy conservation [1], cerebral thermoregulation [2], neuronal detoxification [3], tissue restoration [4], deletion of infrequently used cerebral networks [5] and/or preservation of genetically programmed behaviours [6], one important role of sleep is to subtend memory consolidation processes after learning has ended. Already in 1924, Jenkins and Dallenbach disclosed behavioural evidence in man that sleep after learning pairs of nonsense words prevents the forgetting of this verbal material, whereas memory decays in participants kept awake [7]. Although first

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interpreted by Jenkins and Dallenbach [7] as a passive, shielding effect of sleep against diversion interference from other activities experienced during daytime (see also [8]), many behavioural, neurophysiological and imaging studies have demonstrated since that sleep plays an executive role in memory consolidation (for reviews, see, e.g., [9, 10]). Learning and memory consolidation processes are instances of brain plasticity, itself favoured by sleep mechanisms [11, 12]. In this respect, noninvasive brain imaging studies conducted in man using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) during the last 20 years have significantly contributed to our understanding of the cerebral mechanisms underlying sleep-dependent memory consolidation processes. These studies have investigated brain activity during sleep after learning and/or changes in performance-related cerebral networks during daytime as a consequence of post-training sleep manipulation. Before reviewing these studies in the present chapter, we will shortly introduce the reader to the dominant explanatory models of sleep-dependent memory consolidation in man.

Models of Memory Consolidation in Sleep

Like sleep featuring different substates of vigilance (mostly rapid eye movement [REM] and non-REM [NREM] sleep, the latter subdivided into light stage 2 (N2) sleep and deep slow wave sleep [SWS or N3] in man [13]), memory is not a unitary phenomenon. According to the *two-stage theory*, newly encoded memories are stored in two different long-term memory repositories. In the *transitory* long-term memory store, information is quickly learned but is also only temporarily held and therefore easily forgotten. In the *lasting* long-term memory store, encryption takes place at a slower rate, but information is stored for the long term, up to years or even decades [14, 15]. Although connections encoded in the lasting long-term memory store are relatively weak at initial encoding, repetitive interactions with the transitory memory store allow them to be gradually reorganized and reinforced. This process promotes a progressive transfer of the learned information from transitory to lasting memory stores, where it is progressively integrated into pre-existing networks. Converging evidence suggests that the neurophysiological conditions of post-learning sleep offer optimal conditions for information to transfer from transitory to lasting long-term memory stores [12]. Consequently, sleep would exert a beneficial role at the crucial step where information needs to be integrated in already existing networks. One mechanism by which this information may be processed is the reactivation during sleep of the neural patterns underlying the memory trace, i.e. a "neuronal replay."

The *hippocampo-cortical dialogue* model [16] proposes that memory consolidation takes place through repeated interactions between transitory and lasting long-term memory stores across multiple iterations of the sleep-wake cycle. During a learning episode at wake, information collected at the neocortical level is transferred and transiently stored in the hippocampus. During SWS, however, information

would preferentially flow in the opposite direction, from hippocampal to neocortical stores, a phenomenon favoured by the marked decrease in cholinergic activity during this state of sleep [17]. Consequently, repeated or continued activation of the learned memory trace in the hippocampus during post-learning SWS would eventually lead to a progressive transfer toward neocortical lasting long-term memory stores. Conversely, neuronal replay during REM sleep featuring high cholinergic levels might feedback the replayed information toward hippocampal repositories. Repeated SWS-REM sleep cycles would then consolidate and store memories for the long term.

Building up on this model, it has been proposed that neuronal patterns in hippocampal and neocortical stores are synchronized by the alternation of "up" and "down" states of slow oscillations during SWS [18, 19]. Hippocampal sharp wave ripples (i.e. high-frequency bursts of neuronal activity) and thalamocortical spindles (i.e. waxing and waning oscillations in the sigma frequency range lasting 0.5–3 s) are triggered during the depolarizing ("up") phase of the slow oscillations. Sharp wave ripples synchronize with spindles that then propagate within the neocortex, inducing long-term potentiation (LTP) processes eventually modifying synaptic strengths in interconnected neuronal networks [20]. As a result, hippocampal information progressively transfers to neocortical stores, as predicted by the hippocampo-neocortical dialogue model [16]. An enduring debate is whether information is erased from hippocampal stores upon transfer or hippocampal pointers still contribute retrieving the information stored in long-term memory, as proposed by the multiple trace theory [21–23].

An alternative, but not exclusive, model for memory consolidation during sleep is the synaptic homeostasis theory [24]. This model is built on the assumption that memory acquisition during wakefulness is associated with increased synaptic strength in learning-related cerebral areas. This synaptic growing process progressively induces neuronal saturation and decreased plasticity. Neuronal saturation developed at wake will then lead to proportionally increased slow oscillatory activity in stimulated brain areas during post-training SWS. This model hypothesizes that local use-dependent homeostatic regulatory mechanisms during SWS will progressively downscale synaptic weights. This would eventually restore synaptic plasticity for the next day. Besides, synaptic downscaling would reduce the signal-to-noise ratio for the imprinted information, which would participate in the consolidation of the memory traces embedded in highly saturated synaptic networks. Thus, weak memory traces will be removed and stronger traces reinforced, without the need for a transfer between remote brain structures. Consequently, this theory might be more appropriate to account for the consolidation of memories that are not dependent of the hippocampus, e.g. perceptual or motor memories processed at the neocortical level.

Besides their differences, these two theories are likely to represent complementary phenomena in memory consolidation. Also, it should be noticed that both theories assign a main role to SWS in the consolidation of recent memories, especially considering the synaptic homeostasis theory. However, such conceptualizations negate results from behavioural and neuroimaging studies indicating that REM

sleep also plays an important role in memory consolidation processes. That both SWS and REM sleep might contribute in memory consolidation was accounted more specifically in the dual-process and sequential-process hypotheses. According to the dual-process hypothesis, SWS would be especially suited for the consolidation of declarative memories, whereas REM sleep would subtend the consolidation of procedural memories [25, 26] (but see [9] for a critical review). Alternatively, the sequential hypothesis proposes that effective memory consolidation actually requires information processing through SWS followed by REM sleep episodes [27] (but see also [28]), a precursor of this hypothesis being the proposal that SWS protects recent memories against interference that are then consolidated during REM sleep [29].

Neuronal Replay: Insights from Imaging

In a nutshell, spontaneous "replay" of neuronal activity in learning-related brain structures during sleep was initially demonstrated in the rodent hippocampus [30, 31] and then in the song nucleus in birds [32, 33]. In rodents, it was shown that stimulation during wakefulness of hippocampal place cells (i.e. cells firing when the animal occupies particular locations in the environment [34]) selectively increases firing rates in stimulated cells during subsequent NREM and REM sleep [30], as well as coordinated interactions between hippocampal and neocortical cells [35]. Further studies demonstrated that the temporal sequence of firing patterns within neocortical and hippocampal cells during spatial exploration at wake was partially reproduced during subsequent NREM [35–40] and REM [41] sleep. Rodent and bird studies disclosing the repetition during sleep of neuronal activation patterns observed during a spatial or vocal experience at wake were interpreted as instances of neurophysiological processes subtending consolidation in long-term memory stores (but see [42] for a discussion about differentiated processes between mammals and birds). These studies were at the basis of conceptually similar studies conducted in man that will be reported below. However, it should be noticed that a limitation in these animal studies is that no behavioural measures were taken (but see [33]), thus not allowing to ascertain the relationship between sleep-related reactivation and memory consolidation processes.

Imaging Sleep in Man

In humans, the two most widely used neuroimaging techniques have been PET, measuring regional cerebral variations in glucose or oxygen consumption, and fMRI, measuring changes in blood-oxygen-level-dependent (BOLD) signal, both being considered indirect markers of neuronal activity. Using the PET technique, pioneering studies evidenced distinctive functional neuroanatomical regional correlates of REM

and NREM sleep [43–46]. Further studies conducted using PET and fMRI disclosed the neural correlates of phasic events during sleep such as ponto-geniculo-occipital (PGO) waves subtending rapid eye movements during REM sleep [47, 48] (see also [49] using magnetoencephalography [MEG]) and NREM spindles [50], but also tonic delta activity featuring slow oscillations [51, 52] (for a review, see [53]). Other functional neuroimaging studies demonstrated preserved patterns of brain reactivity to external auditory stimulation during sleep stages (e.g. [54–58]). This suggests that information processing is still possible during sleep, in line with previous studies using electroencephalography (EEG) (for a review, see [59]).

Spontaneous Neuronal Replay in Human Sleep

Evidence for the reactivation of learning-related functional cerebral patterns in man was initially found during REM sleep [60]. In a PET study, participants were scanned while trained on an implicit probabilistic serial reaction task (SRT) in which they were instructed to press as fast and accurately as possible on the response key corresponding to the position of a stimulus displayed on a computer's screen. Unknown to them, the succession of positions followed complex probabilistic rules. Although participants were unable to verbally report the regularities of the sequential material or to reproduce the practiced sequence later on, they gradually developed faster reaction times (RTs) for items following the probabilistic rules than for deviant unexpected locations, which demonstrated implicit procedural learning in this task [61]. Other participants were trained to the task or kept in quiet awake conditions and then scanned while sleeping at night during REM and NREM (N2 and SWS) sleep periods. Results showed increased activity during REM sleep in subjects trained to the task and more so than in untrained participants in the mesencephalon, bilateral cuneus and left premotor cortex already found activated during practice of the SRT task. Furthermore, left premotor cortex activity during REM sleep was functionally more correlated with activity in the left posterior parietal and bilateral pre-supplementary motor areas in trained than in untrained participants, suggesting the optimization of the brain networks subtending visuomotor responses [62]. Finally, to test the hypothesis that reactivation in learning-related areas during REM sleep was specific to the reprocessing of the implicit rules driving the succession of the displayed locations, more than to the mere optimization of basic visuomotor skills, a new group of participants was similarly trained before being scanned during sleep, but this time using a fully random sequence of stimuli [63]. This latter study demonstrated reactivation in learning-related areas (i.e. the cuneus bilaterally) during REM sleep in subjects trained to the probabilistic SRT task but not in those trained to the random material. This indicates that reactivations were indeed related to the implicit acquisition of the probabilistic rules that defined stimulus sequences. Cuneus activity during REM sleep also correlated with rCBF variations in the striatum, a key area in probabilistic sequence learning [61], significantly more in participants

trained to the probabilistic than to the random task. These results supported the hypothesis that REM sleep is deeply involved in the reprocessing and optimization of the high-order information contained in the material to be learned. Besides, cuneus activation during REM sleep positively correlated with performance levels achieved at the end of learning, suggesting that post-learning reactivation during sleep is modulated by the strength of the memory traces developed during the learning episode [63].

Although brain activity was recorded during all stages of sleep, no effects were observed during NREM sleep periods using the probabilistic SRT task described above, at variance with the many animal findings of neuronal reactivation during NREM sleep. However, rodent studies mostly used hippocampo-dependent spatial orientation tasks, which was not the case of the probabilistic SRT task in which learning is subtended by striato-cortical networks. Therefore, participants were trained in a further PET study on a spatial navigation task in which subjects had to learn their way in a virtual town [64]. During practice, performance in spatial navigation was associated with increased activity in hippocampal and parahippocampal regions. During post-training NREM sleep (N2 and SWS), but not during REM sleep, reexpressed activity was found in learning-related brain areas in trained participants, as compared to participants trained on the procedural memory SRT task described above. Furthermore, the amount of hippocampal activation during SWS positively correlated with performance improvement on the next day. Altogether, these results suggested that learning-dependent modulation in hippocampal activity during human sleep reflects the offline processing of recent episodic and spatial memory traces, eventually leading to the plastic changes underlying the subsequent improvement in performance.

Reactivation during sleep was also evidenced using fMRI in visual-learning-related areas after intensive training on a perceptual texture discrimination task [65]. In this study, the authors found increased activity during post-training SWS (as compared to the night before learning) in stimulated areas of the primary visual cortex (V1). Also, the amplitude of the BOLD signal in trained regions during SWS correlated with subsequent behavioural improvements in performance to the task. Finally, sleep spindle-related reactivation after learning paired associates was disclosed using EEG/fMRI [66]. In this study, participants learned face-scene associations or performed on a visuomotor control task and then were scanned during subsequent NREM sleep. Results showed that learning face-scene associations (as compared to visuomotor practice) triggered a stronger combined activation of neocortical and hippocampal regions during subsequent sleep. Noteworthy, reactivations were in temporal synchrony with spindle events, tuned by ongoing variations in spindle amplitude and restricted to the face- and scene-selective visual cortical areas previously activated during presleep learning. Additionally, spindle-coupled hippocampal activation was proportional to the participant's performance at the end of learning. Altogether, spontaneous reactivation studies suggest the reprocessing of previously learned information during post-learning sleep, a reactivation possibly organized by sleep spindles in the case of hippocampal-neocortical memories.

Triggered Neuronal Reactivation During Sleep

Reexpressed activity in learning-related areas during sleep and correlations with overnight performance improvement are positive evidence supporting the hypothesis that neuronal replay is associated with memory consolidation processes. However, positive associations do not allow inferring causality patterns or the directionality of the relationships between behaviour and brain activity. Adopting a different experimental strategy, several researchers have attempted cueing the material learned at wake and then presented the cues during the subsequent sleep episode assuming that the cue would trigger the reactivation of the associated memory trace.

Triggering learned information during sleep has been mainly investigated in the declarative memory domain. In the Rasch et al. study [67], participants had to learn objects' locations in a two-dimensional memory task while a context odour cue was released. During subsequent SWS, representation of the associated context odour, but not of an odour not associated at learning, improved overnight memory performance above levels obtained after a normal night of sleep. However, reexposure was ineffective during REM sleep or wakefulness. Additionally, fMRI data showed that releasing the associated context odour during SWS activated the hippocampal formation, further reinforcing the hypothesis that odour cues had reactivated the declarative memory traces.

Although an advantage of odours cueing is that odours are devoid of awakening properties [68] making these a useful tool in sleep studies, cueing-related improvement of memories in sleep is not restricted to olfactory material. For instance, representation of a clicking noise displayed in background during learning a complex logic task [69] or auditory stimulation after learning Morse code [70] enhanced overnight memory when auditory stimulations were coincident with rapid eye movements during REM sleep. Further using EEG, Rudoy et al. [71] had participants learning object locations, each object being associated with a congruent sound (e.g. meows for the cat image). During a subsequent nap, half of the object-associated sounds were represented. Results showed better recall for cued than non-cued images, suggesting specificity in the triggered reactivations and in the ensuing consolidation for the targeted items. Using a similar experimental protocol and fMRI, participants were scanned during SWS while presented object-associated auditory cues [72]. Despite similar memory performance in the experimental and control conditions, evoked BOLD responses during SWS were higher for cue than control sounds in the right parahippocampal area. Furthermore, parahippocampal connectivity with posterior visual areas was increased upon presentation of cue sounds, an effect interpreted by the authors as indicating that cues-related evoked responses during sleep were not merely limited to the processing of auditory stimulations, but extended to visual areas recruited during the task. This effect is congruent with the report of spindle-related reactivation of paired associates in hippocampal and task-specific face and locations-related areas, as described above [66]. Additionally, activity in thalami, medial temporal lobe (including the hippocampus)

and cerebellum correlated with overnight performance, as well as connectivity levels between the parahippocampal areas and the precuneus.

In their fMRI study, Rasch and colleagues also trained volunteers on a finger-tapping motor procedural memory task, again cued with an odour [67]. However, representation of the cue odour during SWS or REM sleep was ineffective to improve memory, in contrast with SWS-cueing-related improvements observed after the declarative memory task. However, this negative result does not preclude the hypothesis that triggering memories during sleep could boost procedural learning. In this study, odours were not presented coincidently with rapid eye movements like in the Smith and Weeden [69] or Guerrien et al. [70] studies, a temporal coincidence probably difficult to achieve using odours. Also, it is possible that such type of non-hippocampus-dependent procedural memories could not be cued by odours, since odour pathways directly link to the hippocampus. Indeed, in another behavioural study, subjects trained to a melody-playing task in which they sequentially pressed keys following a screen template. Two sequences of key presses were practiced, corresponding to two different melodies. During a post-learning subsequent nap (NREM sleep), one of the two melodies was replayed. Results showed better performance improvement for the sleep-replayed than for the other melody [73], suggesting that cueing during NREM sleep is also beneficial for sensorimotor memories.

Neurophysiological Markers of Memory Consolidation

Many electrophysiological studies have found an association between the overnight consolidation of memories and spindle parameters (e.g. [73–76]) modulated by slow oscillations (e.g. [77–79]), in line with the theoretical assumption that reactivation and consolidation processes are subtended by the interaction between slow oscillations, sharp wave ripples and spindles in NREM sleep. For instance, spindle density positively correlates with performance change in declarative memory tasks [80–84]. Similarly, slow wave activity correlates with performance improvement in both declarative and non-declarative memory tasks [78, 85]. Also, electrical brain stimulation at the frequency of slow oscillations using transcranial direct stimulation (tDCS) during NREM sleep improved overnight performance on a word pairs memory task, above the effect of an undisturbed night of sleep, suggesting a causal role for slow wave activity in declarative memory consolidation [86]. Besides, sleep ripples in the medial temporal rhinal cortex correlate with recognition performance for items studied prior to sleep [87], and intracranial recordings in epileptic patients have shown that sleep ripples are phase locked to spindles and synchronized to slow oscillations [88, 89]. This further reinforces the assumption that (para)hippocampal ripples, spindles and slow oscillations act in synchrony to promote the consolidation of associative and declarative memories, as also demonstrated in animal studies (see, e.g., [90, 91]). To the best of our knowledge, only one neuroimaging study to date disclosed interactions between synchronized sleep spindle activity and memory consolidation for associative material ([66], see above). Further neuroimaging

studies should investigate in depth these issues, but also investigate the role and defining features of phasic and tonic events during REM sleep in relation to reactivation and memory consolidation processes that remain nowadays neglected and misunderstood.

Neuronal Replay: In Wake and Sleep

The identification and characterization of the neurophysiological sleep parameters subtending offline memory consolidation processes should not obscure the fact that memory processes already take place during wakefulness, both during learning and post-training wakefulness periods. In this respect, memory consolidation should be seen as a continuous and cyclic process in which alternating states of vigilance differentially contribute to the storage and updating of information in long-term memory stores. Accordingly, continued activity in learning-related areas during a subsequent attentional task was demonstrated using fMRI both after spatial declarative and non-declarative procedural learning [92]. These results indicated that the human brain already extensively process recent memories during the first hours of post-training wakefulness, even when simultaneously coping with unrelated cognitive demands. Continued neural activation during brief pauses at exploration or a short post-learning period was also observed in animal studies (e.g. [31, 93–97]), similarly suggesting continued processing of recent experience at wake. However, slow frequency tDCS known to promote memory consolidation when applied during NREM sleep [86] was reported to enhance theta activity and memory encoding in man when applied during learning at wake, but not when applied after the end of the learning episode [98], hence casting doubts about the relevance of these wakefulness-related neural activities for memory consolidation per se.

In this respect, differences between wake- and sleep-related triggered reactivations were investigated using fMRI and an object-location task cued by odours [99]. In this study, subjects were trained to an object-location memory task associated with a contextual odour, like in the Rasch et al. study [67] (see above). After training, they were kept awake or allowed to sleep for 40 min. During this wake or sleep period, the contextual odour cue was released for 20 min. Subjects then learned new associations between previously learned objects and their location on the grid, hence creating interference. Finally, they were tested for their memory of the object-location associations learned before the post-sleep (or post-wake) period. At the behavioural level, odour cueing had opposite effects when presented during sleep or wakefulness. Odour-related reactivation during wakefulness destabilized memories as shown by decreased retrieval performance, whereas retrieval was enhanced when the odour was displayed during sleep, in line with prior behavioural studies indicating higher resistance to interference after sleep (e.g. [100]; but see [101]). At the functional neuroanatomical level, presentation of contextual odour cues during the post-training wakefulness period mainly enhanced activity in the prefrontal cortex, whereas odour release during post-learning sleep mainly induced higher activity in

the hippocampus and posterior neocortical areas involved in memory processing and retrieval. Hence, these results suggest that reactivation of memory traces may serve distinct and possibly complementary functions depending on the brain state of wakefulness or sleep.

Finally, the same authors investigated differences between spontaneous and triggered reactivations (i.e. natural vs. cued sleep) [102]. In this latter study, participants learned object-location associations and then were allowed to sleep for either 40 or 90 min without any odour presentation. Data were compared to the 40-min cued odour condition in the study described above [99]. Results showed that natural post-training sleep was beneficial for memory in the 90-min condition only and that memory enhancement in this spontaneous sleep condition was to the same extent as that of the one observed in the odour-cued 40-min post-training sleep condition. This suggests that cueing memories during sleep accelerates the consolidation process by which novel associations are integrated in long-term memory stores. Interestingly, the amount of post-training SWS correlated with performance improvement in the natural 90-min sleep condition, but not in the 40-min cued sleep condition, suggesting that triggered reactivation of learning-related neural patterns might improve memory through different mechanisms than during undisturbed SWS.

Imaging the Consequences of Memory Reactivation During Sleep

An alternative, indirect approach to investigate sleep-dependent memory consolidation processes is to probe related changes in brain activity during the retrieval of the associated material at wake after sleep has taken place or has been suppressed during the post-learning night. In their fMRI study showing higher evoked BOLD responses for cue than control sounds in parahippocampal regions during SWS after learning object-location associations, Van Dongen et al. [72] also investigated post-sleep changes in cerebral connectivity for items cued versus not cued during SWS. Retrieval of reactivated object-location associations, but not retrieval of non-cued associations, correlated with pre- to post-sleep connectivity changes between parahippocampal and medial prefrontal areas. These results indicate that cueing during sleep may also modify connectivity patterns within cerebral networks subtending memory retrieval at wake.

Other studies had participants scanned using fMRI during learning, allowed to sleep or sleep deprived for the post-learning night and then scanned again 2–3 days later during memory retrieval. Recovery nights aimed at scanning participants at similar levels of vigilance to avoid impeding memory-related activations by the known effect of sleep deprivation on brain activity patterns (see, e.g., [103]). One of the first studies showed that sleep deprivation both impact on performance and underlying cerebral activity at delayed retrieval in a procedural motor pursuit task [104]. Also, connectivity between performance-related activity in superior temporal sulcus and cerebellum, and between frontal and supplementary eye fields, was increased in the sleep condition. Similarly, another fMRI study showed sleep-dependent

stabilization in visuomotor adaptation skills [105]. During training, activity in a set of cerebellar, striatal and cortical areas was proportional to performance improvement. During retest, participants deprived of sleep on the post-learning night recruited the cerebello-cortical networks involved at the earliest stages of learning during task performance, whereas participants in the post-learning sleep condition exhibited a similar pattern of cerebral activity during learning and retest. Additionally, increased activity in hippocampal and frontal areas during learning was associated with a better resistance against the detrimental effects of sleep deprivation. Optimization in learning-related networks was also shown after practice on procedural motor sequential finger tapping [106, 107] and visual discrimination [108] tasks. Finally, sleep after implicit learning on the probabilistic SRT task was associated with a diminished differentiation between event-related fMRI responses to items following versus violating the sequential rules, despite similar overnight changes in performance in sleep and sleep-deprived post-learning conditions [109]. Modified responses were found in a set of cortical and subcortical areas previously identified as being part of the networks involved in implicit sequence learning and its offline processing during REM sleep [60, 63] (see above). These results indicate the sleep-dependent development of distinct neurophysiological processes subtending the consolidation of implicit motor sequence learning.

Similarly in the declarative memory domain, sleep and sleep deprivation on the night after training on a virtual spatial navigation task (as used in [64] disclosing hippocampal reactivation during NREM sleep) resulted in similar levels of performance at the behavioural level. However, fMRI analyses also revealed that post-learning sleep promoted a shift in cerebral activity patterns underlying topographical memories [110, 111]. In participants deprived of sleep after learning, performance in route retrieval was mostly associated with hippocampal activity, like during learning. In participants in the post-learning sleep condition, however, navigation performance was additionally associated with activity in striatal areas, suggesting that brain activity is restructured during sleep in such a way that navigation becomes progressively contingent on a procedural-like, response-based strategy mediated by the striatum. In these studies, both neural strategies eventually led to equivalent performance levels as measured in retest sessions, indicating that covert reorganization of brain patterns after sleep is not necessarily accompanied by overt changes in behaviour.

A sleep-dependent evolution in brain patterns underlying verbal memory retrieval was also evidenced on the long term. Indeed, hippocampal activity during retrieval of word pairs was higher 2 days later in participants who slept than who were kept awake the night after learning, but not when tested 6 months later. At variance, an opposite pattern of activity was found in the medial prefrontal cortex with enhanced word retrieval-related activity at the 6-month testing only [112]. Similarly, Takashima et al. [113] evidenced a continuous decrease in hippocampal activity during recognition of learned pictures over a 3-month period, whereas activity in the ventral medial prefrontal cortex gradually increased. Likewise, fMRI studies having investigated the sleep-dependent processing of emotional memories have shown larger stimulus retrieval-related responses 3 days after learning in the hippocampus and medial prefrontal cortex in the sleep than in the sleep-deprived condition. This short-term increase was coupled with higher sleep-dependent connectivity and an

additional involvement of emotion-related amygdala responses [114] and then followed by increased connectivity patterns between long-term neocortical stores and emotion-related areas when retested 6 months later [115]. Altogether, these studies are consistent with the hippocampo-neocortical dialogue hypothesis featuring a progressive transfer of information from the hippocampus toward neocortical stores over time and sleep, which might be modulated by additional parameters such as emotion or contextual information.

Dreams and Neuronal Replay

Neuroimaging techniques have been used to record brain activity during post-learning sleep under the assumption that reproduction and triggering of learning-related cerebral activity patterns during sleep reflects the ongoing processing of memory traces eventually leading to their consolidation in long-term repositories. To conclude this chapter focused on imaging memory reactivations in man, we will argue that reactivation processes may also be investigated and accessed at the behavioural level through the study of dreams and sleep disorders.

Dreams, like any mental production, are grounded in brain activity [116–118] and experienced daily events are often incorporated into dreams [119, 120]. This suggests a possible link between the incorporation or recently learned information into dreams and their neuronal replay-related consolidation in memory during sleep. Supporting this hypothesis, information items repeatedly accessed during sleep and elaborated for insertion into ongoing dream experiences are better retained at delayed recall [121]. Also, task-related dream imagery during NREM sleep in a nap after topographical learning in a virtual navigation task was strongly associated with performance improvement, which was not the case for task-related thoughts during waking [122], suggesting that dream experiences indeed reflect memory processing during sleep.

By definition, dream reports can be reported upon awakening only, i.e. in a different state of vigilance than when the dream is experienced, leading to the fact that various factors may bias a posteriori dream descriptions (e.g. forgetting, a posteriori reconstruction, censorship or introspective abilities). In this respect, the study of sleep disorders featuring spontaneously enacted verbal or motor activity while sleeping might offer promising perspectives to visualize “online” the expression of dreams and their relationships with memory consolidation processes. For instance, loss of muscle atonia in REM Behaviour Disorder (RBD) may be associated with a dream-like enactment featuring pseudo-hallucinatory and repeated limb movements involving complex violent (fights) and nonviolent culturally acquired behaviours [123] associated with increased activation in sensorimotor structures during the RBD episode [124]. In a seemingly similar manner, sleepwalking features a dissociation between activation of thalamocingulate pathways and persisting deactivation of other thalamocortical arousal systems [125], associated with abnormal behaviour, wandering and/or speech during NREM sleep that may match dream reports upon awakening [126, 127]. The hypothesis that recent learning at wake would be

replayed and expressed in abnormal sleep patterns was specifically tested in two populations of patients with RBD and sleepwalkers trained to repeat a sequence of arm movements [128]. After learning in this variant of the SRT task, subjects spent the night in the laboratory. Video-polysomnography recordings evidenced the reproduction of a large fragment of the learned motor sequence during a sleepwalking episode in one patient. Also, analyses of video recordings conducted by judges naive to the experimental manipulation classified on average more movements as similar to the learned motor sequence in trained than untrained sleepwalkers. Although a definite reproduction of the learned motor sequence could be observed in one patient only out of 19 sleepwalkers, and no such reactivation was found in any RBD patient, this result indicates the behavioural expression of the ongoing processing of a recent memory trace during SWS. Whether this behavioural expression is associated with memory consolidation and subsequent performance improvement remains to be ascertained in future investigations.

Interestingly, but maybe also surprisingly, the suggested relationships between memory consolidation and post-learning dream mentation [122] or dream-like enactment [128] have mostly disclosed a role for NREM sleep, which might be consistent with the proposal that episodic memory sources are on average more present in NREM than REM sleep [129]. In this respect, it should be considered that not only spatial navigation but also the explicit learning of a motor sequence involves hippocampal regions and that initially increased hippocampal activity during motor learning was associated with the initiation of sleep-dependent memory consolidation processes [130]. These elements would be consistent with the proposal that isolated episodic elements reported in dreams are the consequences of neuronal replay and the ongoing hippocampo-cortical dialogue [131] that mostly takes place during SWS. In this view, we have shown in this chapter consistent neuroimaging evidence that hippocampus-related experience is repeatedly reactivated and transferred to the neocortex integrating new information in long-term memory. Hippocampo-neocortical transfer is also driven by phasic activity such as hippocampal ripples, which are discrete neuronal bursts themselves associated with thalamic and cortical spindles. These phasic events may favour the transfer of discrete quanta of information, making likely the reactivation of isolated elements of recent memories during sleep and then during dreams. According to Schwartz [131], this would explain why incorporations of daytime-experienced information during dreams are rarely an exact reproduction of this event but rather the expression of parcelled features. At variance, old memories already integrated within interconnected neocortical networks (but also more semanticized) might be more completely integrated in our dreams.

Further studies combining neuroimaging techniques with the collection of dream-related mental and neural activities in healthy populations and in sleep disorders should probe these hypotheses, and continue investigating how neuronal replay in REM and NREM sleep stages shapes sleep-dependent memory consolidation processes in man.

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Part V
Computational Modeling of Coordinated Neural Activity

Chapter 12
Models and Theoretical Frameworks for Hippocampal and Entorhinal Cortex Function in Memory and Navigation

Nathan W. Schultheiss, James R. Hinman, and Michael E. Hasselmo

Abstract The hippocampus and related medial temporal lobe structures subserve both navigation and memory. These seemingly disparate functions have been characterized extensively at the cellular, network, and systems levels, leading to models of the hippocampus at different levels of abstraction. Mechanistic models relating neural activity to spatial and/or mnemonic function often rely on representations of individual neurons, synapses, or network structure, while theoretical models of the hippocampus incorporate and attempt to reconcile aspects of the hippocampal codes for space and/or past experience. In this chapter we first provide a brief introduction to the research history and concepts relating the hippocampus to memory and navigation, incorporating an overview of some of the influential models and theories that have been proposed to capture aspects of the hippocampus's role in mnemonic or spatial processing. We then describe the anatomy of the hippocampal-entorhinal circuit, emphasizing the rough division of labor across hippocampal subregions and entorhinal cortex related to the computational demands of navigation and episodic memory. Next, we discuss the role of oscillations and cross-frequency coupling in coordinating neural activity to encode spatially and temporally sequenced information about ongoing or remembered experience. Finally, we discuss an important conceptual framework that links numerous experimental observations of hippocampal spatial and mnemonic function based on commonalities between map-based and self-motion-based navigation strategies on the one hand and semantic and episodic memory on the other.

Keywords Hippocampus • Entorhinal cortex • Memory • Navigation • Oscillation • Theta • Gamma • Pattern separation and completion

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The hippocampus and related medial temporal lobe structures subserve both navigation and memory. These seemingly disparate functions have been characterized extensively at the cellular, network, and systems levels, leading to models of the hippocampus at different levels of abstraction. Mechanistic models relating neural activity to spatial and/or mnemonic function often rely on representations of individual neurons, synapses, or network structure, while theoretical models of the hippocampus incorporate and attempt to reconcile aspects of the hippocampal codes for space and/or past experience. In this chapter we first provide a brief introduction to the research history and concepts relating the hippocampus to memory and navigation, incorporating an overview of some of the influential models and theories that have been proposed to capture aspects of the hippocampus's role in mnemonic or spatial processing. We then describe the anatomy of the hippocampal-entorhinal circuit, emphasizing the rough division of labor across hippocampal subregions and entorhinal cortex related to the computational demands of navigation and episodic memory. Next, we discuss the role of oscillations and cross-frequency coupling in coordinating neural activity to encode spatially and temporally sequenced information about ongoing or remembered experience. Finally, we discuss an important conceptual framework that links numerous experimental observations of hippocampal spatial and mnemonic function based on commonalities between map-based and self-motion-based navigation strategies on the one hand and semantic and episodic memory on the other.

Hippocampal Mnemonic Function

It is now widely accepted that the hippocampus plays a critical role in the formation and intermediate storage of episodic memories, that is, memories of life events or "episodes" typically incorporating objects and/or people of some relevance and unfolding in a particular location within a limited time frame. Early insights into the brain systems responsible for memory were derived largely from studies of amnesic patients with focal brain lesions caused by disease, injury, or in some cases medical treatment [1–3]. Perhaps the most notable case, patient H.M. (Henry Molaison, 1926–2008), exhibited anterograde amnesia such that he was no longer able to form new episodic memories after undergoing surgery to ameliorate intractable epilepsy which involved bilateral removal of his anterior hippocampus and adjacent structures including the amygdala and entorhinal cortex [1]. Although his intellect, his ability to transiently store and use information in working memory, and his ability to acquire new motor or procedural skills were spared [4, 5], H.M. exhibited temporally graded retrograde amnesia whereby his memory for relatively recent events (prior to the surgery) was impaired while older memories remained intact. The sparing of H.M.'s childhood memories was a striking illustration that episodic memories are initially dependent on the hippocampus, but with time and perhaps repeated recollection or experience of similar events, memories of the more distant past seem to become independent of an intact hippocampus.

The amnesic consequences of H.M.'s surgery (and many other cases of humans with hippocampal damage) were instrumental in establishing theories and models

of multiple memory systems in the brain that distinguish implicit memory for skills and procedures, priming effects, and perceptual learning, from explicit forms of memory including semantic memory for factual information and episodic memory [6]. Hippocampal lesions in humans cause impairments on tests of recollection-based recognition memory, free recall of lists of items, and cued recall of paired associates [1, 3, 7]. In rats hippocampal lesions cause impairments in tasks requiring relational memory such as the transitivity and transitive inference tasks [3] and tasks requiring aspects of sequence memory such as the order of items in a list [8] or the end of overlapping lists [9]. Hippocampal lesions also impair trace conditioning in classical conditioning paradigms [10]. Hippocampal models using rate-coded neuronal activity have simulated performance on free recall, cued recall [11], and recollection-based recognition [12]. The critical role of the hippocampus in episodic memory has been modeled as encoding and retrieval of a sequence of patterns [13–16] or of a complex spatiotemporal trajectory associated with specific items or events [17]. Hippocampal models have also captured the temporal gradation of the hippocampal dependence of episodic memory [18, 19], such that episodic associations are initially formed in the hippocampal formation and then reactivated during quiet waking or slow-wave sleep leading to long-term representations in the neocortex.

Integrating several of the key features of hippocampal-dependent episodic memory outlined above, the "hippocampal memory indexing theory," proposed originally by Teyler and DiScenna [20] and revisited recently by Teyler and Rudy [21], advocates that episodic memory traces in the hippocampus do not themselves possess the content of remembered experiences. Rather, neocortical activity patterns representing the features of an experienced episode become associated in the hippocampus forming an index. In the contemporary formulation of indexing theory, subsequent activation of the hippocampal index by a subset of the features of the original experience can then reactivate the full content of the memory through the hierarchy of reciprocal connectivity between the hippocampus, entorhinal cortex, and lower-order sensory and associational cortices. Indexing theory points to possible differences in hippocampal and neocortical induction of long-term synaptic modification to help explain the fast formation of the hippocampal index and the slower process of *systems consolidation* whereby episodic associations are trained in the neocortex with repeated activations of the index. This aspect of indexing theory is proposed to underlie the observation that older memories are more resistant to disruption than memories of the more recent past (Ribot's law) [22] and is useful in interpreting the temporal gradation of retrograde amnesia exhibited by humans with hippocampal damage.

Navigation by Cognitive Maps and Path Integration

The role of the hippocampus in navigation and spatial coding began to be appreciated largely with the seminal observation of O'Keefe and Dostrovsky [23] that hippocampal principal cells fire in well-defined locations within an environment.

O'Keefe and Nadel [24] subsequently proposed that populations of these "place cells," each coding for a particular location, form a "cognitive map" of an environment by which navigation can be guided. Such map-based or *allocentric* navigation [25] relies on knowledge of the static spatial relationships between features of an environment [26] and supports self-localization in terms of the collective activity of place cells, i.e., the place code, within the cognitive map of a given environment. Alternatively, *egocentric* navigation, also known as path integration or dead reckoning, depends on neural integration of self-motion information, including heading directions and distances (or speeds and times), relative to a known starting point [27]. Thus, the spatial coding mechanisms exhibited by hippocampal formation structures comprise two subsystems for navigation distinguished primarily by their dependence on environmental or self-motion information. However, map-based and path integration strategies for navigation depend on some of the same neural machinery or computations, i.e., networks of spatially or head direction-tuned neurons (discussed further below), and they are complimentary such that both probably function in all environments to greater or lesser degrees. However, under conditions where environmental cues are limited, or in novel environments where landmarks have little a priori significance, the ability to navigate may depend more strongly on an animal's knowledge of how it reached its current location than on local environmental landmarks.

Given the interconnectedness in these strategies for navigation, it is not surprising therefore that allocentric and egocentric navigation strategies rely on some of the same neural processes. For instance, self-localization by path integration requires knowledge of a starting location. Thus, path integration may also be understood as a mechanism whereby existing cognitive maps (of familiar environments) are extended to incorporate new locations or to link existing maps together. In this scenario, an existing map functions as the known starting point for path integration-based navigation, and exploration of areas outside the existing map creates associations incorporating the new spaces and extending the map.

Since the discovery of place cells, other forms of spatially tuned neurons have been identified that contribute to the putative cognitive map. Most prominent among these are grid cells, which also fire in spatially restricted locations within an environment, but in contrast to the selective representation of a single location by individual place cells, grid cells exhibit multiple firing fields arranged at the vertices of tessellated triangles (or overlapping hexagons) covering the 2-dimensional extent of open field environments [28]. Grid cells are found in the deep cortical layers of the entorhinal cortex (EC) as well as in the pre- and parasubiculum, but are most abundant in layer II of the EC. Layer II grid cells have generally been considered to be entorhinal stellate cells which, in contrast to pyramidal cells, are intrinsically oscillatory neurons exhibiting subthreshold membrane potential oscillations (SMPOs) and subthreshold resonance in the theta frequency band (6–12 Hz). Models of grid cell spatial periodicity generally fall into one of two classes: network attractor (NA) models and oscillatory interference (OI) models. Several early implementations of OI models were based on the intrinsic oscillatory dynamics of stellate cells, but recent work suggests that grid cells also include pyramidal cells in the

superficial layers of the entorhinal cortex [29, 30]. More contemporary grid cell models have used network oscillations or a combination of oscillations and attractor dynamics [30–32], but the cellular and/or network mechanisms underlying the spatially periodic firing patterns of grid cells remain unproven.

We discuss the hippocampal subfields in greater detail later in the chapter, but it is useful to note that layer II grid cells project to the early stages of hippocampal processing, i.e., the dentate gyrus and CA3 hippocampal subfields, whereas grid cells in the deep layers of the entorhinal cortex receive hippocampal output from CA1 and the subiculum. Thus, entorhinal grid cells appear both at the last cortical processing stage prior to the hippocampus as well as at the first cortical stage receiving output from the hippocampus proper and are likely to possess very strong bidirectional interactions with the hippocampal place code. Moreover, a subset of hippocampal place cells and deep-layer entorhinal grid cells respond to a combination of spatial and directional parameters such that these conjunctive place- or grid-by-head direction cells fire action potentials within their spatial firing fields but only when the animal traverses a field with its head facing in a particular direction [33]. This more complicated set of firing contingencies implies the integration of spatial and directional information at the level of individual neurons. In fact, a significant fraction of neurons in the dorsal presubiculum (postsubiculum) [34, 35], retrosplenial cortex [36], parasubiculum [37], and medial entorhinal cortex [33, 37] respond to the direction that an animal is facing rather than where it is currently located. These head direction cells are understood to provide an internal compass contributing to the ability to navigate.

In addition to place and grid cells, spatial features of an environment are also encoded by boundary vector cells, or "border cells," found in the medial entorhinal cortex [38] and subiculum [39], and which fire preferentially along stable borders of an enclosed space [38]. Some cells also fire in response to objects located within an environment, and these seem to be preferential for objects deemed to be more stable features of the environment, i.e., immovable, rather than transient placements of movable objects. Leaving aside precise delineation of what constitutes a feature *of* an environment from what constitutes an object *within* an environment, the responses of such cells to objects within an environment begin to suggest that the hippocampal-entorhinal circuit encodes not only environmental space but, even at the level of individual neurons, also calculates the spatial relationships of items within an environment. Thus, within the hippocampal-entorhinal circuit, the ingredients necessary for mapping space, self-localization, localization of items within certain spaces, and the heading of self-motion are encoded in the firing properties of individual neurons.

Remapping

The place fields of individual place cells (and the spatial relationships between them) differ across environments, such that the patterns of place cell activity constitute distinct maps of different locations using overlapping neuronal populations.

Like place cells, grid cells exhibit remapping between environments or in novel contexts. This points to interactions between the entorhinal cortex and hippocampus, providing a flexible representation of space in different environments and under different motivational contexts. Unlike place cells, however, grid cell remapping consists of differences in spatial phase, i.e., lateral shifts of grid fields, and the angular orientation of the axes along which grid fields are aligned. Also, whereas different subsets of place cells seem to be active in different environments, grid cells seem to be active in all environments, and only the locations of their firing fields are remapped. Interestingly, in contrast to their grid-like spatial tuning in open field environments, in segmented or repeating environments such as a spiral maze [40] (personal communication with Dr. M. P. Brandon) or hairpin maze [41], grid cells exhibit firing fields on each segment with relatively fixed spatial relationships to the individual segment. This pattern of firing behavior may suggest that grid cells are specialized to respond to spatially regular features of an environment rather than directly coding for particular locations.

The increased specificity of spatial information encoded by place cell firing (coding for a particular location) relative to grid cell firing (coding for numerous locations) is consistent with the positioning of the hippocampus at the top of hierarchically organized levels of neocortical processing stages, i.e., at greater "neural distance" from the primary sensory cortices, which for memory models allows the hippocampus to associate highly processed information patterns rather than requiring associations be made between the innumerable raw features of experience. This line of thinking would suggest that place cell spatial firing specificity might depend on integration of spatial information from grid cells. Grid cell activity influences the firing fields of place cells as demonstrated with inducible activations and inactivations of layer II of the medial entorhinal cortex that cause remapping of place cell firing fields in specific and repeatable patterns [42, 43]. However, place cell firing patterns can be largely spared by manipulations that disrupt grid cell firing [44, 45], and Brandon and colleagues [46] have recently extended this finding by demonstrating that intact grid cell function is not necessary for establishing new hippocampal place cell firing fields in novel environments. Furthermore, grid cell function depends on excitatory hippocampal input to the entorhinal cortex [47]. Thus, the relationship between the lattice-like spatial tuning of grid cells in EC to the specific place tuning of place cells in the hippocampus is not fully captured by a feedforward conceptualization of spatial information extraction, suggesting instead that more complex interactions within the hippocampal-entorhinal circuit underlie the formation and stability of cognitive maps for space.

Spatial Memory Tasks and Models

Motivated by the clear involvement of the hippocampus in spatial functions, and by the fact that using animal models for memory tests requires making measurements of behavior or neural activity (rather than self-reporting as in humans),

hippocampal-dependent tasks often incorporate aspects of both mnemonic and spatial functions to evaluate memory in terms of an animal's ability to navigate based on previous experiences. In rats, hippocampal lesions cause impairments of memory-guided behavior and a diversity of models capture performance on such tasks. Models using firing rate representations of neurons often start with representations of place cell firing as a basis for goal-directed planning in a number of tasks, including the open field [48–50], the Morris water maze [51, 52] as well as spatial alternation [53], and a multiple-T choice task [54]. Some of the models of goal-directed behavior have used replay of previously experienced spiking activity to more rapidly build the representations of the environment for goal-directed behavior [54, 55]. Hippocampal models have also addressed physiological data showing correlations between hippocampal spiking activity and a number of different variables of behavior. Early models showed how place cells could arise from competitive self-organization of inputs from sensory cues [56, 57] or from error-correcting rules guiding formation of place cells [58]. Later models simulated place cell responses based on path integration of self-motion information for self-localization [49, 51, 59, 60]. These models also incorporated multiple different maps to account for the remapping of place cell responses based on changes in behavioral stimuli or task demands.

The models of path integration for place cell responses were precursors to the models addressing the potential mechanisms for the generation of grid cell firing patterns [27, 61–64]. Recent models have addressed how place cells could arise from the properties of grid cells in the entorhinal cortex [27, 65]. Changes in place cell responses which occur after movement of environmental boundaries led to development of a model of place cells based on boundary vector cells [66, 67]. Models have also demonstrated how context-dependent spiking activity can depend upon variables other than current location, including the presence of specific sensory stimuli or on prior history [53]. An important model of the effects of Hebbian synaptic plasticity [68] generated the experimentally verified prediction that the firing fields of place cells tend to shift backward with experience [69].

These models and a host of related findings have led to contemporary theories of hippocampal function which we discuss throughout the remainder of the chapter.

The Hippocampal-Entorhinal Circuit

Thus far we have described aspects of the mnemonic function and spatial processing in the hippocampal formation structures, and we have provided an overview of the hippocampal neural code for space. In this section we review in greater detail the hippocampal-entorhinal circuit and highlight significant features of the anatomical projections therein with respect to the computational demands of memory and navigation.

The hippocampal formation is comprised of the dentate gyrus, the cornu ammonis regions (CA3, CA2, and CA1), subiculum, pre- and parasubiculum, and the entorhinal

cortex (EC) [70]. Highly processed information from neocortical associational areas reaches the hippocampus via perforant and temporoammonic pathway projections from the entorhinal cortex. The hippocampus then projects back to neocortex via CA1 and the subiculum and EC, placing the hippocampal-entorhinal circuit at an ideal anatomical position to "watch" patterned neocortical activity during behavior, i.e., during memory encoding, and also to access or influence neocortical activity during planning or memory retrieval.

In behaving animals incoming sensory information is routed largely from primary sensory cortices, through higher-order sensory areas which extract multidimensional features from the "raw" sensory inputs, to high-order association cortices such as the perirhinal and postrhinal cortex that provide highly processed information to the superficial layers (layers II and III) of the entorhinal cortex. The superficial layers of the EC provide the primary cortical input to the hippocampus, with layer II of the EC projecting to the dentate gyrus and CA3 and layer III projecting to CA1 and the subiculum. Within the hippocampus, excitatory projections maintain a primarily feed-forward pattern. The granule cells of the dentate gyrus send axons to CA3, known as the mossy fibers, which terminate on the proximal apical dendrites of pyramidal cells in stratum lucidum. The pyramidal cells of CA3 project to CA1 via the Schaffer Collaterals, but also send a vast set of associational collaterals to other CA3 pyramidal cells. This is a strikingly unique feature of CA3, as such an extensive network of associational projections is not found in any of the other hippocampal subfields. The pyramidal cells of CA1 project back to the deep layers of the entorhinal cortex (layers V and VI) and also forward in the hippocampus to the subiculum, which in turn also projects to the deep layers of the entorhinal cortex. Outputs from the deep layers of the EC complete the hippocampal-entorhinal loop by projecting to the superficial layers of the EC, but also project back to the higher-order associational cortical areas that funnel information into EC.

The different hippocampal subfields (dentate gyrus, CA3, and CA1) have been modeled as subserving different functional aspects of memory. Generally, the dentate gyrus has been modeled as performing pattern separation, CA3 as performing pattern completion, and CA1 as performing comparative operations or novelty detection. Unique aspects of the physical circuitry of each subregion have partly motivated the demarcation of functions to each region.

Dentate Gyrus

A critical problem that a memory system must solve is how to encode similar, overlapping, yet not identical, memories. This function, commonly referred to as pattern separation, was originally attributed to the dentate gyrus in the seminal modeling work of David Marr [71]. Pattern separation has been modeled as an orthogonalization, because it reduces the magnitude of the dot product between any two given input vectors of neural activity. This is purportedly achieved as a result of increasing sparseness of representations from the entorhinal cortex to dentate gyrus.

In rats, the entorhinal cortex contains about 250,000 neurons with which to represent information, yet the dentate gyrus consists of approximately 1.2 million neurons, close to a fivefold increase [72, 73]. Thus, activity patterns in the entorhinal cortex can be separated into sparse representations in the dentate gyrus [74]. Additionally this process has been modeled as benefiting from synaptic modification of inputs to the dentate gyrus, thus generating self-organization of distinct, random cell assemblies [11, 75–77]. The dentate gyrus is unique as it continues to have neurogenesis into adulthood. This too has been modeled as enhancing pattern separation mechanisms [78] and thereby reducing the interference between similar representations [79]. The dentate gyrus has also been modeled as a latent attractor, regulating remapping of place cell responses in different environments [80].

CA3

Another challenge that a memory system must overcome is how to retrieve a representation given an incomplete set of cues or inputs. The extensive excitatory recurrent connections among the pyramidal cells of CA3 led Marr to model the region as performing autoassociative encoding of input patterns [71], a process commonly termed pattern completion. As described earlier in the context of indexing theory, Hebbian synaptic modification of excitatory recurrent synapses during encoding forms associations between the elements of an input pattern, allowing pattern completion during subsequent retrieval. During retrieval, a partial cue consisting of a subset of active neurons causes activity to spread across previously modified synapses to cause activity in other elements of the pattern, resulting in a pattern of activity more closely matching the originally encoded pattern. This basic mechanism of autoassociative memory function has been central to many models of region CA3. McNaughton and Morris described the role of recurrent connections for both autoassociative pattern completion and encoding of associations between a pattern at one time and the subsequent pattern at a later time step [81]. The encoding and retrieval of sequences in region CA3 has been extensively modeled with simplified spiking neurons [16, 82]. Multiple cycles of the spread of excitatory activity can result in explosive activity unless it is balanced by inhibitory feedback, in which case the network can converge to an attractor state, matching the initial encoded memory pattern. Attractor dynamics in region CA3 have been used for retrieval of encoded memory patterns in a range of hippocampal models [11, 12, 75, 83, 84]. The modeling of attractor dynamics builds on extensive earlier analysis of the memory capacity of recurrent networks [85] that was applied to models of hippocampal function [75, 83, 86], including models of multiple attractors [86]. The capacity limits of hippocampal circuits could constrain its role in holding intermediate-term episodic memories that are eventually used to update neocortical representations. Attractor dynamics in CA3 have also been used to model place cell activity [59, 60], as well as grid cell firing in the medial entorhinal cortex [27, 61, 87].

CA1

Based on clear differences in anatomical connectivity, region CA3 and CA1 have been proposed to have different roles in prediction based on prior experience [88]. In striking contrast to CA3, region CA1 has a marked lack of excitatory recurrent connectivity, and CA1 receives two major sources of feed-forward excitation. First, layer III of the entorhinal cortex terminates in the stratum lacunosum moleculare and, second, CA3 pyramidal cells synapse in the stratum radiatum. The existence of these two input streams has led to CA1 being modeled as performing a comparator function of these two inputs [11, 89, 90]. Such a function has been employed to set the levels of acetylcholine to modulate the dynamics of encoding and retrieval both in a simulation of region CA1 [90] and in a network simulation of hippocampal memory function [11]. The place cell responses in region CA1 have been modeled using arrays of sensory features linked to place cell responses by self-organization of afferent synapses from the entorhinal cortex [57, 91, 92] or using error-based learning of associations with location [58].

Entorhinal Cortex

As described earlier, the entorhinal cortex provides the primary input to the hippocampal formation, with entorhinal cortex layer II projecting to the dentate gyrus and region CA3 and layer III projecting to region CA1. Extensive modeling has addressed the mechanism and role of grid cells in the medial entorhinal cortex of the rat. Grid cells have been modeled based on interference between oscillations with frequencies shifted by the velocity of the rat [62, 66, 93, 94]. This model predicted [62, 66, 93] that the difference in spatial frequency of grid cells at different positions along the dorsal to ventral axis of the medial entorhinal cortex could arise from differences in the intrinsic oscillation frequency of entorhinal neurons. This prediction was supported by intracellular recording data showing a gradient of intrinsic subthreshold membrane potential oscillations and resonance [63, 95, 96] and unit recording data showing a gradient of intrinsic periodicity in autocorrelations [93, 97]. Other models have proposed that grid cells arise from attractor dynamics [27, 61, 87, 98] or self-organization of afferent input to the entorhinal cortex [64].

The excitatory pathways in the hippocampal-entorhinal circuit are all embedded within highly organized GABAergic interneuronal networks in each subregion. Within the hippocampus, there exists a massive heterogeneous population of GABAergic interneurons, and each interneuron subtype preferentially receives specific afferent input and has axonal arborizations targeting specific somatodendritic aspects of the principal cells. The excitatory projections within the hippocampus contact select portions of pyramidal cell dendrites, as well as particular subsets of GABAergic interneurons that provide both feed-forward and lateral inhibition.

Considerably less is known about the diversity of GABAergic interneurons in the entorhinal cortex. However, recent work has shown that stellate cells in layer II of the EC make very few, if any, direct synaptic connections but rather are primarily coupled indirectly via GABAergic interneurons.

Medial Septum

The hippocampal formation receives subcortical input from the medial septum (MS) which is critical to the generation and coordination of the theta rhythm (discussed later in the chapter) throughout the hippocampal-entorhinal circuit. Cholinergic projections from the MS traverse promiscuously through all layers of the hippocampus and entorhinal cortex, modulating local activity through extrasynaptic release of acetylcholine. In contrast the GABAergic projections from the MS show remarkable specificity, terminating selectively on perisomatic regions of GABAergic interneurons and generating theta-rhythmic disinhibition of the principal cells in the hippocampus and entorhinal cortex.

Cholinergic input to the hippocampus has been modeled as having several effects beneficial for encoding new information [11]. Medial septal cholinergic neurons provide modulatory tone that regulates intrinsic neuronal properties of hippocampal neurons, and this cholinergic tone has been proposed as a mechanism for regulating the dynamics of encoding and retrieval in the hippocampus [84, 90]. High levels of acetylcholine are observed during active waking, concomitant with theta oscillations, and models have shown acetylcholine leads to increased spike output in response to input from the entorhinal cortex through depolarization and a suppression of spike frequency adaptation, as well as enhanced synaptic modification. Cholinergic input from the medial septum also reduces the recurrent excitation arising from CA3 by presynaptically inhibiting glutamate release. Models have shown how this reduction in CA3 recurrent excitation reduces the possibility that stored representations in CA3 will interfere with the encoding of new representations [11, 84, 90]. During quiet waking and slow-wave sleep, acetylcholine levels decrease, which could allow the transmission of CA3 representations through the retrohippocampal output pathway to drive neocortical consolidation of hippocampally stored representations [99].

In addition to playing a role in regulating the dynamics of encoding and retrieval, models have also addressed the role of the medial septum in pacing theta rhythm oscillations [100] and make use of this baseline theta rhythm oscillation for oscillatory interference models of grid cells [62, 93]. The importance of theta oscillations in the maintenance of grid cell spatial periodicity is supported by the finding that medial septal inactivation reduces theta oscillations and eliminates grid cell spatial periodicity [44, 101]; however, recent findings demonstrate grid cells in the entorhinal cortex of bats that don't exhibit theta rhythmicity [102] or theta frequency intrinsic resonance [103].

Coordination of Neural Activity by Oscillatory Rhythms

Theta Generation and Coordination

As the functional roles of oscillatory dynamics have begun to be appreciated in the past few decades, the role of the theta rhythm (6–12 Hz in rats) in the hippocampus and related structures has been the focus of considerable theory and modeling in studies of memory and navigation. Throughout the hippocampal formation, theta and gamma oscillations present in the local field potential reflect the spatiotemporal summation of excitatory and inhibitory postsynaptic potentials impinging upon the laminarly structured architecture of the somatodendritic field, as well as intrinsic membrane potential oscillations of principal cells [104–110]. It is important to differentiate the different roles played by different neuronal populations in the generation of theta. The medial septum is generally thought to provide *rhythm* generation, while superficial EC neurons and CA3 pyramidal cells are thought to provide the *current* source for the local theta rhythm. While EC and CA3 neurons have the intrinsic ability to generate theta-rhythmic activity, neurons throughout the hippocampal formation spike in phase relation to the theta rhythm [111]. Stellate cells in layer II of the EC show resonance in the theta frequency range, have subthreshold membrane oscillations potential in the theta frequency range, and ultimately spike at theta frequency. Lesions of the EC virtually abolish theta in the hippocampus, leaving only a small, presumably CA3-mediated theta oscillation in CA1. This is supported by the finding in the whole-hippocampus in vitro preparation within which theta rhythm activity emerges intrinsically and which can be paced by selectively driving parvalbumin-positive interneurons [112, 113] with optogenetic techniques [114, 115]. While theta rhythmicity can be generated by different neuronal populations within the hippocampal formation, they are all thought to be coordinated by the medial septum. As described in the previous section, the MS provides both GABAergic and cholinergic projections throughout the hippocampus and entorhinal cortex, with the GABAergic projections synapsing preferentially onto inhibitory interneurons within its target regions, and many of these GABAergic neurons burst at theta frequency. This theta-rhythmic pacing of local interneuronal activity creates rhythmic temporal windows within which spiking of local principal cells can occur. Thus, while components of the hippocampal formation have the intrinsic ability to generate theta-rhythmic firing, theta-rhythmic firing is ultimately temporally coordinated by the medial septum. The manner in which the MS similarly coordinates theta frequency oscillations within and between medial temporal lobe structures remains a significant focus for further study. Furthermore, the distinct effects of and probable interactions between the cholinergic and GABAergic projections from the MS also require further description.

As a rule of thumb, oscillatory activity in the brain has been suggested to reflect computation or coordination of activity across different spatial scales such that higher-frequency activity reflects local processing, whereas lower-frequency activity reflects longer-distance interactions including coordination between nuclei. Gamma frequency oscillatory activity (40–100 Hz) is observed in brain structures

throughout the neocortex and has been proposed to play a role in the integration of sensory information into conscious percepts [116–119], i.e., the binding problem, as well as in attention. In the hippocampus and related structures, gamma is thought to represent the specific content about ongoing experience, typically of highly preprocessed information ascending to the hippocampus from association cortices which, if it is behaviorally significant, may be encoded into memory. Within this framework the ensemble of cells that are active within the temporal windows defined by gamma cycles act as a unitary chunk of experience. As is discussed below, the temporal organization of gamma-linked ensembles within cycles of the slower theta rhythm may serve to compress information about sequential events, items, or places that are experienced on a behavioral timescale onto a neural timescale [120–122]. In this way the spatial and temporal sequence of an episode, including the sequence of locations visited or the order of events within a memory, is encoded in the nested cycles of oscillations within different frequency bands. Thus, these nested oscillations may serve the necessary function of coordinating neural activity to reflect the causality flow between events composing an episode in time or between locations composing a trajectory in space.

Theta Phase Precession

The spiking activity of the hippocampus shows clear relationships to local field potential oscillations. In particular, the firing of place cells on a linear track shows a systematic change in phase of firing relative to theta rhythm oscillations [122, 123]. When the rat first enters the field of firing of a place cell, the spiking occurs at late phases, and then it shifts to earlier theta phases as the rat moves through the place field. This phenomenon is referred to as theta phase precession. A number of models have addressed theta phase precession using different mechanisms. These can be grouped into three broad categories: (1) In models of phase precession from sequence readout, each location cues the retrieval of a sequence of place cell spiking activity due to Hebbian modification of associations between place cells firing to adjacent locations [13–15, 53]. (2) In models of phase precession from oscillatory interference, precession arises from interference between oscillators with different frequencies. This can involve interference of intrinsic oscillations with network oscillations [123, 124] or between oscillations in different groups of neurons [125]. The same mechanism has been used to model theta phase precession in grid cells [62, 126]. (3) Lastly, phase precession has also been modeled as a consequence of progressive change in depolarization relative to network theta. In these models, precession arises from a gradual change in depolarization that results in spiking at a different phase of theta [69, 127]. Recent intracellular recordings from awake head-fixed mice running in a virtual world have tested predictions of these different models [128]. The intracellular membrane potential shows subthreshold oscillations that shift in phase relative to network oscillations, consistent with the oscillatory interference model rather than the sequence readout models. The data also show a depolarization of membrane potential within the place field.

Cross-Frequency Coupling

Initial descriptions of the relationship between theta and gamma frequency oscillations in the hippocampus pointed to several different ways in which these two oscillations interact in vivo in the rat. First, it was observed that gamma power (or amplitude) was higher during the presence of theta than when theta was absent [107, 129]. Second, higher-frequency theta oscillations were associated with higher-frequency gamma oscillations [107]. As theta frequency ranged from 6 to 10 Hz, gamma frequency maintained an approximately tenfold greater frequency, e.g., when theta frequency was 8 Hz, gamma frequency was 80 Hz. Third, gamma power was shown to fluctuate according to theta phase, such that gamma power was largest near the peak of locally recorded theta and smallest near the trough [107]. These initial observations were made in the dentate gyrus subregion of the hippocampus, and shortly thereafter it was shown that the same three relationships maintained between theta and gamma in the hippocampus also held in the superficial layers of the entorhinal cortex [130].

Throughout the hippocampal formation, gamma oscillations are phase modulated by the local theta rhythm, but the frequency composition of the gamma rhythm can vary both within and between regions of the hippocampal formation [131]. In CA1 the frequency distribution of gamma oscillations is bimodal with peaks around 45 and 100 Hz (slow and fast gamma). These two different frequency gamma oscillations are both modulated by the phase of the local theta oscillations, but have different preferred phases. The slow gamma has a preferred phase on the initial part of the descending theta phase, while the fast gamma has a preferred phase around the trough of theta [131]. Furthermore, during fast gamma in CA1, there is increased gamma coherence between CA1 and medial entorhinal cortex, whereas during slow gamma there is increased gamma coherence between CA1 and CA3. This suggests that the frequency of theta-modulated gamma plays a role in routing information between the different regions of the hippocampal formation [131].

Theta-gamma cross-frequency coupling has been shown to be related to the performance of an item-context association task in rats [132]. Learning in the item-context association task is associated with an increase in the theta phase modulation of gamma power in the CA3 subregion of the hippocampus, and such cross-frequency coupling remains high when rats maintain a high level of task performance. Additionally, theta power has been shown to be positively related to the degree of modulation, but theta power could not explain all of the variability in the theta modulation of gamma. Thus, similar to the previous reports discussed above, the power of theta appears to play a role in the degree of gamma modulation, but in this case the modulation increases in relation to the learning process as well [132]. The comodulation of theta and gamma power has also been related to performance on a radial water maze task [133]. In this case, theta-gamma power comodulation was higher when rats correctly retrieved the goal arm in the maze than when the incorrect arm was chosen. Inactivation of the MS/dbB (diagonal band of Broca) with muscimol decreased theta-gamma power comodulation as well as rats' performance on the task [133].

Computational models addressing the functional purpose of such theta-gamma coupling have focused on a potential role in various types of memory. Almost immediately following the original demonstration of hippocampal theta-gamma cross-frequency coupling [107], Lisman and Idiart presented a computational model proposing that gamma oscillations nested within theta cycles could maintain a set of items (or units of information) for subsequent recall during a short-term or working memory task [120]. The model suggested that the psychophysically determined average number of items that could be stored in short-term or working memory could arise by maintaining each item in successive gamma cycles and repeating that order of items in gamma cycles on successive theta cycles. Thus, the number of items that could be stored on successive theta cycles depends on the number of gamma cycles occurring during each theta cycle. Given the frequency of gamma observed in the hippocampus, the number of items corresponds to the average number of items (7 ± 2) that humans can maintain in working memory [134]. Additional evidence for this model consists of the fact that for each additional item added to a list of items to be maintained, an additional ~35–40 ms is added to a subject's reaction time for identifying whether a probe item was actually in a studied list, and this duration is on the order of a length of a single cycle of gamma frequency activity [135].

Based on this suggested role of theta-gamma cross-frequency coupling, several recent studies have investigated whether such coupling is present during working memory performance in humans. In a study testing several predictions put forth by computational models, Axmacher et al. investigated the role of theta-gamma cross-frequency coupling in the human hippocampus during a working memory task [136]. Theta phase modulation of gamma power was found during successful working memory maintenance, and the greater the number of items that had to be maintained, the slower the modulating theta frequency [136]. The longer oscillation cycles of this slower theta rhythm could accommodate additional theta-nested gamma cycles, potentially allowing more items to be maintained in working memory.

In addition to the human hippocampus, cross-frequency coupling of theta and gamma has been observed in the human cortex as well. Subdural electrocorticogram (ECoG) recordings were obtained from a group of epilepsy patients while they performed a number of different cognitive tasks [137]. The amplitude of high-frequency gamma oscillations (80–150 Hz) was found to be phase modulated by theta at sites across a large area of cortex, as the 8×8 grid of electrodes employed covered frontal and temporal cortical regions. The degree of modulation was positively correlated with the amplitude of theta at a given electrode site (similar to the findings from rats) and the sites showing significant modulation varied (but were repeatable) based on the demands of the task. While cortically recorded theta oscillations may be volume conducted from hippocampal sources, cortically generated gamma oscillations do maintain a relationship with hippocampal theta oscillations. Just as the power of gamma oscillations in the hippocampus and entorhinal cortex are phase modulated by the theta oscillations generated in those regions, the power of gamma oscillations generated in cortical sites is phase locked to theta oscillations generated in the hippocampus [138].

Integration of Hippocampal Theories

As reviewed in this chapter, numerous studies have demonstrated that the hippocampus and related structures are critical to spatial processing necessary for navigation and to episodic memory. Several hippocampal models represent how the task requirements of navigation and memory, e.g., pattern separation and completion, can be implemented by subregions within the parahippocampal region. Recently, Buzsaki and Moser have proposed that commonalities between the task requirements for navigation and episodic memory suggest a cohesive theory of hippocampal function, i.e., a shared neural algorithm that subserves both spatial and mnemonic functions [139]. Pointing to "clear parallels between allocentric navigation and semantic memory, on one hand, and path integration and episodic memory on the other," Buzsaki and Moser propose that "the same mechanisms that define unique positions and their relationships in a map can be used to define or symbolize events, objects, and living things." Based on this rationale, Buzsaki and Moser hypothesize that the role of the parahippocampal system in navigation may have evolved to also support episodic memory, such that, firstly, the spatiotemporal sequences of locations that an animal visits can be represented internally, i.e., encoded, in the nested temporal activity of neuronal assemblies and, secondly, that representations of this nature can be used to code nonspatial information items and sequences. A recent study by Pastoll and colleagues demonstrated that precisely timed gamma oscillations emerge in tissue slices driven by theta-rhythmic optogenetic stimulation [140]. This finding illustrates that local network circuitry is able to generate the cross-frequency coordination of oscillations even without an intact animal, i.e., without the specific experiential content thought to comprise the information carried by gamma frequency activity. In the context of indexing theory introduced early in the chapter, this suggests that the hippocampal formation is both watching *and structuring* information coming from associational cortices, and if that content is sufficiently behaviorally significant, it can be recorded into memory, having already been structured by nested oscillations of neural activity to reflect the spatial and temporal sequencing of behavior and experience.

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Chapter 13
Information Encoding and Reconstruction by Phase Coding of Spikes

Zoltan Nadasdy

Abstract Each part of the central nervous system communicates with the others by means of action potentials sent through parallel pathways. Despite the progressively increasing spatial and temporal variation added to the pattern of action potentials at each level of sensory processing, the integrity of information is retained with high precision. What is the mechanism that enables the precise decoding of these action potentials? This chapter is devoted to explaining the transformations of sensory input when information is encoded and decoded in the cortical circuitries. To unravel the full complexity of the problem, we discuss the following questions: Which features of the action potential patterns encode information? What is the relationship between action potentials and oscillations in the brain? What is the segmentation principle of spike processes? How is the precise spatiotemporal pattern of sensory information retained after multiple convergent synaptic transmissions? Is compression involved in the neural information transfer? If so, how is that compressed information decoded in cortical columns? What is the role of gamma oscillations in information encoding and decoding? How are time and space encoded? We illustrate these problems through the example of visual information processing. We contend that phase coding not only answers all these questions, but also provides an efficient, flexible, and biologically plausible model for neural computation. We argue that it is timely to begin thinking of the fundamentals of neural coding in terms of the integration of action potentials and oscillations, which, respectively, constitute the discrete and continuous aspects of neural computation.

Keywords Neural code • Phase • Spike • Local field potential • LFP • Subthreshold membrane potential oscillation • Gamma • Theta • Synchrony • Interference • V1

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Analog and Digital Components of the Neural Code

The Importance of Neural Coding

Information processing in the nervous system has been evolving under the conflicting constraints of speed, reliability, metabolic costs, and size to ultimately shape the structure and wiring of the brain. To maximize speed, neurons developed myelin shields and nodes of Ranvier. For reliability, massive parallel axon bundles are formed. To minimize metabolic cost, neurons migrate to layers in order to provide better access to blood vessels. To minimize the size, cell bodies are arranged into heavily convolved but essentially 2D sheet-like structures such as the cerebral mantle, with long myelinated axonal connections between them. To keep the bandwidth of connections proportional to the increasing area of the cerebral mantle, messages are simultaneously transferred between these structures via parallel fiber tracts. However, our understanding of the biological principles of encoding, transferring, and decoding parallel messages is incomplete. Keeping the robustness and accuracy constraints in mind, we propose a biologically plausible theory for information encoding and decoding.

Understanding the neural coding is important for a number of reasons. One practical reason is to be able to read the signals from the brain in order to control external devices or actuators that augment or restore disabling conditions, such as neural prosthetics and other types of brain-machine interfaces. Second, it would allow us to treat neurological diseases such as epilepsy and Parkinson's disease by restoring compromised information processing in the brain. Third, the nature of the code determines how we think about biological computations and may inspire artificial intelligence. Lastly, it reveals the limitations of our cognition and clarifies our place in the universe in general.

The Problem of Conductivity and Synaptic Divergence

Sensory information in the central nervous system is transmitted through parallel pathways in the form of action potentials (APs), also, when extracellularly recorded, referred to as "spikes." While the rapid sequence of visually evoked APs form dense pockets of spikes at the level of retinal ganglion cells, these packets gain a triple-fold increase in temporal variation as they reach the primary visual cortex V1 (Fano factor = 0.11, 0.20, 0.33, respectively [1]), and the variance of arrival times exceeds 50 ms (ranging from 34 to 97 ms; 66 ± 10.7 ms) [2, 3]. When trying to tease apart the sources of this variation, we must consider two factors. One is the trial-by-trial variation of spike latencies at different stages. The second is the heterogeneity of conductivity in axonal transmission. The trial-by-trial variation is partially explained by decreasing firing rates and decreasing refractory periods along the visual pathway from the retina to the visual cortex [1]. In contrast, the single-trial desynchronization

of spikes that increases progressively along successive stages of the visual pathway can be explained by the strikingly heterogeneous conductivity of axon fibers. For instance, the conductance velocity of M and P cell axons forms bimodal, almost nonoverlapping, distributions, where the M pathway responds as much as 20 ms earlier in layer 4B than does the P pathway [2].

The first problem is that due to the known heterogeneity of the axonal composition of these pathways, one would expect an originally synchronized volley of spikes induced at one end—for instance, by simultaneous stimulation of a set of photoreceptors—to arrive with as much as 50 ms jitter of latencies to the cortical targets in layer 4B. However, this progressive jitter poses a major computational challenge for explaining how a dispersed pattern of APs can retain the integrity of the code and effectively able to excite target neurons in the cortex with a ~10 ms precision, i.e., the integration time window of pyramidal cells [4–6]. We propose that despite the trial-by-trial variability of spikes and the conductivity differences between axons, the integrity of the spike code is preserved along the visual pathway due to a common oscillatory drive, which resolves simultaneity at the level of precision afforded by the frequency of oscillation. In addition, the same oscillatory drive may also map the spatial relationship between cells onto different phases of the common oscillation, a mechanism that we explain in details below (see section "Sensory Encoding-Decoding Circuits").

The second problem is the divergence of synaptic connectivity in the sensory pathways. Continuing the example of the visual pathway, retinal ganglion cells in the mammalian brain establish synaptic terminals on several LGN neurons [7]. An even larger number of LGN neurons converge on single granular layer neurons in V1. However, the geniculo-cortical divergence is greater still than the retino-geniculate divergence: about 40 V1 neurons are connected to each LGN neuron. As a result of this divergence and reconvergence, a significant spatial blurring is imposed on the sensory input. We are then faced with yet another serious computational problem: how is the precise spatial mapping between the retina and visual cortex, upon which our photoreceptor resolution visual acuity relies, retained despite such highly divergent retino-geniculo-cortical connections? Likewise, sections "LGN-V1 Projection" and "Reconstruction of the Information from Phase Code" will answer this question.

Deterministic vs. Nondeterministic Brain

Despite the deterministic nature of Hodgkin-Huxley neurons [8], current models on neural coding are dominated by the assumption that spike processes are "stochastic," i.e., nondeterministic. This is based on observations of the large variance of spike trains following repeated presentation of a "frozen-noise" stimulus [9]. In contrast, we argue that spike processes are deterministic at a >5 ms scale [10–12], if we consider the precision of neurons' own temporal reference, i.e., the neuronal clocks.

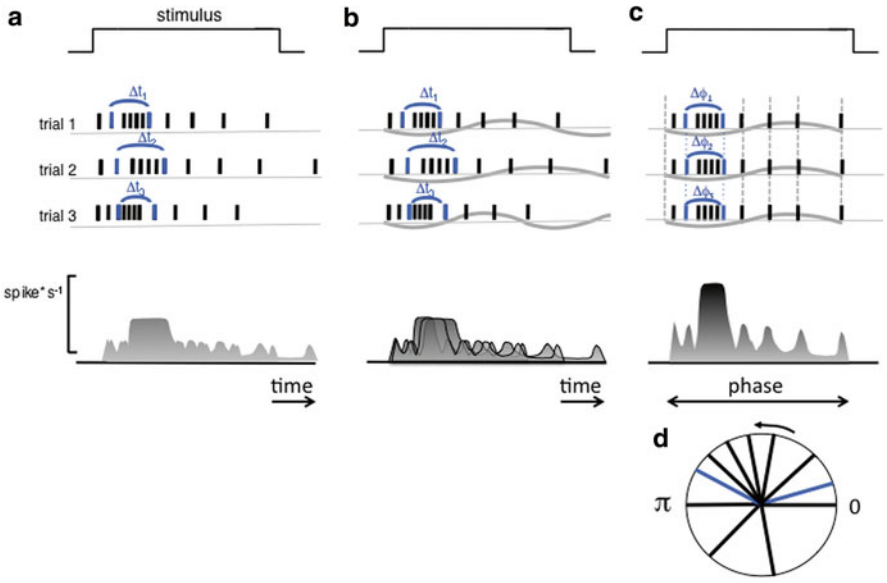

Fig. 13.1 The relativity of spike timing uncertainty. The *cartoon* illustrates how the trial-by-trial reproducibility of an action potential sequence in response to sensory stimulation is dependent on the intrinsic frequency variation of membrane potential oscillations. (**a**) Under a "frozen-noise" stimulus condition, when the patterns of visual motion stimuli are identical in each trial, the experimentalist observes large intertrial variance in spike timing ($\mathbf{\Delta}t_1 \neq \mathbf{\Delta}t_2 \neq \mathbf{\Delta}t_3$) and concludes that responses of neurons are stochastic. (**b**) In contrast, when local field potentials (LFPs) are recorded in conjunction to single units, the correlation between population depolarization (negative phases) and spike timing is evident. Note that the spike train in trial 2 is a stretched out version of the spike train in trial 1. (**c**) After warping the spike times to the simultaneous LFP by computing the phase of the spike relative to the LFP, spikes line up across trials ($\mathbf{\Delta\Phi}_1 = \mathbf{\Delta\Phi}_2 = \mathbf{\Delta\Phi}_3$). The precise alignment is evident when comparing the traditional peristimulus time histogram (PSTH, *bottom* **a**) with the peristimulus phase histogram (PSPH, *bottom* **c**), as the latter one is sharper and larger in amplitude than the former. The combination of spike timing variances is signified by the decomposition of the traditional PSTH to single-trial PSTHs (*bottom* **b**)

In order to take the neuronal clock into account, instead of aligning the spike trains to stimulus onset and measuring the absolute time of spike occurrence, we align them to the neurons' intrinsic oscillations. These oscillations can be recorded intracellularly as subthreshold membrane potential oscillations (SMOs) and extracellularly as local field potentials (LFPs). The relationship between SMO and LFP is still unresolved, but the high correlation between them suggests that the LFP is a sum of local SMOs combined with postsynaptic potentials [13] (see section "Correlation Between Subthreshold Membrane Potential Oscillations and Local Field Potentials"). The alignment can be achieved by first converting the oscillations to phase and then by replacing spike time by the phase of oscillation (Fig. 13.1). Spike phase combined with firing rate has demonstrated superior performance in information transmission [7–9]. However, knowing the relevant frequency of the internal clock that provides optimal segmentation is critical.

Without knowing the frequency of segmentation, information carried by spike trains is underestimated and the spike process appears nondeterministic. In the rest of the chapter, we argue that the key to unlock the neural code is to understand the subtle biophysical relationship between APs and subthreshold membrane potential oscillations (SMO). If the oscillation field of local SMOs is organized topographically, it will control the firing probability of large populations of neurons in a spatially ordered fashion, a principle that phase coding exploits.

Despite numerous qualifications, single neuron biophysics maintains that neurons generate APs when the combination of excitatory postsynaptic potentials (EPSPs) elicits a wave of depolarization that, upon reaching the axon initial segment, exceeds the neuron's threshold. In addition to the EPSPs, the membrane potential of neurons periodically fluctuates around a mean due to the intrinsic subthreshold membrane potential oscillation (SMO). The SMO makes the neuron most excitable when the membrane potential is near threshold. During this depolarization phase, neurons are more likely to fire APs than during a hyperpolarized phase.

Two Information Transmission Logics in One Brain

Messages between neurons with the highest precision are exchanged across chemical synapses as a sequence of APs. Thus, APs are the smallest indivisible units of the code. Without them, there is no information processing, perception, coordinated movements, memory, or consciousness. However, they are not the only form of communication between neurons. Neurons communicate through electrical synapses, such as gap junctions [14], as well as through ephaptic conductance [15], which enable the sharing of subthreshold membrane oscillations within a local population of neurons. What are the functions of these two signals, and why are there two kinds? While APs encode the messages in discrete, binary values, SMOs change continuously. It is easy to see the analogy with the difference between digital and analog signal processing. If APs are the signals that communicate the absence or presence of a sensory/neural event, then the SMO may provide the reference to read that message. How? Before answering this question, we will outline a model of a complete processing cycle from the sensory input to the cortical stimulus representation. First, let's see the correlation between APs and SMO. Then we will review spike-field correlations, because usually only LFPs are accessible. Finally, we review the status of correlation between SMO and LFP.

Correlation Between the Phase of Membrane Oscillations and Action Potential

The mechanism by which neurons coordinate APs with SMO is inherent to the process of AP genesis. We discriminate between four different mechanisms: (1) neurons are endowed with resonant properties. The membrane potential fluctuates without any

synaptic drive to the cell [16–18], even in isolated cells [19]. The spontaneous fluctuation is limited to a narrow frequency range, which varies between structures but is shared among neurons of the same structure. This is the characteristic resonant frequency of the neuron at which a frequency-modulated input current would drive the cell membrane with the smallest attenuation [20]. Since the SMO frequency is the characteristic resonant frequency of the neuron, AP-evoked synaptic input arriving in-phase with the depolarization phase of SMO will be more likely to reach the threshold and reproduce an AP than off-phase input. Consequently, if rhythmic APs impinge on the cell at its characteristic resonant frequency and synchronize with the SMO, then each AP will be relayed reliably. Conversely, the SMO selectively relays the synaptic input that arrives in-phase with the membrane depolarization cycles. (2) Moreover, the SMO can be entrained by concerted synaptic input. (3) Synchronization of SMO can occur as a result of release from inhibition; for example, when a spontaneous excitation is followed by mutual inhibition by inhibitory interneurons, such as proposed in the olfactory bulb between mitral cells through granule cells [21–23]. (4) In addition, the SMOs of nearby neurons influence each other through GABAergic synapses, glia, and electric synapses, leading to a fast SMO synchronization with a small phase gradient induced by propagating waves. The concept that these four adaptive resonances, in concert, enable spikes to embed in the fabric of membrane oscillations is critical to the argument we make for phase coding.

Correlation Between the Phase of Local Field Potentials and Action Potentials

The correlation between action potentials and LFP has been widely reported in a number of species under a variety of mostly awake experimental conditions [24–30]. Interestingly, what drew the most attention to this correlation was not the phase locking between spikes and LFP per se but rather the systematic drift in phase (the "phase precession" of spikes) relative to the theta oscillations recorded from hippocampal pyramidal cells and interneurons. Since those early reports [31, 32], phase precession has been confirmed in a number of other areas including the entorhinal cortex [33] and the primate visual cortex [34]. The other line of evidence is derived from studies on spike-field coherence. The coherence between local spiking activity and distant LFP elucidates the direction of causal influence between cortical areas [35].

Phase precession was first described between single unit activity and LFP recorded from rat hippocampi as a systematic shift in spike probability relative to the phases of successive theta oscillations while the animal was traversing through a place field. Because place cells, by definition, are most likely to fire in restricted spatial locations, it is difficult to determine whether the phase precession is independent or dependent on the spatial location. Before we can determine the function of

phase precession, we need to understand the relationship between APs and intracellular SMO under the same behavioral condition. By using an elaborate virtual reality paradigm on head-fixed mice, Harvey et al. were able to obtain simultaneous intracellular and extracellular recordings from the same hippocampal pyramidal cells and determine the relationship among spikes, LFP, and SMO [36]. It turned out that APs were always aligned to the depolarized phase of the subthreshold theta cycle. Thus, no phase precession was observed between spikes and the SMO of the same neurons. At the same time, the spike phase precession was maintained relative to the extracellular theta-band LFP. This discrepancy between the intracellular (SMO) and extracellular (LFP) theta phase precession can only be explained by assuming that the phase of extracellular theta drifts relative to the intracellular theta SMO. How is that possible?

We propose that a systematic drift of the LFP phase relative to the SMO phase can reliably reproduce the observed phase precession of APs relative to LFP, while also explaining the lack of precession relative to SMO. Such systematic drift is consistent with the propagating theta oscillations in the hippocampus [37, 38]. To explain spike phase precession, consider an array of neurons. Each neuron intrinsically generates voltage oscillations at $\boldsymbol{\theta i}$ frequency synchronized across the array with a constant phase delay between them. Also, consider a point in extracellular space representing where an electrode picks up the voltage fluctuation $\boldsymbol{\theta e}$ emanating from the surrounding neurons as LFP. Further assume that traveling theta waves sweep across the array of neurons and synchronize with local $\boldsymbol{\theta i}$. Because the extracellular electrode integrates voltage from a spherical volume of ~150 μm diameter that includes thousands of neurons, some of these neurons start the SMO earlier while others start it later. Thus, for the theta field to synchronize with early and late SMOs, the $\boldsymbol{\theta e}$ frequency must be slightly lower than $\boldsymbol{\theta i}$, causing a discrepancy between intracellular and extracellular theta oscillations (Fig. 13.2). When the spike phases of a given neuron are referenced to the $\boldsymbol{\theta e}$ extracellular electrode, it will show a precession. Meanwhile, the same spikes referenced to the neuron's own intracellular SMO ($\boldsymbol{\theta i}$) will be precisely aligned at depolarization peaks, nearest to threshold. Note that the direction of precession, whether it is a progressive phase advancement or phase lagging, depends on the direction of $\boldsymbol{\theta e}$ propagation relative to the direction of phase gradient $\boldsymbol{\theta i}$. If the traveling theta wave is moving in the direction of the SMO phase gradient, then the spike process produces phase advancement; otherwise it produces phase lagging (Fig. 13.2).

Other examples for coordination between LFP and spike processes were observed in primates. In a reaching task, correlations between spike and LFP between the dorsal premotor area of frontal cortex and the reach region of the parietal cortex increased when the monkey was making free choices instead of instructed choices [39]. In another experiment, primates were trained to hold two items in working memory. During memory encoding, the phase of spikes associated with those items in the prefrontal cortex were segregated relative to a 32 Hz oscillation according to the order of memory items [40]. In general, LFP was found to correlate with spike synchrony [41].

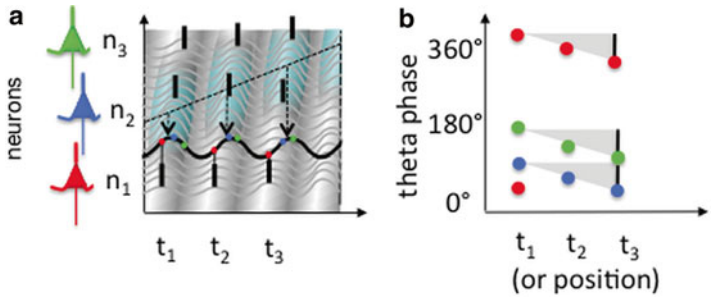

Fig. 13.2 A model of theta phase precession in the hippocampus. (**a**) The scheme depicts the field of theta oscillations in the hippocampus. The *gray-shaded* area represents the field of synchronized SMO waves with a phase gradient across a population of neurons. Each sine wave is a neuron. Three neurons on the *left* (n_1, n_2, n_3) represent place cells as they fire at the peak of SMO when the animal is crossing the place field. Consistent with electrophysiology, the spikes are aligned to the SMO peak of the same cell. At the same time, a traveling theta wave (*cyan shading*) is sweeping through the cell population while maintaining synchrony with the cellular SMOs. The wave front (*dashed line*) displays a slower propagation than the SMO. The extracellular electrode detects the LFP (*black sine wave*) as the integral of the voltage fluctuation deriving from local SMOs as well as from the traveling theta wave. Because the theta wave is traveling, $\boldsymbol{\theta e < \theta i}$. White crosses signify peaks of the traveling theta wave. When spikes (*black ticks*) of the *red*, *blue*, and *green* neurons are projected to the LFP, the spike phases display a progressive advancement across successive oscillations (*red*, *blue*, and *green dots*). (**b**) The phase precession from (**a**) as typically represented on the time/position and phase axes. The *black bar* signifies the phase precession

Correlation Between Subthreshold Membrane Potential Oscillations and Local Field Potentials

Although, based on the correlation of APs with SMO phases (see section "Correlation Between the Phase of Membrane Oscillations and Action Potential") and LFP phases (see section "Correlation Between the Phase of Local Field Potentials and Action Potentials"), a tight coupling between SMO and LFP would not be surprising; such a relationship is not necessary. Relatively few studies have addressed this question directly. Among those, significant correlation between local subthreshold oscillations and local field potentials was found in low (1–25 Hz) [13] and high (>25 Hz) frequency bands with the expected polarity reversal between intra- and extracellular potentials [13, 21]. We know even less about the mechanism of the transfer between SMO and LFP.

To explain such correlation, the SMO must synchronize between neurons to be able to generate LFP, which integrates over the membrane oscillations of thousands of neurons. However, the mechanism of such synchronization is poorly understood. For instance, SMOs may synchronize at low frequencies through the glia surrounding neurons. Neuroglia have been known to buffer and redistribute local extracellular K^+ and are thus able to transfer slow wave oscillations and spike-wave seizures

[42]. Astrocytic calcium transients have also been shown to display oscillatory activity [43].

Subthreshold oscillations synchronize with LFP in the motor cortex [44], and they do so even across the central sulcus between somatosensory and motor cortical areas at 20–40 Hz but with a 180° phase reversal between superficial and deep layers [45]. Abundant correlation between LFP and SMO was observed in the barrel cortex of behaving mice during quiet wakefulness but not during whisking [46].

As mentioned before, neurons are also capable of synchronizing their SMO through ephaptic coupling, which has proven to be effective at synchronizing APs in slice while synaptic transmission was pharmacologically blocked [15]. In contrast, the old model, based on current source-density analysis [47, 48], postulated an entirely synaptic origin of LFP. Although the mechanism that links SMO to LFP is still hypothetical, the old model needs a revision in light of new data showing substantial contribution of synchronized SMO to LFP. Moreover, extraneuronal components such as glia and astrocytes may play a role in transferring and integrating SMOs across the extracellular space to create LFP.

After discussing the critical components of phase coding and the coherence between SMO and APs, we now turn our attention to a model of phase coding in action.

Sensory Encoding-Decoding Circuits

Sensory organs are topographically organized. The retina, inner ear, olfactory neuroepithelium, and cutaneous receptors are all 2D surfaces. Except for the olfactory pathway, these 2D surfaces project through massive parallel pathways to the secondary interface that is the thalamus. The rest of the chapter will focus on the mammalian visual pathway, but the same principles can be generalized to other sensory systems. Visual coding has three critical stages: retina, LGN, and V1. From V1 to higher cortical areas, the same principles apply. We will first describe the retinal encoding on the example of mammalian visual system, then the information compression at LGN, and finally the decoding in V1 by information reconstruction.

Retina-LGN Projection

Sensory encoding in the mammalian visual system takes place in the retina by the retinal ganglion cells. These cells are topographically organized, where each retinal ganglion in the fovea represents a 0.5–2° receptive field of the eye-centered visual field. Light from this receptive field elicits a spike train in the retinal ganglions, which is modulated by two processes: (1) the extrinsic luminance contrast and (2) the intrinsic retinal waves, i.e., local membrane oscillations, which we described earlier as SMO. In this spike train, information is multiplexed in short (~300 ms) packets, consistent with the notion of “retinal functional units” (RFU) [49]. We

further propose that the two components, the light-induced and intrinsic oscillations, each contribute to the code differently. The light-induced component generates a burst of APs, which encodes luminance contrast by two distinct mechanisms (Fig. 13.3a): (1) by *frequency coding*, where the firing rate is proportional to the stimulation of the on/off center after subtraction of the stimulation of surround for on-center cells and off-center cells, respectively [50, 51], and (2) by *latency coding*, where the latency of the elicited burst is inversely proportional to the luminance [37, 39]. The retino-geniculate pathway also keeps the two types of codes separated in two different channels. One channel operates at low frequency bands (<30 Hz) and transfers the average firing rate. The other channel operates at gamma frequency bands (40–80 Hz) and converts the spike latency to oscillation cycles [53]. As we had proposed previously, the position of the retinal input, encoded by the phase, is also included to this channel [54].

How is the fine retinal position encoded? Because RFUs are evoked upon visual transients such as saccadic eye movements and microsaccades, they trigger short traveling waves of gamma oscillations (wave-packets) [49]. Intriguingly, retinal ganglions are able to resolve fine textural details at less than about one-fifth of a receptor diameter resolution with "hyperacuity" [55, 56]. On a theoretical ground, the eye would not be able to capture these high-resolution details unless it first converted them to the temporal domain. Whenever the eye (or the object relative to the eye) moves, the motion of the luminance transient generates a temporal offset between the SMOs of adjacent ganglion cells, captured as a phase difference of the oscillations. Hence, instead of the spatial receptor density, what really constrains the spatial resolution is the temporal resolution of those cells. Fortunately, the smallest spatial and temporal window has been determined and found to be 2–3 arc-min and 20–30 ms, respectively [55]; it closely matches the duration of a gamma cycle. It is reasonable to assume that the search for the smallest discernible spatial difference (such as contour discontinuity or texture) detectable by a moving eye based on the phase difference between the activities of two neurons takes a gamma cycle. In summary, we propose that an RFU is able to scan-in a patch of high acuity texture during a microsaccade or post-saccadic fixation from the fovea and convert it to a code that is a combination of (a) firing rate, (b) firing latency, and (c) spike phase relative to the intrinsic gamma SMO. These packets are sent to the LGN (Fig. 13.3b).

At this point we are ready to define the construction of the retino-geniculo AP packets. Luminance contrast induces latency-encoded AP bursts in a group of retinal ganglions. Next, single spikes from the bursts are aligned with the stimulus-induced gamma oscillations. This stage is called "gamma alignment" (Fig. 13.3, [41, 44]). When these responses are measured in absolute time, the AP latency is quantized in gamma cycles, and the textural information (e.g., hyperacuity) is encoded by the gamma phase. In summary, the sequence of retino-geniculate APs compresses three types of information: the luminance proportional firing rate (<30 Hz), the gamma-aligned latency at 40–80 Hz resolution, and a ~1 ms precision AP phase code, which reflects textural details in supra-photoreceptor resolution.

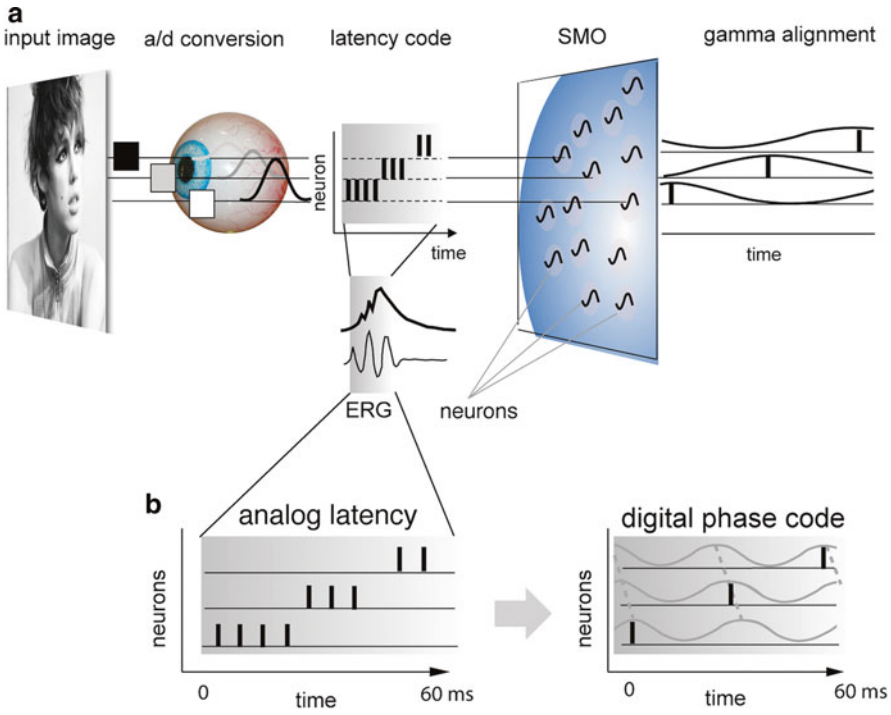

Fig. 13.3 Gamma alignment in the retina. (**a**) Visual encoding starts with a luminance-induced burst in the retinal ganglions, where the burst latency is inversely proportional to the luminance. Certain spike elements of the burst are sampled through local gamma oscillations (SMO) that are topographically organized (gamma alignment). (**b**) Major information processing steps in the retina-LGN-cortex circuitry. The first two steps are the conversion of bursts to gamma-aligned spike patterns. Because of the constant phase gradient between adjacent ganglion cells, spike phases represent the relative spatial position, while the gamma cycle represents stimulus intensity. The third step is code compression in the LGN through dispersion. The fourth step is reconstruction based on interference. The *inset* under latency code in (**a**) represents the electroretinogram (ERG) recorded from the back of the eye. The ERG captures the retinal functional unit (RFU ~300 ms), which is a briefly evoked gamma frequency oscillation that also contains the packet of spike message

Gamma Alignment

While the frequency-encoded quality directly affects the likelihood that an LGN target neuron will relay the message to V1 through LGN, the gamma-aligned code is a complex temporal code (see section "Deciphering the Phase Code") that has to be decoded. The gamma SMO will transfer only those AP components of the burst pattern that coincide with the depolarization phases of gamma. When spike bursts are selectively eliminated by allowing only APs that are in-phase with the depolarization peaks of gamma SMOs to be processed, gamma SMOs attach a spatial phase tag to the

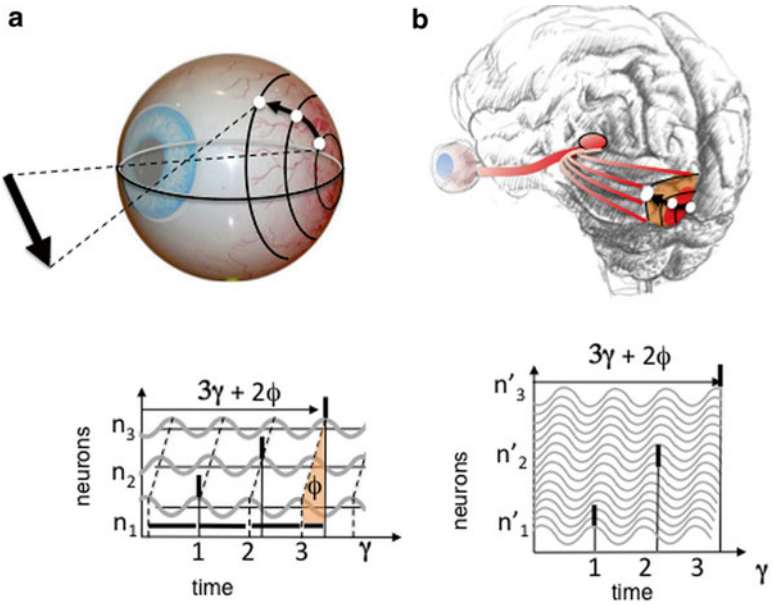

Fig. 13.4 Mapping of retinal topography on V1. (**a**) When a motion stimulus is projected on the back of the eye, the stimulus components activate a set of photoreceptors along a line in the retina. These components elicit successive spikes in n_1, n_2, and n_3 neurons. Because the spikes are aligned to the gamma SMO, their latency is $nk \times \gamma + n \times \phi$, where n is the number of neurons, k is a velocity constant, and ϕ is the phase gradient (here $3\boldsymbol{\gamma} + 2\varphi$). (**b**) The sequential activation in the retina will generate a similar pattern of activity and topography when reconstructed in the cortical columns of V1. What was radial in the retina is longitudinal in V1. The cortical projection of the motion trace (*top panel*) and its neuronal reconstruction from phase-coded sensory input (*lower panel*). An array of cortical neurons receives three spikes, which are projected on all neurons in V1. However, the only neurons responding are the ones that share the exact phase of the input APs. The reconstruction is based on the same wave function as described above ($nk \times \gamma + n \times \phi$)

temporal code (Fig. 13.3a). This phase tag can be decoded as long as the retina and LGN are sharing the same gamma clock, and transient gamma couplings between the retina and LGN have been supported by a number of observations [26, 49, 53].

Topography of Retinal Gamma

What is the biological function of gamma alignment? The answer derives from the spatial topography of gamma oscillations in the retina (Fig. 13.4). Gamma oscillations are topographically organized in the retina, because every eye or head movement induces a whole field visual transient, or because objects move in space with inertia and generate local transients. These transients activate the 2D matrix of photoreceptors simultaneously. Those photoreceptors converge on the retinal ganglion cells and generate a packet of gamma oscillations in each ganglion cell, which

organizes itself in a simultaneous wave sweeping through the 2D matrix of ganglions. Due to the constant phase lag between adjacent photoreceptors, the induced gamma has a phase gradient. Depending on the type of motion, this phase gradient has different geometries.

The Origin of Retinal Gamma

The origin of gamma oscillation in the retina is still unresolved. Retinal waves were proposed on a theoretical basis [57] and later discovered in the developing retina [58], but their role in wiring the retino-geniculate projections is controversial [59]. Gamma oscillations are still prevalent in the retina after birth [26, 49, 52]. We propose that these oscillations are intrinsically induced in the retinal ganglions but extrinsically triggered by saccades or microsaccades, which, in turn, modulate the luminance field. The same frequency oscillations appear in the LGN phase-coupled with the retina [26, 49, 52].

The retina-LGN gamma coupling can be accomplished in two different ways. One is a direct projection from the retinal ganglia to the LGN. This can be achieved through the gamma-band 40–80 Hz spike channel [52]. The other is indirectly through eye movements. The retina does not receive feedback from LGN. However, eye movements are under cortical and subcortical control (frontal eye fields and superior colliculus, respectively), through which waves of activity are generated. Such wave-triggering eye movements are the microsaccades: 1° ~20 ms duration. Microsaccades, discovered by Robert Darwin (Charles Darwins' father) in 1786 [59], cover the retina across a range of several dozen to several hundred photoreceptor widths. The duration of microsaccades closely matches the gamma oscillations. During one microsaccade, the retina is able to scan 2–120 arcmin of the visual field, and the lower band is the same minimal displacement as for hyperacuity. Because the microsaccade causes a translational motion of all textures and edges, this transient generates the gamma oscillations wrapped into an RFU as described above (see section "Retina-LGN Projection"). The contrast transients evoke a gamma SMO that travels across the retina with the speed of microsaccades. The induced gamma SMO will couple frequency with neurons in LGN by pacing LGN's own gamma SMO.

Since luminance contrast is latency encoded, the larger contrast signal generates an earlier burst of APs relative to the gamma wave onset (triggered upon the microsaccade) than smaller contrast. The burst duration/frequency is proportional to the intensity of light. Adjacent retinal ganglions will engage the microsaccade-triggered gamma oscillation with a slight latency difference as contrasts deriving from the same object traverses sequentially through them. Thus, microsaccade-triggered gamma oscillations traveling over a small distance in the retina have an intrinsic phase difference.

For the LGN to faithfully communicate the gamma-aligned information to cortical targets, it needs to preserve the AP-gamma phase relationship, because the object-specific information is encoded relative to the gamma oscillations.

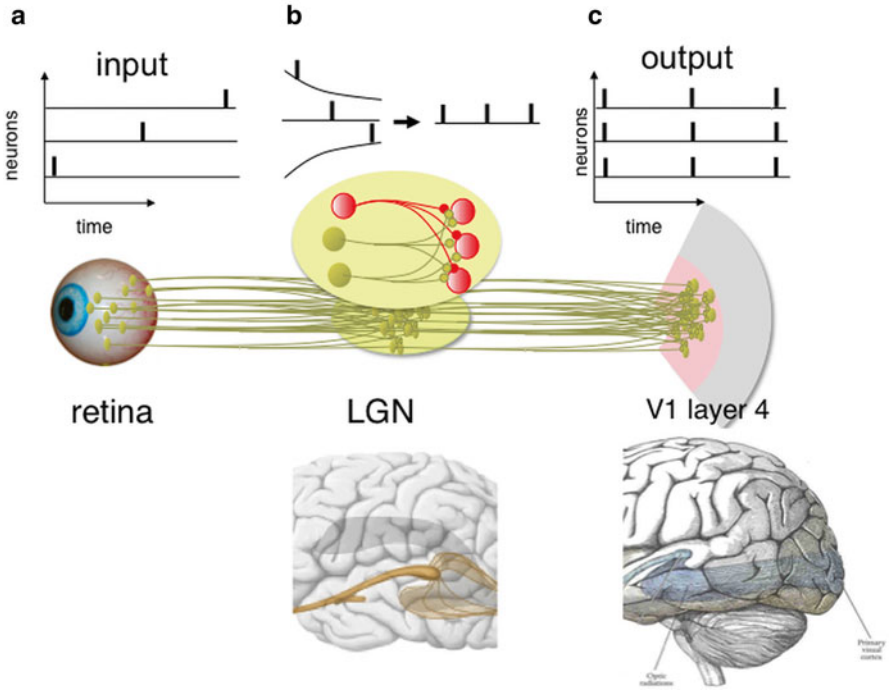

Fig. 13.5 Information transfer through the retino-geniculo-cortical pathway. (**a**) The gamma-aligned action potential (AP) pattern from retinal ganglions is transferred to the LGN through the optic tract. (**b**) In the LGN, the AP pattern from different fibers is dispersed through divergent synaptic connections, which led to merging of the AP patterns, resulting in potentially confused AP origin and spatial blurring. Nevertheless, the spatial information is retained by the precise phase of APs. (**c**) As a result of merging APs from different neurons, a compressed code is broadcasted to the visual cortex V1 where neurons decode the spatial information from the phase

Therefore, the retinal gamma oscillations with the correct gamma phases have to be communicated with the LGN. This is established by the retinal-LGN gamma coherence. A profound retina-LGN coherence in the 60–120 Hz frequency range was found in multiunit data [61]. Information encoded in gamma-aligned spikes is then compressed before transmitted to cortical targets, which is the subject of the next section (see section "LGN-V1 Projection").

LGN-V1 Projection

When the gamma-aligned code arrives to LGN, it will be transferred through the relay cells to V1 (Fig. 13.5). The retinal input acts through monosynaptic excitatory connections, which contribute 5 % of the total relay cell input [62]. The remaining 95 % derives from cortico-LGN feedback connections and interneuronal input.

There are at least three classes of LGN neurons in terms of temporal characteristics of responses to retinal input: one with sustained responses, another with transient responses, and a third heterogeneous class [63]. The reproducibility of relay neuron responses is very robust and precise in time [1]. The same study also reported that the Fano factor of burst responses remained sub-Poisson if they only considered the first spikes of each burst. This precision is critical because most cell-to-cell and trial-by-trial spike time variance observed in V1 recordings derives from the latency encoding of the original burst responses in the retina and not from the uncertainty of LGN responses. Therefore, we attribute the LGN response latency differences to the gamma alignment of the retino-geniculate signal.

The feedback projection that dominates the relay cell input is critical. This input usually occupies the distant dendrites, and as such, it has a modulatory rather than direct influence on the responses of LGN neurons. We assume the main contribution of this feedback is to synchronize relay cell activity with V1 gamma. Since the evoked retinal gamma imposes gamma-band coherence onto the LGN neurons through the retino-geniculate input, the corticothalamic feedback closes the loop between the retina and V1. We hypothesize that the entire trisynaptic feedforward retino-geniculo-cortical pathway intermittently engages to a coherent gamma phase lock. Visual information is most efficiently transmitted during these phase locks. Because the gamma is topographically organized over the retina, and retina is topographically mapped on LGN as well as on V1, the topography of the retinal gamma phase gradient must be preserved across both retinotopic maps, LGN and V1. Note that the overarching gamma coherence does not mean zero-phase-lag synchrony between retina and LGN and V1. The conductivity imposes a slight delay between the gamma cycles at successive processing levels, but it is inconsequential because all neuronal computations are performed relative to the local gamma.

Most importantly, the projection neurons in LGN display a synaptic dispersion through the collateral synaptic divergence of axons impinging on the relay cells (Fig. 13.5b, c). The result of this divergence is critical because it distributes the gamma-aligned input over a group of relay cells. Therefore, the topographically organized spike packets will be spatially blurred. A given thalamic relay cell's $R_{x,y}$ input represents the output of the retinal ganglion $G_{x,y}$ mixed with the output of neighboring $G_{x\pm n,y\pm n}$, where x and y are the retinal coordinates and n is a number of neighbor retinal ganglion cells collaterally terminating on the $R_{x,y}$ cell. Does this convergence have a detrimental effect on the code conveyed to V1? It depends on whether or not the topography of retinal projections can be recovered in V1. Given the approximately same number of input and output axons, any dispersion of axonal projections across neurons comes with convergence of axons on the same neurons. Hence, dispersion and combination of APs across neurons happen at the same time. Combining the AP packets derived from different ganglion cells intersperses the individual APs across neighbors by merging them like a zipper. The result of merging is that the same packets will be transferred through neighboring axons. This will compress the code and will also greatly improve the reliability of transfer between LGN and the cortex. The code compression is achieved by collapsing the messages sent in parallel independent channels into fewer independent channels.

Nevertheless, the total number of channels may remain the same but communicate redundant information. By the reduction of independent channels, the reliability improves because the compressed code is cloned in multiple axons. Then, error correction is possible between noisy fibers at the terminals, because all axons convey the same temporal pattern of APs; therefore, if one axon transfers an incomplete AP sequence, the other axons can correct for that postsynaptically by overlapping terminals. The other biological advantage is that the same information can be routed to multiple cortical areas. Thus different areas can compete and parse the same code according to different aspects. This advantage may not be significant in the sensory pathway because the divergence between LGN and cortical targets is limited. However, it *is* significant when the corticocortical transfer is considered. Our next question regards how the original spatial specificity of the retinotopic code is recovered. Without that, there is no use for neural encoding and code compression.

Reconstruction of the Information from Phase Code

V1 receives simultaneous spike trains through a massively parallel fiber bundle of optic radiatum, which emanates from the small nuclei of LGN bilaterally like the horn of a phonograph. The fibers are retinotopically organized, and this makes the projection on the granule cells of V1 also retinotopic. Every $G_{x,y}$ retinal position corresponds to a $V1_{x,y}$ location. However, since the retinal output is dispersed by the divergent transmission through LGN, those x,y positions in the LGN-V1 pathway are no longer fiber specific (Fig. 13.3b). The question is: how can the position code be recovered from the compressed multiplexed information?

The circuitries of the cerebral cortex are organized into columns, small cylindrical volumes with an intricate internal wiring scheme [64]. Pyramidal neurons in the column generate SMO at 20–60 Hz (gamma/beta) frequency range. In our model, each column is an independent gamma generator of its own by inducing gamma oscillations that spread from the center to the periphery of the column. We further assume that different columns may couple by phase locking their gamma oscillations while they remain independent from other columns. Phase coupling does not imply phase synchrony. When phase coupling is established between two columns, their gamma oscillations display a constant phase lag. If we strategically place electrodes over a small area of the cerebral cortex, we are able to measure these phase-locked and slightly asynchronous oscillations as wave propagation. These waves are generated by local SMOs displaying a phase gradient. The role of these SMO waves is to periodically depolarize a group of pyramidal cells in the column in a radial order from the center to the periphery. Thus, neurons that undergo phasic depolarization are more sensitive to the input that arrives in-phase during that interval. Conversely, neurons that receive input in-phase with their SMO are more likely to generate APs than neurons for which the same input is not in-phase with the local SMO. How exactly does the reconstruction work?

Key Concepts of Information Reconstruction

Interference Principle

For the reconstruction of sensory information from spike phases to work, the cortical field of gamma oscillations must be phase locked with the gamma oscillations of the retina. This phase locking is provided by the above-described retino-thalamo-cortical loop. Given the temporal coherence and spatial mapping between the gamma oscillation field in the retina and the gamma oscillation field in V1, the compressed code from LGN meets with a gamma field in V1 layer 4B. The AP sequence arrives at the granule cells in the form of synchronous volleys through parallel axons, but only a small fraction of EPSPs will coincide with the depolarized state of granule cells' SMO and be able to reach further to layer 2/3 pyramidal cells within the same column. At the same time, EPSPs that do not coincide with the depolarization phase of SMO will fail to initiate APs. These signals are not transmitted further within that column. As a consequence of the topological one-to-one mapping between the sensory neuromatrix and the cortical neuromatrix, these coincidences between SMO and EPSP will occur in cells that are in topological register (Fig. 13.4). For instance, concentric circular waves in the retina induce linear traveling waves in V1 because the fovea projects to the posterior pole of the calcarine fissure while the periphery projects to the anterior boundary of V1. Linear waves in the retina induce waves in V1 along the anterior-posterior axis, where the retinal periphery maps to the anterior V1. On the other hand, linear waves in the retina are mapped along the dorsal-ventral axis of V1, where the upper retinal hemifield projects to the ventral V1 (Fig. 13.4). Despite the geometrical distortion, the topological mapping is conserved.

Deciphering the Phase Code

All sensory information can be described by four variables: the intensity I (here defined as luminance), the coordinate of the sensory receptor $[r,\theta]$ relative to other receptors within the sensory organ, and time t of the activation time. In the visual modality, $I_{r,\theta,t}$ represents the luminance I at radial coordinate r and angular position θ of the retinal ganglion at time t. (For the sake of simplicity, we neglect channels of other sensory qualities, such as the color channels, but they can be easily included.) These coordinates must project on specific cortical columns of V1 at retinotopic coordinates $V_{x,y}$ without the requirement of a one-to-one projection. The problem the nervous system must solve is how to accomplish this one-to-one projection without a prewired direct axonal projection from the retina to V1 (Fig. 13.4).

As discussed earlier, retinal ganglions convert the luminance to latency, and these latencies map on the nth gamma cycle, where n is inversely proportional to $I_{r,\theta}$. Then, by synaptic convergence, the parallel latency-encoded trains of spikes are merged into fewer channels than the number of retinal photoreceptors without

changing their temporal relationship. These channels transfer the retinal signal to the V1 through LGN. In the compressed spike train, the AP's timing is controlled by two parameters, the integer number of gamma oscillations (γ) encoding luminance and the gamma phase (φ) encoding the r,θ polar coordinates. Here, the phase φ derives from the phase difference between γ oscillations in the center and the periphery of the retina ($\varphi = \gamma_{\text{central}} - \gamma_{r,\theta}$) as a result of spreading gamma oscillations in the retina. The latency of the AP evoked by the transient $I_{r,\theta}$ on the retina arriving in LGN is $t_{\text{AP}} = t_0 + \Delta t_c + n \times \gamma + \varphi$, where t_0 is the time of stimulus, Δt_c is a constant conduction delay, and φ is a cortical position-dependent phase difference within a γ cycle. Here $\varphi < \lambda_\gamma$, where λ is the length of a gamma cycle and n is the latency in gamma cycles that an $I_{r,\theta}$ induces. Thus, the code conveyed by each spike is quantized by the γ cycles and φ phase. If we assume that Δt_c is constant within a group of axons, the relative spike latency at a given neuron is simply $n \times \gamma$ cycles $+ \varphi$ phase, by construction. This relative time is transferred in packets between the retina and the LGN, containing the complete topographical information about the intensity of light exposing the retina at any position. In these packets, spike phases label the position of retinal input, while relative spike latency encodes luminance. However, for this phase information to be readable by neurons at the decoding site, these neurons need to access the γ reference, either the original or a copy of it. The simplest means would be to transfer γ along with the packets. However, an oscillation, being an analog quantity, cannot be transmitted by axons since they are restricted to the binary (digital) data transmission of APs. Rather, since gamma is ubiquitous and intrinsically generated in multiple sensory and cortical structures, it only needs to be synchronized across these areas. Sufficient evidence for this cross-areal synchronization is described in sections "Retina-LGN Projection," "Gamma Alignment," "Topography of Retinal Gamma," "The Origin of Retinal Gamma," and LGN-V1 Projection."

The cross-areal gamma coupling brings local gamma oscillations into coherence intermittently. Coherence is achieved when the SMOs of synaptically connected neurons in the retina, LGN, and V1 display successive gamma cycles with the same frequency but a constant delay. This is equivalent to stating that the phase gradient between cells A and B in the retina is equal to the phase gradient between corresponding cells A′ and B′ in the LGN or V1. This requirement is fulfilled by definition, because corresponding cells are not defined based on topographic register but instead by the phase gradient. Thus topography is defined by the topology of cross-areal phase coherence, which nevertheless provides a relatively consistent one-to-one relationship.

When the gamma coherence is established between LGN and V1 and the compressed spike message is transferred, all V1 neurons within the LGN projection field receive the exact same AP sequence simultaneously in a pattern of synchronized volleys (Fig. 13.6). As the volley of APs reaches the layer 4B granule cells, it will be relayed to layer 2/3 pyramidal cells and generate excitatory postsynaptic potentials (EPSPs) at every synapse upon which it terminates. By this time the gamma coherence should be established between the LGN and V1, which depolarizes the layer 2/3 cells periodically. The spike input and depolarization waves set the

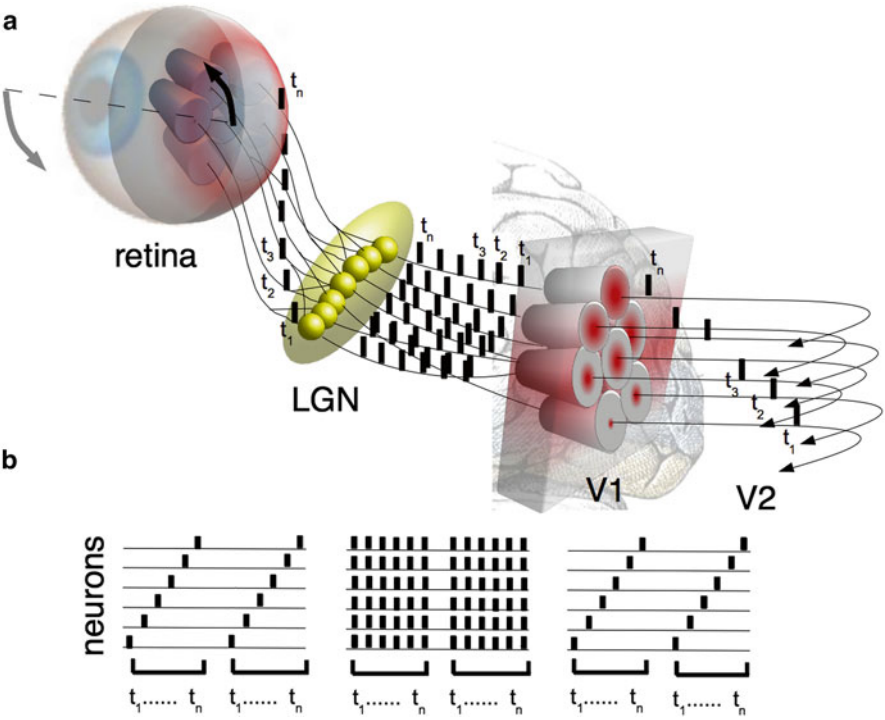

Fig. 13.6 Information reconstruction in the visual cortex. (**a**) The cartoon illustrates the parallel information flow from the retina through the LGN to V1. The reconstructed AP pattern maps on the columnar architecture of V1. Each column generates its own gamma SMO, which spreads radially from the column center. The column at which the SMO was at its peak when the input from the LGN arrived responded first to the input volley of APs (t_1). As the SMO wave unfolds in space and time (expanding *red shading* in columns), subsequent volleys coincide with the SMO peak at different neighbor columns and generate a spatial pattern that reproduces the topography of the pattern of the visual input on the retina. The output of V1 is compressed again before it is projected to V2. (**b**) The corresponding sequence of APs in time from (**a**). The AP pattern evoked by visual input in the retinal ganglions is broadcasted as a gamma-aligned code to the LGN, where it is compressed and transferred as parallel spike volleys to V1. The columns in V1 decode it by phase coincidences of spikes with SMO, and original spike sequences are recovered

condition for some selected layer 2/3 pyramidal cells to be able to fire APs. However, only those pyramidal cells that receive input from granule cells while their membrane is depolarized by the peak phase of gamma SMO will fire APs. Although other pyramidal cells will not transfer the input at that time, they may fire when the coincidences between the local SMO depolarization and the input from the granule cells occur. Because the topographic distribution of gamma phase gradient over V1 reflects the topography of the retina, the coincidence of EPSP and SMO is established over specific pyramidal cells, exactly those that are in topographic register with the retina (Figs. 13.4 and 13.6). These coincidences will reconstruct the original

sensory input from the compressed code similar to holography, where the 3D shape of an object is "drawn" in space as an interference pattern between the phase-modulated laser and the reference laser beam. However, instead of lasers, the nervous system utilizes its own ubiquitous coherent oscillation, the gamma, to reconstruct information encoded in phase. Because the phase coincidence between gamma SMO and sensory input does not typically happen in a single neuron, but in many neurons simultaneously, the reconstruction operates on a field. This notion is captured by the interference principle described in section "Interference Principle" [53, 56].

Note that the reconstruction is highly sensitive to the topography of oscillations and the oscillation gradient over the cortical area of projection. In addition, it is sensitive to noise, which is a subject of other studies.

Corticocortical Information Exchange

One can assume the same mechanism to be in place for corticocortical information transfer. First, APs of cortical pyramidal neurons in layers 5–6 have to be converted to latency code as $\gamma+\varphi$ in each cortical column before it is transferred to another column. This is achieved through converging/diverging synaptic connections, similar to the sensory nuclei of the thalamus (see section "LGN-V1 Projection"). The spikes generated in different neurons, each aligned to the local gamma phase, will merge on output layer neurons maintaining $\gamma+\varphi$ phase on all output neurons. These neurons fire APs in synchrony and relay the same spike times in parallel channels through a bundle of axons terminating at multiple distant cortical areas, reaching as far as the opposite hemisphere through the callosal interhemispheric connections. Because the originally labeled-line code is now compressed into the same code in every output neuron of the given column, it is critical that the originally labeled information can be decoded in different areas without addressing each axon by its origin. The challenge and its solution in the corticocortical transfer are similar to that of the sensory transfer. It also transfers topographically organized information via channels with topographically uniform content.

Topography

Phase coding generates topographic patterns in the brain that are not unfamiliar to us. We demonstrated by simulations that a layer of uniformly distributed neurons, which collectively support sinusoid plane wave propagation of SMOs, generate representations typical of grid cells observed in the rodent brain [53]. If gamma serves as the reference wave for neural information processing and it provides the temporal unit for reconstructing information from phase, uniformly distributed gamma generators in the neocortex self-organize into columns where the local gamma radially propagates within each column. Then it is conceivable that a neighborhood of columns is able to synchronize information processing cycles in a form of continuous spatial

wave function as long as the SMOs of constituent columns are coherent. In contrast, columns with incoherent SMOs could maintain segregated information processing. The independence of two adjacent gamma generators is maintained within the radius of a complete gamma cycle in space, and so does the coherence maintained over multiple spatial gamma cycles. The radii of gamma generators depend on the propagation speed. We demonstrated by simulations that the phase gradient that provides maximal precision of reconstruction from gamma phases, i.e., the propagation speed of gamma waves in the cortex, must be close to 0.1 mm/ms [53]. Intriguingly, this is very close to the empirically described values across species and preparations [65–68]. Given the propagation speed and the oscillation frequency gamma, the cortical columns must be about 1 mm in diameter, which closely matches to the 500 μm–2 mm cortical column size. Decreasing the frequency of SMO increases the estimated column diameter, which is the case in the motor and premotor cortical areas.

We discussed earlier that propagating theta oscillations cause AP phase precession when measured from extracellular electrodes while the same APs maintain their phase lock to the intrinsic SMO (see sections "Correlation Between the Phase of Membrane Oscillations and Action Potential" and "Correlation Between the Phase of Local Field Potentials and Action Potentials"). This result is also supported by empirical results [36–38]. Here we illustrate how phase coding generates a biologically plausible topography before selective wiring takes place: we modeled the self-organization of orientation maps in the primary visual cortex without orientation selectivity being assigned. First, we constructed a retinal array of 36×36 neurons consisting of 81 neuron groups. Each individual group collected the input of 16 ganglion cells. These ganglion cells encoded the visual input by gamma-aligned spikes as described in section "Gamma Alignment". The visual input was modeled by a set of orientated sinusoid gratings with a single-cycle spatial frequency (Fig. 13.7). The total 1,296 ganglion cell model converged on an array of 81 LGN neurons, each transferring the compressed code from 16 ganglions to the cortical array of 36×36 neurons, interfacing with the retina. These cortical neurons were also assigned by gamma SMOs with the same spatial phase gradient as the ganglions. According to our simulations, the model cortical layer reconstructed the phase-encoded stimulus with a characteristic spatial transformation. Each different orientation was mapped on a slightly phase-shifted area of the cortical cell array because the gamma phase difference in the time domain naturally mapped onto a spatial phase difference between locally generated gamma SMOs. Because gamma SMO displayed a similar spatial phase gradient both in the retina and in the cortex by construction, this spatial phase gradient enforces the mapping of different stimulus orientations to different spatial phases. When the reconstruction from phase takes place in the cortex, the originally phase-encoded APs will coincide with the cortical SMO of those neurons that are in the same topological position. Because of the retinotopy of cortical cells, the topography of APs in the cortex roughly reproduces the retinal input [53]. When we superimposed neuronal responses to different orientations, we observed a typical pinwheel pattern, characteristic of the empirical pinwheels observed in columnarly organized visual cortical architectures [69]. We emphasize that there was neither a particular projection imposed on the architecture nor was orientation selectivity assigned to the cells in the model. Nevertheless, a pinwheel

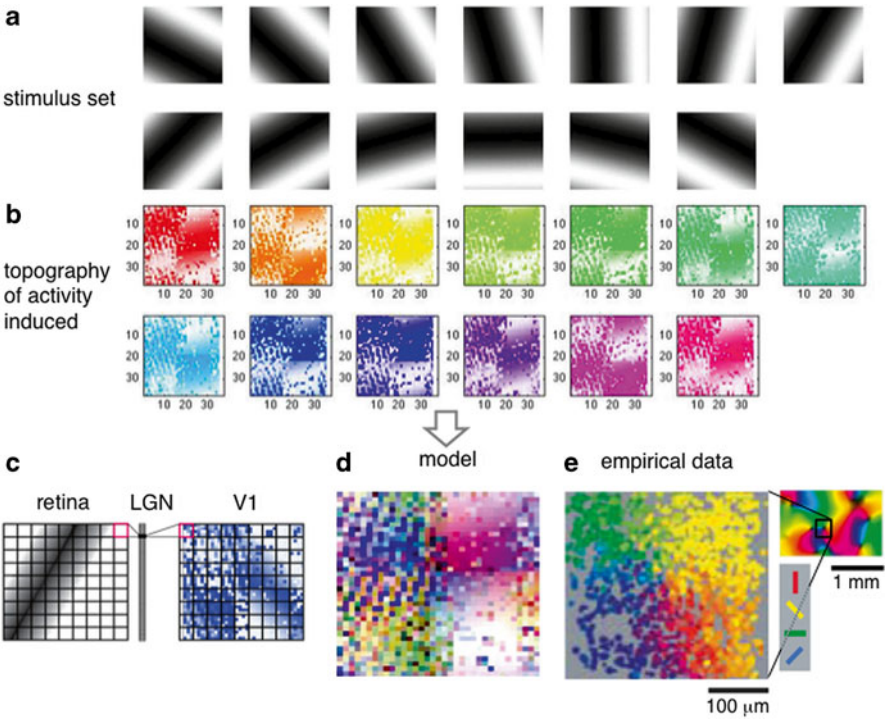

Fig. 13.7 Computational model of the self-organization of visual orientation maps. (**a**) A set of oriented grating stimuli was applied to drive retinal ganglions, one orientation at a time. The square-shaped stimulus covered the entire area of the retina. (**b**) The cortical activity induced by the corresponding stimulus set in (**a**). The hues of colors represent the activity of neurons at the given point of the 36×36 neuron space. (**c**) The luminance values were processed through latency-encoding gamma alignment. Compression into 81 channels took place at the LGN and the final step of reconstruction in V1. (**d**) The combined orientation responses in V1. *Colors* in (**b**) are superimposed. (**e**) Empirical results of pinwheel structure [69]. Note that although orientation selectivity was not wired in the system. Nevertheless, phase coding generated an orientation-selective pinwheel structure

structure evolved from mapping the original temporal phase offsets into space. This illustrates how orientation selectivity may emerge from phase coding, while these emergent maps can stabilize by means of spike time-dependent plasticity that strengthens the synaptic connections over time.

Time in the Brain

Tracking the real time of events in our environment is critical for survival. All physical and social interactions are time dependent. Often there is a very narrow time-window of interaction with the environment, which, if missed, can have dramatic

outcomes. For monkeys to grab a branch while jumping from tree to tree or for humans to steer a car away in intersection to avoid a collision, timing is vital. To achieve this temporal precision, the brain needs to integrate across a number of parallel sensory channels and across different modalities, such as between sound and visual motion. The inherent problem of sensory processing is delay, the time it takes for the brain to access the true time of events. It takes time to compute time. There are three problems: one is the combined effect of conductivity and cumulative synaptic delay that sets the boundary for perceptual delay and reaction time. The second is the variance of these delays across axons and fiber bundles and sensory pathways (see section "The Problem of Conductivity and Synaptic Divergence"). The third is the discrete nature of sensory processing.

Conductance delay itself would not be a problem as long as the brain can compensate for that delay, and Libet's subjective referral is one example of how that can be accomplished [70]. However, the problem of heterogeneity of axon conductivity is difficult to explain away [71, 72]. The time scale of the variations of thalamocortical delays in the visual pathway (>20–40 ms) exceeds the time window of spike time-dependent plasticity (±10 ms, [73, 74]). Hence it is critical for the brain to accomplish the level of precision necessary for cortical neurons, as coincidence detectors [75], to detect true coincidences in the physical world. How can the brain combine color with motion when the latency difference between the two pathways is larger than 20 ms?

The solution we propose is plausible based on physiological and anatomical facts. According to phase coding, neural fingerprints of sensory events carry their own time tags. The spike-train packets encode the complete spatiotemporal pattern of a sensory event. The delay between two events is captured by the gamma cycles between them, and more refined discrimination is achieved on the spatiotemporal domain as phase differences. Instead of registering events in absolute time, the phase captures the relative time of sensory events such as a texture moving across a small patch of retina.

Because space is converted to time, time in the neural code is inextricably connected to space. Most importantly, the embedded time code makes the timing of sensory events immune to distortions due to the variance in conduction delays.

The notion that the brain references the times and locations of events by the cycle and phase of ongoing oscillations was corroborated by recent magnetoencephalographic evidence: perceptual adaptation to audiovisual asynchrony correlated with the change in the phase of entrained cortical oscillations in the auditory cortex relative to the visual stimuli and predicted the individual's perceived simultaneity of audiovisual events [76]. In support of the notion of discrete sensory sampling, gamma frequency oscillations have been observed in the insect nervous system, specifically in the mushroom body, in fish, and also in the mammalian nervous system [77, 78] (see section "The Origin of Retinal Gamma" above). Moreover, one gamma cycle is 20–25 ms long and matches the average critical fusion frequency (15 Hz rod-mediated vision and 60 Hz at very high illumination intensities) [79]. Motion perception in the mammalian brain relies on this discrete sampling of visual space. In summary, we propose that the temporal basis of transferring time-labeled

spatial information in a broad range of species and sensory organs is gamma SMO-based. This mechanism guarantees the separation of the temporal information in the spike packets from the transfer delay and processing time due to conduction delays in neuronal circuitries.

Benefits of Phase Coding

What are the biological advantages of phase code? Why perform so much work only to encrypt sensory messages for mere tenths of a millisecond before decoding? This brings us back to the issue of why coding is necessary at all. The answer applies to other biological systems using coding, such as DNA with its complementary nucleotide sequences. That is, the information in these messages has to (1) be maintained in time, (2) be transferred over a distance, (3) be read by diverse targets, (4) support selective partial readout, (5) be noise resistant, and (6) be reproducible. We argue that phase coding in the brain meets with these requirements:

1. Phase code maintains information by explicitly encoding time and space. Because time between events is encoded by the distance the gamma wave travels and distance is encoded in phase, time and space are inextricably combined in the phase code by the sequence of APs. These sequences can be maintained and reproduced in synaptic circuitries by known plasticity rules and reverberations.
2. Phase code can be broadcasted over a distance as binary code by APs. Delays do not affect the code because the code contains time.
3. The code must be accessible to be read by multiple targets since the sensory information has to be processed by those multiple targets (e.g., the retinal input is used by the optic tectum and thalamic targets).
4. Different subsystems read different parts of the code. Thus the code has to be composed such that these parts can be parsed. The gamma SMO provides a biologically plausible reference for the parsing because it is locally generated and ubiquitous. The interference principle implements the target selective readout (section “Interference Principle”).
5. Noise resistance. The code has to be transferred with minimal distortion. This is provided by the code compression. Merging spikes across parallel channels makes the code self-correcting, because if one AP fails to be transferred, divergent connections at the next level will fill in from neighbor axons.
6. Reproducibility. The code can be maintained in polysynaptic circuitries as in (1) and is accessible for other structures at other times. The code can also be recompressed in the cortical columns before transferring to other columns. Cortical columns naturally reproduce the sensory information and distribute them to vast numbers of cortical columns.

In addition to these benefits, sensory systems are able to enhance the spatial resolution of the signal by intrinsically induced or movement-evoked traveling waves of

membrane potential over the receptor surface. One example for enhanced spatial resolution was hyperacuity (discussed in section "Retina-LGN projection"), which illustrates how converting spatial information on the temporal domain can increase the spatial resolution of the transmitted sensory signal. Hence, at cortical targets, the information can be reconstructed at higher than receptor resolution.

Finally, phase coding is not simply an encoding and decoding principle that can restore the original information with 100 % accuracy. The cortical representation is not meant to be an identical reconstruction of the retinal image. Instead, because of the target diversity and partial readout principles (3 and 4), different structures extract different components of the sensory information. One manifestation of such distortion is the topographical mapping of angular space to the topography of visual cortex. Another manifestation is the mapping of visual orientations in retinal coordinates to cortical orientation space, which maps the temporal interference pattern into a spatial phase map. It then reproduces the empirical pinwheel structure without predefined orientation selectivity (section "Topography").

Transformations of the code and selective readout at different levels of information processing are constrained by the topology of oscillation fields at those levels. The relationship between the retinal oscillations and oscillation fields in V1 determines the information that will be read out as well as of the nature of the distortion of the code. However, instead of compromising the code, this distortion enhances its properties, as the orientation mapping enhances the abstraction of orientation features from the retinal image. Hence, subsequent processing stages are able to extract different features from the input by simply changing the structure of the oscillation field. Because phase coding redefines the goal of neuronal computation by focusing on the transformation of oscillation fields between interfacing stages of sensory and cortical processing, it will force us to develop a new computational toolset for investigation of the interaction between the discrete APs and the continuous field of membrane oscillations at multiple scales. This approach will ultimately deepen our understanding of how local cellular mechanisms of information processing make up the fabric of large-scale computations in the brain.

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Chapter 14
Reinforcement Learning and Hippocampal Dynamics

Adam Johnson and Sarah Venditto

Abstract Recent experimental findings on hippocampal representational dynamics such as route replay and sweeps match intuitive notions from reinforcement learning including transiently representing potential trajectories and reward locations. We explore these intuitions within a formal reinforcement learning framework and examine how these representational dynamics might be integrated with reinforcement learning algorithms. We suggest that hippocampal representational dynamics can be best integrated within a model-based reinforcement learning framework and show how this framework can be used to cultivate specific quantitative predictions for the control processes that direct and utilize hippocampal representations.

Keywords Hippocampus • Memory • Reinforcement learning • Reward • Replay • Sweeps • Generalization • Planning • Consolidation

Introduction

Hippocampal function is typically explained in terms of a set of fundamental representations or memory contents that inform behavior. The foremost of these hypothetical representations is the cognitive map in which hippocampal place cells represent an animal's position within a behavioral task [1]. Although a swath of hippocampal research has focused on understanding how an animal finds and represents its place within an environment, the recent discoveries of hippocampal representational dynamics such as route replay and sweep activity suggest new research avenues.

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These dynamic spatial representations provide deep intuitions into how an animal can find its way, remember its past, and even imagine its future and further connect the place cell literature with the larger hippocampal memory literatures [2–5].

The move from hippocampal representations as mere reflections of an animal's current spatial location and previous locations to hippocampal representations as vehicles for active learning and decision-making processes poses a series of theoretical challenges. The most important of these challenges are centered on the control processes that govern and interact with hippocampal representational dynamics. In order to address these challenges, we adopt a reinforcement learning approach [6]. The primary thrust of reinforcement learning (RL) is the development of a set of actions that maximizes the acquisition of reward. Within RL, hippocampal representational dynamics can be understood as members of a class of covert cognitive actions that animal can employ to better solve a behavioral task [7]. But how should these covert actions be implemented? The following discussion explores how hippocampal dynamics might be embedded within and interact with RL computations.

Beyond Simple Location: A Brief History of Hippocampal Representational Dynamics

Early studies of off-line hippocampal activity showed that task-related place cell activity persists beyond task performance [8, 9]. Further investigations showed that the temporal organization of off-line replay largely reflected previous behavior and suggested replay associated with sharp-wave ripple complexes could be understood as temporally compressed records of previous experience [10–13]. A number of later findings showed similar sharp-wave ripple-associated replay dynamics during awake online behavior [14–16]. These results showed that the hippocampus supported a set of representational dynamics that reinstantiated an animal's developing experience within a task.

Early findings on hippocampus-based forward replay were viewed as residual reverberatory dynamics embedded within hippocampal circuits. Forward replay was thought to be the product of sequential activation of place cells and spike-time-dependent plasticity. Online and off-line replay dynamics were explained as interactions between the animal's position and experience within the particular task [16–19]. And the increased likelihood of replay that included the animal's current location during awake online replay could be accommodated by including heightened disinhibition of the animal's current location [17]. Because spike-timing-dependent plasticity and simple disinhibition could explain the observed forward replay dynamics, hippocampal replay could be construed as passive, bottom-up processing: hippocampal forward replay dynamics were an epiphenomenal by-product of behavior. Their contribution to reinforcement learning was simply that they afforded RL systems an opportunity to vicariously practice the task in between actual behavioral trials [20].

More recent experimental findings have complicated passive, bottom-up views of hippocampal representational dynamics. The discovery of backward replay [14, 15, 21] poses a distinct problem for spike-timing-dependent plasticity models of passive replay. Remote replay [22] and replay activity that spans multiple sharp-wave ripples that may be separated in time [23] challenge initiation of replay based on disinhibition associated with the animal's current location. And increased replay activity associated with novelty within a task [24, 25] and novel reward [26] appears to require even more complex neuronal explanations. While cellular and circuit level explanations for these findings will certainly be found, these findings suggest that hippocampal representational dynamics may be functionally organized according to more cognitively oriented, top-down processes. Two sets of experimental findings appear to support this claim: hippocampal sweeps and replay of novel trajectories [27–29].

Hippocampal sweeps are representational dynamics associated with vicarious trial-and-error behavior within spatial decision tasks [28, 29]. Vicarious trial-and-error (VTE) behavior occurs as an animal approaches a choice point; it is characterized by a series of spatially directed feints toward each potential choice [30, 31]. Tolman's early descriptions of VTE suggest that the animal represented information related to the outcome of each potential choice option such that the animal could vicariously sample and evaluate each choice option. Hippocampal place cells associated with the spatial location of potential choices become active while the animal pauses at the choice point. This activity appears to instantiate the core representational dynamics necessary for evaluation of spatial choice.

Although previous work suggested that hippocampal replay can reinstantiate previous spatial experience, whether the hippocampus might construct novel replay activity that moved beyond experience remained an open question. Gupta et al. [27] found novel spatial trajectories embedded within hippocampal replay of a spatial decision task. These replay dynamics mixed forward and backward replays and appeared to match a set intuitive representational dynamics that an agent with knowledge of the task might use to solve the task. Furthermore Pfeiffer and Foster [32] showed that place cells predict an animal's trajectory in a two-dimensional environment and appear to allow an animal to represent the goal location. And unlike previous work that showed replay activity that reflected general task experience [16], these predicted trajectories developed flexibly, often producing novel trajectories to the goal location.

These experimental findings highlight the importance of looking beyond passive, bottom-up explanations on hippocampal representational dynamics toward explanations that emphasize active regulation of hippocampal dynamics by higher-order cognitive processes and their interaction with ongoing behavior. Backward route replay, hippocampal sweeps, and novel trajectories within replay each fit intuitive explanations for task solution and enhanced performance through based on reinforcement learning. But how do they fit within a more formal RL framework?

Reinforcement Learning

RL as Predictive Maximization

The goal of reinforcement learning is to learn a policy $\pi(s,a)$ that maps states to actions ($s \rightarrow a$) and maximizes future reward receipt. In simple terms, a policy can be understood as a table that specifies what action the agent ought to select in each state. A state is formally defined in terms of the task. For example, state within a tone-based delayed conditioning task is indicated by the tone cue, while a state within a spatial task might be given by a particular location or maze region. Some modeling approaches assume that the task state is fully observable (e.g., the tone), while other modeling approaches assume that it must be inferred from available task cues (e.g., a particular region of a spatial maze). Future reward receipt or the return, R_t, is given by

$$\mathrm{R_t} = \sum_{k=0}^{\infty} \gamma^{\mathrm{k}}\, \mathrm{r_{t+k+1}}$$

where r_t is the reward at time t and γ is the discount factor. The discount factor is typically introduced in order to make the equation tractable for R_t in continuing tasks such as random foraging tasks where there is no natural end point for a single trial. The discount factor can be neglected or set to $\gamma = 1$ in repeating tasks with terminal states, which clearly indicate the end of a single trial. We return to this point below.

The value of a policy is given by its expected return. Since a policy is a mapping of states to actions, the value of a particular state given the policy can then be expressed as the expected sum of discounted reward for all available future states.

$$\mathrm{V}^{\pi}(\mathrm{s}) = \mathrm{E}_{\pi}\left\{\mathrm{R_t} \mid \mathrm{s_t} = \mathrm{s}\right\} = \mathrm{E}_{\pi}\left\{\sum_{k=0}^{\infty} \gamma^{k}\, \mathrm{r_{t+k+1}} \,\middle|\, \mathrm{s_t} = \mathrm{s}\right\}$$

Defining the value of a policy as a function of state $V^{\pi}(s)$ forms the basis of the Bellman equation and provides the fundamental intuition behind reinforcement learning [33]. The result of this formulation is that specific states can be used to predict expected future rewards given a policy.

$$\mathrm{V}^{\pi}(\mathrm{s}) = \mathrm{E}_{\pi}\left\{\mathrm{R_t} \mid \mathrm{s_t} = \mathrm{s}\right\} = \sum_{a} \pi(\mathrm{s,a}) \sum_{\mathrm{s}}^{'} \mathrm{P}\left(\mathrm{s}^{'} \mid \mathrm{s,a}\right)\left[\mathrm{R}^{\mathrm{a}}_{\mathrm{s,s}^{'}} + \gamma\, \mathrm{V}^{\pi}\left(\mathrm{s}^{'}\right)\right]$$

Here $P(s'|s,a)$ denotes the probability that an action a in state s will lead to a subsequent state s' and $\mathrm{R}^{\mathrm{a}}_{\mathrm{s,s}^{'}}$ denotes the reward probability for a given action a in state s leads to state s'. The Bellman equation forms the basis for evaluating a particular policy and plays a critical role in the search for an optimal policy [6]. The use of recursion in Bellman equation [that describes the value of a policy at one state $V^{\pi}(s)$ as a function of the value of the policy at a subsequent future state $V^{\pi}(s')$] gives rise

to the prediction error in model-free temporal difference learning. And the $P(s'|s,a)$ term which describes the dynamics of the task and the $R^{a}_{s,s'}$ term which describes the reward contingencies of the task give rise to the task model in model-based reinforcement learning approaches.

Model-Based Versus Model-Free RL

The Bellman equation forms the basis for two major computational approaches to value function learning and policy development. The first approach, often referred to as *model-based RL*, requires that the reward function $R^{a}_{s,s'}$ *ss* and the transition dynamics $P(s'|s,a)$ are either learned or previously known in order to compute the value function. Model-based RL uses a model of the task—estimates of $P(s'|s,a)$ and $R^{a}_{s,s'}$ —to learn the optimal policy. If we assume that the agent has no previous knowledge of the task, model-based RL can be viewed as a two-stage learning process. In the first stage the agent learns a model of the task-based reward functions and transition dynamics, and in the second stage, it uses these models to construct a value function in order to optimize reward receipt on the task. Although these stages are ordered since policy development is contingent on learning the reward and transition functions, the two stages are generally interleaved so that optimal policy development reflects task learning.

The second approach, referred to as *model-free RL*, uses sample data to estimate the value function without explicitly learning the reward function $R^{a}_{s,s'}$ or transition dynamics $P(s'|s,a)$ embedded within the task. In this case, model-free RL approaches use the set of task-based observations $[s,a,s',r]$ as samples from the reward and transition dynamics distributions in order to develop value function and policy learning without explicitly attempting to learn the reward and transition models.

Temporal difference learning is among the simplest and most well-known model-free RL approaches and can be viewed as an extension of associative appetitive learning [6, 34, 35]. Temporal difference-based value function learning is a simple modification of the Bellman equation in which the temporal difference is computed by comparing the expected value of a state $V(s)$ and the sum of a reward and the value of a discounted subsequent state, $r+\gamma V(s')$. If the value function is accurate, the temporal difference is zero, but if the temporal difference is nonzero, the prediction error given by $\delta=[r+\gamma V(s')-V(s)]$ can then be used to update the estimated value function

$$\mathrm{V}(\mathrm{s}) \leftarrow \mathrm{V}(\mathrm{s}) + \alpha\left[\mathrm{r} + \gamma\,\mathrm{V}\left(\mathrm{s}'\right) - \mathrm{V}(\mathrm{s})\right] = \mathrm{V}(\mathrm{s}) + \alpha\delta$$

where α is the learning rate and γ is again the discount factor. The appeal of temporal difference learning as a model of biological reinforcement learning comes from its computational simplicity and studies of the neural activity of midbrain dopamine neurons that reflect these prediction errors. Dopamine neurons in the ventral

tegmental area display activity that is highly consistent with prediction errors on a variety of learning tasks [36, 37].

Each of these approaches has merit—in terms of pure computation and in terms of explanations of neural basis of reinforcement learning. Model-based RL is typically viewed as fast adapting since an agent learns the structure of the task as well as what actions are best, while model-free RL is typically slower but requires much less computational machinery since it learns only what actions are most rewarding [38]. As a result, model-based RL has been used to explain flexible, goal-directed learning and model-free RL to explain habit learning [38]. Model-free RL computations are thought to depend on dorsolateral striatal circuits as lesions of this area compromise habit learning [29, 38, 39]. In contrast, model-based RL computations are thought to depend on prefrontal cortical and hippocampal circuits as lesions of these areas compromise goal-directed behavior [29, 38].

Where Does the Hippocampus Fit Within RL?

Early reinforcement learning models viewed the hippocampus as providing location-based state information. These models used temporal difference learning algorithms to develop spatial- or location-based value functions that were then used to solve spatial learning tasks [20, 40]. While temporal difference (TD) learning-based approaches could simulate acquisition of spatial learning, they did so too slowly: basic TD models of the water maze failed to capture one trial learning dynamics [40], and similar models of sequential spatial decision tasks also failed to capture the speed of task acquisition [20]. The failure to adequately capture the speed of hippocampal learning within RL models has been addressed in two ways—the development of generalizable representations and the introduction of explicit model learning.

Generalizable Representations

Generalization within RL is typically introduced by constructing hierarchical state and action representations that increase task acquisition rates [41, 42]. Hierarchical representation-based approaches effectively fold the state space or action space onto itself such that reward observations (and the prediction errors they produce) can be mapped onto multiple states/actions simultaneously. The mapping of these reward observations onto multiple, often hierarchically organized states and actions massively facilitates value function learning and policy development. Foster et al. [40], for example, introduced a goal representation that could be generalized across variable platform locations in addition to a standard place representation in order to model learning on the water maze. This form of generalization facilitates learning through a hierarchical spatial-action representation and was critical for modeling the development of single-trial learning within water maze.

The simplest example of generalization is the use of eligibility traces within TD learning. An eligibility trace $e(s)$ is usually represented as a leaky integrator or exponential decay function that indicates how recently a particular state has been encountered. Once computed, it can be used to map the prediction error δ onto each state according to how recently it has been encountered.

$$\delta_{\text{update}}(s) = \delta \cdot e(s)$$

Given that $\delta_{\text{update}}(s)$ now is defined for all states, the entire value function can be simultaneously updated according to temporal difference learning value function update shown above. The process of sharing information associated with a reward observation in order to simultaneously update multiple components of a value function is the hallmark of generalization within RL frameworks. Generalization does not require explicit use of model-based RL or nonlocal representations; it can occur by representing an agent's current state/action as a multifold set of hierarchically organized substates and/or sub-actions.

An example of this multifold representation can be drawn from spatial representations across the dorsal/ventral axis of the hippocampus. Rather than representing the position of the animal within a single hippocampal map, this view holds that an animal's position is simultaneously represented across multiple hippocampal maps that vary in spatial resolution. The small place fields of the dorsal hippocampus represent the animal's fine-scale position in its environment, while the larger place fields of the ventral hippocampus represent its larger-scale position [43]. Treated in this way, spatial learning develops quickly because ventral hippocampus provides a state space over which a low-resolution value function can be learned while the dorsal hippocampus provides a state space over which high-resolution value function can be learned. A simple prediction of this view is that specific lesions of the hippocampus should differentially affect spatial learning: lesions of the dorsal hippocampus should compromise the high-resolution value function and produce more broadly distributed search, while lesions of the ventral hippocampus should compromise the low-resolution value function leaving more focal search intact but compromising learning at much larger scales. This multifold view of hippocampal representations is consistent with the findings from specific lesions over small spatial scales [44].

Although the above treatment does not explicitly explain how generalization might affect hippocampal representational dynamics such as hippocampal sweeps and replay, it provides several important intuitions to which we briefly return to in our subsequent discussion of planning.

Model-Based Learning and Simulating Task Experience

Model-based RL algorithms learn explicit models of the transition and reward structure of a task. These models are then used to simulate task experience in order to facilitate value function learning and policy development. Learning models of a

behavioral task allow immediate construction of value functions and policies as an alternative to using previously stored or cached value functions and policies.

The distinction between constructing a policy on the fly and retrieving a cached policy immediately raises questions about which is more appropriate. Retrieving a cached policy is generally faster than constructing the policy de novo and reduces computational load; however, a previously cached policy may not integrate new task information or current motivational status [38]. In an idealized version of model-based RL, model-based simulation occurs instantaneously and provides a complete value function and policy update after each time step [38]. While the ideal approach provides maximum adaptive flexibility, it is also likely computationally prohibitive for anything beyond the simplest of tasks. Instead, cached value functions and policies are likely used in highly standardized domains, while constructed value functions and policies are used in highly variable domains that must integrate new task information and motivations.

These intuitions should deeply inform when and where we expect hippocampal representational dynamics to occur and what we expect these dynamics to represent. More specifically, computationally efficient model-based RL suggests learning can be split into two functional domains: general value function and policy learning that reflects the stable task components and specific value function and policy learning that updates local, temporally variable task components. The distinction between construction of local, temporally variable value functions and policies and global, stable value functions and policies is similar to the distinction between working and reference memory made by Olton et al. [45]. If the hippocampus updates or contributes to the construction of local, temporally variable value functions and policies, the spatial representational dynamics of the hippocampus should reflect these locations.

Backward Versus Forward Replay

Theoretically, backward replay may have a privileged role over forward replay in fast construction of local, temporally variable value functions by mapping rewards backward without discounting. Forward replay, in contrast, likely captures the general statistical structure of the task and compensates for the possible idiosyncratic, inefficient local policies that would develop as a result of isolated backward replay. If backward replay is primarily used to update local, temporally variable value functions and policies while forward replay is primarily used to update global, temporally consistent value functions and policies, we should expect to see different distribution of these types of replay across task performance and rest periods: backward replay that facilitates local, temporally variable value functions and policies should increase relative to forward replay during task performance and decrease following task performance. Indeed, Wikenheiser and Redish [46] found that during task performance, forward replay occurs as often as backward replay while forward replay occurs more frequently than backward replay during post-task sleep.

Local Versus Remote Replay

Efficient value function and policy updating suggests that segments of an agent's history that produced large changes in the value function should be replayed more often than segments of an agent's history that produced little change in the value function (see Sutton and Barto [6] on prioritized search). During early learning trials, states that are in close temporal proximity to reward quickly increase in value while states that are farther away display little change. As learning proceeds, the value function stabilizes for states in close proximity to reward and the value function for states further from reward begin to undergo larger changes. As a result, the region of greatest change in the value function moves away from reward locations across learning. Such changes in the value function may account for increased replay after changed reward contingencies [26], increased representation of goal locations [32], and the development of remote replay [22].

Until this point, the type of replay we have described to facilitate learning within a model-based RL system has been a purely passive reflection of task statistics. Each of the hippocampal representational dynamics (backward/forward, local/remote) can be understood as specifically driven by quickly integrating unexpected reward into current value functions and policies. We now turn to planning and evaluation in which an agent (or animal) must represent and evaluate different potential options. This evaluative process requires a subtle change in the statistics that inform hippocampal representational dynamics.

Hippocampal Dynamics in Planning

Planning ostensibly refers to a model-based RL approach wherein temporally or spatially distant outcomes are represented and evaluated. Within model-based RL, the transition model $P(s'|s,a)$ is used to represent future outcomes while the reward model is used to construct the value function for a particular choice. In short, planning requires that an agent vicariously represents and samples from each possible option in order to construct a value function with which to compare available options. This technical definition elucidates the difference between passive decision-making processes in which each option is sampled according to the transition model probabilities and active decision-making processes in which each option is sampled according to other criteria (e.g., expected value, resolution of uncertainty, etc.).

Planning dynamics are dependent on the task structure and the task representation. More specifically, where planning occurs within a task is dependent on the how the animal represents the task [47] and the working memory capacity of the individual animal. A locally constructed value function can be constructed from a distance via the generalization processes outline above and subsequently maintained until the critical choice point. However, maintenance of the value function prior to the choice point is dependent on the availability of adequate working memory resources; without these resources, planning is worthless.

Johnson and Redish [28] showed that hippocampal sweeps associated with vicarious trial-and-error behavior develop at a high-value choice point within a set of spatial decision tasks. Sweep activity developed across early trials and then decayed as stereotyped behavior developed in a spatially stable sequential decision task but persisted after development in a cued spatial decision task in which the reward location was contingent on an auditory cue. In these cases, dynamic hippocampal representations associated with planning occurred at choice locations during online task solution. In contrast, Singer et al. [48] showed that replay activity prior to a trial represented multiple potential trajectories during early learning regimes. Furthermore, higher coherence within these replays predicted better behavioral performance. Finally, Pfeiffer and Foster [32] showed that replay activity predicts an animal's future trajectory with a particular emphasis on goal locations. This representational emphasis of goal locations may be associated with the construction and subsequent maintenance of a local, temporally variable value function in much the same way that hippocampus-based working memory supports radial arm maze performance [49].

Extending Model-Based RL to Memory Consolidation: Information as Reward

The contribution of hippocampal replay to reinforcement learning is a relatively recent development. It has traditionally been viewed primarily within the context of memory consolidation and the formation of robust, stable memories [50, 51]. Within this context, reactivation of previous experiences enhances synaptic connections, usually within neocortex, making the memory more robust against potential mnemonic interference. One of the primary difficulties encountered within the consolidation literature is the temporal variability of consolidation processes. Consolidation is usually understood as a slow, gradual process [51]; however, a variety of studies suggest that consolidation can occur very quickly. A recent experimental study by Tse et al. [52], for example, showed consolidation of single-trial learning (signaled by hippocampal independence) was complete in less than 48 h when animals were provided appropriate behavioral training.

Reinforcement learning may offer some insight into this apparent conflict between typically slow consolidation processes and sudden hippocampal independence. The goal of RL is the maximization of reward. Our previous discussion has shown that hippocampal representational dynamics such as replay contribute to reinforcement learning. However, our discussion has focused on an arbitrary reward currency applicable to appetitive learning with food, water, intravenous drugs administration, or medial forebrain bundle stimulation. If we posit that a reduction in the uncertainty of a task representation—information gain—is form of reward currency [53], the entire previous discussion can be applied to memory consolidation. The upshot of applying RL to consolidation processes is the specific focus of hippocampal replay dynamics on particular aspects of the task where replay will most enhance consolidation. This allocation process emphasizes reactivation of coherent, but not quite stable memory representations that will undergo the greatest stabilization through replay. As a result, specific training conditions such as those

used by Tse et al. [52] should increase the speed of memory consolation. Though speculative, the information gain proposal offers a natural connection between the RL literature, particularly work by Friston and colleagues [54], and computational theories of memory consolidation.

Conclusions

Our treatment of hippocampal representational dynamics within the context of RL was motivated by a series of experimental results suggesting that the behavior of these dynamics followed core intuitions of reinforcement learning. We suggest that hippocampal representational dynamics including replay and sweeps can be understood as critical components of a model-based RL process. The RL literature has been circumspect on the contribution of the hippocampus to reward learning and has instead focused on the more readily identifiable contributions of striatum and prefrontal cortex [38]. However, we believe our approach to hippocampal dynamics provides a theoretically well-grounded and intriguing way to examine the contribution of the hippocampus to RL, particularly as it provides a natural framework for understanding the interactions between the prefrontal cortex as a controller and the hippocampus as an actor within a memory space.

Within our model-based RL approach, the prefrontal cortex biases hippocampal representational dynamics toward behaviorally salient features of the task where policies must be flexibly updated in order to produce optimal behavior. The hippocampus performs two functions. First, it provides the memory substrate for representing remote locations and constructing extended policies associated with plans for future behavior. Second, the hippocampus provides a set of memory stability signals that replace reward signals and can be used to direct reactivation in support of memory consolidation rather than drive reward acquisition. If the prefrontal cortex drives hippocampal dynamics, inactivating prefrontal cortex will leave intact bottom-up dynamics like spike-timing-dependent plasticity-based replay while abolishing top-down dynamics like remote replay and sweeps. This perspective is consistent with proposals that the prefrontal cortex is the critical control element for flexible, goal-directed behavior [38] and may explain why so many tasks can be learned without a hippocampus, albeit much more slowly.

While the hippocampus is critical for many learning tasks, situating the hippocampus within the context of reinforcement learning has been difficult. We hypothesize that much of this difficulty has been the consequence of an attempt to identify the hippocampus as supplying critical information general reinforcement learning rather than supporting critical dynamics associated with model-based RL. Model-based RL supports the behavioral flexibility that hippocampal-dependent tasks require and utilizes dynamics similar to the representational dynamics observed in the hippocampus. Framing hippocampal dynamics as supporting model-based RL offers a set of computationally tractable, quantitative predictions that can be used to further explore hippocampal function and its diverse contributions to learning and memory.

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Chapter 15
Off-Line Replay and Hippocampal-Neocortical Interaction

Szabolcs Káli

Abstract This chapter focuses on possible computational functions of hippocampal replay. First, we briefly review essential data and theories on the function of the hippocampus in long-term memory, focusing on its proposed role in memory consolidation. We then describe a combined hippocampal-neocortical model which allows the simultaneous but distinct treatment of episodic and semantic information and study the relationship between hippocampally initiated replay and different aspects (storage, access, and decoding) of long-term declarative memory in the face of representational change. We show that replay may not provide a plausible way to establish in neocortex durable episodic memories which are independent of the hippocampus. We then turn to the question of maintaining access to episodes in the presence of the hippocampus and demonstrate a possible role for replay in this process. Finally, we examine the acquisition, consolidation, and maintenance of general semantic information and compare it with episodic memory. The last part of the chapter describes our recent efforts aimed at the identification, using combined physiological and modeling tools, of cellular and network mechanisms of the generation of hippocampal sharp wave-ripples and associated replay of neuronal activity sequences.

Keywords Hippocampus • Episodic memory • Semantic memory • Memory consolidation • Network dynamics • Sharp wave • Ripple oscillation • Simulation

Hippocampal Functions

To date, most characterizations of the function of the hippocampus fall into three broad categories: memory, spatial processing, and conjunctive coding. Based originally on neuropsychological data from humans, memorial theories posit that the hippocampus is responsible for storing certain classes of memories in such a way

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that they can be recalled based on partial or altered cues [1–4]. The role of the hippocampus in memory may also involve a consolidation process, whereby reactivation of the memory traces stored in the hippocampus results in a gradual reorganization of neocortical memory representations [5, 6].

Spatial processing theories were originally based on behavioral and selective lesion data from a variety of animal species and, most spectacularly, neurophysiological data from rats on the existence in the hippocampus of neurons (called place cells) whose activity signals the animal's position in space [7]. These theories hold that the hippocampus plays a central role in manipulating information about space, potentially implementing or supporting key operations such as the construction and use of internal maps of the layout and contents of the external world [8–10].

Finally, conjunctive coding theories, based originally on data from animal conditioning, suggest a particular role for the hippocampus in creating, and perhaps teaching the neocortex about, unitary codes to represent complex combinations of potentially multimodal stimuli [11, 12].

All of these theories appear to capture some critical aspects of hippocampal function, but neither of them, by itself, seems powerful enough to describe the entire, bewilderingly rich collection of experimental observations about the hippocampus and its interactions with other brain areas. Instead, the actual neural operations carried out by the hippocampus can probably support a variety of behavioral functions, also depending on a number of factors such as the species considered, task, context, and behavioral state. Several authors have argued for the unification of memorial and spatial accounts of hippocampal function [8, 13, 14], and some models have explicitly shown how aspects of hippocampal architecture traditionally considered to be necessary for its memorial functions may also support spatial processing [15, 16]. Unifying accounts of memory and conjunctive coding have also been proposed [17].

Memory and the Hippocampus

Roles of the Hippocampus in Memory

The hippocampus is known to be involved in the storage, access, and decoding of episodic memory (i.e., autobiographical event memory) and semantic memory (which we define here as the storage and retrieval of structured information not specific to one particular episode), two subtypes of declarative memory which have been characterized in detail both experimentally and computationally. Long-term declarative memory requires the integrity of the hippocampus (HC) and adjacent cortical areas of the medial temporal lobes (MTL) [18]. Clinical studies in humans and animal experiments indicate that damage to these regions results in amnesia, whereby the ability to acquire new declarative memories is impaired (this is termed anterograde amnesia) and some of the memories acquired before the damage are

lost (retrograde amnesia; RA). However, the detailed characteristics of these deficits and, consequently, the exact roles of the hippocampus and neocortical areas in different types of declarative memory have long been subjects of great controversy.

RA following hippocampal damage is often found for tasks whose acquisition depends on the hippocampus (i.e., those that are also affected by anterograde amnesia) and sometimes also for tasks unaffected by anterograde amnesia (for a review, see [19]). In many cases, retrograde amnesia has been shown to be temporally graded; i.e., remote memories are recalled better than recent ones, the exact opposite of the pattern found in normals. This phenomenon has been known for more than a century (for historical references, see [5]). An important insight into the underlying mechanisms was afforded by the discovery that lesions to the medial temporal lobes (MTL) in humans can give rise to temporally graded RA [20]. This finding has now been confirmed by studies of a large number of patients, as well as by controlled lesion studies in several animal species [18].

It was suggested a long time ago that temporally graded RA reflects a gradual reorganization of the neural substrate of memory, and this notion then became linked with the medial temporal lobe through the data described above. Temporally graded RA after hippocampal (or other MTL) lesions has been taken to imply that memories which initially depend on the hippocampus for their successful retrieval are gradually reorganized (or consolidated) through some hippocampally dependent process so that retrieval becomes possible without the hippocampus.

Thus, the hippocampus appears to play at least two separable roles in memory. Since the memory is lost if the hippocampus is lesioned directly after successful acquisition, the hippocampus must have a role in either the storage or the retrieval of the memory at this stage. On the other hand, the consolidation process itself must depend on the hippocampus, since no recovery from retrograde amnesia can normally be observed in the absence of the hippocampus. A detailed analysis of the possible ways in which the hippocampus may contribute to each of these operations is presented next, in the context of a more general examination of the computations that support memory.

General Characterization of Memory Systems

Before going into the specific roles of the hippocampus in declarative memory, first let us step back and consider memory storage from a computational point of view (in the sense of Marr [21]). At this level, memory may be defined as using information from past experiences to aid subsequent performance, and the argument is about optimality, independent of how the required computations are performed. One of the advantages of this level of analysis is that it can make very clear the ways in which memory tasks can differ. One of the important variables is the structure of information in the learning episodes, in particular, whether there is a single or multiple learning episodes, what the nature of the stimuli constituting a single episode

is, and how the experiences in the different learning episodes relate to each other. The other fundamental factor is the information required to solve the task at the time of retrieval and how this relates to the information in the set of learning experiences. This relationship determines the amount and type of information that needs to be preserved about the original experiences. Of course, we generally expect that information from a set of experiences will need to be used in different ways in various tasks, and therefore the information stored during initial exposure must be able to support all these possible future uses. For example, consider the case when there are multiple learning experiences, each of them consisting of the concurrent presentation of a pair of visual stimuli. Then the information that needs to be preserved about these presentations is very different depending on whether the task later will be recognition of the pairs as a whole, recall of paired associates, generalization to new instances of the rule describing the relationship between the stimuli within a pair, or being able to say whether at least one of the stimuli was always a household item.

The argument so far has not depended crucially on the way experiences, recalled memories, and other information are represented, or the form in which memories are stored. However, if we want to extend our analysis to what Marr [21] referred to as the representational and implementational levels, in order to find out how the brain carries out the computations that support memory, we need to take into account the different ways in which information can be represented in the brain. In particular, suppose we want to find the optimal form for the storage of information in a given memory task. This will clearly depend on a number of factors and their associated costs. First, the form in which the original learning episodes are represented is relevant, as are the representations utilized by the output systems, since information needs to be converted from the input format to the stored form during exposure to the learned material and from the stored to the correct output format during retrieval. Depending on the storage format (assuming that the input and output formats are given), one or both of these conversion operations may be computationally expensive (requiring a lot of time or resources). For example, if the task requires the integration of information across different learning episodes, use of a stored format which itself integrates different traces might be appropriate since this could make retrieval much simpler. However, this might come at the cost of having to take into account all previous experiences when storing (the relevant aspects of) a new one. Alternatively, one might consider keeping the stored representations of the different experiences separate and performing the integration at the time of retrieval. On the retrieval side, one of the most important contributions to the cost is probably the time required to generate an answer.

Second, an obvious contribution to the cost of solving a memory task in a particular way comes from the cost of making errors. A third somewhat less obvious contribution is the cost of maintaining the stored information between learning and retrieval. The inclusion of this term provides a simplistic explanation for why short-term memory is mostly activity-based while long-term memory tends to be weight-based. The idea is that storage based on maintained activities is likely to involve lower conversion costs between the stored representation and input and

output formats due to their fundamentally similar nature, but weight-based storage prevails for longer retention intervals because of the lower metabolic costs associated with maintenance. However, other factors like the vulnerability of the stored memory are also likely to play a role. Finally, as already described at the computational level, an efficient memory system should be able to utilize information from a given learning experience in different circumstances, and the form of the stored representation is at the core of such versatility. Of course, it is possible that a single stored representation cannot support all the relevant uses of the information in a learning experience, and this might explain some observed instances of different learning systems apparently processing the same type of information (albeit in different ways).

An example of such a possible conflict between different utilizations of the same experiences (one that is very much relevant to the main topic of our discussion) is provided by the analysis of [6]. These authors suggest that there may be a computational reason for a division of labor between the hippocampus and neocortex. They argue that discovery of shared structure in an ensemble of inputs (which is thought to be necessary for successful learning in most complex tasks) crucially depends on making slow, gradual changes to the internal parameters of the learning system based on multiple, interleaved presentations of representative samples from all areas of the input space. In a system designed to extract general structure, attempts to learn new, specific information without interleaving it with examples that conform to the structure already learned result in the phenomenon called "catastrophic interference," a dramatic impairment for previously acquired information following even moderate amounts of new learning. Thus, the neocortex, which is assumed to be responsible for the acquisition of general information, is unsuited for rapid learning of specific events and needs to be supplemented by the hippocampus that performs this latter task (but is not capable of extracting generalities).

Next, we would like to consider the roles of the hippocampus in memory in a neurobiological context, which requires making explicit our assumptions about the substrates of representation and learning in the brain. First, we assume that perceptual and other inputs, cues for memory retrieval, and the retrieved memories themselves are all represented as specific patterns of activity across large numbers of neurons, often distributed in several different brain areas. Experiences of events activate neurons in a large number of brain areas that process stimuli of different modalities, and recall of the episode leads to the same (or very similar) pattern of activation in those same areas (perhaps excepting "low-level" sensory areas). Second, it is assumed that memories are stored in the efficacies of the synaptic connections through which one neuron can influence the activity of the other; this may include connections within a brain area as well as connections between different areas. Third, learning involves changes in these synaptic efficacies which depend mainly on the activities of the particular neurons making the connection. Finally, there exist global factors, such as inputs from subcortical neuromodulatory centers, that can influence both neuronal activity and synaptic plasticity in a manner that is not specific to particular patterns of activation.

Hippocampal Involvement in Early Recall

Let us now consider the role of the hippocampus in early recall. In other words, how does the hippocampus contribute to the recall of a memory directly after it has been established? There appear to be two (not mutually exclusive) basic possibilities. One possibility is that some of the information required to identify the memory to be recalled uniquely is actually stored in connections involving the hippocampus. This storage may involve intrahippocampal connections as well as the connections to and from the hippocampus, whose information content is also lost if the hippocampus is damaged. The other possibility is that although all the information about the memory may be stored outside the hippocampus, the hippocampus is somehow required to access this information and translate it into the activity pattern representing the memory.

The simplest version of the storage deficit hypothesis is that the hippocampus stores the memory in its entirety, i.e., a representation of all the information that can later be recalled. As pointed out by [6], the stored representation would not have to be a copy of neocortical activation patterns, but rather a compressed, summary version of them, which may nonetheless carry the same information due to the redundancy of the neocortical representation. Compression and decompression would be carried out by the convergent neocortical projections to the medial temporal lobe and on to the hippocampus, and the divergent back-projections from the hippocampus through the medial temporal cortical regions to other areas of neocortex, respectively. This feature is shared by "indexing theories" of hippocampal function (e.g., [22, 23]), which hold that the role of the hippocampus is to store an index, or list of pointers to the neocortical locations where the different components of the memory itself are stored. According to both Teyler and DiScenna [22] and McClelland et al. [6], very little change in neocortical connections occurs during initial learning; instead, synaptic changes within the hippocampus mediate initial storage, and the original neocortical representation of the memory can be reinstated via the existing mapping between hippocampal and neocortical representations, embodied by the hippocampo-cortical back-projections. Another alternative is that initial learning occurs in the hippocampus *and* in the back-projections to neocortex, which could maintain the correspondence of hippocampal and neocortical representations. A rapid change in the back-projections is actually required to accompany hippocampal learning if the hippocampus creates an essentially random, "orthogonalized" new trace for the new memory, as proposed by some theories of hippocampal function, because, in this case, the existing mapping from hippocampal to neocortical activity patterns may not generalize well to the new memory trace. During retrieval, cues activate the index or compressed representation of the memory in the hippocampus, which in turn activates the corresponding neocortical representation.

Another idea central to several theories of hippocampal function is that the hippocampus binds together information from disparate cortical areas. The hippocampus (and, in fact, entorhinal cortex and, to some extent, the perirhinal and parahippocampal cortices as well) can be seen as a convergence point in the hierarchy

of neocortical areas [24, 25], which, taking into account both forward and backward projections, provides a route of communication between any areas within the hierarchy. In fact, this anatomical binding property is a simple way in which the medial temporal lobe may be critical for memory retrieval independent of the plastic changes happening within the structure—if the areas representing the memory (some of which may also represent retrieval cues) cannot communicate with each other, retrieval will fail, even if all the information stored about the memory is intact. In many theories, this binding role of the MTL is combined with storage of information within the MTL.

On the other hand, there have also been several proposals according to which the hippocampus does not store memories at all. Instead, it may serve as a modulatory center; its role may be to enable "chunking" (the formation of new associations) in neocortex [26] or to "imprint" or "rehearse" memories in neocortex [27]. Alternatively, it was proposed that the hippocampus may implement the "orienting subsystem" in "adaptive resonance theory," processing information about novelty of stimuli and signaling to neocortex the need to form new representations [28].

Hippocampal Involvement in Consolidation

Now let us turn to the role of the hippocampus in consolidation. First of all, consolidation should involve changes within neocortex, whereby whatever role the hippocampus initially played in the recall of the memory (be it storage or retrieval related) can now be assumed by the neocortex itself, independent of the presence or absence of the hippocampus. Second, as already discussed, consolidation should require the active participation of the hippocampus. Issues now concern the locus and nature of neocortical changes, as well as the nature of hippocampal involvement. Regarding the nature of cortical changes, if we assumed that information crucial for the recall of the memory was initially stored within the hippocampus, this information must somehow be transferred to neocortex during consolidation. This transfer should not be thought of as direct copying of synaptic efficacies from one brain area to another; as well as being physically unfeasible, such a process would also be useless since a given pattern of synaptic efficacies may have a completely different meaning in different neural contexts. Rather, the transfer of information should occur through the spread of activation from one brain area to another, resulting in activity-dependent synaptic changes in the participating areas.

One way in which such transfer can work is the following. Imagine that the information initially stored in the hippocampus can be used to reconstruct the neocortical activity pattern that characterized the original episode. During several such reactivations, perhaps spread over a relatively long time, associations between neocortical areas or neurons can be built up gradually (in line with the proposal discussed above that the neocortex learns slowly), and these associative connections could then support memory retrieval. Some version of this idea plays a major role in most theories of consolidation [1, 5, 6, 22, 29–31].

Most of these accounts are not very specific about the mechanism by which new neocortical associations become established. Alvarez and Squire [5] suggest that, as a result of multiple, hippocampally dependent reactivations of the scattered cortical areas representing the memory, direct connections are established between the participating neurons in different areas through Hebbian associative learning. Although Hebbian-type learning is thought to occur between pairs of connected neurons in the brain (indeed, LTP/LTD has been given a Hebbian interpretation), areas of neocortex which process the different modalities that make up an episode do not normally have large numbers of direct connections, and it appears unlikely that cortical learning would require the formation of a large number of new direct long-range intracortical connections. Murre [31] also points out this difficulty and suggests that, instead of direct connections between the participating neurons, the formation of new associations involves the strengthening of existing connections within a chain of neurons connecting the two sites. In addition, it is noted that, rather than being densely or randomly connected, neocortex is better characterized as a loose hierarchy of areas (perhaps with multiple roots or convergence points), with the medial temporal lobe as one of the convergence points [24]. This observation suggests that the way to establish arbitrary new cortical associations should perhaps be sought in the context of hierarchical architectures.

Memory Consolidation and Sleep

There is currently very little direct experimental evidence that would allow us to distinguish between the different possibilities outlined above regarding the nature of the initial involvement of the hippocampus in recall, its role in consolidation, and the nature of neocortical changes during consolidation. However, there is an abundance of data that provide indirect clues about these issues (e.g., on cortical connectivity, hippocampal anatomy and physiology, plasticity, neuromodulation, effects of lesions, and other manipulations in animals and humans). Here we will briefly summarize two sets of data, one from physiology and one from behavioral studies, which together suggest the existence of special brain states (occurring during sleep) where both reactivation of hippocampal memory traces and neocortical memory consolidation seem to take place, perhaps signifying a functional link between the two.

On the physiological side, there is now considerable evidence that the spatiotemporal activity patterns of hippocampal neurons that occur during waking are replayed during subsequent slow-wave sleep (SWS) [32–35] and rapid eye movement sleep (REMS) [36] (reactivation during awake states has also been observed, although that might subserve at least partly different functions [37, 38] SWS reactivation happens during physiological conditions when hippocampal activity patterns are created largely autonomously, and then serve to influence activity in neocortex (unlike during waking, when hippocampal activity is strongly driven by cortical input) [39]. Sharp wave activity in the hippocampus (characteristic of SWS), driving activity in neocortex [40, 41], probably underlies the observed reactivation of neocortical activity patterns [42–44] and is also thought to provide good conditions for

neocortical synaptic plasticity [39, 45]. These experiments have been reviewed in more detail in earlier chapters.

On the behavioral side, there appears to be a link between sleep and memory consolidation (for reviews, see [46–49]). All in all, it appears that both REMS and SWS are likely to be important for memory consolidation, although the degree to which each of them is involved is probably task dependent. Taken together with the physiological data, the evidence seems to support a theory in which consolidation requires both SWS, during which the hippocampus initiates the reactivation of hippocampal-cortical memory representations, and REMS, during which some kind of reactivation may also occur, but is likely to be initiated in neocortex. On a more fundamental level, the apparent basic differences in physiology, and specifically in the nature of information flow in the hippocampal-neocortical network, between awake exploratory states and the states implicated in consolidation (particularly SWS) suggest that the roles played by the hippocampus in recall and in consolidation may be distinct rather than identical.

Off-Line Processing, Consolidation, and Memory Maintenance

An important issue that we have avoided so far is the impact of ongoing learning and neural plasticity on the retrieval of existing memories. If information from new experiences is continuously integrated into the neocortical knowledge base via distributed changes in cortical synapses, neocortical representations must constantly be changing. These changes pose two problems for memory. First, the patterns of neural activity that should inspire the recall of a particular memory are nonstationary. Second, the information recalled from memory has to be interpreted (i.e., decoded) in an ever-mutating code. Despite their pervasive nature, these issues of input and output accessibility have been neglected by most current theories of long-term memory, which concentrate instead only on the storage of information. Here we summarize the results of our study [50, 51] on the possible benefits of hippocampal replay, and in addition to providing an in-depth study of its role in storage, we make the novel suggestion that replay of hippocampal-neocortical patterns during sleep and quiet wakefulness is part of an active process by which the brain ensures that old memories, wherever they are stored, can be appropriately retrieved and understood in the current representational coordinates.

A Hippocampal-Neocortical Network Model

We investigated the issues of acquisition, consolidation, and maintenance of both episodic and semantic memories through the explicit implementation, simulation, and analysis of an abstract network model [50, 51], which nevertheless captured many of the critical features of cortical computation and was sufficiently rich in

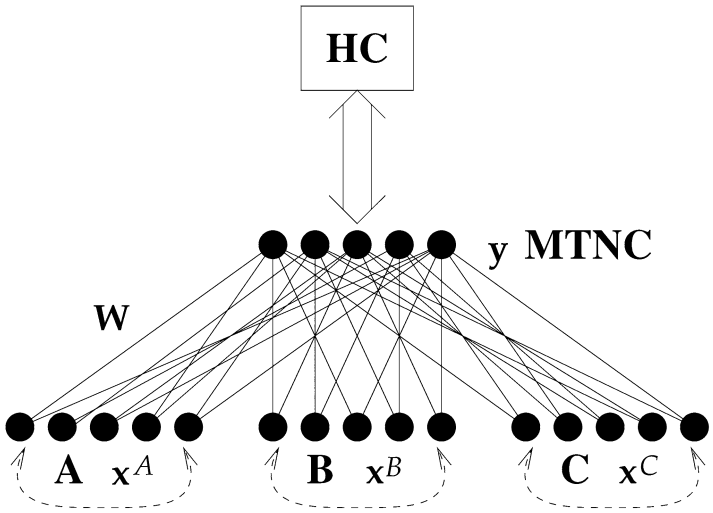

Fig. 15.1 Model architecture. All units in neocortical areas A, B, and C are connected to all units in area MTNC through bidirectional, symmetric weights (W's). Connections between units in the input layer are restricted to the same cortical area and are treated as weak local attractors (*dashed arrows*). These are not explicitly simulated, but (in the absence of feed-forward activation of the area) have the effect of converting top-down input which closely resembles one of the valid input patterns in that area, into an exact version of that pattern. $\mathbf{x}^A$, $\mathbf{x}^B$, $\mathbf{x}^C$, and $\mathbf{y}$ denote activity vectors in the corresponding neocortical areas. The hippocampus (HC) is not directly implemented, but it can influence and store the patterns in MTNC. All communication between the HC and the input areas is via area MTNC

detail to allow us to probe several fundamental questions. Figure 15.1 shows the full model. The neocortical part (all bar HC) has two layers connected in a reciprocal and hierarchical manner [24, 25]. The lower layer (labeled A, B, and C) consists of higher-order association areas from different modalities or processing streams, which are assumed to represent the end result of extracting relevant information from sensory inputs. The upper layer models areas in medial temporal neocortex (MTNC)—namely, entorhinal, perirhinal, and parahippocampal cortices. MTNC is separated because these areas integrate information from all processing streams in each modality and contain the exclusive cortical conduit to the hippocampal formation. MTNC activity can inspire hippocampal recall, which in turn affects MTNC activity, and thus activity in areas A-C. Each area contains a large number of abstract (binary), neuron-like units, which are connected to other units within the area.

A basic tenet of our model is that neocortical representations are acquired and continually adjusted through an unsupervised learning process in which the strengths of a large set of synaptic connections within and between neocortical areas are altered in the light of the ever-changing statistical structure of the input [52]. In such distributed representational schemes, learning that affects the internal representation of some stimulus will also affect the representation of a large array of other stimuli. The neocortical model acts as a probabilistic generative model (the version

used in our model is known as the restricted Boltzmann machine [53]). Unsupervised learning [54, 55] extracts from a collection of inputs in the input areas a set of underlying statistical causes in the form of MTNC activations. The information about the statistical structure of the inputs that is stored in the weights W between area MTNC and the input areas is best characterized as general semantic knowledge, including data on categories, tendencies, and correlations. This type of knowledge is not always considered to be part of declarative memory, although it shares several important characteristics with more conventional types of semantic memory (such as fact memory). For simplicity, we will refer to this type of stored information as semantic knowledge (or semantic memory). Once trained appropriately, the network is capable of "recognizing" (i.e., identifying the probable underlying causes of) novel inputs and of performing cortical pattern completion from partial or noisy inputs by applying appropriate probabilistic updates to neocortical unit activities. If some of the input units (say, those in areas A and B) are clamped by external input so that they are not allowed to change, the samples produced in area C represent the network's inference about probable completions of the pattern in A and B.

In keeping with a wealth of experimental and theoretical data [1–3, 17, 56–59], the hippocampus is assumed to be capable of (1), under appropriate conditions, storing a representation of a hitherto unfamiliar current MTNC pattern in such a way that (2) it can be auto-associatively reinstated when the corresponding hippocampal memory state is activated by pattern completion from an MTNC pattern that is judged as familiar, by being sufficiently similar to a previously stored pattern. Once the mapping between the input areas and MTNC has been established, reinstating the correct set of MTNC activities suffices to reinstate the whole cortical pattern, provided that the neocortical and hippocampal representations are appropriately in register. This allows sampling in the neocortex to converge instantaneously. We also assume that (3) the patterns stored in the HC can be activated intrinsically and randomly (for instance, during sleep [33]), and this, via the generative model, suffices to create the possibility of replay.

In our scheme, episodes are specific items, i.e., completely specified patterns of activity over the units in areas A, B, and C. The quality of episodic recall is judged according to whether the pattern in one area (say, C) for an episode can be recalled through successive sampling iterations (possibly involving the hippocampus) starting from the correct activities for that episode in areas A and B but completely corrupt (random) activities in area C. Recall stops after a fixed number of iterations or if the pattern in area C comes within the local basin of attraction of a valid input pattern in that area.

In order to study both semantic and episodic memory, a relatively rich collection of input patterns is required. Specifically, we consider four different domains of input patterns. In each domain, 10 random binary patterns were generated in each input area. In all but one domain, all 1,000 possible combinations of the valid patterns in areas A, B, and C were considered equally likely. The remaining semantically "structured" domain had inter-areal semantic structure in that each of the 10 possible patterns in area A always appeared with an (different) associated pattern in area C. Any of these A–C pairs could appear with any of the patterns in area B.

All 100 possible combinations of patterns in this domain were equally likely. The unstructured domains allow the study of episodic memory, uncontaminated by semantic knowledge, while the correct recall of paired associates in the structured domain provides a measure of semantic knowledge.

Consolidation of Episodic Memory

We first examined the long-term storage and recall of episodic memories within this framework. For comparison with experimental data [60–63], and earlier modeling [5, 6], we first confirm that our model can capture basic phenomena of hippocampal-dependent consolidation as in the transfer model [18, 64, 65]. We model consolidation by having learning alternate between two types of events, "experience" and "replay." The first corresponds to continued exposure to stimuli from the regular inputs. The second starts from hippocampal reactivation in MTNC of a stochastically selected stored memory pattern. The resulting MTNC activation leads to the reactivation of the input areas (also taking into account the effect of local attractors in each input area). The combined activity leads to weight modifications in the neocortex according to the same learning algorithm used for external input-driven learning [55]. Throughout the consolidation period, blocks of 900 hippocampally initiated learning events alternate with blocks of 100 input-initiated (general training) events. Such a substantial degree of imbalance was required for robust episodic consolidation (see below).

In the first set of simulations, portrayed in Fig. 15.2a, input patterns were drawn from a single unstructured domain. In a first phase of semantic training, 200,000

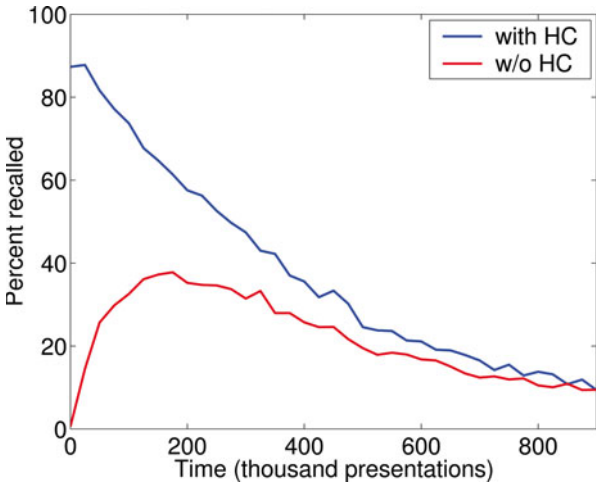

Fig. 15.2 The consolidation of episodic memories. Average recall performance (as percentage of successful recall) on episodic patterns as a function of time. The *blue curve* represents normal controls, and the *red curve* shows the case when the hippocampal module is inactivated for testing. Episodic patterns are stored sequentially, and their strength decays exponentially with a time constant of 200,000 pattern presentations. The curves are averages over all episodic patterns used, aligned at the initial presentations (also the start of consolidation) of the particular patterns

patterns selected at random were presented to the neocortical module, establishing the relationship between the activities in A-C and MTNC. Then, we implemented an experimental paradigm often used in animal studies of retrograde amnesia [60–63], in which animals learn about several different sets of stimuli (e.g., in the context of a sensory discrimination task) at different times before the hippocampus (or some other associated structure) is lesioned. In our case, specific input patterns (involving all three areas) were designated as episodic patterns to be memorized. These were introduced sequentially during subsequent training (with 50,000 pattern presentations between the initial storage of two adjacent episodes). Experimentally, performance on all sets of stimuli is tested after recovery from an operation such as hippocampectomy; in our model, we tested recall without the hippocampus. We implement normal forgetting by awarding hippocampal memory traces an exponentially decaying "strength" that determines the probabilities of both a pattern being selected for replay and successful hippocampal pattern completion during recall.

Figure 15.2 shows the performance of the network as a function of time. The averaged time-performance curves for normals and hippocampals replicate many important characteristics of the experimental data. Normals (blue curve) show the highest performance directly after training and forget gradually over time. Hippocampals (red curve), for whom recall is tested immediately after the lesion, perform at floor if the HC is removed directly after training, confirming its essential role in early recall. However, hippocampals perform more proficiently as more time intervenes between training and lesion, and the difference between hippocampals and normals becomes negligible for the most remote time periods tested. This has been taken as a signal of successful consolidation in several animal experiments and all previous models of memory consolidation [5, 6, 60–63].

Figure 15.3 demonstrates starkly, however, that such consolidation does not by itself lead to long-term stability of episodic memory traces in neocortex. The figure shows the recall probability in the absence of the HC, for episodes which have been stored in neocortex, either directly (through repeated presentations of the patterns to the input layer; light curve in Fig. 15.3) or through the consolidation process described above (the heavy curve in Fig. 15.3 shows results for "consolidated" patterns taken from Fig. 15.2). Comparing the curves, recall performance on the "consolidated" patterns of Fig. 15.2 decays when the HC is switched off in the model and the network is subjected to general training on all valid input patterns and does so at speeds comparable to that for a nonconsolidated pattern. Indeed, the forgetting rate is much higher than that of normals in Fig. 15.2 (note the different time scales), indicating that the decay rate of hippocampal traces determines the normal forgetting rate in our complete model.

True consolidation of episodes is prevented by a novel type of interference between episodic and (general) semantic memories coming from the ongoing semantic plasticity in the cortex. This interference can be countered by frequent hippocampal reactivation of the episodes. Interference is asymmetric in that the effect of storing new episodes on stored general information is found to be much less severe, probably because the episodes conform to the same statistical structure as the patterns on which the network underwent semantic training.

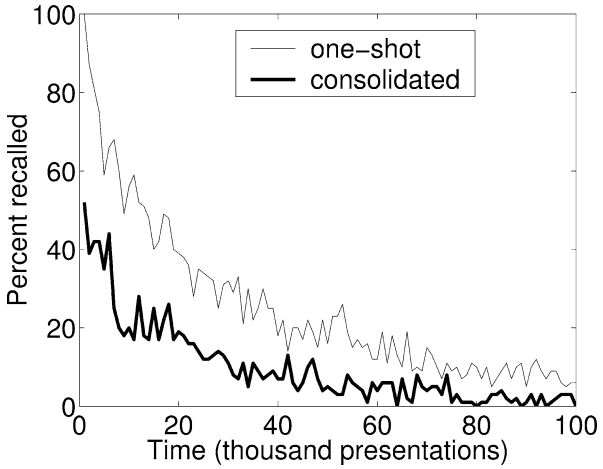

Fig. 15.3 Extinction of neocortical episodic memory due to semantic training. The *light curve* is for an isolated neocortical network trained to asymptotic performance on a particular episodic pattern. The *heavy curve* shows recall performance in the neocortical network as a function of time after the removal of the hippocampus, for a single pattern from among those which were used to construct Fig. 15.2, which has been hippocampally "consolidated" for 250,000 presentations

Acquisition and Consolidation of Semantic Memory

One hotly debated question about declarative memory is whether its different subtypes depend in a similar way on the hippocampus. Above, we argued that episodic and semantic memory present quite different computational challenges. In particular, the rapid, interference-free learning capabilities of hippocampus appear to be especially relevant for episodic learning, while we might expect that the slower, integrative plasticity of neocortex could by itself be sufficient to support semantic learning. On the other hand, a large amount of evidence from amnesic patients indicates that semantic memory can be severely affected by hippocampal lesions (although generally less severely than episodic memory) [64, 66–69]. Therefore, it is important to identify the ways in which the hippocampus can contribute to semantic memory. In this section, we examine two (nonexclusive) possibilities: first, that the hippocampus can aid semantic recall through the episodic storage and retrieval of examples, and, second, that off-line replay of stored examples can facilitate the acquisition of (hippocampal-independent) semantic memories.

Our simulation protocol was as follows. Input patterns were drawn from domains 1 (the unstructured domain used earlier) and 2 (the structured domain) throughout. In the baseline simulation, general neocortical training on patterns from both domains continued throughout, without any hippocampal involvement. We also tested three other conditions where the hippocampus was involved either in recall, replay, or both. In these cases, 50 episodic patterns were stored in the hippocampus after 500,000 presentations. 10 of these patterns were from the unstructured domain 1,

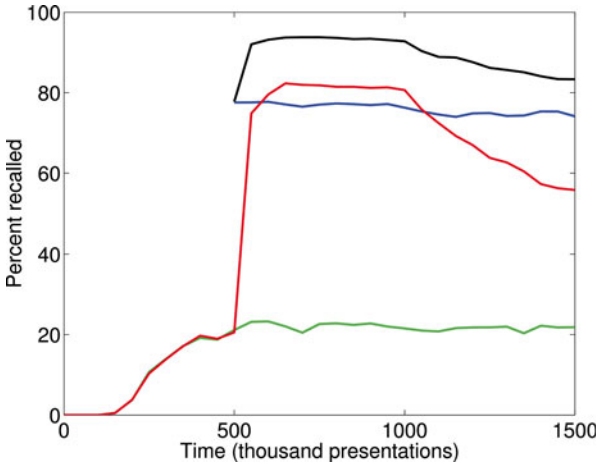

Fig. 15.4 The acquisition and consolidation of semantic information. The curves show the percentage of correct pattern completion in area C for patterns from domain 2. The different curves represent different training conditions, according to the following color code: *green* is pure neocortical learning; *blue* is neocortical learning supplemented by hippocampal learning and recall of episodes (but no replay); *red* is with replay, but without hippocampal involvement in recall; and *black* is with hippocampal replay and recall

and these were the ones used in all tests of episodic memory. The other 40 patterns included each of the 10 valid A–C pairings from the structured domain 2, presented together with 4 of the possible area B patterns—these allowed us to test the effects of episodic storage and replay on semantic memory within the same setup. The stored patterns then became available for hippocampal recall, and there was hippocampally initiated replay of episodic patterns between time points 500,000 and 1,000,000 in some conditions. Hippocampal traces did not decay in these simulations. We monitored semantic recall (the recall of paired associates from domain 2) during these two phases, and then during a subsequent 500,000 presentations of input patterns in domains 1 and 2, during which there is no hippocampal replay in any of the conditions, in order to test the permanence of semantic consolidation.

Our results on semantic acquisition/consolidation are summarized in Fig. 15.4. First, we see that under these conditions semantic learning without hippocampal involvement (green curve) is very slow and may never reach high levels. Episodic storage and recall of examples in the hippocampus (blue curve) brings an immediate increase in semantic recall performance, which goes beyond the level expected from simply getting right those queries involving the exact patterns stored. Hippocampal replay of these examples results in a less immediate, but just as dramatic performance gain, even if the hippocampus is then disabled for testing (red curve), although enabling hippocampal pattern completion during recall leads to a further substantial performance increase (black curve). Somewhat surprisingly, in the replay conditions, there is a slow and moderate decrease in performance once replay

stops. This is surprising because, unlike in the episodic case earlier, now the pattern completion we ask from the network is the only possible one under the full input distribution, so decay occurs despite the absence of contradictory input and the presence of some reinforcement. We believe that decay results from indirect competition from patterns in other domains (in our case, the more frequent "background" patterns) for the internal representational resources of the neocortical network. However, this is not a direct capacity issue since doubling the number of units in area MTNC did not affect the qualitative behavior.

Our results on semantic learning are in accord with earlier results on catastrophic interference described by McClelland et al. [6] and others [70] which concerns representational competition between different semantic memories. According to McClelland et al. [6], consolidation is in general required to integrate new information with previously acquired, richly structured semantic knowledge. By contrast, the computational goal of episodic learning is the faithful storage of individual events rather than the discovery of statistical structure. Thus, consolidation is seemingly inappropriate in any case. If initial hippocampal storage of the episode already ensures that it can later be recalled episodically, then, bar practical advantages such as storage capacity (or perhaps efficiency), there seems little point in duplicating this capacity in neocortex.

Maintaining Access to Declarative Memories

One might conclude from the previous sections that, provided the hippocampus stores the essence of episodes permanently, as suggested in the multiple trace model of Nadel and Moscovitch [71, 72], episodic memory will be unaffected by neocortical plasticity. However, note that the scenario represented by Fig. 15.3 is actually overly optimistic, in that the statistics of the general neocortical patterns remain constant, as if there is no refinement of the existing semantic representation, change in input statistics, or acquisition of a new semantic domain. All of these can occur, at least to some extent, even in the face of hippocampal insult [67–69, 73–75]. Such plasticity will change the cortical representations associated with past episodes. Wherever these episodes are stored, be it in the hippocampus, as discussed above, or the neocortex, semantic cortical plasticity will erode the relationship between inputs coded in the current representation and episodes coded in past representations. In this section we show the severe effect of semantic plasticity and show how hippocampally initiated replay can mitigate it.

In our model, successful recall of an episode stored in the hippocampus depends in two ways on the correspondence between low- and high-level cortical areas embodied by the neocortical network. First, the high-level (MTNC) representation of the recall cue needs to be effective in activating the correct hippocampal memory trace; second, the high-level representation activated by hippocampal recall should effect the recall of the appropriate components of the corresponding episode in lower level areas. Replay may prevent these damaging consequences of

continued neocortical plasticity by maintaining the proper correspondence between hippocampal and neocortical representations.

To assess the effect of neocortical learning on the recall of previously stored episodes, we modified the presentation paradigm for patterns that we used in Fig. 15.4. The first phase of training still consisted of pure input-driven learning using patterns from domains 1 and 2. 50 episodic patterns (10 from domain 1 and 40 from domain 2) were stored at the end of phase 1, and these then became available for hippocampally assisted recall and replay. Training on the same two input domains continued (with hippocampal replay where appropriate) during the next 500,000 input presentations (phase 2). Next, changes in input statistics were implemented by appending phases 3 and 4 to the simulation. In phase 3, input patterns were drawn from domains 1, 2, and 3, while all four input domains were sampled in phase 4. We first did this without replay, to establish a baseline, and then included replay. Unlike the extreme biasing towards replay that was necessary to show (temporary) transfer in Fig. 15.2, replay and experience were equally balanced. In addition, since we were interested in the effects of neocortical rather than hippocampal plasticity, we ignored the decay of hippocampal memory traces in these simulations. In all cases, the quality of recall for the stored episodes was monitored throughout.

Figure 15.5a shows the percentage of correct recall as a function of time after the start of training (the curves themselves start only after the storage of the episodes). Clearly, neocortical learning comes to erase the route to recall, even though the episode remains perfectly stored in the hippocampus throughout.

Figure 15.6a, b indicates the reasons for this behavior. Figure 15.6a shows that continued semantic learning after the storage of the episode causes its MTNC representation to move away from the version with which the stored hippocampal trace is associated. This is dramatically enhanced by the substantial changes in neocortical representations that follow the expansion in the input patterns (at 1 million and 1.5 million presentations), whereupon even the full original episode may fail to activate the corresponding hippocampal memory trace. Figure 15.6b shows that the effect of representational change on hippocampally directed recall in the input areas is also significant. In phase 4, even if the correct hippocampal trace gets activated, the full episode can be successfully recalled only about 40 % of the time, with a large variability between patterns.

These results indicate that episodic memories are fragile. To test how hippocampally initiated replay can help, input-driven training is interleaved with epochs of replay, assumed to take place during sleep. Replay happens just as in the previous section (including the use of the clean-up connections within each lower cortical area which effectively restrict activity to legitimate input patterns).

Figure 15.5c shows the consequence of following the usual consolidation protocol, with plasticity just in the neocortex. Compared with Fig. 15.5a, replay can prevent the degradation of episodic recall due to the introduction of new input patterns. Detailed analysis of the representational changes (analogous to the results in Fig. 15.6; data not shown) suggests that replay works by preventing the MTNC representations of episodes from changing, thereby assuring a continued perfect fit with the stored hippocampal trace.

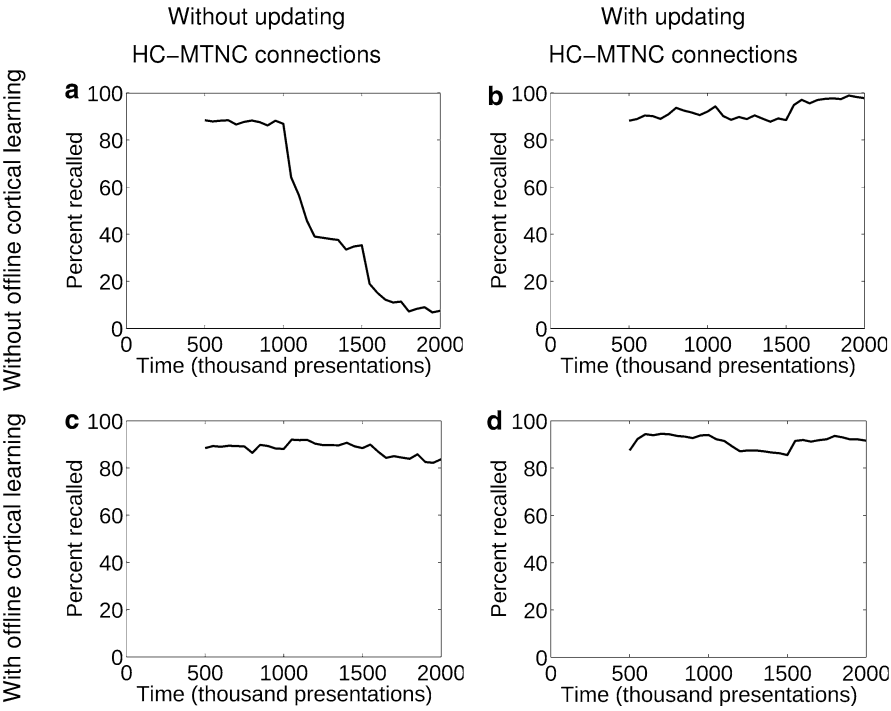

Fig. 15.5 The effects of changes in neocortical representations on the recall of previously stored episodes (**a**) in the absence of hippocampally initiated replay; (**b**) if the correspondence between hippocampal and MTNC representations of the episode is updated during off-line replay; (**c**) if neocortical connections are updated during replay episodes but hippocampal-MTNC connections are not; (**d**) if both neocortical and hippocampal-MTNC connections are updated. The simulation comprised four successive phases, each phase consisting of 500,000 pattern presentations (see text for details)

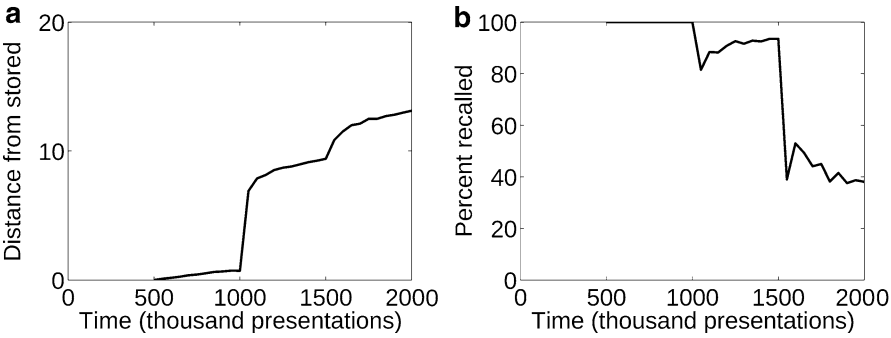

Fig. 15.6 Analysis of the reasons why episodic recall breaks down in Fig. 15.5a. (**a**) shows the distance between the MTNC pattern currently associated with the representation of the episode in the input areas and the MTNC pattern associated with the stored hippocampal memory trace. (**b**) shows the percentage of correct recall in the input areas if we start the recall process from the stored MTNC representation of the episode

We might imagine, however, that constraining new neocortical learning such that the internal representations of all hippocampally stored episodes remain fixed is too stringent a requirement, which could severely compromise the learning capabilities of the neocortical network. Therefore, we introduced and tested the effect of a different sort of plasticity during replay. Here, once the stored representation of the episode is reactivated in MTNC and the representation of the episode is reconstructed in the lower-level areas, the current feed-forward mapping between the input areas and MTNC is employed in order to determine the up-to-date MTNC representation of the episode. This MTNC pattern is then associated with the stored hippocampal episode which initiated the replay, so that the hippocampal and input level representations of the episode are again in register. As evidenced by Fig. 15.5b, this also maintains episodic recall at a high level, despite substantial changes in the neocortical network. For replay to work, it is essential that the episodic patterns be representationally refreshed sufficiently frequently so that the hippocampus and MTNC remain tied. Figure 15.5d shows that combining both forms of replay, with neocortical learning and continually updated HC-MTNC connections, also results in good preservation of old episodes in the face of neocortical representational change but provides no obvious gain over the previous cases.

We also examined the effect of neocortical representational change on semantic memories. Semantic maintenance was measured in the same simulations which were used to demonstrate episodic maintenance, but here we tested semantic memory on patterns from structured domain 2 in the way described earlier. Figure 15.7 is analogous to Fig. 15.5 in using the standard 4 phases of presentation and testing the utility of the two different forms of hippocampal and/or neocortical plasticity during replay. As we have already demonstrated, episodic storage and off-line replay help in various ways to establish high levels of semantic recall. Figure 15.7 shows that, in addition, replay can help maintain semantic memories in the face of changes in input statistics. Without replay, introduction of a new "background" semantic domain disrupted the recall of semantic information from the structured domain (Fig. 15.7a). However, the extent to which the two different types of plasticity during replay that had been introduced earlier contributed to acquisition and maintenance was different from the case of episodes. For episodes, either kind of replay by itself resulted in a similar high level of performance. For semantics, the best performance was afforded by combining during replay the update of neocortical-hippocampal connections with neocortical processing of the patterns reactivated (Fig. 15.7d). However, as in the previous accounts of catastrophic interference in semantic memory [6], the most important contribution comes from neocortical learning on the reactivated patterns (which is absent in Fig. 15.7b), rather than the regular updating of the mapping between hippocampus and neocortex (absent in Fig. 15.7c). With hippocampal replay-assisted neocortical maintenance, recall of previously acquired semantic memories remains at a high level throughout the acquisition of new material, even if the hippocampus is then inactivated during testing (red curves).

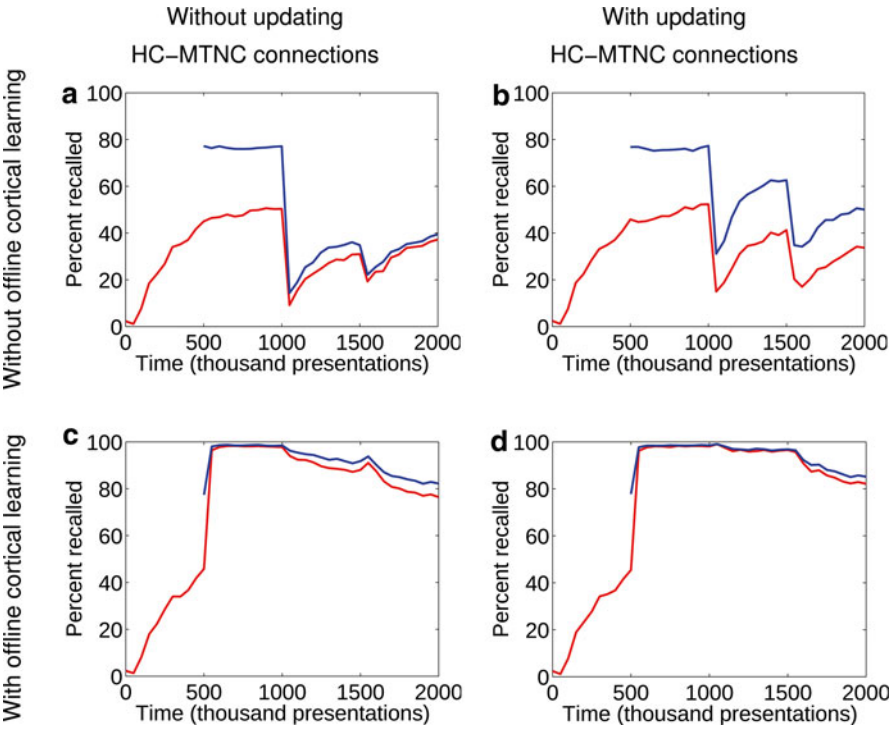

Fig. 15.7 The effects of neocortical learning on the recall of semantic information. Training protocol, replay conditions, and figure layout are the same as in Fig. 15.5. The blue trace in all plots is with hippocampal involvement in recall; the *red trace* is purely neocortical recall

Extending the Hippocampal Index

So far, we have presented a number of ways in which hippocampally initiated replay of episodic memories can aid the acquisition and maintenance of both episodic and semantic information. However, replay might be useful in other contexts as well. For instance, in separate simulations [50], we have shown that replay can be used to extend to semantically related stimuli the set of cues which can directly elicit the retrieval of an episode. Episodes should be retrievable from all input patterns to which they are closely semantically related. The knowledge of semantic relations in the neocortex is implicit in its synaptic weights; and only a portion is directly reflected in the similarity of MTNC codes. However, in the present scheme, this portion alone is what permits hippocampal recall. During replay, semantic cousins of existing episodes can be generated, and associations made between their MTNC representations and the hippocampal traces. Then, in normal operation, the episodes can subsequently be retrieved when the semantic associates are presented.

The Generation of Sharp Waves and Off-Line Replay in a Detailed Hippocampal Network Model

In all the work described so far, we treated the hippocampus as a black box and completely ignored the ways in which it might implement critical operations such as the storage, cue-based retrieval, and autonomous reactivation of memory traces. Such a mechanistic understanding of the operation of hippocampal networks has been the subject of numerous modeling studies (as reviewed in the chapter by Schultheiss et al.). Recently, we have employed a combination of in vitro physiology, pharmacology, and optogenetics experiments along with model-based data analysis and computer simulations to decipher the ways in which hippocampal networks (particularly those in area CA3, which have long been implicated in memory functions) might carry out these operations. As we have discussed briefly in this chapter, and in more detail in other chapters, several distinct patterns of population activity can be recorded in the hippocampus in vivo. These neural activity patterns depend on the behavioral state of the animal and include theta-modulated gamma oscillations as well as low-level irregular activity with periodically occurring large-amplitude sharp wave-ripple (SWR) events. During SWRs, neuronal populations in the hippocampus have been found to replay, on a faster time scale, activity recorded during theta-gamma activity in the exploring animal. Such replay may be important for the establishment, maintenance, and consolidation of long-term memory. Our aim was to develop a mechanistic understanding of cellular and network mechanisms underlying the generation of SWRs in general (also in relation to other population activity patterns such as gamma oscillations and epileptiform bursts) and spatiotemporal sequence replay during SWRs in particular, based on in vitro and in vivo experimental observations as well as computational modeling.

Methods

By improving the preparation and maintenance conditions of in vitro slices, activity patterns identical to in vivo described SWRs and gamma activity can be recorded from the CA3 area of submerged hippocampal slices [76]. Under baseline conditions the slices spontaneously generate SWRs with characteristics similar to those observed in vivo. This preparation has allowed the collection of a large and diverse set of data regarding the properties of SWRs, as well as the characterization of several cell types and synapses which are critical in their generation [77]. Mimicking the increased cholinergic tone during the theta-gamma state in vivo by the application of a low concentration of the cholinergic agonist carbachol (3–10 μM, CCH), the SWR activity can be quickly (1–2 min) and reversibly converted into gamma activity (Fig. 15.8a). By contrast, if cellular excitability is increased by elevating the

extracellular concentration of K^+ or by various other means, SWRs are replaced by larger amplitude epileptiform events [78].

Based on these data and other published results, we developed a large-scale model of the CA3 area of a hippocampal slice. Our model contained 8000 pyramidal cells (PCs) and 150 parvalbumin-containing, fast-spiking basket cells (BCs); some versions also contained (100 instances of) a second type of interneuron which had a longer membrane time constant and provided longer-lasting inhibition to pyramidal neurons. Cells were modeled as adaptive exponential integrate-and-fire neurons [79] whose parameters were set based on whole-cell recordings of the response to injected current steps in the appropriate cell types. Synaptic properties were also determined experimentally. The selection of the final set of model parameters was further aided by phase-plane analysis of the dynamics in a rate-based version of the network. Connectivity was sparse and random. One version of the model contained stronger recurrent excitatory connections within artificially defined subpopulations of pyramidal cells to mimic the effects of prior learning (the formation of cell assemblies). In our model of hippocampal replay, weights were determined via a spike-timing-dependent learning rule applied to the simulated activity of a population of place cells (see below).

Results

We found that our model based on measured cellular and synaptic parameters could faithfully reproduce the experimentally observed SWR activity (Fig. 15.8a–c) as long as we included an appropriate slow feedback mechanism which was responsible for the termination of SWR bursts. Our model allowed us to rule out several potential candidates (such as neuronal adaptation) for the slow feedback process, suggesting that either slowly activating interneuronal feedback (as in Fig. 15.8) or short-term synaptic plasticity of connections within CA3 might terminate SWRs. When we implemented the changes in cellular and synaptic properties measured in the slice following the activation of cholinergic receptors, including increased cellular excitability and reduced efficacy of synaptic transmission, our model replicated the experimentally observed transition from SWR activity to gamma oscillations (Fig. 15.8c, d).

Statistical analysis of the inter-event interval (IEI) distribution of SWRs in vitro suggested that, following an initial "refractory period" after each SWR, the next SWR is initiated stochastically, requiring the simultaneous activation of a threshold number of pyramidal cells. This hypothesis was tested by fitting to the data an analytically solvable model instantiating the above assumptions (Fig. 15.9). This simple model assumes that the number of synchronously firing PCs required for the initiation of an SWR event increases transiently after the previous SWR episode (due to SWR-induced changes in cellular excitability and/or the efficacy of synaptic transmission) and then recovers exponentially to its baseline value. The IEI distributions were fitted assuming a fixed number of cells (10,000) and shared values

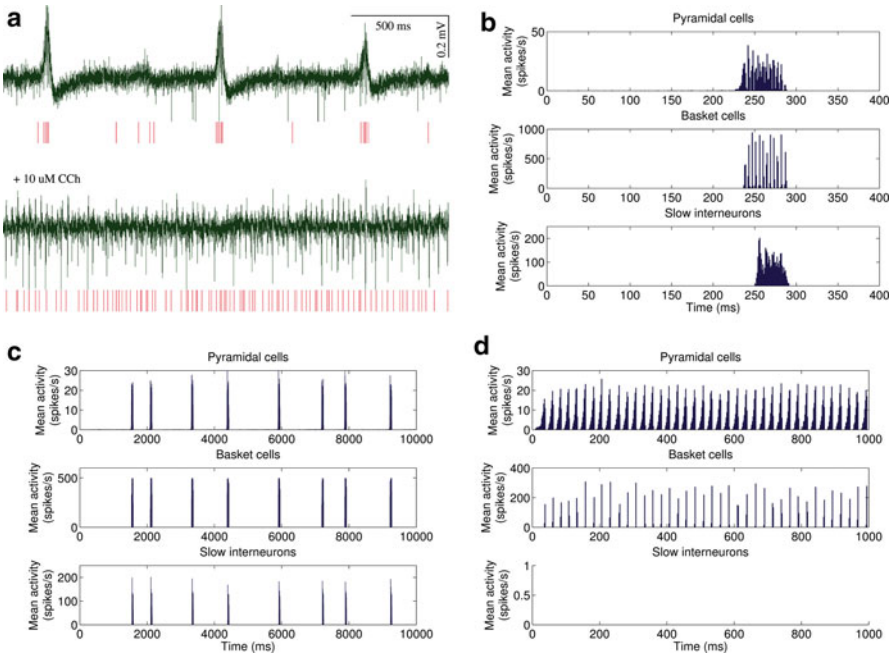

Fig. 15.8 (**a**) Raw field potential recordings (*green*) and multiunit activity (*red*) recorded in the CA3 area of a 600-**μ**m-thick hippocampal slice. Top part, control conditions; bottom part, during the application of 10 **μ**M carbachol. (**b**) Average spiking activity of the three cell populations during a simulated SWR event in the model with slow feedback inhibition (and without learning). (**c**) Irregular SWR activity on a longer time scale in the same model. (**d**) Gamma oscillation in the same network following experimentally determined changes in cellular and synaptic parameters

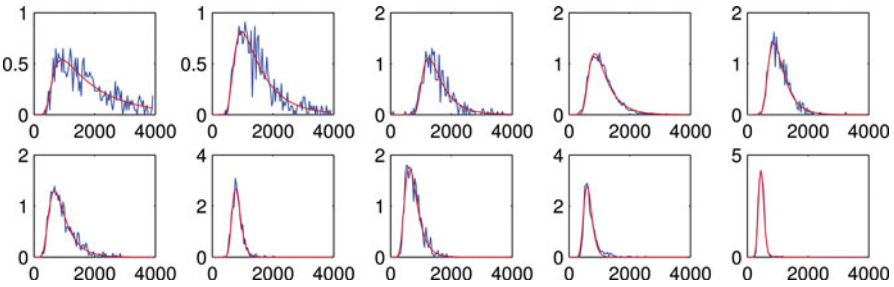

Fig. 15.9 Analytical fits (*red curves*) to the inter-SWR distributions (*blue lines*) in a randomly selected sample of 10 experiments, based on the calculated time until the first coincident firing of a threshold number of PCs; the rate of random firing is assumed to decrease temporarily (and recover exponentially) after an SWR event

for some parameters (such as the length of the coincidence detection window, the baseline firing rate, and the recovery time constant) across slices and separate values for the required level of coincidence and its relative change after SWRs in each slice. This simple mathematical model achieved a uniformly good fit to the variety of IEI distributions in the experiments, showing that a combination of refractory and stochastic mechanisms likely contributes to the initiation of SWRs in vitro. The threshold nature of SWR initiation was also supported by intracellular monitoring of synaptic events before SWR events [80].

Our data and simulations also indicated that perisomatic interneurons (in particular, parvalbumin-containing basket cells, PV+BCs) and their mutually inhibitory synaptic connections play critical roles in the generation of sharp waves and associated ripple oscillations in area CA3. This conclusion was supported by the results of a number of experimental manipulations: (1) cutting the reciprocal connections between PV+BCs (while leaving the recurrent excitatory collaterals intact) desynchronized ripple oscillations (as well as sharp waves) between the two halves of the slice; (2) ripple oscillations could be evoked by optogenetic activation of PV+cells, even after the blockade of excitatory synaptic transmission; (3) optogenetic silencing of PV+cells interrupted and blocked SWR generation [80]. In addition, when we selectively eliminated parts of the SWR-generating model network described above, so that only the mutually interconnected basket cells remained, ripple oscillation could still be evoked by tonic activation of the BCs (Fig. 15.10a); however, ripple synchrony was lost when the inhibitory connections between BCs were eliminated (Fig. 15.10b).

These observations suggest that ripple oscillation during sharp waves are generated via the following mechanism (Fig. 15.10c). First, following an initiation phase governed by refractory and random processes as described above, activity builds up exponentially in the recurrent excitatory collateral system of CA3 (step 1) and starts to drive PV+BCs to fire (step 2). PV+BCs firing at sufficiently high rates synchronize their activity through their mutually inhibitory connections (step 3), and the resulting ripple frequency inhibitory input stabilizes the average firing rate of PCs and modulates their activity (step 4). We refer to such ripple frequency population activity emerging through the interaction of PV+BCs, which is also detectable in the local field potential, as fast interneuronal oscillation (FINO). Similar mechanisms have been suggested for the generation of fast rhythms [81–84], although often in the context of gamma rather than ripple frequency oscillations [85–87]. Gamma oscillations in CA3 are now thought to be generated through a different mechanism known as pyramidal-interneuron gamma (PING), which involves phasic reciprocal interactions between pyramidal cells and interneurons [88].

As accelerated replay of behaviorally relevant sequences of neuronal activity has often been observed during SWRs, we aimed to find out whether sequence replay can be exhibited by our model of SWRs under appropriate conditions. Early models of hippocampal sequence learning, recall, and replay [88–92] showed that appropriately learned, asymmetric connections between CA3 pyramidal cells could give rise to network dynamics which supported the autonomous reproduction of trained sequences. Therefore, we applied a spike-timing-dependent plasticity rule to the recurrent

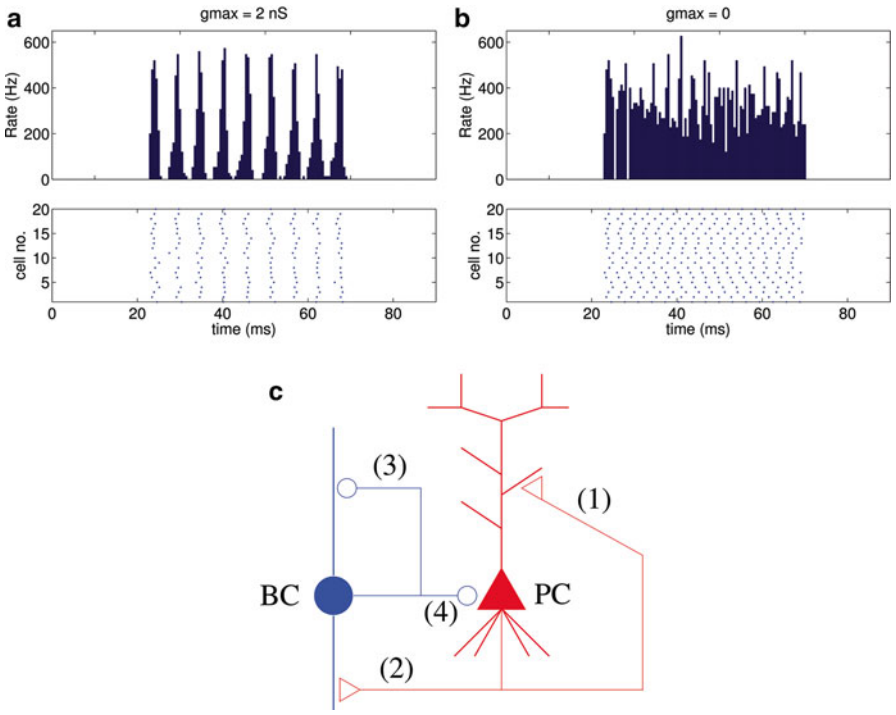

Fig. 15.10 (**a**) Ripple frequency oscillation emerges in a network model of basket cells interconnected by fast inhibitory synapses (delay, 1.5 ms; decay time constant, 1.5 ms; maximal conductance, 2 nS) when cells are driven by a depolarizing current pulse (duration, 50 ms; amplitude, 400 pA), mimicking the optogenetic activation of PV+cells with excitatory transmission blocked in the slice experiments. (**b**) Ripple oscillations disappear, and the average firing frequency of BCs increases if the same stimulation is repeated in the absence of mutual inhibition. (**c**) Schematic representation of the mechanism for the generation of sharp wave-associated ripple oscillations in area CA3 suggested by our experimental and modeling results. Numbers indicate the basic steps in the generation of the sharp wave and ripple components, each of them roughly corresponding to the action of a separate set of synapses in the CA3 network, as described in the main text

excitatory weights during simulated exploration. In this period, the firing rate of PCs depended on the location of the simulated rat (place field) as well as on the phase of a global theta rhythm (phase precession); actual spikes were generated from inhomogeneous Poisson processes. The emerging weight structure then supported the autonomous generation of SWRs in the network in the absence of structured external input, with the firing rates of both PCs and BCs close to the experimentally observed values, and also led to the spontaneous replay of sequences of place cell representations during simulated SWRs (Fig. 15.11). Our results argue strongly for the feasibility of a traditional model of sharp wave-associated replay (see also [93]) and indicate that more exotic explanations of the phenomenon [94, 95] may not be necessary.

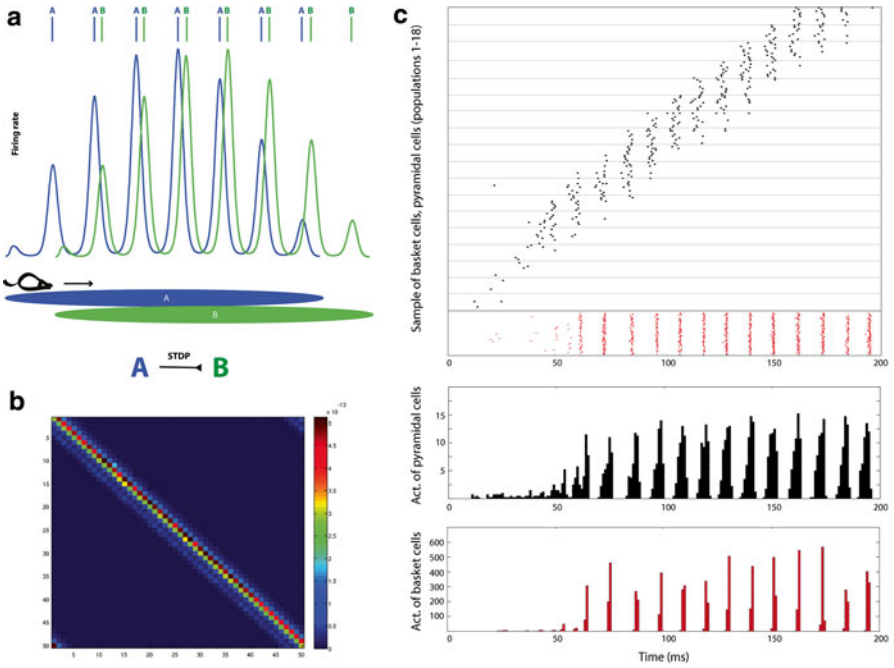

Fig. 15.11 (**a**) Firing rate of two PCs with overlapping place fields during simulated exploration. (**b**) Recurrent excitatory weights between PCs (indexed by place field location) following the application of a spike pair-based additive STDP learning rule during exploration. (**c**) Sequential reactivation of PCs (black raster and histogram) during spontaneous SWR activity; the activity of FSBCs is shown in *red*. In this example, no SWR termination mechanism was included to highlight replay

Conclusions

Off-line memory replay, for which there is increasing neurophysiological evidence, has mostly been viewed as a potential mechanism for the transfer of information from hippocampus to neocortex. We have pointed out the more pernicious and pervasive problems of maintaining access to, and readout from, episodic memories in the light of ongoing representational change, a stability-plasticity dilemma [96] rather as in one standard set of views of the genesis of infantile amnesia [97]. We made the novel suggestion that hippocampally initiated replay is critically involved in this maintenance and demonstrated its efficacy in a model. Our results are also consistent with data showing that the hippocampus can play an important role in normal semantic learning [66, 69] and a temporary role in semantic recall [98, 99]. As in the suggestion of McClelland et al. [6], replay can allow the slow integration of information from episodes into the general cortical semantic knowledge base.

The different types of replay that we explored in our model require different types of coordination between the hippocampus and neocortex, and it is tempting to

associate these distinct modes of processing with different stages of sleep. For instance, autonomous reactivation of hippocampal memory traces, leading to the selective reactivation of corresponding neocortical representations, may preferentially take place during slow-wave sleep. Thus, SWS may be critical for the long-term maintenance of episodic memories and may contribute to the hippocampal enhancement of semantic learning. By contrast, index extension requires extensive stochastic exploration of cortical semantic knowledge, a tempting associate of REM sleep.

Our model may also explain some intriguing recent observations about how compatibility with preexisting knowledge influences the speed of consolidation. Experiments by Tse et al. showed that memory consolidation could be radically accelerated when the information to be stored conformed to a previously established mental framework (or "schema") [100]. In our model, the integration of new specific information into the neocortical knowledge base requires much smaller weight changes and, as a result, can be accomplished in fewer reactivation episodes if the new pattern conforms to the statistical structure already represented by the neocortical network.

One major limitation of our abstract model of hippocampal-neocortical interactions is that it was designed to handle static patterns of neuronal activity. By contrast, experimentally observed replay involves the reactivation of precise temporal sequences of spiking activity. Such details can only be captured by more realistic models, such as the detailed network model of area CA3 presented in the last part of this chapter. This model also allowed us to formulate quantitative hypotheses regarding the initiation, termination, and internal structure of SWR events and confirmed that the measured cellular and synaptic changes are sufficient to explain the observed switching between two fundamentally different types of network dynamics. We also found that using structured rather than random weights substantially altered the global network dynamics, resulting in a sparse participation of pyramidal neurons in individual SWR events and allowing our model to match more closely the corresponding experimental observations.

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