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Richard Courtemanche *Editors*

Neuronal Oscillations of Wakefulness and Sleep

Windows on Spontaneous Activity of the Brain

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Foreword

It is rare indeed that a single volume can intertwine in a delightful and informative set of examples our diverse behavioral modes, from athletics to sleep to epilepsy, with the brain activities that underpin them. The editors and authors have managed to do so. The result is a series of chapters full of ideas, explanations, and hypotheses, all set in a context aimed at readers who have a range of interests: a general interest in the mysteries of the brain and how it could produce behavior and cognition; professional individuals from economists to athletes interested in formalizing these links; academic individuals teaching and learning about how biology can produce behavior; and even philosophers who know that their ideas can be informed by this intertwined approach to brain and behavior.

Sometimes the seemingly esoteric world exemplified by the physicists, engineers, and astronomers who examine oscillatory activities and signal frequencies—and who use the math that goes with these analyses—seems too demanding and almost off-putting for non-experts. The editors have gone to great lengths to avoid this potential problem. As a consequence, they have uncovered for the reader an emerging and exciting field in which we know that we do not know how the brain works, but at the same time are discovering signaling mechanisms never before open to deep analysis.

The electrical activity of the brain has been a subject of fascination for scientists since Victorian times. The first human brain recording was made by Hans Berger in 1924, who referred to his recordings as the *Elektrenkephalogramm* or "Electroencephalogram" (EEG) in English. The literal meaning from the roots of the word is "electrical writing of the brain." The assumption that the electrical signals of the brain must, in some way, convey information about mental activity was present from the beginning: Berger was searching for the physical basis of mental telepathy (Millet 2001). Although today it is thought that the electrical output of the brain is much too weak to have any noticeable effect on the nervous systems of other individuals (with the possible exception of certain electric fish), it was not an unreasonable belief at the time, given the sudden ubiquity of radio communications and the absence of scientific research on the existence (or lack thereof) of telepathy. Science fiction writers further explored this theme, notably in the classic Stanislaw

Lem novel (1961) and Andrei Tarkovsky film (1972) "Solaris," in which an X-ray beam is modulated by a human's EEG in hopes of communicating with an alien intelligence.

One of the most striking results from Berger's 1924 publication was that when the subjects' eyes were closed, the occipital contacts showed a 10 Hz oscillation, which—being the first brain oscillation observed—was dubbed "alpha." Study of changes in the patterns and frequencies of brain oscillations soon proved their utility not only for understanding the structure of sleep, but also for neurological diagnostic purposes. By the end of the 1950s, there was a rich literature available in both of those fields. However, the connection between electrical brain signals and mental activity remained obscure, not least because of the fact that in the conscious waking state and in the "altered consciousness" state of REM (dreaming) sleep, the oscillations that were so clear in deep sleep broke down, producing a "desynchronized," i.e., apparently random, signal. Some researchers despaired of ever understanding any connection that might exist between the observed random electrical activity and the highly structured activity of conscious thought (although occasional anecdotal evidence continued to pique the interest of other observers, e.g., Sacks 1999).

Sensation provides the essential raw material for mental activity, or at least so it can be argued. As early as 1947, electrical brain activity evoked by somatosensory stimulation became amenable to study by means of EEG recording (Dawson 1947) and a large literature on sensory-evoked potentials in all modalities followed. Dawson's original method of showing the typical response to stimulation involved superimposing multiple EEG traces displayed on an oscilloscope following repeated applications of the stimulus, and he immediately pointed out that this method could be greatly improved if the signals could somehow be averaged rather than simply superimposed. There followed a decade of various attempts to realize Dawson's signal averaging concept, and by the early 1960s signal averaging equipment was widely available for research. The concept of stimulus-evoked potentials soon became generalized not only to motor behavior, but even to hypothetical brain states that could be inferred from task conditions, such as the Contingent Negative Variation (Walter et al. 1964) and the Readiness Potential (Kornhuber and Deecke 1965). An entire new field of study of event-related potentials (ERPs) came into being, in which the effects of cognitive factors on gross brain physiology were quantified: the amplitude of the Late Positive Component (or Complex), 450–750 ms after stimulus presentation, can predict whether the presented stimulus item is later remembered (Sanquist et al. 1980); the Early Left Anterior Negativity occurs in response to violation of linguistic conventions (Frisch et al. 2004); the Error-Related Negativity occurs after task errors are made (Falkenstein et al. 1991; Gehring et al. 1993); and the mismatch negativity (MMN) occurs in response to an unusual stimulus in a sequence of stimuli (Näätänen et al. 1978).

Meanwhile, during the same period of time as the development of event-triggered averaging and the study of cognitive ERPs, microelectrode recordings had become possible in awake, behaving animals (Hubel 1959; Evarts 1964). Thus began the era of single-unit electrophysiology in awake animals performing cogni-

tively demanding tasks, expanding the paradigm of earlier single-unit studies of sensory systems that required use of anesthetized animals. During this explosion of cognitive electrophysiology data from single-unit studies and ERP studies, brain oscillations became largely neglected outside of sleep studies, olfactory bulb studies, and clinical applications.

However, microelectrodes also made it possible to record a signal that had not been previously analyzed: the local field potential (LFP). Like the EEG signal, the LFP is generated by a mass of brain tissue containing an enormous number of neurons, but EEG electrodes are placed on the surface of the scalp, whereas LFP recordings are made from microelectrodes that have been driven into the interior of the brain tissue. Combined with appropriate referencing techniques, microelectrodes can provide a more sharply localized view of brain activity and reveal currents that cannot be detected on the scalp. The modern era of LFP oscillation studies might be considered to begin with the publication of a paper by Charles Gray and Wolf Singer titled "Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex" in 1989, in which they report the results of simultaneously recording multiunit spike activity and LFPs from microelectrodes, and cross-correlating the two sets of recordings. Studies of LFP oscillations in other sensory modalities soon followed, and it became clear that the animal's attention can enhance these oscillations (Murthy and Fetz 1992; Fries et al. 2001). No longer appearing random, mass electrical activity in the awake brain was shown to be temporally structured, sensitive to cognitive demands, and intimately related to the timing of single-unit spikes (Singer 2018).

An enormous literature has now accumulated relating the dynamics of LFP oscillations to unit activity and behavioral/cognitive demands. The first chapter of this volume provides an excellent overview of the major highlights of the field during the past 30 years since Gray and Singer's publication. The remaining chapters will bring the reader up to date not only on many additional details of brain oscillations in cognition and behavior, but also on the cognitive roles of brain oscillations during sleep, and some of the implications of disturbed oscillatory dynamics in disorders affecting the brain. We hope that you enjoy these!

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Introduction

Oscillations constitute a universal phenomenon, across biological systems. The oscillatory nature of biological processes results from complex coordinated interactions, which may confer functional advantages in performing physiological functions and maintaining homeostasis. In the central nervous system, oscillations reflect fundamental properties of neuronal activity. Increasing evidence shows that behaviours, cognition, mood, and vigilance states are governed by specific patterns of neuronal oscillations. A deeper understanding of the characteristics and mechanisms of neuronal oscillations is therefore critical to decipher the neurobiological basis of human behaviour.

The field of research on brain oscillations has considerably expanded over the past decade, accelerated through the development of new techniques, such as optogenetics and brain connectivity studies with neuroimaging, allowing a refined investigation of neural oscillations from cellular to system levels. The aim of this book is therefore to provide the reader with an overview of how neural oscillations shape behaviours, mood, and cognition. A comprehensive review of the mechanisms and properties of each type of brain oscillation is beyond the scope of this book. Instead, this volume presents the contributions from distinguished experts in the field, providing a state-of-the-art knowledge on neuronal oscillations in selected topics of cognitive and behavioural neuroscience. While shedding light into the basic physiological aspects of consciousness and cognition, these works also illustrate the relevance of studying brain oscillations in order to bring insight into the pathophysiology of neurological and psychiatric disorders.

Presenting research from both animal and human studies, and using a wide range of techniques, from intracellular recordings to functional magnetic resonance imaging, this book is ultimately organized in two main sections: wakefulness and sleep. Neuronal oscillations have indeed been initially described across various states of vigilance and still constitute the basis for an objective characterization of vigilance states. Neuronal oscillations can also influence information processing in a variety of behaviours and situations, within a variety of local or long-range circuits.

The wakefulness section starts with a review on the role of brain oscillations in sensorimotor functions, by Courtemanche and collaborators. Amilhon and colleagues from the Williams Laboratory then describe the important role of theta rhythms in coordinating neuronal activity between the hippocampus and other brain regions, in the modulation of cognition. Keitel, Thut, and Gross then extensively discuss the differential control of attention by fast and slow neuronal oscillations. The section concludes with a clinical insight on the involvement of high-frequency oscillations such as ripples in certain forms of epilepsy, as reviewed by Levesque, Behr, Gotman, and Avoli. Ripples also spontaneously occur during sleep, and this chapter naturally leads to the second section of the book on neuronal oscillations during sleep.

This second section focusing on sleep opens with a description of the mechanisms and functions of the neuronal oscillations characteristic of sleep, including their possible roles in gating external stimulation during sleep and promoting offline memory consolidation. The focus is particularly made on the thalamocortical oscillations defining non-rapid eye movement sleep, namely sleep spindles and slow waves. This topic is first covered by Timofeev, Bonjean, and Bazhenov, using a cellular perspective and animal models. It is followed by a chapter by Salimi, Perrault, Zhang, Boucetta, and Dang-Vu, which provides a human neuroimaging perspective on the same topic. The involvement of neuronal oscillations of sleep in memory and cognition is further developed in the chapter by Marshall, who discusses the relationships between spontaneous or experimentally induced sleep oscillations and memory consolidation and describes a conceptual model on the possible biological mechanisms for these relationships.

Sleep oscillations also dramatically change across the lifespan. Sergeeva, Vicszko, Owen, and Fogel describe the alterations in neural oscillations of sleep with ageing, as well as the potential mechanisms and functional implications associated with these changes. Like the first section, this section concludes with a clinical perspective as well, in the review of Ferrarelli and Tononi on the disruption of sleep oscillations in mental disorders. With a focus on major depression and schizophrenia, this final chapter discusses how this disruption might inform us on the pathophysiology and management of mental diseases.

With this book, we hope to offer to readers an insightful journey into one of the most fascinating and growing areas of neuroscience. We also hope that the works presented here will encourage experienced as well as emerging scientists to pursue the scope of investigation into the mechanisms and functional properties of neuronal oscillations. Such endeavours will ultimately contribute to a better understanding of the complex processes underlying human behaviours and cognition and may also provide critical information to understand, monitor, prevent, or treat neurological and mental illnesses.

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Abbreviations

AASM	American Academy of Sleep Medicine
AD	Anterior dorsal (nuclei)
AHP	After hyperpolarizing potential
ASDA	American Sleep Disorders Association
BDNF	Brain-derived neurotrophic factor
BOLD	Blood-oxygen-level-dependent
CA	Cornu ammonis
CAP	Cyclic alternating patterns
CL	Central lateral (nuclei)
CM	Central medial nucleus
CMRglu	Brain glucose metabolism
CSD	Current source density
CT	Cortico-thalamic
CTC	Communication through coherence
DAT	Dynamic Attending Theory
DG	Dentate gyrus
DSM	Diagnostic and Statistical Manual of Mental Disorders
EcoG	Electrocorticographic
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EF2	Elongation factor-2
EMG	Electromyogram
EOG	Electrooculography/electrooculogram
EPSCs	Excitatory postsynaptic currents
EPSPs	Excitatory postsynaptic potentials
ERK	Extracellular related kinases
ERP	Event-related potential
FEF	Frontal eye fields
fMRI	Functional magnetic resonance imaging
FO	First order
FRB	Fast rhythmic bursting (neurons)

FS	Fast-spiking (neurons)
GAD	Generalized anxiety disorder
GCL	Granule cell layer
GMV	Grey matter volume
HCN	Hyperpolarization-activated cyclic nucleotide-gated non-selective cation
HD-EEG	High-density electroencephalography
HFOs	High-frequency oscillations
HO	High order
IB	Intrinsically bursting (neurons)
IN	Interneurons
IPS	Intra-parietal sulcus
IPSP(s)	Inhibitory postsynaptic potential(s)
ISA	Integrated spindle activity
LC	Locus coeruleus
LEC	Lateral entorhinal cortex
LFP(s)	Local field potential(s)
LGN	Lateral geniculate nucleus
LTD	Long-term depression
LTP	Long-term potentiation
LTS	Low-threshold spike
MD	Medial dorsal (nucleus)
MDD	Major depressive disorder
MEC	Medial entorhinal cortex
MEG	Magnetoencephalography
mGluR	Metabotropic glutamate receptor
mPFC	Medial prefrontal cortex
MSL	Motor sequence learning
MTLE	Mesial temporal lobe epilepsy
mTOR	Mammalian target of rapamycin
NIMH	National Institute of Mental Health
NMDA	Non-*N*-methyl-d-aspartate
NREM	Non-rapid eye movement
OCD	Obsessive–compulsive disorder
PAC	Phase-amplitude coupling
PCP	Phencyclidine
PET	Positron-emission tomography
PF	Parafascicular Complex of Thalamus
PFC	Prefrontal cortex
PGO	Ponto-geniculo-occipital/ponto-geniculate-occipital
PMT	Pontomesencephalic tegmentum
PSG	Polysomnographic
PTSD	Post-traumatic stress disorder
PV	Protein parvalbumin
PY	Pyramidal

rCBF	Regional cerebral blood flow
RE	Reticular
REM	Rapid eye movement
RF	Receptive field
RL	Large terminals synapses
RS	Regular-spiking (neurons)
SCN	Suprachiasmatic nuclei
SD	Sleep deprivation
SHY	Synaptic homeostasis hypothesis
sLORETA	Standardized low-resolution brain electromagnetic tomography
SMA	Supplementary motor area
SO	Slow oscillations
SOL	Sleep-onset latency
SPWRs	Sharp-wave ripples
STDP	Spike-timing dependent plasticity
STG	Superior temporal gyrus
SUB	Subiculum
SWA	Slow-wave activity
SWS	Slow-wave sleep
TC	Thalamocortical
TDT	Texture discrimination task
TES	Transcranial electrical stimulation
TMS	Transcranial magnetic stimulation
TRN	Thalamic reticular nucleus
VL	Ventrolateral
VPL	Ventral postero-lateral (nucleus); visual perceptual learning
VPM	Ventral posteromedial (nucleus)
ZI	Zona incerta (neurons)

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Part I
Wakefulness

Chapter 1
Exploring Oscillations in Expert Sensorimotor Anticipation: The Tennis Return of Serve

Richard Courtemanche, Daniela Popa, and Clément Léna

Introduction: The Setup and the Return of Milos' Serve by Roger's Brain

As evidenced by the companion chapters in this book, an increasing body of scientific literature has focused on the functional and physiological basis of brain oscillations in the last three decades. In this chapter, we explore the role of oscillations in predictive aspects of movement and action, making opportunistic use of a sport-related situation with time-constrained information processing. The return of serve in tennis encompasses a variety of perception-action couplings constrained by the very short amount of time available … when done well, the experts' brains performs impressive computational feats, likely optimizing inter-areal communication. Sports expert performance seem to be a "final frontier" in terms of experimental accessibility, with substantial gains to be made if we could understand how the perceptual-motor and cognitive systems of athletes, finely honed for hours a day and years of training, optimize brain networks for optimal performance [1, 2]. Since this review can be allowed to speculate, let us look at great subjects for our illustration.

Let us transport ourselves to the 2016 edition of the Wimbledon men's singles tournament, for the semifinal match being played between Milos Raonic, at the time ranked No. 6 in the world, and Roger Federer, ranked No. 3. It is a great matchup, between two opponents at different stages of their career. The mighty Federer, at the time a 17-Grand Slam singles title holder (now at 20, leading the Open Era),

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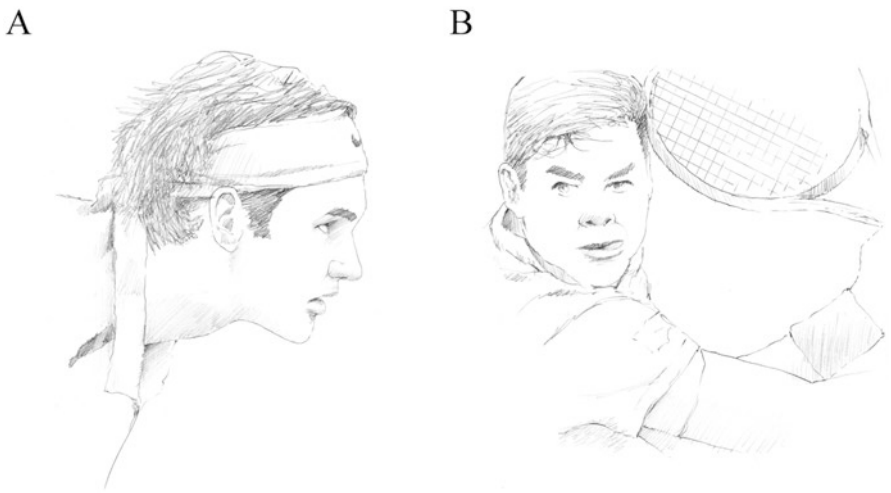

Fig. 1.1 The actors in that Wimbledon semifinal. In the situation presented here, Roger Federer (**a**, left) returns the serve from Milos Raonic (**b**, right). (Artwork courtesy of Mark Winter)

possesses an attacking all-court game, flawless and legendary strokes off both wings, lightning-quick reactions, and tremendous footwork. More than just his results, the way he plays has been described as an example of a "kinetic beauty" [3]. Dominant for years, he has recovered from his injury issues, and drawing upon his invaluable wealth of experience, Roger has had a resurgence. The next-gen Raonic, the first Canadian man to advance this far in Grand Slam singles, has a fantastically precise and powerful serve (he nearly always leads the men's tour in aces) along with a mighty forehand; his volleying and all-court game also make him a solid threat on this surface. So, the blossoming heavy hitter vs. the legendary artist—or should we say, the server vs. the returner (Fig. 1.1).

Centre Court seating is filled to capacity, with 15,000 people absorbed in this confrontation. Wimbledon grass courts bring particular technical challenges: bounces stay low, making spin shots challenging to return, and the ball skids on the slippery grass, resulting in added vigor to otherwise average first serves. However, Roger and Milos are far from average servers. This late into the tournament, the court at the baseline is down to the bare soil (despite the great work of the experienced grounds crew), challenging footwork and rebound adjustments. While this may be, both players are definitely on a good day and evenly matched. What do their brains have to do on a return of serve? In this match, the quality of the serve forces the returner to repeatedly perform nothing less than sensorimotor exploits:

1. To correctly track and perceive the direction, pace, and spin of the incoming serve
2. To make a lightning-quick decision on how to return it
3. To execute the return with millisecond timing coordination

Each receiver's decision is based on the type, location, speed, and spin of the ball from the incoming serve, adapting the return-of-serve movement so that it will convert the point to his advantage. Whether it is Milos or Roger serving, this is indeed a challenge: for tactical emphasis, let us select the situation when Roger is returning Milos' colossal serve, a tough task any day. In the fast-paced conditions of Wimbledon, Roger's brain must perform these return-of-serve operations within 500 ms! [4, 5]. Of course, time constraints also influence the capacity to perceive, think, and act: the return of serve relies on the sensory, central, and motor systems processing at a fast pace, optimizing precision and speed or reaction [1, 2]. Historically, at Wimbledon, success often hinges on who returns better, making it possible to capitalize on return opportunities by breaking the opponent's serve. Drawing upon his fine-tuned skills, training, and vast experience, Roger tries to react optimally to (and likely anticipate) the incoming serve, by using a priori knowledge of serving tendencies and premovement cues.

A service return is, of course, a voluntary movement made by the returner—it is just that it is performed under significant time duress. It is a misnomer to use the term "reflexes" to describe fast sensorimotor voluntary reactions, such as when a lightning-quick serve is successfully returned. Broadcasters might say that the returner shows "great reflexes," an unfortunate choice of words that obscures the perceptual, cognitive, and sensorimotor brain network complexity of the performance. This is becoming less controversial as scientific notions on motor control spread into lay culture. Of course, these quick reactions are not "inborn," as reflexes are, and come from highly practiced perception-action couplings. Indeed, as we will explore further, serve/return-of-serve combinations use networks spanning the whole brain, yet fitting within spatiotemporal constraints. Expertise certainly plays a role: experts in racket sports, compared to novices, identify and use specific cognitive and contextual psychomotor variables to process optimal visual information [6–8]. Particularly in tennis, experts learn to deal with visual occlusion much better than novices, providing evidence that they rely on initial ball trajectory and server pre-impact arm position more than novices [9, 10]. This is very likely what Roger's brain is doing, as for "champions" (that is to say, experts), the ability to perceive is linked with the ability to predict [11].

Strategies to simplify information complexity are useful in deciphering from the many possibilities in the incoming serve, facilitating perception. Tactically, Milos aims to serve either to Roger's forehand side, his backhand, or straight to his body, and of course, he intends to vary his offerings, to decrease predictability. Conversely, Roger is trying to decode Milos' serving patterns, focusing on tactical schemes and in-game context to improve anticipation and return efficiency. For Roger, the short time available to process information favors proactive information gathering strategies—he is often better off anticipating the serve at least partially than to wait for the complete information [12, 13]. As such, properties of the incoming serve (direction, speed, spin) can often be partially predicted by the context or by precontact cues. Roger uses his vast experience to best anticipate, considering contextual indications, filtering out unnecessary information, and focusing his attention on key visual information.

Let us try to quantify Roger's sensorimotor challenge to be successful. For a service speed of 125 mph (at impact; Milos has been known to crank it up to 147 mph), the incoming ball comes at a speed close to 52 m/s. With a server-receiver distance of 24 m (about the length of the court), Roger will have less than half a second (~460 ms) from the serve impact to make contact with the ball [5]. A schematic of the ball travel is shown in Fig. 1.2. Considering a realistic movement time estimated around 200 ms, Roger would have to react before 260 ms from impact, and this includes the three steps outlined above: time to perceive the stimulus, choose and program the response, and execute the return. As the incoming serve can take multiple locations, spins, and speed possibilities, this time delay is short—thus, it is useful to restrict some of these options before impact. In racket sports, for available time delays around 160 to 140 ms before ball contact, players must rely on incomplete information, so use a reasonable anticipation of the incoming shot [14, 15]. In terms of service return expertise, Roger has certainly been at the peak of reaction speed/accuracy and anticipatory performance throughout his career [3, 16], with the likes of current players Serena Williams and Novak Djokovic, and retired Wimbledon legends André Agassi, Martina Navratilova, Martina Hingis, Jimmy Connors, and Steffi Graf. Along with Roger, these great players are exceptional "scholars" of anticipation [17, 18]. Broadcasters hint at anticipatory abilities in these return-of-serve experts; during the Indian Wells Finals broadcast, Tracy Austin said "Agassi sees the ball so early" and "Hingis is anticipating really well," but some believe that these anticipatory skills "cannot be taught, you either have them, or you don't." Hopefully they are in the minority. Rectifying this fallacy, motor control studies show that there is indeed expertise in perception and anticipation, subject to rich learning, as seen in fast ball sports [8, 19, 20]. This is a practiced skill.

Thus, the return of serve is a crucial tennis situation, and with its time constraints, a particularly interesting one to explore brain processes for sensorimotor decision-making. In this situation, how do neuronal populations coordinate? What is the signature of the interacting neuronal activity in the time domain? How does the brain of these tennis virtuosos accomplish these sensorimotor feats under time constraints? Physiologically, these exploits require the interactions between multiple brain areas part of perception, decision, and action networks, and these must be

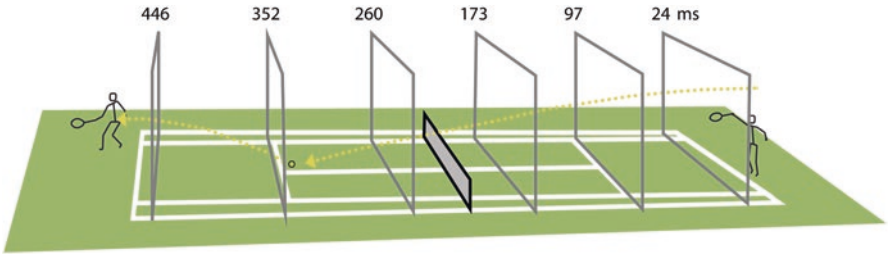

Fig. 1.2 The return-of-serve situation. Milos is serving (right), while Roger is returning serve on the left. The first serve from Milos makes it likely the ball will travel to Roger in less than half a second

optimized to function together in the short amount of time allotted to Roger to make his tennis response. Whether based on complete or incomplete information, these networks are likely recruited in a particular order, manner, and timing. A classical stance would be to describe this sensorimotor process as a serial perception-decision-action flow; in this chapter, we present evidence to modify this scheme with considerations toward an information transmission scheme that would follow a more iterative process [21]. One mechanism likely involved in this communication and transfer of information between areas is synchrony of neural activity [22–24], functioning at the appropriate timescale to support population coding and neuron-to-neuron communication. Such a mechanism has a rich history in the limbic system, which has a strong theta generator in the hippocampus [22, 25], and in coordinated multi-area interactions across the parahippocampal structures (hippocampus, entorhinal, and perirhinal areas), and activity with the olfactory bulb and cortex. Similarly, olfactory afferent pathways and relays show strong rhythms in the coding of olfactory representations [26]. Overall, cortical structures have a rich history in oscillation generation and coding, and coordination across distant and local networks, via task-related temporal properties [27, 28].

Specifically, in this chapter, we aim to present how local networks for perception, decision, and action can communicate across the phases of sensorimotor processing, so that ongoing local operations for perception are produced in the context of the goal to be reached. Local networks and cell firing have been related to both perception/decision or perception/action properties and thus provide strong suggestive evidence of this interaction. Across long-range networks, communication likely makes use of synchronized neural activity, based on oscillations at different frequencies. In a model study of coordinated neural networks, oscillatory activity has the advantage of enhancing the link between areas, while asynchrony leads to a filtering of activity. The dynamic nature of this relation allows flexible routing in neural circuits [29]. Oscillations in sensory and motor areas could be involved, in the beta (10–30 Hz) and gamma (30–80 Hz) ranges [30]. It is also likely that this role in information processing is not strictly passive, as information is fetched using particular carrier waves [31, 32]. “Back-and-forth” coordination between brain areas, using oscillations to control information flow in the time domain, could facilitate the formation of functional networks and optimize the sensorimotor process in time-constrained situations. In the case of the challenge presented to Roger, this process could be key in the successful fast processing of information to efficiently hit the return. In this chapter, we do not have the objective of a fine-grained analysis at a microcircuit level: our text will thus show certain cellular limits, and certain shortcuts in the representation of specific microcircuit oscillatory activity. However, we explore oscillatory mechanisms that would favor optimality in brain sensorimotor processing, and offer hypotheses at a larger scale during this perception/decision/action period.

The Task at Hand: Which Regions of the Brain Are Involved, a Serial or Recurrent Model?

To accomplish a successful return, visual and somatosensory information must be analyzed prior to and during the tennis stroke for optimal ball contact. In addition, Roger must adapt his ball-striking movement (using his arm along with the rest of his body), so he can optimize his posture and racket-wielding, up to the details concerning the optimal wrist angle and racket face (for determining point of impact and generating the ball spin). For each incoming serve, a specific motor sequence is selected and executed. In a classical information processing perspective, this perception-to-action information flow has been modeled as a linear progression [33]; such a process is illustrated in Fig. 1.3, focusing on visual information. This scheme starts with a sensory analysis, goes through sensorimotor matching, motor planning, and finally execution (and then feedback). Figure 1.3 also identifies some brain areas likely involved in the case of Roger's service return. Roger's brain is subjected to the difficult test of integrating the computations from these brain areas working together, in a short amount of time [34, 35]. Of course, the optimal return of serve represents the best choice from a variety of return options. Given Roger's experience, training, and sensorimotor repertoire, his perceptual abilities are polished, decision mechanisms are sharply tuned, and his biomechanical efficiency is world-class. These "embodied decisions," based on environmental affordances identified from the context and current online cues, are also matching Roger's strengths and pre-point intentions [36].

How could the identity and involvement of these brain areas be determined during the tennis stroke? Of course, it is not trivial to measure brain activity in sport situations—these are highly demanding body- and brain-recording conditions; for the current exercise, an approximation can be provided by looking at studies of brain activation during mental imagery of tennis actions. Such studies, using PET and fMRI, show a definite role for parietal and frontal cortical areas in the activity, along with the cerebellum and basal ganglia [37–39]. As a first approximation of the task-related network interactions in Roger's brain, we can tackle a unidirectional

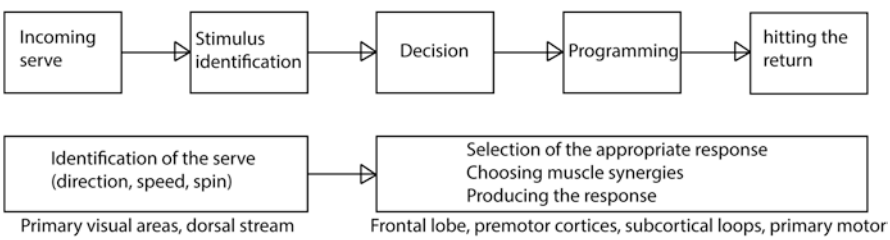

Fig. 1.3 The "serial" stimulus-response process, with associated areas. This is a common process for the identification of interactions in sensorimotor information flow. The details for each step are linear and unidirectional. However, as discussed in this chapter, the dialogues are very likely more bidirectional than unidirectional

flow of information, as a (fairly traditional) description of passage of information between these areas, using visual and somatosensory analysis as a starting point. To describe, Roger's primary visual areas in the occipital lobe have a dominant role in analyzing and scrutinizing visual information and focusing on ball motion [40–42]. His previous experience also enhances his efficiency and speed at perceiving ball motion [43]. Ball motion information travels to the parietal lobe for analysis of the overall path in egocentric (body-centered) coordinates, exploitable by the motor systems [44–46]. Concurrently, information about the body's sensory state and racket position will also be analyzed in the parietal lobe [47, 48]. As it becomes usable, the frontal lobe cortical circuits (including the motor areas and subcortical connections) will use this information for decision-making and motor response programming [21, 49]. Once these movement computations are optimized, the motor areas send commands to the spinal cord, activating the muscle groups according to the appropriate modularity [50]—producing all required forces for executing the return of serve. At a slow timescale, this general flow of information has been confirmed in many imaging studies, and likely is the general blueprint of the "slow flow" of activity in Roger's brain.

In addition to the basic perceptual-motor stream, with this little time available, how can Roger obtain more time to react? He can anticipate the incoming serve, in order to "increase the time available for the return" [4, 5]. Anticipation permits him to cut down on perceptual time and advance toward the movement decision by favoring an option, or by eliminating unlikely-to-occur competing options. It is an important trend in high-performance racket sports that expert players actively seek out visual cues permitting them to anticipate the serve properties before racket contact [6, 8, 10, 20, 51]. Initially a research-only interest, this type of data has been a player secret for years, and has also been embraced by tennis coaches, who have detected and used this knowledge in studying ways to improve return performance, using patterns and context to narrow down the serve/return possibilities in predicting spin and direction [52–54]. To the astute observer (player or coach!), multiple sources of information can help constrain potential options for the incoming serve. Before or during the match, predictive information concerning the opponent's serve can come from the context, for example, in specific documented serving patterns and tendencies in Milos' serving, as well as in recent usage of specific tactics [12, 14, 55]. As the point is initiated, cues can also be used by the expert returner: visual cues prior to ball contact, like the pre-impact angle of the racket, are better identified by expert players, like Roger, than non-expert players [56–58]. In addition, sound at impact can also give information about the spin of the ball, affecting the timing percept of collision and motion [59]. These sources of information, identified before stepping on court, during the course of the match, or during the specific point being played, advantage experts in return-of-serve performance.

In terms of neurophysiological mechanisms, anticipation and the search for specific sensory information can be related to expectancy prediction and inverse modeling of the sensory environment [60–63]. It is interesting to link this sensory-to-motor or motor-to-sensory activity with oscillatory properties present in the specific brain areas involved. Such a series of operations could lead to recurrent expectancy-driven

dialogues between different areas, including between sensory and motor areas, and oscillatory activity could be at the service of such comparisons [64]. While methods for measuring brain activity at a slow timescale show that a general sensory-to-motor progression is taking place, at a faster timescale, dynamic measurements provide evidence of a series of back-and-forth interactions in neural activity—likely with a coordinated set of loops serving to proactively capture information [21]. These loops would process the information by making quick comparisons, in time, of the expected status vs. sensory feedback [64, 65]. In light of Roger's time constraints and the added value of anticipatory processes, we can certainly posit that his brain has developed an efficient and fast way to search for the information he needs. With this exchange of information taking place, the acquisition of information would then be made more often with a purpose, and sensorimotor "action couplings" would be more efficient, even if based on partially incomplete information. In these cases, sensory expectations can serve to guide the acquisition of sensory information from the environment [66]. As described below, this likely gives rise to bidirectional exchanges between sensory and action areas via oscillatory communication loops. A representation of this recurrent scheme is shown in Fig. 1.4.

In the following section, we will evaluate how various oscillatory processes could contribute to the coordination of this mode of communication. We will consider faster (gamma) and slower (beta and alpha) oscillations, and the possible nuances these could bring to the communication channels, be they cortical or subcortical.

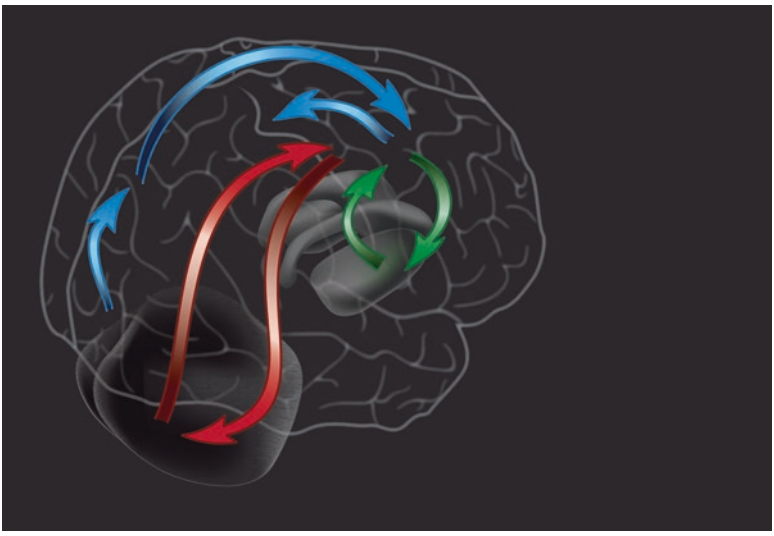

Fig. 1.4 A more recurrent scheme showing interactions between multiple areas of the brain of the returner. While there is a general "slow-flow" from sensory to motor, the recurrent loops will support multiple iterations improving the computations. Blue: cortical loops; Red: cerebro-cerebellar relations; Green: cortico-striatal loops

Perceiving the Incoming Serve: Faster Oscillations—Gamma

The areas involved in vision and ball perception include Roger's visual cortices and parietal areas, where a prominent background influence is given by oscillations in the gamma range. In the somatosensory areas, where body proprioception and touch processing of the racket take place, gamma range oscillations are also present. What follows is a basic picture of the interconnections in the visual and somatosensory flow of information, along with some evidence of the role of oscillatory activity in the visual and somatosensory systems.

Areas for Visual Processing

Many of Roger's brain areas will participate in the processing of visual information from the incoming serve. Upon receiving the sensory input, retinal output neurons process ball motion and flight principally through the magnocellular pathway [67, 68], which reaches the magnocellular portion of the lateral geniculate nucleus, which then project particularly to primary but also secondary visual cortical areas, such as areas MT, MST, and the posterior parietal cortex; these secondary areas focus on motion detection [44]. In this progression, as early as in the primary visual cortex, ball properties become separated: fine-grained ball shape and color properties progress along the ventral stream, which ends in the inferotemporal cortex, while ball motion—location, direction, and speed of the ball—flow through the posterior parietal cortex, along the dorsal stream. The ventral stream has been identified as the "what" pathway for object perception, and the dorsal stream as the "where" pathway for action planning [42, 46, 69–73]. For Roger, the dorsal stream computations form the basis of his goal-directed perception within an egocentric frame of reference, placing the location, motion, and spin of the ball in body-centered coordinates [71]. Since the allowed perceptual time is short, luckily not requiring a sophisticated stimulus identification, Roger always prepares to hit the ball in this return-of-serve situation, even if it has a chance of being out of the service box. What matters is the capacity to determine the finer details of shot selection, strongly based on the incoming ball path; in this case, the dorsal stream plays a very important role in determining where the ball is and how (spinned, fast, far from the body) it is coming, relative to the body [36].

With his vast experience, Roger also knows what to focus on when waiting to receive serve. Focused attentional mechanisms enhance neural processing along the visual stream given to specific stimulus properties. For example, while attending to shape or color, subjects show greater PET activation of the inferior temporal pathway; with the same stimulus presented while attending to the speed of the stimulus, the inferior parietal lobule is more activated [74]. During Roger's return of serve, the dorsal stream is likely processing essential perceptual components. Online information processing about the flight of the ball (and the same goes for tactile/

proprioceptive input as well) will be affected by attention, through modulation of the responsivity of neurons along the sensory processing pathway, which for vision includes the modulation of visual areas V1, MST, and MT [73, 75, 76]. Indeed, attentional focus sharpens the stimulus encoding processes in the ventral and dorsal streams [70]. From this, we can infer that Roger must pay adequate attention to the ball path, optimally encoding ball motion relative to him (in an egocentric frame of reference) in the posterior parietal cortex, leading ultimately to an adapted tennis stroke.

Visual Oscillatory Mechanisms

Electrophysiological synchrony can functionally bring together local computations that require exchange of information in the visual areas about the incoming serve. Various types of synchrony exist, whether anatomical, stimulus-dependent, or emergent [77], and these mechanisms influence group dynamics in visual cortex population coding, especially in early information processing [78]. Supporting synchrony are oscillations in the visual system: a predominant local field potential oscillatory signal recorded in the primary and secondary visual areas are gamma oscillations [79–82]. These oscillations functionally influence cell activity in primary and secondary visual cortices to fire with zero-lag synchrony, and this firing coordination between units form a population coding mechanism bringing together relevant features of the visual scene [83]. This coordinated activity can then support the information code of the incoming tennis ball. Gamma oscillations also influence the filtering of LGN to V1 connections, by modulating the responsivity of layer 4 neurons in V1 to afferent inputs [78]. This would provide a way to select information, out of multiple components of the stimuli, in addition to the object representation at a population level. As such, binding by synchrony of the various components of the visual image constitutes an answer to the binding problem, where multiple elements combine to form a unique percept [84]. In addition, this representation based on synchronous unit firing represents a mechanism for a heightened saliency in the representation—awareness about the stimuli actually require this synchrony [83]—just like when Roger pays special attention to elements helping him to pick up the indicators of the incoming ball flight. The synchronous activation of key populations of neurons seems to heighten the salience property of visual experience, as has been modeled previously [81, 85]. Another added value of oscillations into this information coding process is the temporal predictive capacity of top-down connections provided to the primary sensory areas [86]. Indeed, oscillatory activity could enhance predictive coding [87]. These then can facilitate the process by which action-oriented areas can coordinate and “seek out” the processing of sensory information.

Areas for Somatosensory Processing

For a successful return of serve, Roger's brain obviously must also optimally process somatosensory information. If we limit the description to Roger's "feeling" of the racket grip (touch) and racket arm proprioception (positional input during stroke production), important elements include mechanoreceptor information from the skin and muscles, coursing along the afferent nerves and relays in the spinal cord, to the dorsal column nucleus, the VPL thalamus, finally ending up in the primary somatosensory cortex (areas 3a, 3b) [88]. These areas further project to areas 1, 2, and then 5 and 7, toward the posterior parietal cortex. A continuous barrage of spindle information serves to update posture and limb placement, including serving error correction [89], while palm tactile information permits to regulate prehension forces on the racket. Overall, by feeding this sensory information to action areas, these signals permit to optimize the path of the hitting arm and the position of the racket face.

Somatosensory Oscillatory Mechanisms

Oscillations in the beta and gamma ranges have been recorded within the parietal lobe and more specifically in the somatosensory systems, with and without somatosensory stimulation [90–92]. These oscillations could serve to determine which stimuli are processed within the cortical module, or equally importantly, filtered out [93]. Specifically, gamma oscillations in the somatosensory cortex appear to improve somatosensory processing, as transmission is enhanced for certain types of SI cortical cells by gamma oscillations, which regulate the temporal sharpening of cortical sensory responses [94]. In addition, those oscillations play an important role in the neurovascular coupling in the fMRI response in response to a stimulus [95].

Taken together, we can foresee the potential for multiple network interactions in the visuospatial information processing relating visual and concurrent somatosensory encoding, along the occipital-parietal areas. While a speculation, these interactions should resolve the comparison between the location of the ball and the location of the racket; they would also likely sculpt the evolution of neurophysiological activity across the visual and somatosensory networks, for example, meeting within Roger's parietal lobe. These comparisons should be discernible within the posterior parietal cortex population code, which has an important role in aligning the neuronal response properties in movement perception. The interactions also concern sensorimotor comparisons using the frontoparietal and parieto-frontal connections, to match the feedback from the sensory input with the intent of the action. As such, parietal coding will likely deal with the location of the moving ball in the context of the movement needed to attain it [49]. We make a case that such operations will make use of oscillatory interactions.

Deciding and Producing the Return of Serve: Beta and Alpha Oscillations

Using the continuously updated status of somatosensory input from the arm along with the current visual information on the path of the ball, Roger will use this information during the delay to decide which stroke to hit and to execute the return. Many areas are involved in the decisional aspects of movement and in the execution of action [96, 97], and these areas are much of the same that were described above for returning serve. These include the primary motor and premotor areas, as well as subcortical structures [21]. Sensorimotor programs represent the neural operations performed preceding and during the execution of a motor skill, and involve sensory-to-motor and motor-to-sensory dialogues. In the context of Roger's return of serve, the information about the motion and location of the ball, as well as the up-to-date state of his body, needs to be provided to the frontal lobe for optimized action planning; in return, frontal lobe areas use this self-referenced information about the context, the ball, and the racket to program the optimal motor response [49]. In tennis specifics, the "parietal" motion and locations of the ball and racket, as well as the body configuration, are used to "frontally" compute the optimized return stroke—forehand or backhand—with its arm speed, body/postural configuration, location of impact, and racket trajectory. The programming details required and the computational needs go as far as the specificity of the proper sequence of muscle activations to produce the return.

Cerebral Cortex

Within the frontal lobe, the prefrontal cortex is an important area where sensory information about the ball and the body will assemble, in general profile and in detail. The ventral and dorsal streams—the "what" and "where" visual pathways—converge at this location [98, 99]. The prefrontal cortex weighs the sensory information in the larger context of behavioral imperatives: for example, in adaptation to the environment and homeostasis [100]. In the return-of-serve context, it oversees the motor program within its overall setting: for Roger, it monitors the launching and execution of the service return by evaluating its potential success, and does so using its connections with the basal ganglia. The coordination of neural activity within the frontal lobe generates a wave spanning the prefrontal cortex and premotor areas, which ensure optimization of global aspects of the movement in advance of movement initiation, for example, its direction and target endpoint [46]. The premotor cortex ensures the general strategy of movement and underlying contractions, and is also linked with the sensory guidance of movement [46, 101]. The wave of activity also passes through the supplementary motor area, which coordinates the global aspects of the movement sequence and its bilateral coordination [102]. This leaves the primary motor cortex to compute the forces and combinations of muscles to be

activated to produce the motor response. Although it does not represent the "final common pathway" as it once did [21, 49, 103], the primary motor cortex is intimately involved in the selection of motor pools and modules in the spinal cord for the muscle activity producing the movement-generating torques [50, 102].

Oscillatory Mechanisms in the Cerebral Cortex

Rhythmic activity in the alpha and beta ranges has also been recorded in these frontal areas involved in movement decision, planning, and execution; this oscillatory activity is localized widely in the frontal areas up to the primary motor cortex. Frontal alpha oscillations are prevalent in many alert behaviors, and in upright posture [104–106]. Activity in the beta range is also prominent during the premovement phase in humans, primates, and in many animal models [107]. For the primary motor cortex, these oscillations are more pronounced in the context of sensorimotor preparedness [108–111]. In electrocorticographic (ECoG) recordings of the human motor cortex, a 12–20 Hz rhythm alters the phase of the broadband activity [112]. Alpha/beta oscillations can also modulate cellular activity: Beta oscillations can coordinate the firing of unitary action potentials [113], even in the context of discrete, nonrhythmic behavior [114]. This means that these oscillations also have the capacity to influence the exit properties of the local primary motor cortex networks. Indeed, primary motor cortex LFPs can also show coherence with muscle activity, thus clearly showing an interaction with the downward output [115–117]. Oscillatory temporal driving signals (as seen in LFPs) can thus produce a downward influence, affecting cerebral-to-spinal communications (as seen in EMG) with beta-range components [115]. "Motor" oscillations are not exclusively in the beta range, as gamma-synchronized MEG signals were linked with corticospinal relationships [118]. Overall, oscillatory activity could serve to coordinate the frontal lobe communications, with alpha oscillations coordinating neighboring regions across the premotor cortex [119], and the prefrontal cortex [120]. In essence, communication throughout the frontal lobe appears facilitated by oscillatory activity.

Subcortical Areas: Basal Ganglia and Cerebellum

Communicating cerebral cortical areas also interact with subcortical structures in the analysis of contextual information, and in formulating better efficiency in output. One of those structures is the cerebellum, which links together sensory information and motor commands; as such, it participates in the analysis of sensory information, in its comparison with expected feedback, and in the timing and coordination of movements and muscles [62, 121, 122]. Another set of structures, the basal ganglia, are also involved in the planning of movement, in the coding of sensorimotor sequences, stimulus-response relationships, and in the packaging of

action-related information [123–125]. By receiving from all parts of cortex, and outputting to the frontal cortex (via the thalamus), the basal ganglia mediates planning and execution, especially in the building up, storage, decoding, retrieval, and expression of behavioral action plans [126, 127] and cognitive patterns [128]. Together, the cerebellum and basal ganglia form loops with major portions of the cerebral cortex for optimal processing of sensorimotor information. In primates, many aspects of movement or thought sequencing likely have been more encephalized [129], emphasizing the coordinated action of corticostriatal and cerebrocerebellar pathways. In these networks, the computations concerning the intention, the sensory status, and the motor commands are received from various sources, and integrated with intentional context for improved output. As an example, for optimal processing of sensorimotor information, the cerebellum shares functional information with somatosensory and motor cortices [130, 131]. Cortical connections originate from the frontal and parietal areas to the basal ganglia [125, 132, 133], and from the cerebral cortex to the cerebellum via the pontine nuclei [134–137]. These extensive connections link together the cerebellum and basal ganglia with the cortex, in both directions, as well as between each other [133, 138].

Are these interconnections accessed in a linear progression within a single iteration or using loops with multiple iterations, to process information? During a linear perception-to-action link in a single iteration, a wave of activity goes across the cortex such as in somatosensory processing and visual processing [76, 139, 140]. However, when searching for information, sensory acquisition more likely involves an active process guided by action or decision-based sampling, leading to closed-loop interactions instead of strictly open loop [65, 141]. Multiple motor programming processes involving the basal ganglia and cerebellum operate through loops functioning in parallel with cortical processing; these loops use repeated cyclical activity leading to oscillations [142, 143]. This highlights the extensive integrative computing taking place throughout cortical areas and subcortical structures, via repetitive iterative processes serving to progressively optimize the networks. Thus, the basal ganglia and cerebellar circuits coordinate spatiotemporally with cerebral cortical neural activity, through coordination by coherence, likely under the influence of oscillatory activity.

Oscillatory Mechanisms: Cerebellum

Within the cerebellum, oscillatory activity was first recorded from the olivocerebellar system, with near-10 Hz rhythms detected in climbing fiber activity, potentially serving sensorimotor situations [144–148]. Theta and beta rhythms were also recorded in field potential activity in the granule cell layer (GCL) [143, 149–154]. The cerebellar cortex Purkinje cell layer contains even faster (200–300 Hz) oscillations [155, 156]. The range and types of oscillatory phenomena in the cerebellar cortex have been reviewed by multiple authors [143, 157, 158]. These oscillatory phenomena could influence local network coding. In the awake behaving animal,

the configuration of olivocerebellar networks shows heightened anteroposterior synchrony under the influence of oscillations [146]. Olivocerebellar oscillatory activity also shape mosaics of task-related networks, preceding rhythmic movements [159]. The inferior olive thus acts as a motor pacemaker, influencing networks from the large cerebellar cortex neural sheet at an even finer grain than 10 Hz [147, 160]. Influencing another layer, ~14 Hz rhythmic GCL oscillations are prominent in the primate, and stopped by movement [149], while similar were found at ~7 Hz in the awake rodent [150]. These oscillations are related to GCL unit activity, including Golgi cells [151, 154], and are strongest in movement preparation or during expectancy [151]. GCL 7 Hz and 10–25 Hz oscillations also show synchronized activity with the primary somatosensory cortex during behavior [152, 161]. For the latter, Courtemanche et al. [153] report a basic parasagittal modularity, widening during a sensorimotor task. This influence could radiate to other layers: lateral synchrony is also seen in Purkinje cell simple spikes [162]. Oscillatory activity thus guides information flow throughout the cerebellar cortex and communication throughout the sensorimotor system.

Oscillatory Mechanisms: Basal Ganglia

LFP oscillations are also present in basal ganglia networks [163–168]. Initially considered pathophysiological and due to a loss of dopamine neuromodulation, theta/beta striatal LFP oscillations are now considered to have a functional role [142, 165, 169, 170]. If not maintained within optimal limits, basal ganglia oscillations can lead to an exaggerated oscillatory phenomenon permeating through the system [142, 170–172]. Dopamine depletion clearly entrains striato-pallidal networks in a reverberative state, oscillating to interfere with voluntary movement [173], due to multiple strong oscillatory influences [174].

Nevertheless, oscillations in the basal ganglia have been found in a variety of conditions, and if kept in check, can assist in information flow throughout the structures, contributing to the neural firing and the functional organization of circuits [163, 164, 166, 175, 176]. Oscillatory properties could govern the state of the basal ganglia networks [177], and for purposeful action, theta or beta-level oscillations have been linked with decision-making processes, network coordination, and task-related firing [166, 167, 176]. Sub-band dynamics might even shape subpopulations of cells differently [167]. An overabundance of beta oscillations could, in turn, decrease capacity for local information processing [172]. Functionally, oscillatory properties of the networks could also differ with skill learning: attractor frequencies for unit firing across the striatum will show initial entrainment to gamma rhythms, while later learning will see a greater influence of beta rhythms [168]. Nested oscillations also influence coding, as theta-gamma phase-amplitude coupling can serve to shape long-range interactions, with longer distance influence by the theta rhythm [178]. The dopamine depletion oscillatory pathological manifestations could be due to interference with information processing requirements. For cortico-basal ganglia

coordination, slow oscillatory signals appear to prevent information flow; an exacerbated beta activity, as seen in the case of deficit of dopamine [179, 180], might lead to a loss of capacity for information transmission, in contrast with higher-frequency oscillatory activity [172]. Beta hypersynchronization in the basal ganglia is widely distributed across the networks [181].

As the cerebellum and basal ganglia show oscillatory activity coordinated with the oscillations in the cerebral cortex, there remain many questions concerning the functional role that these subcortical patterns play in the overall brain synchrony, and in the processing of information. One aspect which is clear, though, is that these oscillatory patterns can serve to bring together neuronal populations across these structures. Applying these to Roger's preparation to return Milos' serve, his occipital, parietal, frontal, and subcortical networks could coordinate their activity in order to optimally filter, select, and recruit the necessary and sufficient computing units for analysis and execution. In the time interval starting shortly before Roger's stillness for the return of serve and until his own return ball contact, multiple lines of research point to the use of slow and faster oscillations to coordinate the circuits [22, 182]. This iterative process will be detailed in the next section.

Not a Serial Model: Interactions Through Sensorimotor Synchronous Oscillating Circuits

The previous sections allow one to identify functional correlates permitting Roger to process information during the short time he has to initiate his return in response to Milos' serve. While often portrayed as a serial process—flowing from sensory input to motor response—a major limitation is that linear information flow on its own is rarely computationally successful in precision tasks [21]. A more optimal and accurate processing mode establishes information estimation based on expectancy, and in this case very likely flows through multiple state estimations, with multiple back-and-forths. This process thus emphasizes optimization, with feedback and feedforward loops giving rise to forward/backward exchanges of information between neuronal pools, with the information precision improving with each iteration [183–185]. This is related to the long-known concept of pre-shaping perception through prior experience [21, 186, 187].

Anatomical and physiological clues provide insight into the system organization supporting the role of action as a contextual element in order to seek out information—so that the planned action is not only considered as the culmination of the information processing, but also as an early factor influencing sensory information flow [63]. More precisely, a role in pre-shaping perception can be appreciated with action/output-related sensory modulation that occurs at multiple levels of the nervous system, especially in the context of the filtering out or amplifying sensory input via motor commands. Sensorimotor interaction is already planned in the network organization, with network output (coming from the next step in the path) also

serving as "corticofugal" input. An important function of such organization is to select-in or select-out specific sensory information that have been determined to be useful in the particular context [188–197].

In discussing information flow in human sensorimotor control, the conceptually "more passive" passage of information has been labeled as "reactive," in contrast with the more movement-specific processing of afferent information, labeled as "predictive" [198–200]. Predictive capacity implies learning about the needed sensory input and determining appropriate sensory expectations throughout task execution. This context-specific sensory gating, continuous filtering, and tapering of information likely takes place between cortical areas (such as frontal-parietal interactions), as well as between cortical and subcortical areas [183]. As such, it represents a key process in network optimization which requires bidirectional information flow. During the exchange of information, processing networks are progressively refined to enhance contrast in a task-specific manner. This network selection process is unlikely to be optimized within one iteration; more likely, it will necessitate recurrent interactions (see the information flow scheme in Fig. 1.4) between the various information nodes to achieve convergence. An illustrative example pertains to somatosensory afferent processing, which when timed optimally with rodent whisker activity, shows neural activity traveling back and forth at a preferential 7 Hz rhythm (optimally ranging at theta up to beta) between dorsal column nuclei, thalamic, and somatosensory cortex relays [201].

In sensory state estimations, a similar temporally constrained iterative information-processing scheme likely operates at the level of cerebral cortical areas [65], with rhythmic communication operating as an important mechanism [202]. Network optimization thus appears to coordinate oscillating networks for the exchange of information—mathematically, networks with similar frequencies can synchronize in an economical fashion [203, 204]. The temporal flow of excitation/inhibition in individual neurons would then be mostly controlled by oscillatory influence, giving rise to short periods of activity, also separated by short silences [205]. Conceptually, for optimal communication, oscillations at various frequencies could serve as a "carrier wave," phase-locking cells throughout the local circuits, via feedforward and feedback loops leading to greater synchronized neural activity [86]. During communication, the phase between networks and relative to sensory input can provide important information [206]. Ultimately, operations carried out at the perceptual, cognitive, and motor levels would use interacting synchronization mechanisms, and often specific oscillations, involved at each step.

Getting back to Milos and Roger … as Roger is awaiting to return serve, poised and ready, he is processing incoming information to make a choice and waiting for the proper time to launch his service-return sequence of movements. To this end, as he is immobile—his cortical sensorimotor areas are processing visual and somatosensory information within local (e.g., specific receptive fields) and long-range circuits (e.g., across receptive fields, across limbs, or multi-sensory interactions) and functionally communicating on the basis of oscillatory activity. In the case of sensorimotor behavior, mammalian, primate, and human motor and premotor cerebral cortical areas (LFP, EEG, ECoG) indeed show premovement oscillations, e.g., the

cat waiting for a mouse to appear, or a human waiting for an event to happen, or when preparing to move [107–109, 207–210]. In humans, magnetoencephalography (MEG) has shown such oscillations in sensorimotor preparedness. Transposed to our situation, sensorimotor areas indeed show slower (alpha 8–12 Hz, or beta 10–30 Hz) and faster (gamma 30–100 Hz) activity [211], and would likely do the same in preparation for Roger's imminent service return. This spectrum of oscillatory activity provides a temporal background upon which local networks can effectively separate and communicate together.

Based on these observations, Roger's motor areas, decision areas, and sensory areas likely coordinate on the basis of sensorimotor premovement oscillations, partially illustrated in Fig. 1.5. Of course, the options for Roger's return are partially primed in advance and are likely to influence the speed and efficiency with which he will respond to the serve: a serve corresponding to the prediction will be more efficiently responded, while a non-corresponding serve will trigger a slower response. With the proper methods, it might even be possible to discern the predictive purpose as an influence on the flow of inter-areal communication, on brain synchrony. How neural activity "holds" the stated goal or the expectancy of future events, for comparison with sensory input, is key in understanding the network dynamics. In addition to fast input-output operations, cortical and subcortical networks have relied on oscillatory activity during expectancy periods to optimally prepare the circuits [143, 163]. This represents a strong circuit mechanism for

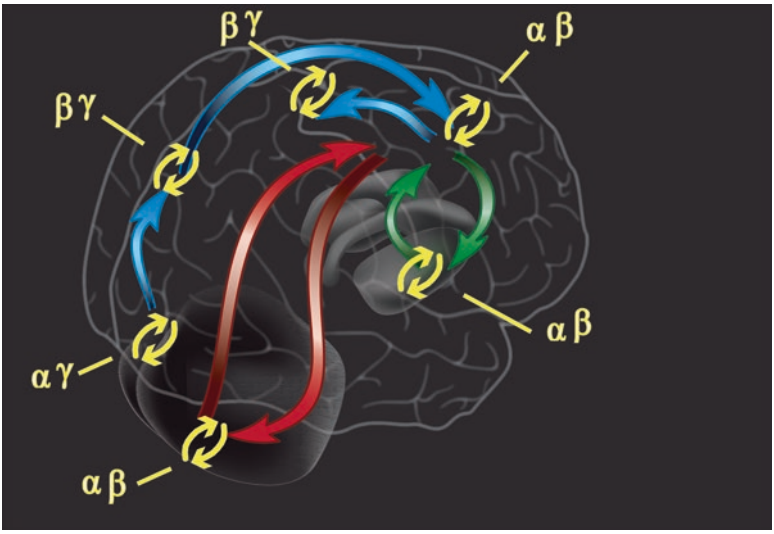

Fig. 1.5 Oscillatory processes added onto the flow of information. Many areas show slower and faster oscillatory processes, which can interact and be concurrent. Oscillatory frequency bands indicated, and are discussed in the text. The oscillations recorded at individual sites could be due to local oscillators (yellow arrows), to long-distance connections (blue, red, green arrows), or a combination of these two. Premotor areas and rostral frontal areas presented together for this figure

population coding in the preparation and performance of a sensorimotor task. These oscillatory networks can also serve network memories and motor learning, and embody time intervals during expectancy. In their greater context, many learning processes are based on temporal relations and coincidence, forging the stabilization of stimulus-response patterns [212–214]. For Roger, we can surmise that with repeated successful service returns in practice and match play, coincident-dependent modifications within his brain have taken place, coordinating the circuits responsible for the optimal adapted service return, fostering the efficiency of his sensorymotor adaptations. The time constraints particular to the return of serve prescribe efficient temporal coupling of the response with the stimulus, and these constraints will also modulate the coupling between the rhythms associated with sensory analysis with those from action areas. Their efficient coordination will insure optimal performance and long-term learning.

Let us return to the overall tennis serve-return timeline. Even if it is likely an oversimplification, let us also consider Milos' serve impact as the starting point, and draw a scenario for Roger's electrophysiology based on the oscillatory properties of the areas presented above. Starting from the sensory realm, the ball is tracked by the visual system in the occipital lobe, where *gamma* oscillations provide visual processing support to permit cells to analyze the position and motion of the incoming tennis ball. At the same time, *gamma* somatosensory oscillations also support touch processing. This will cover the early part of the perceptual process. As the initial ball position and initial somatosensory racket state start to fade, within a few gamma cycles (e.g., 20-ms period), the primary processing regions will engage in *beta* oscillations, enabling this longer-distance carrier wave to recruit neighboring areas in the parietal lobe, with a larger (e.g., 50-ms) cycle period. A similar process then takes place in communications with the prefrontal cortex and premotor areas, where *gamma* precedes *beta*; at the same time, in a short time overlap the primary motor cortex also comes into play. The *gamma-beta* sequence then coordinates both local processing and preparedness for more distant communication. For each *beta* cycle, long-distance networks can perform the multiple iterations necessary for the fine-tuning of information. Bidirectional communication would then coordinate the activity between sensory areas, and between sensory, decision, and motor areas.

This scenario is rooted in empirical and mechanistic support. In addition to the concept of specific carrier frequencies satisfying networks of different sizes [22, 25]—slower for larger networks, faster for local networks—the capacity for circuits to switch oscillatory mode between faster and slower oscillatory processes, or for them to coexist in a local network, can inform us as to the state of information flow for a particular task. Such sensorimotor interactions have been recorded in the cat brain, where oscillatory coherence developed and flowed across the cortical areas during a sensorimotor task [27]. In the context of a visual working memory task, frontoparietal networks synchronize using 15–25 Hz LFP activity as background, with communication in a parietal-to-frontal progression [215]. The carrier frequency for information flow (and its direction, in this case) shows that *beta* oscillations have a role in distant synchronization mechanisms, and at the same time in sensory-to-motor information flow. In the posterior parietal cortex, there also seems

to be a progressive change from 20–40 Hz oscillations to 0–10 Hz oscillations toward movement onset [216]. Finally, the prefrontal cortex can synchronize its activity with parietal areas through oscillations in the *beta* range, and thus exert likely a top-down modulation of the dorsal stream processing [217]. At the same time, it could very well be that the long-range *beta* synchronization mechanism is coordinated with local circuit *gamma* activity. Indeed, *gamma* oscillations show a phase-relation with slower oscillations in the cortex [218]. Cortical-subcortical alignment is also likely to occur; across the cerebellum and basal ganglia, rhythms at these same frequencies also likely align to sensorimotor events, through the subcortical sensorimotor loops [152, 161, 163, 178].

In parallel, attentional processes could represent a functional aspect of behavior linking brain areas together. Using MEG, Siegel et al. [211] recorded slower oscillations (10–50 Hz) across occipital, parietal, and frontal areas as tonic activity present during the waiting period prior to a visual stimulus; they also saw a faster stimulus-triggered 50–100 Hz oscillation in visual and parietal areas. In this context, attentional modulation had a region-specific effect on the frequency of oscillations: in the parietal lobe, the MEG signal showed a suppression of the 5–15 Hz band (close to *alpha*) before stimulus onset, whereas the appearance of the stimulus induced increases in the low-*gamma* (35–60 Hz) band. Thus, during stimulus processing, gamma coherence is prevalent across the dorsal stream pathway, while beta coherence seems to be more prevalent in the parietal-frontal interactions; this is the pattern described above, likely to be taking place in Roger's brain during his return of serve. This seems to hold, with the nuance that in the visual cortex, beta oscillations also appear to facilitate the attention to specific visual locations. Overall, this shows that attentional processes have an effect adapted to the cortical area and information to be processed: more local gamma, more distant beta. Specific synchronization characteristics for more local visual processing contrast with visuotactile stimuli linked with visual processing showed integration in the 7–13 Hz range [219, 220], validating above considerations for slow oscillations going across systems. Idiosyncratic oscillatory tendencies and resonance parameters of the individual networks determine the optimal frequency band for an efficient connection. Oscillatory frequency can thus be positioned in its effects on network size: slower for larger network vs. faster for local network communication [221–223]. We will describe this further in the next section.

Different Frequencies, Different Roles for the Oscillations: Becoming More Predictive

As Roger tries to return Milos' serve, he uses his experience in directing his focus of attention on particular elements of the visual scene, extracting the speed, direction, and path of the incoming serve, while also monitoring his own body position. How the allocation of attention is managed within networks can help understand the

formation of such networks [224, 225] (see also Chap. 3. Oscillations and Synchrony in Attention), even in the case of attention committed to sensorimotor execution. As task-related information is processed, attentional resources are structured, bringing together a network of neurons from the occipital, parietal, and frontal cortices. As he knows quite well what to focus on, Roger's top-down attentional monitoring of incoming information has the effect of increasing the neural activity to the attended features (e.g., including tracking the flight of the ball); conversely, this also decreases the neural activity to features outside the attentional scope. This top-down modulation comes from parietal and frontal sources, influencing the sensory processing in primary and secondary sensory areas [226]. Specifically, goal-directed (top-down) preparation and selection of stimuli include the intraparietal cortex and superior frontal cortex [227]. Interestingly, these areas also harbor oscillatory activity, where in the prefrontal cortex this activity is coherent and synchronized with the neural activity in the areas focusing on perception [217]. Finally, oscillatory activity has been identified in the parietal cortex during spatial sensory processing [216, 228]. These downstream areas could thus influence the gathering of information produced by the perceptual areas.

This task-related communication between frontal and parietal areas based on oscillatory synchronization can be considered as an example of communication-through-coherence [202], where oscillatory properties of local networks in each area are coordinated via long-range connections to ensure the exchange of information. Effective network-to-network communication coordinates the putative oscillators, spatiotemporally influencing the firing of local neurons, and facilitating the synchronous firing of distant neurons. As such, the phase relation and between-neuron synchrony depends on the coherence between neural oscillations in each of these groups [229]. This relation progresses through time, and is likely dynamic across consecutive oscillatory cycles. As Roger's attention is focused on detecting clues as to the serve's pace, spin, and direction, and is improving the accuracy of information decoding throughout the delay, this oscillatory interplay dynamically takes shape, likely through frontal-parietal bidirectional communication. For each service return, Roger's brain computes action selection to match the sensory input in multiple iterations, each providing a progressively more accurate computation. An important question then concerns the optimal "sampling frequency" of coherent oscillations for this sensorimotor updating process to converge. An optimal frequency (or frequencies) would facilitate communication if it is adapted to: (1) communication across shorter or longer distances; (2) the capacity of certain oscillations to affect different cortical layers; and (3) the multi-oscillatory potential effects on the timing of network activity. Below, we propose a hypothesis on the functional role of faster vs. slower oscillations in sensorimotor circuits.

Frequency Specificity

Communication highways must ultimately contact and recruit the desired neuronal populations, and specific oscillatory frequencies can better influence specific population constituents, namely local interneurons, local projection neurons, or in a definite manner, distant units. By their structure and the tally of their component elements, larger neural networks/populations of neurons tend to oscillate more slowly, while smaller populations of neurons tend to oscillate at a faster rhythm [22]. This network phenomenon is based on delays required to complete oscillatory loops across the neural population, following dipoles within the networks. Without being an absolute rule, in general principle, gamma oscillations likely affect local networks of neurons, while beta oscillations likely affect more distant networks, using long-range mechanisms and synchrony [221, 223]. This network behavior for slower and faster oscillations has been empirically confirmed with models using excitatory-inhibitory networks of neurons, with established connection lengths [221]. Specifically, gamma-gamma synchrony stabilizes during the synchronization of two local networks, with gamma activity optimizing at conduction delays of circa 10 ms. However, beta-beta coupling was more efficient for conduction delays around 20 ms. Overall, local network beta oscillations can drive excitatory projection neurons, with excitatory-excitatory coupling insuring long distance synchrony. This provides a modeling result in support of frequency-specific optimization of axonal conduction delay modulating network synchrony. It also provides a strong cellular basis for the selective communication between areas based on local network frequency [202].

Driving Neuronal Response Across the Cortical Modules

These oscillatory influences sweep across all layers of the cortex, and their capacity to influence specific cell types depends on the cells' biophysical properties, connectivity, and position within the cortical layers. Accordingly, specific frequencies carry an optimal influence on units located in particular layers, driving cortical cells of different types, and influencing the input-output properties of cortical columns. As a consequence, an optimized communication frequency will thus determine how many and which units can be recruited by a particular oscillatory pattern across the network, and these will recruit particular units which have a particular connectivity across the canonical cortical network [230, 231]. Oscillatory entrainment of units consisting mainly of interneurons will thus affect cortical layers I–IV, while an entrainment of layers V and VI will drive output units. As LFPs provide a measure of the integrated neurons' synaptic activity and the cells' own local currents, across the local network [232], by recording LFPs and unit activity, we can identify phase-locked units, which are affected by the underlying oscillatory influence. This can trigger action potentials and sometimes bursts of firing, which are optimal for

long-range communication. With its alignment in time of excitation and inhibition, the oscillatory phenomenon can operate as a burst control function [202]. Within smaller cortical circuits favoring gamma oscillations, this faster phenomenon appears optimal to drive the firing of local interneurons located in input and short-distance cortical-cortical connection layers [233, 234]. In gamma oscillations as well, unit and LFP measures reveal a recruitment of inhibitory interneurons to control the firing of excitatory units, leading to gamma generation [235]. In comparison, due to their size and biophysical properties, projection cells such as pyramidal units located in the lower cortical layers require the convergence of multiple excitatory inputs to be driven above firing threshold—which is more easily accomplished via slower oscillatory processes. By driving pyramidal cells, the local circuit can then activate long-range communication connections.

Taking a look at brain areas involved in the return of serve can help illustrate these principles. In the primary visual cortex, unit and slow-wave activity in V1 layer 4 show particular patterns that appear influenced by gamma oscillatory phenomena [236]. With recordings focusing on depth differences and layer specificity across the area, unit firing in V1 in superficial layers shows a relation with gamma oscillations, while unit firing in deeper layers is better related to beta oscillations [237]. This corresponds to a particular connection pattern, where superficial cortical layers are predominantly responsible for local connections, while deeper layers concern more long-range connections [231]. Each layer is thus under the influence of oscillatory activity optimal for their specific input-output properties. This determines the efficiency in oscillations to drive units in these different layers, and the cellular communication using connections going to and receiving from coupled cortical sites. Going further in the visual cortex organization, the consequence is that slower oscillatory influences move toward the dorsal stream, while faster oscillations influence neural activity toward neighboring visual areas. In a related manner, multiple distinct alpha rhythm generators were found in the superficial, granular, and deep layers of the visual cortex. However, recordings from layer 4C and deep layers provide evidence of local generators, suggesting the involvement of the thalamocortical network, which could be involved in a particular alpha-related transmission. However, during the sustained processing requiring visual attention, alpha oscillations were decreased, as was the level of alpha interactions [238]. This shows that alpha and gamma oscillations can coexist in the visual cortex; the coexistence of different types of oscillations has also been seen in other cortical areas. In rodent motor areas, theta-gamma nesting has been found throughout the LFP profiles, and multiple interneurons in superficial layers are phase-linked with gamma oscillatory activity; however, when looking at gamma phase locking, a variety of phases can be discerned for the neuronal firing in deeper layers [239]. This means that in order to ensure motor cortex output, a small network population code based on another type of oscillation than gamma (likely alpha or beta) might be required to drive pyramidal cells in MI. When considering their electrophysiological properties, and the need of the input from multiple converging afferent neurons to drive the downward pyramidal cells, which includes the massive Betz cells (what could be considered

like electrophysiological "inertia"), it is clear that slower oscillations might have an advantage as a neuronal driver in frontal action areas.

Timing of and Multiplexing of Neural Activity

With multiple types of oscillation simultaneously coexisting within cortical modules, it is quite possible that circuit mechanisms favor spatiotemporal linkage between them, serving to define simultaneous populations carrying multiplexed information. This "nesting" phenomenon, with faster oscillations "riding on top" of the slower ones, has been a staple of information processing codes in the hippocampus and cortical structures, and could represent concurrent information storage channels on different timescales, for example, in theta-gamma nesting [223, 240, 241]. This co-patterning of activity, where both slower and faster oscillation patterns show an apparent link together, could represent a cross-frequency coupling phenomenon, and act as a mechanism to coordinate neural populations [242]. A variety of cortical network interactions can give rise to cross-frequency interactions, linking together slow oscillations with fast oscillations [243]; this temporal signature can also change through time, drifting across slower or faster oscillatory modes, according to a process of variable coupling. Another example is when the frontal motor systems enter into beta-range oscillations, followed by a passage into gamma-range oscillations [244]. Thus, in the same networks, a spatiotemporal patterning of slower and faster oscillations can coexist, as recorded with LFPs from a few nearby electrodes—and it is likely to influence neural firing and information processing in the area in a specific manner. As it draws upon and influences different subpopulations, it is quite possible that during this multiplexing, the different oscillations have a slightly different purpose. During treadmill running in rodents, corticostriatal theta-gamma phase-amplitude coupling can be recorded, where theta is the frequency better coupled with neighboring structures [178]. In a short-term memory task in primates, the prefrontal cortex also presents slower and faster neural coding: action potentials were phase-locked at 3 and 32 Hz, both present during the short-term memory delay, with faster oscillations being sensitive to specific information [245]. Cross-frequency coupling would then be an optimal mechanism for linking together distant areas, giving context to local processing networks: the slower interactions that are needed to combine brain activity at behavioral timescales, with the faster local cortical processing that is required to compute local operations [246, 247]. As an empirical support for this, stimulating with transcranial alternating current stimulation in a theta-gamma mode also improved working memory performance [248]. Multiplexing could thus represent a powerful communication strategy for information sharing across multiple cortical biological neural networks, controlling the flow of information at the level of single-unit firing across multiple frequencies optimized for local and global processing [222].

The interpretation of this coexistence of oscillations is the source of ongoing debates. For example, Engel and Fries proposed that beta oscillations could help to

encode the status quo, while at the same time supporting network operations that participate in the attentional top-down surveillance of this status quo. Conversely, an expected change would then trigger a smaller but quicker set of gamma oscillations [223]. Other considerations include a role of beta-band oscillations in the wide-range support of intra-areal coding that can provide local context, particularly in the case of operations taking place in the prefrontal cortex and in the posterior parietal cortex [31]. This multiplexed prefrontal cortex control of behavior is a prominent phenomenon [249]. Even in each frequency band, the different rhythms display a variety in purpose. In essence, these slower oscillations could represent a top-down effect on local networks, in a mechanism analogous to how attention affects local cortical modules [250]. Slow oscillations, with their capacity to coordinate large-scale networks and deep layers of the cortex, represent a plausible way to automate predictive timing [87]. In addition, alpha oscillations could serve as a mechanism to functionally compare sensory input with sensory predictions [251], and they are modulated in anticipation of relevant or irrelevant stimuli [247]. The slower oscillations could be in delta, alpha, theta, or even beta bands. When looking more specifically at the somatosensory system, the slow oscillations could be in the beta range, as beta oscillations could help process somatosensory feedback from the peripheral receptors [252].

In another example, occipito/parietal gamma oscillations are coupled with frontal beta rhythms during mental imagery; in this instance again, cross-frequency coupling could represent a mode of communication emphasizing expectation-based information during imagined movements [253]. In this case, while no movement is produced, the frontal lobe could be verifying the status quo, as the occipito/parietal areas themselves would be free to participate in the imagery process. Specifically, gamma rhythms have been subdivided into different types—a stronger type with active coding, and a weaker type with attention and arousal. A separation between beta rhythms has also been established. What appears key for characterizing the effects of these oscillations on cell assemblies is to understand the mechanistic implications. With a beta-gamma multiplexed influence on the organization of assemblies, the top-down beta influence exerts its effects onto the deeper cortical layers [254]. Comparably, when inspecting the V1–V4-parietal area 7 interactions, this slow/fast rhythm multiplexing is confirmed, with a parietal beta top-down directional enhancement on primary visual cortex gamma during attentional allocation [255].

An interesting aspect is to measure the expectancy elements in isolation, such as when subjects observe a demonstration of a motor activity, which has been identified as a “mirror experience”—this paradigm has been show to affect alpha frequency oscillations in EEG [256]. In the context of this chapter, and in exploring the effects of top-down modulation of sensory processing, it is interesting to consider a study related to the expertise of tennis players in shot direction anticipation [20]. In a mirror-system type observation paradigm, expert tennis players and novices were compared for their EEG activity while watching video of opposing players hitting tennis shots. As expected, subjects who were experienced tennis players were better able to anticipate the direction of the next shot hit by a video opponent. For EEG

measurements, experts also showed a more prominent and earlier μ (mu) and beta desynchronization than less-experienced tennis players. Consequently, this slower μ oscillation could play a top-down role in perception, and be useful in the interpretation of sensory data and in sensory prediction operations. This provides a very practical link with our current return-of-serve situation. In another situation where an arm movement actually takes place, just like Roger's service return colliding with the path of the incoming tennis ball, recording of EEG in sensorimotor-visual matching has shown a prominent of slow (3–7 Hz) activity in the sensorimotor EEG, likely serving to link sensorimotor with visual information in the task [257]. This also highlights the role of slow oscillations in grouping together information being processed within distant brain areas.

Brain Neural Synchrony in the Return of Serve

Finally, we can establish a few basic properties for the tennis-specific information processing, based on the information flow we have discussed in the chapter. So, Roger is ready, poised to return Milos' serve … he is waiting for the cues concerning the serve properties, in order to select which return to execute. We can subdivide Roger's particular task here into a preservice period, a predictive/sensory processing period, and finally a post-service sensory-updating process. Like the predictive/sensory processing period, the pre- and post-service periods quite likely make use of oscillatory synchronous activity in Roger's brain (likely engaging the frontal lobe and associated cortices); however, we will focus on the most interactive sensorimotor period, the middle period right before and during the service return.

Once Milos steps to the line to serve, Roger is already computing the potential identity of the incoming serve [11]. This gives rise to an interaction between prediction refinement processes and sensory processing, likely through a combined slow oscillatory process (within theta/alpha/beta or a combination) to communicate over long distances with a faster local process (gamma), at various ratios throughout the time period. An interesting location where to look for this type of activity would be within the parietal lobe, where indirect connections from the visual system, somatosensory system, as well as action planning "corollary discharges" can get integrated on a fairly large scale [258]. Presumably, this interaction can be characterized by a variable equilibrium between the sensory and motor components permitting to improve the planning of movement iteratively, eliciting a predominance of predictive and reactive operations, at various times. This has implications for the potential, and type, of oscillatory activity to occur:

1. Early in the period, the predictive process dominates, giving rise to a predominance of slower oscillations, for example, during pure anticipation [20, 161]
2. In the middle of the process, gamma oscillations related to sensory local processing increase in importance, accompanying the slower oscillations. This produces a series of complex waves that combine slower and faster oscillations, such as

theta-gamma coupling. This type of activity is seen in many brain areas, including within the parietal cortex during recognition in the rodent [259], and sensorimotor gamma activity can also be under the influence of long-distance connections [260]. This confirms that the different oscillations can have a role while the local and long-range interactions need to take place. More than a mere presence, the disturbance of the slow frequency component during theta-gamma coupling even has a causal effect in humans, affecting information processing and working memory [261]. It is possible that the relative theta-gamma coupling could have a predictable ratio: an hypothesis could be that the more predictive the processing is, the ratio would then tip toward the slow oscillations; conversely, the ratio would tip toward the faster component when the network is more in reactive processing.

3. Finally, during the execution, the processing required is fast and goes through the sensorimotor networks and descending circuits quickly. These are also somewhat aligned with lower motor neuron activity [112, 262], but this activity will shift quickly for preparing for the next shot to hit.

In (2), the hypothesis of predictability of parietal oscillatory and coherence frequency is related to the type of activity sweeping across the parietal cortex. This interaction, focusing on large-network/small-network contrasts across the occipitofrontal transitions, does not negate a type of interaction we have largely omitted—the activity from thalamic neurons and the pulvinar. However, the transition proposed profiles well the activity across frontoparietal networks [247]. By incorporating cellular coding across these networks, we might even be able to identify the potential cellular elements contributing to the theta/gamma frequency shifts, based on how different types of afferent inputs shape the local circuit [64].

Complementing with a Network View

When considering the effects of such oscillatory and coherence processes on network architecture, it is interesting to inspect and represent and analyze the interactions through the graphical network analysis [263, 264]. An advantage of this approach is that we can then represent the dynamical connectivity interactions and get a "topography of synchrony." Locating with precision the elements that synchronize provides a picture of the network architecture exchanging information, even if transient. Such an analysis is becoming increasingly part of the framework of the analysis of interactions in the nervous system [265–269]. Figure 1.6 applies the notions discussed in this chapter in a graphical format. Of course, this would have to be confirmed by fMRI, EEG, NIRS, or MEG, with the subject himself. When compared with other less-experienced subjects, the patterns of activity can then be used as a potential biomarker of expertise. An interesting quantitative approach has been used in NIRS compared to bimanual proficiency in surgeons, where the coordinated activation of networks across the primary motor cortex, the

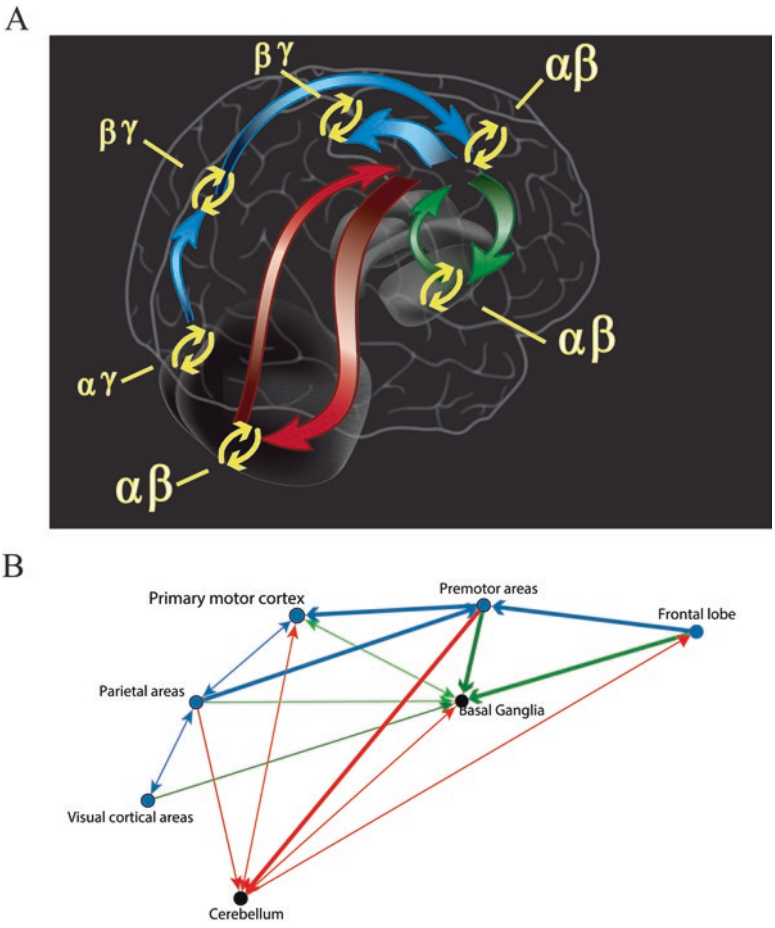

Fig. 1.6 Oscillations serve expertise and anticipation. (**a**) As the returner has trained for many years and become more proficient at identifying the incoming serve direction, speed, and spin through contextual or online cues, the brain oscillatory activity from predictive networks can acquire more importance. As Roger has practiced numerous returns of serve, the predictive alpha/beta bands would have a greater role in the information processing scheme. Note the long-loop arrows from the frontal lobe increasing in importance. (**b**) Corresponding network analysis shows this increased importance with the links represented with the edges from a frontal origin

supplementary motor area, and the prefrontal cortex was a better predictor of skilled performance than the expert observer rating system [270]. Incidentally, the activation of prefrontal cortex decreases while the activation of the primary motor cortex and supplementary motor area increases, with skilled learning.

Back to Function, and Back to the Match!

While we kept in touch with the problem throughout the chapter, all these brain operations must be related back to Roger's return of serve. As we initially described, Roger must choose his service return as well as he can, in the short amount of time provided by the situation. According to tennis experts, Roger can choose between three imperatives on the service return: put the ball back in play (play defensively), counter a hard serve with the goal of giving trouble (to counter-attack), or in the case of a weak serve, to take the initiative (to attack) [55, 271]. With Milos serving, the latter option is definitely off the table. So Roger is trying to return the serve to his advantage, but if he misreads the spin, location, or pace, he will likely have to settle for just putting the ball back in play.

To read the serve, that is the crux of the problem. Expert players try to determine the server's patterns and tendencies, from specific statistical records and rigorous opponent scouting, and during the match, they put a great effort in trying to find cues that will permit to use the return of serve as an opportunity to attack. A break of serve often means the set. Part of the anticipation will be due to the phase of play [272]—the score and its relative risks, and the last string of points, the momentum. The returner will also establish partial information from the opposing player's position after the serve in recent points (serve-and-volley, hugging the baseline), and adapt their own technique, such as shifting their own position in the receiving half-court, or decreasing their return swing length, change spin and/or speed [273]. Likely the type of information requiring the most expertise to recognize are the pre-impact within-service motion cues [10, 57]. This pursuit is largely perceptual-cognitive, and elite players have the advantage of a clear mental representation of the information they are seeking. They more clearly identify the cues, and make the choice swiftly based on partial information [272]. In optimal situations, this choice is devoid of uncertainty, and is in line with their tactical plan. Detecting these cues requires much concentration. An optimized perceptual process, for tennis coaches, requires quieting the mind [274]. In essence, a strong concentration and dedicated attentional focus is necessary to detect the key information permitting the prediction of the incoming serve.

For discussion purposes, we can posit that Roger might have noticed that Milos has a slight trunk rotation difference between a serve down the middle, or toward the outside. Once this cue is detected, Roger can then reevaluate quickly the probability of occurrence of the different potential serves and then anticipate the incoming serve. This cuts down on the decision time, and Roger can start shifting his weight toward forehand or backhand, at the same time initiating the cognitive/action process associated with this serve. These apparently automatic reactions, perfected through years of high-end training, are thus efficient, precise, and adaptable. If Roger can detect, anticipate, and initiate the adapted actions at a high enough rate, the tennis expressions, being "in the zone," and in a "state of grace" are sometimes used [11]. With Roger, this happens more often than anecdotally… Roger's service returns have a timing, fluidity, and adaptability that in addition to his fantastic per-

ceptual and decision-making abilities, he has learned to coordinate together a variety of perceptual instruments or effectors in the participation of his fast-paced action [272]. Years of practice—as Foster Wallace has said, successfully returning a hard-served tennis ball requires special senses—to be able to make adjustments on strokes so well, as they recede from normal consciousness [275].

Conclusion

This chapter aimed to show that just as top-level tennis players anticipate an incoming tennis serve, brain processing also uses predictive information in optimized communication. This predictive activity can be seen in brain coordination patterns in oscillatory activity. Could better-timed oscillatory activity and enhanced coordination help Roger return Milos' serve? Multiple examples show that enhanced synchronization between relevant sensorimotor areas leads to improved performance [219]. This enhancement of information processing would thus support the sensorimotor performance. More specifically, when referring to Roger's brain coordination, one wonders how the brain is coordinated on the days where he is in the zone vs. days when his decision-making and execution are less crisp, less sharp. In this state of grace, are coherent oscillations optimal? More testing will have to take place.

Oh, and the final score for this Wimbledon semifinal: a fantastic five-setter finishing 6–3, 6–7 (3), 4–6, 7–5, 6–3 for Milos. Great match, but he lost in the finals 2 days later to Andy Murray. Roger took his revenge in the quarterfinals the following year, winning the tournament for the eighth time. Over their career, Roger has the edge 11–3. Who says only it only takes a big serve to win? When an unstoppable force meets and immovable object…

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Chapter 2
Theta Rhythm in Hippocampus and Cognition

Bénédicte Amilhon, Guillaume Ducharme, Jesse Jackson, Romain Goutagny, and Sylvain Williams

Introduction

Brain oscillations arise from the coordinated activity of thousands of neurons. Within large neuronal networks, the activity of individual cells sums up to translate into oscillations of the extracellular local field potential (LFP) [1]. These rhythmic variations of the LFP can be recorded at the surface of the skull (electroencephalogram) or by lowering recording electrodes within brain regions. Rhythmic oscillations have been shown to underlie a vast majority of brain functions as diverse as breathing, movement, information coding, and cognitive functions [2, 3]. Accordingly, nearly all brain pathologies have been correlated with a dysfunction of some form of rhythm [4–6]. Oscillations thus play a key role in the brain, and comprehending the mechanisms of rhythm generation and modulation is critical to gain better understanding of brain functions.

The role of oscillations in brain function has been extensively studied in the hippocampus, a brain region located in the medial temporal lobe and named after its

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resemblance to a sea horse [7]. The hippocampus has received much attention for its crucial role in memory formation. In a seminal study, Scoville and Milner described a complete anterograde amnesia and limited retrograde amnesia (around 3 years before the surgery) following bilateral resection of the entire hippocampus and parts of the neighboring regions (i.e., amygdala and entorhinal cortex) [8], results that were later confirmed by others [9, 10]. More refined lesion experiments in rodents [11–13] and primates [14, 15] also demonstrated the role of the hippocampus in memory formation. More recent research has extended the role of the hippocampus beyond memory formation and defined it as a cognitive brain hub involved in multimodal processing of many forms of inputs (somatosensory, olfactory, visual, auditory, magnetoreceptive, time-related, and emotional) [16–20].

The neuronal hippocampal network generates a large collection of brain rhythms across a wide range of frequencies (0.1–500 Hz) [21]. Due to its well-described anatomical organization and neuron types and rich repertoire of rhythms, hippocampal network provides an ideal model for studying the mechanisms and function of brain oscillations. Among all oscillations in the hippocampus, the most prominent recorded oscillation is theta rhythm, a large amplitude oscillation around 3–12 Hz. Theta rhythm in the hippocampus occurs simultaneously with higher-frequency activity in the 20–200 Hz range, collectively referred to as gamma oscillations [22, 23]. Although gamma rhythm can be found in many different behavioral states, it is largest in the hippocampus when occurring simultaneously to theta oscillations and is found "nested" within theta cycles [22]. Theta is evolutionarily conserved and has been recorded over many species including rats [24], rabbits, cats [25], bats [26], monkeys [27], and humans [28, 29], which suggests this rhythm serves fundamental functions in the brain. Theta rhythm is mainly associated with behavioral states such as active processing of sensory information, voluntary movement, and rapid eye movement (REM) sleep [30–32]. When initially recorded in the hippocampus of rabbits, theta rhythm was behaviorally linked to attention and arousal [25]. Since these initial studies, theta rhythm has been suggested to correlate with anxiety [33], movement [24], and various forms of learning [34–37]. The role of theta rhythm in cognitive functions has thus been debated over time, although consensus has been reached today regarding the fact that theta rhythm changes in response to a number of different psychological states [30, 38], and likely represents the multimodal processing that takes place within hippocampal circuits. The study of the relationship between hippocampal cellular activity, theta rhythm, and various forms of cognition has yielded crucial progress in the understanding of the role of theta rhythm in cognitive functions, and will be the focus of this chapter.

Anatomy of the Hippocampal Formation and Theta Oscillators

Large-amplitude signal in the extracellular LFP such as theta rhythm requires that currents flowing through cellular membrane are summated both spatially and temporally [1, 39]. The unique anatomical organization of the hippocampal network

and inputs provides the framework for spatial summation, and strong temporal summation can be achieved through synchronizing mechanisms which will be discussed later in this chapter. The combination of these features therefore makes the hippocampus a powerful theta generator, and an ideal brain region to study the roles of theta rhythm in cognition.

The terms "hippocampal formation" and "hippocampus" can both be encountered in the literature. The hippocampal formation includes the medial and lateral entorhinal cortex (MEC and LEC), the dentate gyrus (DG), cornu ammonis regions CA3, CA2, and CA1, the subiculum (SUB), as well as para- and presubiculum [7]. When referring to the hippocampus, we will be referring to the CA regions and the DG. It is worth noting, though, that in many cases the term "hippocampus" refers to CA regions only [7]. Unlike neocortical regions composed of six cell layers (as the MEC and LEC for example), the hippocampus displays a single layer of tightly packed pyramidal neurons. In CA1 and CA3, this dense cellular layer allows the division of CA regions into distinct layers: stratum oriens, containing the axons or pyramidal cells; stratum pyramidale, containing the tightly packed cell bodies; stratum radiatum, where proximal dendritic arborizations are localized; and stratum lacunosum-moleculare, with the most distal dendrites. In CA3 an extra layer called stratum lucidum can be found bellow stratum pyramidale [7]. Most studies investigating the roles of hippocampal formation subregions have focused on the MEC, DG, CA3, CA1, and the SUB, which will be described here.

Santiago Ramon y Cajal was the first to study hippocampal anatomy in detail [40], using the Golgi impregnation labeling technique. Ramon y Cajal was able to show with remarkable accuracy the patterns of projections within the hippocampus, and constructed the first circuit maps of hippocampal formation networks. The dominant pattern of connections between the different subregions of the hippocampal formation is an ordered flow of axonal inputs and outputs. The MEC, considered as the main entry point of cortical information in the hippocampal formation, "perforates" the hippocampus and forms excitatory synapses on DG excitatory granule cells and inhibitory interneurons [41–43]. Aside from this perforant pathway, the MEC also provides direct inputs from layer III principal cells to CA1 [44] and layer II principal cells to CA3 [45]. Interestingly, the LEC also provides direct inputs to the hippocampus through projections to the CA1 and CA3, yet weakly overlapping with MEC inputs, suggesting a functional dissociation between MEC and LEC pathways [46].

After receiving inputs from the MEC, granule cells in the DG send excitatory axonal outputs to the CA3 region using the mossy fiber projection. CA3 pyramidal cells in turn send excitatory outputs back to adjacent regions of the DG (back-projections), to the CA1 stratum radiatum through a pathway called "Schaffer collateral," and recurrently onto other local CA3 pyramidal cells [47, 48]. The output of pyramidal cells in CA3 has been described as extremely divergent, since a single CA3 pyramidal cell can contact CA1 neurons throughout the entire longitudinal axis of the hippocampus [48]. The CA3–CA1 synaptic connection is among the most studied systems in the brain. Most theories of synaptic and molecular mechanisms underlying learning and memory derive from CA3 Schaffer collateral

stimulation in hippocampus slices. This in vitro model has indeed allowed the demonstration of long-term potentiation (LTP) and long-term depression (LTD) in hippocampal slices, considered as the molecular models of learning [49–51].

The hippocampal formation internal circuit is continued by CA1 pyramidal cells sending axonal outputs to the subiculum and back to the MEC [52, 53]. These CA1 excitatory terminals contact pyramidal cells in the molecular layer of the SUB, which is continuous with stratum radiatum of CA1. The properties of the CA1–SUB pathway have been largely understudied compared to Schaffer collateral pathway, although it has been described that long-term potentiation can arise at CA1-SUB synapses [54, 55]. This connection thus seems to possess molecular and plasticity machineries similar to CA1, and could therefore be also necessary for memory formation and recall.

The SUB is the main output of the hippocampal formation, connecting a vast and functionally diverse array of brain regions [56–58]. Within the hippocampal formation, the SUB sends excitatory projections back to the MEC and LEC, completing the loop. In addition, the SUB is the primary source of hippocampal-subcortical projections (connecting the basal forebrain, hypothalamus, amygdala) and hippocampal-cortical projections (connecting the prefrontal cortex and other associational cortices) [56, 57]. The topography of SUB connections to post-synaptic targets is highly spatially organized. Small clusters of SUB neurons contact targets which are also anatomically bound together. The SUB thus seems organized in modules, selectively communicating with distant brain regions involved in a specific function, suggesting that the SUB, and by extension the hippocampus, is a highly multifunctional structure.

The above-described hippocampal formation network has been extensively studied and is probably one of the best-known circuits in the brain. However, a number of recent studies describe more subtle and less-studied pathways in the hippocampus. The SUB has recently been shown to send back-projections to CA1 [59] and CA3 [60]. Besides, an interactive paper published by van Strien and colleagues summarizes hundreds of understudied projection pathways in the hippocampal formation [46]. Additionally, the CA2 region is highly neglected from most studies of the role of hippocampal subregions. Some recent studies, however, are starting to highlight an important role of CA2 in hippocampus circuits as an important relay between the MEC and CA1 [61, 62].

Finally, an important feature of hippocampal networks is the strong heterogeneity observed along the longitudinal axis of the hippocampus (also called dorsoventral or septo-temporal axis). Differences can be found along the longitudinal axis at the level of gene expression [63, 64], cell properties such as intrinsic pyramidal cell excitability [65], or place field information content and size [66–69], network properties [69], and connections to other structures [46, 53]. Experiments done in an isolated hippocampal preparation demonstrated that the dorsal and ventral networks are independent, suggesting a dichotomization of the septo-temporal areas of the hippocampus [70]. However, fewer studies have been performed on the intermediate or ventral hippocampus compared to the vast body of literature published on the dorsal hippocampus. Refining our understanding of all septo-temporal regions of hippocampal network is crucial to fully understand the multimodal processing taking place in this complex brain region.

The layered organization of the hippocampus is the basis of some of the largest extracellular currents recorded in the brain. Dense excitatory and inhibitory inputs onto hippocampal cells, condensed on specific portions of the pyramidal cell arborization, create massive influx and outflows of ions through cellular membranes. From these anatomically organized ion fluxes arise current sink-source dipoles which translate into large local field potentials, and have been best described in CA1 region [39]. The two sink-source dipoles observed in CA1 are believed to arise from perisomatic inhibition, provided by interneurons, on stratum pyramidale and by strong excitatory inputs from the entorhinal cortex onto pyramidal dendrites in stratum lacunosum-moleculare [39, 71]. The main current generators of theta oscillations are thus located within the hippocampal network.

Hippocampus Cell Properties in Relation to Theta Rhythm

Considering the prominent role of the hippocampus in learning and memory, specific functions of hippocampal formation subregions have been mainly studied in relation to spatial memory. A brief overview of the cell properties in relation to spatial navigation, the interactions with theta oscillations within the hippocampal formation, and functional differences between the MEC, DG, CA3, CA1, and SUB are described in this section.

The MEC contains neurons called "grid cells," as they fire in a pattern that creates a Euclidean map of the environment [72, 73]. The regular spacing intervals provided by grid cell firing are believed to provide a map that can triangulate the animal's position in space. When recording from grid cells in different parts of the MEC, the spacing appears different, thus enabling the mapping of different sized environments. This map of space provided by grid cells is hard wired, difficult to modify, and appears very early in development [74, 75]. The periodic firing of grid cells seems to rely at least partially on theta rhythm in the hippocampal formation [76, 77], but see Yartsev et al. [78]. Grid cells have been found to fire in relation to different phases of the theta rhythm generated locally in the MEC and to carry different spatial information content depending on the preferred firing phase [79]. As described above, the MEC is the main source of cortical inputs to the hippocampus, and is thus responsible for providing sensory information about the environment to hippocampus cells. The MEC provides the hippocampus with information about the position, direction, and velocity of the animals required for hippocampal function. It has been shown that lesions of the MEC perturb the dynamics of place cell firing in CA1, suggesting that this input is important for the formation of a hippocampal spatial map [80, 81]. Inputs to grid cells originate partly from neurons called "head direction cells" located in the anterior thalamus and presubiculum [82–84]. As their name indicates, head direction cells code for the orientation of the animal's head and thus provide a major cue regarding position in space.

The DG, CA3, CA1, and SUB all contain neurons called "place cells." Place cells code for the spatial location of the animal by increasing their firing rate in a specific region of an environment [85–88]. The precision of spatial coding by a place cell depends on how selective the increase in firing rate is for a given location. One of the most studied roles of theta rhythm in the hippocampus is that of organizing the timing of place cells. Theta oscillations are believed to underlie the temporal coding of spatial representation through a mechanism called "phase precession" [89]. Phase precession refers to the progressive change in the relationship between place cell spikes and theta phase as the animal moves through the cells' place field. As the animal advances through the place field, the firing rate of the cell coding for this spatial location increases, reaching a maximum at the center of the place field. Simultaneously, the spikes occur on progressively earlier phase of theta oscillations as the place field is traversed [89, 90]. This progressive sliding in phase locking thus also codes for the position of animals in space, and has even been shown to predict the position in space more accurately than the firing rate of the place cell [91, 92]. The mechanisms underlying phase precession are still unclear, but may rely in part by MEC excitatory input [81, 93]. (See Burgess and O'Keefe [94] and Maurer and McNaughton [95] for reviews). Phase precession in the hippocampus is believed to allow the binding of place cell sequences, representing a trajectory of the animal in space (see the section "Theta Rhythm as a Cell-Assembly Binding Mechanism"). Although extensively characterized in the hippocampus, theta-phase precession has also been reported in SUB principal cells [96], some MEC grid cells [97–99], and interestingly in other brain structures outside the hippocampal formation such as the medial prefrontal cortex [100] and the ventral striatum [101].

Theta Rhythm Generation in the Hippocampus

Understanding the mechanisms of theta rhythm generation and modulation is a key step in understanding how this rhythmic oscillation participates in hippocampal function. Theta rhythm has been recorded throughout the entire hippocampal formation, in vivo and in vitro [102–105]. In all subregions of the hippocampal formation, neuronal activity can be found phase-locked to theta rhythm. Phase-locked cellular activity has indeed been described in the DG [32, 106, 107], CA3 [108, 109], CA1 [106, 107, 110], the SUB [88], parasubiculum [111], and the MEC [102, 112–114]. It thus appears that each hippocampal subregion can generate theta oscillatory activity locally [115]. Distinct groups of neurons therefore need to be coordinated over large distance so that the timing of theta oscillation can be coherent from region to region. The main proposed hypothesis that has dominated in the last few decades is the idea of one central theta pacemaker consisting of the medial septum and diagonal band of Broca complex (MS/DBB or MS), located in the basal forebrain.

The MS Pacemaker Hypothesis

The MS sends direct projections to the hippocampus via three major cell types: cholinergic, GABAergic, and glutamatergic. The glutamatergic septo-hippocampal projection has been described only recently, and relatively little is known about their physiology. (See Colom [116], Fuhrmann et al. [117], Huh et al. [118], and Sotty et al. [119] for a possible role of the glutamatergic MS neuron in theta). Investigation of the contribution of MS neurons to theta rhythm generation and modulation has therefore primarily focused on cholinergic and GABAergic MS projections.

The hypothesis placing the MS as a pacemaker of hippocampal theta rhythm is supported by two main lines of evidence. On the one hand, numerous studies have shown that lesion of the MS results in an almost complete loss of theta rhythm in the hippocampus [25, 120, 121]. On the other hand, a portion of MS neurons show in vivo rhythmic bursting, phase-locked to theta rhythm in the hippocampus [122–125]. Importantly, rhythmically bursting MS neurons display these properties even when the MS is disconnected from most of its afferents in vivo, indicating that this bursting behavior is generated within the medial septum [126]. MS theta-locked bursting neurons have been shown to be principally GABAergic, which places them as leading candidates for the generation of theta rhythm in the hippocampus [122, 124]. In the same line of evidence, GABAergic MS possess the intrinsic capacity to oscillate. In vitro, some MS GABAergic neurons display phasic activity at theta frequency in slices [127], and express hyperpolarization-activated cyclic nucleotide-gated nonselective cation channels (HCN), which have been associated with intrinsic oscillatory properties [128]. MS GABAergic neurons are thus foreseen as the main actors of the MS pacemaker hypothesis. MS GABAergic cells have been proposed to serve this function by directly imposing theta rhythm on hippocampal networks through rhythmic inhibition onto GABAergic interneurons in the hippocampus [129–131].

The role of cholinergic septo-hippocampal neurons has also been investigated; however they do not seem involved in the generation of hippocampal theta rhythm. Cholinergic septal cells have low in vivo firing rates, far from theta frequencies, thus unlikely contributing to the precise timing of hippocampal neurons for theta rhythm generation [124]. Besides, specific lesion of the cholinergic population within the septum does not eliminate theta rhythm, despite an effect on power [130, 132, 133]. Lastly, acetylcholine levels measured in the hippocampus undergo fluctuations at longer time courses than theta rhythm frequency, since acetylcholine levels have been shown to steadily increase during theta episodes [134]. Cholinergic septo-hippocampal projections thus appear to have a modulatory influence rather than a role in pacing hippocampal networks to generate theta rhythm.

Despite strong lines of evidence pointing toward an important role of MS GABAergic neurons in hippocampal theta generation, some experimental observations are in contradiction with this hypothesis. First, theta oscillations recorded at different levels of the hippocampus are not synchronous, although high synchrony would be expected in the case of a single central theta generator [109, 135–138].

When simultaneous recordings of CA3, CA1, and/or MEC subregions are analyzed, theta oscillations can show large phase shifts, i.e., large time lags between the peaks of theta oscillations in each subregion [105, 139, 140]. Such phase shifts are also observed within each subregion [135, 137], further suggesting that a single theta pacemaker is probably not responsible for generating the entirety of hippocampal rhythms. Second, data from MS lesion experiments also question the role of the MS in pacing hippocampal theta. Several reports indeed show that following MS lesion, the power of theta oscillation is greatly reduced, yet the frequency of the remaining activity remains unchanged [141, 142]. Besides, following MS lesions some neurons from the hippocampus and MEC still exhibit theta periodic firing, in the absence of any apparent rhythmic septal inputs [76, 77, 143]. Again, these results underline the potentially important role of local hippocampal networks in the generation of theta rhythm. Therefore, the exact contribution of MS in pacing theta oscillations in the hippocampus remains unclear.

There is no doubt that MS projection neurons play an important role in hippocampal theta; however clear evidence also points toward a contribution from hippocampal self-generated theta rhythm. Rather than a simple pacemaker role of MS cells (notably GABAergic), these neurons may rather provide a synchronizing input to organize the local oscillators and cell assemblies generating theta rhythm [144]. This synchronizing role still needs to be tested experimentally; however recent data has provided the demonstration that hippocampal networks have the capacity of self-generating theta rhythm in vitro [144], further supporting the idea that local hippocampal circuit wiring is crucial in rhythm generation.

Intra-hippocampal Theta Generation

The idea that theta rhythm can be generated locally in the hippocampal network arises from different lines of evidence. The local circuitry in hippocampus slices retains the ability to produce rhythmic network activity when provided with moderate levels of receptor agonists producing tonic excitation [145–149]. In addition, multiple modeling studies have demonstrated that a network limited to a minimal number of the cells types found in CA3 or CA1 is capable of generating theta rhythm [150, 151]. Most importantly, recent evidence has shown that an in vitro preparation consisting of the intact hippocampus disconnected from the MS, thus preserving all intrinsic connections, generates spontaneous theta rhythm in the absence of any pharmacological or electrical stimulation [60, 70, 144, 152, 153]. These studies have shown that the hippocampus contains multiple oscillators located on the longitudinal axis in the SUB and CA3, capable of oscillating independently. Hippocampal networks thus have the ability to generate theta oscillation in the absence of any input, including the MS. Interestingly, the depth profile of theta rhythm recorded in the isolated hippocampus in vitro corresponds to one of the sink-source dipole described in vivo [71]. Indeed, two sink-source pairs exists in the CA1 region in vivo; one is formed by excitatory inputs from CA3 at the level of str

radiatum and inhibitory inputs at str pyramidale, while the second one is located at the level of the distal dendritic region and arises from excitatory inputs from the entorhinal cortex in str lacunosum-moleculare [39, 71]. Accordingly, only a single sink-source dipole exists in the isolated hippocampus preparation [144, 152] while the second dipole arising from entorhinal cortex inputs is absent [39, 71].

Many mechanisms have been described which participate in the generation of theta rhythm in the hippocampus. At the cellular level, single neurons display subthreshold intrinsic resonance. Resonance allows a given cell to respond optimally (i.e., maximally) to an input at a given frequency [154, 155]. Neurons with resonant properties can also transform a nonrhythmic input into membrane oscillations enriched in their resonant frequency [156]. Most importantly, the effect of subthreshold membrane resonance can be communicated to the rest of the network through the spike output of the cell [157]. Many cell types within the hippocampal formation have been shown to display resonant properties at theta frequency including in CA3 [158], CA1 [159], SUB [160], and EC [156]. Although likely contributing to the generation of network rhythms, resonance alone is not sufficient to explain theta oscillations in the hippocampus. Mechanisms promoting synchronous activity between large groups of neurons are needed to coordinate the firing of these cells and create a coherent oscillator. The favored candidates to assume this function are GABAergic interneurons. Over 20 subtypes of interneurons have been described in the hippocampus [161]. Many of them have been recorded in vitro and in vivo in anesthetized or behaving rodents to assess their contribution to theta rhythm. In theory, almost every interneuron subtype could be important in theta generation, as they make complex patterns of connections among themselves and with pyramidal cells [162], and virtually all discharge phase-locked to hippocampal theta oscillations [161]. However, two interneuron populations have received particular interest as key candidates in hippocampal theta generation. First, O-LM interneurons expressing the neuropeptide somatostatin have been suggested as critical components of hippocampal theta generation [148, 150]. The name O-LM comes from their particular morphology with their soma located in stratum oriens (O) and dense axonal arborization in stratum lacunosum-moleculare (LM), contacting the most distal dendrites of CA1 pyramidal cells [163]. O-LM interneurons also have dendritic arborizations spreading over the longitudinal axis, which has been foreseen as an important feature for theta rhythm generation in the hippocampus [148, 164]. Additionally, O-LM interneurons show subthreshold theta resonance [159] and have been shown to fire more reliably in response to inputs at theta frequency [165]. Altogether, O-LM interneurons are believed to be important components of hippocampal theta rhythm generation (but see Kispsersky et al. [166]). The second type of interneurons believed to play an important role in theta generation in the hippocampus is basket interneurons, expressing the calcium-binding protein parvalbumin (PV). PV-positive basket cells densely target CA1 pyramidal cells at the level of the soma, enabling a strong control of pyramidal cell firing [167] and synchronizing them at theta frequency [168]. It has also been shown that silencing even a small number of PV basket cells alters the phase of pyramidal cell firing relative to theta oscillation in the hippocampus [169]. The activity of PV basket cells in vivo is

tightly phase-locked to hippocampal theta and gamma oscillations [170, 171]. And it is now well established that PV interneurons have a causal role in cortical gamma oscillation generation in vivo [172, 173]. Several studies also suggest that PV interneurons are important in the generation of theta oscillations in hippocampus [167, 169, 174–176]. Yet it was only recently, by combining the isolated hippocampus preparation with optogenetics, that a causal relationship between PV interneuron network activity and theta rhythm generation was demonstrated [152]. Indeed, rhythmic activation of PV interneuron network robustly drives intrinsic theta rhythm with a preference for 8 Hz, the frequency of in vivo theta rhythm, and strongly synchronizes PC firing. Notably, silencing the PV network disrupts theta oscillations and decreases the phase-locking of PC [152]. Surprisingly, optogenetic activation or silencing of somatostatin-positive interneurons had a negligible effect on intrinsic theta rhythm, confirming previous studies questioning their long foreseen role in theta rhythm generation [166]. Yet several studies have now demonstrated that somatostatin-expressing O-LM interneurons can powerfully modulate entorhinal cortex inputs onto PCs [152, 177, 178]. PV interneurons are thus instrumental in theta generation within the hippocampus network. Moreover, they are ideally positioned as a relay between septal inputs and the hippocampal network. Indeed, GABAergic projection cells from the septum preferentially targets fast spiking, putative PV basket interneurons [129], and it has been hypothesized that large-scale inhibition of these interneurons could be the mechanism by which GABAergic septal cells exert their control on hippocampal theta rhythm [179]. Altogether, it now appears clearly that theta rhythm generation in the hippocampus is the result of the interaction between intrinsic theta oscillators and multiple external theta oscillators such as the MS or the MEC.

Theta Rhythm as a Cell Assembly Binding Mechanism

Cell Assembly Binding Within the Hippocampus

Within hippocampal network, theta allows the linkage or formation of local neuronal ensembles. This effect is believed to be mediated at least partially by the interaction between theta and gamma oscillations within the hippocampus. Gamma rhythm can be recorded nested within theta cycles, and both the phase at which gamma oscillation are present and the amplitude of gamma cycles can be modulated [180]. Two distinct gamma frequency rhythms have been shown to arise from the MEC and the CA3 [22, 181–183]. The MEC communicates with CA1 neurons preferentially through fast gamma rhythm (around 80–100 Hz) while the CA3 region preferentially uses slow gamma rhythm (around 20–50 Hz) [22, 182]. Frequency-specific communication thus arises between different subregions of the hippocampal formation in the gamma range. Interestingly, these two modes of gamma communication are segregated in time since they are coupled to different phases of theta rhythm

[182]. This phase segregation mechanism thus allows CA3–CA1 or MEC–CA1 communication to remain independent from one another within CA1 networks. As gamma rhythms have been shown to coordinate spike timing and facilitate plasticity [184], MEC and CA3 inputs each have a specific window within hippocampal theta oscillation where synaptic plasticity is favored. This segregation of subregional communication within the hippocampus has been linked with cognitive performances. Gamma synchronization in the CA1–CA3 pathway has indeed been shown to correlate with learning and decision-making in working memory tasks [184, 185]. Theta can thus serve as a synchronizing mechanism to bind locally generated gamma rhythms between different subregions of the hippocampal formation.

Theta rhythm, along with gamma oscillation, also serves as a temporal metric to organize the timing of neurons within the local hippocampal network. As discussed above in the section "Hippocampus Cell Properties in Relation to Theta Rhythm," both grid cells in the MEC and place cells in DG, CA3, CA1, and SUB fire in relation to theta rhythm. Phase precession by place cells codes for the animal's location in space, through the progressively earlier firing of a cell relative to the ongoing theta cycles. Simultaneous recording of many place cells during voluntary movement has allowed a finer understanding of how place cells could underlie spatial navigation and cognition. Several studies have now demonstrated that single theta cycles can contain a compressed spatial representation of the immediate environment of an animal (for example, see Dragoi and Buzsaki [186], Foster and Wilson [187], and Skaggs et al. [188]). This compressed spatial representation consists of sequential firing of consecutive place cells within one theta cycle, spiking in sequential order as the animal advances through the portion of environment coded by these cells. As consecutive place fields overlap, and each place cell undergoes phase precession, each theta cycle can contain a "chunk" of compressed spatial information. Thus, within one theta cycle, the current position of the animal is represented by the most active place cell, as well as locations just behind on the earlier phases, and just ahead on the later phases [186–190]. This information compression represents current location but can also be used to "look ahead" or "look behind" in space, especially at a choice point requiring a decision to turn in the right direction [189, 190]. When the animal pauses at a choice point, a behavior named "vicarious trial and error" can be observed, which consists of alternating head movement toward possible directions to take in order to obtain a reward. During this pause, the spatial representation carried by compressed place sequences within theta cycles can become transiently nonlocal, alternatively representing the future paths rather than the actual location. This predictive aspect of place cell phase precession in relation to theta rhythm has been called "forward sweeps" and was described in both CA3 and CA1 [191–193]. Interestingly, CA1 place sequences can also transiently represent a replay of recent position ("look behind" sweeps) that has been suggested to reflect the encoding of immediate experience [191]. Theta rhythm thus supports the representation of current location and the prediction of future locations ahead of an animal's choice, in order to guide navigation and reward-directed behavior.

Cell Assembly Binding Across Brain Regions

At a larger brain scale, theta rhythm is believed to serve as a cell-assembly synchronizing metric between the hippocampus and distant regions, thus acting as an important mediator of long-range communication in the brain [189]. Within an oscillating network, cell assemblies go through periods of high and low excitability. Cell assemblies from distant regions are assumed to communicate optimally when oscillations are synchronous, i.e., when the periods of high and low excitability happen simultaneously [194]. Thus, through dynamic synchronization of distant networks, cell assemblies can be brought together in a flexible and behavioral state-dependent manner, which would be difficult to achieve through hard-wired networks [194]. Long-range communication via theta oscillations can be studied by measuring the degree of synchrony (or coherence) in the theta frequency range during a given behavioral task. Moreover, if cell assemblies from distant regions are synchronized through hippocampal theta rhythm, neuronal activity is predicted to occur phase-locked to hippocampal theta. It is interesting to note that several studies report examples of both high and low theta-coherence within the hippocampus itself (for example, see Royer et al. [69], Patel et al. [138], Adhikari et al. [195], Bienvenu et al. [196], Gourevitch et al. [197], Jacinto et al. [198], and Schmidt et al. [199]). Yet, a systematic measurement of variations in theta coherence along the septo-temporal axis as a function of behavioral state is lacking, and would most certainly help gain insight into the dynamics of theta oscillations and their role in cognition and behavior.

A well-studied example of the role of theta rhythm in synchronizing brain region activity is the interactions between the prefrontal cortex (PFC) and the hippocampus [200, 201]. The synchronization between the hippocampus and PFC has been studied in the context of various behaviors requiring coordinated activity in these two brain regions. The PFC, especially the medial part, has been shown to have a key role in several cognitive functions, such as some forms of memory, decision-making, and attention (see Euston et al. [202] and Miller and Cohen [203] for reviews). The PFC and hippocampus are anatomically connected, with the ventral hippocampus (CA1 and SUB regions) sending direct projections to the PFC [204, 205]. Accordingly, hippocampal excitatory inputs can activate PFC principal cells, and these synapses have been shown to undergo long-term potentiation [206–209]. Neuronal activity and network oscillations in the PFC have been shown to synchronize to hippocampal theta rhythm in freely behaving rats, during various natural behaviors such as, for example, exploration of an environment, rearing, foraging, or REM sleep [210–213]. The timing of PFC unit phase-locking in relation to hippocampal theta suggests a hippocampus-to-PFC directionality, consistent with the described anatomy [211]. Interestingly, parvalbumin-positive basket interneurons in the PFC have also been shown to strongly phase-lock to hippocampal theta [214]. PFC parvalbumin-positive basket cells are known to exert a powerful control on principal cell activity and network oscillations [152, 167, 172, 173], suggesting that feed-forward inhibition could be one of the cellular mechanisms underlying PFC network entrainment by hippocampal theta.

Several studies have further refined these results by examining the dynamics of PFC-hippocampus theta-synchrony during learning and memory behavioral tasks. The PFC is known to play a key role in working memory, which allows temporary storage of information necessary to accomplish a cognitive task over short periods of time (seconds or minutes). Spatial working memory performances can be measured in rodents in mazes designed to discriminate between "forced" epochs where only one trajectory through the maze is available, versus choice epochs where the animal has to remember immediately previous trajectory to choose the rewarded direction [99, 215, 216]. At the decision point, where the animal must remember the previous trajectory, coherence between PFC and hippocampus network oscillations is increased in the theta-range. Importantly, this increase is greater during correct trials, where the right arm is chosen, compared to error trials or forced turns. In the same spatial working memory tasks, the degree of PFC unit phase-locking to theta rhythm in the hippocampus is also increased at the decision point [99, 215, 216]. Another study used a delayed nonmatching to sample task, commonly used to assess nonspatial working memory performances in rodents, and found similar results with a higher proportion of PFC neurons firing phase-locked to theta rhythm in the hippocampus during correct versus incorrect trials [217]. These results show that synchronization of both PFC units and network activity to hippocampal theta rhythm is correlated with behavioral and cognitive performance, and suggests that coupling of PFC and hippocampus activity through theta oscillations is necessary for information transfer during working memory [99, 215–217]. Benchenane and colleagues examined the time course of synchronization between the PFC and the hippocampus in a Y-maze where rats were tested in an attentional set-shifting task [218]. Coherence between PFC and hippocampus in the theta-range was increased at the decision point and, interestingly, this increase in coherence was greater when the new rule had been successfully learned. Moreover, the number of PFC neurons firing in synchrony to a specific phase of hippocampal theta rhythm increased as well, showing that the mechanisms by which behavioral rules are learned and memorized rely on neuronal and network synchronization through theta rhythm.

The PFC and hippocampus (notably the ventral portion) are also both known to play an important role in anxiety and fear behavior [219–224]. The dynamics of PFC-hippocampus synchronization have been assessed during innate anxiety using classical tests such as the open-field or the elevated-plus-maze [195]. In both anxiogenic environments the coherence of PFC-hippocampal field activities were increased specifically in the theta-range. Besides, analysis of the phase-locking relationship of PFC units to hippocampal theta revealed strong phase-locking to hippocampal theta and suggested a hippocampus-to-PFC directionality. Interestingly, a more detailed analysis of PFC unit firing revealed that a significant portion of neurons fire in a task-related manner, i.e., clearly discriminate open arms or closed arms in an elevated-plus-maze [195]. Moreover, these task-related units are more strongly phase-locked to theta in the hippocampus in comparison to non-task-related units. In addition, an elegant study by Ciocchi and collaborators investigated long-distance targets of CA1 ventral hippocampus principal cells in relation to firing patterns of these cells [225]. Using optogenetic antidromic activation of hippocampal cells, they found that a subset of CA1 principal neurons responds specifically to anxiogenic environments, and that this cell

population preferentially targets the PFC. Sub-circuits within hippocampal principal cells thus convey anxiety-related information selectively to the PFC network. Theta rhythm has also been shown to synchronize PFC units and field potentials to hippocampus theta during conditioned fear [226, 227]. In these studies, authors found that theta rhythm synchrony between the hippocampus and PFC increases during the recall of a conditioned fear-memory, when the mice were re-exposed to the stimuli previously paired to a foot shock. Interestingly, as this fear-memory extinguishes, as shown by the decreased freezing in response to the conditioned stimuli, theta-range hippocampus-PFC synchrony also decreases.

PFC and hippocampus co-operate during various behaviors, in order to ensure adapted behavioral responses, memorization, and decision-making. The vector of such communication seems to be synchrony of single neuronal activity and field potentials in the theta-range frequency. Hippocampal theta rhythm also influences local PFC gamma oscillations which reflect the engagement of local circuits, usually spatially organized within cortical columns [91, 212]. Locally generated gamma oscillations in the PFC have indeed been shown to be phase modulated by hippocampal theta rhythm during natural behaviors such as REM sleep and exploration [212]. Hippocampal theta rhythm thus appears as an important long-range communication substrate with the PFC, modulating single cell, local cell assembly gamma oscillations, and PFC theta rhythm in a behavioral state-dependent manner.

Theta rhythm in the hippocampus has also been shown to synchronize cellular and field activity with several other brain regions that receive direct hippocampal projections. The amygdala, a region crucial to fear behavior, displays theta rhythm coherent to hippocampal theta after fear-conditioning [228] and during fear-memory retrieval [229]. Interestingly, the degree of amygdala-hippocampus theta coherence increase during REM sleep after conditioning predicts fear-memory performances [228]. More recent evidence suggests that specific subtypes of amygdalar interneurons show hippocampal theta-modulated firing in response to noxious stimuli [196]. Therefore, similarly to the PFC-hippocampus system, transfer of information in a behaviorally relevant manner seems to rely on theta synchrony between the amygdala and hippocampus. In addition to PFC and amygdala, another well-studied area, the striatum, is involved in various cognitive functions such as procedural and spatial learning or reward-processing, and receives dense projections from the hippocampus CA1 and SUB regions [230]. Cellular activity and theta oscillations coherent with hippocampal theta can be recorded in the striatum through various behaviors, including spontaneous exploration of an environment [231], reward seeking [232–234], procedural learning [235], or decision-making [236]. Interestingly, some ventral striatal neurons fire in a “ramp” pattern, i.e., progressively increase their firing rate as they approach an expected reward. Such ramping neurons show phase-precession relative to hippocampal theta, a mechanism suggested to link spatial and reward representations through theta rhythm [101]. In addition, in a maze-task involving choice points for reward seeking, striatal neurons coding for reward can be activated during hippocampal “forward sweeps” mentioned earlier [237], again suggesting that space and reward representations generated by hippocampal and striatal activities are linked through theta rhythm [17, 238].

Lastly, some other examples of theta-frequency coupling between the hippocampus and other brain regions during behavior are worth mentioning, such as the lateral habenula [239], ventral tegmental area [240], cerebellum [241], cingulate cortex [242], or olfactory bulb [18]. Interestingly, for some of these examples there is no direct monosynaptic connection between the hippocampus and other structure, suggesting that information transfer through increased theta coherence is a mechanism that can be generalized to the entire brain and does not exclusively depend on hippocampal inputs. Most studies cited above recorded theta rhythm coupling between two regions; yet an increasing number of studies are now extending such simultaneous recordings to multiple brain areas, including or not the hippocampus [228, 240, 243, 244].

Conclusion

Theta rhythm in the hippocampus arises from complex interactions between intrinsic hippocampal theta oscillators and external inputs from other brain regions such as the MS and MEC. Theta emerges as a function of the behavioral state of an animal, and multiple lines of evidence show a role for this oscillation in cognitive functions linked to the hippocampus. The most recently described and fascinating role of hippocampal theta is to serve as a temporal metric, a timeframe, so that distant cell assemblies or networks can synchronize and communicate efficiently. In that perspective, coupling through theta rhythm is likely to underlie most, if not all, cognitive functions of the brain. Altogether, theta coupling appears as a widespread long-range communication mechanism, allowing information transfer across multiple brain regions and behavioral states.

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Chapter 3
Oscillations and Synchrony in Attention

Christian Keitel, Gregor Thut, and Joachim Gross

Introduction

At any given moment our mind focusses on a small number of tasks, thoughts, or sensory impressions. This does not seem to be a deliberate choice; it rather reflects fundamental limits in the ability of a healthy brain circuitry to process all available information in parallel. Fortunately, a number of mechanisms guide the efficient allocation of limited processing resources to behaviourally relevant tasks and sensory input. These mechanisms can be subsumed under the term "attention". In this chapter we introduce the most prominent mechanisms of attention and discuss recent findings about how these relate to oscillatory brain activity.

Mechanisms of Attention

In the 1800s researchers observed that human conscious perception has a limited capacity; participants of an early psychophysical experiment were incapable of reporting a full array of objects briefly flashed to them. However, they could improve performance, i.e. consistently report a subset of the array, when they deliberately

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focussed on specific positions in anticipation of the upcoming array [1]. Similar results were later obtained in experiments using auditory stimuli: focussing on a particular voice among others improved performance in reporting spoken words or elements of a narrative [2].

The above-described experiments established that attention can be allocated *voluntarily* to a portion of space (e.g. parts of a letter array) or a stimulus feature (e.g. voice pitch) of the collective sensory input to facilitate task performance when trying to achieve a specific goal. Nevertheless, high-contrast sensory events such as a loud bang or a bright flash of light will attract attention automatically. In fact, even hearing your name in a background conversation at the proverbial cocktail party can have a strong *stimulus-driven* pull effect on your focus of attention. Both ways to (re)allocate attention have led to the influential "top-down" (goal-directed) vs. "bottom-up" (stimulus-driven) dichotomy in attention research [3–5]. As we will see in the following sections, this distinction continues to inspire research into oscillatory correlates of attention.

In sum, early experimental findings have led to the conceptualization of attention as a selective filter mechanism (or a set of hierarchical filters) that can be adjusted dynamically to meet the demands of current behavioural tasks or allow facilitated responses to rapidly changing situational circumstances. The filter concept thus already implements three characteristic properties that have become subjects of intense research into underlying neur(on)al correlates:

1. The internal representation of an attended stimulus experiences a selective gain as compared with concurrent unattended sensory input.
2. Stimuli outside the focus of attention do not receive in-depth processing—they are effectively filtered out. Note that while this effect can be seen as a consequence of a selective gain mechanism, current research supports the notion of an active suppression of irrelevant input (see the section "Oscillations and Suppression of Irrelevant Information" later in this chapter).
3. Conceiving of the focus of attention as a dynamic mechanism implies that it can move through position and feature spaces to allow for flexible selection (and filtering-out).

In the following sections of this chapter, we review models of how these properties can be formulated in terms of rhythmic brain activity in characteristic frequency bands. Beforehand, we briefly recapitulate prominent models of attention to point out where these fall short and may benefit from integrating concepts learned from the study of brain oscillations.

Models of Attention

Psychological models of attention have evolved during the second half of the last century mostly based on results of behavioural studies. A number of metaphors have been coined in the process to illustrate the selective filter aspect of attention. Whereas a

"bottleneck" was used to describe selective listening [6, 7], visual—more specifically visuo-spatial—attention has been famously likened to a "spotlight" [8] or "zoom lens" [9]. Especially in the visual modality, more complex models have been developed that sought to describe and, ultimately, to predict the characteristic properties of the attentional spotlight. Efforts culminated in the Feature Integration Theory [10], Guided search models [11], and the Theory of Visual Attention [12], among others.

These models were mainly based on abstract psychological constructs such as the spotlight and schematic internal representations of external physical stimulus situations, so-called "feature maps", devoid of any specific neurophysiological substrate. They were nevertheless successful in predicting behavioural performance in visual search tasks. At the same time, advances in neurophysiological techniques increasingly allowed the investigation of the neural substrates of attention. Early electrophysiological experiments found that the neural activity associated with stimulus processing increased when a stimulus was attended. This led to the notion of attention as a response gain ("sensory gain") mechanism [13].

Soon after, recordings of single neuron firing patterns allowed groundbreaking insights into the influence of attention on neuronal stimulus processing. Based on their studies, Moran and Desimone [14] put forward the influential Biased Competition model of attention. When they placed two stimuli in the receptive field (RF) of a neuron that represented an unattended location, its response (spike rate) was a weighted average of the responses to the singly presented stimuli. A stimulus that usually elicited a strong response ("preferred" stimulus) and one that usually elicited a weak response ("poor" stimulus) placed within the same RF gave an intermediate response. Crucially, allocating attention to one of the two stimuli shifted the neuronal response towards the response given when the attended stimulus was presented alone.

These results led them to hypothesize that multiple simultaneously presented stimuli enter a competition for neuronal representation, thereby suppressing each other's processing. They further proposed that attention biases the competition by releasing a selected stimulus from mutual suppression [15]. To date, numerous single-cell studies have supported this assumption [16, 17]. Neuroimaging studies have revealed Biased Competition-like mechanisms in large-scale population responses in the human brain [18–20], although more recent findings question whether these act on all stages of the visual processing hierarchy [21, 22].

Notably, Biased Competition posits a contrast gain rather than a response gain mechanism to enhance the processing of an attended stimulus. The stimulus profits maximally from the attentional bias when it competes with concurrent equally salient stimulation. The bias has little effect when the stimulus is highly salient itself (ceiling effect) or presented among more salient stimuli (floor effect).

Recent progress in single-cell research led to the development of powerful computational models of attention that supersede the original Biased Competition idea in many aspects. To date, so-called normalization-type models represent the state of the art [23]. The term "normalization" refers to the fact that this class of models includes a computational stage at which response magnitudes of individual neurons are divided by the population level activity. The Normalization Model of Attention

by Reynolds and Heeger [23] has especially raised interest because it implements entities that seem closely related to constructs used in psychological theories of attention, but are directly derived from properties of single neuron and population level activity (Fig. 3.1). The Attention Field, for example, resembles aspects of both, the spatial "spotlight" and the "feature maps". One important contribution of this model is that it unifies seemingly contradictory response gain and contrast gain effects of attention on the fly by predicting a simple relationship between the (flexible) size of the attentional focus and the stimulus size.

In conclusion, there is an abundance of theories and models that describe influences of attention on perception and behavioural performance. While some are based on abstract psychological constructs, others are derived from studying single-cell or population-level activity. Importantly, models increasingly converge—psychological constructs can be expressed in terms of neuronal interactions as in the Normalization Model of Attention. Nevertheless, most models can be considered incomplete with regard to two important aspects. First, attending to a stimulus requires the orchestrated activity of widely separated neuronal populations in different brain areas. Current models instead disregard or simplify the underlying

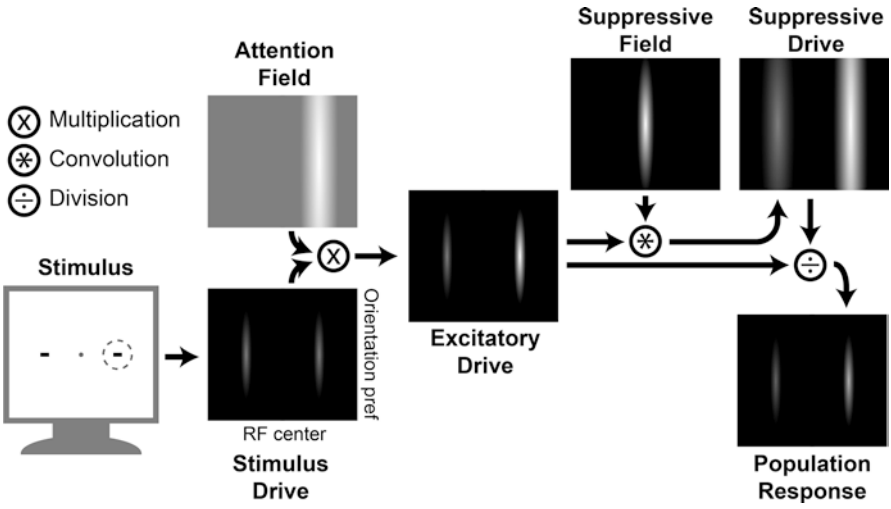

Fig. 3.1 Schematic representation of the Normalization Model of Attention. From left to right: The presentation of the stimulus display leads to the activation of neuronal populations that prefer the orientation of the black bar stimuli and whose receptive fields (RF) encode their locations. This Stimulus Drive can be represented as a two-dimensional position space by feature space maps. Attending to one position is equivalent to multiplying the Stimulus Drive with an Attention Field, which leads to a relative gain effect depicted as the Excitatory Drive. In a second stage the excitatory drive is effectively normalized through a division with the Suppressive Drive (a convolution of the Excitatory Drive and a Suppressive Field that represents lateral inhibition between neurons) to yield the final biased Population Response. (Used with permission from Montijn JS, Klink PC, van Wezel RJ. Divisive normalization and neuronal oscillations in a single hierarchical framework of selective visual attention. Front Neural Circuits. 2012;6:22. Modified after Reynolds JH, Heeger DJ. The normalization model of attention. Neuron. 2009;61(2):168–85)

brain circuitry and anatomical connections between them. Second, we rarely attend to a particular stimulus over an extended period of time. The allocation of attention is a highly dynamic process. Imagine, for example, a typical traffic situation during rush hour. These dynamics require transient and on-demand connections between remote neuronal populations. Models of attention are based on the assumption that these *functional* connections exist, but currently lack further specifications of how they are established.

Attention and Brain Rhythms

Long-range functional connectivity requires anatomical connections such as fibre tracts that link distant areas of the brain. Several anatomically defined networks have been identified whose nodes contribute to various aspects of attention and its influence on perception [24]. Among them, a dorsal fronto-parietal network encompassing the intra-parietal sulcus (IPS), in posterior parietal cortex, a portion of the precentral supplemental motor area, the so-called frontal eye fields (FEF), and early sensory areas, such as visual cortex, comprises the most comprehensively investigated cortical network implicated in the control of attention (Fig. 3.2) [25].

The last couple of years have seen an increasing number of studies reporting that the nodes of the fronto-parietal "attention network" communicate by means of brain rhythms in characteristic frequency bands [26–28]. Crucially, the idea is that these

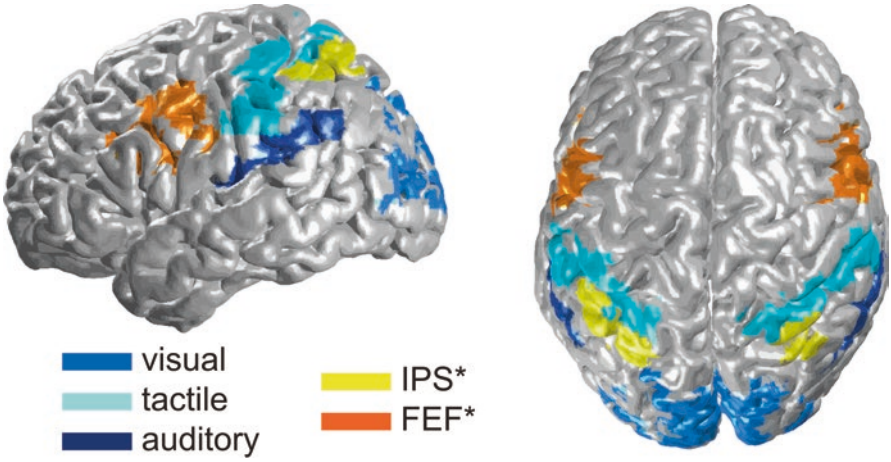

Fig. 3.2 Schematic cortical surface. Areas coloured in shades of blue correspond to the sensory cortices. Yellow and orange areas denote locations of nodes of the fronto-parietal attention network. Asterisks (∗) in the legend signify that the indicated areas are not identical to the nodes, but likely contain them. The yellow areas cover parts of the posterior parietal lobes that enclose the intra-parietal sulcus (IPS) bilaterally. The orange areas give approximate locations of the frontal eye fields (FEF) that can be found in precentral supplemental motor areas

rhythms establish functional connections that convey modulatory influences of attention [29]. Above-described shortcomings of current models of attention can thus be addressed by considering the intrinsic rhythms of the human brain as a key player in intra- and inter-areal brain communication.

In the following, we will relate the selective gain aspect of attention to the selective routing of information between neuronal populations that synchronize their activity locally, within cortical regions, or globally, across cortices, through slower delta (1–4 Hz), theta (4–8 Hz) and alpha rhythms (8–13 Hz), as well as faster beta (15–30 Hz) and gamma rhythms (>30 Hz). The alpha rhythm and its relationship with the second aspect of attention, the filtering-out or suppression of irrelevant, possibly distracting, sensory input will be discussed in more detail in a later section. Furthermore, we will outline that (low-frequency) oscillatory phase may play its part in understanding how the dynamics of attentional gain and suppression unfold in time. Ultimately, we review attempts to integrate these aspects into a coherent oscillatory framework of attention and introduce an approach that links brain oscillations and the normalization model of attention. Neural mechanisms of attention have also been investigated by means of stimulus-driven brain oscillations [30]. The nature of stimulus-driven brain oscillations and their relationship to intrinsic rhythms is currently under debate [31]. An extensive review of findings on (visual) attention by means of frequency-tagging can be found in [32].

Oscillations and Selection of Relevant Information

This section reviews two hypothetical accounts, communication-through-coherence [33] and the phase reset of low-frequency oscillations [34] that model how selective attention influences stimulus processing via brain oscillations.

Communication Through Coherence (CTC)

The CTC framework starts with the observation that any neuronal assembly can synchronize otherwise random firing patterns of individual neurons when activated by a common input [35, 36]. Such *coherent* behaviour of neurons in sensory cortices is regarded as the signature of neural stimulus representation in the animal model [37, 38] and, more recently, in human electrophysiology [39, 40]. More importantly, rhythmic activity of a neuronal assembly entails both periods of high excitability to external input coupled with peaks in spiking activity, as well as periods of low excitability during which neurons cease firing [41, 42]. It is this periodicity in excitability that allows for selective communication with other groups of neurons.

CTC posits that two groups of neurons establish a communication link by synchronizing their rhythmic bursting behaviour and, thus, their excitability cycles [33, 43, 44]. Conversely, communication ceases when two groups desynchronize. A sending and a receiving neuronal assembly that seek to transmit information between

them will do so during their joint phases of maximum spiking activity that coincide with excitability peaks. This coherent, strictly periodic opening and closing of communication "channels" subserves a number of purposes: (1) It ensures that the receiving group of neurons picks up spike bursts emitted by the sending group during its periods of highest excitability while capitalizing on the fact that neurons are particularly sensitive to synchronous input. This maximizes information transfer [45] and renders CTC effective. (2) Communication can be maintained over at least a number of coherent cycles because the sender can easily predict the upcoming excitability peaks of the receiver due to the inherent temporal regularity. This establishes the stability of CTC. (3) A given group of neurons can temporarily synchronize and desynchronize with different other groups of neurons to form transient coherent networks for specific processing tasks. CTC thus allows a selective and dynamic arrangement of functional connections within a network of anatomical links.

CTC does not strictly limit the bandwidth of the frequencies at which groups of neurons communicate with other populations. Frequencies rather depend on the time it takes to transmit signals between sender and receiver [33]. Specific lags are thus mostly determined by synaptic delays and axonal conduction speed [46, 47]. For relatively short anatomical connections, as within brain areas, signals travel quickly and allow for information transmission within one cycle of gamma oscillations (>30 Hz). For long-range inter-area connections, signal conduction times increase. Groups of distant neurons thus typically synchronize at lower, beta-band frequencies [48–50]. The role of gamma and beta rhythms in cognitive processes in general and attention in particular has recently been reviewed extensively in [51, 52].

As a framework for selective and flexible communication, CTC is ideally suited to model the neuronal mechanisms that underlie selective processing of attended over ignored sensory input. As laid out above, an attended stimulus dominates the competition for neural representation. Within CTC, in-depth neural representation of a given stimulus can be expressed as communication between neuronal assemblies that code that stimulus across hierarchical stages of sensory processing. Selective gain can thus be conceived of as selective communication within a cortical network of neuronal assemblies coding the attended stimulus (while excluding concurrent ignored sensory input).

Note that the strict phase-locking of the receiving neural population to one subordinate group of neurons but not the other resembles a winner-take-all mechanism [53, 54] consistent with the Biased Competition account of attention that has been formulated on the level of single neuron spiking behaviour [14, 15]. There, neurons in cortices representing late sensory processing stages have been found to show a characteristic response to an attended stimulus in the presence of irrelevant stimuli as if it were presented alone. Therefore, selective attention described in terms of CTC extends Biased Competition to the level of neuronal populations and links it to intrinsic neural rhythms with a prominent role for gamma band oscillations.

To date, various predictions of a CTC account of selective attention have been tested and confirmed [28, 55–57]. Only recently, Bosman et al. [58] investigated its core assumption in early visual cortices of the macaque brain: they recorded electrocorticograms from two sites in primary visual cortex (V1) that were responsive to two spatially distinct stimuli as well as from one site in higher-order visual cortex

(V4) that received converging input from both V1 sites. They found compelling evidence that the downstream group of neurons selectively coupled to the V1 site that represented the currently behaviourally relevant stimulus, thus corroborating that selective gamma-band synchronization allows for dynamic and exclusive routing of attended sensory input.

Considering the wealth of research on CTC, it can be regarded as an exceptional model for how selective stimulus processing makes its way up the (visual) processing hierarchy. It is less clear, however, how goal-directed (top-down) biases can be implemented by CTC. Put differently, how does CTC model the proverbial spotlight? The top-down direction requires higher-order brain areas to exert processing biases. Indeed, several studies have shown long-range gamma coherence (i.e. "coupling") between early sensory cortices and FEF [28], between homologue areas in different cerebral hemispheres [59], and between motor cortex and peripheral muscle innervation [60]. Although modulations of gamma coupling were substantial, the overall coherence was found to be relatively low. Lisman and Jensen [61] discussed that low coherence might render communication ineffective. In their opinion, long-range gamma coupling might rather be a consequence than a means of neuronal communication over such distances, which makes it an unlikely candidate for conveying direct top-down influences on sensory processing. Below, we discuss how low-frequency brain oscillations (<15 Hz) may enable long-range high-frequency coherence in top-down processing.

Low-Frequency Phase Reset

Rare, high-contrast salient sensory events—ambulance sirens or a camera flash—capture attention automatically, "bottom-up". In most cases we will immediately turn towards the sources of these events involuntarily. With regard to neural activity in corresponding sensory cortices, these salient sensory events have (at least) two effects: First, they elicit evoked responses, an increase in overall activity that occurs strictly time-locked to stimulus presentation [62]. And, more importantly, they reorganize the phase of ongoing oscillations in such a way that a preferred phase occurs at a certain latency after the event, irrespective of the phase prior to the event [63, 64]. This phase "reset" (Fig. 3.3) leads to strong phase synchronization that tunes the cortex to the processing of the properties of the driving stimulus [65]. In detail, phase resets provide organized temporally structured windows of high cortical excitability that can lead to optimal stimulus processing equivalent to a sensory gain mechanism. In contrast, stimuli that occur outside this optimal window arrive at phases of lower excitability and have a processing disadvantage. As a consequence, stimulus-driven phase resets implement a potent mechanism for sensory selection [34].

Extending the phase-reset mechanism to multisensory scenarios, Lakatos et al. [66] suggested that neural processing can be guided by the sensory modality corresponding to the salient event. In case of the ambulance siren, for example, the

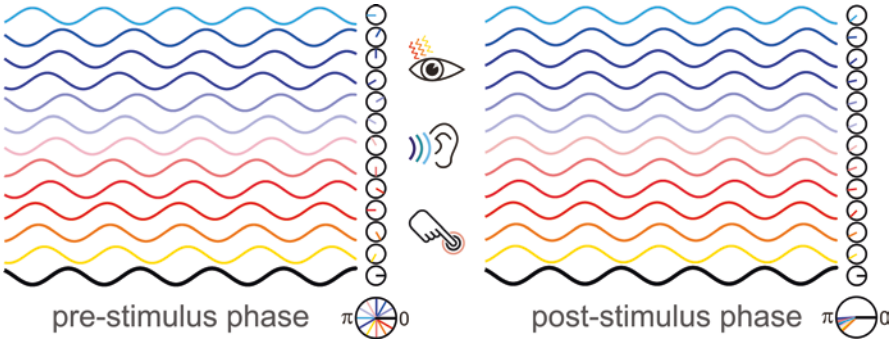

Fig. 3.3 Schematic phase reset. Each coloured waveform represents oscillatory activity in a small neuronal population of a given sensory cortex. (The heavy black line depicts a cosine signal that can be used as a reference.) Prior to stimulation, these populations may oscillate with a random phase relationship (see corresponding phase plots in unit circles next to the waveforms). A salient sensory stimulus can reset oscillatory phase across populations. This leads to a non-random phase distribution, i.e. phase alignment, shortly after stimulus presentation

auditory cortex takes reign over sensory processing. Ultimately, the "leading sense" exerts modulatory influences on early cortical visual and somatosensory processing. These influences can be considered as a cross-modal spread of attention: attending to a specific stimulus in one sensory modality has been shown to selectively facilitate the processing of temporally and spatially congruent input to the other senses [67]. The ambulance siren will likely draw your attention towards a fast-approaching vehicle with blinking lights. This selective bias of processing between senses might aid in extracting and integrating concurrent multisensory input [68].

A crucial precursor was the finding of Lakatos et al. [66] that the phase reset (but not the evoked response) "spills over" to other sensory cortices. A phase reset across senses ("cross-modal") occurred specifically in oscillations within gamma- and theta-frequency ranges, and was most pronounced in the theta band. Especially low-frequency oscillations have proven instrumental in providing temporal reference frames for the encoding of stimuli in sensory cortices [69]. It is thus conceivable that auditory-guided selective processing of visual input is supported by a cross-modal phase reset, where the auditory cortex imposes its temporal reference frame on visual processing.

Lakatos et al. [66] further demonstrated that cross-modal phase resets are only initialized by attended stimuli. More specifically, when attending to auditory input, the presentation of an auditory stimulus will lead to an evoked response and a phase reset in auditory cortex but will only reset phase in visual cortex. The same holds true for visual stimulus presentation while attending to visual input. The presentation of an auditory stimulus during attention to vision, however, still leads to an evoked response and phase reset in auditory cortex (albeit of smaller amplitude) but is ineffective in resetting phase in visual cortex. These findings stress the role of

attention as a dynamic selector of the leading sense as a pace maker in sensory processing.

Although powerful in describing how attention may govern flexible sensory selection, some aspects of the "leading sense" framework need further specification. Similar to CTC, as discussed above, it is unclear how attention is initially allocated to a sense. The notion of cross-modal phase resets emphasizes the role of transient salient sensory events in capturing attention automatically, as in our ambulance example. Nevertheless, most experiments investigating oscillatory cross-modal interactions employed paradigms that required sustained focussed attention to one of two concurrently presented equally salient sensory streams [65, 70]. For that purpose, a higher-order mechanism operating above sensory modalities and exerting such biases must be assumed and remain to be included in the model. As with CTC, a likely candidate is the dorsal fronto-parietal attention network (see "Mechanisms of Attention" at the start of this chapter).

Furthermore, it remains to be seen whether a phase-reset mechanism can be generalized to other stages of stimulus processing. Physically distinct properties of an object, such as "colour" and "motion trajectory" in the visual system have to be selectively processed and integrated within senses as well. It might be an interesting subject of future research whether a phase reset can also account for within-modal but between-feature coupling in visual processing. For instance, will the red ball coded in colour-sensitive visual areas phase reset oscillations in other areas that code its trajectory (or vice versa)? Such a mechanism might prove vital for an efficient assessment of the ball's approach towards oneself and allow for timely evasive action.

Oscillations and Suppression of Irrelevant Information

Another important mechanism by which attention optimizes stimulus processing in the human brain is the suppression of unattended sensory input. Preventing task-irrelevant information from reaching higher processing stages optimizes the use of limited processing resources and avoids interference or competition between irrelevant and relevant information. Ideally, irrelevant information should be blocked at the earliest possible stage, i.e. in early sensory areas. Evidence for task-specific suppression of sensory information is ubiquitous in the neuroimaging literature. Interestingly, recent studies provided compelling evidence that brain oscillations play an important role in attentional suppression. In particular, oscillations at a frequency of around 10 Hz (alpha-band) show task-specific amplitude modulations that are consistent with a role in attentional suppression. This hypothesis has gained early support from studies demonstrating an inverse relationship between alpha amplitude and behavioural performance of target processing [71, 72]. These studies show that even spontaneous fluctuations in occipito-parietal alpha power modulate the perceptual fate of an incoming near-threshold stimulus. Other studies extend this finding by showing that alpha power is related to cortical excitability [73, 74].

But beyond these general findings, evidence is emerging that specifically suggests that alpha band activity transiently inhibits neural populations that process task-irrelevant sensory information. In the following sections we will review and discuss this evidence.

Suppression of Spatial Location

Most of this evidence originated from electrophysiological studies of the classical Posner paradigm—a cued target detection paradigm [8]. Typically, participants fixate on a central fixation cross throughout the trial. A symbolic cue (e.g. visually presented small arrow, word, or tone) instructs the participant to covertly shift attention to the left or right visual hemifield (Fig. 3.4) while continuing to fixate on a central cross. After a delay period (often between 500 and 1500 ms), a target is presented in the left or right hemifield. Behavioural performance is better for targets

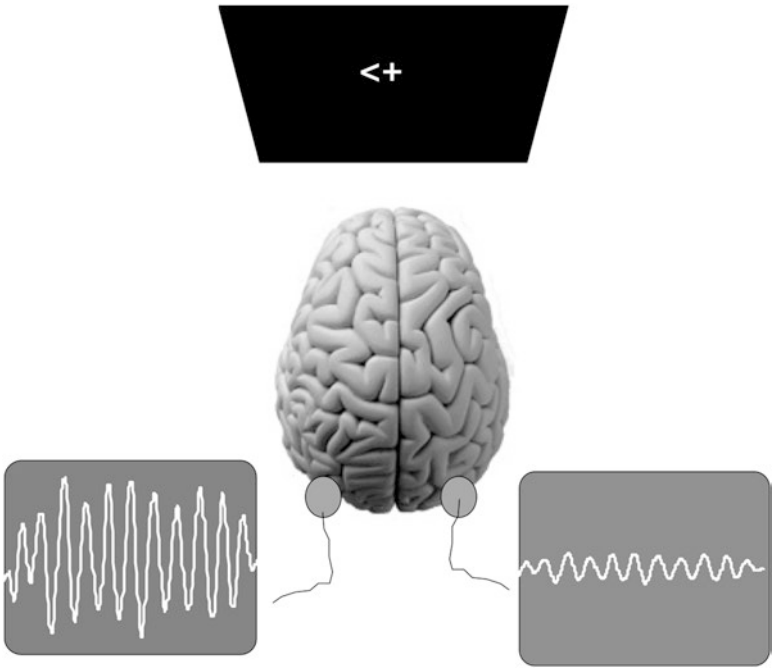

Fig. 3.4 Schematic representation of the modulation of brain oscillations during visual spatial attention. In the commonly used "Posner-task", participants fixate the cross. The < cue instructs them to covertly shift attention (to the left hemifield in this case). The shift of attention leads to a modulation of 10 Hz brain oscillations in occipito-parietal brain areas. The amplitude of 10 Hz oscillations decrease in the hemisphere contralateral to the attended hemifield and increase in the hemisphere contralateral to the suppressed hemifield

presented in the attended hemifield [8]. A number of variations of this classical paradigm exist. The validity of the cue stimulus can be changed (i.e. targets are presented in the uncued hemifield with a certain probability), participants can be instructed to respond (or not) to targets presented in the uncued hemifield, and distractors can be presented at the same time with the target stimulus in the attended or unattended hemifield. The task may involve the detection of near-threshold targets or the identification of a specific target stimulus, etc.

Interestingly, the amplitude of alpha oscillations over occipito-parietal brain areas is modulated following the presentation of the cue stimulus and even reflects the locus of spatial attention (see Fig. 3.4). Specifically, the covert shift of spatial attention to one hemifield leads to a reduction of alpha oscillations in contralateral occipito-parietal brain areas [75–77]. This reduction is sustained in the absence of sensory stimulation during the cue-target interval. These often-reproduced findings indicate a close link between visuo-spatial attention and alpha oscillations. But what exactly is the evidence that link alpha oscillations more specifically to attentional suppression?

Importantly, several studies report an up-regulation of alpha oscillations contralateral to the *unattended* hemifield consistent with a suppression of the visual hemisphere that is less likely to receive target information [26, 78–80]. This is illustrated in Fig. 3.4 where the parietal areas contralateral to the unattended hemifield show an alpha increase in the cue-target interval (before presentation of the target).

Furthermore, the amount of alpha modulation in this type of paradigm has been found to correlate with behavioural performance, indicating a functional role of alpha oscillations in the gating of target stimuli. It is important to note here that it is the single-trial alpha power in the cue-target interval that correlates with subsequent target processing performance. This is consistent with the notion that alpha power reflects the anticipatory attentional bias of location-specific neural populations. However, it remains unclear to what extent this correlation holds for the inhibitory aspect of alpha oscillations. In fact, Capilla et al. [79] found a correlation between anticipatory alpha power and behaviour only for the alpha power decrease contralateral to the attended hemifield, and not for the alpha power increase (thought to reflect sensory suppression) contralateral to the unattended hemifield. Further studies have reported correlations of behavioural performance with a collapsed measure of hemispheric lateralization of alpha power in occipito-parietal EEG electrodes [75, 76].

The correspondence between alpha modulation and shifts of visual attention has been generalized to more complex (and ecologically valid) scenarios. Recently, Tan et al. [81] showed that during a dynamic action observation task alpha modulation spatially coded for the predicted movement end point of the behaviourally relevant stimulus feature (in this case the moving hand of an actor performing a pointing movement). After movement onset, participants dynamically predicted the end point of the pointing movement. The outcome of this prediction was reflected in hemisphere-specific occipito-parietal alpha modulations several 100 ms before the observed movement was finished.

Similarly, the amount of alpha lateralization has been shown to correlate with cue validity [77]. Together, these studies indicate that alpha modulations reflect the

brain's predictions about upcoming stimulus contingencies—important for efficient deployment of limited processing resources.

Suppression of Object Features

Postulating a role of alpha oscillations in attentional suppression of irrelevant information requires further generalization across different tasks, stimulus features, and modalities. Indeed, neural populations processing task-irrelevant object features seem to show increased alpha activity in the cue-target interval. Snyder and Foxe [82] used coloured moving dots as targets and instructed participants via a cue to attend to either one of these object features. Areas of the dorsal visual stream showed increased alpha activity when participants shifted attention to the movement, whereas alpha activity increased in ventral areas when colour was attended. Similarly, Jokisch and Jensen [83] studied alpha modulation in the ventral and dorsal visual stream while participants remembered the orientation or identity of a face in a match-to-sample task. Consistent with the inhibitory role of alpha, they observed an alpha power increase in the dorsal stream during the identity task and in the ventral stream during the orientation task.

Extending these findings, Capilla et al. [79] demonstrated the co-representation of suppression and selection in the alpha band with distinct spatio-temporal signatures. Using a classical Posner paradigm, numbers were presented at near-threshold in the cued or uncued hemifield. Source localization of MEG signals revealed transient alpha power increase following cue presentation in dorsal parietal areas contralateral to the inhibited (unattended) hemifield. In contrast, the occipital ventral area contralateral to the attended hemifield that is associated with processing numbers and letters showed sustained alpha decrease throughout the cue-target interval. The first effect represents an alpha-mediated suppression of irrelevant spatial locations whereas the second effect represents an alpha-mediated priming of neural populations that are expected to receive the target.

Suppression Across Sensory Modalities

Further evidence for a more general role of alpha oscillations in attentional suppression comes from studies investigating other sensory modalities as well as intermodal attention.

The correspondence between visuo-spatial attention and alpha oscillations has been replicated in the somatosensory domain for painful stimuli by May et al. [84]. The authors reported lateralized anticipatory alpha modulation in primary somatosensory cortex. However, it is important to note that while the pattern of alpha lateralization is identical to the visual domain (relatively more alpha suppression contralateral to attended side) there was no evidence of alpha power increasing relative to baseline. This is in agreement with results of a study of tactile attention that also reported later-

alized alpha (and beta) modulation in anticipation of a tactile target stimulus, but similarly failed to find alpha power increase as a sign of active inhibition [85].

Similarly, a study of tactile discrimination found significant alpha suppression contralateral to the attended side, but no significant increase in ipsilateral somatosensory cortex [86]. Interestingly, the same group reported a significant alpha increase in ipsilateral somatosensory cortex that contributed significantly to discrimination performance when distractors were introduced opposite to the attended side [87]. The lack of alpha increases in the previously mentioned studies could simply result from the fact that suppression was unnecessary because no distractors were presented. Therefore, these studies further support the notion of alpha oscillations playing a role in suppressing task-irrelevant information.

Another group of studies investigated the role of alpha in intermodal attention tasks based on the Posner paradigm. Targets could be presented in the auditory or visual modality with a preceding cue instructing participants to focus attention on one of these two sensory modalities [88]. Instructing participants to attend to auditory stimuli resulted in increased alpha power over visual brain areas indicating inhibition of the irrelevant sensory modality. But no increase in auditory areas was reported when attending to the visual domain. Bauer et al. [89] used an intermodal vision-touch attention paradigm and reported stronger alpha suppression in the attended sensory domain. An MEG study by Frey et al. [90] showing alpha modulation specifically in auditory cortex in an audio-visual spatial attention task complemented earlier results.

Finally, an interesting finding relating to the inhibitory role of alpha oscillations was made by Hwang et al. [91]. They studied inhibitory control with the antisaccade task where participants are instructed to make a saccade to the opposite direction of a peripherally presented target stimulus. Here, pre-stimulus alpha power in FEF predicted saccadic inhibition.

Overall, this constitutes considerable evidence for an at least partially inhibitory role of alpha oscillations. Interestingly, recently more direct evidence for a *causal* involvement of alpha oscillations in the suppression of irrelevant stimulus aspects has been gathered. Rhythmic TMS at alpha frequencies was used to specifically entrain alpha oscillations in IPS—an important node of the dorsal attention network engaged during the shifting of visual spatial attention. Simultaneous EEG recordings revealed that this particular TMS protocol transiently increased alpha power and led to a suppression of the contralateral visual hemifield [92, 93].

Oscillations and the Dynamics of Attention

In the previous sections, we have summarized oscillatory mechanisms that may underlie the selection and filtering of sensory input. It is obvious that these mechanisms must operate in a highly dynamic manner: A visual search, for example, entails successive shifts of the spotlight of attention selecting yet unexplored portions of space until the target stimulus is finally found. In a mechanistic interpretation, shifts of attention have been described as cycles of disengaging and shifting the spotlight from a searched location and engaging it onto a new target [3]. This con-

ception acknowledges a fundamental property of all neural processes that subserve attention—they take time. As an example, one cycle of shifting attention from one location to another does not occur instantaneously, but has a given duration. Furthermore, facilitatory effects on selected and suppression of irrelevant sensory input take time to build up [94]. The allocation of attention itself can thus be considered a function of time. In the following section, we focus on how intrinsic neural rhythms can serve as "clocks" of attention and provide a temporal frame for the cyclic dynamics in allocating attention.

Stimulus Anticipation and Temporal Regularities

Previous research led to the notion that our senses capitalize on rhythmic structures in sensory input to efficiently process and predict upcoming stimulation [95]. Predictions based on such temporal regularities indeed improve behavioural performance. For instance, Rohenkohl et al. [96] reported faster reaction times and greater accuracy for temporally predictable visual target stimuli within a regular, as compared with an irregular, stimulus train. Temporal regularities can be used to precisely time the deployment of anticipatory biases on sensory processing.

Without initially making a connection to intrinsic neural rhythms, Large and Jones [97, 98] introduced their Dynamic Attending Theory (DAT). The DAT provides an account for the waxing and waning of attention in time by assuming an internal oscillatory process that is able to "lock on" or "entrain" to temporal regularities in sensory input. This oscillatory conceptualization of attention is closely related to the idea that low-frequency brain oscillations underlie a selective temporal tuning of sensory cortices [34]. More specifically, periods of high and low excitability of delta-theta rhythms are a potential neural correlate of the DAT oscillator model, as pointed out by Henry and Herrmann [99]. Schroeder and Lakatos [34] further suggested that entraining to rhythmic input is metabolically optimal. In case of arrhythmic input, making temporal predictions impossible, the brain needs to resort to an energy-consumptive "continuous" processing mode instead.

Importantly, relating fluctuations in attention to the entrainment of low-frequency oscillations emphasizes the role of their phase on stimulus processing. Recent experimental work has repeatedly confirmed the role of relative delta, theta, and alpha band phase on stimulus perception [100–103]. These studies consistently demonstrated that stimuli presented during high excitability phases were detected faster and more accurately. Moreover, low-frequency oscillations have been shown to entrain to temporal regularities in sensory input through phase alignment [66, 104, 105].

Recent research into auditory speech processing has further recognized the role of entrainment in the selection of complex sensory input [106]. A recent study by Zion Golumbic et al. [107] demonstrated compellingly how low-frequency oscillations in auditory cortices selectively entrained to the speech envelope (i.e. the pitch contour) of an attended speaker in a multiple-speaker environment. Entrainment can thus be regarded as a versatile mechanism of sensory selection.

Active Sensing

Assuming oscillatory entrainment as a general mechanism of selective attention is tempting. However, only a subset of stimuli allows straightforward extraction of temporal regularities. When viewing a painting, for example, despite the absence of any periodic changes in its content, we are still able to perceive and even focus on its constituent elements. How do our perceptual systems exploit the benefits of entrainment in such a situation? Schroeder et al. [108] suggested that in the absence of temporal regularities, sensorimotor interactions lead us to produce rhythmic behaviour that imposes a temporal structure on sensory input. These authors argue that active rhythmic sampling is the rule and not the exception in at least some of our senses. Their "Active Sensing" perspective rests on a number of observations. First of all, free exploration of a sensory situation involves moving our sensors: gaze shifts successively cover areas of interest in visual scenes, and our fingers manipulate objects to experience their physical properties. Respective exploratory movements occur in a near-periodic manner. During free viewing of natural images, saccadic gaze shifts occur at a rate of three per second, and fixation dwell time is ~200 ms on average [109]. Both values correspond well to the frequency and period of delta and theta rhythms. Although corresponding findings remain scarce for active human tactile perception [110], research in the rat model shows a similar periodicity of whisking movements during haptic exploration [111]. Second, just like sensory perception, motor output seems to be slave to the rhythm; motor cortices generally exhibit rhythmic activity in the same characteristic frequency bands as sensory cortices. These rhythms are instrumental in coordinating motor activity, such as planning and executing movements [60]. For example, during slow, precise finger movements a small 5–8 Hz rhythm can be observed peripherally that originates from rhythmic activity in a thalamo-cortical loop and likely supports optimal movement control [112]. Interestingly, participants instructed to simulate Parkinsonian tremor settled naturally into the same 5–8 Hz low-frequency rhythm, highlighting the preference of the human motor system for this frequency range [113]. Third and most crucially, low-frequency cortical oscillations tend to align with quasi-periodic gaze shifts [114, 115] and haptic receptors in the rodent model [116].

Using the visual modality as an example, Schroeder et al. [108] argue that each saccade triggers a volley of "fresh" sensory input that is subsequently processed within a period of high cortical excitability. This period starts with the onset of fixation and ends before the initialization of the next saccade [117]. The concept of Active Sensing thus links rhythmic motor behaviour to rhythms in perception. It posits that we actively sample our (visual and tactile) environment using our sensory organs. Rhythmic sampling routines thereby optimally exploit periodic changes in perceptual processing of sensory input.

Note that Schroeder et al. [108] acknowledge that Active Sensing does not provide a straightforward account of selective attention for the auditory modality. This is simply because we are not able to move our ears to rhythmically sample auditory input. Interestingly, this observation ties in well with recent findings that, unlike in the visual sense, auditory processing might not underlie a low-frequency rhythmical sampling process [118].

Discrete Perception and the "Blinking Spotlight" of Attention

Although the Active Sensing framework possesses high ecological validity—it reflects how we naturally explore our (visual and haptic) environment—it deliberately disregards the fact that we are able to focus our attention on a portion of the visual field that is not in the centre of our gaze. This "covert" form of visuo-spatial attention decouples gaze fixation from selective sensory processing. It allows shifting the spotlight of attention while keeping gaze steady. Attention can thus either be allocated by shifting gaze and fixating a target (termed "overt" attention) or covertly as described before. Importantly though, both mechanisms rely on the same underlying neural circuitry, the fronto-parietal "attention-network" [25, 119].

In a seminal study on the dynamics of FEF control of attention, Buschman and Miller [120] investigated FEF neuronal activity during covert shifts of attention in awake behaving monkeys. These were trained to perform a covert visual search task in a four-item display and respond upon discovery of the target item by making a saccade towards it. While doing so, monkeys obeyed a strictly serial—predominantly clockwise—pattern as reflected in FEF neuronal activity: Neurons exhibited maximal firing when attention was allocated to their preferred location. When a target was presented at their preferred location, firing rates peaked just before the saccade (50 ms). When a target was presented one or two positions further clockwise, firing rates of the same neurons peaked earlier (100 or 200 ms prior to saccade), indicating that the attentional focus moved across successive positions in order to find the target. Importantly, firing rates were modulated by the phase of ongoing beta band oscillations of the LFP. Single-trial variations in frequency of these oscillations were predictive of corresponding saccadic reaction times. Finally, Buschman and Miller [120] were able to conclude that monkeys spend on average 44 ms per item, which corresponded well with the cycle length of observed 18–34 Hz LFP oscillations (40 ms at 25 Hz). In summary, their results provide compelling evidence for a serial periodic sampling of a search display that can be conceived of as successive shifts of the attentional spotlight, and that is implemented via rhythmic beta-band fluctuations in local neuronal excitability.

The findings of Buschman and Miller [120] leave us with the interesting possibility that rhythmic exploratory motor behaviour in terms of Active Sensing [108] might rather be a consequence of an intrinsically periodic sampling of our sensory environment than a cause. In fact, it is a long-standing notion that perception itself is based on taking discrete snapshots in contrast to merely processing continuous sensory inflow [118]. Again, neural oscillations, particularly those in the alpha and theta frequency ranges, have been identified as being instrumental in digitizing continuous input into discrete samples [121]. More specifically, Busch et al. [100] as well as Mathewson et al. [122] found that detection of near-threshold visual stimuli depended on the relative phase of ongoing 7 or 12 Hz oscillations in human EEG recordings, respectively. However, a follow-up study by Busch and VanRullen [123] emphasized the role of attention: Oscillatory phase only influenced the detection of threshold stimuli at attended, but not at unattended, locations. This finding suggests that either attention accentuates perceptual sampling or the sampling process is closely related to sensory input selection by attention.

Accordingly, a number of studies have since reported signatures of attention-based rhythmic sampling in human behavioural performance [124–126]. For instance, Landau and Fries [126] presented participants with two visual stimuli, one within each visual hemifield. They found that accuracy in a change detection task fluctuated rhythmically with a frequency of 4 Hz after cueing participants to attend covertly to the left or right stimulus. Moreover, the rhythm was in counterphase for both stimuli, indicating periodic shifts of attention between them. These findings were replicated by Fiebelkorn et al. [125] remarkably showing a similar 4-Hz rhythmic sampling between stimuli in different hemifields. Moreover, their experiment featured a condition investigating effects of object-based attention: In addition to target events on attended or unattended stimuli, task-relevant events could occur at an unattended location situated on the same "object" (a white bar) as the attended location. Crucially, target detection within objects obeyed an 8-Hz rhythmicity suggesting attentional sampling at a higher temporal rate.

Overall, these findings accord well with the notion of a "blinking" spotlight of (at least visual) attention as proposed by VanRullen et al. [124]. This notion emphasizes the intrinsic rhythmicity in sampling one object discretely or multiple objects successively, and is well in line with the reported phasic neural processes underlying attentional selection. Furthermore, recent results indicate that the blinking-spotlight framework might further elucidate the neural underpinnings of parallel vs. serial visual search, i.e. that target search times remain constant vs. increase with increased display size [127].

Integrating Models of Oscillations and Attention

Taken together, oscillatory accounts of attention mechanisms are able to describe long-assumed properties of the underlying neural processes (e.g. the dynamics of the "spotlight") on the level of communication within and between neuronal populations—a level that is likely the locus of neural representations of our sensory environment, intentions, and thoughts. However, it remains to be shown which of and how all of these mechanisms work in concert to produce, for example, typical scans of a visual search display that involve the selection of a stimulus while filtering out distractors, subsequently moving on to the next stimulus and repeating this cycle until the target is found. Likely candidates for an integrated framework are oscillatory interactions between frequency bands that are usually referred to as cross-frequency coupling [128].

Cross-Frequency Coupling

The most prominent cross-frequency coupling mechanism is phase-amplitude coupling (PAC) where the phase of low-frequency oscillations modulates the amplitude of high-frequency oscillations. PAC is particularly suited as a neural mechanism

that can similarly account for long-range low-frequency biasing signals (phase) that further act upon short-range high-frequency stimulus representations (power) in local neuronal networks [129, 130], both processes of which are required to incorporate all described aspects of attention.

Most vividly captured in the case of visual attention, a phase reset of low-frequency biasing signals can be generated by internal events and exerted by the fronto-parietal attention network [131], or by salient external events in the same or different sensory modalities [66, 132, 133]. These biasing signals determine local excitability cycles and thus regulate the high-frequency activity of neuronal populations that encode sensory stimulation. Evidence for PAC in human cortical activity associated with cognitive functions in general is still sparse but growing [106, 134–136]. Only recently, Szczepanski et al. [137] provided experimental evidence for a PAC that underpinned the control of visuo-spatial attention. In a spatial cueing task they found that the coupling strength predicted reaction times to target stimuli, thus tying PAC to a behavioural outcome that varied with the allocation of attention.

Jensen et al. [130] have proposed a model of coupled alpha and gamma band oscillations that serve in prioritizing visual input. Crucially, the model postulates that a visual scene is decomposed into its constituent objects via a transformation into a temporal code. Different gamma cycles code different objects, and the most salient item is processed first at the onset of increasing local excitability as determined by alpha phase. Importantly, current task demands may modulate the relative saliency of objects. Thus goal-directed attention can modify the order of the temporal code. Moreover, as for example in a visual search, the behavioural relevance of items of the search display can change over time. In that case, the model provides a flexible mechanism of re-prioritizing objects on each new excitability cycle (i.e. alpha phase) according to the strength of their neuronal representation (i.e. gamma power).

Although these findings and ideas show that different oscillatory phenomena associated with attention can be integrated into a consistent unified framework by assuming cross-frequency interactions such as PAC, explanatory gaps still remain to be closed. In the beginning of this chapter we have introduced current models of attention that are based on observations of single neuron behaviour. These so-called normalization models have been widely successful to explain a wide range of effects of attention on stimulus processing while, however, disregarding any oscillatory contributions. Given the explanatory power of oscillatory accounts of attention on the one side, and normalization models on the other side, it is clear that a comprehensive account of human attention (and its underlying neural processes) has to incorporate both aspects.

Hierarchical Normalization and Oscillation Model of Attention

Montijn et al. [138] undertook a pioneering foray into combining oscillations and normalization models. They identified a potential weakness of the normalization model by Reynolds and Heeger [23] when modelling the processing of two close-by stimuli along the visual processing hierarchy. They observed that the neuronal activity

profiles (given by the "Population Response" diagram in Fig. 3.1) increasingly blur into each other at higher processing stages simply because the receptive field (RF) sizes of respective neurons increase. Because attention can only modulate neuronal responses at the spatial scale provided by the RFs at each stage (the "Attention Field" in Fig. 3.1), it loses its discriminative power and similarly enhances the responses to both stimuli. Put differently, a neuron with an RF that fully encompasses both stimuli would respond maximally.

Montijn et al. [138] introduced a possible solution to this limitation by reinstating the discriminability of two stimuli falling within overlapping RFs. They assumed—in accordance with the CTC framework [33]—that neuronal populations coding the stimuli would oscillate at different phases. In fact, their oscillatory extension elegantly maintains unambiguous responses to each of the two stimuli at later processing stages. Now, a neuron with an RF that fully encompasses both stimuli would receive phase-shifted input from neuronal populations coding the stimuli at an earlier processing stage. Modelling the according "Population Response", Montijn et al. [138] were able to demonstrate that such a neuron would only give an intermediate response due to phase cancellation effects. Maximum responses instead were obtained from neurons whose RFs gave a slight preference to one of the two stimuli and thus received dominating input from—or, in terms of CTC, showed coherent activity with—the corresponding lower-tier populations.

Taking into account oscillatory phase thus preserves the possibility to selectively modulate the processing of stimuli at stages of the visual hierarchy on which a selection based on space or feature alone is difficult. In a sense, Montijn et al. [138] amended the original normalization model [23] simply by giving it a time dimension that is required for oscillatory processes to take place. Further modelling showed that this "Hierarchical Normalization and Oscillation Model of Attention" is able to accurately reproduce known effects of attention such as response and contrast gain, as well as the backward progression of the onset (and magnitude) of attentional modulation, along the visual hierarchy as first described by Buffalo et al. [94]. Despite its promise, to date, the model awaits experimental validation.

Conclusion

Expressing mechanisms of attention in terms of brain rhythms is a massively pursued effort in cognitive neuroscience. As we have reviewed in the above sections, three major components of attention that contribute to the preferential processing of behaviourally relevant sensory input can be described from an oscillatory perspective: Selective processing of attended as well as suppression or filtering-out of ignored stimulation, and the dynamic allocation of processing resources.

We have seen that at least two oscillatory phenomena play their part in boosting neural representations of attended stimuli. Neuronal populations can synchronize their firing patterns in the gamma (or beta) frequency range, enabling effective connections along which information can be transmitted. This communication-through-

coherence [33, 44] readily allows a selective routing of information by increasing the coherence between neuronal populations that encode an attended stimulus. As a second complimentary mechanism, low-frequency delta/theta or alpha band oscillations can reset their phase to accommodate incoming stimulation during periods of optimal cortical excitability [34, 133]. One sensory cortex may reset the phase of others, thus tuning them to processing coincidental input in other senses [66, 132]. Such a cross-modal spread of attention may also subserve multisensory integration [68].

The suppression of irrelevant stimulation has classically been linked to oscillatory activity within the alpha band, and has been most extensively studied in the visual domain. Generally, alpha power decreases in cortical regions that process an attended portion of space, and increases in other regions that represent unattended locations [75, 80]. High alpha power thereby indicates decreased cortical excitability and, consequently, reduced stimulus processing [73, 139]. Beyond suppressing unattended spatial locations, alpha power increases have been linked to a selective inhibition of unattended object features, [82] as well as unattended sensory modalities [88, 90].

Neural mechanisms of selective gain and suppression underlie dynamics that follow the phase of intrinsic rhythms. Neural oscillators can entrain to temporally regular sensory input to match phases of optimal cortical excitability with anticipated upcoming stimulus occurrences [96, 97, 99, 133]. In the absence of temporal regularities, some of our senses tend to create periodic behaviour—such as quasi-regular eye movements in vision—to actively produce rhythmic sensory input [108]. Moreover, in the visual domain, rhythmic sampling can even occur in the absence of eye movements, i.e. when gaze remains fixated. Visual search experiments requiring covert shifts of attention still revealed a cyclic sampling of the search display [120]. These and other findings [123, 125, 126] have led to the notion of a "blinking spotlight" of attention [124], i.e. attention itself being a rhythmic sampling process independent of any sensor movement.

In summary, research over the last years has greatly emphasized the importance of brain oscillations for the neurophysiological implementation of cognitive processes of attention. Although significant progress has been made, there is still a considerable gap between psychological theories and behavioural descriptions of attention on one side, and computational models and their neurophysiological implementation on the other side. Narrowing this gap represents a formidable challenge and, at the same time, a highly promising and fruitful endeavour for interdisciplinary scientists.

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Chapter 4
Pathological High-Frequency Oscillations in Mesial Temporal Lobe Epilepsy

Maxime Lévesque, Charles Behr, Jean Gotman, and Massimo Avoli

Introduction

According to the World Health Organization, epilepsy is the most prevalent neurological disorder, with a prevalence of over 50 million and an incidence of 2.4 million per year. Partial epileptic disorders represent 60% of these cases, with mesial temporal lobe epilepsy (MTLE) being the most common type. MTLE is thought to be associated to an initial brain insult such as traumatic brain injury, encephalitis, febrile convulsions, or *status epilepticus*, that is followed by a latent period of many years during which no seizures occur [1, 2]. Based on the results obtained from animal studies, neuropathological changes such as axon sprouting, structural changes in pre- and postsynaptic receptors, changes in voltage-gated ion channels, alterations of homeostatic mechanisms, and neuronal degeneration are taking place during this latent period and could lead in some individuals to the occurrence of spontaneous seizures [3]. Once patients become epileptic, they show partial seizures that originate from the hippocampus or parahippocampal structures [4].

Many antiepileptic drugs are currently available to control seizure occurrence, but approximately one-third of patients are refractory to medication, making MTLE one of the most refractory forms of partial epilepsy in adults [5]. In such patients, surgical resection of the epileptic tissue remains the main therapeutic alternative; in these cases the seizure onset zone and the possible postsurgical neurological deficits must be assessed with multiple and costly tests, sometimes including presurgical invasive procedures such as intracranial EEG recordings.

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MTLE is often associated with brain damage in the temporal lobe such as hippocampal sclerosis, which is characterized by selective neuronal loss in the CA1/CA3 region of the hippocampus and the hilus, along with granule cell dispersion and aberrant mossy fiber sprouting in the molecular layer of the dentate gyrus [6–10]. Removing the sclerotic hippocampus will reduce seizure occurrence, but still approximately 30% of patients are not seizure-free after surgery. Also, in some patients, the seizure onset zone cannot be clearly identified.

In the past 15 years, with the development of new technologies that allow multichannel recordings, high sampling rates (>2000 Hz), and the automated analysis of extensive amount of data, a new window on the pathophysiology of MTLE has been opened.

The discovery of high-frequency oscillations (HFOs, ripples: 80–200 Hz, fast ripples: 250–500 Hz) first in experimental animals [11], then in microelectrode recordings of epileptic patients, [12] and finally in the EEG of epileptic patients [13] has led to promising results in the identification of seizure onset zones in patients with refractory epilepsy. Indeed, it was demonstrated that the removal of brain regions with HFOs is associated to good postsurgical outcomes [14, 15]. In animal models that reproduce the electrophysiological, behavioral, and neuropathological features of MTLE as well as in in vitro conditions, HFOs were shown to be associated to epileptogenesis and ictogenesis [16].

In this chapter, we will review recent studies on HFOs recorded in animal models of MTLE and in epileptic patients. We will discuss their role as biomarkers of abnormal network activities that may sustain ictogenesis and epileptogenesis. For each subgroups of HFOs, namely ripples (80–200 Hz) and fast ripples (250–500 Hz), we will describe their cellular correlates and their relation with epileptogenesis and ictogenesis, as shown by in vitro, in vivo, and clinical studies.

Ripples (80–200 Hz)

Cellular Mechanisms

Ripples are transient events recorded in the EEG that are only visible after the raw signal has been filtered between 80–200 Hz. Under physiological conditions, they are usually observed in the hippocampus [17] and are phase-locked to the negative phase of EEG sharp wave events [18, 19]. Under pathological conditions, they are recorded in temporal lobe structures in association with interictal [12, 20, 21] and ictal activity [22–24]. The mechanisms responsible for the generation of physiological ripples have been extensively studied and will be detailed below. It is, however, actually unclear if pathological ripples share the same mechanisms, but they may represent an exaggerated version of physiological activity [25].

In awake animals, physiological ripples are predominantly recorded in the pyramidal cell layer of the CA1 region of the normal hippocampus, but they have also been observed in the subiculum, entorhinal cortex, and amygdala [26–28].

Ripples are mainly recorded when the animal is immobile or sleeping [16]. They may be triggered by population bursts of highly interconnected CA3 networks, which would produce excitatory postsynaptic potentials (EPSPs) through the CA3 Shaffer collaterals on the dendrites of CA1 pyramidal cells and interneurons [19]. The massive depolarization of interneurons in CA1 may lead to the activation of voltage-dependent channels and sustained firing from basket cells and chandelier cells [28]. The high-frequency firing of interneurons would then lead to inhibitory postsynaptic potentials (IPSPs) in the soma of CA1 pyramidal cells, and the spatio-temporal summations of these IPSPs would result in an oscillation at approximately 200 Hz in the field potential [26, 28]. Ripples would thus reflect summed Cl-dependent IPSPs on the soma of pyramidal cells in response to inhibition from interneurons [28, 29].

Evidence from tetrode wire recordings performed in vivo in awake animals indeed support this hypothesis, since it was shown that the interspike intervals of interneurons matches the frequency of ripples, and that ripples are always associated with interneuronal discharges [30]. Single cell recordings in humans have found a similar mechanism underlying hippocampal ripple generation, since it was found that interneurons are homogeneously involved during ripples, can discharge during each successive ripple, and increase their firing rates before pyramidal cells [31]. More specifically, GABAergic basket and bistratified cells are thought to highly contribute to these oscillations since they increase their firing rates during ripples, whereas oriens-lacunosum moleculare cell firing is suppressed [28, 32, 33]. Pyramidal cell discharges would not be sufficient to trigger ripples, but would be required for their maintenance [34].

It was also proposed that EPSPs in CA1 pyramidal neurons phase-locked to ripples and independent of GABAergic transmission may be responsible for ripple generation [35]. There is also evidence suggesting the involvement of gap junctions in ripple generation, since in in vitro preparations the application of gap junction blockers such as octanol, halothane, or carbenoxolone, reversibly suppresses ripple activity in CA3 [36]. Similarly, ripples recorded in the somatosensory cortex of anesthetized animals are suppressed within a few minutes after the administration of halothane and progressively reappear when its administration is stopped [37]. Ripples recorded in vitro in the resected neocortex of patients with refractory epilepsy are also abolished by carbonexolone [38]. These results thus support previous studies performed in silico, in which the generation of high-frequency neuronal population oscillations (125–333 Hz) was shown to rely on axon/axon gap junctions between pyramidal cells without the involvement of chemical synapses [39]. Gap junctions between interneurons in the hippocampus and neocortex can synchronize pairs of interneurons, thus promoting the synchronous firing of interneuronal populations, which would enhance the coherence of oscillations emerging from the GABAergic neuronal network [40–44].

Physiological ripples associated to large amplitude sharp waves occurring during slow-wave sleep have often been linked to memory consolidation [45]. More specifically, during these transient events, newly acquired items are thought to be reactivated [46] in the hippocampus before being transferred to other cortical areas,

where they would become stable and consolidated during slow-wave sleep [46, 47]. This is supported by studies performed in rats in which the rate of occurrence, frequency, amplitude, and duration of ripples increase following the acquisition of spatial memory tasks [48–50]. Even more convincing evidence showed that when ripples are suppressed with electrical stimulation, memory consolidation is impaired [51]. In humans, the propagation of ripples from the hippocampus to the rhinal cortex is also highly correlated with memory consolidation [52]. Ripples would thus be linked with neural processes related to plasticity [46].

Epileptogenesis

Ripples have been linked to epileptogenesis, i.e. the development of a chronic epileptic state, due to their occurrence in structures that, under normal conditions, do not generate oscillations in these frequency ranges. For instance, in control animals, ripples are never observed in the dentate gyrus. However, in the dentate gyrus of kainate-treated [53, 54] or pilocarpine-treated animals [55, 56], interictal spikes are associated to pathological ripples, mostly during the spike component [57, 58] (Fig. 4.1). Interestingly, these ripples occurring during the latent period can be used to predict epileptogenesis, since all animals that show spontaneous seizures have ripples in the dentate gyrus, suggesting that they may reflect abnormal network activity in this structure [57]. In the chronic period (after first seizure occurrence), we have reported that rates of occurrence of interictal spikes with ripples in the dentate gyrus can also be markers of continuing epileptogenesis, since their rates significantly increase over time in pilocarpine-treated animals with seizures [58]. Such an increase of ripple occurrence was not observed in other regions such as the CA3 region of the hippocampus, entorhinal cortex, and subiculum [58].

In epileptic patients implanted with depth microelectrodes, early studies reported that pathological ripples can occur in the hippocampus, entorhinal cortex, and subiculum [11, 12, 59]. They were shown to occur bilaterally in areas ipsilateral and contralateral to seizure onset [12]. Ripples recorded in these patients tend to occur mostly during slow-wave sleep or quiet rest, with an amplitude, frequency, and duration similar to what is observed in animals (100–600 μV, 60–180 Hz, 50–120 ms) [12, 60]. With the use of EEG recordings, it was shown that in most cases and as it is observed in animal models of MTLE, ripples occur in coincidence with interictal spikes, mostly during the spike component and less frequently during the wave that follows the interictal spike [61]. Some ripples can also occur alone, outside of spikes, on spiking channels, and on non-spiking channels [61]. When comparing the seizure onset zone and regions outside of it, both ripples occurring

Fig. 4.1 (continued) (**b**) Histogram showing the distribution of delays (in ms) between the first cycle of ripple oscillations and the peak of the interictal spike (at 0). The highest probability of onset of ripples occurred during the spike component [58]. (**c**) Representative example of a ripple occurring alone, outside of an interictal spike in a pilocarpine-treated animal. Events in the 250–500 Hz frequency range were not detected as fast ripples due to their too-short duration

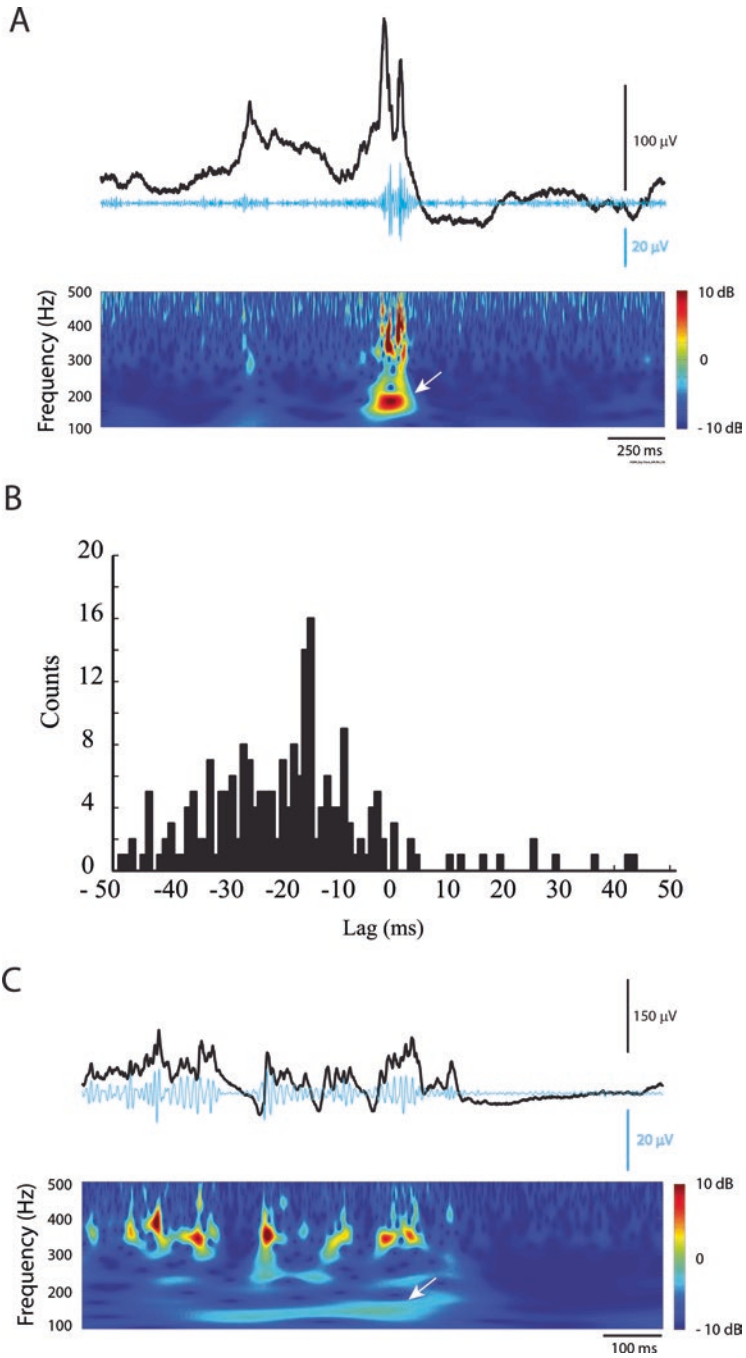

Fig. 4.1 (**a**) Example of a ripple associated to an interictal spike in a pilocarpine-treated animal. The blue line represents the signal filtered between 80 and 200 Hz. The time frequency representation of the activity in the ripple frequency range is also shown. The arrow points to the detected ripple.

on the spike or alone appear to be better markers than interictal spikes to localize the region that generates seizures [21, 61, 62], although another study found no significant difference between ripples occurring in the seizure onset zones and in regions outside of it [21].

These results thus suggest that although ripples can be recorded in the non-epileptic brain, they can be used as pathological markers to identify regions that generate seizures in patients with epilepsy. It is, however, difficult to make the difference between abnormal and physiological ripples, since to date there is no method to distinguish them and they may even be generated by the same neural mechanisms [63]. However, a recent study by Matsumoto et al. [64] showed that in epileptic patients implanted with microelectrodes, pathological ripples differ in amplitude, frequency, and duration compared to physiological ripples. They suggested that pathological oscillations could reflect abnormal neural synchronization induced by normal physiological mechanisms.

Ictogenesis

Numerous mechanisms have been implicated in the initiation and maintenance of seizures, such as failure or increase in inhibition, as well as enhanced excitatory transmission [40]. These neuronal events occurring during ictogenesis are likely to produce HFOs of various frequency bands in the EEG. In patients with mesial temporal lobe seizures, an initial study has reported that ripples can be recorded during the ictal period in regions responsible for seizure generation and in areas of propagation contralateral to seizure onset zones [13]. Further studies performed in vivo in experimental animals have then investigated the role of HFOs in seizures with different onset patterns, namely during low-voltage fast-onset seizures and during hypersynchronous-onset seizures. These two patterns are common patterns of seizure onset observed in patients and in epileptic animals, which are thought to involve different networks and distinct mechanisms of generation [65, 66]. In the pilocarpine model of MTLE [55, 56], seizures that initiate with a low-voltage fast-onset pattern are characterized during the pre-ictal and ictal phases by high rates of ripples in the seizure onset zone [22] (Fig. 4.2). These results thus suggest that this specific pattern of seizure onset could reflect pyramidal cell activity in response to interneuron inhibition. In agreement with this, enhancing GABAergic transmission in vitro induces ictal-like discharges that share morphological features with in vivo low-voltage fast-onset seizures [67] and that are sustained by inhibitory postsynaptic activity dependent on interneuronal discharge [68]. In line with these results, we have recently reported high rates of ripples along with the virtual absence of fast ripples during ictal-like events generated by piriform and entorhinal cortex networks

Fig. 4.2 (continued) ripples and fast ripples during low-voltage fast-onset seizures, in seizure-onset zones, and in regions of secondary spread. Seizures are represented on a scale from 0 to 100% to account for differences in duration. Note the gradual increase of ripple activity before the onset of the seizure and the high rates of ripples compared to fast ripples in the seizure onset zone ($*p < 0.05$) [22]

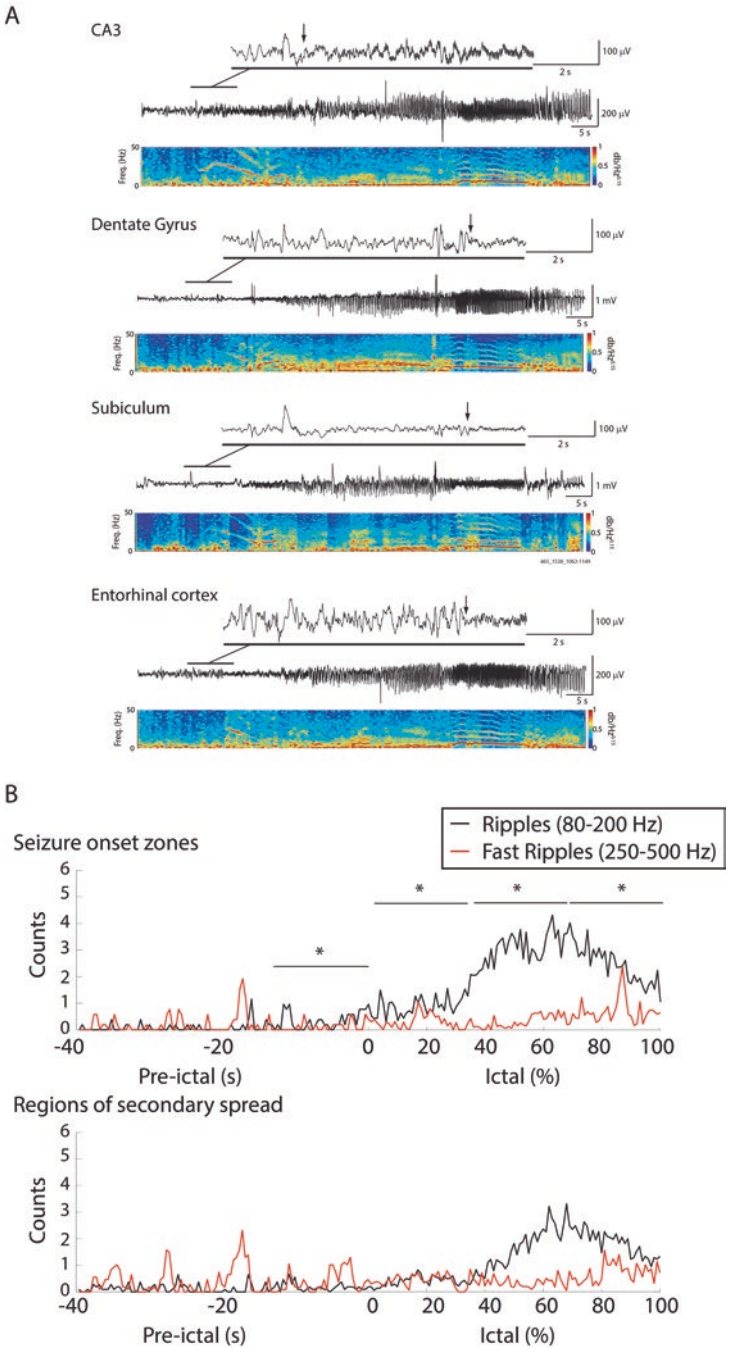

Fig. 4.2 (**a**) Example of a low-voltage fast-onset seizure recorded from four regions of the temporal lobe in a pilocarpine-treated animal. Note the sentinel spike in CA3 and subiculum preceding the onset of fast activity (15–20 Hz, arrow). (**b**) Line plot showing the distribution of

following the administration of 4-AP [69, 70]. It is, however, unclear if ripples recorded during ictal events share the same morphological and physiological properties as ripples occurring during interictal periods.

Fast Ripples (250–500 Hz)

Cellular Mechanisms

In the somatosensory cortex of non-epileptic animals, physiological fast ripples (>200 Hz) are superimposed on the initial slow wave of sensory-evoked potentials and during spike-and-wave patterns [71]. In humans, fast ripples (>300 Hz) overlying the cortical response in the somatosensory-evoked potential have also been observed [72, 73]. These oscillations would reflect the response of populations of pyramidal cells coupled with gap junctions [74] and would not depend on GABAergic postsynaptic currents [75].

In pathological conditions, fast ripples were recorded in the subthalamic nucleus of patients with Parkinson's disease [76–80] or with non-parkinsonian motor disorders [76]. In the epileptic tissue, they have been found in hippocampal and parahippocampal regions of epileptic animals [11, 22, 57, 58] and in the seizure-onset zone in humans [13, 20]. The mechanisms through which fast ripples are generated in the epileptic tissue are actually not well known, but some studies suggest that they depend less on interneuronal activity and more on the activity of clusters of pathologically interconnected neurons. Indeed, fast ripples would reflect hypersynchronized action potentials generated by clusters of principal cells [11, 81–84]. Another hypothesis states that fast ripples would emerge from the desynchronized firing of clusters of pyramidal cells [79, 85]. Since principal neurons cannot fire at more than 200 Hz, it was suggested using in vitro experiments and computational modeling that fast ripples result from the out-of-phase firing of pyramidal cells, at an interval that will produce a field oscillation in the fast ripple (250–500 Hz) frequency range. More specifically, firing delays between neuronal clusters may produce emergent oscillations in the field potential at higher frequencies (>400 Hz) than the pure oscillations produced by the in-phase firing of pyramidal cells (<400 Hz). It was hypothesized that this out-of-phase firing results from cell loss that occurs following *status epilepticus* [79]. However, fast ripples can also be recorded in the tetanus toxin model, which is associated to a minimal neuronal loss [86].

The generation of fast ripples has also been linked to gap junctions, since they are suppressed by halothane in vitro and can be generated in silico from gap-junctionally connected networks of neurons [38, 87]. Interestingly, in vivo, the administration of gap junction blockers (carbenoxolone and quinine) in the entorhinal cortex also decreases the number of fast ripples and the number of cycles per fast ripple in the hippocampus of pilocarpine-treated animals [88]. It would thus be interesting to address the relation between a suppression of hippocampal fast ripples by gap junction blockers and seizure occurrence in animal models of MTLE.

Epileptogenesis

One of the first studies suggesting a link between fast ripples and epileptogenesis was performed by Bragin and colleagues [11] who reported the occurrence of oscillations between 250 and 500 Hz (mean amplitude: 720 μV, duration: 10–100 ms) in kainate-treated rats but not in controls. Fast ripples, as ripples, occurred during slow-wave sleep and immobility, but contrary to ripples, they occurred in regions adjacent to the site of kainic acid injection and in the dentate gyrus and entorhinal cortex ipsilateral to the injected hippocampus. They also found that fast ripples can be associated with interictal spikes or can occur alone. In a subsequent study [89], they analyzed the temporal evolution of fast ripples in kainic acid-treated rats and showed that they appear in the dentate gyrus and entorhinal cortex 10–14 days after intra-hippocampal injection of kainic acid, whereas seizures occurred after 2–4 months. They thus hypothesized that fast ripples could reflect the pathological reorganization of neural networks capable of generating powerful hypersynchronous bursts of action potentials that will initiate epileptogenesis; this view was based on the fact that fast ripples were observed in regions with intense mossy fiber sprouting and that the size (approximately 1 mm^3) [81] and the location of regions generating fast ripples remained stable over months [60, 90].

A link between epileptogenesis and fast ripple occurrence was also shown in the pilocarpine model of temporal lobe epilepsy (Fig. 4.3). As in the kainic acid model, fast ripples in epileptic pilocarpine-treated animals can co-occur with an interictal spike (shown in Fig. 4.3a) [58, 91] or occur alone (as in Fig. 4.3c) [91]. When they are associated with an interictal spike, they preferentially occur during the spike component (see Fig. 4.3b) [58]. We have recently studied their pattern of occurrence over time in pilocarpine-treated animals, and reported that rates of occurrence of interictal spikes with fast ripples in the CA3 region of the hippocampus can predict seizure occurrence between day 4 and day 15 after *status epilepticus* (see Fig. 4.3d, e) [58]. These results thus suggest that the high occurrence of interictal spikes with fast ripples in the hippocampus may reflect a time window during which regions of the temporal lobe undergo meaningful changes in excitability. A subsequent study also performed by our group [91] investigated the relation between HFOs and the two types of interictal spikes, namely those characterized by a spike followed by a wave and those characterized by a spike with no wave [92]. When comparing interictal spike rates in the entorhinal cortex and in the CA3 region of the hippocampus, interictal spikes with no wave and with fast ripples occurred at higher rates in the entorhinal cortex compared to the CA3 region of the hippocampus during the latent phase. During the chronic phase (after the first spontaneous seizure), they occurred at a similar rate in both regions. Therefore, we concluded that spikes with no wave could be a reliable marker of epileptogenesis and could reflect the progressive increase in excitatory drive eventually leading to the onset of spontaneous seizures.

In epileptic patients implanted with depth electrodes, fast ripples mostly occur in mesial temporal lobe structures [11, 12, 20, 21, 59, 61]. Similar to ripples, they occur during periods of rest or sleep, are seen on spiking and non-spiking channels,

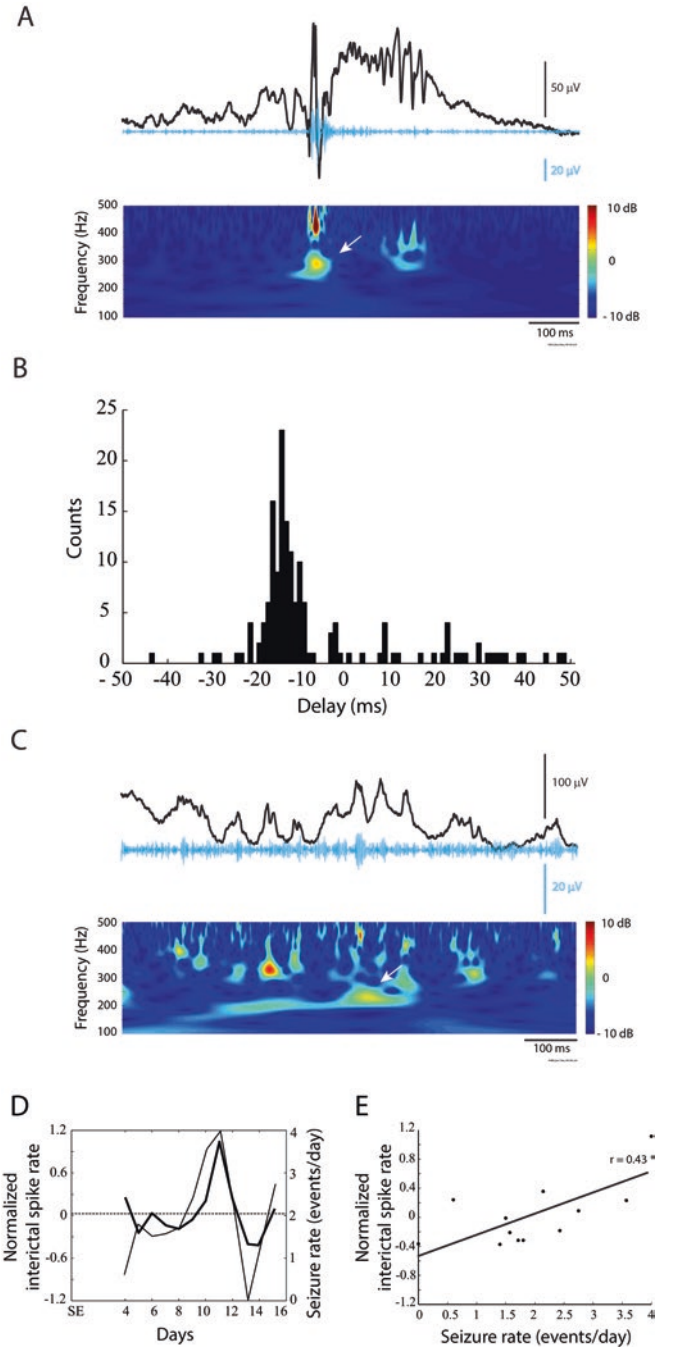

Fig. 4.3 (**a**) Example of a fast ripple associated with an interictal spike in a pilocarpine-treated animal. The blue line represents the signal filtered between 250 and 500 Hz. The time frequency representation of the activity in the fast ripple frequency range is also shown. The arrow points to

and are superimposed on interictal spikes or occur alone. However, contrary to ripples, fast ripples are mainly observed in one hemisphere and close to the seizure-onset zone [11, 12, 20, 21, 59, 61, 62]. Moreover, multiunit recordings obtained from epileptic patients have shown that fast ripples are associated with a higher synchrony of unit activity and are generated by smaller neural networks compared to ripples [20]. Taken together, these results support the hypothesis that, as observed in animal studies, fast ripples are mainly limited to brain tissue capable of generating spontaneous epileptic seizures and could be better markers of seizure-onset zones than ripples or interictal spikes. If this hypothesis is true, the surgical removal of regions containing fast ripples should lead to a favorable postsurgical outcome. So far, some studies have explored this relation in patients with MTLE. Jacobs et al. [14] have shown that the removal of regions containing either ripples or fast ripples is associated to a good surgical outcome. In children with medically refractory epilepsy, the complete removal of regions with fast ripples leads to seizure freedom [93]. Haegelen et al. [62] however found that although the removal of contacts with HFOs was associated to a favorable outcome compared to the removal of contacts with interictal spikes, there was no difference between ripples and fast ripples.

Ictogenesis

Studies on the occurrence of fast ripples during seizures in MTLE have reported that as ripples, they increase in occurrence on the same channels that show interictal fast ripples [94]. However, compared to ripples, they are better markers of seizure-onset zones since they occur more frequently in channels located near the epileptic generator [13]. Moreover, when HFOs are analyzed based on the seizure-onset pattern, fast ripples are more likely to be associated to hypersynchronous-onset seizures [22, 24], which are thought to mainly originate from the hippocampus [65, 66]. In line with this hypothesis, we found high rates of fast ripples in the CA3 region of the hippocampus during the pre-ictal period and ictal period of hypersynchronous-onset seizures in the pilocarpine model of MTLE (Fig. 4.4) [22]. Thus, since fast ripples are believed to reflect the activity of principal glutamatergic cells in the epileptic hippocampus, the initiation of hypersynchronous-onset seizures could

Fig. 4.3 (continued) the detected fast ripple. Other events in the fast ripple frequency range were not detected because of their too-short duration. (**b**) Histogram showing the distribution of delays (in ms) between the first cycle of fast ripple oscillations and the peak of the interictal spike (at 0). The highest probability of onset of fast ripples occurred during the spike component [58]. (**c**) Example of a fast ripple occurring alone in a pilocarpine-treated animal. The arrow points to the detected fast ripple. (**d**) Distribution of seizures (thin line) in pilocarpine-treated animals ($n = 7$) from day 4 to day 15 after SE, and of the occurrence of interictal spikes associated to fast ripples (bold line) in CA3. Note that an increase of seizure occurrence is associated with an increase of interictal spikes with fast ripples [58]. (**e**) Linear regression showing a significant relationship between rates of occurrence of seizures and rates of interictal spikes with fast ripples in CA3 [58]

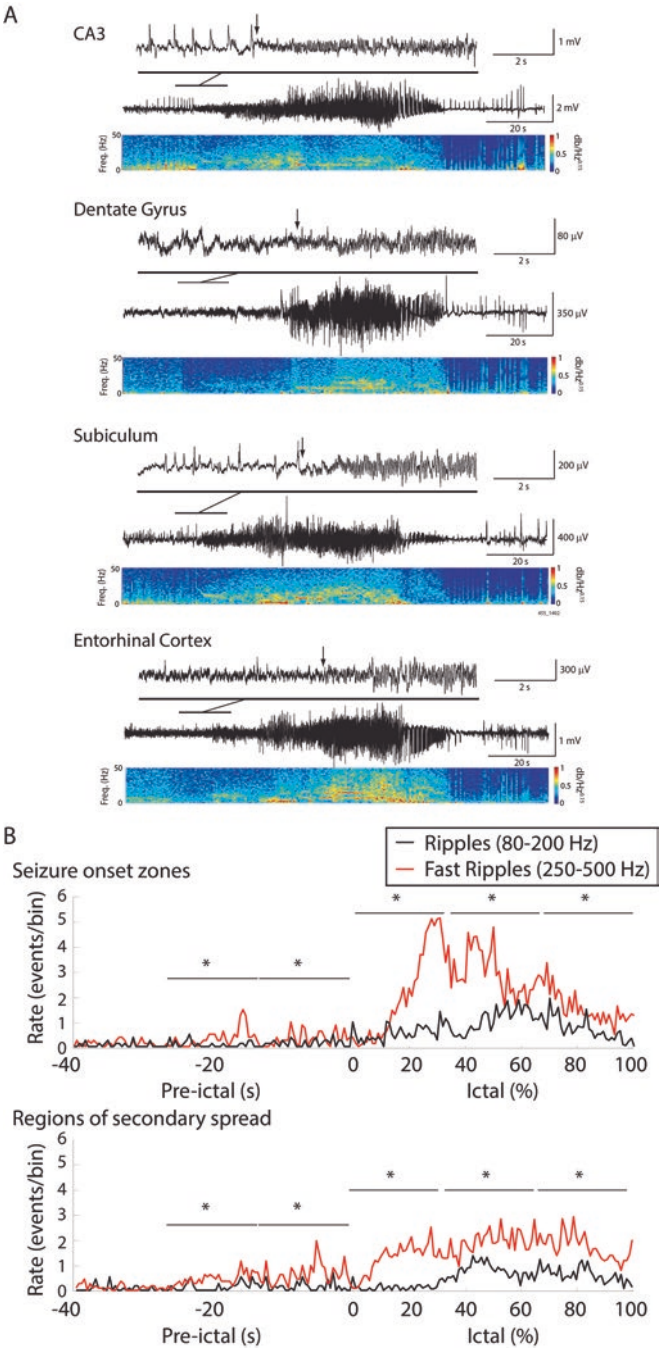

Fig. 4.4 (**a**) Example of a hypersynchronous-onset seizure recorded from the temporal lobe of a pilocarpine-treated animal. Note in CA3 the periodic multiple spikes that precede the onset of fast

depend on these mechanisms [63, 79, 83–85, 95]. However, in epileptic patients, such a high occurrence of fast ripples preceding and during hypersynchronous-onset seizures has not been observed so far [96].

Conclusion

In this chapter, we have reviewed recent findings on HFOs and their relation with MTLE. Oscillations in these frequency ranges appear to be promising biomarkers of the pathophysiogenesis of this disorder, and might help to develop more efficient and targeted surgical and pharmacological interventions. However, further studies are needed in order to understand how these pathological HFOs are generated, and if they are distinct from physiological HFOs, because as stated by Jefferys et al. [16], there is no guarantee that oscillations in the same frequency range represent the same phenomenon. Moreover, it is unclear if HFOs recorded during interictal periods are similar to those recorded during seizures, and if they rely on the same mechanisms. The effect of antiepileptic drugs on HFOs has also not been extensively studied and could lead to the identification of subgroups of HFOs that are sensitive or insensitive to medication. Only one study in epileptic patients has investigated this phenomenon so far, and suggested that HFOs may be sensitive to medication reduction, therefore suggesting that may behave like seizures [97]. Animal studies on the effect of antiepileptic drugs on HFOs during epileptogenesis should be performed.

It is highly likely that future studies will provide a better understanding of these HFOs and their relation with the epileptic tissue that generates seizures. They nonetheless represent an important finding for epileptologists that could have important clinical implications for the diagnosis and treatment of this disorder.

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Fig. 4.4 (continued) activity (15–20 Hz, arrow). (**b**) Line plot showing the distribution of ripples and fast ripples during hypersynchronous-onset seizures, in seizure onset zones, and in regions of secondary spread. Note that contrary to what is observed for low-voltage fast-onset seizures, hypersynchronous-onset seizures are mostly associated to fast ripples in seizure-onset zones and in regions of secondary spread. Note also the high occurrence of fast ripples during the ictal phase in seizure-onset zones and in regions of secondary spread ($*p < 0.05$) [22]

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Part II
Sleep

Chapter 5
Cellular Mechanisms of Thalamocortical Oscillations in the Sleeping Brain

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The thalamocortical (TC) network is a site of generation of various oscillatory activities with distinct mechanisms. It plays a major role in orchestrating discharge patterns of cortical neurons that underly EEG activities between wakefulness and non-REM sleep.

The understanding of the various oscillatory activities generated by the thalamocortical system requires the understanding of two underlying set of mechanisms: (1) *Extrinsic* (or network) mechanisms, which require the interaction of excitatory and inhibitory neurons within a population of neurons; (2) *Intrinsic* mechanisms that depend on the interplay between specific intrinsic currents within a neuron.

Architecture of the Thalamocortical Network

The thalamus, a centrally located brain structure, sits in a strategic position for brain processing and controls the flow of information to the cortex via cortico-thalamo-cortical interactions. Three key areas of the thalamus are described below.

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1. The dorsal thalamus comprises roughly 15 nuclei. Thalamocortical (TC) cells from the first-order nuclei "relay" to the neocortex specific inputs from ascending sensory pathways (e.g., medial lemniscus, optic tract, brachium of the interior colliculus, and brachum conjuctivum). They act as the main gateway to the cerebral cortex. The first-order thalamic nuclei, also called "specific" or "core-forming nuclei" (e.g., VPM, ventral posteromedial nucleus,), receive corticothalamic inputs mainly from cortical layer VI and project into cortical layer IV and V/VI. Corticothalamic projections to those nuclei and thalamocortical projections from those nuclei are reciprocal. The level of membrane potential of TC cells is modulated by inputs from brainstem modulatory systems (e.g., cholinergic, norepinephrinergic, serotoninergic).
2. The second-order thalamic nuclei, also called "nonspecific" or "matrix-forming nuclei" (e.g., CM, central medial nucleus), receive driving corticothalamic inputs from cortical layer V and project onto layer IV, superficial cortical layers, and onto subcortical centers [1, 2]. Importantly, in addition to feedback excitation of cortical areas from which these nuclei receive inputs, they also send broader feedforward excitation to other cortical areas. Corticothalamic fibers provide major excitatory input to the higher order thalamic nuclei.
3. The ventral thalamus, the major portion of which are the thalamic reticular (RE) nucleus and zona incerta (ZI), sits like a shield flush against the anterior, lateral, and ventral surfaces of the dorsal thalamus. The neurons from these nuclei are GABAergic and project to TC neurons to inhibit them.

Axons from layer VI (but not from layer V) cortical pyramidal neurons form synapses into the RE neurons [3, 4]. Another source of excitation of RE neurons is collaterals of axons of TC neurons. The inhibitory input into first-order thalamic nuclei is provided by the RE [5–7], while higher order thalamus receives inhibitory inputs mainly from the ZI [8–10]. ZI has reciprocal connections with cortex, thalamus, brainstem, cerebellum, basal ganglia, and multiple other structures [11]. ZI neurons are interconnected, and strong cortical activation inhibits ZI neurons removing the inhibitory drive they provide to their target TC neurons in the higher order nuclei [12].

Two major types of synapses are formed on TC neurons: round vesicles, large terminals synapses (RL) type, which contains large presynaptic terminals (2–4 μm) with multiple release sites and round vesicles, and small terminals synapses (RS) type, which contains small presynaptic terminals (0.2–0.5 μm) with a single release site. RL synapses are mainly formed on proximal dendrites and RS synapses are mainly formed on distal dendrites [13]. Later, the large synapses were qualified as drivers and small synapses as modulators [14]. While in specific nuclei the drivers are formed by ascending fibers [13], in higher order nuclei at least some of the drivers are formed by axons of layer V corticothalamic cells [14–16]. The presence of driver synapses is possibly not a uniform feature of TC neurons. Our recent intracellular study in mice thalamus in vivo did not identify the presence of synaptic events with features of drivers in parafascicular complex of thalamus (PF), central lateral (CL), and anterior dorsal (AD) nuclei [10].

Most of TC neurons have bushy dendritic arbor with 6–11 sub-trees and from 100 up to 150 end segments [17, 18]. For back propagating signals (i.e., from soma to dendrite) the geometrical ratio [19] at dendritic branching points was estimated to be around 1 in neurons from lateral geniculate (LGN) nucleus [20], and around 1.5 in neurons from ventral posterolateral (VPL) nucleus [18], pointing to either no, or little, electrotonic attenuation of signals propagating from soma to distal dendrites. However, for the forward propagating signals, the geometrical ratio is generally above 3 (above 4 for proximal dendrites) [18], imposing conditions of significant attenuation in amplitude for forward propagating signals, in line with the definition of modulatory effects of distal synapses. The reality is, however, more complex. The distal dendrites of TC neurons are much thinner compared to proximal [18] dendrites; thus the same quantum of neurotransmitter would induce much larger local response in distal dendrites compared to proximal dendrites [21]. A large amplitude signal, generated by local dendritic responses, propagating toward the soma attenuates in amplitude. Therefore, somatic amplitude of the responses to the same stimulating current applied to either proximal or distal dendrites becomes comparable [21]. Still, synaptic boutons driving excitatory postsynaptic potentials (EPSPs) are located mainly on proximal dendrites, and their excitation exerts a stronger excitation on soma compared to individual synapses on distal dendrites.

The neocortex is the major player in the generation of multiple thalamocortical oscillations. It has a complex structure. In this review we will focus only on several elements, which appear to be critical for the generation of TC oscillations. Other important details can be found in our previous review on the topic [22].

Despite its large complexity, the neocortex has a stereotyped organization. One of the examples of spatial stereotypy is the layering of neurons in the neocortex and the specific distributions of different cell types across neocortical layers and areas [23, 24]. The other example is the vertical columnar organization [25–28]. Other studies also point to the stereotyped organization of cortical microcircuits [29, 30], although an unbiased stereology study supports a notion of columnar organization, but questions the uniformity of cortex across areas and species [31]. The major local functional intracortical synaptic pathways start from layer IV, ascend to layers II–III, and then descend to layers V–VI [32, 33]. The axons of TC neurons terminate in the middle layers of the neocortex (primarily layer IV), but some branches of axons ascending from associative and nonspecific nuclei of dorsal thalamus may terminate in layers I and VI [17]. In the cat's visual system, synapses of TC neurons form approximately 5–6% of the total number of synapses on layer IV neurons [34, 35].

The synaptic connectivity in the neocortex is very dense and may span several orders of magnitude. Each pyramidal cell, the main type of neocortical cells, receives from 5000 up to 60,000 synapses [36–39]. Local-circuit synapses have been estimated to account for as many as 70% of the synapses present in some areas of the cortex [40, 41], and pyramidal cells constitute 70–80% of the total number of neocortical neurons [37]. Most of inhibitory synapses are located in the perisomatic region, and most of excitatory synapses are located on dendrites and dendrites spines [37]. According to the cable theory of neuron [19], synapses that are located closer to the place of generation of action potential (axon hillock in most of the

cases, but in some occasions dendritic triggering zones) have a stronger influence on action potential generation than synapses located remotely. However, the influence of remotely connected synapses on the generation of action potentials might be significantly facilitated by a variety of dendritic intrinsic currents [42–53], and simultaneous or close time-related activation of several synapses [54–58]. Shunting effects of network activities on cortical neurons [59, 60], and in particular on their dendrites, might significantly influence the expression of the abovementioned phenomena. In addition to thalamic inputs (see above), corpus callosum neurons, connecting two hemispheres of the cerebrum, provide inputs to neocortical areas. These neurons are located mainly in cortical layers II/III but also in infragranular layers, among them layer V, in different neocortical areas [61–64].

The other inputs to a given cortical area come from ipsilateral cortical fields. A given intracortical excitatory presynaptic axon forms between one to eight synaptic contacts with postsynaptic neurons [65, 66] that elicit excitatory postsynaptic potentials from 0.1 to 10 mV, with a total mean of about 1 mV [65–69]. Similarly to RE neurons, a network of inhibitory interneurons in the neocortex is coupled via electrotonic synapses, at least in young animals [70, 71].

A Description of Intrinsic Firing Patterns and Underlying Currents in Thalamocortical System

Physiology taught us that intrinsic properties of a neuron are defined by two key factors: (1) a unique set of ionic channels specific to a given neuron; and (2) the channel distribution in different compartments of the neuron. The diversity of channels in neurons is large and results in a variety of patterns of action potential generation induced by a constant input.

Thalamic neurons, like cortical neurons, have intrinsic membrane properties that cause their discharge pattern to change as a function of the level of depolarization of the cell. When depolarized, TC neurons discharge in a single-spike mode but when hyperpolarized they display a bursting pattern. Since their level of depolarization is dependent upon the ascending activity system (neurotransmitters systems mostly coming from the brainstem) to the forebrain, the discharge pattern of thalamic cells is modulated by ascending neurotransmitters, which levels are fluctuating throughout the various states of consciousness and sleep stages.

Thalamocortical Neurons

Thalamocortical (TC) neurons, like neurons everywhere in the central nervous system, possess a large set of intrinsic currents in their soma and dendritic membranes that enable them to contribute to the various oscillatory activities and/or mediate

some of them. At the high level, TC cells may exhibit two fundamentally different firing modes as evoked earlier (from tonic firing to a bursting firing pattern). To support those firing modes, several types of ionic conductances, reviewed in greater details below, shape the various peculiar excitatory properties of TC cells and how they respond to inputs: regular and persistent Na^+ conductances (e.g., I_{Na} and I_{NaP}), K^+ conductances (e.g., A-current I_A), Ca^{2+} conductances (e.g., T-current I_T), and the general cation current (h-current I_h). The electrophysiological identification of a TC neuron is shown in Fig. 5.1. Usually, a small depolarization of TC neurons with intracellular DC current pulses only produces a passive response (not shown). Progressive increase in the intensity of the depolarizing current leads to the generation of action potentials followed by increase in their discharge frequency (Fig. 5.1, left). The enhancement of depolarization in TC neurons over the stimulus duration is probably generated by persistent Na^+ current, I_{NaP} [72, 73]. This firing mode of TC neurons is denoted as *tonic firing*. Each fast spike produced by a TC neuron is followed by an afterhyperpolarizing potential (AHP). Neuronal firing is associated with Ca^{2+} influx [74, 75]. Rise of intracellular Ca^{2+} concentration during tonic spiking activates Ca^{2+}-activated K^+ currents ($I_{K(Ca)}$) that produce afterhyperpolarizing potential (AHP) [76, 77]. At the offset of the depolarizing current pulse, most TC neurons generate a medium or slow afterhyperpolarizing potential (Fig. 5.1, left). Application of low-amplitude hyperpolarizing current pulse results in passive responses (not shown). An increase in the pulse amplitude hyperpolarizes the TC neuron to a level of activation of hyperpolarization-activated cation current, I_h, that produces depolarizing sag [52, 78]. Of particular interest is the Ca^{2+} conductance based on T-type Ca^{2+} channels that give rise to I_T. At the offset of the hyperpolarizing current pulse, the TC

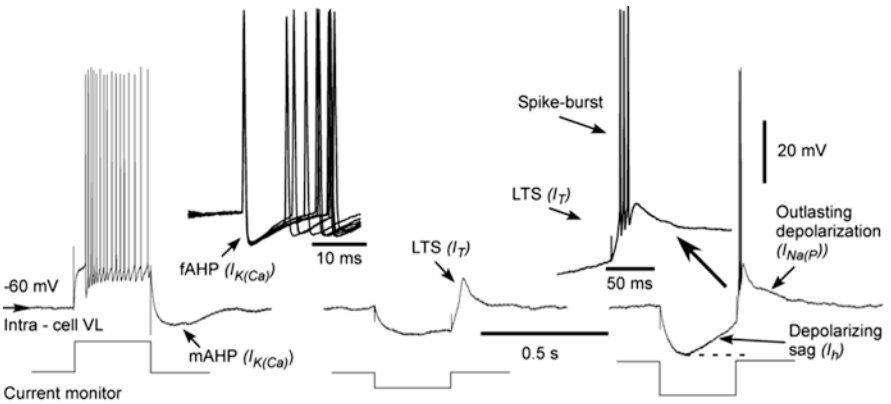

Fig. 5.1 Intrinsic electrophysiological properties of thalamocortical neurons. Barbiturate anesthesia. The membrane potential for this neuron was −60 mV. Depolarizing current pulse elicited tonic firing (*Left*). Each action potential was followed by fast AHP (fAHP). At the end of the current pulse a long-lasting AHP (mAHP) was generated. At the end of small amplitude hyperpolarizing current pulse the neuron generated a low-threshold spike (LTS) in isolation (*Middle*). During large amplitude hyperpolarizing current pulse (*Right*) depolarizing sag was obvious. At the end of the current pulse the neuron generated an LTS accompanied with spike-burst

neuron generates a depolarizing response, commonly called LTS for low-threshold spike, that is due to the de-inactivation of low-threshold Ca^{2+} current, I_T [51, 79–81]. Recent studies suggest that the LTS also contains a component mediated by I_{NaP} [73]. An increase in the amplitude of the hyperpolarizing current pulse produces an increase in both the depolarizing sag and the rebound excitation that leads to a burst of Na^+ spikes (up to eight spikes in the experiment shown in Fig. 5.1). Both spontaneous and evoked LTSs of TC neurons reveal gradual properties [82]. This type of response is referred to as *bursting mode of firing*. Thus, both excitatory and inhibitory inputs are able to induce firing of TC neurons. Excitatory inputs lead to a generation of firing in a tonic firing mode, while LTSs are generated at the end of inhibitory responses and TC neurons fire in a bursting mode. Tonic and bursting firing modes represent two fundamentally different modes of transmission of information. Tonic firing is directly proportional to EPSPs: the larger the depolarization, the greater the response, implying a fairly linear input/output relationship during tonic firing. In contrast, burst firing is an all-or-none response meaning that a larger input does not evoke a larger Ca^{2+} spike, implying a nonlinear input/output relationship. Some studies report the presence of electrical coupling between TC neurons [83], which are believed to play an important role in the generation and synchronization of spindle activities as discussed later in this chapter [84].

Reticular Thalamic and Zona Inserta Neurons

Reticular (RE) neurons are crucial in the generation of sleep rhythms and in inhibiting external signals through TC neurons. As briefly described earlier, the thalamic reticular nucleus is a thin layer of GABA nerve cells that surrounds the thalamus. RE and zona incerta (ZI) neurons release the potent neurotransmitter GABA to their main targets, which are TC neurons in the dorsal thalamus.

RE neurons possess complex intrinsic firing properties, akin to TC neurons, which consist in the bursting and tonic discharge modes. Three currents have been deemed critical to endow them of oscillatory properties sustaining sleep oscillations: I_T, and two calcium-activated currents, $I_{K(Ca)}$ and I_{CAN}, further reviewed below. The bursting mode is exhibited during EEG-synchronized sleep (non-rapid eye movement, NREM, sleep), while tonic discharge is detected during waking and rapid eye movement (REM) sleep [85–87]. These two firing modes depend on the membrane potential of the cell [88–90]. At depolarizing membrane potential (above −65 mV), intracellular injection of positive current pulse induces a train of action potentials. In contrast, intracellular injection of the same current pulse at hyperpolarized membrane potential (below −65 mV) results in the generation of high-frequency (300–500 Hz) bursts of action potentials [91, 92]. Similar firing patterns could also be found during spontaneous activity. Much like TC neurons, a RE neuron fires spikes in tonic mode when depolarized, whereas it fires spikes in a bursting mode upon hyperpolarization. A subgroup (about 30%) of neurons reveals the presence of prolonged hyperpolarizing potentials preceding spindles in RE neurons, which facilitated occurrence of bursts [93]. The high-frequency

bursts in RE neurons are generated through the activation of low-threshold Ca^{2+} current (I_T) [94, 95]. In vitro, an intracellular injection of negative current pulse is typically followed by the generation of rebound LTS and burst of action potentials [94]. Following this LTS, an AHP hyperpolarizes RE neuron and a second LTS is generated as a rebound on this hyperpolarization [91]. Such activity could be maintained for several cycles with frequencies reaching 12 Hz. The low threshold spikes in RE neurons are gradual in nature [96, 97]. Current-clamp intracellular recordings of RE neurons in cats under barbiturate anesthesia revealed the presence of membrane bistability in ~20% of neurons. Bistability consisted of two alternate membrane potentials, separated by ~17–20 mV. While non-bistable (common) RE neurons fire rhythmic spike-bursts during spindles, bistable RE neurons fire tonically, with burst modulation, throughout spindle sequences. Bistability is strongly voltage dependent and only expressed under resting conditions [98], even when LFP shows increased patterns of activity [99].

Reticular thalamic neurons form tight clusters [10]. It is known that RE neurons are interconnected by chemical and electrical synapses [84, 100–102]. One study reports, however, that intrinsic GABAergic connections are present only in young, but not in adult, mice [103]. Clusters of electrically coupled RE neurons generate synchronous activities [104], suggesting that tightly interconnected bursting RE neurons within clusters would induce large inhibitory postsynaptic potentials (IPSPs) in their targets.

External inhibitory input to high-order thalamic neurons is provided by ZI [8, 9]. Despite similar origin and neurotransmitter content, several features of ZI neurons are different from those of RE neurons. First, ZI neurons do not generate spike bursts [105], and they do not receive excitatory feedback inputs from dorsal thalamus [8]. The main excitatory inputs to ZI come from peripheral sensory inputs and from cortical layer 5 pyramidal neurons [106]. It appears that ZI neurons are not connected via gap junctions. ZI neurons are connected via traditional chemical synapses; these connections are formed between different sectors of ZI of the same hemisphere as well as with contralateral hemisphere [11]. This implies that firing of ZI neurons consequently decreases the firing probability of ZI's target neurons. Thus, during sleep or anesthesia, the overall inhibition exerted by individual single-spike firing ZI neurons onto the target TC neurons should be much smaller compared to the burst firing of electrically coupled RE neurons.

Neocortical Neurons

Neocortical neurons reveal at least four distinct electrophysiological types: (a) regular-spiking (RS); (b) intrinsically bursting (IB); (c) fast-rhythmic-bursting (FRB); and (d) fast-spiking (FS, shown in Fig. 5.2) [107–110]. We previously provided a detailed description of firing pattern properties of neocortical neurons and their ionic mechanisms [22]. Therefore, we skip a detailed description here, and instead only emphasize two main points:

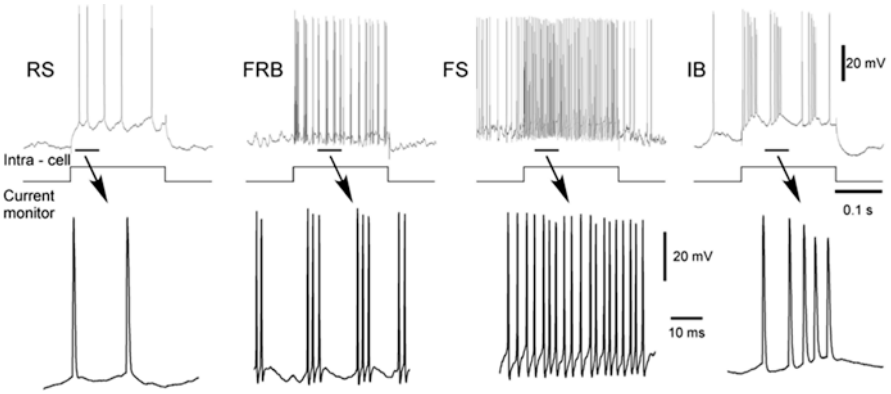

Fig. 5.2 Electrophysiological identification of different cell-classes. (*Upper*) Responses of regular-spiking (RS), fast-rhythmic-bursting (FRB), fast-spiking (FS), and intrinsically bursting (IB) neurons from area 4 to depolarizing current pulses (0.2 s, 0.8 nA). (*Bottom*) Each depolarizing response from each of the cell classes in the upper panel is expanded

1. Only fast-spiking neurons provide linear input-output relation; that is, the increase in their firing rate is linearly proportional to the increase in depolarizing current. The fast-spiking neurons are GABergic and therefore inhibitory [108]. The other types of neurons typically provide nonlinear input-output relation, they integrate inputs and the output signal may be either enhanced, for example, by burst firing, or dampened, for example, because of the fast adaption in regular spiking neurons.
2. The intrinsic neuronal properties are not stable and undergo dynamic changes [110, 111]. The changes in firing patterns can be induced by multiple sources, such as changes in the overall network state [111], membrane potential changes [112], or neuromodulator activities [113]. Because network activities induce continuous changes in extracellular ionic dynamics [114–117], the changes in extracellular ionic concentration also cause changes in intrinsic neuronal responses [118].

Oscillations Generated Within the Thalamocortical System and Their Underlying Mechanisms

Rhythms are ubiquitous in neural systems. The brain exhibits stereotypical synchronized oscillations during sleep. At the macro-level, those synchronous rhythms are detected by EEG recordings and used to differentiate changes in alertness and sleep stages. In humans, NREM sleep is divided into three distinct stages, which manifest themselves by stereotypical activities on the EEG [119]. Of particular relevance for this chapter are NREM stages 2 and 3. Stage 2 is characterized by sleep spindles and K-complexes. Spindles are waxing-and-waning oscillations with frequencies ranging

from 10 to 16 Hz and K-complexes are isolated slow waves, which are largest in amplitude EEG events that can be recorded from a healthy brain. Stage 3 sleep, also called deep sleep or slow-wave sleep, with *delta* waves (1–4 Hz) and *slow-wave* oscillations (<1 Hz).

Those spontaneous activities recorded on the EEG represent the statistical aspect of the continuously fluctuating condition of the brain, and in particular reflect correlated synaptic activity in cortical cells from oscillations of neuronal populations [120]. The thalamocortical system plays a central role in generating and sustaining those NREM rhythms and we describe below the physiological characteristics underpinning the oscillations that are a hallmark of NREM sleep.

Oscillatory rhythms generated in the thalamocortical system may be divided in two main classes: (1) intrinsic rhythms that are generated by a single neuron endowed with pacemaker oscillatory activity as a result of an interplay between specific intrinsic currents and (2) extrinsic (or network) rhythms that emerge from cellular interactions within a network, even if none of the constituent elements is capable of auto-rhythmicity. Excitatory rhythms usually require the interplay of excitatory and/or inhibitory synaptic interactions between neurons of the same or different classes. Intrinsic neuronal currents contribute to the generation of network oscillations. Oscillations may be also generated in a population of non-pacemaker neurons. We next review the major properties and mechanisms of normal (non-paroxysmal) oscillations observed during different sleep stages: slow-wave oscillation, delta, and spindles.

Slow Oscillation (<1 Hz)

While some types of thalamic and cortical oscillations, such as thalamic delta (1–4 Hz) and spindle (10–16 Hz) oscillations, presumably result from the interaction of a few intrinsic currents or a few neurons of different types and could be reproduced with scaled-down computer models (see below), there exist some oscillatory rhythms which are only observed in large enough networks. The slow oscillation (0.3–1 Hz) rhythm is an important example of the latter. The slow oscillation, one of the most important sleep oscillations, is a hallmark of deep NREM sleep (stage 3, also called slow-wave sleep or SWS), dominating cortical activity during early periods of sleep and under some types of anesthesia [121–125]. During a slow oscillation cycle, the entire cortical network alternates between silent (hyperpolarization or "*down*") and active (depolarizing or "*up*") states, each lasting 0.2–1 s. Silent periods are periods of disfacilitation (i.e., absence of synaptic activity), while active periods have intensive synaptic activity leading to the generation of fast oscillations within the thalamocortical system. We describe below the key mechanisms underlying the slow oscillation.

Overview of the Underlying Mechanisms

The slow oscillation is essentially a cortical rhythm. This conclusion is based on three basic observations: (a) The slow oscillation survives extensive thalamic lesions [126]; (b) the slow oscillation can be recorded in neocortical slices [127] and cultures [128–130]; and (c) the slow oscillation is absent in the thalamus of decorticated cats [131].

At least three distinct, nonexclusive, mechanisms were proposed to explain the origin of slow-wave oscillations based on what causes the transition to the active (Up) states of the thalamocortical network: (a) spontaneous miniature synaptic activities (or *minis*) coming from mediator release in a large population of neurons leading to occasional summation and firing [112]; (b) spontaneous intrinsic activity in layer V intrinsically bursting neurons [127]; and (c) self-sustained asynchronous irregular activity in layer V [132]. Despite different underlying hypotheses, all these scenarios involve some form of spontaneous activity of cortical neurons during the silent ("down") state immediately preceding the transition to the active state. Details of these mechanisms are further discussed below in the section "Effect of Slow Oscillations on Information Flow in the Brain."

While most studies have focused on intracortical mechanisms of slow oscillation, some studies pointed to a possible involvement of the thalamus. Following an activation of the metabotropic glutamate receptor (mGluR, mGluR1a), cortical inputs can recruit cellular mechanisms that enable the generation of an intrinsic slow oscillation in TC neurons in vitro with frequencies similar to those observed in vivo [133]. It was suggested that cortical activity can recruit intrinsic oscillatory mechanisms in thalamocortical neurons [133], which could support slow rhythm [134].

Recently, studies combining in vivo recordings in animals and network modeling proposed a new role for thalamocortical interactions during slow oscillations [135, 136]. It was found that thalamocortical inputs critically contribute to maintaining slow oscillation in the intact thalamocortical system. Full or partial cortical deafferentation that removes thalamocortical inputs also disrupts the slow rhythm in the neocortical network. Details of these studies are presented in the section below.

A high degree of local synchrony in thalamocortical network during slow sleep activity [137] is reflected in large-amplitude fluctuations of the local field potential (LFP), with a characteristic positive wave in superficial layers and a negative wave in deep layers recorded during active states of slow oscillation [138–140]; LFP polarity inverts during silent states of slow oscillation. This EEG pattern reflects complex current source density (CSD) profile generated during slow sleep activity, with current sources generally located in superficial layers and current sinks in deep layers during active states and inverse of this during silent states. An LFP model taking into account the strong filtering properties of the extracellular space is necessary to explain such CSD profiles [141].

Effect of Slow Oscillations on Information Flow in the Brain

Intracellular studies on anesthetized and non-anesthetized cats have shown that the hyperpolarizing phase of the slow oscillation is associated with disfacilitation, a temporal absence of synaptic activity in all cortical, TC, and RE neurons [125, 131, 142]. Even a moderate spontaneous hyperpolarization of TC neurons during depth-positive EEG waves is sufficient to displace them from firing threshold, thereby affecting transmission of information toward the cerebral cortex and thus creating disfacilitation [131, 143, 144]. An absolute blockade of information transmission through the thalamus occurs only when prethalamic (lemniscal) stimuli are used by shunting spike generation in TC neurons [131, 143, 145]. Responses to peripheral sensory stimuli still may reach the cerebral cortex during sleep or anesthesia [144, 146–154], but the precision of the cortical network to respond to peripheral volleys during disfacilitation periods is lost [144, 152]. Spike timing is critical in cortical information processing [155] and a minimal time interval of stable TC activity is required to achieve conscious perceptions [156]. Thus, the conscious perception is impaired during sleep and anesthesia, likely because of the loss of precision in the sensory information transfer from periphery to the cerebral cortex. The transmission of peripheral information to the cerebral cortex during periods of disfacilitation still may occur when peripheral stimuli elicit barrages of EPSPs in TC neurons that triggers LTSs crowned by spike-bursts at hyperpolarized voltages and tonic firing at depolarized voltages [144]. During disfacilitation, the membrane potential of cortical neurons is mediated by K^+ currents, primarily leak currents [125]. The long-lasting hyperpolarizations of cortical neurons are absent when brain cholinergic structures are set into action [126, 157] or during REM sleep and waking (Fig. 5.3) [124, 125].

Basic Mechanisms Underlying Generation of Slow Oscillation in Neocortex

Several distinct mechanisms for the origin of slow cortical oscillations were proposed. The first mechanism depends on spontaneous miniature synaptic activities (minis) [158], caused by spike-independent release of transmitter vesicles and are regulated at the level of single synapses [159, 160]. Such spike-independent synaptic release occurs during the silent state of the cortical network, for example, in slices, in the neocortical slabs [112, 161], or during the hyperpolarizing components of slow sleep oscillation. Occasionally, summation of spike-independent minis depolarizes cortical neurons to the level of activation of the persistent Na^+ current [50, 162]. This minis-dependent depolarization may activate IB neurons whose spikes then trigger synaptic potentials that result in depolarization and spiking of a population of postsynaptic neurons; activity spreads, thus triggering the onset of an active state. Shunting inhibition [59, 60] and activity-dependent increase of failures of synaptic transmission [116] significantly reduce the effectiveness of single axon EPSPs, thus preventing the network from overexcitation. Since the number of neurons in slices is small, their interconnections are reduced and are also strongly affected by the thickness of the slice [163]. It is unlikely that minis-dependent spontaneous activity would lead to active periods in slices.

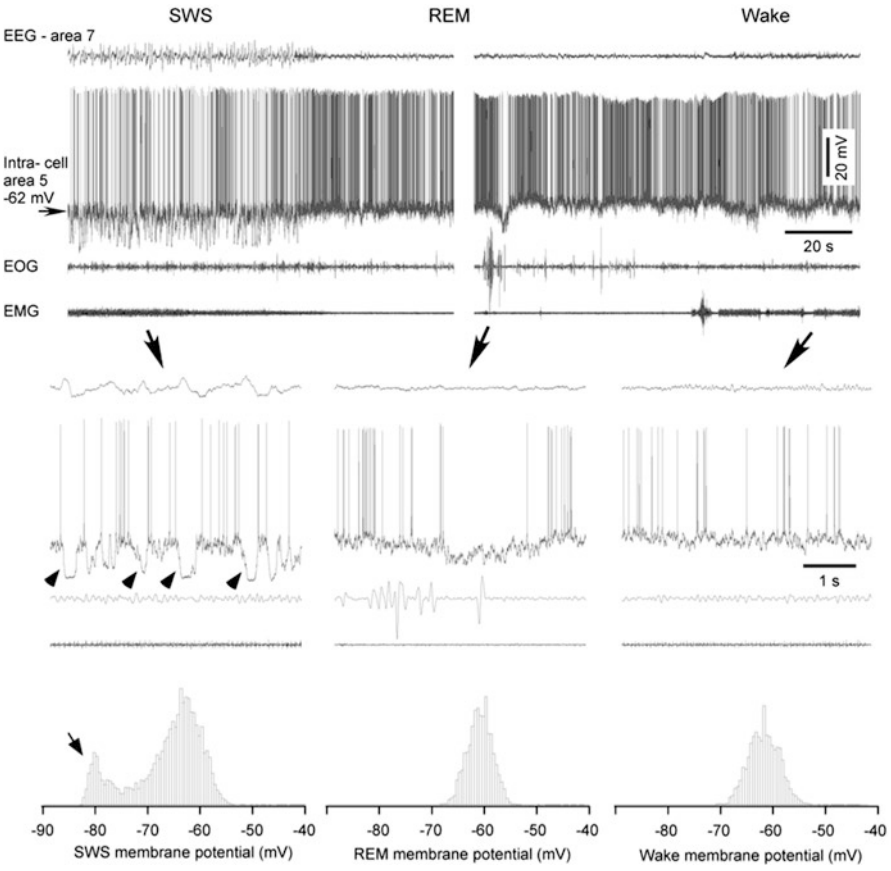

Fig. 5.3 Cortical intracellular correlates of natural slow-wave sleep (SWS), REM sleep, and waking states. The four traces depict (*from top to bottom*): EEG from area 7, intracellular activity of area 5 RS neuron (membrane potential is indicated, −62 mV), EOG, and EMG. High-amplitude and low-frequency field potentials, intracellular cyclic hyperpolarizing potentials, and stable muscle tone are distinctive features of SWS. Low-amplitude and high-frequency field potential oscillations, tonic neuronal firing with little fluctuations in the membrane potential, rapid eye movements, and muscle atonia are cardinal features of REM sleep. Low-amplitude and high-frequency field potential oscillations, tonic firing with little fluctuations in the membrane potential, and muscle tone with periodic contractions are characteristics of the waking state. Parts indicated by arrows are expanded below (*arrows*). Note cyclic hyperpolarizations in SWS (indicated by *arrowheads*) and diminished firing rate during ocular saccade in REM sleep. The histograms of membrane potential in SWS, REM sleep, and wake are illustrated below. Note the bimodal distribution of the membrane potential and the presence of hyperpolarizing mode of membrane potential during SWS (indicated by *arrow*). (Modified from Timofeev, et al. [125])

In isolated small (10 × 6 mm) cortical slabs, relatively rare (3.2 ± 0.3 periods per minute) nonperiodic spontaneous active states were found. These patterns were similar to the active states of slow oscillation, but frequency was low, presumably because a relatively small number of cells was interconnected. Assuming minis-dependent

mechanism of active states generation, increasing the size of the isolated cortical tissue to a gyrus should increase the number of sites where activity could arise [112, 164]. This would lead to an increased probability of occurrence of the active periods, thus attending frequencies similar to those of the cortical slow oscillation. To test this hypothesis, the mean and standard deviation of interburst intervals were estimated with analytical model as a function of the number of neurons present in a network (Fig. 5.4) [112]. For a slab the estimated mean was about 24 ± 21 s; the mean decreased with the size of the network and reached 4.9 ± 2.3 s for a network the size of a gyrus. The study suggested that cortical SWS oscillations could arise from the same mechanisms as spontaneous slab activity in the limit of a very large neuronal population. This hypothesis was probed using a Hodgkin-Huxley-based thalamocortical network model [164]. From the analytical model it was estimated that the mini-dependent mechanism can drive periodic network oscillations at frequencies 0.2–0.5 Hz when the network size exceeded ~10^8 neurons [112]. Computer simulations involving this order of magnitude of conductance-based model neurons is not yet feasible, so the amplitude of miniature events was increased by about 50%. In these conditions slow periodic oscillations similar to those observed in vivo were found (see Fig. 6 in [164]). Each active phase was initiated in one of the cortical pyramidal cells and then spread over thalamocortical network. While thalamic RE

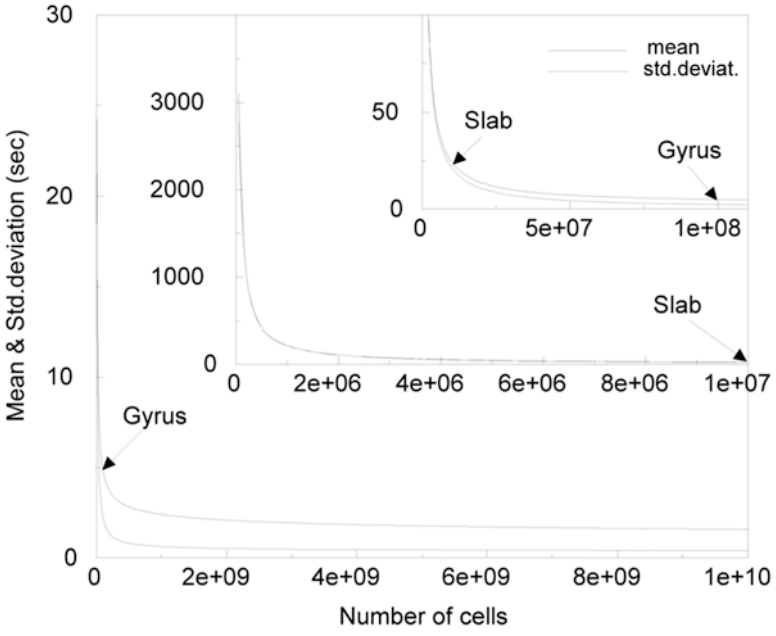

Fig. 5.4 Analytical estimates of the period T and standard deviation σ of the slow oscillation for the networks of diffzerent size. Analytical curves estimated based on in vivo data. Estimated mean of interburst intervals for a slab (about 10^7 neurons) is 24 s (standard deviation is 21 s) and for a gyrus (about 10^8 neurons) the mean is 4.9 s (standard deviation 2.3 s). (Modified from Timofeev, et al. [112])

and TC cells were not necessary to maintain slow sleep oscillations in the model, their presence changed spatiotemporal patterns of slow sleep activity. In a map-based model [165] in which conductances of neurons are neglected and the number of modeled neurons can be of order of ~1.36 millions of cells, the slow oscillation could be reproduced with realistic mini amplitudes and frequencies [166]. In this model, changes in the radius of neuronal connectivity affected the velocity of propagation of sleep slow oscillations.

Our intracellular data strongly suggest that the persistent Na+ current participates in the maintenance of the depolarizing state of the membrane potential (Timofeev, Grenier, Steriade, unpublished observations). This suggestion is based on two facts: (1) Voltage-current characteristics demonstrate the linear relations over a wide voltage range. However, the slope of this linearity is changed and becomes steeper at voltages below −65 mV. (2) At voltages above −65 mV, the spontaneous fluctuations of the membrane potential are flattened. Direct hyperpolarization of neurons below −65 mV produces significantly increased fluctuations of the membrane potential, revealing sharply rising synaptic potentials and indicating that some currents maintaining the membrane potential at a certain level of depolarization are now absent. The persistent Na^+ current in cortical neurons is activated at approximately −65 mV. Furthermore, at these voltages no other intrinsic currents are activated [50]. Thus, it seems that the persistent Na^+ current may contribute to maintaining depolarizing membrane potential that is primarily set up by synaptically generated potentials. This current becomes extremely important in various depolarizing states of cortical neurons. Overall, our data indicate that hyperpolarizing states present during SWS result from disfacilitation and leak currents predominately influence the membrane potential of neurons. The depolarizing states, which are present during the slow oscillation in SWS, as well as throughout REM sleep and waking, are composed of postsynaptic potentials that are amplified by the persistent Na^+ current.

The synaptic depression of active synaptic connections [161, 167, 168], the slow inactivation of the persistent Na^+ current [169, 170], the activation of Ca^{2+}-dependent K^+ current [171], and the activation of Na^+-dependent K^+ current [171] would displace the membrane potential of neurons from the firing level, and the entire network would go to the hyperpolarized or silent state. These observations were confirmed in modeling [164, 172]. Recent experimental results revealed that the downward transition (from active state to silence) in cortical networks is often better synchronized than the upward transition (from silence to active state), and shows no latency bias for any location or cell type [10, 173]. This in vivo result could not be explained by earlier models [164, 172, 174] and suggested that some larger scale biophysical mechanisms may be involved in manipulating the downward transition during slow oscillation [175]. One of the possible mechanisms is active cortical inhibition. Different types of inhibitory neurons are active during depolarized states of the slow oscillation [176]. We demonstrated that strong inhibitory barrages take place 200–300 ms in a subset of cortical neurons, which lead to a decrease in neuronal firing and a reduction of synaptic activities [177]. Indeed, a subset of fast-spiking inhibitory interneurons fire specifically prior to the onset of silent cortical state [178].

Two other studies demonstrated that cortical somatostatin positive interneurons fire prior to the onset of silent states [179, 180]. These interneurons can mediate inhibitory activities recorded prior to the onset of silent state leading to the onset of disfacilitation. Intracortical interneurons possess short axons. Therefore, this activity of cortical interneurons by itself cannot explain long-range synchronization of active state termination. It requires a common input to widespread cortical areas. Several such inputs could play a role in synchronization of onsets of silent states:

1. Thalamic inactivation or cortical isolation dramatically increase jitter of silent state onsets [177], suggesting that firing of some thalamic cells that send axons to widespread cortical areas and that form synapses on inhibitory interneurons can excite them and therefore contribute to synchronous termination of active cortical states. A recent study demonstrated that indeed occasional firing of VPM thalamic neurons that target parvalbumin positive cortical interneurons contribute to the onset of cortical silent states in the barrel cortex [181]. Thus, recent findings demonstrate that either somatostatin or parvalbumin expression in cortical interneurons can contribute to the onset of silent states.
2. Another possibility would be that some subcortical GABAergic inputs would directly inhibit a subset of cortical excitatory neurons. A subset of GABAergic basal forebrain neurons projecting to neocortex discharges spike bursts correlated with cortical slow oscillation [182]. The cortical targets of these neurons are unclear. At least most of the globus pallidum externa GABAergic cells projecting to the frontal cortex target GABAergic interneurons [183]. A subset of CA1 interneurons projects to the retrosplenial cortex [184]. Overall, firing of extracortical GABAergic cells can potentially contribute into the termination of activate states. However, known projections of long-axon GABAergic cells to the neocortex are local (restricted to a given area); therefore, firing of extracortical interneurons cannot in itself explain simultaneous terminations of active states across large cortical territories [10, 177].

In light of those observations, the prevalent hypothesis for the synchronous termination of spontaneous active states is the excitation of a small subset of cortical local circuit interneurons by a common extracortical excitatory drive. We have shown that thalamic inactivation was sufficient to desynchronize the active state termination [177]. It should be noted that although active inhibition does play a role in the termination of active states, it is not an essential factor. Blockage of intracortical inhibition does not prevent termination of active cortical states [175, 185].

Another possible mechanism accounting for the generation of active states during slow-wave sleep (SWS) oscillations is the generation of spontaneous activity by layer V cortical neurons. The dynamics of some intrinsic currents in cortical neurons, including the hyperpolarization-activated cation current, I_h, may mediate the recovery of active states in SWS, in a way similar to the interaction of the low-threshold Ca^{2+} current and I_h in thalamic relay cells that organizes thalamic oscillations in the delta frequency range [78, 186–188]. It was shown using cortical slice preparations that, using relatively high concentration (3.5 mM) of extracellular K^+, cortical slices can oscillate in the frequency range of slow sleep oscillations

[127]. This activity was usually initiated in layer V and propagated over the whole slice. It is not clear, however, how the specific conditions in those slice preparations affected the excitability of cortical neurons and the temporal patterns of their activity. An in vivo study shows that deep layer neurons (including layer V) are the first to show depolarization associated with active state onset and they also fire earlier than other cortical neurons at the onset of active states [139]. A slight increase in $[K^+]_o$ may depolarize some neurons to the firing threshold (see Fig. 2-3 in [127]). In these conditions the relatively large amplitude EPSPs, but not minis, might recruit postsynaptic neurons into active states. Only 5–20 synchronized presynaptic action potentials are needed to fire a postsynaptic neuron in vitro, assuming linear summation [65, 189]. Thus, spontaneous active periods might be obtained in slices that are exposed to a slightly increased $[K^+]_o$ and decreased $[Ca^{2+}]_o$ or any other factor leading to the depolarization of relatively large population of neurons in vitro.

A computer model was proposed where transitions from down (silent) to the up (active) state were initiated by spontaneous spike discharges in a small random group of neurons [174]. Once started, up states were maintained by strong recurrent excitation, and the transitions to the down state were due to a slow Na^+-dependent K^+ current. In vitro studies indicate that a group of neurons, which could initiate active periods, could be either layer V IB neurons [127] or spatially structured neuronal ensembles [190].

In another model, the spontaneous activity raised from recurrent connections between cortical neurons within a given layer (presumably layer V) leads to self-sustained irregular activity states within that layer [132].

The various mechanisms may well coexist, and all contribute to the generation of slow oscillations. Irrespective of the precise mechanism responsible for the slow rhythm generation, long-range excitatory and inhibitory synaptic connectivity likely play a major role in synchronization of transitions between active and silent states of slow oscillation leading to periodic LFP and EEG oscillations observed in animals and humans during deep sleep. The role of the thalamus, as reviewed below, might be to contribute to the long-range cortical generation and/or synchronization of the rhythm.

Role of Thalamus in Slow Oscillation

The relative contribution of the thalamus and cortex to sleep slow oscillation remains a controversial topic. A number of studies [127, 140, 164, 191–195] suggest that the neocortex is, in itself, sufficient to generate the slow activity characteristic of slow-wave sleep via recurrent excitatory and inhibitory intracortical interactions. Other studies, however, showed that the thalamus might actively contribute to the generation of the slow oscillation [133–135]. These results argue for a significant role of the thalamus in patterning the slow oscillation during deep sleep [134].

A recent study revealed that the functional removal of thalamic inputs to the neocortex dramatically reduced the occurrence of active states of the slow oscillation [136]. The remaining active states in the affected region were infrequent and

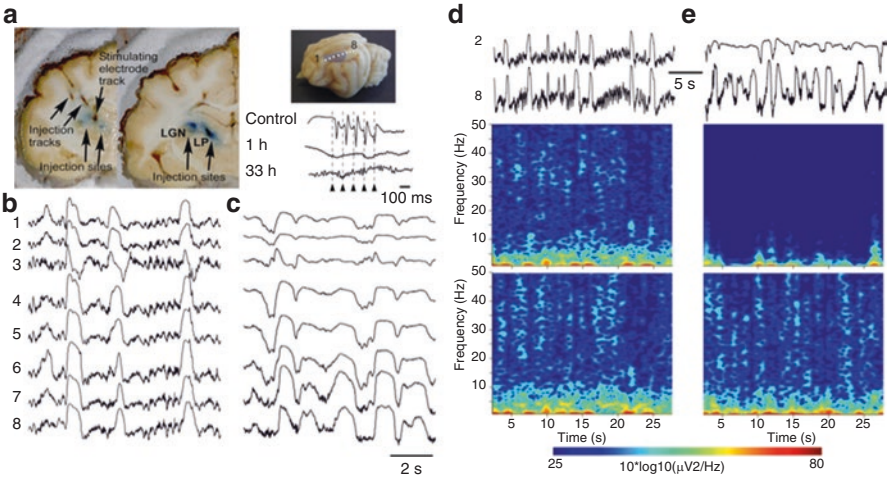

Fig. 5.5 Effects of partial thalamic inactivation on cortical slow oscillation. (**a**) Left, location of QX-314 injection sites (violet area) and stimulating electrode in LP nucleus. Top right, location of cortical recording electrodes 1–8. Bottom right, cortical response to LP stimulation in control and its abolition 1 h and 33 h after inactivation. Multisite LFP recordings (**b**) before and (**c**) 1 h after LP inactivation. Wavelet transform of the LFP signal from electrodes 2 and 8 (**d**) before and (**e**) after LP inactivation

local, explaining the low amplitude LFP in that region (Fig. 5.5). Similar results were obtained after complete isolation of a cortical area (slab), regular active states having been replaced by irregular and infrequent events. It was proposed that the thalamocortical neurons: (1) participate in the generation of active states, (2) contributes to the normal duration of the active states by maintaining recurrent activity, and (3) play a major role in synchronizing the slow oscillation across cortical columns. The modeling study—using a large-scale realistic model of thalamocortical network—revealed that the dense local connectivity was sufficient to generate spontaneous active states, but widespread cortico-thalamo-cortical projections were required to ensure the propagation of the locally generated active states to the rest of the network (Fig. 5.6) [136].

Another line of evidence on active thalamic contribution to generation of cortical slow oscillation comes from thalamic recordings: intracellular recording from a variety of thalamic nuclei in mice shows that neurons within parafascicular and posterior nuclei of thalamus start active states simultaneously, or even before investigated cortical sites [10] (Fig. 7 from [10]), and that thalamic neurons from anterior and ventral group on nuclei [196, 197], or central medial nucleus [198], can even fire prior to onset of active cortical state. However, the fact that some thalamic neurons are activated prior to cortical active state does not necessary indicate that these neurons lead the slow oscillation. Global cortical slow waves tend to start in frontal regions and propagate backward [10, 199]; there are also local cortical slow waves [200, 201]. The fact that the thalamic recording demonstrates an activation prior to

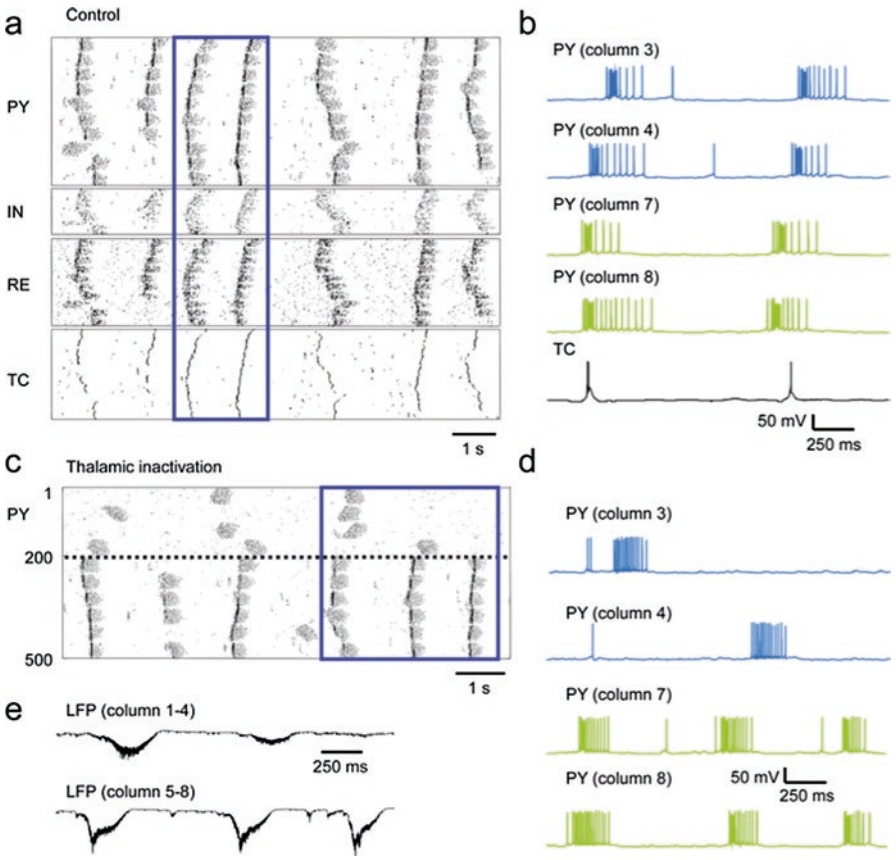

Fig. 5.6 Modeling study of the effect of thalamic deafferentation on the neocortical slow oscillation. (**a**) Slow oscillation in large-scale thalamocortical model. Rastergrams of pyramidal (PY), interneurons (IN), reticular (RE) thalamic and thalamocortical (TC) cells (upper panel). (**b**) Examples of membrane voltage of PY neurons from selected columns and of a TC neuron in control condition. (**c**) Removal of synaptic connectivity from TC neurons to the first four cortical columns (top) reduced active states occurrence. (**d**) Examples of membrane voltage of pyramidal neurons from selected columns after removal of thalamic inputs. (**e**) LFPs in deafferented columns 1–4 were reduced in amplitude in comparison to intact columns 5–8

cortical recording may only suggest that cortical recording was performed in an area that was not leading that particular cycle of the slow oscillation. These results support the studies suggesting the role of the widespread (matrix) thalamocortical projections in the synchronization of another NREM sleep rhythm, cortical sleep spindle oscillations [202].

When the thalamocortical connectivity was abolished to capture the thalamic inactivation, active states of the slow oscillation became desynchronized in the affected cortical areas. Surprisingly, the slow oscillation recovers within hours after disruption of the thalamocortical connectivity [136]. Using computer models, it was

found that following a decrease in the overall level of activity, the normal pattern of the slow oscillation can be recovered by upregulation of excitatory synaptic conductances or decrease in the potassium leak current. Synaptic scaling is known to be involved in homeostatic synaptic plasticity triggered by changing of the overall activity level [203]. Other factors that may contribute to the recovery of slow oscillation after thalamic inactivation include a homeostatic effect on neuromodulation, which can increase excitability by blocking K^+ leak currents [113], and on intrinsic conductances, which can affect the expression of intracellular excitatory and inhibitory conductances [204]. In sum, this study led to the conclusion that the deafferentation-induced alterations of the sleep slow oscillation can be counteracted by compensatory intracortical mechanisms and that the sleep slow oscillation is a fundamental and intrinsic state of the neocortex.

Delta Oscillation

The field potential recordings from the neocortex in both humans and animals during sleep reveal the presence of delta oscillation with frequencies 1–4 Hz. Delta and the slow oscillation represent two distinct phenomena [205], with differences in the dynamics between the slow and the delta oscillations, as the latter declines in activity from the first to the second NREM sleep episode, whereas the former does not. The delta oscillation has likely two different components, one of which originates in the neocortex and another one in the thalamus. Surgical removing of the thalamus or recordings from neocortical slabs in chronic conditions demonstrated significant enhancement of delta activity in the neocortex [206–208]. Little is known about cellular mechanisms mediating cortical delta oscillation. One of the hypotheses suggests that cortical delta activity is driven by an intrinsic discharge of IB neurons [209]. The rationale for this hypothesis is, however, not clear: firing pattern of IB neurons could only be revealed by intracellular application of depolarizing current pulses (see Fig. 5.2); however intracellular recordings from cortical neurons during sleep demonstrated the presence of long-lasting hyperpolarizing, but not depolarizing potentials [124, 125, 210]. Therefore, IB neurons can contribute to the spread of activity, but the initial group of neurons driving delta activity still remains unidentified. Using a supervised learning approach, we recently developed a method of automatic detection of slow waves, which encompasses both slow and delta oscillations [211, 212]. Exploiting this method, at least in mice, we were unable to find differences between slow waves generated during slow oscillation vs. during delta activity. This suggests that slow waves generated by both types of oscillations share the same mechanisms. The differences in frequency between the two rhythms likely depend on activities of neuromodulatory systems. It is well known that activity of neuromodulatory systems is reduced during SWS [213–215],), but some firing of neurons in these structures remain [216–218]. A slight change of neuromodulator content dramatically affects power of slow-wave activities [219]. Thus, we hypothesize that slow waves generated during both delta and slow oscillation share the

same origin. The difference in the frequency of slow vs. delta oscillations can be explained by the difference in the neuromodulatory content. This hypothesis needs experimental confirmation, and the test of this hypothesis is feasible with currently available tools.

Thalamic Delta Oscillation

Thalamic delta (1–4 Hz) oscillation is a well-known example of rhythmic activity generated intrinsically in thalamic relay neurons. These oscillations arise as an interplay of low-threshold Ca^{2+} current (I_T) and hyperpolarization-activated cation current (I_h) and may be observed during deep sleep when TC neurons are sufficiently hyperpolarized to deinactivate I_T [78, 186–188]. The dynamic of I_T was summarized in earlier sections of this chapter. It was explained that sufficiently long and deep hyperpolarization of TC neuron removes I_T inactivation and makes possible rebound burst generation triggered by a depolarized input [79, 82]. An additional factor required for sustained bursting in the isolated TC cell is the presence of I_h [52, 78]. The interplay of I_T and I_h during delta oscillation was first described in vitro [78] and was later studied with computational models [220].

The mechanisms of single cell delta activity can be synthesized as follows: a long-lasting hyperpolarization of a TC neuron leads to a slow I_h activation that depolarizes the membrane potential and triggers rebound bursts, mediated by I_T, which was deinactivated by hyperpolarization. Both I_h (because of voltage dependency) [52] and I_T (because it is a transient current) [51] inactivate during burst, so the membrane potential is hyperpolarized after burst termination. This afterhyperpolarization then starts the next cycle of oscillations (Fig. 5.7).

Synchrony between different TC neurons during delta activity has not been found in decorticated cats [191]. Thus, it is unlikely that thalamic delta activity could play a leading role in the initiation and maintenance of the cortical delta rhythm. However, the presence of a corticothalamic feedback in an intact cortex could synchronize thalamic burst-firing at delta frequency and generate field potentials [188, 221]. In such conditions the cortical network plays a critical role in the generation of delta frequencies. At certain level of leak current (I_{leak}), the "window" component of I_T may create oscillations similar in frequency to the intrinsic thalamic delta oscillation [222].

Sleep Spindle Oscillations

Sleep spindle oscillations consist of waxing-and-waning field potentials of 10–16 Hz which last 0.5–3 s and recur every 5–15 s. In vivo, spindle oscillations are typically observed during light sleep or during active phases of slow-wave sleep oscillations. In cats, the maximal occurrence of sleep spindle was found in motor, somatosensory,

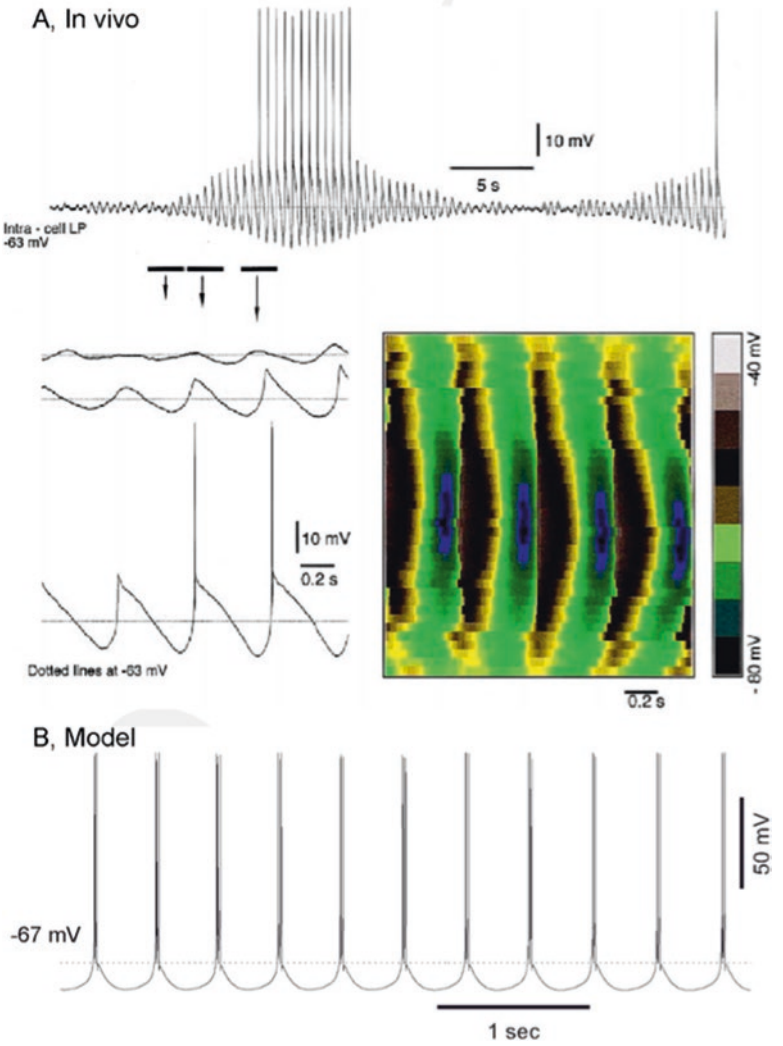

Fig. 5.7 Thalamic delta activity. (**a**) Waxing and waning delta activity in LP thalamocortical neuron in decorticated cats. Ketamine-xylazine anesthesia. Periods of delta-like oscillation start from subtle fluctuations of the membrane potential. The amplitude of such activity starts and declines without changes in frequency (2.2 Hz). Periods indicated by horizontal bars are expended *below*. *Right* topographical plot of delta-like activity emphasizes the stable frequency of delta-like activity regardless of the amplitude of LTSs. From bottom to top, successive sweeps; from left to right, time; voltage is color coded. Intrinsic delta oscillations in the isolated model of a single TC neuron. (From Timofeev, et al. [82].) (**b**) Upon hyperpolarization the modeled TC neuron shows periodic ~2.5 Hz bursting mediated by interplay of I_T and I_h. Blocking either of these two current abolishes oscillations. (From Bazhenov and Timofeev, unpublished observations)

and, to a lesser extent, in associative cortical areas [223]. A presence of spindle oscillations after decortication [191, 224, 225] provides strong evidence for the thalamic origin of this activity. Spindle-like activity was found in thalamic LGN slice preparations of ferrets with preserved interconnections with perigeniculate nucleus [91, 226, 227]. However, spindle activity was not reported in the visual cortex of ferrets, where the LGN nucleus project and thus the mechanisms of spindle-like activity found in the LGN slices from ferrets maintained in vitro may not be directly applied to the interpretation of spindle activity generated in the brain.

Basic Mechanisms of Spindle Oscillations

In vivo, in vitro, and modeling studies suggest that the minimal substrate contributing to the generation of spindle oscillations is generated in the thalamus as a result of interaction between thalamic RE and TC cells [226, 228–231]. According to this hypothesis, RE inhibitory neurons fire a spike burst that elicits an IPSP in TC neurons. At the end of this IPSP the TC neurons generate rebound spike-burst that in turn excite RE neurons, which then generate spike-bursts, starting the next cycle of spindle oscillation. There are at least two sets of data, which demonstrate that this hypothesis does not cover all spindle generating mechanisms:

1. Spindles are generated in isolated RE nucleus [100, 232] and spindles are absent in the dorsal thalamus that is disconnected from RE nucleus [229].
2. During the early 3–4 IPSPs composing the spindle, TC neurons do not display rebound spike-bursts [82], suggesting that the reciprocal TC-RE connections are not contributing to the early phase of a spindle sequence.

Generally, the early part of spindles is not observed or less marked at the neocortical level. A more complex model suggests the presence of at least three phases with different underlying mechanisms that contribute to the spindle generation (Fig. 5.8a) [82]. The waxing phase of spindle oscillations is associated with recruitment of neurons from dorsal thalamic and RE nuclei [122]. During an early phase of spindles, the RE nucleus is driving the spindles by its own mechanisms (see below). The second part of spindles primarily develops as a result of interactions between RE and TC neurons as described above, but cortical firing contributes to the spindle synchronization through the firing of corticothalamic neurons imposing simultaneous excitation of RE and TC neurons. Given robust cortical influence on RE neurons [233], the inhibitory influences of RE neurons onto TC neurons reinforce the spindle. The waning phase occurs as a result of Ca^{2+}-induced cAMP upregulation of hyperpolarization activated cation current, I_h, in TC cells [89, 234, 235], and network desynchronization [82, 236].

In modeling experiments, a single reciprocal RE-TC pair represents the minimal model that is capable to generate spindle-like oscillations [237]. In this model, TC-mediated EPSPs trigger rebound burst in RE cell. In return, RE-mediated IPSPs enhance TC cell hyperpolarization after bursts, thus increasing I_T deinactivation and therefore opening the way for the next rebound burst generated by the TC neuron.

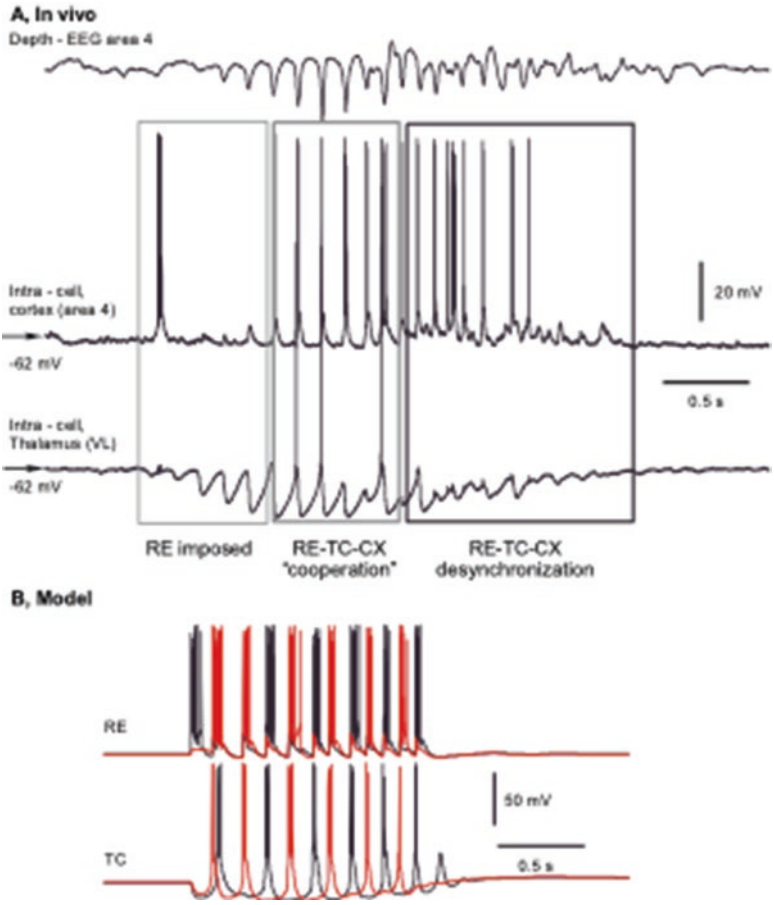

Fig. 5.8 Cellular basis of spindle activity. (**a**) In vivo recordings. Three phases of a spindle sequence. Dual intracellular recording of cortical (area 4) and TC (VL) neurons. (1) Initial phase consists of series of IPSPs in TC neurons that are not followed by rebound spike-burst, suggesting that they are imposed from RE network. Spontaneous firing of some cortical neurons may trigger activities of RE network. (2) During the middle phase of the spindle, the rebound spike-bursts of TC neurons excite both RE and cortical neurons. The activity of cortical, RE and TC neurons is phase-locked. (3) At the end of spindles cortical neurons no longer fire in phase-locked manner. This firing induces depolarization of both RE and TC neurons that create conditions for the spindle termination. (Modified from Timofeev, et al. [82].) (**b**) Computational model. Spindle oscillations in the circuit of 2 RE and 2 TC cells. RE cells fire every cycle of oscillations while TC cells skip every other cycle. Progressive increase of intracellular Ca^{2+} concentration during spindle increases a fraction of I_h channels in the open state. It leads to depolarization that eventually terminates spindle. (From Bazhenov and Timofeev, unpublished observations)

In this model, however, both RE and TC cells oscillate at the same 7–10 Hz frequency [238]. This is not consistent with experimental data where TC neurons do not fire every cycle of oscillations, but intermit bursting with subshreshold oscillations [227]. A simplest circuit model sufficient to generate this type of spindle oscillations includes two reciprocally coupled RE neurons and two TC cells providing excitation to and receiving inhibition from RE neurons [239]. In this model, the RE cells fire at spindle frequency, while each TC neuron generates a burst of spikes every other cycle of oscillations (Fig. 5.8b). $GABA_A$ input from RE neuron is required to provide hyperpolarization that deinactivates I_T channels. For low to moderate levels of $GABA_A$ inhibition more than one cycle of oscillations is required to sufficiently deinactivate I_T; therefore, a TC neuron fires a single burst every few cycles. Enhancing $GABA_A$ inhibition in the model increases the frequency of TC firing and eliminates burst skipping.

Thalamic vs. Cortical Contribution to Spindle Termination

The termination of spindles may be mediated by three different mechanisms: (a) First, during the waxing phase of spindles, TC neurons are hyperpolarized to a level that significantly activates I_h; this current tends to repolarize TC neurons, preventing their rebound spike-bursts. Ca^{2+} accumulation leading to cAMP upregulation of I_h enhances this effect [89, 234, 235]. (b) Second, repetitive stimulation of the dorsal thalamus with low-intensity pulse-trains at spindle frequencies induces decremental responses in RE neurons [240]. This might mediate a depression of inhibition induced by rhythmic volleys from RE neurons to TC neurons [241, 242]. (c) A third mechanism for the termination of spindle depends on desynchronization of activity [82, 236, 243], based on dissimilarity of intrinsic responses in different cortical and TC neurons.

There are several sources of desynchronization that facilitate spindle termination. The first is related to the generation of LTS in TC neurons with different delays from the onset of IPSP. The asynchronous burst firing of TC neurons will keep the membrane potential of RE cells at relatively depolarized steady level, thus preventing the de-inactivation of T-channels and diminishing the probability of burst firing. Barrages of EPSPs from prethalamic relay stations (e.g., cerebellum) may produce a small, but long-lasting, depolarization and decreased input resistance of TC neurons that could desynchronize the thalamocortical network and disrupt the spindles [244]. Because the trains of prethalamic EPSPs would occur only randomly, the most important source of spindle desynchronization, leading to a decrease in their duration, likely comes from long-lasting spike-trains from neocortical neurons. Several specific mechanisms may be involved: (1) First, cortical IB neurons fire with bursts that may significantly outlast the duration of thalamically generated EPSPs [245]. (2) Slightly depolarized FRB neurons (some are corticothalamic projecting cells) could fire high frequencies, non-accommodating trains of spikes throughout the spindle [110]. Those bursting neurons would recruit other cortical neurons into an excited state that is out of phase with the thalamic neurons.

(3) Third, it was shown that short depolarizing inputs to cortical neurons may elicit firing responses outlasting the stimulus by tens of milliseconds [112], producing excitation in the network with up to 180° phase shift. (4) Lastly, strong depolarizing cortical inputs onto thalamic (primarily RE) neurons will prevent LTSs generation and thus will lead to the spindle termination.

An extensive study combining electrographic in vivo recordings in the cat and a realistic thalamocortical network model of spindle activity explored the hypothesis that neocortical feedback actively regulates spindle termination in intact thalamocortical networks [236]. This study showed that the depolarizing action of corticothalamic inputs, which is caused by the lack of precise coordination of thalamic and cortical firing during the later phase of spindles, prevented the de-inactivation of the low-threshold T-type Ca^{2+} channels in TC cells normally involved in spindle generation, and eventually led to the termination of the spindle sequence. This study concluded that spindle termination critically depends on both I_h upregulation and corticothalamic feedback.

Role of RE Nuclei in Spindle Generation

The patterns of spindles and their synchronization are different in the intact brain and in thalamic slices. The depolarizing plateau of the spindle envelope recorded from thalamic RE neurons in vivo [246] was not initially observed in RE neurons from ferret slices that, instead, displayed a sustained hyperpolarization during spindles [226]. This difference may be due to a lack of brainstem activating systems and corticothalamic depolarizing inputs in thalamic slices. More recently, recordings in thalamic slices [247] revealed depolarizing plateaus in about half of the recorded RE neurons during spindles at membrane potentials closer to those recorded in vivo. Spindles have been reported in the deafferented RE nucleus in vivo [229] and in computo [100, 248] but are absent in vitro [226].

One major difference between in vivo and in vitro conditions is that the long dendrites and axonal collaterals of RE neurons are, in all likelihood, cut when slices are prepared; modulatory systems arising from the brainstem are also absent in thalamic slices. The depolarization of RE neurons by inputs arising from monoamine-containing systems, such as the serotonin released by dorsal raphe afferents and noradrenaline released by locus coeruleus afferents, promotes the sensitivity of RE neurons to the IPSPs generated by intra-RE GABAergic connections, with the consequence of generating spontaneous oscillations within the frequency range of spindles [249]. In 2-D network simulations [250], RE neurons organized with "dense proximal connectivity" were examined in a hyperpolarized state (−65 to −75 mV), similar to the in vitro condition when no monoaminergic synapses are activated, and in a more depolarized state (−60 to −70 mV) that would correspond to a weak monoaminergic activity. In the latter condition, the RE neurons generated spindle-like oscillations, whereas in the former condition the oscillatory behavior was absent.

Another proposed mechanism of spindle generation in the isolated RE nuclei depends on the reversed IPSPs between RE neurons. For the reciprocal $GABA_A$

synapses between RE cells, the Cl^- reversal potential is about −71 mV, which is depolarized compared to the reversal potential in TC cells [251]. Thus, at a resting membrane potential of about −78 mV [93, 98, 252] a $GABA_A$ IPSP in a RE cell will be reversed and could trigger a burst of Na^+ spikes [92]. In vivo recordings and computational models of RE cells were used to investigate cellular dynamics at different levels of membrane potential. It was found that reversed IPSPs between RE neurons can directly trigger LTSs bursts at membrane potentials close to those seen during natural sleep [100]. Additionally, a subgroup of 30% of neurons revealed prolonged hyperpolarizing potentials just preceding spindles that would facilitate the reversed IPSP to trigger an initial LTS [93]. Only a fraction of RE neurons needs to be hyperpolarized to generate self-sustained spindle-like activity in the model of isolated RE nucleus [248]. In a one-dimensional RE network hyperpolarized below Cl^- reversal potential, the $GABA_A$-mediated depolarization initiated isolated patterns of spike-burst activity that traveled through the RE network with a velocity that depended on intrinsic and synaptic properties (see Fig. 5-6 in [100]). Similar patterns were described in some other network models [253–255]. In a two-dimensional model of RE network, the activity persisted in the form of rotating spiral waves when the network size was large enough [100]. It produced almost a periodic bursting in RE cells at the frequency about 3 Hz. The frequency of spontaneous oscillations increased up to about 10 Hz, when the resting potential of RE neurons was depolarized more closely to the Cl^- reversal potential.

A possibility of self-sustained activity within RE nuclei suggests a mechanism for spindle initiation. Each sequence of spindle oscillations is followed by waves of activity that persist in the RE network during interspindle lulls and initiate new spindle sequences. These patterns of RE activity could not trigger bursts of Na^+ spikes in the TC cells, which were depolarized after the spindle sequence, until the slow repolarization of TC cells deinactivated the low-threshold Ca^{2+} current and the local RE-evoked IPSPs could initiate a new sequence of spindle oscillations. Therefore, the rate of repolarization determines the duration of interspindle lull. This mechanism is illustrated in Fig. 5.9 with a network model of 100 TC and 100 RE neurons [256].

Role of Thalamocortical Projections in Synchronizing Spindle Oscillations

Human sleep spindles exhibit different synchronization properties when measured by EEG or magnetoencephalography (MEG) during simultaneous EEG/MEG recordings, whereby the EEG signal shows strong cross-pair coherence (Fig. 5.10a) unlike the MEG signal (Fig. 5.10b) [257–259]. Current source density profiles of cortical depth electrode recordings of sleep spindles during presurgical exploration of human epileptic patients have suggested that spatially coherent spindles could be generated by upper cortical layers while spatially incoherent spindles could be generated by middle cortical layers [202].

This hypothesis was tested using biologically plausible computational model using two parallel thalamocortical pathways (*core* and *matrix*)—pathways that were suggested from studies in primates, but whose functional role has remained

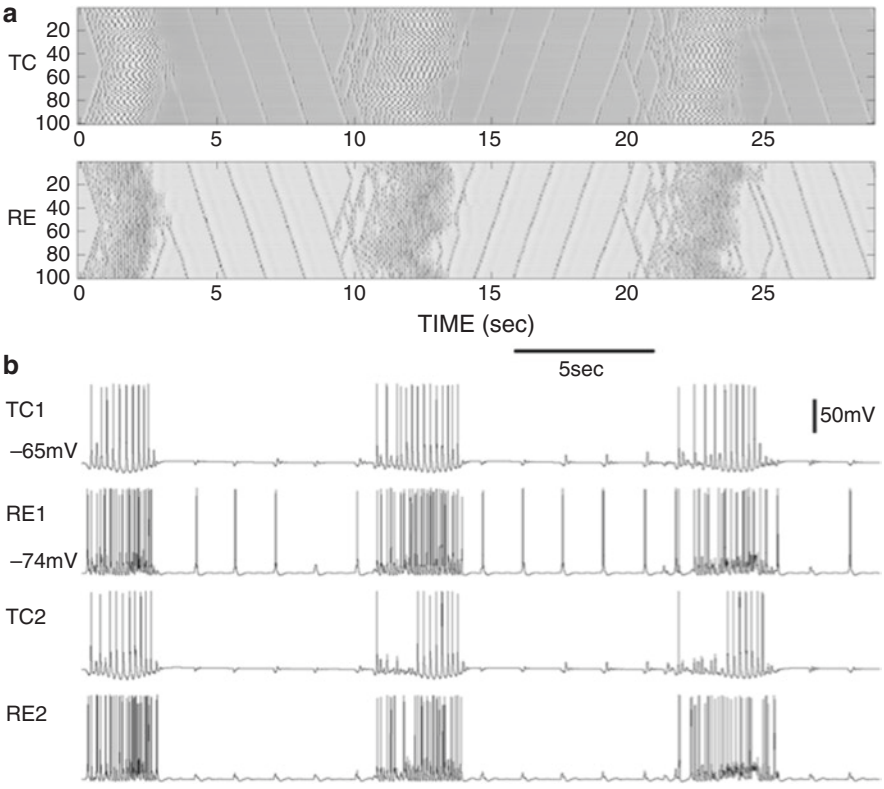

Fig. 5.9 Initiation of spindle sequences in RE-TC network with periodic boundary conditions. (**a**) The sequence of spindle oscillations was initiated at $t = 0$ by the local stimulation of TC cell #1 (left upper corner of the panel) and then propagates in both directions with constant velocity. After 2–4 s the spindle sequence is terminated because of the Ca^{2+} upregulation of I_h current and is followed by localized patterns traveling through the RE nuclei. This activity triggers a new spindle sequence at about t = 10 s. (**b**) Membrane potentials for two RE-TC pairs. (Modified from Bazhenov, et al. [256])

elusive [260, 261]. In this model, the breadth of connectivity in the core and matrix were investigated by carrying out simulations in which the matrix thalamocortical and corticothalamic connections became increasingly diffuse (wider footprint), whereas connections in the core pathway remained focal. The two pathways only differed in their respective connectivity profile and otherwise shared the same properties.

When the connectivity profiles of the matrix and core (i.e., TC → [PY, IN] and PY → [TC, RE] connections) were identical, the characteristics of spindle activity were similar in both networks. Particularly, the degree of synchrony in the two pathways during spindle sequence was indistinguishable. When the thalamocortical and corticothalamic connections fan-outs of the matrix significantly increased while maintaining constant focal connectivity in the core, the cortical spindle activity

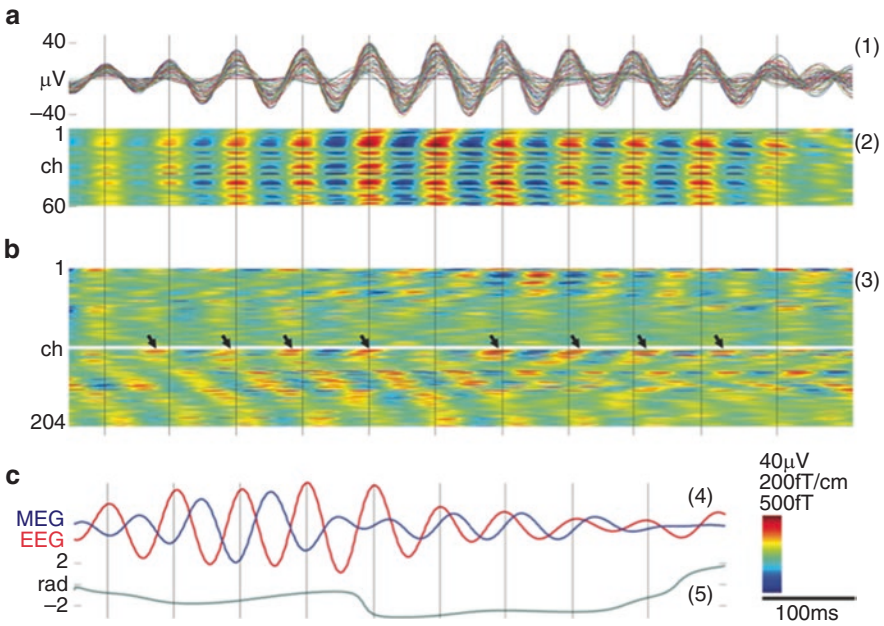

Fig. 5.10 Spindle recordings with EEG versus MEG sensors. (**a**) Referential EEG waveforms from 60 scalp channels during a single spindle, superimposed in (1) and shown with voltage color coded in (2). EEG appears highly synchronous across the scalp. (**b**) MEG spindle recorded by 204 gradiometers simultaneously with the recordings shown in (**a**). MEG appears highly variable and asynchronous across the scalp. The EEG peaks, marked with vertical lines, show no regular relationship with MEG peak activity. The arrows mark the peaks of a particular MEG channel that initially precedes and later follows the EEG peaks. These are typical findings in seven healthy subjects during natural nocturnal sleep. (**c**) Superposition of two of the largest amplitude EEG and MEG waveforms during a single spindle (1) further shows that EEG and MEG have variable relationships during spindles. The instantaneous phase lag, found via the Hilbert transform, varies considerably. (Modified from Dehghani, et al. [258])

appeared more synchronous in the matrix compared to the spindle activity in the core. The study concluded that the difference between core and matrix pathways in thalamocortical fan-out explains best the discrepancies in spindle synchronization between scalp EEG and MEG [202].

Fast and Slow Spindles

Several studies demonstrated that cortically recorded spindles oscillations are not homogeneous, but can be split on at least two types: fast spindles (12–15 Hz) and slow spindles (9–12 Hz). The fast spindles in humans can be recorded over the centroparietal region, and the slow spindles are predominantly recorded over frontal cortical areas [262, 263]. The mechanisms of these two types of spindles appear to be different [264]. This conclusion is based on the following facts: (a) The frequency

of two types of spindles is different. The difference in frequency could be explained by different dynamics of intrinsic neuronal currents of thalamic neurons mediating spindle generation in frontal vs. centroparietal regions (see sections above), but such differences were not yet reported; (b) Spindle oscillations interact with the slow oscillation. In accordance to classical spindle description, the fast spindles are usually triggered at a transition from silent to active states of slow oscillation, but slow spindles are usually either independent of slow oscillation or they onset at a transition from active to silent states [262, 263]. (c) Optogenetic excitation of reticular thalamic nucleus neurons in mice triggered spindle activities in somatosensory cortex without any spindle oscillation in the corresponding thalamic nuclei [265], suggesting that at least some cortically recorded spindles do not have thalamic origin. Although the frequency of those spindles was not presented, those could be slow spindles, because the fast spindles are clearly controlled by the slow oscillation. (d) Systemic administration of T-type Ca^{2+}-current antagonist flunarizine reduced only fast spindles, suggesting their "classical" mechanism of generation; by contrast, administration of voltage-dependent Na^{+} channels antagonist carbamazepine reduced only slow spindles [266]. (e) Finally, individual spindle waves in the motor cortex, the area where fast spindles are most commonly found, were phase-locked to neuronal firing in corresponding thalamic Ventral Lateral (VL) nucleus, while individual spindle waves in frontal cortex, the area where slow spindles are generated, were not phase-locked to neuronal firing in corresponding thalamic medial dorsal (MD) nucleus [264]. Therefore, properties of fast spindles only correspond to the "classical" mechanisms described above. The mechanisms of generation of slow spindles remain to be investigated. The slow spindles could originate from the neocortex. At least, upon stimulation, the isolated neocotical slabs are able to generate oscillations with frequencies around 10 Hz [267], i.e., the frequency range of slow spindles.

Possible Physiological Role of Oscillations

The role of sleep has been one of the most fundamental scientific questions for which only unclear and partial answers have been provided thus far. No single theory of sleep function is widely accepted, but many ideas fall into two categories, not mutually exclusive: theories of *restoration* and theories of *adaptation*. As part of those theories, a growing body of evidence has pointed toward a critical role of sleep in memory consolidation. With the help of circumstantial observations, it has been hypothesized that the stereotypical oscillations mainly present during NREM sleep could support a fundamental role in the memory consolidation processes through various cellular and molecular mechanisms.

It is thus likely that sleep, which occupies about a third of our lives, plays a critical role in memory processes. Specifically, sleep influences unconscious post-encoding processes that result in long-term memory consolidation. The effect of sleep on memory consolidation was first observed in behavioral studies where there was an improvement in the performance for various memory tasks after sleep

compared to a similar period of awake state [268, 269]. This improvement was observed in declarative, procedural, and emotional memory tasks [270–273]. The declarative memory tasks have been shown to involve the hippocampus, while procedural memory is thought to be hippocampus independent. The improvement in performance also occurs for shorter duration of sleep, including naps [274, 275]. The accumulating evidences from behavioral studies have shown a significant effect of sleep on memories. Moreover, another component of sleep—REM sleep (not discussed in the present chapter)—was also hypothesized to facilitate procedural memory. It is not impossible that different types of memory formation (e.g., declarative vs. procedural) require different forms of sleep phases and involve significantly different cellular and molecular processes. In sum, both neural and molecular mechanisms are not fully known on this fascinating topic and require further research. We synthetize below what is known.

Slow Oscillation, Delta

When the brain falls asleep, the spatiotemporal patterns characterizing waking in the corticothalamic system [124, 125] are replaced by low-frequency synchronous rhythms that are relatively insensitive to incoming signals [122]. Studies have reported that slow-wave sleep (SWS) may be essential for memory consolidation and memory formation [276–278]. It has been proposed that synaptic plasticity associated with brain rhythms could contribute to the memory formation [279]. What are the alternations of synaptic plasticity associated with sleep slow oscillation?

In cortical pyramidal neurons, each synapse contains one active zone with 2–20 docked vesicles [280–282]. Some in vitro studies indicate that, at most, a single vesicle can be released in response to an action potential [283–287], while others found evidence for multiple quantal release [288–293]. In any case, only one or few vesicles could activate a postsynaptic neuron when a presynaptic cell fires a spike. In these conditions, changes in release probability would have a dramatic effect on postsynaptic responses. One of the critical factors regulating the vesicle release is $[Ca^{2+}]_o$. The baseline $[Ca^{2+}]_o$ in vivo is around 1.2 mM [294] and decreases with an increase in the level of neocortical activity [114, 116, 294]. The release probability at a synapse critically depends on $[Ca^{2+}]$ [163, 295–297]. The spontaneous decrease in $[Ca^{2+}]_o$ during depolarizing phases of slow oscillation is thus associated with an increase in synaptic failures; in contrast, the efficacy of synaptic transmission increases during silent phases of slow oscillations [116]. Thus, we postulate here that sleep slow oscillation contributes to the reshaping of synaptic efficacy. Traveling of slow waves during sleep in preferential directions [11, 112, 199] could lead to sequential firing of neurons—reactivation or replay—underlying synaptic changes during sleep. These changes in the synaptic efficacy acquired during SWS could be either permanent or transient, but still may remain for long periods of time.

System-Level Reactivation, Replay, and Plasticity During Sleep

Reactivations of specific neural activity patterns have been observed in different brain areas including the hippocampus, amygdala, neocortex, and striatum [298–314]. Consolidation is believed to involve synaptic changes throughout the neocortex, reflecting the integration and refinement of memory representations [315, 316]. Recent evidence suggests that replay may also indicate planning of future behaviors [317–319].

While hippocampal reactivation has been intensively studied (e.g., reviewed in (Sutherland and McNaughton [301]), less is known about properties and interactions of thalamic and cortical reactivation processes. Significant correlations were found between the cue-related activation of the thalamus, cerebellum, and hippocampus during sleep and the performance of subjects post-sleep [320]. The connectivity between hippocampus and prefrontal cortex has been found to increase after a task in which cues presented during SWS were increasing subject performance in memorizing cue-items associations [320]. The medial prefrontal cortex (mPFC) is involved in the consolidation of spatial memory in rats [321] and exhibits significant reactivations after a positively motivated spatial task [308]. This area is also leading in novel object recognition tests (rodent analog of declarative memory) [322]. These reactivations are correlated with the density of down-to-upstate cortical transitions and with K-complexes [323], further pointing to a crucial role for thalamic-mPFC projections in reactivation. The reactivation episodes in mPFC are coordinated with those of the hippocampus and with the occurrence of sharp wave-ripples (SPW) during sleep [311], compatible with their known coordination during awake learning [324, 325].

If sleep-dependent memory consolidation is a fact proven by many publications, the mechanism of this consolidation is a matter of discussion. It is likely that long-term synaptic plasticity underlies memory consolidation, but the direct supports of this hypothesis are scarce [326].

Regarding sleep-dependent synaptic plasticity during memory consolidation, there are at least two major hypotheses: sleep-dependent synaptic downscaling (recently renamed SHY for synaptic homeostasis hypothesis) [327, 328] and sleep-dependent synaptic consolidation [329]. Overall, the idea of SHY is that the waking state is associated with progressive facilitation of synapses mediating learning, and sleep—in particular SWS—downregulates synapses that become ready for learning during next day. The sleep-dependent synaptic consolidation hypothesis suggests that sleep oscillations contribute to synaptic facilitation. We recently published a review paper analyzing these two hypotheses [330] and we suggest that at the present time molecular [331, 332], electrophysiological [331, 333, 334], and structural [335, 336] evidences provide only indirect, or do not provide at all, support for SHY. The hypothesis of sleep-dependent synaptic consolidation gains more support. The NMDA receptors, CaMKII, and ERK and PKA activity [337], translation of ARC and BDNF [338] key plasticity related molecules are increased during sleep. The mGluR5 receptor, the key molecular element of learning and memory, is upregulated at the beginning of light (mainly sleep) phase of sleep-wake cycle in rats

[339]. During wake, there was a progressive increase in GABA receptors on the membrane of excitatory neurons and internalization of GluA1 receptors, which was recovered during consecutive sleep, pointing to downregulation of cortical excitability during wake [340]. The evoked potential and synaptic responses after sleep period are dramatically potentiated [154], and V1 response potentiation, associated with a shift in orientation preference in visual system, occurs only after sleep [341–343]. A vast majority of cortical neurons, except those with high firing rates, progressively increase their firing rates during sleep [344]. In adult mice the density of excitatory cortical synapses is increased at the beginning of the dark (mainly wake) phase of the sleep-wake cycle [345]. And finally, there is a remarkable, sleep-dependent branch-specific spine formation after a period of learning [346]. All these evidences point to overall sleep-dependent strengthening of cortical excitatory synapses. However, the causal role of sleep-dependent synaptic strengthening in memory consolidation is not demonstrated yet.

A new working model on the topic proposes that waking experiences trigger transient plastic changes in cortical circuits and synapses that are further processed during sleep, and sleep-related protein synthesis at these wake-primed synapses mediates structural changes related to long-term information storage [347].

Spike-timing-dependent plasticity [348, 349] can potentially constitute a mechanism contributing to sleep-dependent synaptic plasticity changes. In anesthetized animals, standard stimulation protocol applied during silent phases of slow oscillation yield result similar to the one obtained in cultured neurons [350]. The same study demonstrated that during active phases (UP states) of slow oscillation, the synaptic depression dominated. Because the onset of active states during SWS is characterized by (a) synaptically driven depolarization and (b) spike that occur after some relatively short period of time, it is likely that spike-timing-dependent plasticity produced by spontaneous brain activities would trigger synaptic facilitation [351]. Because active states of slow oscillation were mainly associated with spike-timing-dependent synaptic depression and the waking state is essentially a very long active state, it is likely that the waking state would induce long-lasting synaptic depression. There have been only few computational studies on synaptic changes during sleep [352, 353]. One study [352] reported that when spike-timing-dependent plasticity (STDP) was included in the cortical model of “Up” and “Down” states, the network self-organized, strengthening connections leading to reactivation of precise temporal sequences. Our recent study [354] suggests that interaction of the hippocampal input and slow oscillation in the thalamocortical network leads to input-specific reorganization of synaptic connectivity that favors pattern of slow oscillations implied during stimulation phase.

Spindles

Studies have shown that sleep-related spindle oscillations are essential for memory formation [355], and demonstrated the presence of efficient spindle-dependent short- and middle-term synaptic plasticity (reviewed in (Steriade and Timofeev [278]). It was suggested that the rhythmic spike-trains or spike-bursts fired by cortical and thalamic neurons during low-frequency sleep oscillations may be involved in the consolidation of memory traces acquired during wakefulness [122, 278]) by massive Ca^{2+} entry in cortical pyramidal neurons. Spindling may activate the molecular "gate" mediated by protein kinase A, thus opening the door for gene expression [356], a process that may allow long-term changes to subsequent inputs following sleep spindles. Spindles contribute to the reactivation of hippocampal-neocortical memories for face-scene associations during post-task sleep in humans [357]. It is worth noting that these hemodynamic studies demonstrate selective but regional reactivation, indicating that the evidence for replay in humans is thus far indirect. In the rat, the density of sleep spindles increase after learning or retrieval in paired-associate or spatial tasks [323, 358].

The easiest model to study plasticity associated with spindle oscillations are augmenting responses, which represent a neuronal response for a train of electrical stimuli applied with spindle frequency (8–14 Hz). Augmenting responses are defined as potentials with progressively growing amplitudes starting with the second or third stimulus in a pulse-train [359]. There are thalamic and cortical components of augmenting responses. Experiments in decorticated cats demonstrated the presence of augmenting responses in thalamus [240, 241, 359, 360]. There are at least two types of intrathalamic augmenting responses. The first one is high-threshold, which occurs as progressive depolarization associated with the decrease in IPSPs produced by preceding IPSPs [240, 241]. This type of augmenting responses likely depends on the high-threshold Ca^{2+} currents [80] in TC neurons. To obtain the high-threshold augmenting responses, the discharge pattern of RE neurons has to be decremental [240]. The second type of augmenting response is based on progressively growing low-threshold responses. It results from the enhancement of Cl^{-}-dependent IPSPs, giving rise to postinhibitory rebound bursts, followed by a self-sustained sequence of spindle waves [240, 241]. This type of responses associated with increased number of spikes in RE neurons that follow each consecutive stimulus [240]. The low-threshold augmenting responses are significantly reduced during cholinergic activation [240]. Dual intracellular recordings in anesthetized cats show that thalamically evoked augmenting responses of neocortical neurons are associated with secondary depolarization (mean onset latency of 11 ms) that develops in parallel with a diminution of the early EPSPs [361]. The rebound spike bursts initiated in simultaneously recorded TC cells preceded by ±3 ms the onset of augmenting responses in the cortex and were identified as a primary cause of cortical augmenting responses [143, 361]. Thalamic stimulation is more efficient than cortical stimulation at producing augmenting responses. Despite this, the cortical network has its own "machinery-enabling generation" of augmenting responses.

Experiments in slices maintained in vitro suggested that the primary cause of augmenting responses depends on IB neurons' intrinsic properties [362–364]. Later, in vivo and modeling studies demonstrated that synaptic plasticity may be a primary source of augmenting responses in isolated neocortical networks [365, 366].

Neuronal plasticity induced by augmenting responses recorded in vivo in cortical slabs was compared to plasticity that develops from natural spindles in intact-brain preparations [366]. In isolated slabs (~10 mm long, 6 mm wide and 4–5 mm deep), the greatest increase in the amplitude of depolarization and the most dramatic increase in the number of action potentials with successive stimuli at 10 Hz was found in fast-spiking (FS), presumably local inhibitory, neurons. In the intact brain, cortical stimuli applied during the depolarizing envelope of spindle sequences accompanied by firing elicited an enhancement of the control response, which lasted from tens of seconds to several minutes (Fig. 5.11, left column). Testing cortical excitability with repeated pulse-trains giving rise to augmenting responses (Fig. 5.11, right column) revealed that, first, the IPSP of the control response was progressively reduced in amplitude and replaced by an early depolarization and, second, single stimuli applied after the rhythmic pulse-trains elicited exclusively depolarizing responses, an enhancement that remained unchanged for several minutes. This enhancement was not voltage-dependent, as it was observed with little changes at rest and after a slight DC hyperpolarization. One possible mechanism for increased responsiveness depends on high-frequency firing in response to rhythmic, repeated pulse-trains. This firing would result in activation of high-threshold Ca^{2+} currents and elevated $[Ca^{2+}]_I$ that, in association with synaptic volleys reaching the neuron, may activate protein kinase A [367] and/or Ras/mitogen-activated protein kinase [368]. These enzymes are known to be involved in the processes of memory consolidation.

NREM sleep oscillations (slow-wave and spindles) affect information processing. A study by Dang-Vu et al. [369] showed that sound processing during non-REM sleep is constrained by fundamental brain oscillatory modes, which result in a complex interplay between spontaneous and induced brain activity. In line with previous studies, it was hypothesized that synaptic blockade in the thalamus filters out sensory transmissions to the forebrain during sleep spindle because the burst firing mode distorts the transmission of sensory inputs to the cortex in a nonlinear fashion. This study showed that a distortion of sensory information at the thalamic level, especially during spindles, functionally isolates the cortex from the environment, and therefore might provide unique conditions favorable for off-line memory processing.

Fig. 5.11 (continued) (*During*) and after spindle (*After*). Right column: three traces depict control response to the cortical stimulus applied close to the recorded RS cell (*Before*), responses to a pulse-train at 10 Hz applied 12 min after rhythmic pulse-trains (*During*), and response to a single stimulus (same parameters as *Before*) applied 16 min after the onset of pulse-train stimulation (*After*). Enhanced responsiveness lasted for 15 min. (Modified from Steriade and Timofeev [279])

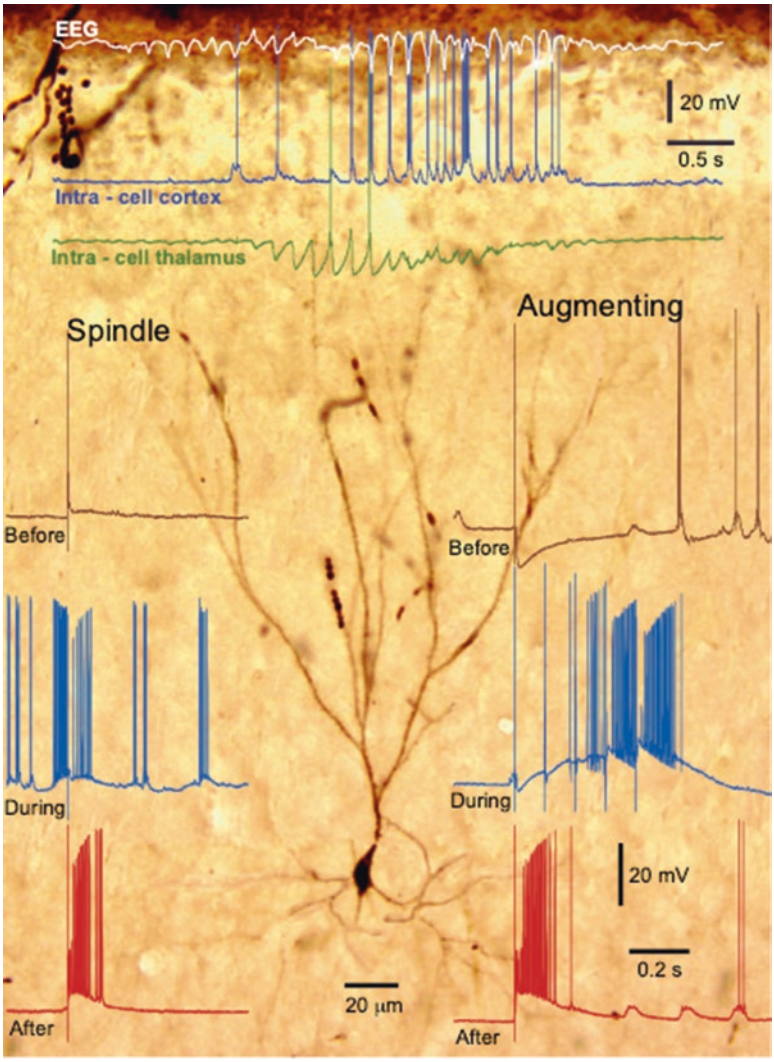

Fig. 5.11 Long-lasting changes in cortical responsiveness after spindles and augmenting responses. Cats under sodium pentobarbital (top three traces) and ketamine-xylazine anesthesia. Top three traces depict a spontaneously occurring spindle sequence, with simultaneous recordings of field potentials from the depth of cortical area 4 and dual intracellular recordings from area 4 cortical neuron and thalamocortical cell from ventrolateral (VL) nucleus. Note sustained activity in cortical neuron despite the fact that the spindle sequence was terminated in VL cell terminated the spindle sequence. *Below*, neuronal plasticity in fast-rhythmic-bursting (FRB) neuron from area 21 following spontaneously occurring spindles (*left column*), and in regular-spiking (RS) neuron from area 7 following augmenting responses (*right column*). Middle part depicts the morphologically (Neurobiotine staining) identified RS neuron whose electrophysiological activity is depicted in the right column. *Left column*: three traces show responses of FRB neuron to control cortical stimuli (*Before*), during spindle sequence

Conclusion

Oscillatory rhythmic activities are an emerging property of the living brain. In this chapter, we described the known mechanisms and the current knowledge on the functional role of major sleep oscillations generated by the TC system. We postulate that the slow brain oscillations (sleep spindles, delta, and slow oscillations) generated within the TC system are not an epiphenomenon, but serve to influence the synaptic plasticity that affects memory consolidation. Thalamocortical system is not separated from the other part of the brain. It seems that interaction to TC system oscillations (slow oscillation and spindles) with hippocampal ripples dramatically increases memory consolidation [370]. Therefore, future studies interaction of TC system activities with other brain structures would lead to a full understanding of functional significance of TC sleep oscillation.

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Chapter 6
Neuroimaging of Brain Oscillations During Human Sleep

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Introduction

Increasing body of evidence suggests the importance of neural oscillations in sleep homeostasis. In order to directly study the morphology and topography of sleep oscillations, early studies resorted to electroencephalography (EEG)—a noninvasive technique, widely used in the field of sleep [1]. EEG records the electrical activity of the brain with a remarkably high temporal but low spatial resolution. Notably, compatibility of EEG with some other imaging techniques (e.g., PET, MEG, fMRI) permits simultaneously combined recordings, and thus improved spatial resolution. Functional neuroimaging studies during sleep provide insights into the changes in brain activity across sleep-wake cycles. Over the past two decades,

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these studies have primarily focused on evaluating the differences between the neural activities across sleep stages and wakefulness [2, 3]. For this purpose, earlier works used positron-emission tomography (PET), a technique that allows indirect examination of the global or regional cerebral blood flow (rCBF) with the use of $H_2{}^{15}O$, or brain glucose metabolism (CMRglu) with ^{18}F-FDG.

Using PET, the comparison of wakefulness and NREM sleep mostly demonstrated decreases in global [4] and regional [3, 5–8] CMRglu or rCBF during NREM sleep. These hypo-activations were observed in brainstem, thalamus, basal forebrain, basal ganglia, and cerebellum, as well as associative cortices (i.e., prefrontal cortex, anterior cingulate, and precuneus). However, one PET study after controlling for the whole brain decrease in absolute metabolism identified relative CMRglu increases in the basal forebrain, hypothalamus, ventral striatum, amygdala, hippocampus, and pontine reticular formation [9].

Unlike the findings of NREM sleep studies, the comparisons of REM sleep with wakefulness showed both increases and decreases in regional brain activity during REM sleep [6, 10–13]. In particular, during REM sleep, increases in rCBF and CMRglu were reported in thalamus, pons, basal forebrain, amygdala, hippocampus, anterior cingulate cortex, and temporo-occipital cortices. Conversely, decreases were observed in dorsolateral prefrontal cortex, posterior cingulate gyrus, precuneus, and inferior parietal cortex.

PET, despite its limited temporal resolution, allows indirect study of brain oscillations. Hofle et al., using PET, investigated neural correlates of spindles and slow waves during NREM sleep by correlating rCBF observed in $H_2{}^{15}O$ PET with EEG spectral power within frequency range of spindles (sigma) and slow waves (delta), respectively. In a sample of six healthy, sleep-deprived volunteers, sigma negatively correlated with rCBF in medial thalamus. On the other hand, increase in delta activity was associated with decreases of rCBF in thalamus, reticular formation of brainstem, cerebellum, anterior cingulate, and orbitofrontal cortex [14]. In contrast to Hofle et al. findings, another study using a larger sample size found no associations between delta activity and thalamic activity, but mainly a negative correlation between delta activity and rCBF in the medial prefrontal cortex, which further highlights the importance of (anterior) cortices in generating slow waves during NREM sleep [15].

More recently, the emergence of functional magnetic resonance imaging (fMRI) technique enabled researchers to closely study the neural correlates of sleep through detection of blood-oxygen-level-dependent (BOLD) signal. In fact, fMRI is a non-invasive tool with higher temporal and spatial resolution compared to PET, and identifies local changes in relative blood oxygenation levels associated with periods or events of interest. Simultaneous fMRI-EEG recordings can provide further insights into neuronal network activations associated with various sleep features [16]. In the field of sleep research, fMRI, despite its advantages, bears some limitations, too. Substantial acoustic noise and the need for lying still in position during the scan can limit the applications of this technique for longer sleep recordings [17]. Also, due to MRI's strong magnetic field, scanning cannot be performed in the presence of ferromagnetic foreign bodies or metallic implants such as pacemakers, aneurysm clips, and some cardiac stents. More notably, EEG signals recorded inside

fMRI scanners suffer from artifacts induced by the scanner, which indeed require extensive artifact removal post-processing [18, 19].

In line with the findings of previous PET studies, early fMRI studies also reported localized hypo-perfusions during sleep compared to wakefulness [20, 21]. Overall, these PET and fMRI works mainly examined the changes in neuronal activations across sleep stages; hence the neural correlates of spontaneous sleep oscillations occurring within sleep stages remained understudied. Higher temporal resolution of fMRI allows the study of BOLD responses time-locked to occurrences of spontaneous sleep oscillations, whereas with PET, brain responses are averaged over the course of scanning. More recent fMRI studies, by assessing the brain activations time-locked to spontaneous brain oscillations during sleep, evidenced the pivotal role of these phasic activities in regulating functional properties of sleep.

In addition to classical neuroimaging techniques, magnetoencephalography (MEG) and high-density electroencephalography (HD-EEG, 64 electrodes and above) have been increasingly used in the field of sleep. MEG and HD-EEG recordings reflect the neuronal activity with a temporal resolution as high as 1 ms. In both techniques, source localization algorithms have been developed to allow for the identification of cortical signal sources. However, these techniques are limited in terms of pinpointing neural sources in subcortical and deep brain structures as compared to the neuroimaging techniques mentioned earlier (i.e., fMRI and PET) [22]. MEG and HD-EEG applications in sleep research have also contributed to a better characterization of typical microstructural figures such as spindles and slow waves.

In this chapter, by focusing on the functional brain imaging techniques, we will review the mechanisms involved in regulations and functions of sleep through the investigation of brain rhythms that compose its microarchitecture. The first section will primarily entail human fMRI studies on neural correlates of sleep spontaneous oscillations (i.e., spindles, slow waves, and REM phasic activity). In addition, we will elaborate on MEG and HD-EEG findings on these rhythms. In the second section, we will highlight the role of spontaneous brain activity in regulating external sensory information during sleep. Finally, in the third section, we will discuss how neuroimaging studies have provided insight into the involvement of sleep oscillations in off-line memory consolidation during sleep.

General Characteristics of Brain Oscillations During Sleep

Human sleep consists of two general states: REM sleep and NREM sleep. REM sleep is the sleep stage in which most dreams occur and is characterized by rapid eye movements, increased respiration rate, and metabolic rate, desynchronized brain activity, along with muscle atonia. In contrast, NREM sleep consists of decreases in muscle tone, heart rate, breathing rate, blood pressure, and metabolic rate, as well as progressive synchronized brain activity. NREM sleep is further subdivided into three distinct stages: N1, N2, and N3, as defined by the 2007 American Academy of Sleep Medicine (AASM) [23]. Stage N1 is the transition from wakeful-

ness to sleep and is characterized by slow eye movements, decreased muscle tone, and mixed frequency brain activity within alpha (7–12 Hz) and theta (4–7 Hz) frequency range. N2 is defined as an intermediate sleep with the appearance of two characteristic grapho-elements: spindles and K-complexes. On one hand, spindles are waxing and waning rhythmic waves that oscillate within sigma frequency band, at 11–16 Hz, with varying amplitude and a minimum duration of 0.5 s. On the other hand, K-complexes are slow-high amplitude EEG waveforms (0.5–1 Hz) consisting in a brief negative sharp wave immediately followed by a positive component. They occur mostly spontaneously but can also appear triggered by an external stimulus. As the brain synchronizes further and NREM sleep deepens (N3), the K-complex turns into slow oscillations (SO)—thought to share similar generating mechanisms [24]. Oscillating at less than 1 Hz at high amplitude (peak-to-peak >75 μV), SO—in the scalp EEG—can be characterized as a biphasic wave with a sharp negative peak and a positive half wave. Other oscillations occurring during NREM within the frequency range of the delta band are called delta waves, oscillating at 1–4 Hz. Distinct by their site of origin and underlying cellular mechanisms [24], SO (<1 Hz) and delta waves (1–4 Hz) when combined are called slow-wave activity (SWA) and dominate the N3 EEG activity. Stage N3, also known as slow wave sleep, is defined by the increased occurrence of these slow waves, occupying more than 20% of the EEG period [23].

Electrophysiological studies investigating NREM sleep in animals, particularly in cats, have shown that spindles and slow oscillations are generated through an interplay of synaptic mechanisms and voltage-gated currents in thalamic and cortical areas [25]. In fact, spindle generation is largely modulated by a population of GABAergic neurons located in the reticular (RE) nucleus of the thalamus, also known as the spindle "pacemaker." This notion stems from studies in which Steriade and colleagues examined spindle activity in a group of RE neurons which were disconnected from the rest of thalamus and cerebral cortex through transection [26]. They reported that spindle activity was preserved within the deafferented reticular thalamic nuclei, while no spindle activity was observed in the thalamocortical networks disconnected from these GABAergic neurons. However, a study using computer modeling and in vivo multisite recordings from the thalamus and cortex of cats demonstrated that the cortex has a pivotal role in the initiation and termination of spindles [27]. Hence, more complex mechanisms underlie spindle generation. In brief, occasional summation of spontaneous miniature EPSPs in the cortex depolarizes the membrane of pyramidal (PY) neurons, which subsequently induce spikes in the thalamic RE neurons [27]. GABAergic RE neurons, upon receiving strong cortical inputs, repeatedly fire onto glutamatergic thalamocortical (TC) neurons, which in turn induce inhibitory postsynaptic potentials (IPSPs). Temporal and spatial summation of these IPSPs lead to the de-inactivation of low-threshold calcium currents, which ultimately triggers spike burst activities projected onto cortical neurons. These phasic firings are eventually detectable on the EEG as spindle sequences [28]. Upon initiation of spindles by cortical discharges, these phasic events are sustained through a local interplay between thalamic RE and TC neurons, independently from cortical activity. On the other hand, during spindle termination, cortical PY neurons

fire desynchronized with respect to thalamic activity. This out-of-phase firing of PY neurons depolarizes both RE and TC neurons, which in turn inhibits the de-inactivation of the low threshold calcium currents necessary for spindle generation [27]. Hence, the initiation and termination of spindles critically depend on cortico-thalamic feedback [29] and appear related to the slow oscillation state.

It has been suggested that spindles and delta waves (1–4 Hz) share comparable mechanisms. Indeed, some studies revealed the presence of delta waves in the TC neurons when sufficiently hyperpolarized by RE neurons. Moreover, similar to spindles, a corticothalamic feedback synchronizes delta oscillations in TC neurons and thus delta potentials in the cortex [30, 31]. However, besides thalamic-generated delta waves, other types of delta waves only triggered in the cortex have been recorded in thalamectomy studies on cats [32, 33]. Indeed, some cortical neurons (called intrinsically bursting neurons) are endowed with intrinsic properties reflecting delta activity [34]. The mechanisms of these cortical delta waves are much less understood, but they might be induced by the onset of the depolarizing component of the slow oscillation triggering a few cycles of delta oscillations [24]. Slow oscillation is also another type of cortically generated oscillations at less than 1 Hz. Slow oscillations (SOs) were initially observed in intracellular recordings of anesthetized cats [35], followed by subsequent recordings in naturally sleeping cats [36] and humans [37]. These studies reported preservation of SO activity in the cortex of thalamectomized cats [32].). However, no such activity was observed in the thalamus of decorticated animals [31]. Collectively, these findings characterize SOs as cortically generated waves that can be recorded in most cortical areas [25]. These rhythms are described as biphasic oscillations consisting of a “down” state, during which neurons are hyperpolarized (silent), as well as an “up” state, during which cortical neuronal excitations lead to high-frequency brisk firings. A few animal studies suggested that SOs are not purely cortical phenomena but are rather generated through an interplay between the cortex and thalamus [38, 39]. These studies demonstrated a dramatic decrease in expression of SOs in the deafferented cortical areas of the sleeping cat. Lemieux et al. reported that SOs started to recover 12 h after deafferentation of the cortex from thalamus [39]. Indeed, Steriade et al. observed normal slow wave activity in the cortex of the cats 2 days after cortical deafferentation [32]. Hence, it is plausible that it is the interplay between cortico-cortical and thalamocortical networks that contributes to the generation and full expression of SOs. The importance of the slow oscillation (<1 Hz) resides in its capacity to group other NREM sleep rhythms (spindles and delta waves, and fast frequencies such as hippocampal ripples) within its upstate phase. Indeed, during the depolarizing phase of the SO, there is a synchronous firing of the RE neurons and cortical neurons, which modulates the synchronous appearance of spindles. Thus, SOs likely reflect the cortico-thalamic inputs required for the generation and coherence of spindle waves [40]. This co-occurrence between spindle and SO upstate has been thought to underlie synaptic plasticity [41] and, more specifically, promotes long-term memory consolidation through a triple-phase locking between cortical, thalamic, and hippocampal rhythms [42, 43]. Specifically, hippocampal ripples [44] associated with memory reactivation tend to nest into spindles troughs

[45], which themselves reach neocortical networks during SO upstates and thereby initiate the hippocampal-neocortical dialogue necessary for memory consolidation [42, 43].

In human studies, scalp- and intracranial-EEG recordings as well as functional imaging divided spindles into two types depending on their frequency and topographic distribution [29]. In particular, spindles are predominantly detected in central and parietal areas with an average frequency of 14 Hz, while they can be less frequently detected in the frontal areas with an average lower frequency of 12 Hz [46]. The topology-dependent variations in spindle frequency led to the distinction between two spindle types: (1) fast spindles predominantly detected over the centro-parietal regions and within the "fastest" part of the sigma band (13–16 Hz) and (2) slow spindles prominent in frontal areas and named "slow" because they oscillate between 11 and 13 Hz [47]. The range of the slow spindle in the sigma band actually varies across studies—for example: 11–13 Hz in Schabus et al. [48] but 8–12 Hz in Marshall, et al. [49] and 9–12 Hz in Molle et al. [50]. Furthermore, human studies on SO-spindles coupling in human using scalp and intracortical EEG recording revealed that fast spindles preferentially occur during the transition from the down- to the upstate of SO [43, 50], and display stronger coupling with hippocampal activity compared to slow frontal spindles [45, 48]. By contrast, slow spindles preferentially occur during the transition from the up- to downstate [43, 50, 51]. It has been shown that fast spindles precede slow spindles by about 500 ms [50]. Indeed, the depolarizing SO upstate would drive the thalamic generation of fast spindles, while the slow spindles would occur later during waning depolarization at the transition into cortical hyperpolarization. From these findings, it has been suggested distinct mechanisms where centro-parietal fast spindles reflect thalamocortical activities while frontal slow spindles are functionally related to cortico-cortical interactions.

Finally, while spindles are segregated between centro-parietal and frontal areas, high-density EEG recordings described SOs as traveling waves, originating predominantly in the prefrontal-orbitofrontal regions and propagating in the antero-posterior axis through the cingulate pathways [52, 53].

Similar to NREM sleep, REM sleep also exhibits spontaneous brain activity. Particularly, phasic activity during REM can either be observed as sawtooth waves detected on EEG or, more frequently, as ocular saccades on electrooculography (EOG) recordings. In cats, ocular saccades during REM sleep have been associated with prominent activities in the pons [54], lateral geniculate bodies of thalamus [55], and occipital cortex [56]. These phasic activities—collectively called ponto-geniculo-occipital (PGO) waves—are the hallmark of mammalian REM sleep. Immediately prior to the appearance of PGO waves, animal studies evidenced increased firing in brachium conjunctivum and a cessation of firing in dorsal raphe nuclei, which suggests pons as the primary site of PGO wave generation [57–59]. PGO wave generation is directly modulated by aminergic, cholinergic, nitroxergic, GABAergic, and glycinergic cells of the brainstem. Additionally, suprachiasmatic, amygdaloid, vestibular, and brainstem auditory cells are involved in indirect modulation of the PGO system [60].

Animal studies have evidenced a key role for PGO waves in off-line memory consolidation [61–63], brain maturation [64–66], brainstem activation [67], transfer of eye movement information to sensory visual system [68], as well as synchronization of fast oscillations (30–40 Hz) [69]. In addition, human studies have investigated the possibility of an association between rapid eye movements of REM sleep and PGO waves. One study, using direct intracerebral recordings in the striate cortex of an epileptic patient, reported the presence of monophasic and diphasic potentials during REM sleep [70]. Also, subsequent human EEG studies observed transient occipital and/or parietal potentials synchronous to rapid eye movements [71]. These results indicated that rapid eye movements during REM sleep are possibly induced by similar or identical mechanisms to PGO waves observed in animals.

Although the topography of sleep neuronal oscillations has been unveiled through animal and human EEG recordings, there is still a gap in knowledge about the neuronal networks recruited by these oscillations. As discussed below, functional neuroimaging studies have significantly contributed to advancement of knowledge in identifying cortical and subcortical structures associated with the initiation or modulation of human sleep oscillations.

Neural Correlates of Sleep Spindles in NREM Sleep

PET has a limited temporal resolution, which restricts its ability in detecting short phasic events such as sleep spindles. However, one study evaluated the neural correlates of sleep spindles through indirect detection of spindles by associating rCBF observed in $H_2{}^{15}O$ PET with EEG spectral power within spindle frequency range [14]. By using the PET scans of six healthy but sleep-deprived volunteers, Hofle and colleagues found a negative correlation between EEG spindle spectral power and rCBF in thalamus. The association between spindle generation and thalamus further support the key role of this structure in the generation of sleep spindles. However, the negative direction in such correlation appears surprising, which could in fact be due to PET limited temporal resolution. More specifically, coalescence of spindles and slow waves may explain the decreased thalamic perfusion. In fact, when averaging rCBF over the course of scanning, the associated "down" phase of slow oscillation could have imposed a more influential metabolic impact on the thalamus. This negative correlation could alternatively be explained by the induction of IPSP in glutamatergic TC neurons of dorsal and intralaminar thalamic nuclei, as a consequence of spindle generation. Finally, in a study done by Gais et al., the divergence observed between the spindle spectral power and discrete spindle events suggests that these two measures are not completely comparable [72]. Therefore, the negative association between thalamic perfusion and spindle spectral power may not be entirely linked to spindles per se.

Given the limitations of PET, more recent studies benefitted from fMRI in order to directly detect brain activities time-locked to spindle events. Indeed, Schabus, et al. investigated the neural correlates of sleep spindles in 14 healthy, non-sleep-deprived volunteers, using simultaneous EEG-fMRI [73]. Using an automatic algo-

rithm, the spindles were detected off-line during N2 and N3 stages of NREM sleep. Functional MRI data revealed significant brain activations time-locked to spindle occurrences (as compared to baseline NREM sleep brain activity) in the following structures: lateral and posterior parts of thalamus, anterior cingulate cortex, insula, and superior temporal gyrus. In contrast to the findings of the previous PET study, which suggested a decrease in brain activity during NREM sleep compared to wakefulness, fMRI studies showed transient, but consistent, increases in BOLD signal in specific brain areas associated with spindles. Most importantly, thalamic activations during the phasic spindle activity support the role of this structure in sleep spindle generation [25]. In addition to the thalamus, a few cortical areas were found involved in the modulation of spindles, in line with recent computer modeling and in vivo recordings demonstrating the importance of cortico-thalamic projections in the initiation and termination of spindles [27].

As previously discussed, it is hypothesized that spindles exist in two subtypes, differing in frequency and topology [46, 50]. In order to confirm this hypothesis, in the same study, Schabus and colleagues used specific band-pass filters on EEG Cz signal to distinguish slow spindles (11–13 Hz) from the fast ones (13–15 Hz). For slow spindles, they observed a brain activation pattern very similar to the common spindle network reported above. However, fast spindles were characterized by more global cortical activation expanding to the mid-cingulate cortex and somatosensory areas. Direct comparison of brain activity associated with these two spindle subtypes revealed a greater BOLD response in the hippocampus and medial prefrontal cortex (mPFC) in relation to fast spindles. This increase in hippocampal activity is in agreement with behavioral [72, 74] and EEG [50] studies proposing a key role for fast spindles in off-line memory consolidation. Moreover, an fMRI study demonstrated increased connectivity between hippocampal formation and neocortical regions during fast spindle activity of stage N2 sleep, suggesting a global information transfer between hippocampus and neocortex in interaction with these spindles in the fast sigma range [75]. Fast spindles were also associated with increased activation in pre- and postcentral gyrus, which supports a sensorimotor processing role for fast spindles [76–78]. Interestingly, a simultaneous EEG-MEG study linked fast spindles with more frequent activation in postcentral areas, while slow spindles were associated with activation of precentral areas [79]. These differences in cortical activation patterns between the two spindle subtypes suggest distinct underlying neural circuits, which lead to propagation of these oscillations toward the cortex. Finally, investigation of anatomical regions that may contribute to interindividual differences in sleep features revealed that differences in gray matter volume (GMV) of the anterior and posterior regions of the insula as well as the primary auditory cortex were related to slow spindle frequency, whereas GMV in the hippocampus was associated with fast spindle frequency. However, GMV of the thalamus did not predict interindividual differences in spindles [80]. These functional and structural findings on the neural correlates of spindles are in line with the proposed role of spindles in protecting sleep in face of external stimulation [81, 82], as well as an

active role in the hippocampo-thalamo-cortical dialogue necessary for sleep-dependent memory consolidation processes [83]. These hypotheses will be addressed more specifically later in this chapter.

Topological dynamic changes of sleep spindles throughout the course of cortical maturation have been studied using HD-EEG recordings. Kurth and colleagues studied the pattern of changes in sigma spectral power activity during the cortical maturation in the first two decades of life using this technique [84]. Researchers reported a predominant sigma power over prefrontal areas with an extension toward central and occipital regions of the brain with age, suggesting that cortical maturation during the first two decades of life influences the topology of sigma activity.

In summary, the occurrence of spindles during NREM sleep was found associated with specific fMRI activations in the lateral and posterior parts of thalamus, anterior cingulate cortex, insula, and superior temporal gyrus. In addition to this common spindle network, slow spindles also activated superior frontal gyrus while fast spindles elicited brain responses in hippocampus, mesial frontal cortex, and sensorimotor cortical areas. Brain responses in hippocampus and mesial frontal cortex related to fast spindles support the role of these phasic fast brain activities in memory processing during NREM sleep (see below) (Fig. 6.1).

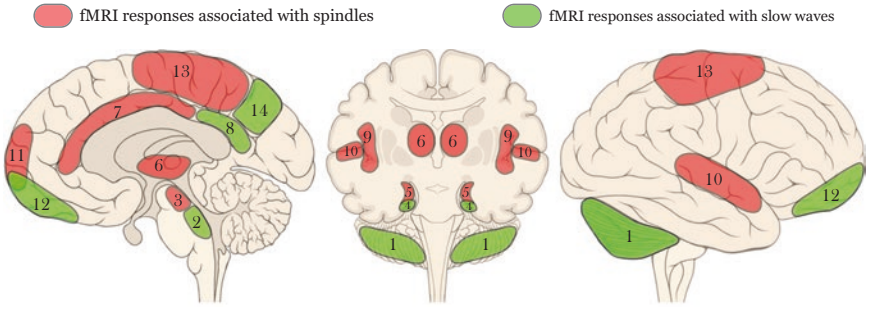

Fig. 6.1 Functional MRI responses associated with spindles and slow waves. Combined EEG-fMRI studies have examined brain responses related to spindle and slow waves. Schabus and colleagues reported increased BOLD signal related to spindles in various cortical and subcortical brain areas including midbrain tegmentum, hippocampus, thalamus, anterior and mid-cingulate, insula, superior temporal gyrus, medial prefrontal cortex, and sensorimotor cortex [73] Dang-Vu et al., by investigating BOLD responses time-locked to slow waves, reported increased brain responses in cerebellum, pontine tegmentum, parahippocampal gyrus, posterior cingulate, inferior frontal gyrus, and precuneus [88]. (Prepared with illustrations by Patrick J. Lynch and C. Carl Jaffe. http://creativecommons.org/licenses/by/2.5/)

Neural Correlates of Slow Oscillations in NREM Sleep

Hofle and colleagues, in the same PET study that investigated the association between rCBF and spindle activity, likewise evaluated the neural correlates of slow oscillations in a sample of six healthy volunteers [14]. EEG spectral delta power in the frequency range of 1.5–4 Hz showed a negative correlation with rCBF in the thalamus, brainstem, cerebellum, and anterior cingulate cortex, as well as orbitofrontal cortex. In a subsequent $H_2{}^{15}O$ PET study, using a larger sample size, Dang-Vu and colleagues found a negative correlation between rCBF and slow wave activity in ventromedial prefrontal cortex, basal forebrain, putamen, insula, posterior cingulate gyrus, and precuneus [15]. However, contrary to the Hofle et al. data, no significant correlation was found in thalamus, brainstem, and cerebellum. In fact, although these results support the role of cortex in generating slow waves, they do not exclude the role of thalamus in slow wave modulation [85]. Particularly, in line with previous findings, these results illustrate the contribution of insular and frontal cortices in initiation of slow waves [52, 53, 86, 87]. Notably, the negative pattern of correlation observed between rCBF and delta spectral power seems contradictory to cortical structures' role in modulating slow oscillations. However, similar to what was previously discussed in PET spindle results, this phenomenon could be explained by a variety of reasons, such as PET's limited temporal resolution, as well as more prominent metabolic effect of slow oscillations' "down" state over the course of scanning.

fMRI technique allows a more direct detection of brain responses associated with slow oscillations, with a higher temporal resolution compared to PET. A subsequent analysis, in the same fMRI dataset that assessed the neural activations due to the spindles [73], evaluated the neural correlates of slow waves using an automatic detection algorithm during stage N3 NREM sleep [88]. Data analysis revealed a significant increase in BOLD signal in medial and inferior frontal cortex, parahippocampal gyrus, precuneus, posterior cingulate cortex, brainstem (pons), and cerebellum during slow waves compared to the baseline brain activity during stage N3 NREM sleep. In agreement with PET [14, 15] and EEG [52, 86, 87] results, increased responses in frontal areas of the brain further supports the role of frontal cortex in slow wave generation. These cortical activations were further evidenced by findings of an HD-EEG source modeling study investigating cortical sources of slow oscillation. In this high-resolution study, Murphy and colleagues reported that slow oscillations are associated with large currents in the medial, middle, and inferior frontal gyrus, anterior cingulate, precuneus, as well as posterior cingulate [53].

The critical role of pontomesencephalic tegmentum (PMT) in the generation and tonic maintenance of wakefulness is well documented in the literature [25]. However, a study in naturally sleeping rats discovered a temporal correlation between PMT and slow wave activity [89]. In particular, the researchers demonstrated that locus coeruleus (LC) neurons, a substructure of PMT, preferentially fire during the transition from the "down" state to the "up" state of slow waves, while

the medial prefrontal cortex neurons fire around the peak of slow wave. These results suggest that the firing of LC neurons prior to medial prefrontal cortex can indeed provide a facilitative neuromodulatory input to increase cortical excitability for slow waves. In fact, as both electrophysiological data in animals and functional neuroimaging results in humans suggest, persistence of phasic brainstem activity during deepest stages of sleep might further enhance synaptic plasticity.

Dang-Vu et al. in the same fMRI study also showed that wave amplitude has an effect on the structures recruited by slow waves [88]. In particular, by evaluating the differences between medium amplitude (75–140 μV) slow waves—corresponding to delta waves—and high amplitude (>140 μV) slow waves, authors discovered increased brain responses in frontal areas (i.e., medial prefrontal cortex and inferior frontal gyrus) in association with delta waves. The latter results were supported by Saletin and colleagues, who reported in their study on structural brain correlates of sleep features that interindividual differences in slow wave (0.75–4.75 Hz) amplitude were associated with GMV of the medial prefrontal cortex, while slow wave density during NREM was correlated with the GMV of the basal forebrain, a region involved in the homeostatic regulation of sleep [80]. On the other hand, high-amplitude slow waves were associated with increased responses in the pons, cerebellum, and parahippocampal gyrus. Notably, activation of mesio-temporal areas during high-amplitude slow waves is in agreement with the results of a transcranial direct current stimulation study, in which the induction of slow-oscillation-like potential fields enhanced hippocampal-dependent memory consolidation [49].

One HD-EEG study provided a fine characterization of slow waves across NREM sleep stages. By comparing late-night sleep (cycles 3 and 4 of NREM sleep) and early-night sleep (cycles 1 and 2 of NREM sleep), researchers found a decrease in slow-wave amplitude, slope, and activity across the night [90]. Interestingly, since the slope of slow waves during sleep is believed to represent a direct reflection of synaptic strength [91], it was interpreted from these results that the cortical synaptic strength decreases throughout the night. Similarly to spindles, dynamic changes in slow waves have also been studied through the course of cortical maturation. In the same HD-EEG study of spindles [84], Kurth and colleagues demonstrated that, during the first two decades of life, the peak of maximal slow waves activity (1–4.5 Hz) shifts from the posterior to the anterior regions of the brain along the direction of brain maturation (postero-anterior axis), suggesting that SWA can indeed reflect cortical plasticity during development.

In sum, slow oscillations were associated with increased fMRI responses in the parahippocampal gyrus, precuneus, posterior cingulate cortex, brainstem, and cerebellum, as well as medial and inferior frontal cortex. These responses were modulated by the amplitude of the slow oscillation, in such a way that only high-amplitude slow waves activated mesio-temporal areas, possibly reflecting the need for a higher degree neural synchronization in order to recruit networks associated with off-line memory consolidation.

Neural Correlates of REM Sleep Phasic Activities

In addition to NREM sleep, a few neuroimaging studies also investigated neural networks associated with the brain spontaneous phasic activities during REM sleep. Only one human study used $H_2{}^{15}O$ PET technique to evaluate neural correlates of rapid eye movements—the hallmark of REM sleep [92]. In fact, Peigneux and colleagues found positive correlations between the density of rapid eye movements and rCBF in the lateral geniculate bodies of the thalamus and occipital cortex (the two sites in which PGO waves are most commonly recorded). In a subsequent work, an event-related human fMRI study evidenced increases in BOLD signal in thalamus and occipital cortex, in a close temporal relationship with incidence of rapid eye movements during REM sleep [93]. More recently, a similar study evaluated brain activations time-locked to the occurrence of rapid eye movements in healthy subjects [94]. Their data demonstrated increased BOLD responses in the pons, thalamus, and primary visual cortex—the three areas known to be involved in PGO wave generation in cats. In addition, the authors found increased activations in putamen, anterior cingulate cortex, and parahippocampal gyrus, as well as amygdala, during phasic REM sleep.

Collectively, the abovementioned studies evidenced increased responses in the areas where PGO waves were most consistently recorded in animals [55, 56]. They are also in line with deep brain stimulation studies in humans, which revealed the presence of biphasic waves during REM sleep in the pedunculopontine nucleus [95], subthalamic nucleus [96], and medial temporal lobe [97]. Not only does neuroimaging show evidence for the existence of PGO-like activity in humans, but also it suggests that the generation of rapid eye movements during REM sleep involves neural processes similar to those recruited by PGO wave generation. However, it remains unclear whether these phasic activities play a role in functional brain processes such as neural plasticity or memory consolidation in humans.

Neural Correlates of External Information Processing During Sleep

Sleep is widely associated with decreased level of consciousness. In fact, it is commonly believed that during sleep, the brain is isolated from the external environment. However, several neuroimaging studies evaluated brain activation upon presentation of acoustic stimuli during NREM sleep and revealed that, despite the common belief, the brain continues to process external sensory information even during the deep stages of NREM sleep. Using a simultaneous EEG-fMRI technique, Portas and collaborators examined the neurophysiological responses associated with auditory stimulation [98]. The researchers exposed the participants to two types of acoustic stimuli: pure tones and the subject's own name. The primary analysis revealed sound-related bilateral activations in the thalamic nuclei, the

auditory cortices, and the caudate nucleus during NREM sleep. In particular, when the subjects were exposed to their own names (compared to the beep tone), left amygdala and left prefrontal cortex showed a higher degree of activation. The increased activity in these two regions was more pronounced during NREM sleep as compared to wakefulness. Notably, the findings of this study highlight the ability of the sleeping brain in detecting external stimuli, and more importantly processing the meaningful events. In contrast to Portas et al. data, other fMRI studies reported decreased responsiveness to external stimuli during NREM sleep, which supports the concept of brain isolation during sleep [99, 100]. Using oddball paradigm in a series of fMRI studies, Czisch et al. observed that presentation of the rare tones during stages N1 and N2 of NREM sleep was associated with decreased BOLD responses in motor, premotor, superior, and medial frontal cortex, as well as amygdala [99]. The same group also reported a positive correlation between stimulus-induced negative BOLD signals and delta power, suggesting the cortical deactivation as a sleep-protective measure against external auditory noises [20].

In order to further investigate the role of NREM sleep in modulating sensory modalities, another group conducted a study using visual stimuli as external cues [101]. They observed decreased BOLD signal in occipital cortex in association with visual stimuli, which further supported the presence of sleep-protective measures during NREM sleep. It thus remained controversial whether the brain is equipped with a deactivation mechanism protecting itself from sensory stimuli during NREM sleep, or can still be stimulated in order to partly process external information during sleep.

A body of evidence in both animals [102] and humans [103] suggests that ongoing brain activity modulates responses to external stimuli. Hence, it could be hypothesized that the two major spontaneous brain activities during NREM sleep—sleep spindles and slow waves—are involved in modulating neuronal responses to external stimuli. In agreement with this hypothesis, some human event-related potential (ERP) studies evidenced enhanced increase in positive component (P2) and decrease in negative component (N1) of ERP response during coalescence of spindles with auditory stimuli [104, 105]. Along similar lines, another ERP study evaluated the effects of slow waves on the short and long latency components of potentials evoked by sensory stimuli [106]. The results demonstrated an increase in the amplitude of potentials during the negative phase of slow waves, while evidenced a decrease during the positive phase of slow waves. More recent EEG studies also reported a modulation of ERP responses by spindles and the slow oscillation phase [107, 108].

Together these studies demonstrated a modulatory effect for spindles and slow waves on processing the external sensory information during NREM sleep. However, the abovementioned ERP studies were limited in detecting the underlying neural structures involved in these regulatory processes.

Dang-Vu et al. investigated the neural networks recruited by external stimuli presented either during or outside sleep spindles in 13 healthy non-sleep deprived volunteers, using simultaneous EEG-fMRI [81]. The subjects were randomly exposed to pure tones (beep tones with a frequency of 400 Hz and duration of 300 ms) during

NREM sleep. Subsequently, the temporal occurrence of the beep tones was used as a basis to classify the tones into outside (TN) or within-detected spindles (TS). Researchers evidenced increased activity in primary auditory cortex and thalamus associated with TN. This was consistent with the findings of the Portas et al. fMRI study. In addition, presentation of TN tones increased activations in the brainstem (encompassing the cochlear nuclear groups, trapezoid bodies, and superior olivary complex), as well as cortical structures reminiscent of the slow-wave network, i.e., middle frontal gyrus, precuneus, as well as posterior cingulate gyrus. Contrary to TN, presentation of TS did not trigger consistent activations in primary auditory cortex or thalamus. A more pronounced response in primary auditory cortex with TN (as compared to TS) suggested a protective role for spindles by reducing the consistency of external information processing to cortex [81]. In another study, Dang-Vu and collaborators looked further into the protective role of spindles in preserving sleep [82]. They exposed 12 healthy volunteers to various naturalistic auditory stimuli during NREM sleep and demonstrated that in subjects with higher spindle density, sleep stability was better preserved in the face of noise. The inhibition of external stimulation processing during spindles raises the question of the type of information actively processed during sleep spindles. As alluded above, evidence suggests involvement of sleep spindles in off-line memory consolidation. This topic will be discussed in the next section of this chapter.

It is widely known that external sensory stimuli can trigger slow oscillations called K-complexes, which are present during stage N2 and N3 of NREM sleep. The controversy on the functional role of K-complexes is reflected in the existence of different hypotheses such as their involvement in arousal phenomena, sleep protection, or sleep state differentiation (as stage N2 hallmark). (For review, see Colrain [109]). To further address the interplay between slow oscillations and sound processing, Dang-Vu and colleagues further examined TN tones, this time in respect to their temporal occurrence with K-complexes [81]. They classified TN stimulations into two groups based on whether K-complexes followed the TN exposure (TNK) or not (TN0). As expected, both TN0 and TNK elicited activation in regions previously observed with TN tones, including primary auditory cortex, thalamus, brainstem, cerebellum, posterior cingulate gyrus, and precuneus. However, by comparing TNK and TN0, authors reported larger responses in primary auditory cortex and ventral prefrontal cortex in association with TNK. Notably, these findings are in agreement with Czisch et al. fMRI findings, in which various cortical areas including auditory cortex were found to be more activated by acoustic stimuli (rare tones) that were specifically followed by K-complexes [99]. These results suggest that K-complexes are associated with enhanced processing of sensory stimuli at the cortical level and fail to validate the involvement of these oscillations in sleep protection against a sensory stimulus. In a follow-up analysis, the same group aimed to investigate the brain response to external auditory stimuli, this time in relation to the phase of the underlying slow oscillation during N3 NREM sleep [110]. For this purpose, Schabus et al. classified the tones delivered during stage N3 NREM sleep based on their temporal occurrences relative to the peak negativity of slow oscillations. The tones appearing up to 300 ms prior the

peak negativity of slow oscillations were called "TPre," and the ones within 300 ms of post-peak negativity of slow waves were labeled as "TPost." Functional MRI analyses revealed no significant differences in thalamic or primary auditory cortex activation between TPre and TPost. Although the primary cortex responded equally to both TPre and TPost, the response in superior temporal gyrus (STG), as a higher auditory associative cortex, was significantly higher during the positive slope of the slow waves (TPost) compared to TPre. These results suggest a key role for the phase of slow oscillations in modulating the response to external sensory stimuli at higher cortical levels. Collectively, these results demonstrate that spindle activity and slow oscillations during NREM sleep modify responses to external sensory stimuli.

Neural networks modulating processing of sensory information during REM sleep have not been studied as exhaustively as during NREM sleep. One fMRI study investigated neuronal reactivity to acoustic stimulation in three subjects [111]. In this study, Wehrle and collaborators differentiated the periods with more abundant rapid eye movements (phasic REM sleep) from the ones with lower amounts of rapid eye movements (tonic REM sleep). The results showed activation in primary auditory cortex during tonic REM sleep while no activation was observed during phasic REM. This suggested that phasic REM period was a state of functional brain isolation from external stimuli. However, the study was limited by the low sample size, and future studies should incorporate more subjects when investigating the role of phasic REM in the modulation of sensory information.

Functional neuroimaging has thus shown that sleep is not characterized by a constant reduction of brain responsiveness. Instead, neuroimaging has shown that ongoing brain activities, including spindles and slow waves, modulate neural responses to external stimuli during NREM sleep. Spindles reduce the consistency of sensory information transmission to the cortex. This cortical processing is also strongly influenced by the phase of the slow oscillation, with a broader transmission during the transition to the depolarizing phase of the wave. Recently, the development of closed-loop stimulation paradigms allowed the auditory stimulation to be targeted to specific sleep oscillations and phases, supporting the importance of timing in sensory processing during sleep. Ngo and colleagues developed an online closed-loop feedback system, in which the auditory stimulation was applied in synchrony with the SO negative half-peak of the ongoing EEG activity [51]. They found that in-phase stimulation enhanced SO amplitude and the synchronization of spindles to the SO upstate, along with greater declarative memory performance compared to out-of-phase stimulation and sham stimulation [51, 112, 113]. These findings are in line with the conclusion that sensory stimulation will be processed differently depending on spindles and SO phase. They also show that, in turn, the timing of sensory stimulation during sleep modulates ongoing brain oscillations with subsequent effects on memory performance, in line with a role for sleep oscillations in memory consolidation (see next section). Further neuroimaging studies are needed to fully understand the underlying neural mechanisms of these stimulus-entrained sleep oscillations (Fig. 6.2).

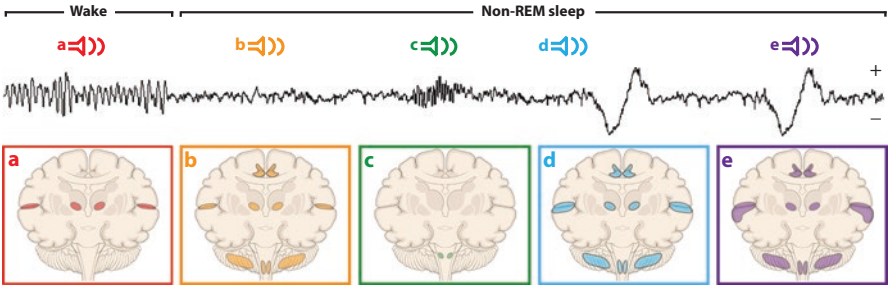

Fig. 6.2 Major brain oscillations during NREM sleep modulate brain responses to external stimuli. Few studies have characterized brain responses to auditory tones during wakefulness and NREM sleep. Dang-Vu et al. demonstrated that during NREM sleep, spindles reduce the consistency of brain responses to external auditory stimuli, while the triggering of evoked K-complexes is associated with enhanced processing of external information [81]. In a subsequent study, Schabus and colleagues added to this knowledge by reporting that also the phase of the slow wave is important in modulating the brain responses to auditory noises during NREM sleep [110]. Clusters with different colors represent fMRI responses related to tones during specific periods as follows: a = tones during wakefulness; b = tones during NREM sleep in absence of spindles; c = tones during spindles; d = tones during NREM sleep inducing a K-complex; e = tones during the ascending phase of the slow wave. (Prepared with illustrations by Patrick J. Lynch and C. Carl Jaffe. http://creativecommons.org/licenses/by/2.5/)

Functional Neuroimaging of Sleep Oscillations in Relationship to Memory Consolidation

A wide range of experimental data has implicated human sleep in the consolidation of memory. Prior research has examined the role of REM sleep, NREM sleep, and several sleep oscillations in long-term memory [114, 115]. A common hypothesis in the field of sleep research, called the "dual process" hypothesis, conceptualizes that the role of NREM and REM sleep is different depending on the type of memory. More specifically, it stipulates that NREM is more beneficial for declarative consolidation, while REM is linked to procedural and emotional memories [114, 116–118]. However, several studies have challenged that concept by showing that NREM sleep also seems necessary to the consolidation of procedural and emotional memories [119, 120]. More recent findings support the "active system consolidation" hypothesis, which stipulates that freshly encoded memories are reactivated during NREM sleep, a process that promotes the redistribution of memory traces from temporary to long-term store (e.g., from hippocampus to neocortex in the case of declarative memories), with a stabilization of this reorganization taking place during subsequent REM sleep through synaptic consolidation processes [83, 121–123]. Indeed, it has been suggested that the repeated reactivation of a memory trace allows its strengthening in cortical long-term storage, where it will be integrated into pre-existing networks of associated memory traces [124, 125]. Reactivation during sleep was first shown in hippocampal place cells in rats [126, 127], and then in humans with the observation of neural replay during sleep shown with PET [10,

128] and simultaneous EEG-fMRI [129]. For example, using PET, Peigneux and collaborators observed that the areas (hippocampus and parahippocampal areas) activated during a spatial virtual navigation task were reactivated during subsequent N3 sleep [128].

Evidence behind the theory that spindle oscillation is a central marker of neuronal plasticity and memory consolidation includes various studies in rats and humans showing that spindle density and activity increase after declarative and procedural learning, along with gains in subsequent memory performance [72, 74, 119, 125, 130–140]. But few studies actually investigated spindle-related brain activations during NREM sleep. In 2012, Bergmann and colleagues aimed to connect spindles to the reactivation of newly acquired hippocampal-neocortical declarative memory traces [141]. In nine partially sleep-deprived healthy volunteers, they used simultaneous EEG and fMRI to identify brain regions coupled to fast sleep spindle amplitude. They focused on fast spindles only, as previous data have indicated neocortical-hippocampal connectivity to more strongly interact with fast spindles [75]. Subjects were asked to perform either a declarative learning task (i.e., face-scenes associations) or a visuomotor control task prior to sleep, and were then instructed to perform a cued recall after sleep. Prior learning of face-scene associations more strongly activated neocortical and hippocampal regions during fast sleep spindles modulated by their amplitude, as compared to the control task [141]. In addition, a better immediate recall performance at the declarative task prior to sleep predicted a larger hippocampal activity increase with fast spindle amplitude of the subsequent sleep period. More recently, Jegou and colleagues conducted a simultaneous EEG-fMRI study during a declarative memory learning task (i.e., face sequences), subsequent nighttime sleep (up to 3 h of sleep in the scanner) and recall after sleep, to assess brain responses related to spindles after learning [142]. This study was conducted on a slightly larger sample of 14 healthy volunteers, and all subjects were monitored for the absence of sleep deprivation prior to the experimental session. The control condition consisted in a repeated session of a similar protocol after 1 week of daily reexposure to the same learning task, ensuring that participants had little or no new material to learn while being exposed to the same stimulus content during the control session. Results showed that regions involved in learning the task, i.e., fusiform gyrus, were reactivated during sleep following learning, and particularly during fast sleep spindles (as compared to slow spindles) (Fig. 6.3A). Furthermore, the fusiform gyrus was also activated during the recall of the task after sleep in proportion of the overnight change in recall performance. During fast spindles following learning, there was a trend for a correlation between hippocampal activity and recall performance change after sleep [142] (Fig. 6.3B).

The latter findings support the “active system consolidation” hypothesis mentioned above, which advocates that sleep states allow an active reorganization process that stabilizes the labile neural representation of a new information into a consolidated memory trace [83, 122, 123]. For declarative memories, thalamocortical sleep spindles—fast spindles particularly—would facilitate the transfer of short-term memory traces encoded in the hippocampus into long-term storage sites in the neocortex. Importantly, this process would involve cortical SO and hippocampal

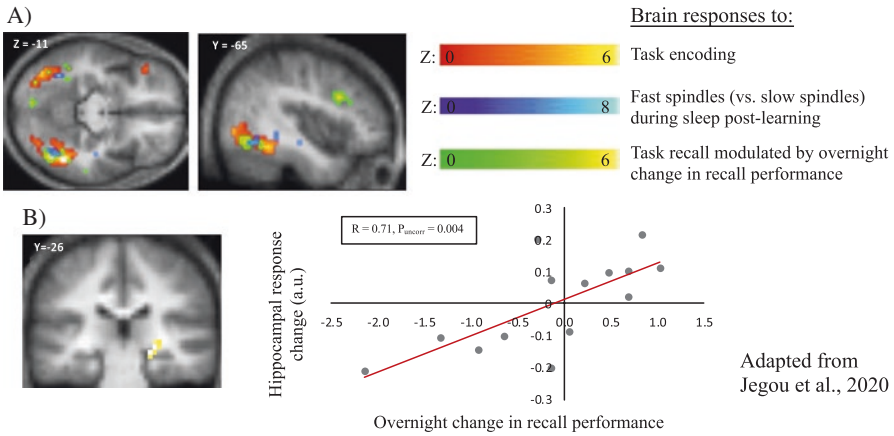

Fig. 6.3 (**A**) Regions activated (i.e., Fusiform Gyrus) during encoding are reactivated during sleep following learning, especially during fast spindles. (**B**) Subjects who presented a larger response in the hippocampus during fast spindles tended to have better overnight improvement in memory performance at post-sleep recall, which further emphasizes fast spindle's role as mediator of the hippocampus-cortex dialogue. Adapted from Jegou et al. [142]

sharp-wave ripples, as fast spindles are synchronized to the upstate of SO and in turn synchronize ripples [43, 50]. This triple phase-locking would allow the transfer and the integration of the declarative memory traces from the hippocampus into the neocortex via plastic changes in the cortical synapses [42, 43, 45, 143–146].

As for the consolidation of procedural memories, it has recently been shown that sleep-dependent motor learning would also involve a dialogue not only between the hippocampus and the thalamus but also with the striatum (i.e., putamen) and motor cortical regions. Similar to declarative memory consolidation processes, this hippocampo-striato-thalamo-cortical synchronization appears mediated by spindles [136, 147, 148]. Fogel and colleagues investigated BOLD activation linked to spindles following procedural learning using simultaneous EEG-fMRI. Participants performed a motor sequence learning (MSL) task and a control task on separate nights in the MRI scanner, each followed by an EEG-fMRI sleep session and a post-sleep retest session. MSL learning and spindles during subsequent NREM sleep were associated with overlapping activations in the striatum (i.e., putamen), hippocampus, and motor cortices. Interestingly, the extent of the striatum reactivation during spindles was not only correlated with the gains in performance, but also with changes in striatal activation from pre-sleep learning to post-sleep retest [148]. Using the same dataset, Boutin and colleagues performed EEG source reconstruction and coherence-based metrics on spindle epochs to investigate functional connectivity between specific seed regions (e.g., hippocampus, putamen) and other cortical/subcortical regions in relation to overnight performance changes [147]. They found that gains in performance were positively correlated with coherence between putamen and cortical regions (i.e., motor area, parietal areas), but also between putamen and hippocampus,

hippocampus and thalamus, and putamen and thalamus within the spindle frequency band. Their findings suggest that spindles facilitate the reorganization of procedural memory traces by functionally binding activities of the thalamus, hippocampus, motor cortical regions, and putamen. The putamen appears to have a central role in the consolidation and reorganization of motor sequence memory during NREM sleep [149], and spindle activity appears to drive and enhance the connectivity of the putamen during NREM sleep throughout this memory consolidation process.

Beyond declarative and procedural memory consolidation, visual perceptual learning (VPL) has also been shown consolidated during sleep [150]. Indeed behavioral studies have consistently shown VPL performance improvements after sleep [129, 151–153]. A study by Bang et al. sought to determine which oscillatory activity—slow waves or sleep spindles—plays a role in VPL consolidation during NREM sleep [154]. Participants performed a visual texture discrimination task (TDT) during an fMRI session, followed by a MEG-EEG sleep recording, and finally a retest after sleep. Results indicated that only the slow spindle EEG activity during N2 sleep was significantly greater after learning, with a larger increase for the trained visual region compared to the untrained region. A significant correlation was also reported between the difference in slow spindle activity (between trained and untrained regions) and performance improvement. These results support the involvement of slow spindles, localized in early visual areas, in the consolidation of TDT.

Conclusion

Sleep is not simply a state of decreased responsiveness, but rather an active state regulated by various neural activities contributing to the physiology of sleep. Previous PET studies demonstrated increases in brain activity during REM sleep, and reported hypoactivations during NREM sleep, denoting REM sleep as an active state and NREM sleep as a state of brain quiescence. However, progress in functional neuroimaging techniques such as combined EEG/fMRI unveiled a new understanding of NREM sleep by demonstrating brain activations time-locked to occurrences of two of the major brain oscillations during NREM sleep, spindles and slow waves. In fact, decreased brain activity during NREM sleep, as reported by PET, along with transient surges in neural activities observed in fMRI studies suggest that NREM sleep consists of a decreased level of baseline activity interrupted by periods of higher activity.

These phasic oscillations have various functional significances during NREM sleep, including the modulation of responses to the external stimuli and the consolidation of memory traces during sleep. Sleep spindles preserve sleep stability by contributing to a gating process during which transmission of external auditory stimuli to the cortex is decreased, while slow oscillation upstate enhances the processing of external information at the level of the auditory cortex. Therefore spindles and slow oscillations during NREM sleep determine the fate of incoming stimuli.

Neuroimaging studies conducted during sleep to specifically address the role of sleep oscillations in memory consolidation have started to emerge. These studies collectively support the role of spindles in the consolidation of different types of memories. Spindles were found involved in declarative memory consolidation, motor skill learning, and visual perceptual learning. Notably, the studies detailed in this section were performed on young, healthy subjects. Recent neuroimaging studies, to be covered in another chapter of this book, have investigated the effect of aging on sleep-dependent memory consolidation.

Future research must further explore the various oscillations that exist within sleep microarchitecture, as current research has been mainly focused on sleep spindles and slow waves. For example, ponto-geniculo-occipital (PGO) waves, a hallmark of REM sleep in animals, have been experimentally shown to enhance memory consolidation [63]. However, in humans, the underlying mechanisms mediating the role of REM sleep in memory consolidation have yet to be elucidated [155]. Future efforts will ultimately allow a better understanding of the precise role of sleep oscillations in memory consolidation which, in turn, will provide better insight into the neurobiological mechanisms underlying sleep-dependent memory consolidation. Finally, neuroimaging research should also aim at further investigating the relationship between sleep oscillations and sleep disorders, such as insomnia or central disorders of hypersomnolence, in order to shed light on their underlying neural mechanisms.

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Chapter 7
A Role for Neuronal Oscillations of Sleep in Memory and Cognition

Lisa Marshall

Sleep and Memory Across Species

This chapter deals with oscillations of neurons and networks that are relevant for different cognitive processes, in particular for memory retention in animals and humans during sleep. This first section gives a brief insight into sleep and memory in nonmammalian species.

The greatest amount of research on neuronal oscillations and plasticity has been conducted in vertebrates, more specifically on mammals. Studies on simpler invertebrate models—most notably the fruit fly and honey bee—have the advantage that the process of memory formation can more easily be dissected, from systems down to the molecular level, than for higher-order animals [1, 2]. Despite well-established proof of memory and plasticity in these species, behavioral rather than electrophysiological definitions of sleep are up to now mostly employed [3, 4]. Only very recently were 7–10 Hz oscillations discovered in the spontaneously sleeping fly [5]. In the olfactory nervous system of the Drosophila, several memory traces associated with short-term, intermediate, and long-term memory after conditioning with odors have meanwhile been reported [6]. For odor as well as for visual memories, a dynamic interaction between different brain regions across time reminiscent of memory in higher-order animals occurs [7, 8]. Neuronal oscillations in the honey bee brain have not been published. Yet, not only was sleep found relevant for consolidating navigation memory [9], but presentation of a contextual odor during sleep enhanced subsequent retention performance [10]. Although the dependence on neuronal activity during sleep has, to the authors' knowledge, not yet been investigated, separate studies have revealed in crayfish both brain electric activity characteristic of sleep [11], as well as evidence of spatial and motor learning [12, 13].

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Avian non-rapid eye movement (NREM) sleep is dominated by slow-wave activity, with slow waves found to propagate within the hyperpallium, yet sleep spindles and hippocampal sharp-wave ripples (SPWRs) have not been detected [14–16]. Studies relating neuronal oscillatory activity to memory consolidation are not as fine-grained as in mammals, yet sleep-dependent memory consolidation together with increased slow EEG activity occurred in visual imprinting [17], and a spatial discrimination task [18]. In seeming accordance with the absence of hippocampal SPWRs in birds, which in mammals are closely coupled to neocortical activity [19, 20], conclusive evidence for a hippocampal to extra-hippocampal transfer of information for long-term storage in birds is lacking [14].

Neuronal Oscillations in Sleep

From the above, it is evident that neuronal oscillations of sleep and their putative function cannot a priori be addressed universally across species. Even within mammals, distinctions between different preparations of the same tissue are necessary, as evidenced, e.g., by different cortical layers from which the cortical slow oscillation has been found to initiate in the brain slice of ferrets vs. human patients [21, 22]. Nevertheless, deductions on the mechanisms and function of human sleep spindles are necessarily often made on the basis of activity within brains or brain tissue of laboratory mammals.

Sleep Spindles

In essence, sleep spindles are generated by rhythmic spike-bursts in GABAergic cells of the thalamic reticular nucleus, which induce inhibitory postsynaptic potentials (IPSPs) in target thalamocortical cells, e.g., via corticothalamic input. The hyperpolarization with deeper NREM sleep of the membrane potential in these thalamocortical cells de-inactivates the Ca^{2+}-dependent current, I_t, activates the intrinsic I_h current, and enables generation of a low threshold calcium spike crowned by high-frequency bursts of fast Na^+-mediated action potentials [23–25]. The bursts of thalamocortical neurons induce in cortical neurons rhythmic excitatory postsynaptic potentials (EPSPs) and occasional action potentials. Synaptic interactions between reticular and thalamocortical neurons represent the spindle pacemaker, in particular during the mid-portion of a spindle. On the other hand, the cortex appears to be involved in spindle synchronization during spindle initiation as well as in the desynchronization of thalamic activity during spindle termination [25, 26]. In contrast to the abovementioned tonic shift toward hyperpolarization with deeper NREM sleep, recent simultaneous intracranial thalamic and cortical recordings in humans suggest that cortical slow oscillation down states and subsequent thalamic down states lead to a phasic hyperpolarization which presents the prerequisite for spindle generation [27]. Gardner and colleagues [28] recently differentiated between cortical subnetworks

activated in the medial prefrontal cortex (mPFC) in rats during spindle initiation and termination. During spindle initiation firing of "early" cells was strongly entrained and in-phase with spikes from cells of the thalamic reticular nucleus, whereby firing was antiphase during spindle termination. Interestingly, spindle length correlated most robustly with the ongoing activity of inhibitory reticular thalamic cells [29]. Neuronal firing patterns, cellular location, and spectral-temporal evolution of individual spindles were taken to suggest that across spindle epochs, distinct cortical subnetworks are differentially engaged.

Changes in intraspindle frequencies were found by several studies recording local field potentials (LFPs) in the mPFC [28, 30, 31]. The reports on the direction of frequency change from spindle onset to offset were, however, inconsistent. Interestingly, the two studies in humans show decreases in intraspindle frequency for fast and slow spindles [30, 31], whereas in rodents, increases were observed [19, 28]. Frequency changes are suggested to depend on thalamocortical (hyper)polarization level [19, 28, 30–33].

The existence of multiple spindle generators in humans has been concluded using various techniques: combined EEG and magnetoencephalogram (MEG) measurements, high-density EEG with source imaging [31, 34, 35], and intracranial recordings [30, 33]. Aside from existing in the neocortex and thalamus reliable spindles, detected within the range of 9–16 Hz, also appear to occur in the parahippocampus and hippocampus [30, 36]. As reflected in the EEG, slower spindles detected intracranially in humans occur predominantly in anterior regions, or have a greater percentage of anteriorly localized sources, and faster spindles are more pronounced in parietal regions [30, 33, 35, 37]. Regarding the timing of slow vs. fast spindles EEG, foramen ovale and intracranial depth recordings have indicated that fast posterior spindles precede slow frontal spindles by about 500 ms [30, 38, 39]. In a study recording simultaneously EEG and MEG, it was proposed that the ~150 ms earlier occurrence of MEG spindles, in the vast majority of cases, may reflect an initial local spindle source which then recruits active networks and shifts frontally, enabling subsequent detection in EEG derivations [31]. Using intracranial depth electrodes, Andrillon and colleagues distinguished a greater number of locally—as compared to globally—occurring sleep spindles, in particular in the beginning of nocturnal sleep. Notably, larger amplitude spindles were, more frequently, global than local in nature, i.e., occurring in concordance in different cortical and brain regions. Differences in timing of spindles between different cortical regions has been suggested to reflect propagation along the thalamic reticular nucleus rather than through intracortical pathways [30]. Interestingly, although cells of different thalamic nuclei revealed different preferred firing phases relative to the slow oscillation, timing was still dependent upon the ongoing cortical network pattern and also the exact activity of thalamocortical cells [40]. The distribution of current source density sinks and sources across cortical layers in humans gives strong support to the concept that thalamocortical core and matrix projections are reflected in different spindle features, at least when measured intracortically [41].

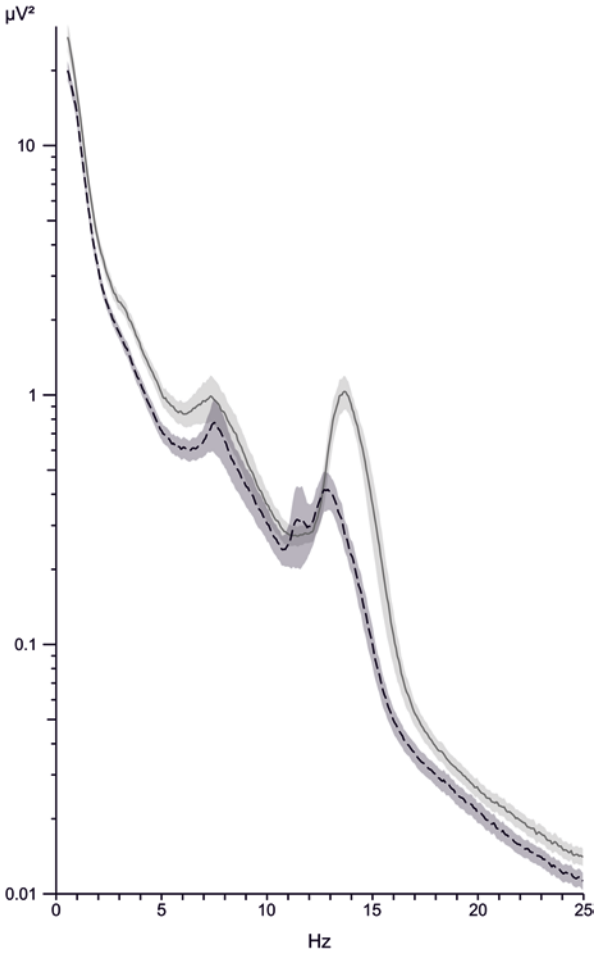

Fig. 7.1 Gender differences in sleep spindles: Mean (±SEM) spectral power for all epochs of stage 2 sleep across nocturnal sleep at Pz. Continuous gray lines, female; dashed black lines, male. Mean fast spindle power (11.5–15 Hz) was significantly higher in females than males (13.8 ± 0.1 Hz vs. 13.1 ± 0.2 Hz, $p < 0.01$, $N = 34$, 17 females; Aumann & Marshall, unpublished results)

A characteristic, frequently measured, feature of discrete spindles is their density. Comparisons in this measure between groups are hampered by the use of different recording derivations and detection algorithms, as well as by the use of different sleep spindle frequency bands. Further factors contributing to variance include the sleep stage and/or time intervals within which spindle power or discrete spindles are analyzed, and subject age and gender, aside from nontrivial interindividual differences [42, 43]. Especially fast spindles reveal pronounced gender differences in frequency and amplitude (Fig. 7.1).

The putative effects of these variables should be sufficiently reported and/or controlled when investigating the interaction with cognitive tasks. Within- and

between-subject comparisons can be differentially biased by these parameters. Some examples of variations are given below.

Spindle densities of 4–6/min are frequently reported in young, healthy (<30 years) subjects when spindle density was computed on the bases of calculating the root mean square of the spindle band signal or detected visually [44–48]. Studies reporting densities of only 2–3/min [49, 50] had investigated relatively older subject populations (mean age of 36 years), which may explain the relatively low spindle density [50], since density declines with age [48, 51]. The effect of analyzing spindle density within epochs of different sleep stages was documented in a study employing young (mean 25 years), healthy male subjects. Fast spindles (12–15 Hz) measured over averaged centro-parietal sites during stage 2 sleep revealed here a density of 5.8/min, whereas slow spindles (9–12 Hz) over fronto-central locations during slow-wave sleep (SWS) averaged only 3.4/min. Slow spindle density during stage 2 sleep and fast spindle density during SWS were intermediate [47].

Spindle density and spindle frequency measured intracellularly from 12 different neocortical regions along the caudo-rostral direction in humans correlated positively [33]. In line with this, both spindle frequency and spindle density can reveal a strong negative correlation with slow-wave activity during NREM sleep ($r = -0.81$, $p < =0.005$, and $r = -0.73$, $p = 0.02$, respectively) [30]. Slow and fast spindles also differ in the variability of their peak frequency between SWS and stage 2 sleep, with fast spindle frequency being more consistent. Slow spindle peak frequency in the above study was about 1 Hz slower in SWS (with a mean of 10.2 Hz) compared to stage 2 sleep (Fig. 7.2) [30, 47].

Slow-Wave Activity and Slow Oscillations

SWS is characterized by cortical slow wave activity (SWA, <4 Hz) and the sleep slow oscillations, which in human EEG[1] and rat LFP are ~0.8 Hz and ~1.4 Hz, respectively [52].

Delta activity (typically 1–4 Hz) is a historically older term, which distinguishes between two types of oscillations generated as the result of either (synaptic) cortical or (intrinsic) thalamic activity [53]. The sleep slow oscillation is well defined down to the cellular level, where it was initially described [54, 55]. It is generally acknowledged that during the sleep slow oscillation neurons (excitatory and inhibitory) undergo a bistable state lasting each hundreds of milliseconds during which either membrane depolarization and vigorous firing (up state), or hyperpolarization and neuronal silence (down state) dominate [56–59]. Initial EEG and LFP measurements suggested widespread cortical activity, yet high-density EEG demonstrate that slow oscillations and slow wave activity can also be locally regulated [56, 60, 61]. In fact,

[1] Note that slow oscillation will be used here as defined electrophysiologically, i.e. human EEG large amplitude oscillations during NREM sleep, >−80 μV negative peak, >140 μV peak-to peak, in a 3.5 Hz low-pass filtered signal, with lengths between positive-to-negative zero crossings from 0.9 to 2 s [39].

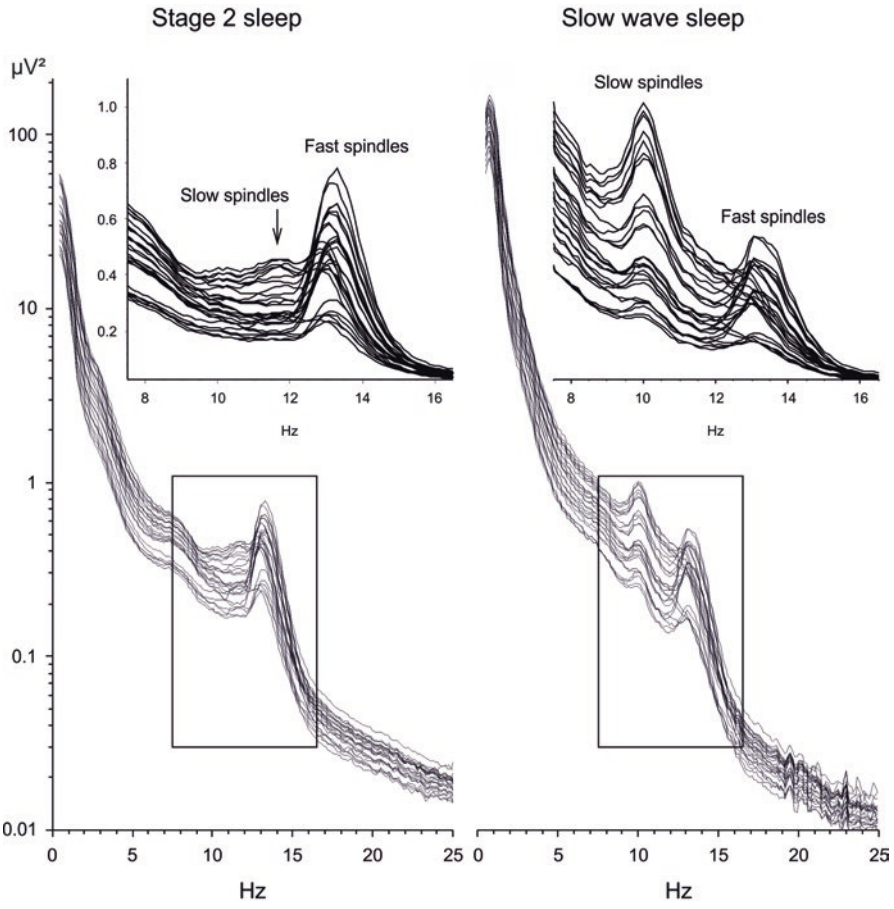

Fig. 7.2 EEG power during NREM sleep across the whole night. EEG power during stage 2 sleep and SWS reveal pronounced differences within the spindle frequency bands. Insets show enhanced views of spindle activity. Although there are clear peaks for slow and fast spindle activity during SWS, only fast spindle activity shows a clear peak during stage 2 sleep. Lines represent the 27 EEG channels. (Republished with permission of American Academy of Sleep Medicine. Mölle M, Bergmann TO, Marshall L, Born J. Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. Sleep. 2011;34(10):1411–21; permission conveyed through Copyright Clearance Center, Inc.)

the molecular and cellular mechanisms for the contribution of local brain activity to the regulation of sleep per se [62], and to the initiation and maintenance of the slow oscillation state [63, 64], are becoming increasingly evident. Further features of the slow oscillation (or SWA) per se, such as anterior to posterior propagation [61], dynamical changes across the night [56, 65, 66], or basic cellular/network generators and the specific contribution of cortical inhibitory interneurons, are not to be presented here, but have been reported elsewhere [57, 67–70]. Although the concept has for long prevailed that slow oscillations were generated exclusively by intrinsic and

synaptic mechanisms within the neocortex, recent data argue toward the relevance of the thalamocortical network for understanding slow oscillation generation in natural sleep and anesthesia [71].

Sleep spindles occur consistently during the up state of the slow oscillation. Less known is that slow and fast spindles occur at different phases of the slow oscillation. Indeed, slow frontal and fast centro-parietal spindles in humans differ in other features aside from frequency and topography. Phase-amplitude cross-frequency coupling between the slow oscillation and each of the two spindle bands with center frequencies fc = 10.5 Hz and fc = 13.5 Hz within SWS of each subject revealed that the amplitude of the slow spindle did not couple as consistently to the phase of the slow oscillation as that of the fast spindle. Significant coherence for fast spindles at Pz (Fz) was measured for 49 (42) out of 54 subjects, whereas for slow spindles at Fz (Pz) within the same SWS epochs significant phase-amplitude coupling [72] was only calculated for 20 (6) of the 54 subjects (D. Aumann and L. Marshall, preliminary results). A comprehensive investigation into differential coupling characteristics was recently conducted by cox and colleagues [73].

Induced Oscillations in Sleep

The relevance of induced oscillations and phase relationships can be well investigated by applying low-intensity sensory stimulation during sleep. Tones, acoustic bursts, or verbal stimuli can induce spindle or K-complex-/slow oscillation like cortical responses in EEG [74–79]. The relevance for memory consolidation was initially investigated by Ngo and colleagues [75], and subsequently by others as reviewed in Wilckens and colleagues [80]. Ngo and colleagues showed that the delivery of an auditory tone which induced a potential in-phase with the ongoing rhythmic occurrence of a slow oscillation led not only to an enhanced slow oscillation rhythm, but also to increased fast and slow spindle power. Above all, stimulation led to increased retention of words in a paired-associate learning task. Phase-independent auditory stimulation, however, did not improve declarative memory performance [81]. Therein slow oscillations and slow-wave activity were enhanced, but both fast and slow spindle power were decreased. These and other data argue that a specific constellation of neuronal oscillations, such as slow oscillations together with sleep spindles, are of functional relevance for memory consolidation [69, 82, 83]. Transcranial magnetic stimulation (TMS) has also frequently been employed to modulate neuronal oscillations [84–87], and to induce local processes of plasticity in subsequent sleep [88, 89], but to the author's knowledge no study incorporates the modulation of higher cognitive processes by TMS during sleep while recording any kind of brain electric activity in humans.

Another method of probing the interaction between oscillatory activity and memory processes during sleep is by transcranial application of weak electric stimulation. In particular, oscillatory stimulation has been impressively shown in vitro to entrain local field potentials after several stimulation cycles [90]. In principle,

due to its low current strength (typically between 0.25 and 2 mA) weak electric stimulation only modulates neuronal networks at the subthreshold level. Thus, effects of oscillatory weak electric stimulation are more moderate and act via different mechanisms than those produced by auditory stimulation [90, 91]. This putative subthreshold action means also that responses to weak electric currents are strongly dependent on the ongoing brain electric activity. Furthermore, as shown by experimental data and on theoretical grounds, oscillatory weak electric currents or fields are most effective at the resonance frequency of the network [92, 93]. Indeed, slow oscillating stimulation applied during NREM sleep has been shown to enhance power in the slow oscillation, spindle frequency bands, and/or retention of declarative but not non-declarative memories [94–97]; yet a lack of modulation has also been reported [80]. Along the same vein, retention of a declarative memory was impaired by ~5 Hz weak electric stimulation, i.e., at a nonresonant frequency, which also suppressed EEG slow oscillation and slow spindle power [97]. Interestingly, when applied during REM sleep ~5 Hz oscillatory tDCS had no effect on memory consolidation, but enhanced gamma band activity (25–45 Hz) in the poststimulation interval. It might therefore be hypothesized that lucid dreaming, which is associated with enhanced gamma band activity over the frontal cortex [98], may be susceptible to this stimulation. In fact, recently, 40 Hz oscillatory stimulation applied during REM sleep was effective in enhancing both endogenous gamma band activity and self-reflective awareness in dreams [99].

The feature that weak electric stimulation is strongly dependent on brain state is not only a virtue of the method in that the system is minimally disturbed by manipulation, but also a caveat. The efficacy of weak electric stimulation is dependent on covert properties, i.e., properties of the brain neuronal activity escaping measurement. During application of slow oscillatory weak electric stimulation phase ampli-

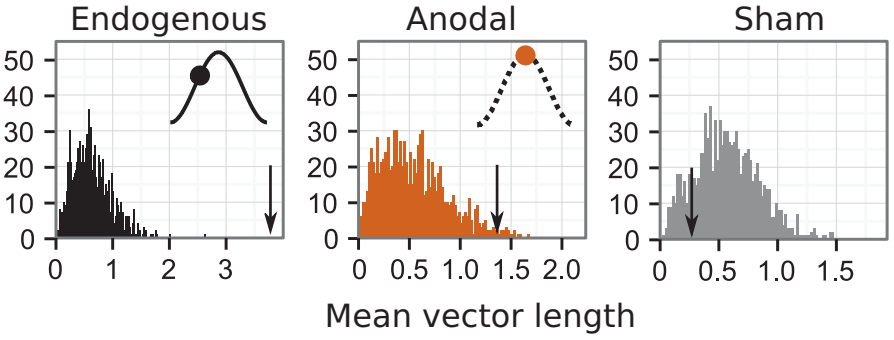

Fig. 7.3 Mean vector length reflecting coupling strength of fast spindles at Pz to the endogenous slow oscillation (left), anodal transcranial slow oscillatory stimulation (middle), and a virtually generated sham signal. Whereas coupling to the endogenous oscillations is highly significant ($p < 0.001$), coupling to the weak electric stimulation is weaker ($p < 0.05$). (Adapted by permission from Springer Nature. Campos-Beltrán D, Marshall L. Electric stimulation to improve memory consolidation during sleep. In: Axmacher N, Rasch B, editors. Cognitive neuroscience of memory consolidation. New York: Springer; 2017. p. 301–12)

tude coupling to spindles reached significance, but coupling strength was much weaker than between endogenous oscillations (Fig. 7.3). As will be described in the following, neuronal activity reflected in oscillatory potential fluctuations does not only effect cognitive processing during sleep, but presleep experience in turn also modifies neuronal oscillations of sleep. Thus, the efficiency of weak electric stimulation may well be significantly influenced by the extent of presleep learning, or existing interindividual trait-like electrophysiological features [100, 101].

Optogenetic activation of channelrhodopsin2-expressing thalamocortical neurons enabled the systematic modulation of cortical slow oscillation frequency in anesthetized rats [102]. The highest amplification of endogenous slow oscillation EEG power occurred when optogenetic activation was applied at the prevailing slow oscillation frequency.

Sleep's Influence on Memory

Although the impact of sleep deprivation on numerous cognitive functions has been reported [103, 104], the effect of specific neuronal oscillations in sleep on cognitive aspects has been most intensely investigated for memory consolidation. Within the process of memory formation, the consolidation of a memory occurs following learning, i.e., uptake and encoding of the contents to be remembered. The retention of a memory reflects the consolidation and is typically measured as the difference in performance between retrieval of the stored memory (recall performance) and encoding/learning performance.

Historically, the first experimental evidence for a positive influence of sleep on retention of memory came about 90 years ago from Jenkins and Dallenbach [105]. This finding was, however, explained within the framework of the passive interference reduction hypothesis, which posits that sleep is beneficial for memory due to less interference from external stimuli.

Results of some studies [106, 107] argued that it was not just sleep per se that was relevant for memory, but the temporal proximity of sleep to the learning. A recent study employing both 12- and 24-h retention intervals with sleep and wakefulness in different orders underlined the relevance of the proximity of sleep to learning for the consolidation of spatial associative memory [108]. But training-induced changes in SWA despite a delay before sleep were also recently reported [109]. The consolidation theory (first put forth by Müller and Pilzecker in 1900) expressed that memories initially exist in a labile state before they go into a longer term storage form [110]. More direct evidence in favor of the consolidation function of sleep did not arise until more detailed features of sleep and sleep types—such as REM sleep and the cyclic organization of sleep [111, 112]—were described.

Already in the 1970s interactions between type of material learned and different benefits of sleep dependent upon sleep stage were reported [113–115]. (For a review, see Cipolli [116].) A further conceptual advancement was the dual process

hypothesis, which explicitly stated that SWS, which is dominant in humans during the first half of the night, is beneficial for the consolidation of declarative memory. Sleep during the second half of the night (REM sleep predominant), on the other hand, is proposed by the concept to be most beneficial for procedural memories. The sequential hypothesis in contrast underscores the relevance of the cyclic succession of NREM and REM sleep (for in-depth recent reviews on studies supporting these theories, see Rasch and Born [70], Giuditta, et al. [117], and Rauchs, et al. [118]). Both hypotheses posit an active role of sleep and ongoing neuronal activity to memory consolidation (as opposed to the passive interference reduction hypothesis). A third concept contrasting to the active consolidation theory is the opportunistic consolidation hypothesis. Here it is put forth that any brain state (not, e.g., SWS per se) occurring in close temporal proximity to learning is beneficial to memory consolidation, such as quiet wakefulness or also certain drugs, as long as the hippocampus is not occupied in encoding new memories [119].

Sleep has often been shown to be more beneficial for the consolidation of emotional vs. neutral memories. REM sleep, REM-rich sleep periods, in particular phasic REM epochs, have been found beneficial in regard to the consolidation of memories with high emotional valence, for preserving emotional reactivity, fear conditioning, and extinction, in both humans [120–124] and rodents [125, 126]. During REM sleep pontine-geniculate waves arising from the brainstem and theta oscillations in the amygdala, hippocampus, and medial prefrontal cortex, and most importantly their coherent occurrence, appear to be the most relevant underlying neuronal rhythms of the forebrain [126–128]. Significant differences between humans and rodents have, however, been measured regarding consistency and topography of hippocampal and cortical theta waves [129]. Successful fear extinction memory was dependent upon phasic pontine wave activity during post-training REM sleep arising from glutamatergic cells with high-frequency (>500 Hz) spike bursts (3–5 spikes/burst) on the background of tonically increased firing rates (30–40 Hz) [125]. It is beyond the scope of this chapter to report in depth on putative mechanisms of neuronal oscillations and their generators affecting memory; for this recent comprehensive reviews are referred to [42, 130–132].

Aside from specific neuronal oscillations, sleep and distinct sleep stages are associated with other physiological parameters, most apparently changes in neuromodulatory tone and neurotransmitter activity, but also autonomic events, which may contribute essentially to sleep-dependent plasticity [70, 133–135]. These physiological effects of sleep also need to be considered when drawing conclusions from the impact of specific sleep stage suppression on the relevance of that particular sleep stage for a specific cognitive function [136, 137].

In addition to the consolidation of memories learned before sleep, sleep-dependent generalization, or the incorporation of recent into existing memories, as well as sleep's role in selective forgetting are processes receiving increasing attention. Whether reactivation occurs during REM sleep, SWS, or both is an ongoing question [138–141].

Post-learning Neuronal Oscillations

Since neuronal activity during sleep is linked to prior neuronal activity [142, 143], it is not surprising that presleep learning and cognitive activity overtly modify the macroscopic neuronal oscillations and activity during sleep, specifically sleep spindles and slow wave features [39, 46, 52, 62, 144–147]. Several developments emerging in the second half of the twentieth century were essential in forwarding research on postexperience neuronal oscillations and/or brain electric activity in association with memory. One was the emergence of concepts for neurophysiological memory trace formation, according to which information is transferred to the neocortical long-term memory store via hippocampo-cortical connections during hippocampal SPWR events of slow-wave sleep (SWS) [148–151]. Later developments incorporated mechanisms of long-term potentiation (LTP), the relevance of behavior, and state-dependent changes for defining neuronal oscillatory patterns into the two-stage model [148, 149, 152]. There was also an upsurge in the interest of linking patterns of brain electric activity to biochemical states of neurons during sleep subserving neuroplasticity, in particular the putative role of spindle oscillations in provoking a massive Ca^{2+} entry into neurons and long-term changes in cortical networks [153–156]. In most recent years, Ca^{2+} imaging has much contributed to elucidating the participation of different cell types to neuronal oscillations in sleep [68, 69]. A third development was the renewed interest in hippocampal place cells [157] in association with theta oscillations during exploratory behavior in rats. Mostly during SWS, postexperience spatially selective firing of hippocampal place cells and hippocampal spatiotemporal activity patterns were investigated [142, 143, 158–162]. Results emerging from this time, on the temporal relations between hippocampal SPWRs and thalamocortical sleep spindles, have since obtained extensive support, and finely tuned interactions between neocortical, hippocampal, and thalamic firing and local field potentials (LFPs) have been demonstrated [19, 20, 73, 131, 163–165]. Experience-dependent reactivations during sleep have been mostly investigated in the hippocampus and neocortex, but particularly in relation to the motor system reactivations in other brain regions, e.g., the striatum are shown [70, 166–173]. A further boost in knowledge and in the search for answers to newly arising questions on spatial and temporal relations between brain regions involved in postexperience sleep came with the increased use of fMRI during human sleep (see Chap. 6 of this volume: Functional Neuroimaging of Brain Oscillations during Human Sleep).

Investigations into post-learning neuronal oscillations in human EEG during sleep also gained momentum toward the end of the twentieth century due to technical advancements in long-term data recording and analyses, which enabled digital time-saving detection of electrical events throughout a period of nocturnal sleep to become a standard procedure.

In this chapter the distinction between neuronal oscillations being induced by prior-learning and contributing to cognitive processing in sleep is artificial and drawn mostly from different experimental approaches. The following studies describe neuronal oscillations induced by presleep learning as compared to those of a non-learning control, preferably of comparable sensory input and/or cognitive load.

In the same laboratory in which studies in humans first indicated that SWS-rich sleep in the first part of the night was beneficial for declarative memory formation, and REM-rich sleep in the second half of the night was relevant for procedural memory [174], the impact of learning on spindle activity was intensively investigated. Gais and colleagues [46] found significantly higher spindle density in stage 2 sleep within the first half of the night after learning on a declarative task paired-associate lists of unrelated words, as compared to a within-subject non-learning control task matched for visual input and difficulty. The difference in spindle density was most pronounced at Fz within the first 90 min of sleep. Neither spindle density in SWS nor any measure of EEG power or time spent in any sleep stage differed between the two experimental conditions. Similarly, Schabus and colleagues [175] found higher spindle activity of detected spindle events during stage 2 sleep following an association task of randomly related word pairs as compared to a matched control condition. The spindle activity measure also correlated strongly with the overnight change in memory performance. Subsequent to exploring a maze as compared to no exploration, spindle activity as well as time spent in sleep stage 2 were reported enhanced (Fig. 7.4) [176].

Memory content can also be relevant for subsequent neuronal oscillations in sleep: for instance, both SWA and sleep spindles were found to increase after learning words of sparse (or low) as compared to high semantic neighborhood density [177].

Conditions at learning furthermore impact post-learning neuronal oscillations: post-learning EEG power in the slow oscillation frequency, time spent in stage 4 sleep, and spindle count in SWS were enhanced when subjects expected to be retested on the learned material as compared to subjects without this expectation [178]. In a similar vein, parietal fast spindles over the left hemisphere reflected best the

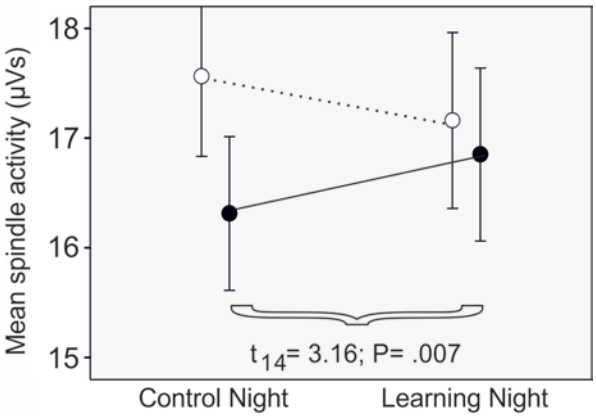

Fig. 7.4 Post-learning modification in fast spindle activity. Mean (±SEM) spindle activity revealed a relative increase in subjects improving on the memory task, but a relative decrease in subjects who did not improve. (Modified with permission from Schabus M, et al. Individual sleep spindle differences and their relation to learning-related enhancements. Brain Res. Vol. 1191. P. 127–35. © 2008. With permission from Elsevier)

effect of instruction at learning, to either remember or forget presented words. As compared to wake, sleep selectively facilitated the class of cued items to be remembered, but not the words to be forgotten. Investigation of other electrophysiological events was not reported. Figure 7.4 shows an increase by learning of spindle activity, but only for those subjects which revealed good memory performance [179].

sLORETA (standardized low-resolution brain electromagnetic tomography), an EEG-based neuroimaging technique, identified for the spindle time course a repeating loop of activity throughout a network in the superior parietal, temporal, and inferior frontal cortex [180]. These regions reveal not only fMRI correlates of fast spindles but were previously found to promote successful instructed-remembering over forgetting [179, 180]. Another study showed that odor cues associated with words presented in left or right hemifields could locally induce fast spindles during NREM sleep [168].

The integration of words in the "mental lexicon" rather than consolidation per se also correlated with spindle count: a larger increase in lexical competition, i.e., the slower response time (an indication of successful addition to the mental lexicon) of test familiar base-words to familiar control base-words, was associated with a greater spindle count. In contrast, the overnight increase in consolidation of novel words per se, tested as recall or recognition of the novel words, did not correlate with spindle count [141].

Post-learning effects of the procedural tasks, particularly in regard to changes in sleep spindles and rapid eye movements, were investigated intensely by Smith and Fogel. It was hypothesized and verified vastly in experiments, that simple motor procedural learning tasks are associated with stage 2 sleep modifications, in particular spindle density, while implicitly learning procedural rules and new cognitive strategies ("cognitive procedural") were associated with increases in density of rapid eye movements [44, 181, 182].

Four simple motor tasks requiring the refinement of motor skills, and not requiring the learning of rules or the development of a strategy—pursuit rotor, a simple version of the mirror tracing task, ball-and-cup game, operation—increased sleep spindle density as well as duration of stage 2 sleep across the night compared to a non-learning control group of six female subjects. In group comparisons of slightly larger sample size, mirror tracing led to an enhancement in REM density [181]. Subjects conducting both the mirror tracing and tower of Hanoi tasks before sleep, i.e., tasks with a large procedural component, revealed significant enhancements in the number of rapid eye movements in later sleep cycles as compared to a control group. No changes in sleep architecture of any type were found, neither spindle density nor EEG power of any frequency band were measured [183]. The relevance of REM density for consolidation is presumably linked to increased P-wave or ponto-geniculo-occipital (PGO) wave occurrence [184, 185]. As far as known to the author, no direct modulation of PGO waves has occurred parallel to any measurement of cognitive or mnemonic parameter.

Interestingly, long-range coupling within MEG delta activity during NREM sleep was recently reported subsequent to conducting a mirror tracing task. The coupled brain regions had been previously identified based on their enhanced involvement during the visuomotor mirror tracing task as compared to a control task in which slow (0.1 Hz) fluctuations in beta band power became synchronized [186].

Motor sequence learning tasks are widely used in sleep research, most frequently reported to increase number and/or duration of spindles, or spindle power, with striatal involvement developing over time [70, 169, 187, 188]. The combination with imaging methods is also particularly advanced for motor-related paradigms [189]. Correlative analyses have shown for discrete spindles that their amplitude can predict overnight gains in performance on an explicitly learned motor sequence task. Correlations were additionally found between BOLD activity in motor-related brain regions and spindle amplitude [190]. A MEG study revealed enhancement of both fast spindles and delta MEG activity during SWS of the first sleep cycle as compared to pre-training sleep. The most prominent region of interest displaying modifications in sigma and delta MEG power was the supplementary motor area (SMA), as detected via source localization [191]. The serial reaction time task can be employed to contrast implicit and explicit learning and the effect of sleep on gaining explicit sequence knowledge [124]. Subjects who had or had not acquired explicit sequence knowledge prior to sleep differed in their level of EEG slow spindle power during SWS [192]. Resting state fMRI during wakefulness, immediately after acquisition of an explicitly or implicitly learned serial reaction time task, revealed a differential involvement of brain regions including the frontal cortex [193].

In a motor adaptation task, a local increment in slow-wave activity over parietal regions and a less robust increase in spindle power as compared to a non-learning control were reported, with a positive correlation between SWA increase and performance improvement [61, 109]. Increased SWA over the frontal cortex, up to 60 min post-training without any change in spindle frequency band, was observed in rats following a task known to elicit long-term potentiation [194].

Conclusion

Taken together, the picture that the sleep-dependent consolidation of declarative vs. non-declarative memory contents represents a dichotomy and is simply attributed to disparate brain structures and mechanisms has greatly diminished. At the same time, the picture is quickly developing that fine-tuning among neuronal oscillations within and between different structures represents the essence of communication within the brain. The latter has been longer discussed regarding working memory function [195], but less in respect to cognitive processing during sleep [196–198]. Oscillatory field potential activity incorporates both general global and network-specific local components. Local aspects are defined not only topographically, but also by coherence strength among networks, by the sleep stages and times of the sleep period at which these oscillatory events mainly arise, as well as through slight variations in oscillatory frequency [196, 199]. In the conceptual Fig. 7.5 neuronal oscillations of memory and cognition are imbedded in the biological system. It reflects the basic principles of experience impacting postexperience neuronal activity. The latter is strongly dependent upon salience and emotional valence of the presleep experience, affecting strength of encoding or innervation of the relevant

brain regions and networks. During sleep basic state-dependent neuronal oscillations and experience-dependent neuronal reactivation (super firing or subthreshold modulation) interact. Tonic and phasic neuromodulatory activity as well as other non-neuronal central-nervous or peripheral inputs signaling immunologic, metabolic, and epigenetic events or processes [62, 200, 201] can further modify the fine-tuning of inter- and intraregional neuro-oscillatory interactions of the brain. On the other hand, neuro(glial)-oscillatory networks can feedback on other systems ranging from the molecular level, e.g., through fluctuations in intracellular ionic concentrations, to global system-wide effects, e.g., via interactions with circadian clock mechanisms.

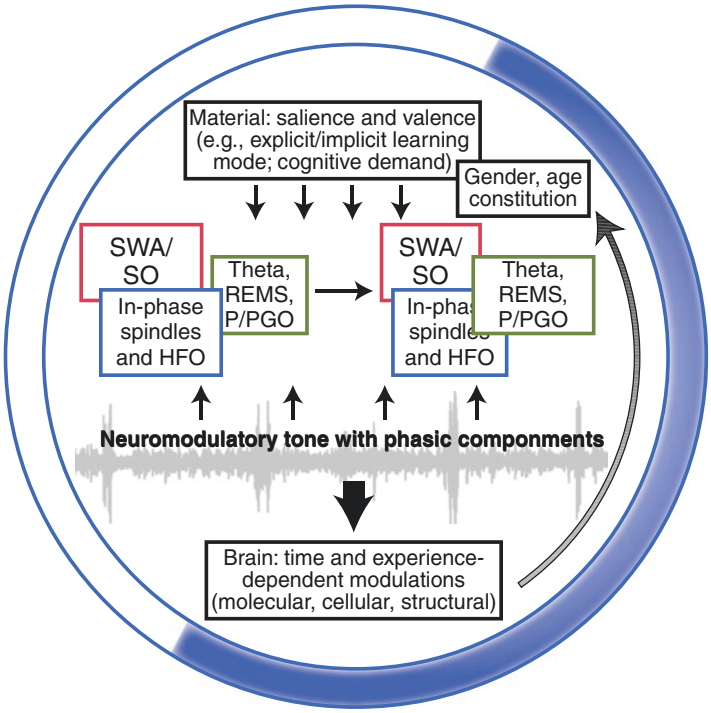

Fig. 7.5 Speculative conceptual framework for neuronal oscillations of memory and cognition within the biological system. The dynamically changing neuronal oscillations and electrophysiological events occurring across the sleep period (SO/SWA, spindles, HFO, theta, REMS, P/PGOs) result mainly from state-dependent neuronal oscillations and experience-dependent neuronal reactivation. Features affecting postexperience modifications are indicated at the top. Neuronal oscillatory activity affects not only ongoing membrane polarization levels, but can induce structural changes (e.g., at dendritic spines and interregional connectivity) in the brain, as indicated at the bottom. The long thin gray arrow on the right indicates that the latter serve to update the biological system for newly incoming information. The expression of neuronal oscillations is also dependent upon trait-like, persistent state and developmental features indicated by gender, age and constitution (see text for more details). *SO/SWA* sleep slow oscillation/slow wave activity, *REMS* rapid eye movements of REM sleep, *P/PGO* P-waves/ponto-geniculate-occipital waves, *HFO* high-frequency oscillations (>30 Hz)

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Chapter 8
Sleep Oscillations and Aging

Valya Sergeeva, Jeremy Viczko, Adrian M. Owen, and Stuart M. Fogel

Sleep Oscillations and Aging

Alongside a healthy diet and regular exercise, sleep is one of the pillars of good physical and mental health, as well as having important links to longevity [1, 2]. However, as we age, the quantity and quality of sleep are drastically reduced (Table 8.1). Subjectively, individuals, and in particular women, report frequent and early awakenings, disturbed or easily disturbed sleep, decreased total time asleep, and excessive daytime sleepiness with increasing age [3–5]. This is consistent with the age-related changes in the neural oscillations that characterize sleep states, including rapid eye movement (REM) and non-REM (NREM) sleep.

In the young adult, Stage 1 sleep (NREM1) is characterized by the disappearance of alpha activity that typically predominates the electroencephalogram (EEG) of eyes-closed wake, and is replaced by low-amplitude, mixed-frequency activity and vertex sharp waves and a slowing of the background frequencies. EEG features such as k-complexes, sleep spindles, and slow-wave activity (SWA) characterize Stage 2 sleep (NREM2), and the predominance of SWA characterizes "deep," slow-wave sleep (SWS). During REM sleep, the electroencephalogram (EEG) from polysomnographic (PSG) recordings (which typically also includes electrooculogram (EOG), electromyogram (EMG) and other polygraphic peripheral signals) returns to low-amplitude mixed-frequency EEG, with trains of sawtooth waves, along with other features such as muscle atonia and rapid eye movements.

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Table 8.1 Summary of age-related changes in the features of sleep, in NREM1, NREM2, SWS, and REM sleep

	Onset, maintenance, and arousal activity	NREM1	NREM2	SWS	REM
Early childhood (<1 year old)	Short SOL, particularly REM onset Disorganized, short sleep episodes	Not present/ negligible	Almost none/ disorganized	SWS activity starts to emerge at 2–6 months	Majority of sleep time
Childhood (1–12 year)	Undisturbed sleep epochs lengthen	Smallest proportion of TST (<5%)	Adult features emerge and proportion of TST increases	Maximal SWS at this age, decreases thereafter	Proportion reduced, related to NREM increase Follows regular ultradrian cycle, maximal second half of night
Adolescence (12–18 year)	Shift from morningness to eveningness begins Increase in TST	No age-related change	Occupies approximately 45–55% of the night	Starts to decrease	Marginal increase
Early/ middle adulthood (18–65)	Marginal changes in onset and maintenance into middle adulthood Major disruptions related to environmental over biological disruptions (e.g. child-raising, career or job-related influences)	Gradual increase with age	Greater variability in spindles Reduction of spindle activity Reduced K-complex production	Occupies about 15–25% of the night Notable decrease in SWS and its characteristics (starting middle-age, especially in men) Great variability in SWA characteristics	Marginal increase Small increase in latency to REM Decreased REM density Reduced arousal threshold Spectral power faster and less synchronized across cortex

(continued)

Table 8.1 (continued)

	Onset, maintenance, and arousal activity	NREM1	NREM2	SWS	REM
Late adulthood (65+)	Increased time to sleep onset Declining sleep efficiency Decreased arousal threshold and increased arousal frequency	Notable increase associated with sleep onset, decreased sleep maintenance and increased arousals Higher proportion of TST (<10%)	Relatively the same compared with the previous age group Greater variability in spindles Further reduction of spindle activity Further reduced K-complex production More fragmented	Greatly reduced (especially in men)	Stable in amount until final decade of life Small increase in REM latency Decrease REM density Decreased arousal threshold Spectral power faster and less synchronized across cortex

Age-related changes in the neural oscillations of sleep may provide insight into the physiological changes that accompany the aging process and to their structural and functional consequences.

This chapter will focus on the age-related changes in the neural oscillations of adult sleep across the different sleep stages. We will also briefly discuss some of the functional consequences of these changes, focusing on studies in humans. Reviews focusing on animal models of sleep and aging are sparse and is beyond the scope of this chapter, but can be found elsewhere [6–8].

Sleep Architecture

The composition of normal, healthy sleep over the course of the human life span is a moving target, evolving drastically as we are born, develop, mature, and age. However, physiological changes cannot be assumed to be in lock step with chronological age, reflected by the enormous variability of how age-related changes in sleep present themselves. This is compounded by evidence suggesting that many age-related changes in sleep are related to changes in homeostatic and circadian control [9–14], or are the result of medical comorbidities [15, 16], rather than related to the aging process per se [16–19]. Disentangling the effects of aging on sleep is further complicated by the impact of side effects from medications [4] and the cumulative effects of lifestyle choices [17, 18] over the course of the life span.

From birth and during the first few years of life, the architecture of sleep and the organization of the sleep-wake cycle dramatically change. Initially, REM sleep predominates the sleep period and there is an absence of SWS and spindles in NREM sleep. Periods of sleep and wake are disorganized, and do not align well with the young adult 24-h cycle until after 2–3 months of age [20]. By 2 years of age, sleep becomes consolidated into longer periods, daytime naps become shorter [21], and the EEG features of NREM2 (e.g., spindles) and SWS (e.g., SWA) gradually emerge [22]. During childhood, the sleep cycle continues to look more adult-like, with the lengthening of the 90-min ultradian NREM-REM cycle typically observed in the sleep of young adults. The proportion of SWS is greatest in childhood and declines into adolescence [22], along with a shift from morningness to eveningness (for review see Crowley K [23] and Crowley J, et al. [24]), peaking around 22 years of age [25].

The proportion of the various stages of sleep continues to change from adulthood until past the age of 70 years. For example, studies consistently report age-related reductions in total sleep time, sleep efficiency, SWS, and increased wake after sleep onset. However, there are less consistent findings with respect to age-related reductions in NREM1, NREM2, and REM. A meta-analysis revealed that in healthy individuals, starting in middle-age and progressing across the life span, the latency and proportion of NREM1 and NREM2 are significantly increased, whereas the proportion of REM sleep is reduced [26]. One of the most consistent and marked changes in sleep architecture with age is a reduction in SWS [27–31]. SWA during NREM, and in particular during SWS, is thought to be a marker for sleep homeostatic function, as increased SWA is observed following increased time awake [32–34], physical exertion [35], and new learning [36–38]. Interestingly, large gender differences in SWA are apparent over the life span, as well as marked interindividual variability between the sexes. For example, SWS declines in men, but remains relatively stable in women [39]. This reduction, in and of itself, would result in reduced SWA, but in addition to this, SWA is reduced during SWS as well [40]. The reduction in the duration of SWS is likely due to a deterioration in the generation of delta activity, and, in parallel, may contribute to an increase in NREM2, given that the distinction between NREM2 and SWS is that the latter is defined as having more than 20% delta activity [41, 42]. REM sleep also declines with age, but is observed in both men and women [43] with a reduction in the density of eye movements [44, 45]. By contrast, NREM1 increases with age, and is thought to represent an increase in lighter, more fragmented sleep that is observed in men but not women [39]. Finally, NREM2 remains relatively stable in both women and men [39]; however, one of the defining characteristics of NREM2, the sleep spindle and the related sigma activity, becomes more variable [44] and is significantly reduced with age [14, 28, 46–48]. The reduction in spindle activity is thought to contribute to age-related deficits in sleep-dependent memory consolidation [49]. Thus, it is crucial to consider the changes in the neural oscillations of sleep with age in order to understand the physiological and functional consequences of age on sleep.

Taken together, some important general conclusions can be made about the age-related change in sleep from sleep architecture data alone. With increasing age, sleep tends to become lighter, more fragmented, marked by a reduction in the neural

oscillations associated with sleep homeostasis and sleep maintenance, and may have important implications for daytime functioning, cognition, learning, and memory. Later sections will focus in more detail on the age-related changes in the neural oscillations that characterize the various sleep states described above, and briefly highlight some of the functional correlates and consequences of these changes. However, first, changes in the timing, initiation, and maintenance of sleep and homeostatic processes will be reviewed next.

The Timing, Initiation, and Maintenance of Sleep

The timing, quantity, and quality of sleep is regulated by the interaction of two main processes: sleep pressure and circadian rhythms [33, 34]. Aging has a putative impact on the integrity of both of these processes, thereby affecting sleep and related neural oscillations. There are two primary outcomes of aging on the sleep-wake cycle: (1) a reduction in the amount and depth of sleep, and (2) the shift from eveningness to morningness. (See Bliwise DL [50] for review and Bliwise DL, et al. [51]; however see Dijk DJ, et al. [52] and Duffy and Czeilser [53] for compelling data from forced desynchrony protocols that suggest otherwise.) Circadian rhythms are regulated by the suprachiasmatic nuclei (SCN) of the hypothalamus. When these nuclei are damaged or lesioned, circadian rhythms are attenuated or abolished [54]. Age-related degeneration of the SCN neurons or of the signal pathways that entrain these rhythms may underlie age-related changes in the timing, propensity, and structure of sleep. However, the biological mechanisms that lead to the buildup of sleep pressure are less clear, and the impact of age on these systems also remains to be fully elucidated. Recent studies in rodents, however, have identified that levels of endogenous sleep factors, such as adenosine and nitric oxide, increase during prolonged wakefulness and induce sleep [55]. Both adenosine and nitric oxide exert their sleep-regulating effects on the basal forebrain. Studies in rodents suggest that an age-related attenuation of the wake-promoting signals in the basal forebrain [56] may underlie age-related changes in sleep homeostasis.

Sleep Homeostasis

The homeostatic buildup of sleep pressure is associated with the amplitude and dissipation of SWA [57, 58]. Sleep restriction studies have demonstrated that SWA is enhanced when sleep pressure is increased via sleep restriction, and SWA is inhibited when sleep pressure is reduced via sleep period extension [59, 60]. The wake-related increase in SWA is observed predominantly in frontal regions [61]. Studies have shown that this increase is use-dependent, whereby SWA is increased locally with increased activity in the contralateral somatosensory cortex to somatosensory stimulation [62], and a reduction with immobilization [63], thus suggesting that the buildup of SWA with prolonged wakefulness is homeostatically regulated and is

use-dependent, possibly reflecting the biological systems-level need for synaptic homeostasis. A reduced buildup and dissipation of SWA with age [64] suggests that either the capacity to produce sleep is reduced [65], sleep pressure is reduced with age [66], or homeostatic regulation of sleep is impaired [67].

Circadian Modulation of Sleep

Homeostatic sleep pressure is not the only force regulating sleep-wake patterns and the neural oscillations of sleep. Sleep spindles, but not SWA, are strongly modulated by circadian rhythms, in tandem with the melatonin rhythm [14, 68, 69]. Interestingly, this is consistent with previously mentioned studies, which found that sleep spindles are one of the neural oscillations that are significantly reduced with age [47]. Thus, the reduction in spindles with age may be the result of reduced or deregulated circadian control of spindle activity [14, 64]. Dijk et al. also revealed that REM sleep and alpha activity during REM sleep [70] were modulated by the body temperature circadian rhythm. Thus, there are several EEG markers of the circadian rhythmicity of sleep; however it appears that SWA is modulated by sleep pressure determined by time spent awake, and that spindle-related activity during NREM sleep and alpha activity during REM sleep are under circadian control. It has been proposed that the phase advanced circadian rhythmicity associated with aging reflects that either the circadian pacemaker may not be functioning [9], the biological signals may be attenuated, or input to the SCN is reduced (e.g., yellowing and clouding of the retinas) [71].

Age-Related Changes in NREM1 Oscillations, Sleep Onset, Arousals, and Sleep Fragmentation

NREM1 is the first and "lightest" stage of sleep following wakefulness, marked by less than 50% alpha activity, and its EEG features such as vertex sharp waves and low-voltage, mixed-frequency EEG mark the transition from wake to sleep. The amount of time spent in NREM1 is typically <5% of the night in healthy young adults but gradually increases into middle and late adulthood. A meta-analysis revealed an increase of 5% between the second and seventh decades of life [26]. This effect was reported to be larger for men; however the opposite trend has also been observed [39, 72]. For both genders, this overall increase in NREM1 sleep stems from an increase in sleep-onset latency (SOL), as well as a failure to maintain sleep, with a significant increase in the number of arousals throughout the night [52]. Most investigations are limited to macro-level descriptions of NREM1 (e.g., the total amount of time spent in NREM1). Because NREM1 is linked with wake-to-sleep transitions and arousal activity [73, 74], both of which significantly increase over age, this section will further detail age-related oscillatory changes in sleep onset and arousals.

Sleep Onset

Sleep-onset latency (SOL) is defined as the time it takes for an individual to transition from wakefulness to sleep at bedtime. It has been shown to progressively increase with age [26]. By contrast, awake, resting, eyes-closed EEG activity is characterized by alpha (8–13 Hz) and beta (12–30 Hz) frequencies. Descending toward sleep onset, cortical activity becomes more rhythmic and synchronized, with a visible increase in slow, synchronized, waveform amplitudes. The most prominent changes in oscillatory activity are apparent in alpha wave activity over the occipital lobe when eyes are closed [17]. The increase in SOL due to aging occurs gradually, but it becomes most notable into the sixth decade of life and beyond [26]. In one study, the mean amount of time spent awake after lights off was nearly double for the elderly participants (nearly 30 min) as compared to young adults (~15 min) [18]. However, this increase in mean SOL might be in part due to the significant increase in SOL variability that comes with age [28]. Indeed, increased SOL has been shown to vary greatly between individuals as well as within an individual, the latter relating to previous accumulation of sleep pressure [11, 12]. In addition, shifts in sleep time occur with age, whereby earlier-to-bed, and subsequently earlier-to-rise, times [75] are observed. This shift from eveningness to morningness in late adulthood has been hypothesized by some as a reduction in the ability of the circadian arousal system to withstand homeostatic sleep pressure [11, 76]. Thus, the overt signs of age-related changes in sleep, including SOL, seem to be at least partially associated with the changes of the circadian [9, 13] and homeostatic relationship [11, 12] which, though antagonistic, operate together to produce an entrainable sleep-wake cycle.

Arousals

Arousals from sleep are usually discrete bursts of synchronized alpha activity (~8–12 Hz) and appear as distinct events from the ongoing EEG. They typically intrude into the lighter stages of sleep, lasting longer than 3 s [41], and reflect an elevated level of cortical activation relative to sleep. Arousals can be elicited by either exogenous or endogenous stimulation. Controversy exists regarding how best to classify and categorize arousals. For both the American Sleep Disorders Association (ASDA) and the American Academy of Sleep Medicine (AASM) criteria, intra-scorer reliability is reportedly low [21] (see Ramanand et al. [77] or Halász et al. [78] for suggested alternatives). According to the most encompassing and broadest categorical definitions, described in Halász P et al. [78], arousals can be classified into three types: (1) behavioral arousals, otherwise known as a movement arousals, whereby any peripheral muscle activation is accompanied by changes in any or all other EEG channels; (2) cortical arousals, a transient shift in desynchronized EEG activity occurring independently of other behavioral, muscular, or autonomic events; and (3) subcortical arousals, a transient EEG pattern associated with

a brief autonomic event [78]. Arousals do not always result in an awakening from sleep and may occur both locally or more broadly across the scalp [79]. In terms of aging, Zepelin et al. [80] reported a substantial decline in the arousal threshold across all stages of the night (i.e., comparatively weaker external stimuli disturbs sleep more easily). This reflects an overall reduction of sleep intensity with increased age, in effect making sleep lighter and more difficult to sustain. Arousals within NREM2 most significantly increase with age [52], occur more abruptly [81], and may lack the transient increases in delta frequency activity that commonly precede an arousal event in young adults [73, 74, 77], although the rate at which older adults fall back to sleep appears to remain the same [10]. Thus, taken together, age-related increases in arousals may not necessarily reflect a diminished need or propensity for sleep.

Functional Significance of Age-Related Changes in NREM1, Sleep Onset, and Arousals

Increased sleep fragmentation and arousals are associated with excessive daytime sleepiness; nocturnal insomnia; nocturnal wandering; cognitive decline; increase in the number of daytime naps; decreases in effectiveness of recovery sleep; and changes in attention, learning, affect, and mood [23, 82–84]. A variety of primary sleep disorders that become more common with age also contribute to disturbed sleep as indicated by a greater frequency of arousals including sleep-disordered breathing, periodic limb movement disorder, restless leg syndrome, chronic pain, frequent bathroom trips, bereavement, neurodegenerative disorders, depression, and many more [17, 23, 26]. While obstructive sleep apnea and medication-related effects are major contributors of sleep disturbances in the elderly, another critical factor underlying sleep quality and maintenance is the integrity of cortical functional organization. A loss in efficacy of the circadian system, cortical, and subcortical arousal, and sleep-promoting regions will all result in reduced sleep efficiency and sleep maintenance [11, 85–87]. In summary, a wide variety of factors contribute to increased arousals during sleep with aging, and thus arousals can serve as a valuable index of sleep disruption; however, they cannot inform us of the underlying neurobiological cause of fragmented or disturbed sleep.

Age-Related Changes in NREM2 Oscillations

In healthy young adults, NREM2 sleep typically occupies about 45–55% of the night's total sleep time [22]. During this stage of sleep, the EEG becomes more synchronized relative to wake or NREM1, electromyogram activity decreases, and the individual's awareness of the external environment is diminished. The characteristic features of NREM2 sleep are sleep spindles and K-complexes [41]. Evidence suggests

that total time in NREM2 sleep increases over the period between middle age and old age [26, 48], while others show only relative increases in NREM2 for men but not for women. In women, these awakenings may be explained by independent and unsynchronized activation of multiple cortical sites that leads to non-synchronized neural activity [88].

Spindles

Age-related changes in NREM2 can also be described in terms of neural oscillations. Sleep spindles characterize NREM2 and are brief bursts (<1 s to ~3 s) of oscillatory activity within the sigma band, with a frequency of ~11–16 Hz with a waxing and waning amplitude that is discrete from the ongoing EEG. There is evidence suggesting the existence of two types of sleep spindles [89, 90]. Slow sleep spindles are in the ~11–13.5 Hz frequency band and are distributed over frontal sites. Fast sleep spindles occur within the ~13.5–16 Hz frequency band, have a posterior distribution, and occur predominantly over parietal and central sites [91]. Sleep spindles are thought to originate in the thalamus, and are a result of the synaptic interactions between thalamocortical neurons and rhythmic depolarization [92], modulated by GABAergic pathways [93, 94], although Bonjean et al. [95] provide evidence suggesting that spindles are initiated cortically.

Age-related characteristics of spindles including the duration, amplitude, and density (Fig. 8.1) decrease with age [44, 47, 96]; however, some studies have shown that spindle density increases with age [97, 98]. Interestingly, some studies suggest that not all spindle characteristics are uniformly affected by age. For example, the reduction in spindle density progresses with age [48, 99], but is reduced to the same extent in men and women [100]. Moreover, spindle frequency is increased in the elderly [14, 28, 46, 48, 99], which is consistent with an overall reduction of frontal slow frequency EEG that is observed with age [40], suggesting that fast and slow spindles are affected to a different extent with age. The periodicity of spindles also changes with age, whereby the inter-spindle interval shortens and the duration of a series of spindles decreases [48]. Another factor complicating the assessment of age-related changes in spindles is that the variability in spindles are great both between individuals and within individual NREM cycles [48, 101, 102], and the difference between young and older individuals changes dynamically as a function of time of night, and across individuals, depending on interindividual variability in spindle density [44]. Moreover, age-related changes in spindles do not occur uniformly across the scalp. Spindle density in elderly adults differs at prefrontal and frontal sites, whereas reduced spindle duration is observed at parietal and occipital areas [47]. Finally, it remains unclear whether older adults generate fewer spindles, or if age-related changes in spindles make them more difficult to identify (e.g., due to reduced duration and amplitude), a methodological issue that remains to be fully resolved, and may have implications for the interpretation of age-related changes in the features of sleep such as sleep spindles.

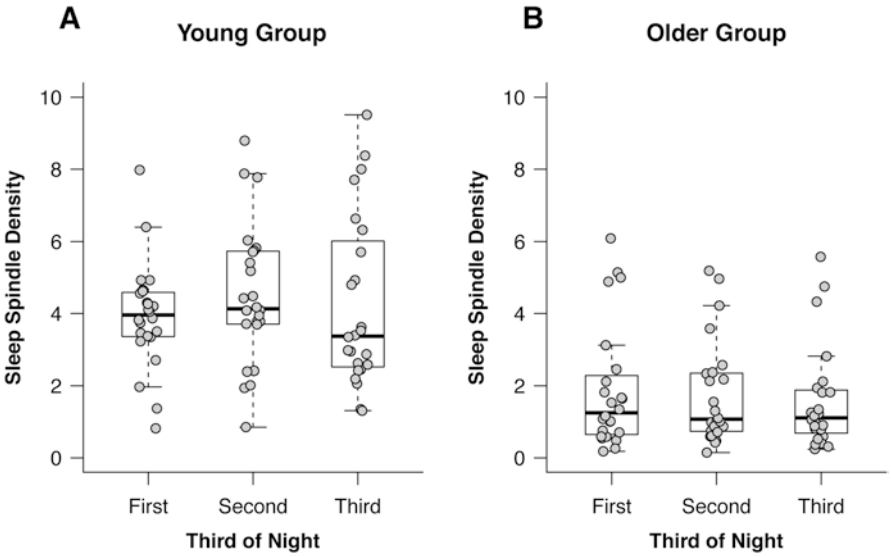

Fig. 8.1 Spindle density in older (**b**) and younger subjects (**a**) in each third of the night. Sleep spindles are significantly reduced in older (60–85 years) as compared to young (age 17–24 years) individuals. The age-related difference in spindle density was consistent over the thirds of the night and did not significantly change over thirds of the night as a function of age. (Peters, R. et al. (2014). Plos One, 9:3, e91047. https://doi.org/10.1371/journal.pone.0091047.g002)

The aging process results in marked changes in spindles and their characteristics; however the underlying physiological changes that accompany changes in the features of the EEG remain to be fully elucidated. Changes in density and duration of spindles may occur due to changes in thalamocortical and intracortical circuitry [103–105]. More specifically, spindle production may be affected due to a decrease of GABAergic neurons, such as those in the reticular nucleus responsible for gating thalamocortical oscillations including spindles. Decreased spindle amplitude may be the result of cortical cell loss associated with the aging process, and the large-scale synchronization of those cells may also affect the frequency of sleep spindles [28, 48]. In addition, the level of circulating melatonin decreases with age, and it is suggested that this could underlie the reduced sleep spindle production, particularly in men [106]. The impact of the structural and functional neural changes, from the molecular to the systems level, associated with aging on sleep oscillations remains to be thoroughly investigated and understood.

K-Complexes

Another characteristic feature of NREM sleep is the K-complex. K-complexes are slow, large-amplitude cortical events that consist of a negative sharp wave (>100 μV), followed around 350–550 ms by a slower positive component, and

terminate with a final negative peak occurring around 900 ms. K-complexes have a total duration of ≥0.5 s and are maximal at frontal derivations [41]. K-complexes and slow oscillations are generated in the thalamus, although their morphology and propagation across the scalp are influenced by cortical cells [107]. With normal aging, the average number of K-complexes is reduced from about 1–3 per minute in younger adults to 0.7–1.7 per minute in elderly individuals [108]. This is consistent with age-related neural degeneration, and reduced gray matter volume [109]. However, the functions of K-complexes are still not fully understood, and some debate exists about whether it is a partial arousal, or an inhibitory process that serves a protective function from external stimuli [28], although recent functional neuroimaging studies suggest that the K-complex reflects a cortical response in auditory cortex to sounds, whereas sound processing during spindles is distorted [110].

Functional Significance of Age-Related Changes in NREM2 Oscillations

Sleep spindles are thought to serve several functions, such as protection from external stimuli [123, 124]. Given their role in protecting sleep from noise, fewer spindles with age may contribute to fragmented sleep [46, 101, 125]. Spindles are also important for the optimal consolidation of procedural (e.g., skills, reasoning, and rule-learning) and declarative (e.g., facts, figures, and events) memory [49, 126–129]. Spindle activity has been implicated in synaptic plasticity [130–132], suggesting that they play an active role in the sleep-dependent consolidation of new learning. Age-related changes in sleep have been shown to have a negative impact on overnight memory consolidation for procedural skills [133, 134], and spindles have been shown to be related to this deficit [102]. Thus, an age-related reduction of spindle activity may help explain age-related, sleep-dependent deficits in memory consolidation. Reduced spindles in the elderly are associated with a reduction of the spindle-related, overnight changes in activity in structures important for skill learning, e.g., putamen and cerebellum in young, but only the cerebellum in older individuals (Fig. 8.2) [49], suggesting that a spindle-related, sleep-dependent increase in activity in structures such as the putamen appears to be crucial for off-line improvements, for which older individuals do not derive the same benefit, due to an age-related reduction of sleep spindles.

However, sleep-dependent memory consolidation in older individuals for declarative memory appears to be intact [135], as does the relationship between spindles and declarative memory performance in elderly women [136]. Finally, interindividual differences in spindles are related to cognitive abilities such as visuospatial ability [126], verbal learning potential, verbal fluency, and visual attention [127]. However, it remains unclear if the relationship between interindividual differences in sleep spindles and cognitive abilities such as IQ deteriorates in elderly populations.

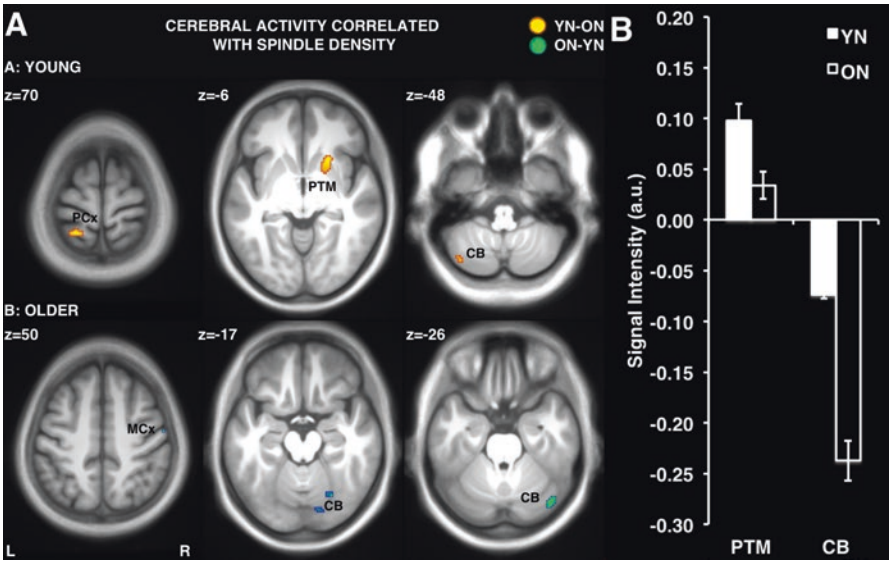

Fig. 8.2 (**a**) Overnight differences in cerebral activation during practice of a motor skill task, correlated with spindle density in young subjects (Young Nap: YN-ON) vs. elderly subjects that slept (Older Nap: ON-YN) groups. (**b**) Mean signal intensity (percent overnight change) for significant clusters in the putamen and cerebellum correlated with spindle density. *PCx* parietal cortex, *MCx* motor cortex, *PTM* putamen, *CB* cerebellum. Error bars represent standard error. (From fMRI and sleep correlates of the age-related impairment in motor memory consolidation. Fogel SM, Albouy G, Vien C, Popovicci R, King BR, Hoge R, et al. Human Brain Mapping. 35:3625–45. © 2013. Reproduced with permission from John Wiley and Sons)

The functions of K-complexes are still largely unknown, but some debate exists whether it is a partial arousal related to information processing [137, 138], sensory processing [110], or an inhibitory process that protects sleep from external stimuli [28]. Reduced K-complexes and the associated increased arousals with age may suggest the former, although this possibility remains to be investigated. Further investigation of K-complexes employing neuroimaging techniques may provide insight into whether sensory processing associated with K-complexes is related to reduced sleep quality with age.

Age-Related Changes in Slow-Wave Sleep Oscillations

In young healthy adults, SWS typically occupies about 15–25% of total sleep time, primarily concentrated in the first half of the sleep period [22]. During this stage of sleep, slow waves dominate the EEG, electromyogram activity remains low, and awareness of the external environment is greatly reduced. The main physiological marker of SWS is SWA, also called delta waves, has a frequency of 0.5–2 Hz, and

large peak-to-peak amplitude of at least 75 μV. Delta waves are thought to reflect the large-scale synchronous firing of cortical neurons, originating from the thalamus [111]. More specifically, the oscillations appear between the two states: the "up" state (depolarizing and generating action potentials) and "down" state (hyperpolarizing and terminating action potentials; for review see Contreras et al. [112]).

Slow-Wave Activity

One of the most prominent transformations of sleep in the elderly is the decrease in amount of SWS. Decreased SWS begins as early as middle age [11, 26, 31, 50, 113–117], and occurs across all circadian phases [118]. Not only do the elderly spend less time in this stage, they tend to have a longer onset for deep sleep [113]. One meta-analysis demonstrated that there is a 2% linear decrease in amount of time spent in SWS and SWA per decade of increasing age [26]. There is some evidence that this decline is gender-specific and happens only in males [39, 100, 115]; however, there is considerable variability in the characteristics of SWS among the elderly [113]. The amplitude and dissipation of SWA reflects homeostatic sleep pressure, and is amplified and increased with prolonged wakefulness. Interestingly, when subjected to sleep deprivation, the resulting enhanced SWA is attenuated in older adults as compared to young adults that experienced the same level of sleep deprivation [84]. Despite the fact that older individuals spend less time in SWS, daytime napping is not more frequent with age, perhaps suggesting that increased age lessens the need for sleep, or perhaps reduces sleep homeostatic regulation of sleep [76].

With increasing age, slow wave density [119] and delta power of the EEG are reduced [11, 120, 121]. Older individuals tend to have smaller and less frequent slow waves compared to young adults [31, 50, 113, 117, 120], even after sleep deprivation [84]. Gender differences have also been observed for delta amplitude, whereby slow waves in females are 40% larger than in males [122]. Slow waves in the elderly also tend to have a lower slope [50, 119, 120]. These age-related differences suggest that more time is required to synchronously group large populations of neurons that produce scalp-recorded SWA. Over the course of natural, healthy aging, gray matter is reduced [109, 116], which in turn would be expected to result in decreased SWA.

Functional Significance of Age-Related Changes in SWS Oscillations

Finally, given the links between SWA and memory consolidation and synaptic homeostasis [36, 139], it is reasonable to hypothesize that age-related changes in SWS may result in deficient synaptic homeostasis and impaired memory and cogni-

tion with age; however this hypothesis remains to be conclusively tested. Recent evidence is limited, but has shown that age-related verbal memory impairments were associated with decreased SWS [140], and higher SWA was found to be associated with better overnight declarative memory retention [141]. Moreover, by interfering with SWA (via acoustic neurofeedback) decreased declarative memory encoding was impaired in the elderly [142]. Together, these studies suggest that memory processing in the elderly remains dependent on SWA for consolidation to be optimized, and reduced SWA in the elderly has a negative impact on memory consolidation. However, this remains controversial [135, 143], and further research is required to elucidate the relationship between the marked age-related changes in SWA and its impact on cognitive function.

Age-Related Changes in REM Sleep Oscillations

During REM sleep, cholinergic, glutamatergic, and dopaminergic neuromodulatory tone increases resulting in low-amplitude, high-frequency cortical EEG activity. Mixed-frequency, wake-like EEG persists throughout REM, including increases in alpha, beta, and gamma coupled to the theta range, and interhemispheric gamma (~30 Hz) coupling is highest in REM [144]. Unsurprisingly, one of the characteristic features of REM sleep is the presence of rapid eye movements. Rapid eye movements appear on the EOG as conjugate, high-amplitude, sharply peaked, horizontal eye movements. The cerebral neurophysiological process underlying rapid eyes movements are ponto-geniculate-occipital (PGO) waves [145]. Until only recently, human PGO activity was only presumed to underlie REM activity, as PGO activity is predominantly subcortical, and not detectable with superficial EEG recording. However, evidence now exists, from deep brain recordings in epileptic patients and neuroimaging studies that confirm REM-PGO activity in humans [146, 147]. Furthermore, PGO and rapid eye movements are associated with facial and distal limb twitches occurring in REM sleep [148], which are also observed in rodents. However, other than these twitches, baseline EMG is typically lowest in REM sleep, resulting in muscle atonia of the major muscle groups, which is congruent with near abolishment of noradrenergic tone. While PGO waves are not detectable with traditional scalp recordings, sawtooth waves are recordable from the surface of the scalp, and are another less-studied archetypal characteristic of REM sleep. With a much lower amplitude than slow-wave activity, sawtooth waves have a frequency range between 2 and 7 Hz, emerge most clearly over central regions [41], and have a distinctive shape from other more gradual slow activity. Age-related changes in sawtooth waves remains to be an area requiring further investigation.

Ohayon et al. [26] report a slight decrease (about 4%) of REM sleep in older versus younger adults; however the amount of REM sleep remains fairly stable into late adulthood. Remarkably, another meta-analysis found the amount of

REM sleep remains stable until the ninth decade of life, at which point the amount of REM sleep significantly drops off below 10% of the night (down from ~20% in preceding decades) [43]. Latency to first REM period exhibits only a small decrease across adulthood [26]. The density of rapid-eye-movements decreases with age [45], as does the arousal threshold [80], leading to an increased number of awakenings from REM with increasing age. However, REM density has been shown to be at the same level as young subjects over the course of the night [44].

Into middle and old age, REM power below 10 Hz decreases [40, 149] and appears to topographically shift theta power toward frontal and central derivations [40]. Sample entropy is a measure of signal irregularity, predicted by the log-rhythmic ratio of high-frequency activity (alpha and beta range) to low-frequency activity (delta and theta range). From middle to old age, sample entropy increases indicating a change in spectral power favoring faster (desynchronized) activity with increasing age [86] and global reduction in slower frequencies. Mutual information of the EEG between cortical regions (i.e., degree of interdependence) is typically lowest during wake, highest in SWS, and declines into old age. More specifically, interdependency of alpha and beta activity is reduced, suggesting that cortical synchronization during REM sleep is reduced in the elderly [88] and that the EEG is more wake-like than in younger individuals.

Functional Significance of Age-Related Changes in REM Sleep Oscillations

It is rather difficult to interpret these modest age-related changes in REM sleep in terms of how they might relate or contribute to waking behavioral and cognitive function, as the precise function of REM sleep is still under debate. REM sleep has been implicated in the consolidation of particular types of procedural memory, particularly when the learning involves the acquisition of an entirely new schema, rule, or skill [150–153]. Whether this holds true with age is unclear. Hornung et al. [154] found that REM deprivation did not reduce procedural consolidation in the elderly as compared to young adults. REM sleep is also involved in processing emotional content (for review see Rasch et al. [155]), and it remains to be investigated whether REM serves the same function later in life. Disruptions of REM sleep and higher REM frequencies are associated with insomnia, which is more common in elderly populations, and is associated with a reduction in the subjective feeling of being well rested [156], a common complaint among the elderly. It remains to be investigated whether REM sleep, although relatively well preserved with age [44], may influence subjective sleep quality, and whether REM sleep plays the same role for memory and emotional processing over the course of the life span.

Other EEG Perspectives and Future Directions

The majority of this chapter has discussed sleep oscillations (e.g., features such as spindles, K-complexes, vertex waves) and viewed primarily through the lens of conventional categorizations of sleep states. Working within this framework bears the benefits of well-understood terminology and common parametric measurements. Importantly, other perspectives and approaches exist from which we might also derive meaningful information about the age-related changes in sleep oscillations. Briefly, we will describe two other approaches that may be beneficial to the investigation of age-related changes in sleep in the future, as relatively little scientific evidence exists using the approaches described next.

Cyclic Alternating Patterns

The identification of cyclic alternating patterns (CAP) [157, 158] in sleep EEG have been slow to gain widespread adoption despite value in describing and characterizing arousal-associated sleep pathophysiologies [78, 159, 160]. Central to this framework is that arousal activity is interpreted as a functionally integrated part of ultradian sleep cycling. This is in contrast to the traditional perspective of arousals as random and disruptive. The CAP-based approach identifies arousals (taken together with the other phasic events of sleep such as delta bursts, vertex sharp waves, K-complexes, intermittent alpha activity, as "Phase A" events) into a model that boasts better predictions of arousal and micro-arousal behaviors throughout the night [157]. The details and background are too extensive to be covered in this section (for review see Parrino et al. [161]). Briefly, CAPs occur in a structured way based on the slope of the sleep trajectory (i.e., whether transitioning "down" to SWS versus "up" into REM), classify patterns of activity in terms of arousal synchronicity, and are a marker of sleep instability.

Most CAP research has been done on middle-aged and young adults, with only one study characterizing life span patterns in the ratio of CAP activity to total NREM activity [162]. In this study, the distribution of CAP activity (and subtypes of "Phase A" therein) were found to vary by age group, with the young adults (31.9%) showing the lowest amount of CAP activity (55%), followed by middle-aged adults (37.5%), teenagers (43.3%), and finally the elderly (55%). The latter group showed more de-synchronous CAP than the other groups which, taken together, is consistent with reduced sleep efficiency as previously described. Given the relationship of CAP to sleep quality and efficiency, especially in terms of arousal and ultradian regulation, future research could capitalize on this novel framework, which may reveal valuable information about the nature of age-related changes in the rhythmic structure of sleep oscillations.

Sleep Microstates

Beyond the classic definitions and classification systems [41, 42], another method of describing sleep is the analysis of sleep microstates; brief (e.g., <1 s) prototypical topographic maps thought to represent distinct spatiotemporal states of the spontaneous fluctuations of the scalp potential field over time. Microstates are topographically defined, and this approach is well suited to describe the dynamic EEG changes across sleep-wake states, whereby spatiotemporal EEG activity is averaged across all electrode sites on a subsecond timescale to extract discrete segments of stability [163, 164]. Wake resting state has been effectively summarized as sequencing between four main microstate maps, characterized by their own distinct topography. These four maps are highly associated with default mode and resting state network activity as measured by functional neuroimaging [165], leading to tentative hypotheses that microsecond fluctuations of microstates are intrinsically associated with resting blood-oxygen-level-dependent (BOLD) activation [166, 167], only reflecting large-scale activity within the dynamics of the subsecond time-course [168].

While microstates have demonstrated some clinical utility [169, 170] and provide useful insight into waking resting state function and process, to our knowledge, only one study to date has applied a microstate approach to sleep. In their study, Brodbeck et al. found that the microstates observed in waking rest were also observed during sleep, even when the acute phasic graphoelements (e.g., K-complexes, slow oscillations) were removed from analyses [168]. When NREM sleep stages where evaluated in terms of microstate parameters (mean microstate duration, ratio total time and global explained variance, and transitional probability), they reported NREM1 being the most similar across all parameters to wake. NREM2 was found to be the most different across microstate parameters versus other sleep stages. In NREM3 all microstates were expressed for nearly double the durations as in wake, indicating microstate stability in this stage of sleep. Surprisingly, NREM1 and NREM3 shared one prominent microstate topography, and across deepening sleep, the microstate with the most frontal topographic distribution was reduced.

Microstates are interpreted as implying fast dynamic information processing, and are believed to be correlated with mentation, and indicators of the integrity and function of underlying cortical networks [169]. Given known structural and functional age-related changes in circadian and homeostatic neural systems [10, 13, 76, 84, 171–173], studies evaluating age-related changes with microstate parametrics could provide new insight into the qualitative and quantitative changes associated with normal and disordered sleep.

Conclusion

With age, the most striking and consistent changes in the neural oscillations of sleep are reduced SWA and sleep spindles, whereas REM sleep is strikingly preserved until the very late stages of life. In general, sleep becomes increasing lighter and more fragmented with age, particularly for men, and there is an increase in the electrophysiological signatures of wake and arousal intruding into sleep. While the functional and structural neural changes that accompany the aging process would seem like ideal candidates to explain the changes in sleep oscillations with age, much work remains to identify the impact of the aging process on the brain and the related changes in neural oscillations during sleep. The functional significance of these changes are not yet well understood in terms of the role that sleep plays for synaptic plasticity, memory, and daytime functioning. Future research could elucidate how better sleep could contribute to healthy aging for the mind, brain, and body.

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Chapter 9
Sleep Oscillations and Psychiatric Disorders

Fabio Ferrarelli and Giulio Tononi

Introduction

Neuropsychiatric disorders are rapidly increasing in prevalence and severity, especially in young adults, thus representing a health care emergency worldwide [1]. Schizophrenia, affective disorders including major depression and bipolar disorders, dementia, and substance use disorder represent about 13% of the overall burden of disease, a number higher than cardiovascular diseases as well as cancer [2]. Notwithstanding their overwhelming impact on the patients and the entire society, still little is known about neurobiology of major psychiatric disorders, despite the fact that their clinical characteristics have been described more than a century ago.

Historically, the syndrome of manic-depressive insanity, which nowadays includes both major depressive and bipolar disorders, was first conceptualized by Emil Kraepelin in the sixth edition of his psychiatry textbook in 1899 [3] whereas the term schizophrenia was introduced by Eugene Bleuler at a meeting of the German Psychiatry Association in Berlin in 1908 [4]. Furthermore, over the past several decades a variety of distinct, diagnostically separated psychiatric disorders have been introduced based on a series of signs and symptoms of mental illness. This effort resulted in the publication of the influential Diagnostic and Statistical Manual of Mental Disorders (DSM), the fifth edition of which (DSM-5) was released in 2013. However, while the DSM is an invaluable clinical tool that provides a common language and set criteria to reliably reach diagnostic consensus across different mental health providers, such a tool has not helped to further our under-

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standing of the etiology and pathophysiology of the most common psychiatric disorders.

A major limitation of a clinically based classification is that it considers different disorders as clearly distinct entities; by contrast, biological boundaries between disorders are often much more tenuous and inconsistent. Additionally, it is becoming increasingly clear that a novel approach to diagnostic classification is needed, which more closely reflects the underlying functions as well as dysfunctions of the brain [5]. This approach, which is strongly supported by the National Institutes of Mental Health (NIMH), emphasizes the role of findings from basic sciences, and especially neuroscience, in formulating and testing hypotheses on defective brain mechanisms underlying the most common psychiatric disorders [6]. Among those findings, neuronal oscillations have been consistently shown to be implicated in critical healthy brain functions—including memory, learning, and plasticity—and increasing evidence indicates the presence of oscillatory abnormalities in psychiatric patients during both wakefulness and sleep.

In what follows we will discuss the relationship between brain oscillations, particularly those occurring during sleep, and psychiatric disorders. We will begin by describing the main characteristics of neuronal oscillations. We will then explain why sleep and sleep-specific oscillations can provide unique insight into a healthy brain function as well as into the neurobiology of some psychiatric disorders, and support those claims with a series of recent findings. Finally, we will elaborate on how future studies on sleep oscillations may help identify both the molecular mechanisms and the neural circuits implicated in the neurobiology of some psychiatric disorders, including schizophrenia and major depression, which in turn may lead to novel pharmacological and non-pharmacological treatment targets for those disorders.

Neuronal Oscillations: General Characteristics

One of the fundamental properties of neuronal populations is their ability to resonate and oscillate at different frequencies [7]. Intra- and extracellular electrophysiological studies have shown that periodic changes in the membrane potential of individual neighbor neurons create extracellular currents, which can be measured by electrical recordings from the scalp as EEG oscillations [8]. Those oscillations therefore reflect periodic fluctuation of excitability in groups of neurons, which in the mammalian forebrain can occur in several oscillatory bands, from ultraslow (0.05 Hz) to ultrafast (500 Hz) frequencies [9].

The most commonly described frequency bands in the human brain include delta, also called slow-wave activity, or SWA (1–4 Hz); theta (4–8 Hz); alpha (8–12 Hz); beta (12–30 Hz); and gamma (>30 Hz). During sleep, the low beta range (12–16 Hz) is usually described as sigma or spindle activity band because of sleep spindles, waxing and waning fast oscillations predominantly occurring during light non-rapid eye movement (NREM) sleep (N2). In contrast, slow waves are observed during deep NREM sleep (N3) and represent the most common oscillations recorded during SWA

[10]. Slow, low-frequency range oscillations provide the largest contribution to scalp-recorded EEG activity because the power density of EEG is inversely proportional to frequency (f). Additionally, changes in the slow frequency phase is associated with modulation in the amplitude of higher frequencies [11], and such modulation can occur both at rest and while performing a task. This suggests that several oscillatory rhythms can occur simultaneously in the same brain regions [12], and that neuronal oscillations can also interact with each other, as suggested by the finding that global, widespread slow cortical oscillations can regulate the occurrence of fast oscillations in the thalamus as well as the hippocampus during sleep [13].

The presence of brain oscillations across different mammalian species underscores the important role of those rhythms in relation to brain activity and connectivity. While brain size increases hundreds- to thousands-fold from the smallest to the largest mammals, the time/frequency content of neuronal oscillations vary little across species [14]. Thus, those rhythms represent a critical, phylogenetically preserved property of the brain, despite ever changing in volume and complexity of its structure. At the same time, the properties of neuronal oscillations are the result of the physical architecture of neuronal networks, including types and ratios of neurons available (i.e., number of excitatory neurons vs. inhibitory interneurons), axons caliber and conduction time, as well as synaptic path lengths and delays [15]. Based on those anatomical and functional constraints, it is generally assumed that the period of an oscillatory activity, and its associate frequency content, is determined by the size of the neuronal populations engaged, as well as by the level of activity and connectivity of the individual neurons involved. Higher frequency oscillations (i.e., high beta to gamma range bands) tend therefore to occur locally and are generally confined to a small neuronal group, whereas slower oscillations (delta to low beta frequency bands) unfold over longer period of time and can involve spatially remote brain regions [12]. It is, however, important to notice that in different behavioral conditions (i.e., while asleep), those slower oscillations, and especially slow waves, can occur both globally and locally as a result of the bistability of cortical neurons slowly oscillating between up and down states, and this phenomenon is regulated during sleep based on the preceding waking activity [16].

During wakefulness, oscillations in various frequency bands can be observed in different brain areas, both at rest and while performing a task. Eye closure induces widespread alpha-band (α, 8–12 Hz) oscillations in occipital-posterior parietal cortical areas [17], whereas 7–12 Hz EEG oscillations (mu rhythms, μ) are commonly observed over the sensorimotor and parietal areas during immobile wakefulness [18]. Those rhythms are thought to reflect the resting or "idling" state of the related cortical regions, as α activity usually subsides after opening the eyes whereas μ oscillations are blocked by movement [19]. Oscillatory activity in faster frequency ranges (i.e., beta and gamma) can be usually elicited by performing cognitive tasks [20] or measuring steady-state evoked responses [21]. More recently the intrinsic oscillatory frequency, or natural frequency, of different brain regions was characterized by employing a combination of transcranial magnetic stimulation (TMS) with high-density (hd)-EEG. This TMS/hd-EEG study established α-range oscillations (8–13 Hz) in the occipital cortex, low beta (13–20 Hz) oscillations in the parietal

cortex, and high beta/gamma oscillations (>20 Hz) in the frontal cortex. Notably, each region maintained its own natural frequency even when activated indirectly after TMS of another cortical area, thus suggesting that the observed oscillations reflect local neuronal mechanisms [22]. A comprehensive description of brain oscillations occurring during wakefulness has been presented elsewhere [8, 18, 20] and is beyond the scope of this chapter, which is instead focused on sleep-specific neuronal oscillatory activity in relation to psychiatric disorder.

Sleep and Sleep-Specific Brain Oscillations

Sleep offers a unique window into brain function. During sleep the activity of neuronal populations can be monitored and probed for an extended period of time with superior temporal resolution. Furthermore, with the development of high-powered computers as well as novel EEG caps, it is nowadays possible to perform high-density 256-channel scalp recordings, thus greatly improving the spatial resolution provided by standard, low-density EEG montages. Sleep EEG recordings also minimize waking-related confounding factors, including fluctuation in attention and variation in cognitive capacity. This is important when performing EEG recordings in healthy individuals to assess for resting, baseline level of function of specific cortico-cortical and cortico-subcortical circuits. It is even more relevant in psychiatric patients, given the role of active symptoms, motivation, and/or cognitive dysfunction in affecting the ability to generate oscillatory patterns.

Traditionally, sleep is divided in NREM, or dreamless sleep, and rapid eye movement (REM) sleep, when most of the dreaming activity occurs. NREM sleep is further divided in three stages, from light (N1) to deep (N3) sleep. A night of sleep usually consists of four to five cycles, each beginning with NREM and ending with REM sleep. Each cycle lasts approximately 90 min, with deep NREM sleep occurring mostly in the first half and REM episodes in the second half of the night (Fig. 9.1). Each of those stages has characteristics EEG features (Fig. 9.1, Table 9.1). During NREM sleep the two most commonly observed rhythms are slow waves—1 Hz oscillations characterized by large amplitude, positive–negative deflections mainly occurring during N3 sleep—and sleep spindles, 12–16 Hz waxing and waning oscillatory activity mostly present during N2 NREM sleep. Those rhythms have characteristic topographies, with slow waves showing the strongest activity in prefrontal areas, whereas sleep spindle power is maximal in a centroparietal region (Fig. 9.1). In addition to occurring spontaneously during NREM sleep, slow waves and spindles can also be evoked noninvasively and reliably by TMS [23], as well as by auditory stimuli, and their activity has been associated with improved cognitive function, including learning and memory consolidation [24]. Those sleep-specific brain oscillations have been consistently observed in mammals as a reliable marker of sleep need and plastic changes [25], and are thought to reflect the activity of complementary cortical and thalamic circuits [10, 26]. The electrophysiological and molecular, as well as network, characteristics of both slow waves

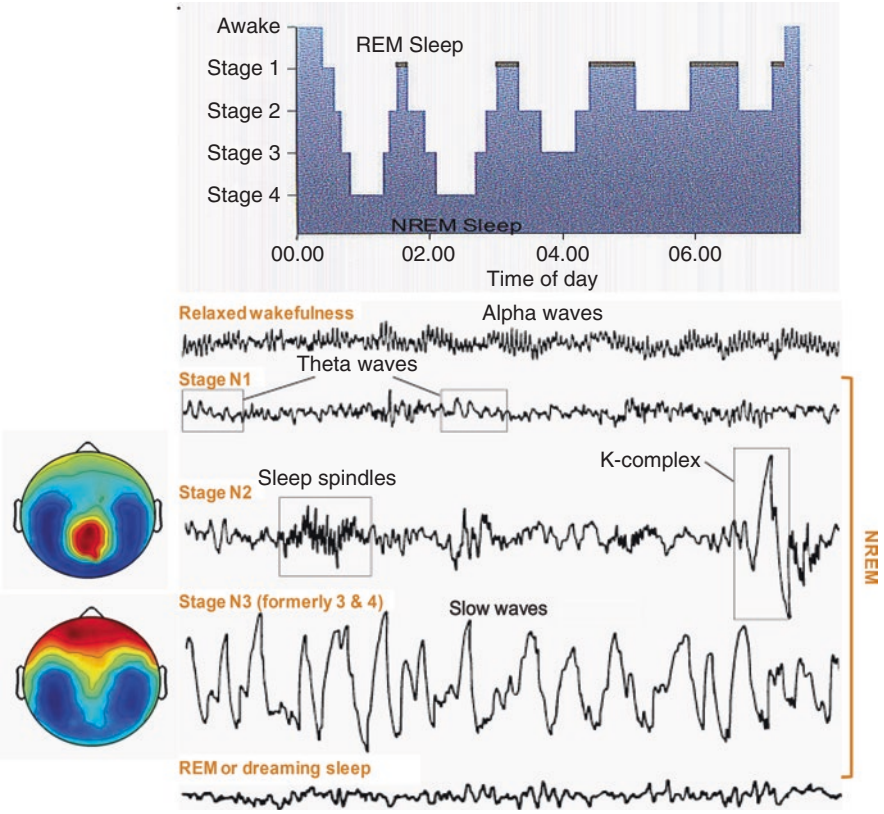

Fig. 9.1 Sleep hypnogram, sleep stages with related EEG rhythms as well as slow wave and sleep spindles topography. *Top*: sleep hypnogram of a healthy adult. Each sleep cycle is characterized by a NREM and a REM episode. However, NREM sleep dominates the first half of the night, whereas progressively longer REM episodes occur towards the end of the night. *Bottom*: Each sleep stage is characterized by a specific EEG activity, including sleep spindles for NREM N2 and slow wave for N3. The topography of those two rhythms is displayed on the bottom left

and asleep spindles have been extensively described by in vitro, in vivo, and in silico studies. Furthermore, increasing evidence has linked those sleep-specific brain oscillations to learning, memory, and plasticity across several mammalian species, including healthy humans, and some recent studies have established slow waves and sleep spindle abnormalities in psychiatric disorders, in particular major depression and schizophrenia patients. Notably, brain oscillations occur also during REM sleep, especially in the theta range (4–8 Hz), both in the hippocampus and the neocortex. However, this chapter will focus on studies investigating NREM-predominant sleep oscillations, including slow waves and sleep spindles, in psychiatric disorders, which will be reviewed in what follows.

Table 9.1 Stages of sleep-electrophysiological criteria

	EEG	EOG	EMG
Wakefulness Stage W	Low-amplitude, mixed frequency; alpha rhythm (8–13 Hz) with eye closure, attenuating with eye opening	Eye movements and eye blinks (0.5–2 Hz)	High tonic activity in skeletal muscles
NREM sleep Stage N1	Low-amplitude, mixed frequency; theta rhythm (4–7 Hz), with vertex sharp waves (V waves, ≤0.5 s)	Slow eye movements (SEM)	Slight decrease in tonic muscle activity
NREM sleep Stage N2	Low-voltage background activity with sleep spindles (11–16 Hz bursts) and K-complexes (biphasic negative–positive waves lasting ≥0.5 s)	No eye movements	Further decrease in tonic muscle activity
NREM sleep Stage N3	High-amplitude (≥75 μV), slow (≤2 Hz) waves lasting ≥20% of the epoch	No eye movements	Low tonic activity
REM sleep	Low-voltage, sawtooth waves (2–6 Hz), predominant theta activity	Rapid eye movements (REM)	Muscle atonia with phasic twitches

Slow Waves and Sleep Spindles

Electrophysiological and Molecular Characteristics

Slow waves are ~1 Hz oscillations characterized by large amplitude (>75 μV), positive–negative deflections generated by cortical neurons and propagated by cortico-cortical and cortico-thalamo-cortical circuits. Slow waves predominate during N3 NREM sleep, which is also called slow-wave sleep (SWS), and were first described with intracellular recordings in neurons of different cortical areas in anesthetized cats [27]. The cortical nature of the slow oscillation has been confirmed by its preservation in the cortex after thalamectomy, its absence in the thalamus of decorticated cats, and its presence in isolated cortical slices [28]. Slow waves are the most prominent EEG features occurring during NREM sleep, and are generated by groups of neurons oscillating between a hyperpolarized, or "down" state, when neurons are silent, and a depolarized, or "up" state, when neurons are firing [10]. The down state is due to disfacilitation, which is the removal of synaptic excitatory inputs in cortical neuronal networks, as well as hyperpolarizing K^+ currents [29]. The up state consists of non-*N*-methyl-D-aspartate (NMDA) mediated excitatory postsynaptic potentials (EPSPs), a voltage-dependent persistent Na^+ current ($I_{Na(p)}$), as well as fast inhibitory postsynaptic potentials (IPSPs) reflecting the action of GABAergic local-circuit cortical cells [27], whereas its duration seems to be regulated by extracellular Ca^{2+} currents. Specifically, it has been suggested that the depletion of extracellular Ca^{2+} during the depolarizing phase of the slow oscillation produces a decrease

in synaptic efficacy, which in turn determines the disfacilitation and the occurrence of a new down state [30].

Sleep spindles are waxing and waning, 12- to 16-Hz neuronal oscillations that characterize light, N2 NREM sleep, although they are also observed during SWS. Sleep spindles are generated within the thalamus, and are then synchronized and maintained at the cortical level. It was originally hypothesized that GABA-ergic neurons of the thalamic reticular nucleus (TRN) are the pacemaker of sleep spindles. The TRN is the only purely inhibitory nucleus of the thalamus, is heavily interconnected with most thalamocortical (TC) neurons, and pioneering studies from the Steriade group demonstrated that TRN neurons can generate sleep spindles in isolation, whereas spindles disappear within the TC network after disconnection from the TRN [31]. More recently, several in vivo, in vitro, and in silico studies have demonstrated that the interactions of chemical synapses and electrical coupling among inhibitory TRN neurons lead to generation and synchronization of spindle sequences within this nucleus [32]. Even if spindle rhythmicity can be produced and maintained within the TRN without necessarily requiring inputs from TC and cortical neurons, corticothalamic (CT) inputs are thought to play an important role in providing an excitatory drive that initiates spindle activity in reticular neurons. The importance of those CT inputs is supported by experiments showing that excitatory postsynaptic currents (EPSCs) elicited in TRN neurons by stimulation of CT axons are 2.5 times larger than in TC neurons, and that GluR4 receptor subunits of CT synapses on reticular neurons are 3.7 times more numerous than in TC neurons [33, 34]. Thus, although slow waves are generated primarily in the cortex whereas spindles are initiated in the thalamus, both rhythms tend to implicate the entire thalamocortical system [28]. Slow waves and spindles have also been described as coalescent, global oscillations, largely based on intracellular recordings from cortical and thalamic neurons in cats showing that the excitatory component (“up” state) of a slow oscillation is often followed by a sequence of spindle waves [35]. However, more recent work employing simultaneous scalp EEG, intracerebral EEG, and single-unit firing in multiple brain regions of neurosurgical patients demonstrated that the majority of slow waves and sleep spindles occur locally as discrete, isolated events, thus suggesting that these brain oscillations can be segregated both spatially and temporally [16].

Role in Plasticity, Memory, Learning

Converging evidence suggests a link between sleep activity and neuronal plasticity, especially in regard to the beneficial effects of sleep on learning as well as memory acquisition and consolidation [36]. Several studies have shown that sleep enhances both declarative and procedural memory in a variety of tasks [37], with virtually no evidence for the opposite effect, that is sleep weakening or removing memories [36]. Furthermore, when compared with the same duration interval during

wakefulness, post-learning sleep promotes the retention of declarative information [38, 39] and improves performance in procedural skills [40–42].

The role of SWA and sleep spindles in those cognitive processes has been increasingly investigated over the past several years. The first of a series of studies performing sleep hd-EEG recordings in healthy humans demonstrated a local increase in sleep SWA in sensorimotor areas after a visuomotor learning task, but not after a kinematically equivalent motor control task with no learning involved, and the post-sleep task performance improvement was positively correlated with the local increase of SWA [43]. Another study obtained similar results when using a declarative learning task that led to increased SWA at left frontal locations during post-training sleep, which correlated with post-sleep improvements in memory performance [44]. A more direct link between SWA and cognitive performance was demonstrated by Marshall et al., who induced slow oscillations by transcranial application of oscillating potentials during NREM sleep and showed that this boosting of slow waves enhanced the retention of declarative memories in healthy individuals [45]. This result was confirmed by another study employing the same transcranial slow oscillation stimulation paradigm before an afternoon nap, wherein an increase in sleep SWA predicted a post-nap improvement in encoding on all three declarative tasks, picture recognition, cued recall of word pairs, and free recall of word lists, whereas procedural finger sequence tapping skill was not affected [46]. Following a different but complementary approach, two studies employed an acoustic slow-wave suppression paradigm, which significantly decreased SWA without affecting total sleep time or REM sleep, and found that the slow-wave reduction significantly affected perceptual as well as visuomotor learning [47, 48]. Similarly, in a study where participants' left arms were immobilized for 12 h, their motor performance deteriorated and SWA over the controlateral sensory-motor area was significantly decreased during subsequent sleep compared to pre-immobilization baseline nights [49].

Whereas the role of slow-wave activity in learning and memory is well established, there is some recent, increasing evidence suggesting that sleep spindles are implicated in memory consolidation and plasticity [50], and can be considered a proxy measure for the individual's learning potential [51]. Both animal and human studies have shown an increase in spindle density and/or activity during non-REM sleep after learning [52–55]. Enhanced spindle activity was observed after acquisition of both declarative memory tasks and procedural motor skills, and in some instances this enhancement correlated with the overnight improvement in task performance [56–59]. Furthermore, this spindle activity increase was localized in cortical areas most strongly involved in the prior learning of the task, including the prefrontal cortex after encoding of difficult word pairs [44, 56], the parietal cortex after a visuospatial task [57], and the contralateral motor cortex following finger motor-skill learning [58].

The exact mechanisms through which slow waves and sleep spindles facilitate synaptic changes underlying memory and learning are still unknown.

However, it has been demonstrated that there is a specific temporal relationship between the occurrence of slow oscillations and sleep spindles during NREM sleep across several species (e.g., mice, rats, cats, and humans) such that spindle activity increases during the up state while it is suppressed during the down state of a slow oscillation [13, 28, 60]. Furthermore, sleep spindles have been shown to be temporally coupled to sharp wave-ripple complexes [61, 62], which consist of sharp, fast depolarizing waves generated in the CA3 region of the hippocampus, on which high-frequency oscillations (100–300 Hz) generated in hippocampal CA1 and called ripples are superimposed [63]. Individual ripple events tend to occur during spindle troughs [62], and it has been suggested that ripple-spindle events represent a hippocampal-neocortical transfer of information, whereby ripples with their associated hippocampal memory reactivations occur during the waning phases of the spindles [64]. Thus, one hypothesis attempting to account for the coalescence of all those rhythms during NREM sleep has proposed that the feed-forward control of slow oscillations over ripples and spindles enables transferred information to reach the neocortex during widespread neocortical depolarization (e.g., on the up state of the slow oscillations), which facilitates the induction of persistent neuronal synaptic changes and the storage of information in the cortex [36]. In contrast, another leading hypothesis, the synaptic homeostatic hypothesis (SHY), proposes that memory consolidation is a by-product of a global decrease in synaptic strength occurring during sleep [65]. Specifically, any information encoded during wakefulness leads to an increase in neuronal synaptic strength, which during subsequent sleep is reduced to a level that is sustainable in terms of energy, space, cellular supplies, and signal-to-noise ratio, thus resetting synapses' ability for future encoding. Various synaptic rules implementing activity-dependent depression during sleep are compatible with the renormalization process predicted by SHY, including (1) a downscaling rule where all synapses decrease in strength proportionally, but those that end up below a threshold become ineffective [66]; (2) a modified spike-timing dependent plasticity (STDP) rule by which stronger synapses are depressed less than weaker ones [67]; and (3) a "protection from depression" rule [68, 69], wherein a neuron that fires strongly during sleep, rather than potentiating the associated synapses as in the awake state, protects them from depression. Altogether, down-selection ensures the survival of those circuits that are the "fittest" because they were strengthened repeatedly during wake or integrated with previously formed memories, whereas synapses that were rarely strengthened during wakefulness are depressed and eventually eliminated. These two hypotheses about the function of sleep and the role of sleep-specific brain oscillations are not mutually exclusive, as it has been recently suggested that slow waves contribute to both synaptic homeostasis by downscaling cortical synaptic connections as well as to memory consolidation through reactivation and strengthening of hippocampus-dependent episodic memories [70].

Slow Waves and Sleep Spindles Abnormalities in Psychiatric Disorders

Anxiety, Obsessive-Compulsive Disorder (OCD), and Post-traumatic Stress Disorder (PTSD)

Although insomnia and other sleep disturbances are commonly reported in patients affected by anxiety, OCD, and PTSD disorders, only a handful of studies have investigated sleep variables in those patient populations. Among the studies on anxiety disorders, one found an increase in the sleep SWA of a subgroup (13, or 24%) of patients ($N = 54$) diagnosed with panic disorder. However, the overarching goal of this work was to establish epileptic abnormalities in those patients, and slow-wave parameters were not further investigated [71]. Two studies performing EEG sleep recording in generalized anxiety disorder (GAD) as well as major depressive disorder (MDD) patients found increased NREM N2 sleep in the former compared to the latter group [72], whereas GAD patients had diminished NREM N2 sleep [73], as well as SWS [72], compared to healthy controls. However, neither slow-wave nor sleep spindle activity were directly assessed. Finally, an increase in the number and duration of slow waves combined with a reduction in their amplitude was reported in a study investigating the effects of Flurazepam on sleep EEG activity in four healthy subjects, whereas no data are available on psychiatric patients [74].

Insomnia is one of the most commonly reported PTSD symptoms and is thought to affect primarily NREM sleep. A meta-analysis of polysomnographic studies conducted on military veterans and civilian adults with PTSD found more NREM N1 sleep, less slow-wave sleep, and greater REM density compared to subjects without PTSD [75]. Some EEG studies have shown greater beta activity during NREM sleep in individuals diagnosed with PTSD, whereas others reported reduced beta power during REM sleep in adults with PTSD relative to control subjects [76]. However, neither slow-wave nor sleep spindle activity has been specifically investigated in those patients, with the exception of a study showing reduced SWS and total slow-wave range integrated amplitude, calculated with a period amplitude analysis according to Feinberg et al. [77] in male subjects with combat-related PTSD compared to combat-exposed healthy controls [78].

The literature on sleep findings in OCD is also very limited. An initial study reported decreased total sleep time, increase in NREM N1 and N2 sleep, decreased SWS, and shortened REM latency in OCD patients compared to healthy controls [79]. The reduction in SWS was replicated by Kluge et al. [80], whereas Robinson et al. found significant negative correlations between OCD symptom severity and the duration of both NREM N1 and N2 sleep [81].

Schizophrenia and Other Psychotic Disorders

Sleep disturbances have been consistently observed in psychiatric patients, and especially in individuals with schizophrenia [82]. Sleep abnormalities are often heralding symptoms of a psychotic break and can predict an acute decompensation in remitted schizophrenia patients [83], whereas sleep deprivation can precipitate psychosis even in healthy subjects [84]. Sleep abnormalities are thought to be a core feature of psychotic disorders, given that they are observed in prodromal individuals [85]; medication-naïve, as well as unmedicated patients [86]; and are often associated with worse cognitive function [87], one of the most persistent and treatment-refractory deficits observed in schizophrenia patients [88]. The most commonly reported abnormalities in sleep architecture in psychotic patients include an increase in sleep latency, increased waking after sleep onset, and reduced sleep efficiency [89]. A reduction in deep NREM sleep, or SWS, has been reported in different groups of schizophrenia, including medication naïve [90] and unmedicated [91] patients, but overall SWS deficits have been inconsistently found and appear to affect just about 50% of psychotic patients [86].

A growing number of studies have investigated changes in sleep EEG activity, and especially in slow waves and sleep spindles, in schizophrenia, and in other psychotic disorders. In two initial studies Keshavan et al. found reductions in the delta (1–4 Hz) as well as theta (4–8 Hz) frequency bands in a subset (N = 19) of 30 schizophrenia patients in relation to control subjects [91], whereas Hiatt et al. reported a decrease in delta frequency activity in 10-min segments of NREM sleep periods in five unmedicated schizophrenia patients [92]. However, a number of more recent studies failed to establish any difference in SWA [93, 94], as well as several slow oscillation parameters [95, 96] between patients with schizophrenia and healthy individuals. Those inconsistent findings about reduced SWA in schizophrenia confirm previous reports that slow-wave deficits may involve just a subgroup of those patients. Consistent with this assumption, lower SWA has been more often reported in institutionalized patients with profound cognitive impairment [89], as well as in schizophrenia patients with prominent negative symptoms [97].

Several studies have investigated sleep spindle activity in psychosis. Hiatt et al. reported higher spindle density during the first NREM sleep episode in five schizophrenia patients relative to healthy subjects [92], whereas two other studies performing sleep EEG recordings in nine [98] and 11 [90] schizophrenia patients and normal controls found no difference in spindle parameters between groups. Notably, all those investigations were conducted on a fairly small number of patients, and employed a very limited number of channels (C3 and C4). By contrast, more recent work from our group employing hd-EEG system (256 channels) demonstrated profound deficits in sleep spindle activity in schizophrenia patients compared to healthy and psychiatric controls. In an initial study we recorded 18 patients with schizophrenia, 17 healthy controls, and 15 depressed patients, and found a marked decrease in spindle range power as well as in several sleep spindle parameters, including amplitude, duration, and number in schizophrenics compared to individuals from

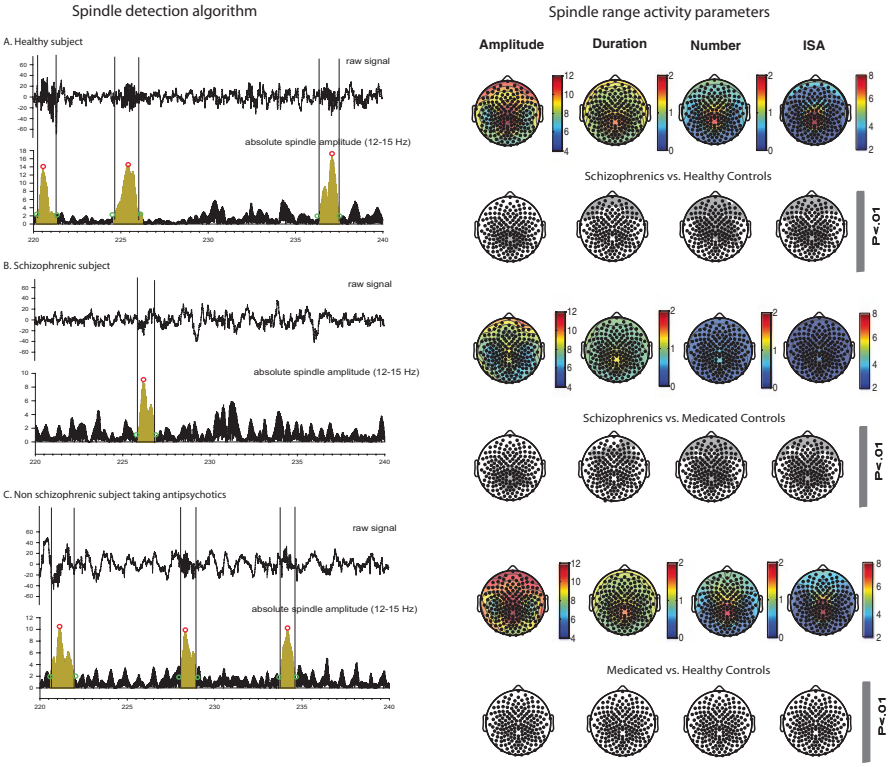

Fig. 9.2 Schizophrenia patients have marked deficits in several sleep spindle parameters compared to healthy and antipsychotic medicated controls. *Left panel*: The top traces show a 20 s NREM sleep epoch, with vertical lines enclosing sleep spindles whereas the lower traces display the rectified EEG signal filtered in the spindle range (12–16 Hz) for a healthy subject, an individual with schizophrenia, as well as a medicated psychiatric control. *Right panel*: Color plots represent the topography of several spindle parameters in schizophrenia patients, healthy subjects, and medicated psychiatric controls. Non color plots depict the topography of electrodes showing a significant reduction (gray area, Statistical non-Parametric Mapping, $p < 0.01$) in spindle parameters in schizophrenics compared to individuals form the other two groups [96]

the other two groups during the first NREM sleep cycle [95]. An in-house algorithm was developed for spindle detection (Fig. 9.2, left panel) and a fourth parameter, integrated spindle activity (ISA), which was calculated by integrating the absolute amplitude of each detected spindle divided by the total NREM sleep duration, had the largest effect size, to the extent that ISA values did not overlap between 16 of 18 schizophrenia patients and both healthy and depression subjects. In a follow-up whole-night sleep hd-EEG study on 49 medicated chronic schizophrenia patients, 44 normal subjects, and 20 non-schizophrenia psychiatric patients receiving antipsychotic medications, we confirmed those spindle deficits in a larger group of schizophrenia patients and established that those deficits were present throughout the night [96]. Furthermore, there was no difference in the spindle activity of the

other two groups, thus suggesting that spindle deficits are unlikely to be related to antipsychotics and could possibly be specific to schizophrenia patients (Fig. 9.2, right panel). In this study we also investigated SWA as well as several slow-wave parameters, including incidence, amplitude, and down and up slopes, and found no difference between schizophrenics and both healthy and psychiatric controls. Those findings further suggest that sleep spindle deficits may be uniquely implicated in the pathophysiology of psychotic disorders, and schizophrenia in particular [99].

In an attempt to assess whether those deficits are present at illness onset as well as in family members of schizophrenia probands, Manoach et al. compared sleep spindle activity in 26 antipsychotic-naïve individuals newly diagnosed with psychosis, 19 young nonpsychotic first-degree relatives of schizophrenia patients, and two samples of healthy controls matched to the patients ($N = 25$) and relatives ($N = 12$) [100]. They found that first-break schizophrenia patients had significantly reduced spindle activity compared to both healthy controls and early course patients with other psychotic disorders, and that relatives of schizophrenia patients also showed reduced spindle activity compared with controls. The authors also examined the relations of spindle parameters with cognitive measures and symptom ratings and reported that reduced spindle activity correlated with impairment in cognitive executive functions as well as with higher level of positive symptoms in first-break patients with schizophrenia [100]. Whereas more studies on larger groups of patients are needed to fully establish the pervasiveness of spindle deficits in schizophrenia, those convergent findings from different research groups suggest that spindle abnormalities are present at the onset of acute psychotic symptoms, persist throughout the course of the illness, and may account for some of the cognitive deficits commonly experienced by schizophrenia patients.

Mood Disorders

Sleep disturbances, including insomnia and hypersomnia, are part of the DSM criteria for mood disorders, and patients with depression frequently complain of difficulty falling sleep, experience repeated awakenings during the night, and report non-restorative sleep [101]. Insomnia often precedes or co-occurs with mood disorders, whereas it tends to present at the same time or following the onset of an anxiety disorder [102]. Traditional polysomnographic sleep studies have shown that in MDD patients REM sleep propensity is increased, leading to reduced REM latency and increased amount of REM sleep, whereas the time spent in SWS and the proportion of overall deep NREM sleep is decreased, as reviewed in Benca et al. [103]. Since slow waves are the main oscillations occurring during deep NREM sleep, numerous sleep EEG studies have investigated SWA in those patients. SWA findings in depression employing EEG with limited, mostly central derivations have been inconsistent, with decreases [104, 105], increases [106], and nonsignificant differences [107, 108] compared to healthy controls, including differential effects of age and sex [109]. Other sleep studies utilizing hd-EEG montages have also failed

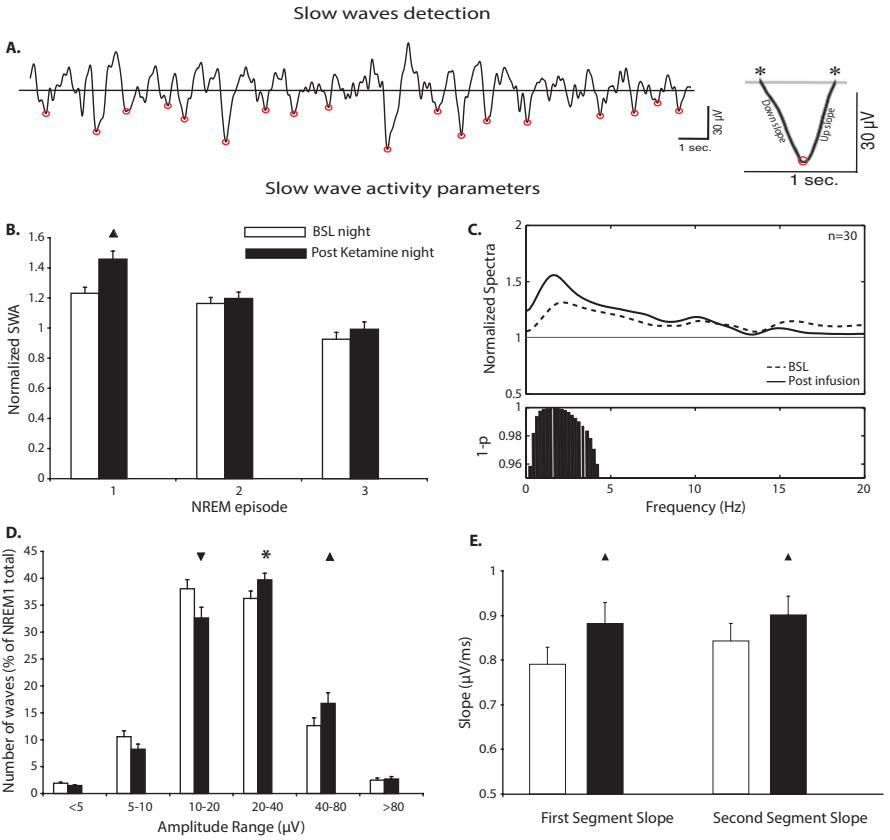

Fig. 9.3 Treatment-resistant MDD patients have an increase in SWA as well as higher amplitude and slope of sleep slow waves after ketamine infusion. (**a**) Slow waves occurring during NREM sleep were detected with an automated algorithm, and slow wave incidence, amplitude, and down and up slopes were measured. (**b**) SWA was significantly increased during the first NREM sleep cycle in MDD patients after ketamine infusion (black bar) compared to baseline nights (white bar). (**c**) Normalized average power spectra for the first NREM episode of baseline night (dashed line) and post-ketamine infusion night (solid line). Black bars indicate significantly different bins ($p < 0.05$, uncorrected). (**d**) Decrease in low amplitude and increase in high amplitude slow waves after ketamine infusion. (**e**) Increase in both segment slow wave slopes post ketamine during the first NREM sleep episode. Black triangles indicate significance and direction of effect ($p < 0.01$). Asterisk (∗) reflects a trend towards significance ($p < 0.1$) [112]

to clearly establish SWA differences between depressed patients and healthy subjects [95, 110, 111], although it was found that patients with MDD and hypersomnia had reduced SWA compared to non-hypersomniac patients [111] in a parieto-occipital region, and that female patients with MDD had significant increases in SWA in multiple cortical areas relative to control subjects [110]. By contrast, a recent study assessing the effects of ketamine on mood, brain-derived neurotrophic factor (BDNF), and SWA—as well as several slow-wave parameters, including incidence, negative peak amplitude, and down- and up-slopes—in treatment-resistant

MDD patients reported an improvement in depressive symptoms shortly after ketamine injection, which was associated to higher SWA during the first sleep cycle (Fig. 9.3) [112]. The authors also found that the increase in sleep EEG power was specific for the SWA range, and was accompanied by higher amplitude waves as well as increased slow-wave down- and up-slopes. Furthermore, in those patients who responded to ketamine, defined as a greater than 50% reduction in depression score 4 h after the infusion, changes in BDNF levels were proportional to changes in EEG slow-wave parameters. Possible explanations for the discrepancy between those slow-wave findings in depression are the severity of symptoms (e.g., in this last study the authors enrolled treatment-resistant MDD patients), as well as a more in-depth analysis of slow-wave EEG features.

Neuronal and Molecular Mechanisms Underlying Slow Wave/ Sleep Spindles Abnormalities in Psychiatric Patients

The two main oscillatory activities occurring during sleep are slow waves and sleep spindles, and generated and modulated within the thalamocortical system, although slow waves are primarily initiated in the cortex and then travel across the brain through cortico-cortical and cortico-thalamo-cortical connections, whereas spindles oscillations are initially produced in the thalamus and then propagate to the cortex via thalamocortical pathways. In reviewing sleep oscillation abnormalities in psychiatry, the most promising findings include deficits in sleep spindle activity in schizophrenia as well as abnormal slow-wave parameters in severely depressed, treatment-resistant MDD patients. In what follows we will discuss how the neuronal and molecular mechanisms associated to those sleep oscillations relate to the neurobiology of those major psychiatric disorders.

Schizophrenia and Sleep Spindle Deficits

Converging evidence from animal studies suggest that the neuronal substrates underlying sleep spindles involve a cortex-thalamic reticular nucleus-thalamus circuitry. The thalamic reticular nucleus (TRN) is considered the spindle pacemaker, and thalamic reticular nucleus/thalamus circuits can generate spindles in isolation, whereas cortical inputs contribute to initiate and amplify sleep spindle oscillations [32]. Notably, all recent studies reporting spindle activity deficits in schizophrenia found that spindle incidence, which likely reflects the activity of intrathalamic circuits, was the most reduced spindle parameter in schizophrenia patients and correlated with the clinical symptoms and impaired cognitive performances in those patients. Moreover, one of those studies established that schizophrenia patients had no deficits in cortically generated slow-wave parameters, thus

suggesting that a dysfunction of a TRN/thalamus circuit may be primarily responsible for spindle deficits in schizophrenia [95, 96, 113]. Corticothalamic afferents may also play an important role, as suggested by neuroimaging [114], electrophysiological [115], and postmortem [116] studies reporting corticothalamic connectivity deficits in schizophrenia. The TRN is strategically placed between the thalamus and the cortex, and receives excitatory afferents from both cortical and thalamic neurons while sending GABA-ergic inhibitory projections to the other thalamic nuclei. Cortical afferents to the TRN greatly outweigh thalamic projections, and it has been recently shown that the prefrontal cortex diffusely projects to frontal as well as sensory thalamic reticular sectors, which may regulate the ability to perform tasks in the context of competing sensory inputs [117]. The TRN also appears to be implicated in blocking or selectively enhancing the transmission of peripheral stimuli to the cortex through sensory gating and attentional modulation, respectively. Intracranial recordings in primates have shown that visual attention regulation involves both higher activity in the lateral geniculate nucleus (LGN) and reduced firing of the TRN [118], whereas pharmacologically induced decrease in TRN firings result in P50 auditory gating deficits [119]. Sensory gating and attention deficits occur in several groups of schizophrenia patients, including first-break and medication-naïve patients [120], and a functional magnetic resonance imaging (fMRI) study showed an increased hemodynamic response in the thalamus, which was correlated with abnormal P50 responses in schizophrenia patients compared to healthy subjects [121].

Another thalamic structure likely to be implicated in the sleep spindle deficits is the medial dorsal (MD) nucleus. The MD is a major higher order (HO) thalamic relay that receives driver inputs from cortical layer V neurons, whereas first-order (FO) thalamic nuclei, such as the lateral geniculate nuclei (LGN), receive most of their driver inputs from subcortical sources [122]. In a recent study we found that the MD nuclei, but not the LGN or the whole thalami, were significantly smaller in schizophrenia patients compared to healthy controls [123]. Furthermore, left MD volumes were correlated with left frontal EEG spindles in both healthy and schizophrenic subjects, a finding consistent with electrocorticogram recordings in humans, demonstrating an implication of MD and TRN in the sleep spindle activity observed in the prefrontal cortex [124].

Regarding the molecular mechanisms underlying sleep spindle deficits, an important role is likely played by Ca^{2+} channels (Fig. 9.4). Electrophysiological recordings in awake and attentive primates have demonstrated that the MD nucleus has much greater rebound burst firing activity compared to the LGN [125], and this higher burst propensity is related to greater expression of voltage-dependent transient (T-type) Ca^{2+} channels [126]. Neurons in the TRN also rely on high concentration of intracellular Ca^{2+} to sustain the rhythmic burst discharges necessary for spindle generation, which include low-voltage gated T-type Ca^{2+} channels (T channels) and the small-conductance Ca^{2+}-activated type-2 K+ channel (SK2) [127]. During NREM sleep, a progressive hyperpolarization of TRN neurons favors the activation of T channels that rapidly and transiently depolarize the membrane voltage and elicits bursts of action potentials [128]. Reticular cells express two T channel subtypes

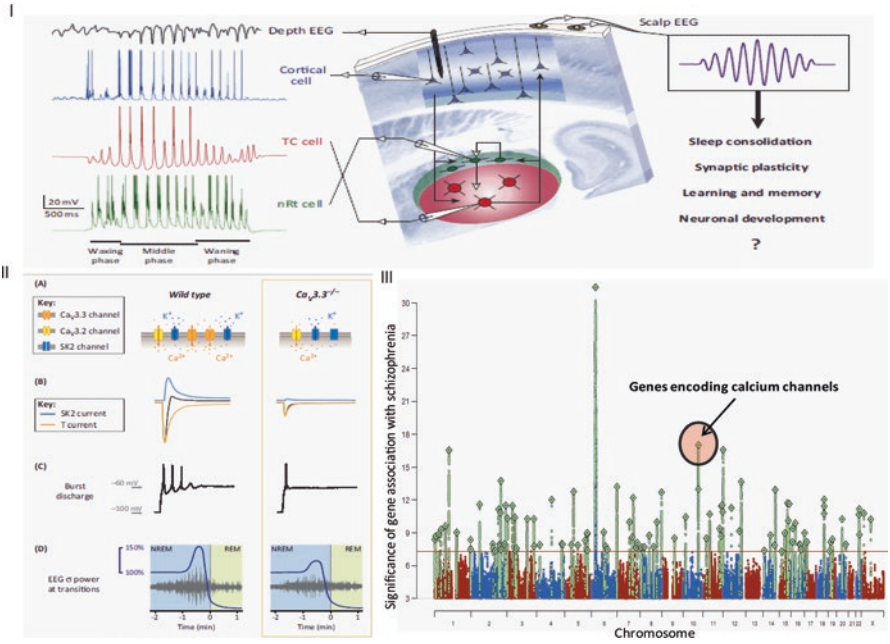

Fig. 9.4 Sleep spindles, which are generated by a TRN-Thalamus-Cortex circuit, are implicated in processes found to be defective in schizophrenia patients and require Ca^{2+} channels showing strong genetic association to schizophrenia. (I) Spindles are generated within the thalamus by TRN cells providing rhythmic GABAergic inhibition to thalamocortical (TC) glutamatergic neurons, which entrains TC rebound burst activity that is transferred to the cortex. Sleep spindle are implicated in several processes, including plasticity, memory, and learning found to be defective in schizophrenia patients [127]. (II) In $Ca_v3.3^{-/-}$ Knockout mice the burst discharge of TRN neurons associated to higher spindle activity during NREM sleep is reduced compared to wild-type animals [127]. (III) Manhattan plot of genome-wide association meta-analysis of single nucleotide polymorphisms (SNPs) with schizophrenia. The red line shows significant level, SNPs in green indicate independent genome-wide significant associations, including genes encoding for Ca^{+} channels [160]. (Reprinted from Trends in Neurosciences, Vol. 36(12). Astori S, Wimmer RD, Lüthi A. Manipulating sleep spindles—expanding views on sleep, memory, and disease. P. 738–48; ©2013, with permission from Elsevier)

encoded by the CaV3.2 (CACNA1h) and the CaV3.3 (CACNA1i) genes [129], which are highly expressed on the dendritic branches [130]. This organization enables amplification of synaptic inputs via low-threshold Ca^{2+} spikes and enhances dendritic responsiveness to somatic voltage fluctuations, and genetic deletion of CaV3.3 channels strongly reduces cellular T currents and prevents low-threshold bursting elicited through somatic hyperpolarization [131]. Intriguingly, a gene encoding a T-type calcium channel (CACNA1i, which encodes CaV3.3) has been recently implicated in schizophrenia by two large genetic studies [132], whereas another study has shown that CaV3.3 calcium channel, which is highly expressed in the TRN, is the major sleep spindle pacemaker in the thalamus [131].

Another molecular mechanism associated with sleep spindle deficits in schizophrenia may involve abnormalities in GABA-ergic neurotransmission. Recent electrophysiological recordings in rats showed that during development, GABA currents induce depolarization in TRN neurons, which is responsible for the bursting activity observed during spindles [133]. These findings suggest that GABA currents/receptors in the TRN play a critical role in the development of sleep spindles and are consistent with the involvement of GABA in the neurobiology of schizophrenia [134]. The presence of GABA impairments in schizophrenia is also suggested by data from postmortem studies, which found a reduction in glutamate decarboxylase 67, an enzyme involved in GABA synthesis, and in GABA membrane transporter density in cortical interneurons in schizophrenia patients [135]. Additionally, treatment studies have shown that clozapine, one of the most effective antipsychotics, is associated with enhanced thalamocortical GABA activity in schizophrenia patients, and the beneficial effects of electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) are related to increased GABA-mediated inhibitory neurotransmission on excitatory cortical neurons [136]. Outside of the TRN, which consists of GABA-ergic inhibitory neurons, most neurons in the thalamus and in the cortex are glutamatergic and increasing evidence point to reduced binding or expression of thalamocortical NMDA glutamatergic receptors in schizophrenia. Postmortem studies found reduced NMDA glutamate receptors in both MD thalamus and prefrontal cortex in schizophrenia patients [137]. Pharmacological manipulations with NMDA antagonists, including ketamine and phencyclidine (PCP), produce schizophrenia-like psychosis in healthy humans, and animal studies have shown that asenapine and clozapine, two second-generation antipsychotics, could revert a PCP-induced hypoactivity of NMDA receptors in both MD thalamus [138] and prefrontal cortex [139]. Injections of NMDA antagonists in the TRN rat brain trigger delta-range rhythmic bursting, thus suggesting that NMDA hypofunction regulate TRN-generated delta band EEG oscillations, a waking thalamocortical dys-rhythmia established in schizophrenia [140]. Furthermore, 2-deoxyglucose imaging data in mice characterizing the acute effects of ketamine on brain functional connectivity found ketamine-induced impairments in a circuitry involving TRN, MD thalamus, and prefrontal cortex [141].

Treatment-Resistant Depression and Slow-Wave Abnormalities

One of the main mechanisms thought to underlie SWA abnormalities in patients with MDD is a defect in cortical synaptic plasticity. Several sleep EEG studies in healthy subjects have demonstrated that slow waves can be considered an EEG marker of synaptic changes in the cortex. Manipulations leading to strengthening in local cortical areas, including controlateral sensorimotor cortex following rotation learning tasks and high-frequency TMS, lead to local increases in SWA during subsequent sleep [43]; by contrast, interventions leading to synaptic depression, such as a 12-h

arm immobilization, resulted in a localized reduction in the controlateral sensorimotor SWA [49]. Furthermore, large-scale computer simulations, supported by experimental findings from electrophysiological recordings in both rats and epileptic patients, have demonstrated that sleep slow waves directly reflect the overall synaptic activity of underlying neuronal circuits [142, 143], and that the slopes of sleep slow waves represent a highly sensitive marker of the synaptic strength of those circuits [144].

Undoubtedly, the strongest evidence indicating a defective SWA in MDD comes from the finding of an increase in several slow wave parameters, associated to mood improvement, in treatment-resistant depressed patients after a single dose of ketamine [112]. It has been therefore suggested that the mechanisms of action of ketamine at the molecular and synaptic level are likely to play a critical role in regulating sleep SW and mood [145]. Ketamine affects primarily the glutamatergic neurotransmitter system. Glutamate is synthesized in presynaptic neurons, is released into the synaptic cleft, and binds to ionotropic NMDA or AMPA postsynaptic receptors (Fig. 9.5). Activation of NMDA receptors leads to eukaryotic elongation factor-2 (EF2) phosphorylation via EF2 kinase, which in turn downregulates BDNF translation. Ketamine blocks NMDA receptors, which leads to reduced EF2 phosphorylation and de-suppression of BDNF translation [146]. BDNF is a neurotrophin with important functions in neuronal development and neuroplasticity, and several recent studies have established a close relationship between SWA and BDNF, including an increase in SWA following intrahemispheric infusion of BDNF and a decrease in SWA with BDNF antagonism [147]. SWA is also increased by behavioral interventions modulating neuronal expression of BDNF [148], as well as the plasticity-related genes Arc, Homer, and NGFI-A [148]. A strong link between BDNF, sleep SWA, and mood was reported by clinical studies showing that human carriers of the BDNF Met allele of the Val66Met polymorphism have reduced production of sleep slow waves [149], and that individuals with this polymorphism were less likely to respond to ketamine than the Val/Val allele [150]. BDNF also enhances TrkB signaling, which leads to the transphosphorylation and the activation of extracellular related kinases (ERK) and protein kinase B(PKB) as well as the suppression of glycogensynthasekinase-3(GSK-3). ERK and PKB then activate mTOR (mammalian target of rapamycin), a large serine/threonine kinase that regulates the initiation of protein translation; mTOR is ubiquitously expressed in the brain and can control new protein synthesis required for synaptogenesis [151], for example by increasing the synthesis of synaptic proteins as well as the number and function of dendritic spines in the prefrontal cortex of rats [152]. In another recent study, rapid activation of the mTOR signaling pathway resulted in increased synaptic spine density and diameter as well as increased EPSCs in the medial prefrontal cortex (mPFC) in rodents, and those changes were associated with antidepressant responses that persisted for up to 1 week in a forced swim model of depression [153]. Furthermore, several classes of AMPA potentiators, including ampakines, have shown antidepressant efficacy in preclinical studies [154, 155], and it has been shown that chronic AMPA treatment resulted in a dose-dependent antidepressant effect in both the forced swim test and sucrose preference test in a rodent model of depression [156]. A similar mechanism may underlie the rapid antidepres-

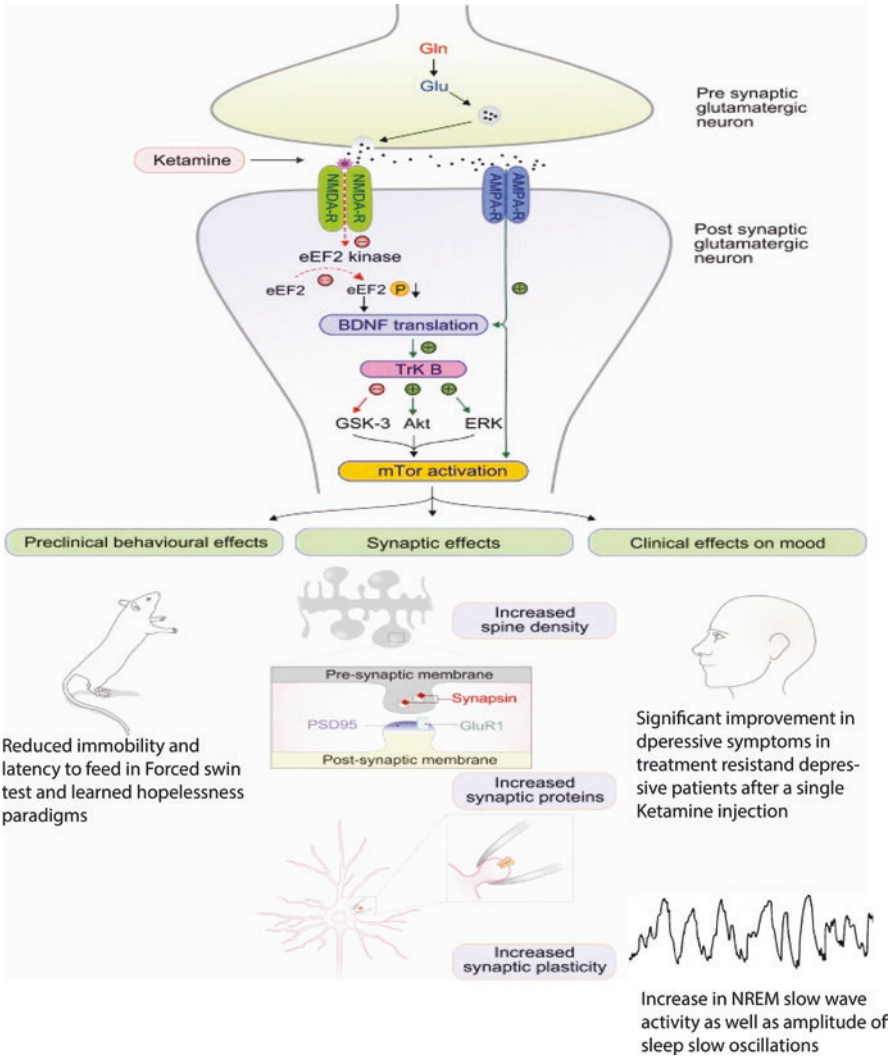

Fig. 9.5 Hypothesized mechanism of action of ketamine on glutamatergic neuro-transmission, which results in higher level of synaptic activity and efficacy, as reflected by an increase in several SWA parameters, as well as in an antidepressant response in both animal models of depression and treatment-resistant MDD patients. (Reprinted from Journal of Affective Disorders, Vol. 156. Naughton M, Clarke G, O'Leary OF, Cryan JF, Dinan TG. A review of ketamine in affective disorders: Current evidence of clinical efficacy, limitations of use and pre-clinical evidence on proposed mechanisms of action. P. 12–35; © 2014, with permission from Elsevier)

sant effects of ketamine in treatment-resistant MDD patients via NMDA receptors blockade and increase in AMPA throughput, which is turn leads to higher BDNF release, Trk B receptor activation, stimulation of mTOR signaling and local protein synthesis, as shown in Fig. 9.5.

Conclusion

In this chapter we have described the main characteristics of EEG oscillations, which are proxy measures of the activity of underlying neuronal circuits, and explained why oscillations occurring during sleep, when confounds like presence of symptoms and level of cognitive effort are minimized, can help revealing intrinsic defects in specific neuronal populations in psychiatric patients. We have then shown that the two fundamental NREM sleep oscillations, slow waves and spindles, are generated and sustained by complementary thalamocortical circuits, and have presented recent work demonstrating marked sleep spindle deficits in patients with schizophrenia as well as slow-wave abnormalities in individuals with treatment-resistant MDD.

Specifically, spindle impairments were reported in both chronic [95, 96] and first-break schizophrenics [100], whereas they were not present in non-schizophrenia psychiatric patients taking antipsychotics [96] nor in early course patients with other psychotic disorders [100]. Spindle deficits were observed in first-degree relatives of schizophrenia probands [100], thus suggesting that those deficits are unlikely to reflect an antipsychotic side effect or a general feature of psychosis, but are rather a biological feature of schizophrenia that is present at illness onset, persist throughout its course, and may represent an endophenotype of this illness [99]. Spindles are generated by the TRN with other thalamic nuclei, and are then synchronized and sustained in the cortex, and in a recent study a TRN-thalamus-prefrontal cortex circuit was found to be defective in schizophrenia patients compared to healthy subjects [123]. Slow waves have been implicated in the pathophysiology of depression based on the robust and rapid antidepressant efficacy of sleep deprivation (SD), which leads to increased SWS during recovery sleep, thus indicating a deficient production of slow waves in patients with depression [157]. Recent work from Zarate et al. has demonstrated that single-dose ketamine infusion was associated with higher level of SWA in treatment-resistant MDD patients, which also leads to a significant, acute improvement in mood [112]. The authors also reported an increase in high-amplitude slow waves as well as in slow-wave slope in those patients, consistent with a primary deficit in synaptic strength that is acutely reverted by ketamine [112, 158]. A defect in the synaptic activity of large populations of cortical neurons, which are responsible for generating sleep slow waves, may also underlie the variety of symptoms and cognitive impairments commonly observed in MDD patients. Altogether, those findings are very promising, and highlight the relevance of this approach in elucidating the neurobiology of major neuropsychiatric disorders, especially schizophrenia and depression.

Future studies are needed to establish the extent of sleep oscillation abnormalities in psychiatric patients. In regard to schizophrenia, it will be critical to confirm spindle deficits in large groups of patients, especially at illness onset, as well as to see whether some abnormalities in spindle activity can be observed during the prodromal phase in individuals at high risk of conversion to psychosis. It would also be important to follow both schizophrenic and MDD patients longitudinally to see how

those abnormalities in sleep oscillations evolve over the course of the illness based on the clinical phenomenology (e.g., presence and intensity of symptoms). So far, a clear impairment in SWA has been established only in severely depressed, treatment-resistant MDD patients, and therefore it would be relevant to assess whether slow-wave abnormalities are a state or trait marker, and how SWA renormalization may predict mood improvement in depressed patients.

Finally, pharmacological as well as non-pharmacological interventions should be developed to revert sleep slow oscillation deficits in psychiatric patients, and to assess how this affects the course of their illness. As an initial step in that direction, it has been proposed that effects of ketamine and other agents with acute antidepressant efficacy on SWA should be extensively tested in MDD, including drug-free and first-episode patients [145]. Furthermore, it has been recently suggested that "synthetic" sleep spindles can be induced by transcranial electrical stimulation (TES) during sleep in schizophrenia patients to supplement their low incidence of spindles [15], whereas in a pharmacological study it was found that eszopiclone significantly increased sleep spindles in patients with schizophrenia, and this increase was correlated with overnight motor sequence task improvement [159].

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