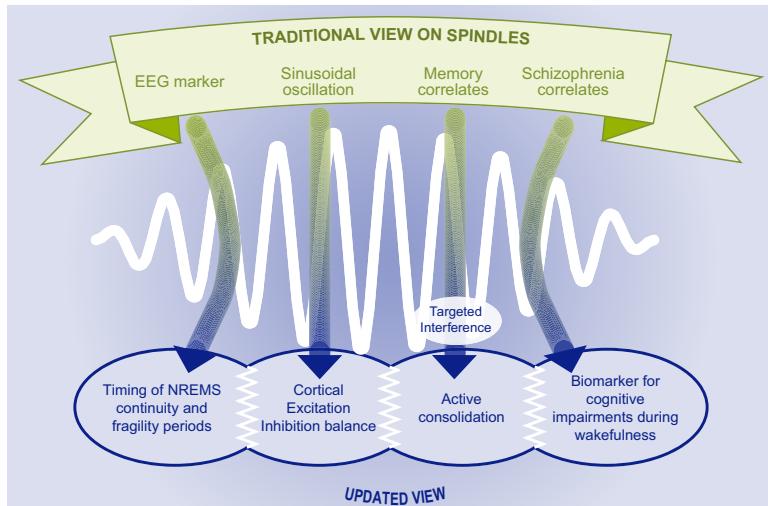


SLEEP SPINDLES: MECHANISMS AND FUNCTIONS

GRAPHICAL ABSTRACT



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KEYWORDS

ion channel; schizophrenia; sleep disorders; sleep regulation; thalamus

CLINICAL HIGHLIGHTS

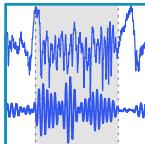
- Sleep spindles are an electroencephalogram (EEG) hallmark of the N2 stage of non-rapid-eye-movement sleep (NREMS) and belong to the most heritable EEG signatures.
- Sleep spindles can be detected automatically, but results need to be assessed by visual scoring experts.
- Sleep spindles are a predominantly local thalamocortical event that dramatically alters activity in grey matter of cortex. EEG surface measures are but an approximation for the substantial spatial and temporal impact of spindles on cortical activity. To monitor these in humans, novel neuroimaging techniques need to be coupled to EEG.
- Sleep spindles evolve with a characteristic profile along the lifespan that parallels cortical maturation in early postnatal periods, throughout adolescence, and aging.
- Higher sleep spindle densities correlate with longer N2 sleep duration and greater resilience to external perturbation.
- Sleep spindles cluster on an infraslow time scale of ~50 s, which is thought to correlate with periods of NREMS fragility. In some sleep-related movement disorders, involuntary limb movements occur periodically on this time scale.
- Sleep spindle density correlates with markers of intelligence, but also with several disorders leading to cognitive deficits and dementia. A better understanding of their spatiotemporal distribution could ultimately become useful for diagnostic purposes.
- A number of disease-linked genes are highly enriched in thalamic spindle-generating circuits, including several underlying attentional disorders and schizophrenia.
- Sleep spindles are modified by wake-related experiences and contribute to the consolidation of memory. They are

thus candidates for targeted interference in efforts to modify, and possibly strengthen, memories acquired during the day.

SLEEP SPINDLES: MECHANISMS AND FUNCTIONS

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Fernandez LMJ, Lüthi A. Sleep Spindles: Mechanisms and Functions. *Physiol Rev* 100: 805–868, 2020. First published December 5, 2019; doi:10.1152/physrev.00042.2018.—Sleep spindles are burstlike signals in the electroencephalogram (EEG) of the sleeping mammalian brain and electrical surface correlates of neuronal oscillations in thalamus. As one of the most inheritable sleep EEG signatures,

sleep spindles probably reflect the strength and malleability of thalamocortical circuits that underlie individual cognitive profiles. We review the characteristics, organization, regulation, and origins of sleep spindles and their implication in non-rapid-eye-movement sleep (NREMS) and its functions, focusing on human and rodent. Spatially, sleep spindle-related neuronal activity appears on scales ranging from small thalamic circuits to functional cortical areas, and generates a cortical state favoring intracortical plasticity while limiting cortical output. Temporally, sleep spindles are discrete events, part of a continuous power band, and elements grouped on an infraslow time scale over which NREMS alternates between continuity and fragility. We synthesize diverse and seemingly unlinked functions of sleep spindles for sleep architecture, sensory processing, synaptic plasticity, memory formation, and cognitive abilities into a unifying sleep spindle concept, according to which sleep spindles 1) generate neural conditions of large-scale functional connectivity and plasticity that outlast their appearance as discrete EEG events, 2) appear preferentially in thalamic circuits engaged in learning and attention-based experience during wakefulness, and 3) enable a selective reactivation and routing of wake-instated neuronal traces between brain areas such as hippocampus and cortex. Their fine spatiotemporal organization reflects NREMS as a physiological state coordinated over brain and body and may indicate, if not anticipate and ultimately differentiate, pathologies in sleep and neurodevelopmental, -degenerative, and -psychiatric conditions.

ion channel; schizophrenia; sleep disorders; sleep regulation; thalamus

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I. INTRODUCTION

Sleep spindles refer to a well recognizable, burstlike sequence of 10–15 Hz sinusoidal cycles in the electroencephalogram (EEG) of sleeping mammals. The name stems from the envelope of a sleep spindle waveform that resembles the shape of the wool-spinning device. It is now 80 yr ago that sleep spindles were first observed in pioneering electroen-

cephalographic studies on naturally sleeping humans (383, 384) (sect. II). It took another 50 yr to localize a subcortical pacemaker and to understand that cortico-thalamocortical (TC) loops in the forebrain are required for sleep spindles to appear at the cortical surface (sects. III–V).

Since these landmark discoveries, sleep spindles have led to insights into novel organizing principles of mammalian sleep and into how sleep relates to cognitive abilities and disease. Their phasic appearance over a hierarchy of time scales divides non-rapid-eye-movement sleep (NREMS) into time windows with variable cortical states and sensory arousability. Sleep spindles are now becoming a tool to monitor the inner workings of TC loops as they are unconstrained by wakefulness-related activity. These advances increase their diagnostic and therapeutic usefulness (sect. X) and refine approaches to explore their roles in memory consolidation (sects. VIII and XI). There are expectations that sleep spindles may ultimately tell us about the development, efficacy, and plasticity of the forebrain circuits that make us intelligent individuals (sects. VI and VII). The genetic, circuit, and behavioral links between sleep spindles

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on the one hand, and selective attention and memory formation on the other hand, are a remarkable development in this direction (sects. VIII and IX).

Despite this progress, many elementary questions remain open. Whereas we know a lot about subcortical origins of sleep spindles, what a cortical spindle is in terms of its neuronal activity profile across cortical layers is just beginning to be addressed. Although the methodology of sleep spindle detection is in steady improvement, where and when they appear on the cortical surface once generated in thalamic circuits is not yet clear. Consequences on cellular

Ca^{2+} and signaling pathways, gating of synaptic plasticity, and their role in the complex sequence of events leading to sleep-dependent memory consolidation are other aspects awaiting to be clarified (sects. VI and VIII). Progress on the role of sleep spindles in healthy sleep, and their implication in pathology, requires more insight into these mechanistic questions.

II. HISTORICAL LANDMARKS

Research on sleep spindles originates with pioneering work in EEG and neuroanatomy, but progress regarding their mechanisms and roles continues to today (FIGURE 1A).

A. Electroencephalographic Identification

The German neurologist Hans Berger (1873–1941), considered the father of human EEG recordings, recorded oscillatory events in the 10 Hz range during states of decreased vigilance and avertin anesthesia (58; for review, see Ref. 298). Shortly thereafter, American researchers (64), including notably Alfred Lee Loomis (1887–1975), a patron of scientific research and technological development, carried out all-night recordings of human sleep and coined the names “K-complexes” and “spindles” for two characteristic spontaneous EEG patterns (383, 384) (FIGURE 1B). Loomis’ recognition that spindles populate light periods of NREMS and are predominant over the vertex are landmarks in sleep-centered research on sleep spindles.

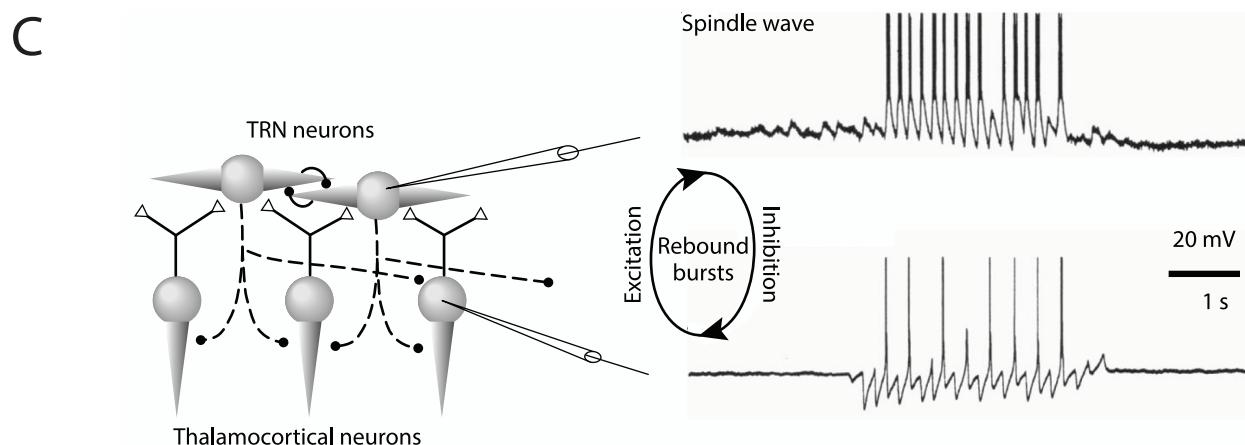
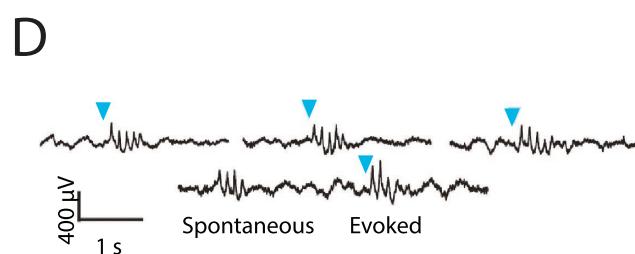
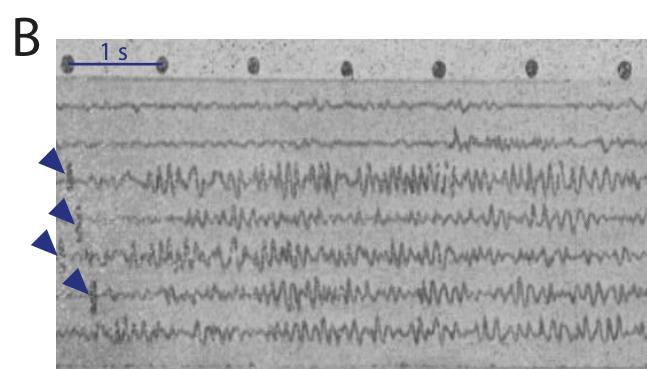
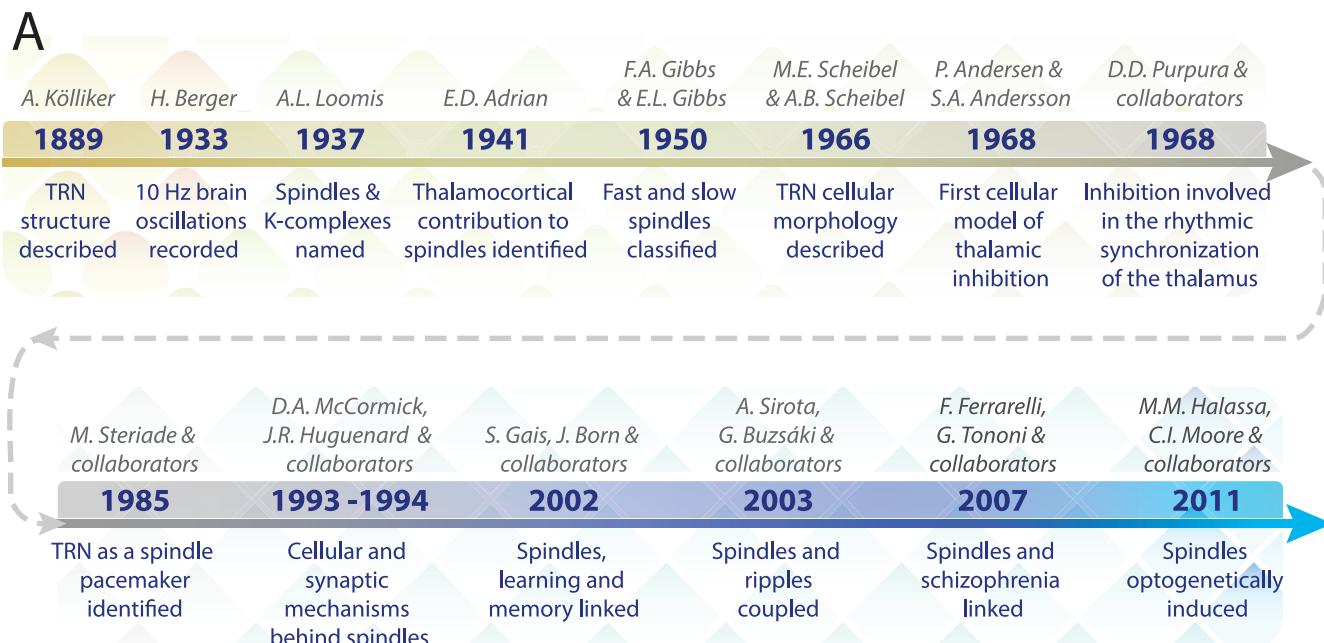
B. Thalamic Origin of Sleep Spindles

The subsequent decades are marked by the search for the origins of sleep spindle generation and the existence of possibly different sleep spindle types, notably the “fast” (generally >13 Hz) and “slow” (generally <13 Hz) spindles (237). When the British electrophysiologist and Nobel Prize

FIGURE 1. Chronology of landmark events in the identification of sleep spindles. *A*: chronology chart of key dates in the history of sleep spindle and thalamic reticular nucleus (TRN) research. Names of pioneer scientists are given above the chart, “& collaborators” indicates that other scientists active at the time contributed importantly. See text references for further details. Key descriptions of the discovery are given below the chart. *B*: first illustration of sleep spindles by Loomis et al. (383). Seven short stretches of an electroencephalogram (EEG) recording of a sleeping human subject are shown. Top 2 traces: subject sleeps undisturbed. Bottom 5 traces: sleeping subject was exposed to brief acoustic stimuli once per minute (arrowheads denote time of stimulus). In the bottom trace, the acoustic stimulus fell outside the displayed portion of the figure. Rhythmic deflections in the 10–14 Hz range were observed upon applying acoustic stimuli, which were termed “spindles because of their appearance in the record”. [Adapted from Loomis et al. (383), with permission from The American Association for the Advancement of Science.] *C*: first cellular and synaptic analysis of the mechanisms of sleep spindle generation based on reciprocal synaptic interactions between TRN and thalamocortical (TC) neurons. Cells are symbolized as cell bodies (circles) with dendrites (cones) and axons (continuous or dotted lines). Continuous lines and open triangles denote axons forming glutamatergic synapses; dotted lines with closed circles denote axons forming GABAergic synapses. Note the formation of reciprocal synapses between the two cell populations. Synaptic events and action potential discharge patterns are shown for two cells (shown impaled by sketched microelectrodes). Note the repetitive burst discharge in both cell types and the arrival of repetitive inhibitory postsynaptic potentials in the TC cell. Circle with arrowheads denotes the cyclical synaptic interaction between the two cell types that leads to repetitive inhibition in the case of TC cells, followed by rebound bursting and synaptic excitation of TRN cells. [Adapted from Bal et al. (45), with permission from John Wiley and Sons.] *D*: first optogenetically elicited sleep spindles in mouse EEG. Blue arrowheads denote application of light pulses to channelrhodopsin 2-expressing TRN cells in mouse. A spontaneous spindle event is also shown. [From Halassa et al. (266), with permission from Springer Nature.]

Winner Edgar Douglas Adrian (1889–1977) noted that spindle rhythms could be recorded from the cut end of TC fibers in cat, neuronal mechanisms came to center stage regarding their origin (6). More than two decades later, the American neuroscientist Dominick D. Purpura's (1927–2019) intracellular recordings from cat thalamic neurons revealed rhythmic inhibitory synaptic events in phase with cortex (502), suggesting an intrathalamic origin for spindle

generation (19). The thalamic reticular nucleus (TRN) turned out to be a major intrathalamic sleep spindle pacemaker. Pioneering intracellular recordings in anesthetized and sleeping cat TRN in the research group of the Romanian physiologist Mircea Steriade (1924–2006) (568, 571) and cellular studies in brain slices from ferret and rodent (287, 572) laid the groundwork for the notion that the TRN generates sleep spindles in reciprocal synaptic interactions



with TC cells (FIGURE 1C). The optogenetic triggering of sleep spindles through TRN stimulation in mouse now opens opportunities for controlling their spatiotemporal occurrence and for advancing insight on their functions (48, 266) (sects. VIII, X, and XI) (FIGURE 1D).

C. Histological Identification of the TRN

Thalamic circuits are the major site of origin for sleep spindles, wherein the TRN is thought to act as a “pacemaker” (see sect. V). The first histological recognition of the TRN as a distinct nucleus dates back to almost 130 yr, when Nissl coined the name “Gitterschicht” (layer of lattices) to describe TRN and portions of adjacent thalamic nuclei, a name motivated by their gridlike appearance in transillumination microscopy (331, 457). This name was later replaced by “nucleus reticularis” (442) and “noyau rayé” or “noyau grillagé.” The gridlike appearance results from bundles of penetrating TC and corticothalamic fibers (530) for which the TRN serves as a guidepost in early development (428). The TRN is a major contributor to a broad and powerful synaptic inhibition in dorsal thalamus (19, 437, 465, 502, 536). To date, important extrathalamic forms of inhibition are described, but their role in sleep-related inhibition of thalamus is not known (263).

III. DEFINITIONS AND MEASUREMENTS

The definition of the American Association of Sleep Medicine (AASM) for a sleep spindle in adult human NREMS is that of a “train of distinct waves with frequency 11–16 Hz (most commonly 12–14 Hz) with a duration ≥ 0.5 s, usually maximal in amplitude using central derivations” (292). In children, definitions are similar but vary from infants to adolescents (252) (sect. VII). The AASM definition relies on a spindle’s cortical surface manifestation and is of practical use for scoring and diagnostic purposes in humans, carnivores, and rodents (FIGURE 2A). However, it assumes that 1) sinusoidal waves at the cortical surface are a faithful reflection of a true TC spindle event and 2) all spindles that are generated reach the cortical surface. As this review will show, this EEG-based quantification of sleep spindles is an

approximation for the true nature and spatiotemporal distribution of sleep spindles.

This section surveys methodologies of sleep spindle quantification based on the AASM definition. Major advances have been achieved through cross-validating methodologies across research groups, and through a number of open source spindle detection routines (for recent reviews and developments, see Refs. 126, 462).

There are two basic methods via which EEG activity in the sleep spindle frequency range is quantified. The first one is based on the spectral power of the recorded signal within the borders of the spindle frequencies, referred to as the sigma band (FIGURE 2, B–D). This measure regards sleep spindle activity as a broad category of oscillations, from background to transient forms irrespective of the exact occurrence of discrete events in time (186, 336). The second major approach instead focuses on identifying precisely these individual spindle events using a variety of strategies for pattern recognition (FIGURE 3).

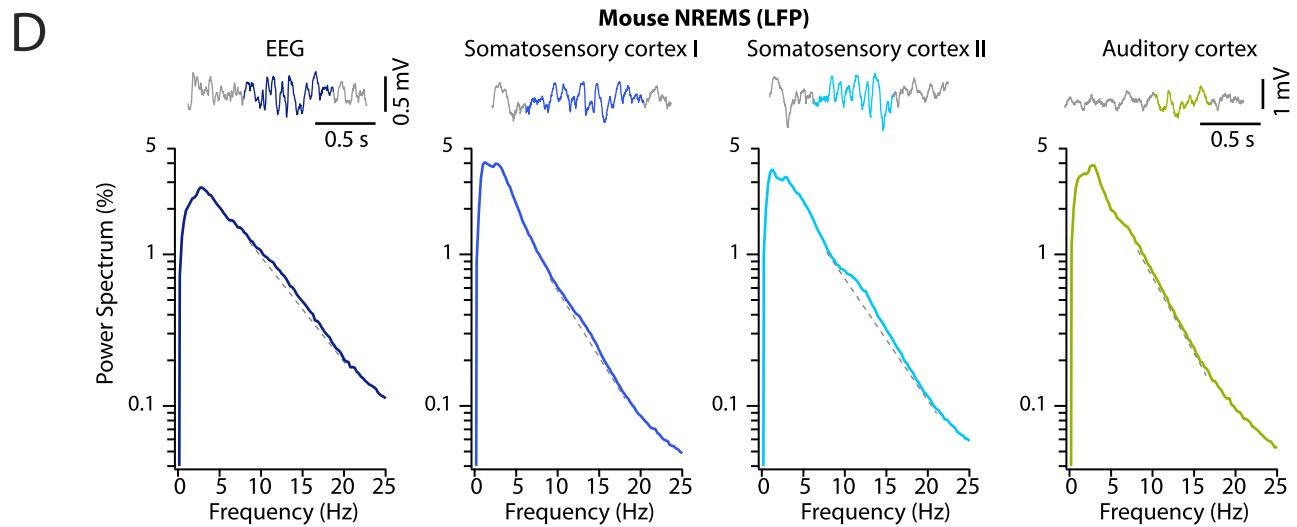
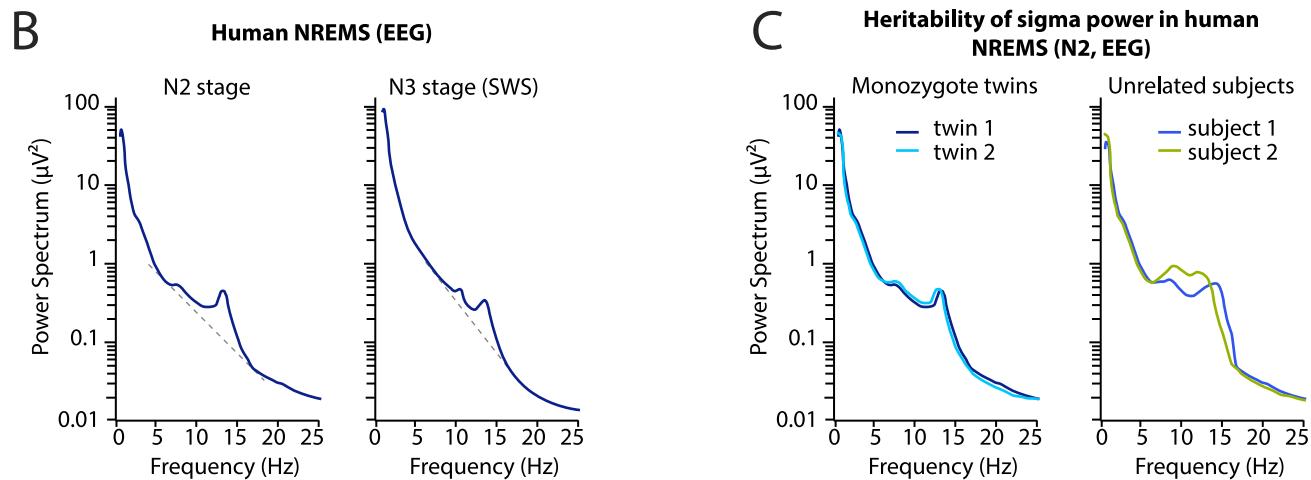
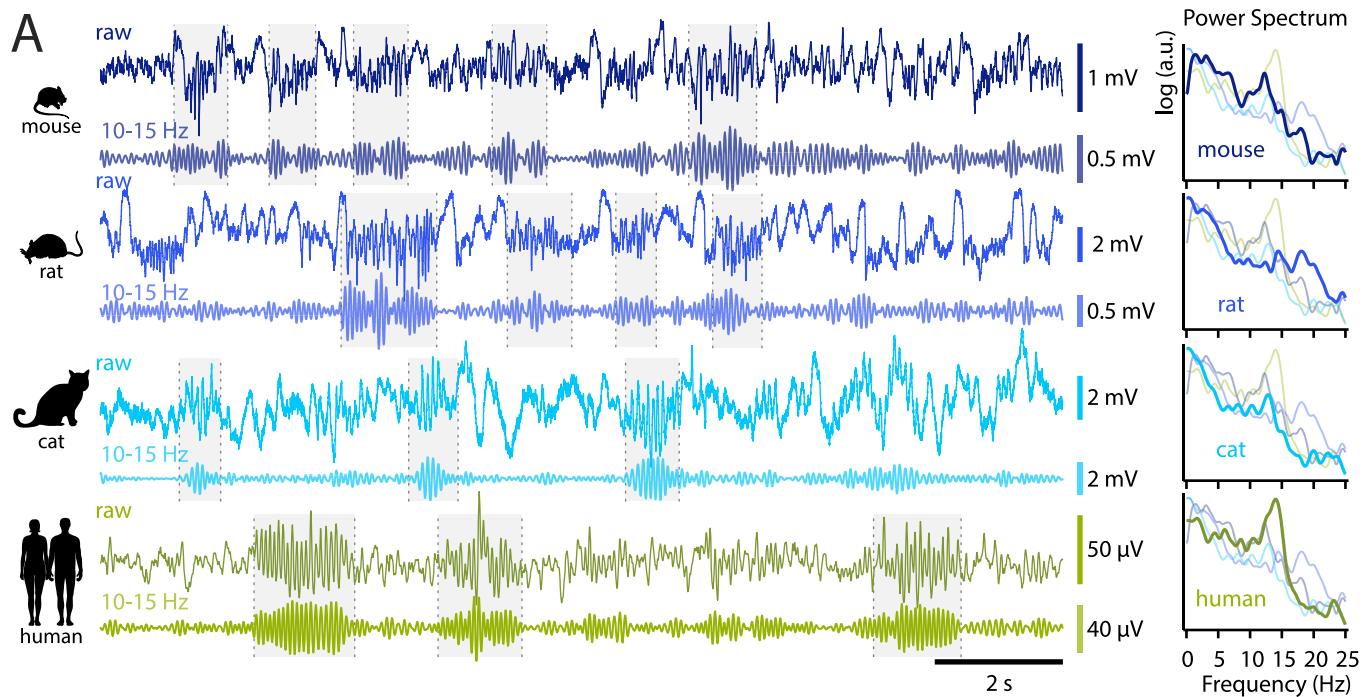
A. Power in the Sigma Frequency Range

1. Sigma power in humans

Spindle quantity and dynamics are measured through total or mean power values in the sigma range (often referred to as “sigma power”) within 7 up to 16 Hz, typically between 10 and 15 Hz (292) (FIGURE 3A). Sleep spindles contribute importantly to the sigma frequency band in humans (170, 631) and in mice (204). Sigma power is widely used to describe spindle dynamics, regulation, and properties during the different sleep stages, at varying cortical sites, and according to demographic parameters. This also holds true for portions of the sigma frequency band that approximate “fast” and “slow” spindles (sects. IVA and VID).

Sigma power in humans shows a stable local maximum in the all-night NREMS EEG power spectrum. These values are derived from standard recording configurations that typically include central recording sites (7, 16, 41, 73, 86,

FIGURE 2. Electrophysiological manifestations of sleep spindles across mammalian species. A: representative 15-s traces of non-rapid-eye-movement sleep (NREMS) from mouse barrel cortex (see Ref. 204 for details), rat hindlimb cortex (see Ref. 542 for details), cat (area 5, parietal-associative cortex, local field potential recordings in deep layers), and human [N2, C3 electroencephalogram (EEG) derivations referenced to mastoid]. The rat trace was provided by Julie Seibt, the cat trace by Laura M. J. Fernandez and Sylvain Crochet, and the human trace by Sandro Lecci and Francesca Siclari. Top traces are unfiltered, and bottom corresponding traces are filtered between 10 and 15 Hz. Vertical dotted lines, gray shadows, show sleep spindles. Smoothed power spectra of the traces on the left are shown on the right, same color code. B: characteristics of sigma power peak in human NREMS. Typical absolute EEG power spectra for all-night human N2 and N3 sleep stages in a log-linear plot to highlight the characteristic power peak falling within the 10–15 Hz band. Dotted lines denote the power increase around the sigma frequency band through connecting adjacent portions of the spectrum. Note that this increase includes, but is not limited to, the 10–15 Hz band. C: heritability of sigma power peak. Representative power spectra of monozygotic twins and unrelated age-matched individuals. D: power spectra of mouse NREMS in EEG and in three different cortical areas obtained via local field potential (LFP) recordings (see Ref. 204 for details). Note that sigma power manifests as a “shoulder” on the power spectrum and varies across areas. [Species cartoons are adapted and modified from Servier Medical Art (CC BY 3.0).]



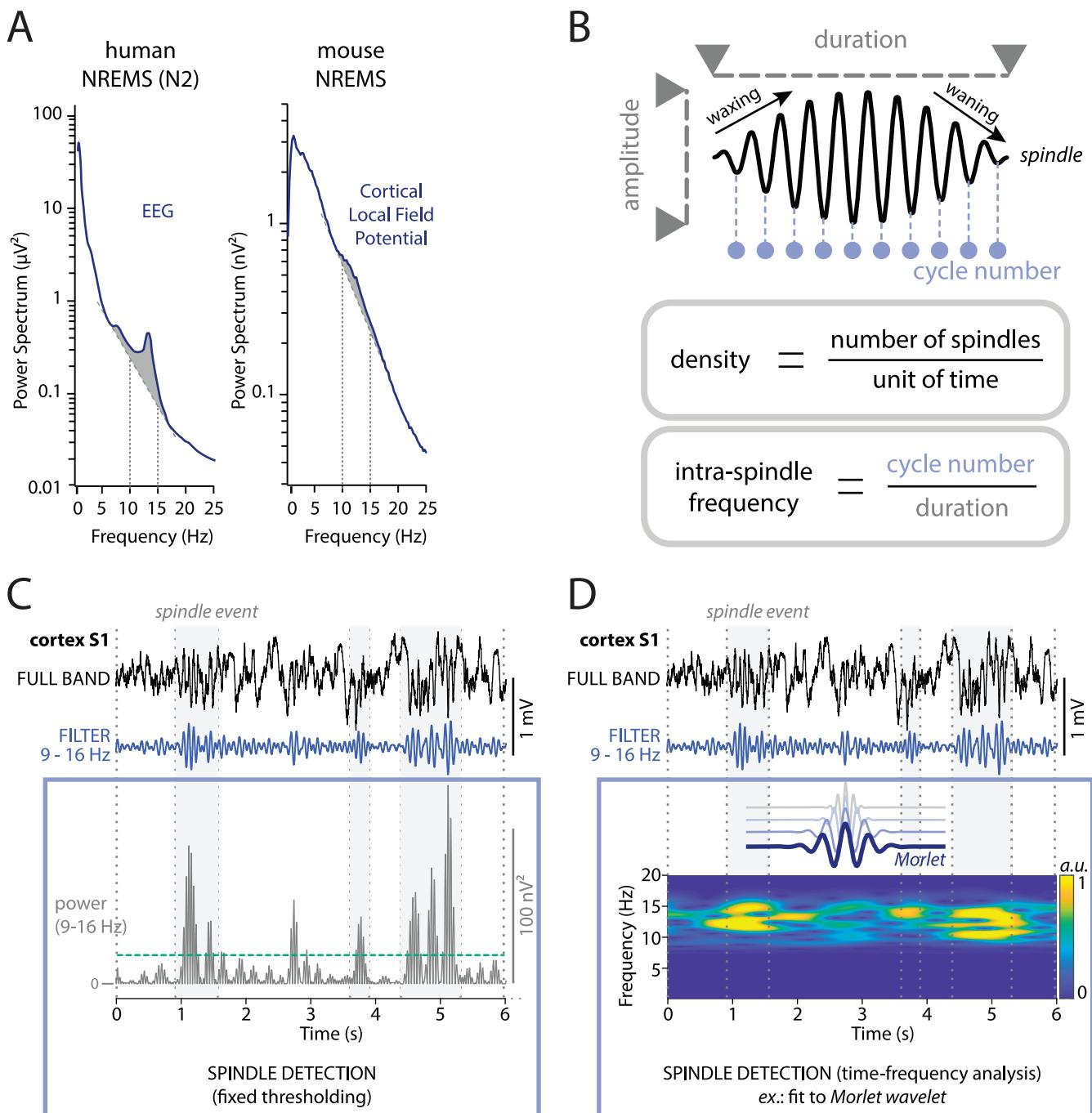


FIGURE 3. Quantification of sleep spindle activity. *A*: sigma power measurements. Gray shaded area shows power levels that go beyond the close-to-monotonically decaying behavior of the non-rapid-eye-movement sleep (NREMS) power spectrum in human (left, N2) and mouse (right, NREMS). Vertical dotted lines show the 10–15 Hz frequency band within which power levels are typically calculated, for example, through integrating the area underneath the curve. *B*: parameters describing a discrete sleep spindle, which is symbolized as a waxing and waning sine wave. *C* and *D*: detection of discrete sleep spindles through automated methods involving fixed thresholding (*C*) or time-frequency Wavelet (*D*) analysis. Top traces show local field potential recordings in mouse primary somatosensory cortex during NREMS and corresponding band-pass filtered signal (9–16 Hz; see Ref. 204 for details). The fixed thresholding method (*C*) applied to the square of the band-pass-filtered signal (see Ref. 204 for details) identifies three sleep spindles (vertical dotted lines). The time-frequency analysis using Morlet Wavelet transformation (*D*) applied to the same band-pass-filtered trace (resolution of 0.1 Hz) identifies three regions of high amplitudes that coincide with the spindle events detected through fixed thresholding.

154, 155, 200, 227, 292, 501, 555, 642). In NREMS stage N2, there is a characteristic peak of sigma power that lies prominently within the 12.5–14 Hz frequency range (133, 154, 155, 432) (FIGURE 2B). In sleep stage N3, an additional shallower peak at lower (<12.5 Hz) sigma band frequencies often appears or becomes more prominent than in N2 (133, 432). These two peaks are characteristically different among individuals and remain stable across nights, equal to an individual's EEG “fingerprint” of NREMS. They correspond to the appearance of fast and slow sleep spindle events that show characteristic temporal and spatial dynamics in the course of a night (see sect. IVA).

Several small-scale twin studies suggested that the sigma fingerprint is heritable (16, 86, 154, 155) (FIGURE 2C), which points to genetic determinants. A large-scale sample study (>11,000 subjects, >16,000 h of N2 sleep) analyzed genome-wide single-nucleotide polymorphisms to demonstrate a strong heritability of absolute and relative sigma power compared with other power bands of the NREMS and the wake EEG (501). Sleep spindle parameters, notably density, were influenced by the same genetic variants as relative sigma power and N2 duration, suggesting a common genetic basis. The heritability of sleep spindle mean frequency was instead not genetically correlated with density, suggesting that frequencies are genetically independent. Fast and slow spindle densities also seemed to be determined by genetically nonoverlapping mechanisms. An individual's sleep spindle characteristics are thus laid down in several dissociable sets of genetic factors. These characteristics also correlate with cognitive abilities and are altered in neurological disorders (sects. IX and X), which explains the interest in sleep spindles as biomarkers for inherited brain functions and disease risks.

2. Sigma power in rodents

The rodent NREMS power spectrum measured through EEG shows a small “shoulder” of the NREMS spectrum from 8 to 20 Hz rather than a discernable peak in the sigma range both in mouse (34, 204, 476) and rat (433) (FIGURES 2D AND 3A). A first reason for this comparatively weak presence of sigma power is that rodent NREMS has so far not been subdivided into stages based on the enrichment of sleep spindles, such as the human N2 stage. As there is now evidence that mouse sleep does show stages with properties similar to human N2 and N3, sigma power can be reevaluated according to this refined scoring [as presented in a preliminary study (341)]. A second reason is that there are differences in area distribution that are not adequately represented at the EEG. For example, relative sigma power is high when measured locally using local field potential (LFP) recordings over mouse barrel cortex, the area encoding the representation of mouse whiskers (204) (FIGURE 2D). In this area, discrete sleep spindles between 9 and 16 Hz are also visually identifiable (204, 542) (FIGURE 2, A AND D). A third reason is that there are species-specific differences in the

wiring of TC circuits (sect. VE), which affects their strength and cortical representation. Fourth, spindle activity in rodents is not strictly confined to the 10–15 Hz sigma power band. EEG power dynamics in mouse NREMS evolve coherently over 9–25 Hz, as evident in particular during “intermediate” sleep (34, 144) (sect. IVA). Spindle-like discrete events were also observed in the β (16–30 Hz) frequency range (38, 542) (FIGURE 2A). These factors all contribute to uncertainties in sleep spindle quantification in rodents that are reflected in variable borders for the frequency band chosen to quantify spindle activity. These range from comparatively broad [11–19 Hz (221); 7–15 Hz (266); 6–20 Hz (38)] to narrow [10–15 or 11–15 Hz (34, 476)]. Together, the representation of sigma power and of sleep spindles varies between rodent and human, and differences may be further exacerbated by the spatial averaging of EEG recordings.

B. Discrete Spindles

Spindle detection methods aim to determine phasic spindle events characterized by an amplitude, duration, frequency, and density (FIGURE 3B). In humans, the conspicuous properties of spindles, notably the sharp appearance above background, the near-sinusoidal and symmetrical waxing and waning waveform, and the characteristic frequency range have rendered visual detection by an expert scorer the gold standard for their quantification (631). However, visual scoring is slow, feasible only for limited data sets, prone to errors, and bears the risk of subjective judgements based on variable expertise. Reliable visual scoring of discrete spindles in rodents is also difficult for reasons mentioned above (sect. IIIA). Automated detection methods overcome these issues and can be additionally adapted to reproduce visual scoring results from particular patient groups, recording conditions, and research questions. Currently, such approaches are in ongoing development and include measures to validate these across research and patient groups. Open access software and the sharing of large data sets are essential for such efforts (for recent reviews and developments, see Refs. 126, 462).

1. Visual detection

The reliability of visual detection between experts is generally considered to lie at >80% (95, 290, 508, 661) and improves further once the number of included expert scorers is larger and consensus rules are applied (631, 641). The best documented case involves 24 experts scoring a total of 2,000 human spindles in N2, yielding an intraspindle frequency of 13.3 ± 1 Hz (mean \pm SD), an amplitude of $27 \pm 11 \mu\text{V}$ (25 μV for males, 30 μV for females), and a duration of 0.75 ± 0.27 s (631). These values were symmetrically distributed around the mean and conform with the values of the AASM definition except for a fraction of spindles (14%) with duration <0.5 s. Spindle densities, al-

though averaging at 2.3 ± 2 spindles/min for N2, were asymmetrically spread to values up to 10 spindles/min. This study sets a gold standard for sleep spindle characteristics in a middle-aged, mixed-sex population and shows that amplitude, frequency, and duration vary fairly symmetrically around a mean, but that there is a large interindividual variability in sleep spindle densities. These parameters are relevant for studies interested in how sleep spindle properties relate to differences in cognitive abilities or to disease (sects. VIII–X).

2. Automated detection

There are excellent overviews of the most widely used algorithms (126) and some of the newest developments in the automated detection of sleep spindles (461). The first step in automated detection is to extract nonstationary phasic events within the sigma frequency range that cross a minimal threshold amplitude (FIGURE 3, C AND D), which is then followed by additional criteria depending on the choice of the thresholding method.

A) **FIXED THRESHOLDING.** The procedure is generally as follows: 1) preprocessing and band-pass filtering of EEG data in the chosen sigma frequency band; 2) a thresholding of spindle amplitudes, typically done on the rectified signal; and 3) thresholding of spindle duration. The spindle-shaped waveform is typically not included as a criterion. While *step 1* involves the choice of appropriate filtering and additional preprocessing steps, there are different ways to carry out *steps 2* and *3*. A sequential thresholding, whereby *step 3* follows *step 2*, was introduced in 1994 (535). Sequential thresholding is computationally easy, but the drawbacks are low specificity and precision, due to accumulating uncertainties in the sequential choice of thresholds. This concerns in particular the amplitude threshold in absolute values (for review, see Refs. 126, 458) or relative to a baseline (204, 434, 458). Fixed thresholds also risk not to account for changing spindle properties, such as those occurring over the night or across different brain areas. Therefore, most studies introduced additional criteria. Examples are 1) the ratio of amplitudes in the sigma versus the alpha band to exclude potential low-frequency spindles in the alpha range in humans (535), 2) further extension of the amplitude criterion to more frequency bands (17, 261, 528), 3) introduction of both a lower and upper threshold for spindle amplitude (206), and 4) introduction of a sensitivity index to reduce excessive event detection (461). A physiologically motivated criterion is based on the timing of sleep spindles with respect to the phase of other sleep rhythms, such as the slow oscillation (SO) (433, 434) (sect. VIE). Inclusion of a temporal coupling of spindles to the SO was essential for a robust quantification of discrete spindles in mice (204, 319).

B) **ADAPTIVE THRESHOLDING.** This refers to studies that adapt thresholding methods to account for the variabilities of

spindle properties across individuals, sex, age, sleep stages, and recording conditions (e.g., the derivation). In humans, the individual adjustment method makes use of the individual power peaks in the sigma range (67, 68). Such methods provided additional details on the topological differences of fast and slow spindles, their age dependence, and the dynamics of discrete spindles across sleep stages (68, 458, 602).

C) **TIME-FREQUENCY ANALYSIS.** This approach analyzes frequency and temporal occurrence of discrete spindle events simultaneously through using continuous wavelet analysis. Some of the first studies used weighted sums of predefined templates to approach the waveform of spindles (187, 661). Widely used nowadays are Morlet Wavelets, which are sine waves multiplied with a Gaussian function, as these come closest to the visual gold standard (628, 631) (FIGURE 3D). Examples are population studies on the genetic and demographic determinants of spindles (501) and on memory consolidation (77). Time-frequency analysis has higher time resolution and appropriate representation of the nonstationary nature of spindles, taking also into account their waxing and waning characteristics. Still, the ambiguities of thresholds for the frequencies and amplitudes remain and approaches to determine these vary (597). Besides the continuous wavelet transform (5, 628), other methods involve complex demodulation that readjusts threshold parameters for detection every 60 s (509), matching pursuit strategies (188), expanded wavelet transforms (344), or multitapered spectral analysis (497). These approaches are suitable for particular purposes, such as determining spindle variability across the night and across individuals (509), their superposition (661), including other waveforms, such as K-complexes (188, 344), detecting sleep spindles without requirement for prior sleep scoring (597), or assessing altered spindle properties in patients with epilepsy (355). Wavelet-based methods outperform threshold-based methods in direct comparisons (631).

D) **QUANTIFICATION BASED ON INTRACRANIAL RECORDINGS.** With the availability of intracranial recordings from humans and animals, the localization and spread of spindle activity across layers provided useful additional criteria, such as the presence and localization of current sources in distinct cortical layers (261).

3. Machine-learning based quantification

Machine learning techniques work with algorithms that use signal features to recognize patterns in a supervised or unsupervised manner. In supervised learning, machines are fed with training data sets in which spindle waveforms are prelabeled, whereas unsupervised learning departs without preindications. Many approaches are currently being developed (3, 12, 62, 421, 467, 620), and one of their most promising aspects is that they use visual scoring for training

algorithms developed by machines. This brings their performance closer to human scorers (see, e.g., Refs. 62, 421).

C. Outlook

Sleep spindles are traditionally defined by their surface correlates, but these are loosely connected to true spindles in the brain. Surface events are additionally distorted by the EEG recordings across the highly resistive skull. EEG sleep spindles are thus a valid measure for NREMS, its overall spectral dynamics, and its regulation, but they do not adequately represent the spatial distribution of sleep spindles on the cortical surface. This limits their use as signatures of local sleep and as biomarkers for cognition, learning, and disease in all of which sleep spindles need to be tracked in a local manner and with ideally little ambiguity regarding their origins. For such goals, better spatial resolution is required, for which magnetoencephalography and local electrical recording techniques seem adapted for the case of humans (sect. VI). Optogenetically generating sleep spindles at defined sites in rodents will be instrumental in delineating the relation between sleep spindle origins and their surface appearance, which can ultimately provide mechanistically guided hypotheses for humans.

Many surface spindles are visually obvious, but equally many are ambiguous events. The graphic information provided by an EEG event (amplitude, frequency, duration, approximate location) is often insufficient to disambiguate it from background or from its nesting within other sleep rhythms. Publicly available large data sets and open access software facilitate the establishment of consensus criteria across groups and reciprocal tests of reproducibility. Comparison between visual scoring and the chosen automated detection routine becomes more the rule than the exception in both humans and animals, with a clear assessment of sensitivity and precision and ideally the inclusion of several experts (126, 340, 631). Progress in this respect also applies to rodents (612). Still, whatever the species, sleep spindle analysis will always need to be adapted to the scientific goals, for example, determining specific spindle characteristics in a within-subject comparison is not the same as coming up with sleep spindle distributions in demographic studies. As awareness for species-specific differences and similarities becomes part of regular exchange, and as understanding of their spatial arrangement improves, their use as biomarkers can be brought to a more analytical level.

IV. ROLE IN SLEEP'S MACRO- AND MICROARCHITECTURE

Human sleep spindles recorded through EEG mark several characteristic moments as sleep evolves during a night. They appear at the onset of NREMS stage N2 (10, 186), when consciousness fades. They are present in the EEG

throughout NREMS, but best visible during N2 (292), while being absent during N1 and rapid-eye-movement sleep (REMS). In rodents, power in the 10- to 20-Hz frequency range is present across the many NREMS bouts of their resting phase that are not typically divided into stages (see, however, a preliminary study, Ref. 341). Sleep spindles are also regulated by homeostatic and circadian processes (72), making them part of the restorative and adaptive functions of NREMS.

NREMS can last for minutes to hours, but its spectral profile is not steady in time. Sleep spindles as brief bursts naturally contribute to heterogeneity. Spindles additionally cluster over several time scales in rodent and human, segregating NREMS into spindle-poor and spindle-enriched periods. This periodic grouping of sleep spindles divides NREMS in mouse into alternating sequences of high and low arousability. There are thus substages within an apparently consolidated NREMS bout. We discuss here how the dynamics of sigma power and sleep spindles contribute to the macro- and microarchitectural organization of NREMS. We will use the terms *sigma power* and *sleep spindles* to refer to the corresponding EEG hallmarks (see sect. III). In later sections, thalamic “spindle-like rhythms” will refer to activity in the spindle-generating thalamic neuronal circuits. The term *slow-wave activity* (SWA) summarizes power in the 0.75- to 4- or 4.5-Hz frequency range. It is subdivided into power in the range of the cortical SO (~0.5–1.5 Hz) (sect. VIE) and power in the 1.5- to 4-Hz frequency range, also referred to as “delta power.”

A. Dynamics Across the Undisturbed Night

1. Sigma power

The first spectral quantifications indicated that a power peak in the sigma frequency band (10–15 Hz), centered around 13–15 Hz, appears in early sleep stages (stage C according to Ref. 510) and largely persists all the way to deep sleep (stage E) across central, frontal, and parietal derivations (185, 186, 307).

Today, power in the sigma (10–15 Hz) band and SWA are the two major hallmarks of human (7, 73) and rodent (221, 596) NREMS. Total power in the sigma band comprises a few percent of SWA during both the N2 and N3 NREMS stages in human (176), but relative power peaks are greater and more consistently localized in the sigma band in N2 compared with N3 (133). Sigma power is thus useful for distinguishing N2 and N3 sleep stages (73, 153, 176). Sigma power increases within minutes at the onset of each of the four or five NREMS cycles during a human night's sleep, and absolute power densities almost double in late compared with early NREMS cycles (176) (FIGURE 4A). During the first one or two human NREMS cycles, the time course of sigma power density shows the shape of the letter

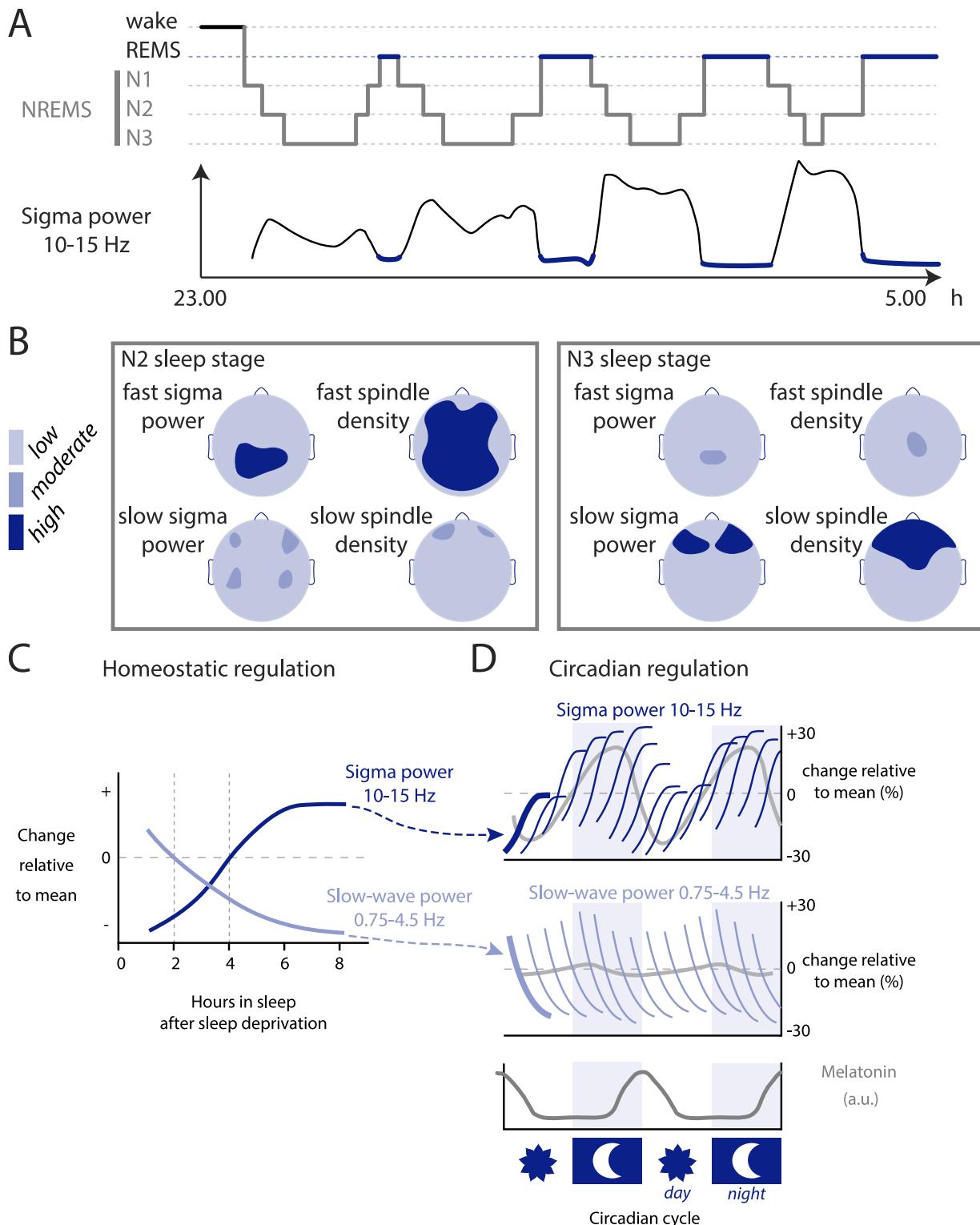


FIGURE 4. Dynamics and regulation of sigma power and sleep spindle characteristics across the undisturbed night. *A*: overnight time course of sigma power across a typical human night, shown as a hypnogram on the top. Note the U-shaped waveform in every non-rapid-eye-movement sleep (NREMS) cycle and the increase in sigma power later in the night. Time axis of sigma power also applies to the hypnogram. REMS, rapid-eye-movement sleep. *B*: topography of fast and slow sigma power and sleep spindle densities for N2 and N3 human sleep. Note the correspondence between both measures and the distinct topographies for fast and slow spindles (see also sect. VI*C*). *C*: homeostatic regulation of sleep, schematically illustrated through showing mean relative changes of sigma activity and slow-wave activity (SWA) across a night after sleep deprivation. *D*: circadian regulation of sigma power and SWA, schematically illustrated as changes relative to the mean as a function of time of day (see Ref. 174 for further details). The circadian time is indicated below through light and dark phases and the melatonin variations.

U (153, 176, 276), with values declining towards the middle of a cycle where N3 sleep is prominent, and sharply increasing in the last 10 min when N2 resumes. These dynamics are also present for higher frequencies within the sigma range, spanning into the beta range up to 20 Hz (7, 176). In rats and mice, a 10–20% increase in sigma power density occurs throughout the 12-h light (resting) phase (220, 596, 634).

In humans, the two peaks of sigma power typically found during N2 and N3 (sect. IIIA) differ in their anteroposterior distribution on the cortical surface, such that slow peaks (<12.5 Hz) are found preferentially anteriorly and fast ones (>12.5 Hz) posteriorly (133, 152, 306, 432, 445, 643, 658) (**FIGURE 4B**). These two peaks correspond to “fast” and “slow” spindles (sect. VID). Fast spindles make a major contribution to the increase in EEG power in the course of NREMS (7, 176, 276). In rodents, frequency differences are moderate (~1 Hz) (319), but relative sigma power is particularly high over somatosensory areas including barrel cortex (204).

2. Sleep spindles

Discrete spindles dominate in the N2 stage of human NREMS, with 2–8 spindles/min in N2 and 1–6 spindles/min in N3, values that are found consistently in central EEG derivations, from small-sample to large-population studies using visual scoring by experts and nonexperts, as well as automated detection methods, and combinations thereof (23, 41, 153, 176, 228, 501, 528, 555, 631). The high centroparietal sigma power density correlates with the greatest density of spindles (153, 186, 624, 658, 661) (**FIGURE 4B**), and it is from these areas that spindle counts are typically made. Total counts of spindles per time spent in N2 in the course of a night amount to 1,000–2,000 (e.g., Refs. 215, 216, 438, 528). Spindle density, amplitude, and duration increase over successive NREMS cycles in human (153, 176, 255, 658). The U-shaped time course of sigma power matches with the time course of sleep spindle amplitude and activity (176).

Properties, density, and topography of sleep spindles are distinct between N2 and N3. N2 spindles are more frequent as well as larger in amplitude and in activity integrated over time (133, 176, 228, 658) (**FIGURE 4B**). There is a good correspondence between the centrally strong fast sigma power and the presence of fast and large spindles in N2. A slow sigma power peak often appears at frontal sites in N3 that correlates with slow spindle densities (133). In mouse NREMS, the largest and fastest discrete spindles have so far been documented in the barrel cortex (204), one of the mouse’s primary modality for active exploration and experience-dependent learning. There are also slow spindles during the N2 stage of human NREMS, but these are less dense, smaller, and spread across parietal and frontal sites. Fast spindles during N3 occur with comparable amplitudes

but more moderate density at central sites. There are estimates that 50–70% of all sleep spindles are temporally coupled to the cortical SOs in both human (432, 453) and mouse (204, 319). These percentages depend on criteria used to extract SOs and spindles; nevertheless, they indicate that a substantial number of sleep spindles occur with no SO being co-detected. The SOs initiate and synchronize spindles through corticothalamic feedback (sects. V, B and C, and VID). SOs are more frequent during N3 than N2, and spindle-only events are predominant during N2. SOs during N2 are also called K-complexes. K-complexes and SOs of N3 probably arise from two different synchronization processes that involve subcortical and intracortical mechanisms, respectively (553). There may thus be sleep-stage-dependent differences in how SO-spindle couplings are mechanistically generated (sect. VIE) and contribute to memory formation (sect. VIII).

3. Regulation of NREMS macroarchitecture

Sleep spindles are not only markers of NREMS but determine its architecture. The so far best-powered study, involving >11,000 individuals and corrected for multiple covariates such as age and sex, shows that the density of sleep spindles in N2 correlates positively with N2, but negatively with N3 and REMS durations (501). This correlation could be related to shared genetic bases (sect. IIIA). However, optogenetic enhancement of spindle-like rhythmicity in mouse produced a direct stabilizing effect on NREMS duration, supporting a protective action of sleep spindles (318, 449). Systematic differences in sigma power between chronotypes (sect. IVC), between sexes, and across the menstrual cycle (sect. IVD) further suggest an interplay with circadian, sex, and hormonal influences on sleep. Above 40 yr of age, the dynamics of sleep spindles within and across subsequent NREMS cycles are attenuated, but correlations with sleep architecture become stronger (353). Sleep spindles may thus become more relevant determinants of sleep quality once SWA decrements with age (353, 501) (sect. VIIIB).

The stabilizing effect of sleep spindles on N2 duration could arise in part from the momentary dynamics of sigma power before NREMS ends. The transitional period to REMS, called “intermediate” sleep, shows a surge in sigma power for 30–50 s in the EEG (221, 650) and in local field potential recordings from sensory cortex (362, 542, 576). It is found in mouse (221, 240), rat (246, 542, 596, 639), and cat (248), and it seems to be present in humans (7, 186, 343, 501). Sigma power surges were also described for transitions from NREMS to full wakefulness (56, 362, 542), although they are less prominent (501, 596). During intermediate sleep, spindles are larger and longer than during regular NREMS in cats (247), and fast spindle density transiently increases in humans (501). Genetically boosting spindle generation lengthened the phase of intermediate sleep (650), while suppressing it attenuated intermediate

sleep (33, 144). Momentary dynamics of sleep spindle activity thus define transitional periods of NREMS. This possibility is part of ongoing research in the context of the infraslow dynamics of sigma power and sleep spindle clustering (sect. IVE).

B. Homeostatic Regulation

Homeostasis ensures a balance between sleep and waking, such that average reference levels of sleep are kept constant over successive sleep-wake cycles. It is a basic regulatory principle that, together with the circadian regulation of sleep, ensures both timing of sleep and adaptation to acute sleep needs. The amount of SWA is a reliable and quantitative marker of sleep homeostasis across mammals (590). Homeostatic upregulation of SWA in response to sleep deprivation leads to less fragmented sleep and a higher arousal threshold, promoting sleep quality. In contrast to SWA, sigma power or spindle densities in rodent and human are downregulated after sleep deprivation (172, 174, 283, 624) and instead increased after napping (170, 644) (FIGURE 4C). Sleep spindles are thus suppressed once sleep pressure is high. Under such conditions, sleep benefits supported by sleep spindles, such as variations in arousability (sects. IVE and VIF) and facilitation of memory consolidation (sect. VIII), seem to be downregulated to boost the restorative effects of sleep enriched in SWA.

The opposite regulation of SWA and sigma power is widely used to describe sleep homeostasis. In humans, this regulation shows a threshold: when mean power between 0.35 and 3.5 Hz went beyond $\sim 50,000 \mu\text{V}^2/\text{Hz}$ at central derivations, sigma power density was suppressed (7, 176), whereas this was not the case for moderate increases in low-frequency power (23, 176, 600). An overall negative correlation between absolute delta power and power across 11–19 Hz was also found in mice (221) and in local recordings in cat thalamus (349). Homeostatic downregulation principally targets the density of sleep spindles rather than their properties (329). The opposite regulation is due to a sharing of the neuronal mechanisms underlying sleep spindles and delta rhythms, both of which arise in thalamus. Thalamic cells can generate both spindle-like and low-frequency rhythmic activity in the delta range, occasionally even simultaneously, but only within a limited voltage range (46, 141). Activity in the delta range is prevalent once the membrane potential of thalamic cells hyperpolarizes (204), as is the case when sleep deepens. In humans, fast sigma power shows dynamics running more strictly opposite to those of SWA. This is also the case for sigma power in sensory cortical areas in rodents (204). The neuronal mechanisms underlying spindles and low-frequency rhythms could thus preferentially overlap in sensory TC loops (8, 172, 353).

C. Circadian Regulation

Sigma power density is the most consistently regulated circadian marker of the NREMS EEG spectrum, with power moving between $\pm 15\%$ around the 24 h-mean (172, 174). This circadian regulation renders sigma power strongest during habitual sleep times and could contribute to NREMS continuity at moments when sleep pressure is low, such as in the early morning hours (FIGURE 4D). Circadian variations in sigma power are phase-locked to those of melatonin, a marker for the circadian cycle, but they run in opposite directions for the intermediate (12.25–13 Hz, 150% of mean) and the upper (13.75–15.5 Hz, 70% of mean) portion of the band (179). The former peaks before the maximal melatonin secretion, whereas the latter reaches its minimum at this point (8, 179) and could involve a regulation of both spindle density and amplitude (328, 636). The circadian regulation weakens in subjects >40 yr (501).

The circadian regulation of sleep spindles is mediated by hormonal and neuropeptidergic signaling mechanisms. Oral administration of melatonin in humans enhanced sigma power density (178). Systemic infusion of melatonin agonists in rodents promoted burst discharge in the TRN through activation of melatonin type 2 receptors and boosted power in the sigma band (463), suggesting that melatonin directly targets cellular mechanisms of spindle generation. Vasoactive intestinal peptide also acts on thalamic neurons (579). There also exists a projection from the suprachiasmatic nucleus to the paraventricular thalamic nucleus (460), raising the possibility of a synaptic regulation of thalamic circuits. Furthermore, the peripheral clock gene *npas2*, which belongs to a family of transcription factors implied in sensing cellular energy state, affects sigma power (220). The product of *npas2* is expressed in TC cells. The circadian regulation of sleep spindles could thus further depend on the metabolic status of thalamic cells.

Young adult morning and evening chronotypes differ by >2 h in terms of sleep timing, by ~ 30 min in sleep duration, and by a few percent in sleep efficiency and time spent in N1 (435). Morning chronotypes show a more rapid decline in SWA across NREMS cycles (435), higher sigma power levels, and an overall larger increase in this power band in successive NREMS cycles (436). Chronotypic differences thus show spectral characteristics that indicate a more rapid dissipation of sleep pressure across the night.

D. Sex Differences

Sex differentially affects sleep quality, architecture, and circadian regulation in an age-dependent manner (for review, see Ref. 99). Sleep duration, efficiency, and quality is generally better in women than in men, and women tend to show smaller differences between morning and evening

chronotypes (435). The sex-specific timing of the release of melatonin, growth hormones, and prolactin are important factors in these differences (357), but sex-specific neural wiring and hormones of the estrous cycle contribute. Both young and middle-aged women show NREMS EEG spectra with higher absolute spectral densities than age-matched males (98, 171), and the rising phase of slow waves is steeper, which is taken as a measure for higher synaptic strength (100). Power differences persist across sleep cycles (435), benzodiazepine regulation (177), and across ages (99). Sex differences are less pronounced in normalized spectra, which has led to the suggestion that skull thickness could play a role (171). However, EEG power spectrum differences were found to be largest in the high-frequency portion of the sigma band (13–15 Hz) (435), and the density of fast but not slow spindles in adult females was higher (501). Absolute sigma power was also markedly larger in females of some laboratory mouse strains (220). Moreover, a higher density of discrete spindles seems to be consistently observed in women (227, 291, 501), and fast spindles have higher amplitudes, densities, and durations (423, 603). Sex differences in spindle-related EEG properties correlate with sex-specific cognitive abilities during wakefulness (sect. IX). The fast spindle range (14–15 Hz) and power up to 17 Hz are regulated by the female ovarian cycle, with decreases present in follicular and increases in luteal phases (156, 183). These alterations coincide with decreased sleep quality around the time of ovulation and their normalization with onset of the luteal phase. The surge of progesterone and allopregesterone levels during the luteal phase prolongs opening times of γ -aminobutyric acid type A (GABA_A) receptors (42) and strengthens sleep spindles (sect. XIA). During pregnancy, along with an overall progressive decrease in low-frequency components of the NREMS EEG power spectrogram, a ~30% attenuation of the high-frequency sigma power component is the most marked change (83).

E. Infraslow Dynamics and NREMS Microarchitecture

Early analyses suggested that sleep spindles modulate the microarchitecture of human sleep (191, 443). The microarchitecture of sleep complements its basic macroarchitectural division into three NREMS stages N1–N3 in human (one in rodent and cat) and into REMS. Even when such a macroscopic sleep stage continues uninterrupted, its electrical signatures vary momentarily. Particularly relevant are variations that show characteristics resembling wakefulness, such as a transient decreases in low-frequency rhythms and the appearance of theta and gamma rhythms and/or muscular activity. Such microarchitectural arousal-like events occur in all mammals and have been variably characterized as “transient phases of activation” (531), “cyclic alternating patterns” (588), and “microarousals” (268) in human, “low-amplitude” sleep (59) in cat and rodent, and “low” states in mouse (430). The dynamics of sigma power

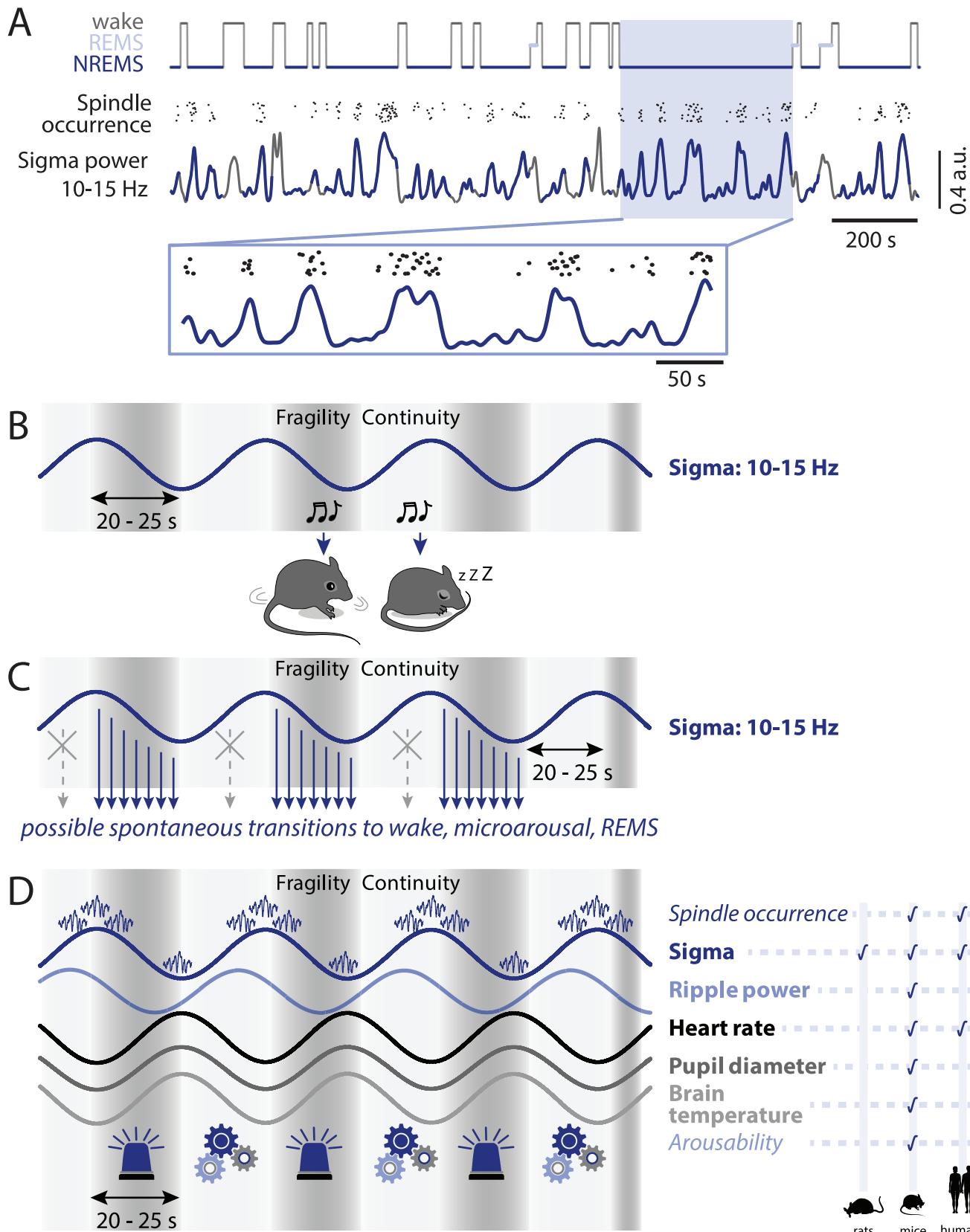
and sleep spindles seem to be of fundamental relevance for the microarchitecture of NREMS, because they indicate variations in NREMS stability. So far, this stability has been mostly characterized regarding disruption by sensory stimuli (sects. IVE and VIF), but there are first indications that it may be relevant for the timing of microarchitectural events, such as microarousals.

1. The 0.02-Hz oscillation of sigma power

Recent studies show that sleep spindle activity varies on top of a comparatively constant level of SWA. These alterations are described by an infraslow periodicity clustered around 0.02 Hz, hence the name the 0.02-Hz oscillation. This oscillation is most pronounced for the sigma band, but exists also in adjacent theta and beta bands (362) (FIGURE 5A). According to the 0.02-Hz oscillation, sleep spindles occur clustered over intervals of ~50 s, and these clusters are interspersed by relatively spindle-free periods. In humans, the 0.02-Hz oscillation was most prominent during NREMS stage N2 and for fast sleep spindles (362). Independent observations that sleep spindles reappear periodically on the time scale of tens of seconds in human N2 (28, 359, 561) and in mouse (142) corroborate the idea that there is a clustering of spindles on an infraslow time scale. The 0.02-Hz oscillation thus defines substates of NREMS that differ by their relative presence of sleep spindles.

2. Fragility and continuity periods of NREMS, defined by the 0.02-Hz oscillation

The 0.02-Hz oscillation is of interest for the microarchitecture of NREMS because it coincides with different levels of sensory arousability (362, 657). When probed with an acoustic stimulus, mice wake up during periods when spindle occurrence declines or is low, which constituted a fragility period (FIGURE 5B). In contrast, spindle-enriched periods, also called continuity periods, protect from arousal. Similarly, when light was shone to the eyes of a mouse in NREMS when pupil diameter was low, SWA in the EEG was relatively preserved, consistent with the continuity phase of NREMS (657). The 0.02-Hz oscillation of sigma power hence marks a microarchitectural variation of NREMS in terms of arousability in response to sensory input. The possibility that the 0.02-Hz oscillation is a generalizable hallmark for NREMS fragility periods that sets permissive windows for termination of NREMS is currently being investigated and follows pioneering work looking at spectral dynamics at moments of NREMS exit (97, 191, 219, 443) (FIGURE 5C). In particular, the above-mentioned alternation of NREMS between fragility and continuity periods predicts that microarousals occur preferentially during the declining phase of the 0.02-Hz oscillation. This would yield predictive power to the 0.02-Hz oscillation that could be useful in anticipating moments of NREMS fragility in diagnostic or therapeutic settings. In support of a role



of the 0.02-Hz oscillation in microarchitectural variations of NREMS, the surge of sigma power typical for intermediate sleep corresponds in duration to a maximum of the 0.02-Hz oscillation, and it is continuous with preceding cycles of the 0.02-Hz oscillation.

3. Autonomic correlates of fragility and continuity periods

The subdivision of NREMS into fragility and continuity periods based on variable acoustic arousability is also evident in oscillatory variations of autonomic physiological parameters (FIGURE 5D). Variations in the heart rate and in pupil diameter are time-locked to the 0.02-Hz oscillation in mouse (362, 657), and there was also a consistent phase relation of heart rate and sigma power in human (362). In mouse, both heart rate and pupil diameter increased during fragility and decreased during continuity periods, respectively. This fits with the idea that the autonomic control of cardiovascular and pupillary functions changes according to when arousals become more or less likely. Thalamically evoked cortical spindle activity in anesthetized cat also attenuates spontaneous activity of γ -motoneurons in the spinal cord, which innervate skeletal muscle spindles (280). Whether altered spinal reflex sensitivity is an additional peripheral correlate of the 0.02-Hz oscillation remains to be seen.

4. Neuronal correlates of fragility and continuity periods

The 0.02-Hz oscillation in sigma power correlates with a grouping of local cortical sleep spindles and with multiunit activity in thalamus, and it is accompanied by small local thalamic increases in brain temperature (142). It is thus genuinely associated with spindle-generating thalamic circuits. It is present in all cortical areas recorded so far, although it is most pronounced in centroparietal areas in human and in somatosensory cortices in mice and smaller in frontal and occipital areas (362). Moreover, hippocampal activity becomes engaged in the rhythm, as ripple activity (150–250 Hz) is positively correlated with the 0.02-Hz oscillation. Hippocampal ripples, an extensively studied neural correlate of hippocampal memory replay during sleep, appeared preferentially during the continuity period while

disappearing during the fragility period. The continuity period is thus marked by neuronal activity patterns engaged in memory consolidation (sect. VIII). An intriguing and tightly phase-locked correlation between sigma power and neuronal activity was additionally obtained through imaging intracellular Ca^{2+} concentrations in apical dendrites of cortical layer V pyramidal cells (542). These measures show that sleep spindles contribute to a periodic alternation of two cortical states defined by a set of layer-specific cellular and dendritic activity patterns. Further research will show how these cortical states regulate sensory processing during NREMS and contribute to fragility and continuity periods. They will be discussed in the context of the cortical state during NREMS (sect. VI).

5. Relation of the 0.02-Hz oscillation to other infraslow variations in the sleeping brain

Brain activity at frequencies in a broad infraslow range (0.01–0.1 Hz) during sleep or anesthesia is not new (for review, see Ref. 633) and in fact was proposed in 1957 to cause slow variations in cortical excitability (14). The 0.02-Hz oscillation currently stands next to at least two other major measures of infraslow activity in the sleeping brain, to which it shows several interesting similarities but also differences (FIGURE 6). First, it is important to note that the 0.02-Hz oscillation is a band-limited power oscillation (FIGURE 6A), but there are also infraslow (0.02–0.2 Hz) direct components of the full-band EEG signals in humans that typically are filtered in conventional EEG recordings (617) (FIGURE 6B). These signals are broadly phase-locked to faster frequency bands typical for NREMS, including also the sigma band, but there is currently no evidence for a preferential coupling. Moreover, a phase-amplitude coupling to discrete EEG events such as K-complexes, arousals, and interictal epileptic events was described. This suggests that the 0.02-Hz oscillation is not exclusively driven by infraslow direct EEG components. Next, there are correlated infraslow dynamics in blood oxygenation level-dependent (BOLD) signals in functionally interrelated brain areas, as measured through functional magnetic resonance imaging (fMRI) (145, 405, 427) (FIGURE 6C). These dynamics have given rise to the definition of several resting state networks that are active in synchrony during NREMS (218). These hemodynamic signals were positively corre-

FIGURE 5. Infraslow dynamics of sigma power and of its additional central and physiological correlates. *A, top*: representative hypnogram for a mouse at the beginning of the light phase, which corresponds to the beginning of the night in this species. *Middle*: corresponding sigma power dynamics, calculated as described in Ref. 362. Spindle occurrence is indicated by black points on top of sigma power, with spindles detected as described in Ref. 204. Portions of the trace underlined in blue are shown at the bottom. Note the oscillatory-like behavior of sigma power during non-rapid-eye-movement sleep (NREMS) bouts according to the 0.02-Hz oscillation (362). REMS, rapid-eye-movement sleep. *B*: schematic illustration of fragility and continuity periods defined by the 0.02-Hz oscillation of sigma power, as probed by auditory awakening in mouse. Fragility and continuity periods that are associated with different levels of arousability (362) are indicated through gray shading and two different symbols. *C*: schematic illustration of preferential moments of NREMS exit to other vigilance states as suggested by the 0.02-Hz oscillation (97). *D*: summary of central and peripheral physiological measures that correlate with the 0.02-Hz oscillation in sigma power described to date (142, 359, 362, 542, 657). Checklist highlights current state of knowledge according to species. [Cartoons are adapted and modified from Servier Medical Art (CC BY 3.0).]

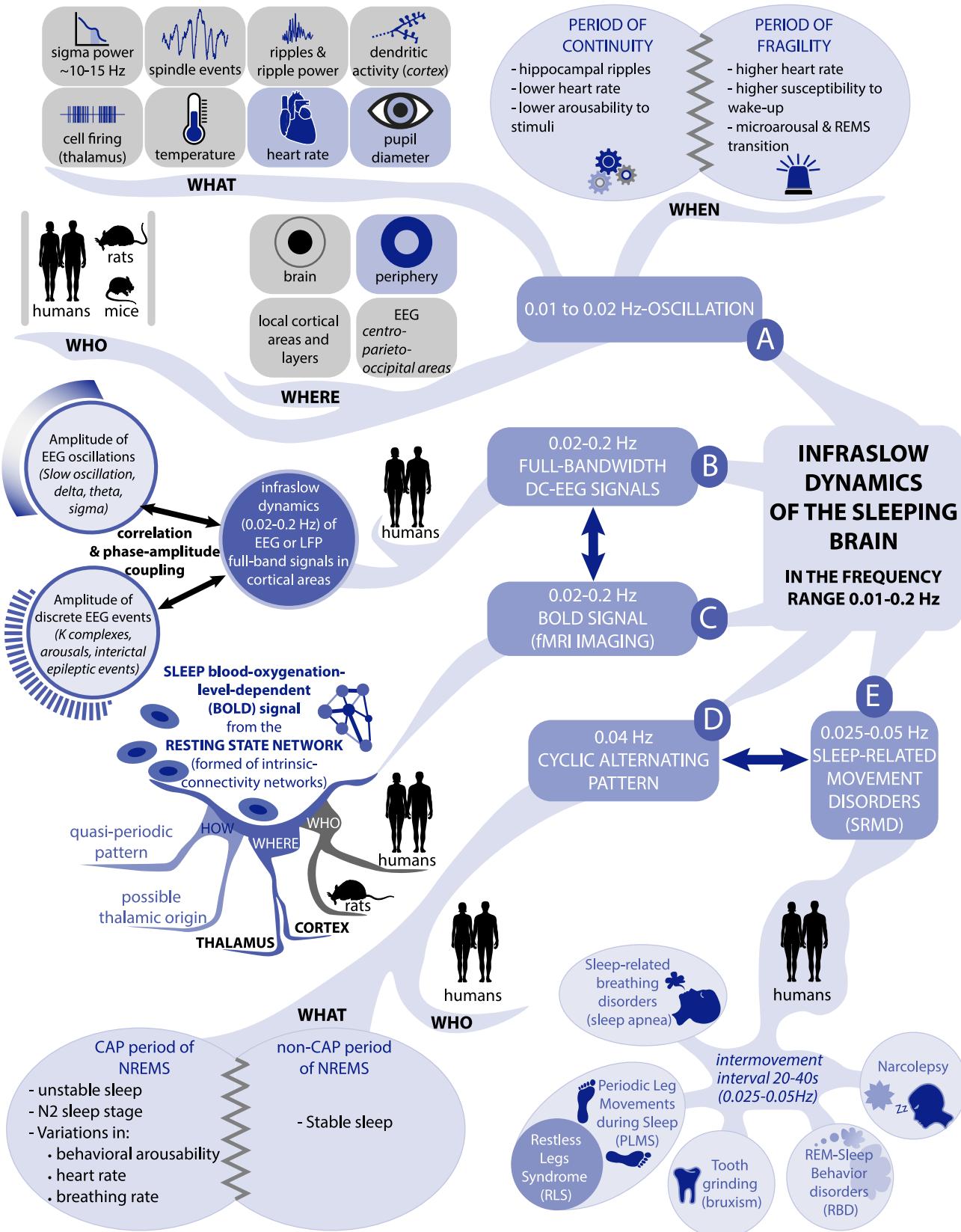


FIGURE 6. Mindmap scheme summarizing infraslow manifestations in the sleeping brain and body and their interrelations. All manifestations within 0.01–0.2 Hz are integrated. A–E follow the paragraphs lettered similarly in the text (sect. IV E). NREMS, non-rapid-eye-movement sleep; REMS, rapid-eye-movement sleep; EEG, electroencephalogram; CAP, cyclic alternating pattern. [Cartoons and symbols are adapted and modified from Servier Medical Art (CC BY 3.0).]

lated with electrical manifestations on the infraslow level in thalamus (487), while they were negatively correlated with cortex. Combined EEG and fMRI recordings in cat and human also suggested that hemodynamic and electrical signals at the infraslow time scale were correlated and perhaps reflected the same underlying processes (253, 275, 470). Most recently, infraslow EEG patterns were proposed to drive hemodynamic and cerebrospinal fluid pulsations during NREMS (225). Given that the 0.02-Hz oscillation reflects a clustering of sleep spindles in which thalamic activity is important, it is, therefore, possible that the 0.02-Hz oscillation is a surface manifestation of these hemodynamic correlations.

Infraslow activity patterns have also been observed through visual observation of phasic events in human NREMS. The cyclic alternating pattern (CAP) is based on visually recognized repeated sequences of transient EEG events on the infraslow time scale that show abrupt variations in their spectral composition (587) (**FIGURE 6D**). CAPs appear preferentially at moments of N2 onset or termination, whereas the 0.02-Hz oscillation runs throughout NREMS periods. The relation to sleep spindle dynamics is not fully established, but spindles occur preferentially during the B- rather than the A-phase of CAP (400). The CAP periods are considered unstable periods of NREMS, during which activity in the periphery is increased and the tendency for sleep interruption is enhanced. Many autonomic parameters, such as heart and breathing rates, are modulated in phase with CAP. The tendency for arousals, leg movements, and bruxism is also enhanced during CAP periods. In spite of these similarities, the relation between CAP and the clustering of sleep spindles has to be established before further comparisons can be made (400).

Sleep-related movement disorders bring infraslow rhythms to abnormal arousal behavior of clinical relevance. Periodic leg movements are widespread in sleep of adult healthy humans (258) and an important manifestation in sleep-related movement disorders, such as restless leg syndrome, sleep apnea, narcolepsy, and REMS behavior disorder (208). Infraslow periodicities are also found for bruxism. Analysis of intermovement intervals shows a broad peak on the infraslow time scale, over which autonomic parameters and arousals can be modulated and strikingly phase-locked. Although the relationship between infraslow brain activities and periodic leg movements is still unclear, pathological motor activity manifests preferably with CAP periods, as well as with cortical or autonomic arousals on the infraslow time scale.

6. Possible origins of the 0.02-Hz oscillation

Current evidence indicates that the 0.02-Hz oscillation is the EEG manifestation of a pervasive brain- and body-wide oscillation that impacts on behavioral arousability, global and local brain activities, and cortical cellular and dendritic

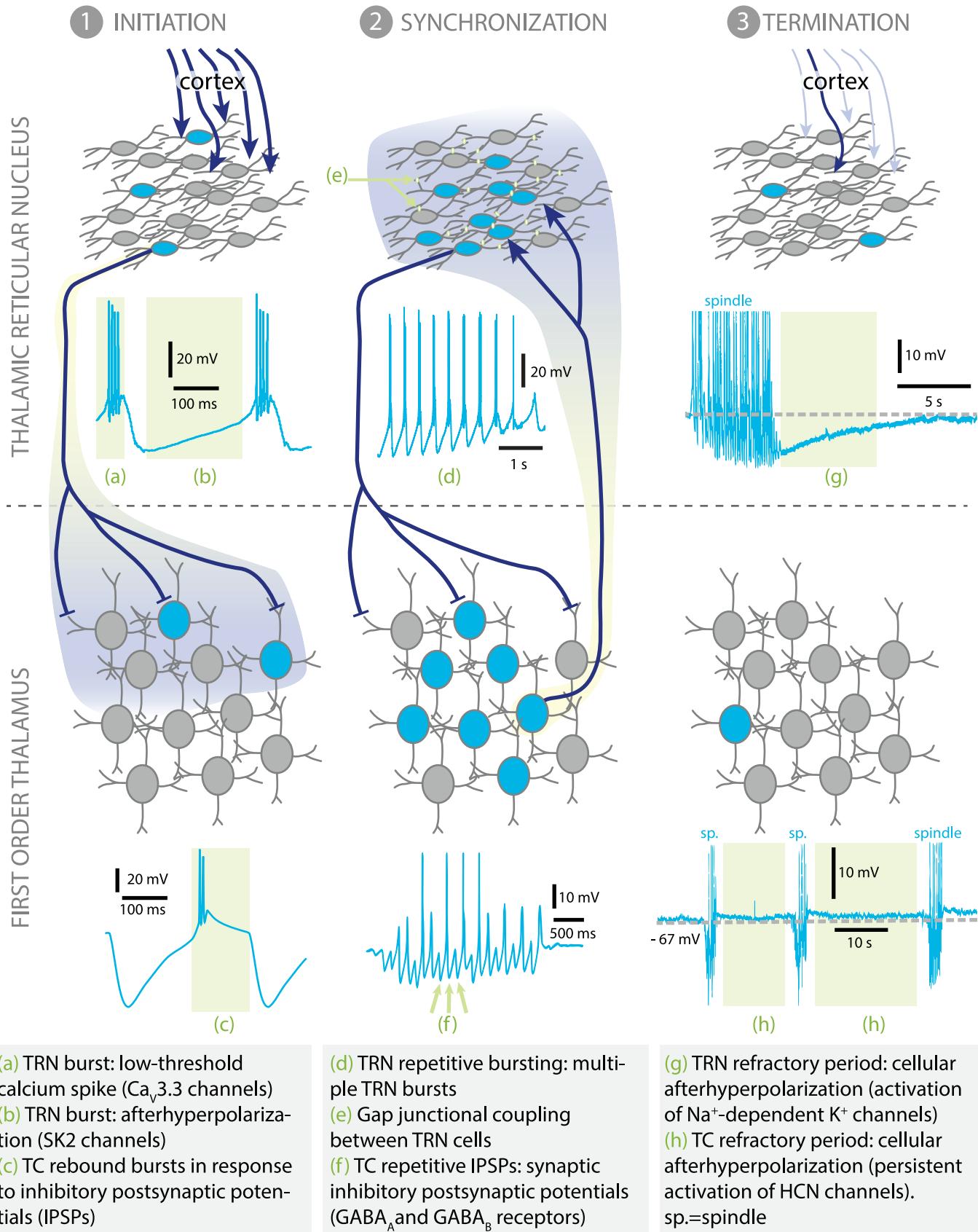
activity. Do the 0.02-Hz oscillations have a neural origin, perhaps even an identifiable pacemaker? Alternatively, does it emerge out of interacting circuits containing neuronal and non-neuronal elements and local blood flow? The phase-locking between sigma power and autonomic output renders brain areas involved in both forebrain modulation and autonomic interesting for further study. For example, the noradrenergic locus powerfully modulates the TC system (413), it is involved in pupil diameter regulation (511), and it shows spontaneous activity on the infraslow time scale (594).

F. Outlook

Human and rodent research together establish a triplicate nature to sleep spindles: They are individual events, portions of the spectral sigma power band, and they appear as groups on the infraslow time scale. With combined human and rodent studies, these manifestations have unraveled some quintessential roles of sleep spindles for NREMS as a vigilance state. Studies in humans have demonstrated their uniquely high heritability and roles for sleep architecture and regulation, while rodent sleep spindles, as smaller and less distinct events, have raised insight in their grouping and the microarchitectural division of NREMS into fragility and continuity periods. Rodent sleep spindles indicate that the presence of sleep spindles may be associated with the functional specialization of sensory cortices, while human fast and slow spindles point to an additional diversification in frontal versus centroparietal areas. This documents that insights gathered from animal and humans, as much as there are species differences, help to derive evolutionarily conserved and possibly more advanced, human-specific spindle functions.

V. NEUROPHYSIOLOGICAL MECHANISMS

Electroencephalographic sleep spindles are a surface manifestation of a synchronized neuronal oscillation that takes its origin within the thalamus. Thalamic networks generate sleep spindle activity even when surgically disconnected from cortex (568, 571). Furthermore, thin brain slices, in which only portions of thalamic circuits are preserved, also generate this oscillatory “spindle-like rhythm” (287, 572). Spindle pacemaker mechanisms are thus fail-safe even in small circuits, pointing to robust cellular and synaptic implementation (for reviews, see Refs. 217, 414, 565, 567, 572). We summarize here how thalamic spindle-like rhythms are initiated, synchronized, and terminated (**FIGURE 7**). The TRN, the “sleep spindle pacemaker” (sect. II), is the focus of our summary. We highlight mechanisms that are of possible relevance for the link of sleep spindles to memory consolidation (sect. VIII), cognitive abilities (sect. IX), and disease (sect. X). We also point out species differences.



A. The TRN

The TRN forms a thin [0.3–0.5 mm maximal thickness in mouse and rat, 0.5–0.7 mm in rabbit, 1–1.5 mm in cat and monkey (109, 389, 660) and 3–6 mm in human] but extended sheet of cells that surrounds the thalamus like a calyx (109). Its embryologic origin is distinct from that of dorsal thalamus (499). Projections from TRN to all dorsal thalamic nuclei are largely ipsilateral, as documented in rat (244, 269, 332, 386, 491), cat (601, 655), and monkey (337). Contralateral projections are sparse and so far not verified functionally (50, 332, 380, 472, 503). The major glutamatergic innervation of TRN derives from the dorsal thalamic nuclei and from corticothalamic projections. The TRN is thus a collection of locally projecting neurons interposed between thalamus and cortex, generating potential anatomical substrates for spindle-like rhythms in all dorsal thalamic nuclei.

Across mammals, the TRN is one of the most prominent brain nuclei synthesizing GABA (29, 151, 378, 477, 562) (for a full review of species, see Ref. 135), and expressing GABA-synthesizing enzymes (281, 464, 562, 583) and vesicular GABA transporters (266). TRN-mediated synaptic inhibition is essential for thalamic spindle-like rhythms. In rodents, TRN represents the major source of inhibition in all thalamic nuclei, but there are also local interneurons in at least some nuclei in rodents (295) and throughout dorsal thalamus in carnivores and primates (29). There additionally are powerful extrathalamic inhibitory afferents (263), for which the roles in sleep spindle generation are unclear.

B. Initiation

Synaptic inhibition generated by TRN cells is particularly vigorous when these cells discharge action potentials in a “burst” mode (FIGURE 7, “Initiation”). A burst contains 2 to >10 action potentials at frequencies of up to several hundreds of Hz (180, 440, 446, 536). Burst discharge is highly dependent on membrane potential: only when values fall below about -55 mV can the ionic mechanisms underlying burst discharge be activated. Such hyperpolarization is typical for periods of sleep onset when ascending neuromodulatory input weakens (81). Hence, “low-threshold” burst discharge is the dominant discharge mode of TRN cells during sleep spindles. When monitored during NREMS, TRN burst discharge often coincides with the beginning of an EEG sleep spindle, intensifies as the spindle

evolves, and phase-locks with its cycles, as shown for cat (570) and rat (90, 230). Even burst discharge in a single TRN neuron only generates spindle-like rhythms in brain slices (320). Optogenetic TRN burst triggering in naturally sleeping (266) or anesthetized mice (48) and in brain slices (607) also produces spindle-like rhythms.

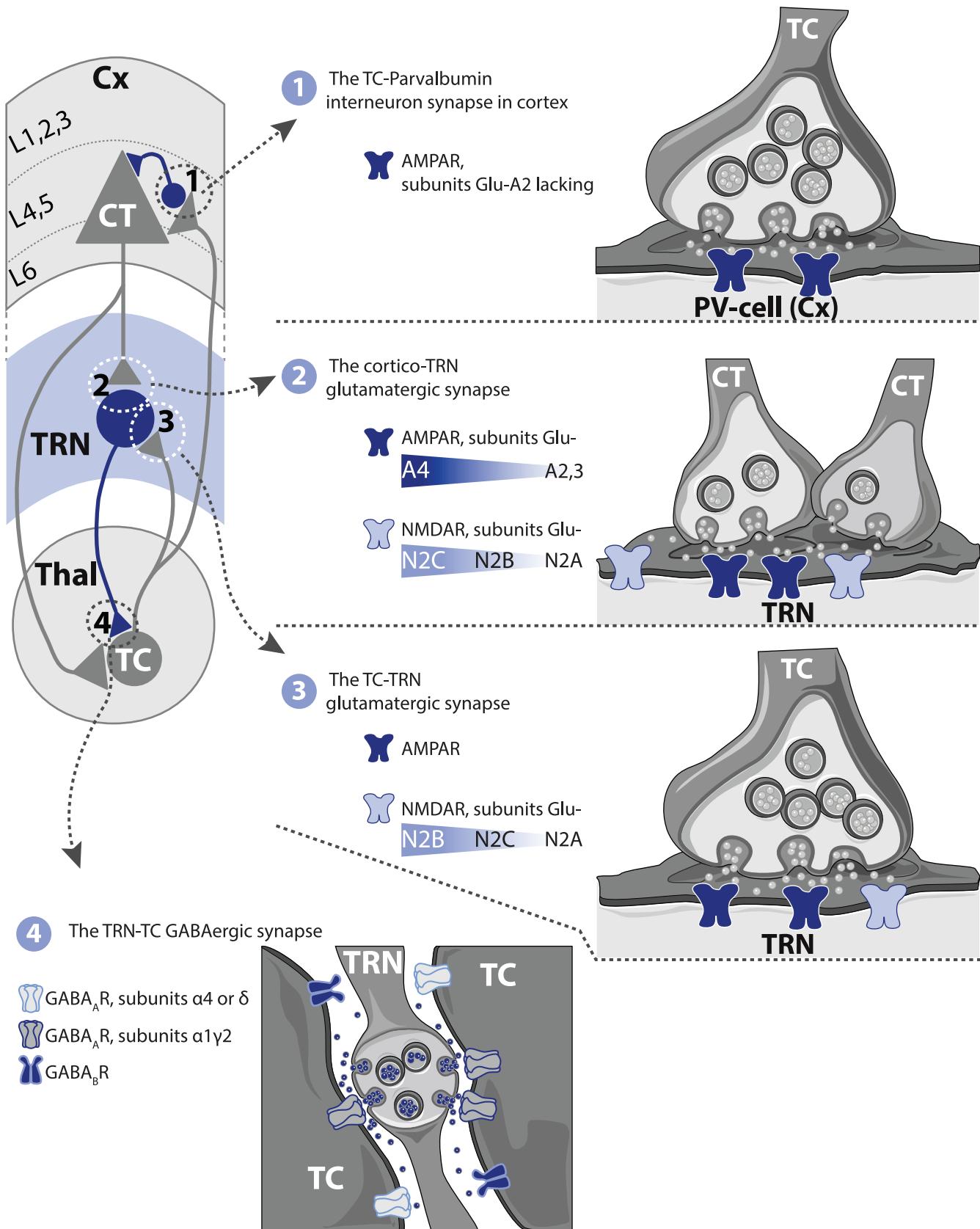
1. Cellular and molecular mechanisms of TRN burst discharge

The ion channels underlying burst discharge belong to the low-threshold Ca^{2+} channels of the Ca_V3 channel family (478). TRN cells express both the $\text{Ca}_V3.2$ and the $\text{Ca}_V3.3$ isoforms (34, 372, 378, 476, 581), but bursting is mainly generated through $\text{Ca}_V3.3$ channels (34, 159). The *CACNA1i* gene encoding the $\text{Ca}_V3.3$ channels is on the list of risk genes for schizophrenia, a neuropsychiatric disorder associated with reduced sleep spindle density (sect. XIE). TRN dendrites express these channels at high levels, including the most distal dendritic compartments (138). TRN dendrites are thus powerful sources of low-threshold Ca^{2+} currents that underlie the TRN cell’s strong capacity to generate action potential bursts (169). Ca^{2+} -dependent K^+ channels of the SK2-type are activated by the Ca^{2+} ions entering through $\text{Ca}_V3.3$ channels and induce a burst afterhyperpolarization, thereby ensuring that bursting is short and can occur repeatedly, which is relevant for the amplitude of EEG sleep spindles (37, 144). Reduced SK2 channel function in TRN was described in mouse models of attentional disorders (sect. IXD) and of the epileptic encephalopathy called Dravet syndrome (sect. IXB). Additional important roles in shaping repetitive burst discharge were described for $\text{K}_V3.1$ and 3.3 channels (196), $\text{Ca}_V2.3$ channels (630), and Ca^{2+} -dependent cationic and persistent Na^+ currents (224, 321). Together, TRN cells express a unique combination of ion channels on their dendrites that make them become vigorous bursting cells in a hyperpolarized range of membrane potentials.

2. Synaptic initiation of TRN burst discharge

Important for the control of sleep spindle initiation, and its timing relative to other sleep rhythms (sect. VIE), is the synaptically triggered activation of low-threshold bursting. The coupling of synaptic input to postsynaptic bursting is well-described for cortical layer 6 afferents to TRN (hereafter referred to as corticorectal afferents) and is based on a number of structural and molecular particularities of the corresponding synapses. Corticorectal

FIGURE 7. Circuit mechanisms of sleep spindles. Main ionic and synaptic mechanisms of initiation, synchronization, and termination are shown separately. Cell populations for thalamic reticular nucleus (TRN) (top, oval cell bodies, bipolar dendrites) and for thalamocortical (TC) cells (bottom, round cell bodies, radial dendrites) are used to indicate the recruitment of cells into the rhythm qualitatively with color coding of cell bodies. Synaptic connections are indicated through arrows (excitatory) or lines (inhibitory). Thick lines symbolize axons that are primarily active, and thin lines symbolize inactive axons (in case of cortical afferents). a-g correspond to key events symbolized through representative electrophysiological traces.



synapses are made on distal TRN dendrites (102). There are numerous postsynaptic GluA4-containing α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) (242) that generate rapid excitatory postsynaptic potentials (161, 233), which leads to postsynaptic $\text{Ca}_v3.3$ channel activation (138, 476) (FIGURE 8, “Synapse 2”). Extrasynaptic GluN2C-containing N-methyl-D-aspartate receptors (NMDARs) on TRN cells may further regulate burst discharge through controlling resting membrane potential (659) and through regulating $\text{Ca}_v3.2$ channel expression (205). In addition to corticoreticular afferents, TC-TRN excitatory synapses trigger TRN burst discharge, constituting a further source for spindle initiation (46, 234) and synchronization (see below).

3. TRN-mediated synaptic inhibition of TC cells

Bursting TRN cells convey reliable and powerful synaptic inhibition through a series of structural and functional peculiarities of the synaptic contacts onto TC cells. TRN-TC synapses are formed between highly arborizing axons with densely aligned axonal swellings (129, 379), the majority of which contain two to five release sites (69, 629) and face dendritic trees of possibly different TC cells, enabling shared and simultaneous inhibition (FIGURE 8, “Synapse 4”). TC cells express postsynaptic $\alpha 1$ - and $\gamma 2$ -containing GABA_A receptors and show a hyperpolarized reversal potential for Cl^- , which leads to large inhibitory postsynaptic potentials (IPSPs) when GABA_A receptors are opened (287, 606). Upon burst discharge, GABA accumulates and spills over the synaptic cleft (51). This leads to a phasic recruitment of nonsynaptic, $\alpha 4$ - and δ -containing GABA_A receptors in addition to the synaptic GABA_A receptors (273, 274, 518, 650), rendering burst-mediated inhibitory postsynaptic events disproportionately larger and slower than the single action potential-mediated ones (287, 322, 323, 538). Additionally, extrasynaptic GABA_B receptors contribute to phasic inhibition during TRN burst discharge (323), but their contribution appears to be species dependent (51, 323). Presynaptic GABA_B homoreceptors on TRN-TC terminals (360) and heteroreceptors at the TC-TRN terminals play modulatory roles (607). A tonic form of inhibition through extrasynaptic δ -containing GABA_A receptors keeps the resting membrane potential of TC neurons hyperpolarized and facilitates rebound bursting in response to phasic inhibition (125). Tonic inhibition is caused by vesic-

ular GABA release (79) and by ambient levels of taurine (304). There may also be regulatory interactions between GABA_A receptor- and GABA_B receptor-dependent signaling mechanisms (117). Together, TRN burst discharge provides strong and synchronous inhibition of TC cells, which is critical for spindle-like thalamic rhythms. The studies detailing the molecular identities of GABA_A receptors also indicate that nonsynaptic receptors could represent a pharmacological target to enhance sleep spindles specifically when TRN discharges preferentially in bursts (518) (sect. XIA).

4. Rebound excitation in TC cells

TC cells generate rebound burst discharge in response to IPSPs arriving from TRN (46). TC bursting is shorter, more stereotyped, and occurs over a more restricted range of membrane potentials (less than about -65 mV). Therefore, when a spindle initiates, TC bursting often does not occur until several IPSPs are received. TC cells thus need to be trained into bursting through TRN inhibition. The burst characteristics of TC cells arise from the $\text{Ca}_v3.1$ channels (20, 296, 363) that are most highly expressed in primary dendrites (648). Once activated, the TC-TRN synapse releases glutamate with high release probability to activate non-GluA4-containing AMPARs (234, 426, 475) as well as GluN2B- and GluN2C-containing NMDARs (33) (FIGURE 8, “Synapse 3”). TC axons give off collaterals in the TRN on their way to the cortex (11, 209, 223) and produce a topographic innervation of TRN (345). The TC-TRN collaterals of first-order thalamic nuclei mostly occur in an open-loop manner, such that TC cells project to TRN cells adjacent to the ones by which they were originally inhibited. These open-loop circuitries allow for a lateral spread of glutamatergic excitation within TRN that can sustain a propagation of spindle-like rhythms (320, 322). There is only a small fraction (<10%) of closed-loop projections between TRN-TC cell pairs (234, 273, 323). The fraction of TRN cells receiving input from more than one thalamic nucleus is also minor (345). Together, primary thalamic circuits support local spindle-like rhythms that can initiate in single or few connected TRN-TC cell pairs and spread laterally. In comparison, this type of rhythm generation seems weaker in higher-order thalamic nuclei (610) (sect. VE).

FIGURE 8. Molecular properties of four major synapses that underlie robust sleep spindle generation within thalamus and cortex. The thalamocortical (TC) circuitry is shown schematically on the left, with numbers 1–4 pointing to the four synapses for which structural and molecular details are schematically illustrated on the right and below. Details of TC-corticothalamic (CT) and CT-TC synapses are not illustrated here, although also important for spindle generation. For the selected glutamatergic synapses, the focus is on the molecular composition of AMPA and NMDA receptors. For the GABAergic synapses made by thalamic reticular nucleus (TRN) cells on TC cells, these concern the molecular composition of GABA_A receptors. Note that molecular details are listed only for subunits for which roles in receptor properties and/or localization were recently identified. Note further that illustrations point to the clustering of presynaptic terminals in the case of corticothalamic synapses made onto TRN cells, and for the multiple release sites formed by single TRN terminals onto TC cells. Cx, cortex; PV, parvalbumin. For cortex, layers 1–6 are schematically indicated. A single triangle symbolizes thalamorecipient layers 4–6, but corticothalamic feedback arises from layers 5 and 6. [Synapse cartoons are adapted and modified from Servier Medical Art (CC BY 3.0).]

C. Synchronization

We discuss here intrathalamic and corticothalamic mechanisms that favor or constrain synchrony in thalamic circuits (**FIGURE 7**, “Synchronization”). At the beginning of a spindle, TC cells receive comparatively weak IPSPs and discharge bursts inconsistently, but both processes strengthen towards the middle of a spindle. More TRN cells thus discharge synchronously at this point, causing stronger inhibition and more reliable rebound (48, 320, 518). Still, recordings from individual TC cells in the slice (46) or during natural sleep in mouse (48, 610) show that synchrony is limited: IPSPs are variably sized and a TC cell discharges a burst not more than once or twice during a spindle. Thalamic network synchronization appears thus comparatively modest, indicating that robust mechanisms limiting synchrony are in place.

1. Mechanisms promoting synchrony

Because of its strong control over TRN cells, cortical input is very important for the spatial and temporal synchrony of thalamic spindle rhythms (123). The majority of corticoreticular projections arises from layer 6 neurons of the corresponding cortical column (75, 76, 166, 223, 387, 515, 601). Corticoreticular projections are topographically aligned and form terminal axonal arborizations in the shape of “slabs” of dense innervation that cover portions of the longitudinal extent of TRN sectors (75, 76, 116, 137, 387) (sect. VE). Sleep spindle synchrony may thus occur along sectorial boundaries and lead to predominantly local spindles (sect. VIC) that may propagate secondarily (123). When cortical synchrony is high, such as in anesthesia (119, 168), TRN sectors may be simultaneously recruited and lead to more global spindles. However, it is largely unclear how the extent and temporal sequence of TRN sector recruitment contributes to the spatiotemporal patterns of EEG sleep spindles.

Within thalamic circuits, an important prosynchronizing mechanism is the open-loop wiring between TC and TRN cells. Several TRN cells adjacent to the one that first discharged in bursts receive excitatory synaptic potentials (EPSPs) from TC cells, such that more TRN cells become recruited and spindle activity starts to engage larger thalamic territories (322). Additional synchrony may be provided by dendro-dendritic contact sites between TRN neurons that were found in cat (65) and rat (151, 165, 493, 655). An important role is played by gap junctions that were described morphologically (165, 466, 493, 655) and through identifying the gap junctional connexin-36 proteins. These proteins were so far described in parvalbumin-expressing TRN cells, where they are located on closely apposed portions of TRN dendrites and in vicinity to asymmetric, presumably glutamatergic synapses (377). Gap junctional coupling is stronger for burst rather than single action potential discharge due to the low-pass filtering

properties of the gap junctions (351, 382). The organization of gap junctional contacts across TRN shows a prevalence within sectors, whereas axo-dendritic connections could reach beyond sectors (160). In the somatosensory sector of young rodent, groups of about nine TRN neurons were typically coupled by gap junctions (364). The majority of these groups were oriented along the slabs, but there was also coupling across slabs. Gap junctions could help synchronize spindle-like rhythms within TRN sectors. The strength of gap junctions can be regulated both through acute activation of metabotropic glutamate receptors (382) and in the long term (350), suggesting that excitatory activity such as that associated with wake-related experience and learning modifies the electrical coupling of TRN cells (sect. VIIIA).

2. Antisynchronizing mechanisms

TRN cells inhibit each other through both GABA_A and GABA_B receptors (521, 605) and via axo-dendritic synapses that were found in rat (466, 563), ferret (521), cat (165, 294, 530, 655), and monkey (30, 649) and that involve $\alpha 3$ - and $\beta 3$ -containing GABA_A receptors (107, 217, 288). Weakened antisynchronizing mechanisms are a common denominator in several forms of generalized epilepsies (sect. XB). Lateral inhibition acts in a twofold manner (217). First, inhibition provokes transient membrane hyperpolarization (160, 521, 551) and/or shunting of excitatory events (606). Second, lateral inhibition shortens the duration of TRN cell burst discharge (45) or prevents it entirely (558). The important antisynchronizing action of lateral inhibition is amply demonstrated through genetic or pharmacological means (288, 521, 559, 622, 632). A strong case for axonally mediated lateral inhibition in adult TRN was made for the *scn8a* gene that encodes the Na⁺ channel Nav1.6 (399). This channel is hypofunctional in some non-convulsive epilepsies in humans. Selective suppression of *scn8a* gene expression in mice produced axonal propagation failures specifically in intra-TRN collaterals and spike-and-wave discharges (SWDs), a hallmark of generalized epilepsy (sect. XB). An additional important antisynchronizing contribution is provided by the astrocytic release of endozepines that are ligands for the benzodiazepam-binding site of synaptic GABA_A receptors (107). Endozepines tonically potentiate synaptic inhibition in TRN, and they suppress SWDs. Similarly, pharmacologically strengthening intra-TRN inhibition through the antiepileptic benzodiazepine agent clonazepam blocks SWDs (287, 558, 559).

The TRN cells stain positively for a number of neuropeptides, including in particular neuropeptide Y that is released from mouse TRN cells upon high-frequency stimulation and that produces a slow, second-long membrane inhibition in synaptically connected TRN cells (577). Somatostatin expression was also verified for human, primate, feline, and mouse TRN cells (55, 87, 251, 464), with the peptide localized in dendrites in rat (578). Exogenous application of

somatostatin exerted antioscillatory effects through both pre- and postsynaptic mechanisms (578). As somatostatin-expressing TRN cells appear to constitute a neurochemically and functionally separate group of TRN cells that does not or only partially overlap with the ones expressing parvalbumin (13, 113), there could be cellular subtype-specific forms of lateral inhibition. There is also evidence for anti-synchronizing effects by thyrotropin-releasing hormones (80), cholecystokinin (130), and prolactin-releasing peptide (373), which modulate cellular membrane potentials. The potential of these, and other, modulatory substances for sleep spindles is currently underexplored but likely powerful. Neuromodulation through neuropeptides also involves TC neurons (for review, see Ref. 414).

D. Termination and Refractory Period

A sleep spindle is limited in duration to 0.5–3 s and followed by a refractory period of 5–10 s. Through refractory periods, sleep spindle recurrence is limited in time over intervals of seconds. Refractory or silent periods were demonstrated for spindle waves in brain slices (44, 394), for evoked spindles in anesthetized cat (120), and for human NREMS (561). Sleep spindle termination and the subsequent generation of a refractory period probably arise from a combination of intrathalamic, cortical, and brain stem mechanisms (FIGURE 7, “Termination”). The exact timing of sleep spindles is probably relevant in the orderly replay of memory traces (sect. VIIIB), as also noted in recent inferential studies (sect. XIB).

1. Thalamic mechanisms

Repetitively bursting TC cells generate an afterdepolarization *in vitro* that decays slowly over 5–20 s (44, 370) and that suppresses rebound burst generation in TC cells (44, 394). The afterdepolarization is mediated through a persistent activation of hyperpolarization-activated cation-non-selective (HCN) channels (44, 395, 397). The signaling mechanism involves Ca^{2+} entry via $\text{Ca}_v3.1$ channels followed by Ca^{2+} -mediated cAMP synthesis that activates cAMP-sensitive HCN channels and stabilizes their open conformation (396). HCN channel subunit expression is variable across thalamic nuclei in rodents (315), with the slow and highly cAMP-sensitive HCN4 subtype enriched in somatosensory thalamus, which contributes to strong sleep spindles in rodent somatosensory cortex (sect. IVA). Another process contributing to sleep spindle termination and refractoriness is a gradual hyperpolarization of TRN cells during repeated cycles of bursting that is caused by Ca^{2+} - and Na^+ -dependent K^+ currents in ferret (321). Indeed, the number of action potentials per TRN burst decreased during a spindle in naturally sleeping rat (48).

2. Cortical mechanisms

A computational study suggested that cortical desynchronization could attenuate the driving role of cortico-

thalamic input for thalamic spindle-like rhythms and contribute to their fading away (71). An increased jitter in simultaneous recordings of cortical and TRN units supports this possibility (230, 482, 611), but the proposed weakening effect on thalamic circuit reverberations could not be seen in simultaneous unit recordings from TRN and TC cells (48).

3. Brain stem mechanisms

Unit activity in locus coeruleus, the major site of noradrenergic afferents into the TC system, decreases before an EEG spindle in sleeping rat and rapidly increases towards its end (32). This suggests that noradrenaline release could initiate sleep spindle termination. This possibility is supported by optogenetic stimulation of locus coeruleus during hippocampally measured sleep spindles (580).

E. Heterogeneity in Thalamic Sleep Spindle-Generating Circuits

In addition to primary thalamic nuclei, the TRN also innervates higher-order, midline, and intralaminar thalamic nuclei, but their engagement in sleep spindles has not been studied systematically. Connectivities and densities of TRN innervation are, overall, lower in these nuclei. Additionally, not all TRN sectors are equal. The purpose of this section is to point out that such heterogeneities could give rise to heterogeneity of cortical sleep spindles. In addition to TRN, there are other sources of heterogeneity. An influential proposal classified monkey TC projections into core and matrix pathways based on whether they innervated cortical areas focally in layer 4 or more diffusely and predominantly in layer 1 (310). This subdivision comprises the sensory first-order nuclei within the core and the intralaminar nuclei within the matrix. In humans, current-source density analyses indeed point to possibly two sources for cortical sleep spindles (see sect. VIB). In mouse, in contrast, higher-order thalamic nuclei seem to be relatively poorly engaged in spindle-like rhythms (610).

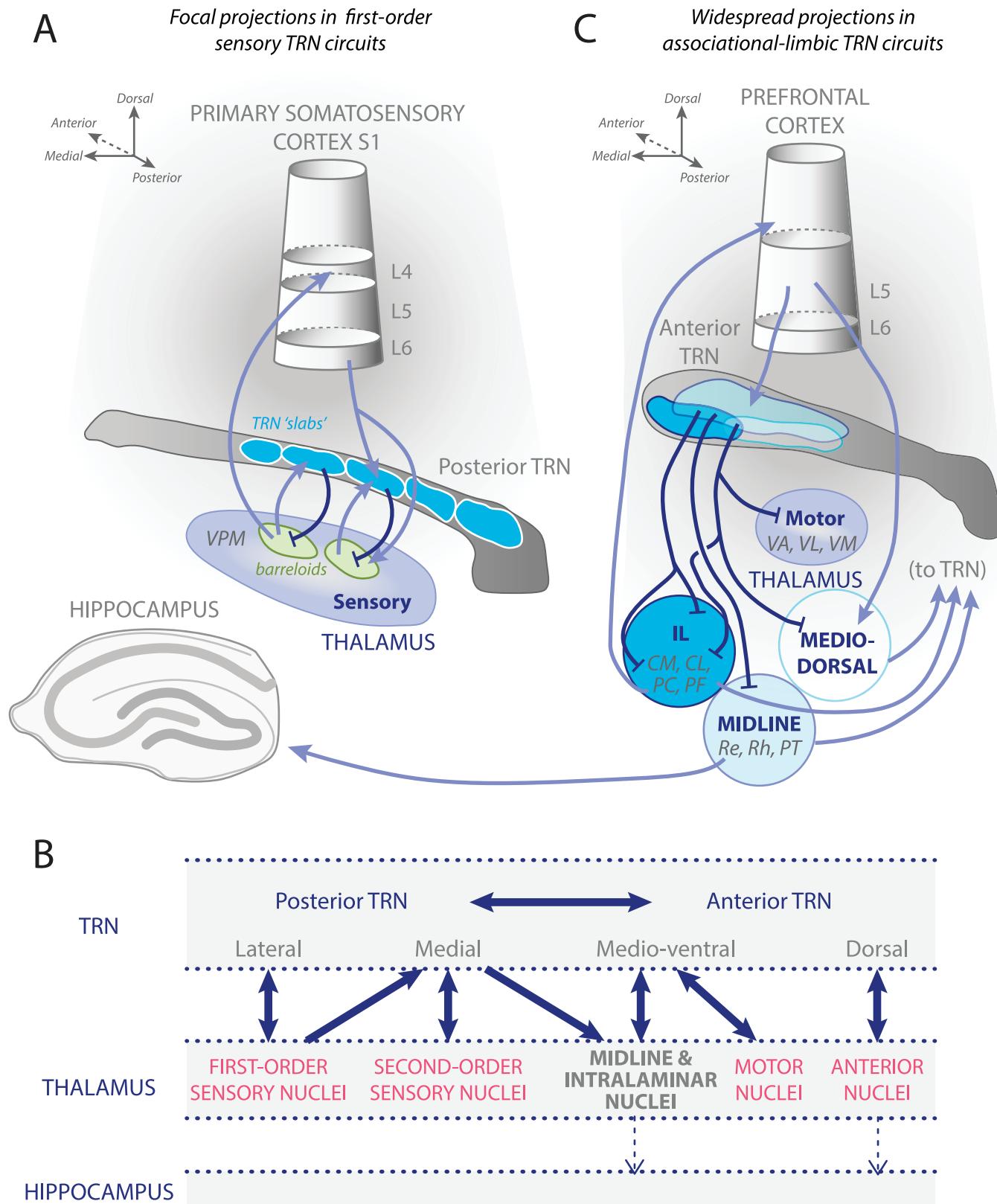
1. Cellular heterogeneities

TRN cells show several cytoarchitectonic differences in carnivore (109, 389), rabbit (389), and rat (389, 512, 562). Small cells form more diffuse axonal arborizations that do not respect the boundaries of thalamic barreloids, whereas larger cells form highly focal projections within barreloids (129). Different dendritic arborizations correlate with the preference of synaptic over electric coupling (160). These morphological observations are the first evidence that not all TRN cells may be equally engaged in sleep spindle generation.

Heterogeneities also exist in electrophysiological characteristics. Nonbursting TRN cells were first found in the ros-

tralateral sector of the urethane-anesthetized cat (118) and in rat slice preparations (84, 365). Visually responsive TRN cells projecting to the first-order dorsal lateral geniculate nucleus showed a higher burst propensity than cells project-

ing to the higher-order lateroposterolateral nucleus (324). Furthermore, somatosensory TRN cells showed many release sites when focally projecting and only a few release sites when diffusely projecting (129). With the use of optogeneti-



cally guided identification of TRN sectors, burst discharge was found to be strong in somatosensory and auditory sectors of TRN and weak in sectors innervated by the mediodorsal nucleus (204). Burst discharge propensity, critical for generating vigorous inhibition, thus seems more pronounced for sensory sectors at least in rodents. Furthermore, mouse TC cells in first-order somatosensory thalamic nucleus received clear repetitive IPSPs during NREMS, whereas these were barely evident in higher-order somatosensory nuclei (610). Heterogeneities in TRN bursting could lead to varying strength of spindle-like rhythms and could determine the spatial distribution of cortical sleep spindles (sect. VIC).

TRN cells are now divided into two largely separate groups according to the expression of the neurochemical markers parvalbumin or somatostatin, as demonstrated immunohistochemically (109, 143, 251, 311, 464) or through the use of Cre-reporter lines (13, 113). Parvalbumin-expressing cells burst more vigorously than somatostatin-expressing cells and their optogenetic activation provoked more robust field potential oscillation in the cortex (113). The detailed projection patterns of these cells seem to be substantially overlapping, but also partially complementary, with parvalbumin-expressing cells projecting primarily into first-order sensory thalamic nuclei, whereas somatostatin-expressing cells additionally target intralaminar nuclei. There could also be sector-specific differences in corticoreticular innervation (13, 113). These properties render parvalbumin-expressing TRN neurons most apt to promote thalamic spindle activity locally, whereas somatostatin-expressing TRN neurons could act more globally across thalamic nuclei, providing possible cellular correlates for “global” and “local” sleep spindles (sect. VIC).

2. Heterogeneities in synaptic connectivity

Further heterogeneity arises from anatomical and functional studies of TRN innervation of different dorsal thalamic nuclei. These heterogeneities are critical for the cortical organization of sleep spindles and may additionally contribute to species differences.

Primary sensory sectors of TRN provide focalized and dense projections, with the large majority of TRN cells

targeting exactly one nucleus in a topographical order (489, 492) (FIGURE 9A). For example, a TRN cell being part of the receptive field of a mouse whisker forms an axonal arborization that is in precise alignment with the corresponding thalamic barrelloid in the ventral posterior medial nucleus (167). These focal cells are additionally interconnected by gap junctions (364). TRN cells projecting to higher-order thalamus are located in the same sector as the first-order projecting cells, but are located more medially (490, 492) (FIGURE 9B). Axons reaching higher-order nuclei tend to have a lower density of terminal arborizations and fewer putative contact sites (490). Focally projecting cells were also found in cat visual TRN (601), whereas somatosensory TRN neurons arborized in both first- and higher-order nuclei (655). In cat and monkey, but not in rodent, local interneurons are additionally present in first-order thalamic nuclei (29) that are targeted by cortical, reticular, or thalamic afferents (546). Primary TC circuits in rodents are thus principally wired for local spindle-like rhythms. In contrast, in higher mammals, TRN inhibition is to a larger extent shared between thalamic nuclei, which could generate spatially more extended sleep spindles.

The motor sector of the TRN is located in an anteromedial to ventral position (347, 492). The TRN sector projecting to ventral anterior and lateral thalamic motor nuclei also projects to the intralaminar centrolateral and the mediodorsal nucleus (346). Shared inhibition between intralaminar and motor nuclei is also present in cats (502), possibly giving rise to spindles that cover both motor and prefrontal cortical areas.

The TRN sectors projecting to intralaminar and midline thalamic nuclei occupy most of the rostral pole of the nucleus. There is a substantial overlap with cells projecting to the mediodorsal nucleus, and projections are made through small terminal arborizations (127, 332, 492) (FIGURE 9C). There is notably a set of TRN neurons in the anteroventral portion that project to the rhomboid and reuniens thalamic nuclei (332), which reportedly project to hippocampus (103). There is additional evidence for cross-modal inhibition between sensory, motor, and intralaminar nuclei of the dorsal thalamus in young rodent (136). The innervation of intralaminar nuclei by TRN, notably the central medial and the central lateral nuclei, seems particularly dense in the cat

FIGURE 9. Heterogeneity in the wiring of thalamic reticular nucleus (TRN) circuits across its different sectors. *A*: wiring diagram for the somatosensory TRN sector in rodent. Note that this sector forms topographically organized and reciprocal connections with the corresponding sensory thalamus, the ventroposterior medial nucleus (VPM). This topography is evident as focalized reciprocal connections between portions of the TRN sector (“slabs”, blue areas with white borders) and the thalamic barrelloids (green areas). The vast majority of TRN cells in this sector project only to VPM. *B*: schematic wiring diagram between different TRN sectors in rodent that is based on anatomical and functional studies. Double-headed arrows show reciprocal interactions, and single-headed arrows show unidirectional projections indicative of open-loop connectivity. Dotted arrows point to anatomically identified projections towards hippocampus. *C*: wiring diagram for associational-limbic TRN sectors. Note that sectors overlap and TRN cells may project to more than one thalamic nucleus. In particular, motor thalamic nuclei are innervated by TRN cells located in associational-limbic sectors. IL, intralaminar nuclei; CM, central medial nucleus; CL, central lateral nucleus; PC, paracentral nucleus; PF, parafascicular nucleus; Re, reuniens nucleus; Rh, rhomboid nucleus; PT, parataenial nucleus; VA, VL, and VM, ventral anterior, lateral, and medial motor nuclei, respectively.

(574), and vigorous spindle-like rhythms were observed in cat central lateral nuclei (473).

The anterior thalamus is part of the limbic circuits (299) and innervated by the anterodorsal portions of TRN (243, 244). Optogenetic stimulation of these areas produced spindle-like activity in prefrontal cortex and hippocampus (354), suggesting a pathway that links thalamic to hippocampal spindles. In support of this possibility, limbic TRN cells are active during NREMS (264, 482) and hippocampal spindles were phase-linked to SOs in anterior thalamus in a human focal epilepsy patient (523).

F. Outlook

Reciprocal synaptic circuits between TRN and TC cells are the basic functional unit in which thalamic sleep spindle rhythmicity emerges. How and where are such units active in the heterogeneous networks formed by cortex, TRN, and thalamic networks? We know little about when thalamic spindle rhythms arise locally, within a few reciprocal TC-TRN cell groups, or about the conditions that can lead to activation of entire or several TRN sectors. These spatial dimensions are some of the principal determinants of the cortical territories engaged by sleep spindles. Invasive recordings from diverse types of thalamic nuclei and subnetworks of TRN cells in rodent are a valuable step to clarify the conditions that lead ultimately to local or global cortical sleep spindles. The spatial confinement of spindle rhythms within or across thalamic nuclei, the particular roles played by simple sensory versus more complex thalamic nuclei, and the recruitment of TRN subnetworks are central to understanding their manifestations at the cortical level and alterations of these as a result of learning or disease.

VI. CORTICAL STATES AND THEIR ORIGINS

Modern neuroscience techniques now replace the classical view of sleep spindles as sinusoidal electrical signals with the description of a distinct profile of neuronal activity across cortical layers. This profile is caused by the rhythmic synaptic currents generated by repeatedly bursting TC axons. We discuss here how TC excitatory input transforms excitation and inhibition across layers and affects activity of pyramidal cell dendrites. Sleep spindles, in part also together with other sleep rhythms, induce a specific cortical state that alters the way information is transformed and routed. Its elucidation in cellular and synaptic terms is a prerequisite to understand the diverse roles of spindles for the brain.

A. Recruitment of Cortical Circuits

1. Anatomy of the TC microcircuitry

TC monosynaptic projections relay thalamic activity to cortex. The detailed wiring is well-described for rodent barrel cortex (202), but general principles apply to many major first-order TC circuits in mammals. Briefly, TC cells project monosynaptically to excitatory regular-spiking neurons of probably all cortical layers. The majority of synapses is formed between layers 3–6, with peak synaptic bouton densities established in layers 4 and 5B (for review, see Ref. 520). Monosynaptic projections from thalamic nuclei to cortex additionally recruit a feedforward inhibitory circuit through predominantly fast-spiking interneurons intercalated in disynaptic pathways (140, 226, 302, 327, 496, 532, 569). Parvalbumin-positive interneurons discharge action potentials with a high probability upon arrival of a TC impulse (43) (**FIGURE 8**, “Synapse 1”). Among the several structural and synaptic mechanisms involved, the expression of AMPARs lacking the GluA2 subunit provides rapid activation kinetics and a high single-channel conductance. In comparison, the impact of TC synapses on principal excitatory neurons is lower. An analogous feedforward inhibitory wiring exists for higher-order, motor, and mediodorsal TC circuits. Here, synapses are predominantly made in upper cortical layers (36, 53, 162, 496). In the case of intralaminar nuclei, TC projections innervate interneurons in outer portions of layer 1 (139). In principle, there thus exist several TC projection systems with several cortical target layers within which sleep spindles can be generated. Possible consequences of more than one TC projection system have been explored computationally according to a subdivision into “core” and “matrix” projections (sects. VE, and VIB).

2. Activation of cortical interneurons by sleep spindles

During thalamic spindle activity, many TC cells discharge bursts, which leads to repeated release of synaptic glutamate onto their cortical targets (33, 217, 286, 414, 572). Temporal summation of synaptic inputs is more rapid and sustained for parvalbumin-expressing feedforward interneurons than for principal excitatory cells (282). Therefore, excitatory neurons will receive a dominant disynaptic inhibition that curtails the direct monosynaptic excitation (**FIGURE 10**). Consistent with this, discharge patterns of principal neurons in rodent prefrontal, secondary motor, parietal, or auditory cortices were weakly modulated during sleep spindles (38, 482, 542, 543), whereas fast-spiking interneurons increased discharge rates vigorously and in a phase-locked manner (38, 482). Strong phase-locking between spindle-activated principal neurons and interneurons consistent with feedforward recruitment was also found in human intracranial recordings in temporal lobe (483) and for layer 2/3 in rat motor cortex (38). Many cortical

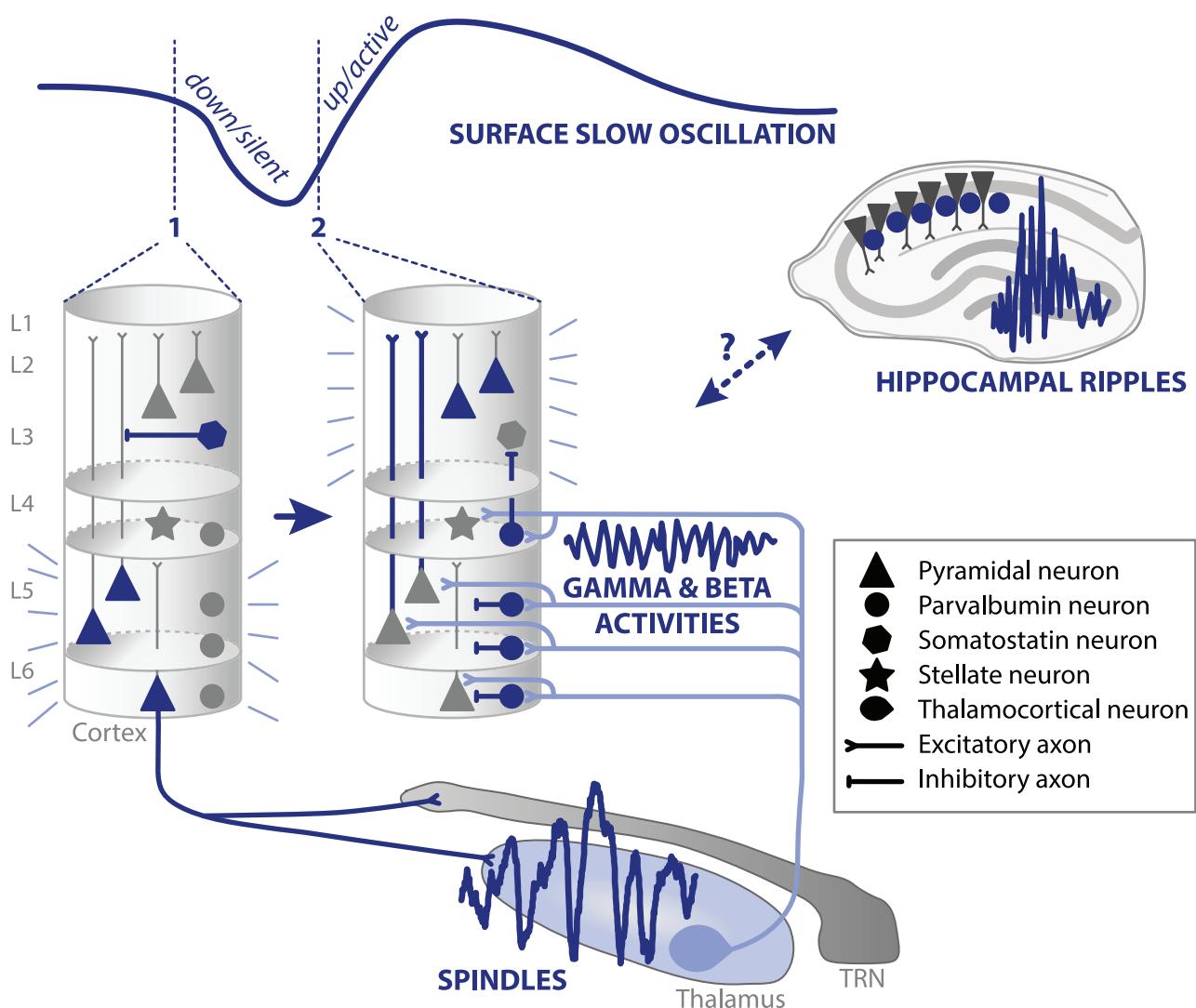


FIGURE 10. Overview of putative cortical state induced by sleep spindles generated on the active state of the slow oscillation. Cortical columns are schematically depicted with cell types symbolized as indicated. Dark blue labeling denotes activated states (action potential discharge in somata, elevated intracellular Ca^{2+} levels in dendrites). Note that sleep spindles recruit feedforward inhibition in deep cortical layers. This leads to inhibition of pyramidal cell somata and an increase in dendritic activity, presumably through parvalbumin neuron-mediated inhibition of dendrite-targeting somatostatin neurons. For simplicity, the cell bodies of these neurons are depicted only for layers 2/3. Additionally, thalamocortically mediated sleep spindle activity may trigger beta and gamma rhythms in cortex. How these rhythms coordinate with hippocampal ripples remains open, as schematized in the figure.

parvalbumin-positive interneurons inhibit somatostatin-positive interneurons, among which some target the apical dendrites of cortical pyramidal neurons. As a result, dendrites will become relatively disinhibited. Altogether, burst of action potentials arriving in TC axons impact on both the excitation-inhibition balance within cortex and on dendritic excitability. Recordings obtained under anesthesia support the idea of a rapid, and possibly differential, recruitment of inhibitory neuronal classes (121, 271). Most direct evidence was provided by two-photon Ca^{2+} imaging of genetically identified neurons residing in layer 2/3 over sensorimotor areas (451). Parvalbumin-positive cells were activated, while the activity of somatostatin-positive cells within the same layer instead became suppressed. Additionally, when there was a SO-spindle event

(sect. VIE), the differential regulation of parvalbumin- and somatostatin-positive interneurons was preceded by a relatively stronger activation of principal cell somata, suggesting that somatic spikes precede dendritic disinhibition. These would be conditions potentially favoring spike-timing-dependent plasticity. Additionally, intracortically projecting layer 6 cells could convey inhibition, but their NREMS activity patterns are not known (74).

3. Modulation of dendritic activity by sleep spindles

Alterations in dendritic activity result from a spindle-specific regulation of cortical inhibitory circuits (FIGURE 10). Dendritic activity was first implied in sleep spindles based

on local cortical recordings in barbiturate-anesthetized (92) and “encéphale isolé” cats (300) and on modeling work (121). Through fiber-optic Ca^{2+} imaging in rat apical dendrites of upper cortical layers, dendritic Ca^{2+} levels for layer 5, but not layer 2/3 apical dendrites, were shown to correlate tightly with the time course of sigma and beta (16–30 Hz) power (542). This correlation evolved on the time scale of tens of seconds, suggesting that the grouping of sleep spindles on the infraslow time scale is linked to dendritic excitability (sect. IVE). This is an important step forward showing that spindle-rich periods generate a unique cortical state to which dendritic activity contributes.

B. Current-Source Density Profile

Current-source density analysis localizes the electrical sinks and sources generated by synchronous synaptic activity. Sleep spindles in rats produce a sink in deep layers during spindle troughs (556), which corresponds to TC afferents targeting primarily deep cortical layers. Recent laminar recordings of human frontal or temporal lobe sleep spindles, however, detected two types of sinks in middle and upper cortical layers, corresponding respectively to layer 5b and layer 2/3 pyramidal cells (261). This could be explained by two different TC projection systems acting as a source for cortical spindles, such as the different projections of first-order and higher-order thalamic nuclei. Earlier divisions of TC projection systems into core and matrix systems in primate support this possibility computationally (310) and suggest that EEG primarily samples the surface-projecting core projections (70).

C. Global and Local Sleep Spindles

The fine spatial distribution of sleep spindles is smoothed by the spatial averaging properties of EEG sleep spindles (222). Still, it is the EEG that has shaped the view of sleep spindles as globally synchronous brain events (2, 120), while local spindles were attributed to pathological conditions (122, 249). True sleep spindle distributions are, however, likely highly nonuniform, as now indicated by recording techniques that capture spatially more confined signals. The current major division between “local” and “global” events is based on whether or not they appear on all or just a few sites of a given multisite recording configuration, such as a grid of regularly spaced electrocorticogram electrodes (479, 485) or a set of independent intracranial field and unit electrodes targeted to specific areas (23, 453, 479). In humans, sleep spindles were found throughout the majority of the cortical surface, with overall highest sleep spindle densities in frontal cortices and over the somatomotor and visual regions and lower levels in temporal lobe (23, 485). Spindles appeared singly in one of several cortical areas and independently between ipsi- and contralateral sites in >50% of the cases (23, 453, 479). Magnetoencephalogra-

phy (MEG)-guided source reconstruction supports the idea of local spindles through showing that surface events coincided with multiple asynchronous sources (158). However, electrodes spaced at smaller and more regular distances also identified more global spindles, in particular over prefrontal and superior temporal gyrus (485). Over the course of NREMS during a night, only about two-thirds of local spindle events were linked to the local SO, with the tightest coupling for fast centroparietal spindles (23). Local sleep spindles showed a propagation along preferential pathways involving frontal and temporal lobes (441, 485), an observation that could have implications for the phase-locking between sleep spindles and ripples (sect. VIE). It is fair to conclude from these data that, in spite of the limited resolution of multisite recordings, spindles appear to be a mostly local sleep event. This sets them apart from SOs that appear globally for major portions of deep NREMS (23, 453). Local sleep spindles are widely distributed across the cortical surface and show characteristics and density that are region- and lobe-dependent. More global events preferentially occur in frontal-temporal regions, and it is in these that sleep spindles may propagate.

D. Fast and Slow Sleep Spindles

Gibbs and Gibbs (237) classified human spindles into two or three types, which they named fast, intermediate, and slow spindles based on the location of the sigma power peak around 14, 12, and 10 Hz. Borders between fast and slow spindles are commonly set around 13 Hz, but they vary between studies, while intermediate spindles are no longer used for classification. This distinction is additionally linked to location: spindle-related power with a spectral peak around 14 Hz is located posteriorly, whereas slow spindles between 10 and 12 Hz are located anteriorly (237). The fast spindle peak is prominent in N2, and the slow one appears variably in N2 and/or N3 (sect. IVA). From the moment of falling asleep to the onset of SWA, local, fast, and centroparietal spindles are initially generated, whereas slower, more anterior, and more global spindles are found later (553) (FIGURE 4). However, there seems to be no clear border between fast and slow spindles but rather a continuum of frequencies from parietal to frontal areas (479, 485). Fast and slow spindles were also observed in intracranial and foramen ovale recordings (23, 112, 479), supporting their existence in local, deep brain areas, in particular in hippocampal, parahippocampal, and entorhinal areas (23, 445, 479, 485).

On the basis of differences between fast and slow spindles regarding their genetic determinants (sect. IIIA), their spatiotemporal appearance during NREMS (sect. IVA), their local and independent appearance (453), their homeostatic and circadian regulation (sect. IV, B and C), sex differences (sect. IVD), pharmacological regulation (39, 306), profiles across the lifespan (sect. VII), hemodynamic correlates (see

below), coupling to the SO and hippocampal ripples (sect. VI^E), and roles in memory formation (sect. VIII), it has been argued that they may arise from different sources and constitute separate TC events. Source-reconstruction analysis through nonstationary fitting (661), low-resolution brain electromagnetic tomography (18, 553), or principal component analysis (619) indeed points to two cortical sources for spindles that are located posteriorly, in superior parietal regions, and anteriorly, in lateral frontal regions. The precuneus, a higher-order sensory area, appeared as a source for fast spindles and the prefrontal cortex for slow spindles (18, 553).

Compared with EEG in which source localization is highly approximative, MEG signals can more faithfully help to determine local sources of current dipoles, because magnetic fields are less distorted by the resistive properties of the biological tissue than the extracellular field electrical potentials, permitting millimeter resolution. MEG data revealed multiple sources for EEG spindles that seemed active in close temporal and spatial succession (388), occasionally associating a spindle with up to 15 underlying sources (158, 549). MEG also showed that two similarly looking spindles detected at one EEG lead had different origins, amplitudes, and phase relationships (158). Moreover, spindles detected via MEG but not EEG indicated that they might occasionally be generated without reaching the cortex (404). MEG data also suggest that some fast and slow spindles might arise from a joint source developing sequentially (256, 609). Thus a large, posteriorly located power at fast frequencies could be active early in a spindle, whereas power in the slower range would rise later and more anteriorly (157, 326). A single spindle might thus arise along a postero-anterior direction of a single thalamic spindle generator. This is a plausible possibility given the multiple and heterogeneous thalamic nuclei that could potentially contribute to a spindle, and wherein propagation from more posterior sensory to more anterior nonsensory areas has been proposed (sect. VE).

Although rodents do not show clearly distinct fast and slow spindles, recent rodent work suggests that thalamic mechanisms may indeed shape spindle properties. In mouse, sleep spindles appear fastest and largest over somatosensory cortex for which the corresponding TRN sector showed highest oscillatory burst discharge propensity (204). In contrast, anterior spindles were slower and connected to TRN sectors with weaker burst capacity. Surface spindle characteristics may thus effectively be co-determined by the properties of the thalamic pacemakers present within the same TC loops (sect. VE).

fMRI measures region-wide changes in oxygen consumption in response to neuronal activity. The temporal resolution of fMRI is low, but it has provided correlative insights into sleep spindle origins based on hemodynamic correlates.

These data support a common origin for both spindles in thalamus but different activation patterns in cortex. Both spindle types shared activation of anterior cingulate cortex and the left insula (22, 525), but fast spindles expanded more broadly across cortex, showing strongest activation in sensory-motor cortices, supplementary motor areas, and portions of motor-related cingulate cortex, whereas slow spindles correlated mostly with activity in superior frontal gyrus. Additionally, the temporal synchrony of fMRI signals was strong between the cortical network activated by fast spindles and the hippocampus (525) and the subiculum (22), a component of the limbic circuit. These patterns support a differential propagation of thalamic spindle rhythms towards their cortical targets, although the resolution was probably not high enough to differentiate between different thalamic regions of activation. Overall, the findings are also consistent with a differential recruitment of sensory and associative TC loops during thalamic spindle rhythms (sect. VE) (FIGURE 9B). Later studies including drug-treated and partially sleep-deprived epileptic patients and less rigidly defined spindles reproduced some of these findings (96, 599).

The existence of possible alternative spindle pacemakers has been revived with the observation that the zona incerta, a ventral continuum of the TRN, can generate rhythmic activity in the sigma frequency range, in particular upon stimulation of the central thalamus (376). As the zona incerta is just one of several extrareticular sources of thalamic inhibition forming giant synapses (263), the possibility exists that extrathalamic sources contribute to power in the sigma frequency band, and to fast versus slow spindles.

E. Temporal Coordination with Other NREMS Rhythms

1. Coupling to the cortical SO

Across species, sleep spindles are found time-locked to particular phases of the SO, generating a cross-frequency phase-amplitude coupling that is considered essential for brain communication and plasticity (FIGURE 10). The SO is a spontaneous, ~0.5–1.5 Hz rhythmic activity pattern during NREMS that originates in the recurrent networks of cortex, whereby spontaneous activity in layer 5 cells acts as a trigger (522, 573). During the SO, excitatory and inhibitory neurons throughout cortical layers engage into recurring “active” and “silent” states. Corticothalamic projection neurons can recruit thalamic sleep spindle circuits (sect. V, B and C), giving rise to a temporal sequence whereby the active state of a cortical SO is accompanied by a sleep spindle.

In naturally sleeping mice (204, 319), rats (433, 556), and humans (1, 434), 50–70% of all sleep spindles measured through EEG or LFP recordings occur consistently in tem-

poral alignment with the active state of SO and across central and frontal derivations. During N3 sleep, when SOs are strongest, this grouping effect is also evident for the topography of sigma power over the human brain (134). The coupling between SOs and sleep spindles could cause specific excitability changes that favor memory processing (sect. VIII). For example, a SO-spindle event activated cortical pyramidal cells more effectively than a spindle alone (sect. VIA). Moreover, optogenetic triggering of synchronized thalamic activity to mimic spindles during active states of the cortical SO enhanced hippocampal-dependent memory in mice, whereas this was not the case for the silent state (354). An enhanced coupling of SO to sleep spindles was reported in humans after a declarative learning task (432). However, at a local level, spindle-only events also occurred that were independent of the local SO (453). Moreover, these spindle-only events became more frequent in later NREMS cycles, where N2 is prevalent and SOs are more local and smaller. The role of SO-spindle coupling in different sleep stages thus needs to be clarified (sect. VIII, *B–D*).

2. Coupling to hippocampal ripples

Hippocampal sharp-wave ripples contain brief, high-frequency network discharges called ripples (80–100 Hz in humans, up to 250 Hz in rodents) that arise within the feedforward circuitry of the CA1 pyramidal layer during NREMS (89, 229) and that are involved in replay of wake-related hippocampal activity (504). A phase-amplitude coupling between sleep spindles and ripples exists on the time scale of individual spindles and on their infraslow grouping. First, ripples couple to the SO and to sleep spindles on the time scale of seconds, as observed for sleep spindles recorded in prefrontal (552) and somatosensory cortices (556). Hippocampal units fired most after active states of the SOs in deep cortical layers, implying a preferential cortico-hippocampal direction of activation (556). Second, hippocampal units discharge phase-locked to individual spindle cycles detected in the cortex with a precision of tens of milliseconds (556). This tight temporal relationship implies an excitatory pathway from spindle-generating circuits through which hippocampal units can be rapidly recruited (FIGURES 9, **B** AND **C**, AND 10). In support of this, intrahippocampal recordings reveal the existence of spindle-related hippocampal sinks (564, 576) that are phase-aligned with ripples. In the end, a coupling of SO, spindles, and ripples is achieved through the synaptic integration of cortical and hippocampally located rhythm generators. In this process, fast spindles appear to be primarily involved (564). It is noteworthy that this coordination involves only a small fraction of spindles and an even smaller one (<10%) of hippocampal ripples. This minor fraction leaves room for this percentage to be increased in case of enhanced memory processing. Third, spindle and ripple activity are positively correlated on the 0.02-Hz time scale (362, 556). This indicates that recurring NREMS periods of ~25 s du-

ration show a hierarchically organized sequence of rhythms that interface between cortex, thalamus, and hippocampus.

The anatomical pathways underlying the cross-frequency phase-amplitude coupling between SOs, spindles, and ripples are an ongoing topic of investigation. A recent study using high-density electrocorticographic recordings covering frontal, parietal, and temporal cortices suggests that spindles propagate in a counterclockwise direction from frontal to temporal to parietal areas (441). Sleep spindles indeed do invade the hippocampus and generate prominent current sinks in the CA1 hippocampal area, notably in the distal stratum lacunosum moleculare (576), an important site for dendritic integration and synaptic plasticity. Both CA1 and entorhinal cortex pyramidal cells are strongly phase-entrained into the spindle rhythm, suggesting that it is through a cortical-entorhinal pathway that spindle rhythms are relayed into hippocampus. The circuit mechanisms for this propagation are thought to involve midline thalamic nuclei, such as the nucleus reuniens, for which anatomical projections to hippocampal, entorhinal, and subiculum areas were reported (616). An additional pathway could involve anterior thalamic nuclei that also innervate hippocampus (sect. VE) (FIGURE 9*B*).

3. Coupling to beta and gamma bands

Spindles trigger increases in power in the beta (from 15 to 25 Hz) and the gamma band (from 25 to 100 Hz) as they occur on the active state of the SO in rat, cat, and human (134, 434, 566, 614). Both phase-coupling and amplitude modulations are strongest at sites of greatest EEG spindle activity and variable for high (40–80 Hz) and low gamma frequencies (30–40 Hz) (40). These phase relationships are preserved between rodent (482) and human (23, 441). There is some evidence that this phase coupling relates to an ordered recruitment of fast-spiking interneurons in cortex around spindle troughs from both anesthetized rats (500) and sleeping rats (38). In the latter case, unit recordings in rat layer 2/3 secondary motor and parietal cortex identified five subgroups of basket cells that all fired at or slightly before the spindle troughs, but that generated action potential discharge at ripple or gamma frequencies (38).

F. Sensory Gating

Sleep fundamentally alters the way by which the brain responds to sensory input. Sleep spindles play a key role as they involve thalamus and cortex, both of which regulate sensory information flow. Sensory processing during NREMS is not a downscaled version of wake-related sensory processing. Instead, sensory stimuli received by the sleeping brain are constrained such that a behavioral response is suppressed (64, 272), although cognitive processing remains possible to some extent (24, 495). Sleep spindles contribute to both; they are protective against stimuli,

but they are also reactive elements actively participating in NREMS-specific cognitive elaboration.

1. Sleep spindles as protective elements

Tests of arousability in humans and rodents through acoustic stimuli suggest that spindles protect NREMS from being disrupted (148, 246, 650, 652). This is the case for NREMS onset (652) and during N2 and N3 (148). Promoting sleep spindles through benzodiazepines in humans (309) or through genetic overexpression of SK2 channels in mice elevates arousal threshold (650). The 0.02-Hz oscillation correlates with varying behavioral arousability in humans and animals (sect. IVE). In humans, behavioral arousability further correlates with power in the alpha range (8–13 Hz) (417), which also fluctuates on the infraslow time scale but with lower amplitude (362). In undisturbed NREMS, the density of spindles correlates with the duration of N2 stage sleep in human (sect. IVA). Sleep spindles thus shield NREMS from sensory or spontaneous disruption.

Thalamic first-order nuclei represent the first stage of sensory processing, and they have commonly been regarded as a “gate” that closes during sleep. Burst discharge generated during sleep spindles distorts the proportionality between the excitatory input a TC cell receives and its action potential output, and could thus plausibly represent such a gate (415), to which synaptic inhibition by TRN contributes (361). However, sensory evoked responses appear in cortex even in the presence of a spindle (25). This suggests that sleep spindles modify sensory processing at the cortical level.

Early studies found that spindle-rich intermediate sleep in cat modulated the cortical response to direct stimulation of the TC afferent fibers (248). The monitoring of sensory evoked responses while subjects remained asleep revealed that sensory stimuli were actively processed in cortex. Evoked responses are composed of multiple, partially overlapping components that occur at various latencies, reflecting different stages in the sensory reception process (94, 115). Reflective of the sleeping brain’s effort to protect sleep from sensory perturbation are response components with latencies >300 ms (N350, N550, P900 in human) (115, 454) that are typical for central and frontal cortical areas once subjects enter NREMS and stop responding actively to a stimulus. Three studies note that these late components were enlarged when the acoustic stimulus coincided with a spindle (350 ms, 550 ms) (128, 193, 526). In contrast, auditory responses recorded locally in primary auditory cortex of rat were unaltered by the presence of a sleep spindle (543). This indicates that cortical sleep spindles control how sensory information spreads from its site of arrival. Evidence supporting this was found for nociceptive stimuli (108)

or through functional imaging of acoustic evoked responses (146).

2. Sleep spindles as reactive elements

Sensory stimuli themselves modify sleep through interacting with the ongoing oscillations. Various types of nonarousing sensory stimuli increase spindle density during N2 in the cortical areas encoding the sensory stimulus (524), often in combination with a K-complex (N550 potentials) that precedes sleep spindles (25, 150, 267). A refractory period of 2–3 s follows, during which power in the sigma frequency range is suppressed (24) and the probability that another sleep spindle can be evoked is reduced (28). Strikingly, during this refractory window, sensory evoked potentials appeared in motor cortex in case subjects were trained before to execute a motor response to the auditory stimulus (25). This effect was specific for N2 and not seen in N3. The presence of sleep spindles thus generates a cortical state that permits interareal cortical communication, which substantiates interpretations from circuit studies (sect. VIA).

G. Outlook

Major human and animal studies establish sleep spindles as a primarily local event that fundamentally shapes the way the cortex operates. Strikingly, this action on cortex outlasts the duration of individual spindles to cover refractory periods and periods defined by the grouping of spindles on the infraslow scale. As sleep spindles emerge on different spatial scales within thalamus, in a temporally synchronous or asynchronous manner, the scales over which cortical states permitting interareal communication, while prohibiting sensory flow-through, are far from clear. To what extent the cortical SO is involved in this organization is another burning question. Bringing together the striking actions on cortical states with the complexity of the spatial organization of spindles seems a daunting task. Do we need to deal with “default” spindles that bring about cortical states and sensory disconnection more globally to ascertain the NREMS state? Do we have to consider, on the other hand, more specific local events that are coupled to hippocampal ripples to ascertain memory-related functions? Rodents allow a greater range of methods to manipulate sleep spindles locally and to track their spread within and across thalamic nuclei. Creative approaches using combination of opto- and chemogenetics could be a way to elicit local spindles and identify pathways across thalamus and cortex that shape cortical states. Probing through MEG in humans could fertilize these hypotheses, and in turn become inspired by insights from animal experiments.

VII. SLEEP SPINDLES ACROSS THE LIFESPAN

Duration and architecture of sleep change substantially across the lifespan. Not only does the typical amount of time spent in sleep decline from 16–20 h for newborns to 7–8 h in adults and <7 h in elderly, but sleep patterns across the day change and so do times spent in NREMS versus REMS (for basic information, see <https://www.sleep-foundation.org>). These alterations are in part congruent with the fact that the needs for the distinct benefits of sleep, such as restoration, neuroplasticity, and brain development, differ across the lifespan of a mammal. However, the brain also changes in structure and function across ages, which in turn will also affect sleep. The postnatal development of SWA and sleep spindles in NREMS from the first months to the aged brain has been particularly revealing for the interplay between sleep and brain structure (FIGURE 11).

A. Prenatal Spindle-like Activity

Activity patterns containing spindle-like activity are among the first signatures of sleep to appear at prenatal stages of rodent and mammals. Recordings from prematurely born babies show that periods of greater or lesser agitation emerge in middle gestational periods, in the absence of clear sleep and wake periods. EEG data are available from ~25–28 wk of gestation (182, 348, 618). At these earliest periods, signals consist of irregular periods of synchronization in the low-frequency range (0.3–1 Hz) on an otherwise largely flat EEG, referred to as “tracé discontinu” (182). Starting around 28 wk, the prenatal EEG undergoes profound periods of synchronization that become more frequent and bilaterally organized and that start being correlated with behavioral signs of rest. So-called “spindle bursts” are conspicuous and abundant hallmarks of the immature EEG starting around this period, and their occurrence is an important predictor for healthy neural development (298, 374, 646).

Spindle bursts are part of “delta brushes” that are composed of an isolated delta wave (0.3–2 Hz, depending on the exact prenatal age) and spindle bursts that ride on the ascending slope of the delta wave, as well as small gamma components. The frequencies of the spindle bursts vary widely and range from anywhere between 5 and 30 Hz, with peaks typically falling into the spindle and beta frequency range (12–20 Hz) (646). Delta brushes are most frequent in gestational weeks 28–34, with 5–10/min, as assessed in low-risk preterm babies (381). This is the period where bodily movements in utero increase in complexity and variability (260) and where the cortical subplate, lying between cortical layer 6 and the white matter and serving as a hub for setting TC connectivity, is maximally developed (313). After this period, delta brush occurrence is reduced and disappears upon birth (<1/5 min). Delta brushes can

also be elicited through sensory stimulation, where they appear in the cortical areas corresponding to the activated sensory modality (106, 114, 425). In rodents, the equivalent of delta brushes are spindle burst-only events that occur over comparable developmental periods and that reflect a primitive sensory responsiveness of local TC loops in response to spontaneous activity in its future sensory input (589). This function may go beyond sensory areas, as spindle burstlike activity was also found in hippocampus (431) and in prefrontal cortex (297). Mechanistic studies in rodents support the idea that neonatal spindle bursts are immature versions of TC oscillations that are distinct from mature spindles. For example, there is a thalamic contribution to spindle burst generation (317, 654). Moreover, if neurons in the cortical subplate that play an instructive role in the formation of TC projections are eliminated, neonatal spindle bursts are suppressed (591).

B. Postnatal Maturation and Adolescence

After birth, brain growth, development, and synaptic refinement continue throughout adulthood (239), but major events take place during early postnatal, prepubertal, and adolescent periods. As electrical events that depend on the TC circuit but also on cortical thickness and excitation-inhibition balance, spindle properties are modified during both early and later phases of brain development (FIGURE 11). Moreover, fast central and slow frontal spindles segregate developmentally according to the differential maturation of cortical brain areas. Briefly, grey matter grows massively within the first 2 yr of age, then more slowly until adolescence, after which it starts to decline gradually (239). The functional development of the spindle-generating thalamic circuitry also takes place at early postnatal stages, as studied in rodent (e.g., Ref. 471). White matter tracts are instead largely in place at birth, but myelination strengthens gradually throughout adolescence (239). Increases in synaptic density vary with cortical area and evolve in postero-anterior regions (289). Sensory circuits show highest synaptic densities in the first 1–2 yr, followed by a decrease until prepubertal stages (289). Frontal circuits are delayed but catch up in synaptic density levels after ~3–4 yr, reach a maximum at prepubertal stages, after which a decline until adolescence starts (289). These alterations overall match with the posterior-anterior maturation of cortical thickness (545).

1. Developmental time course in early postnatal periods

Sleep of human infants shows little detectable sleep spindles until ~4–9 wk of age. Delays are found in rodents (312) and ferrets (416) that coincide with the time of thalamic circuit maturation. Human sleep spindles appear as small-amplitude prespindles that mature within ~2 wk in terms of regularity, amplitude, and preferential occurrence around po-

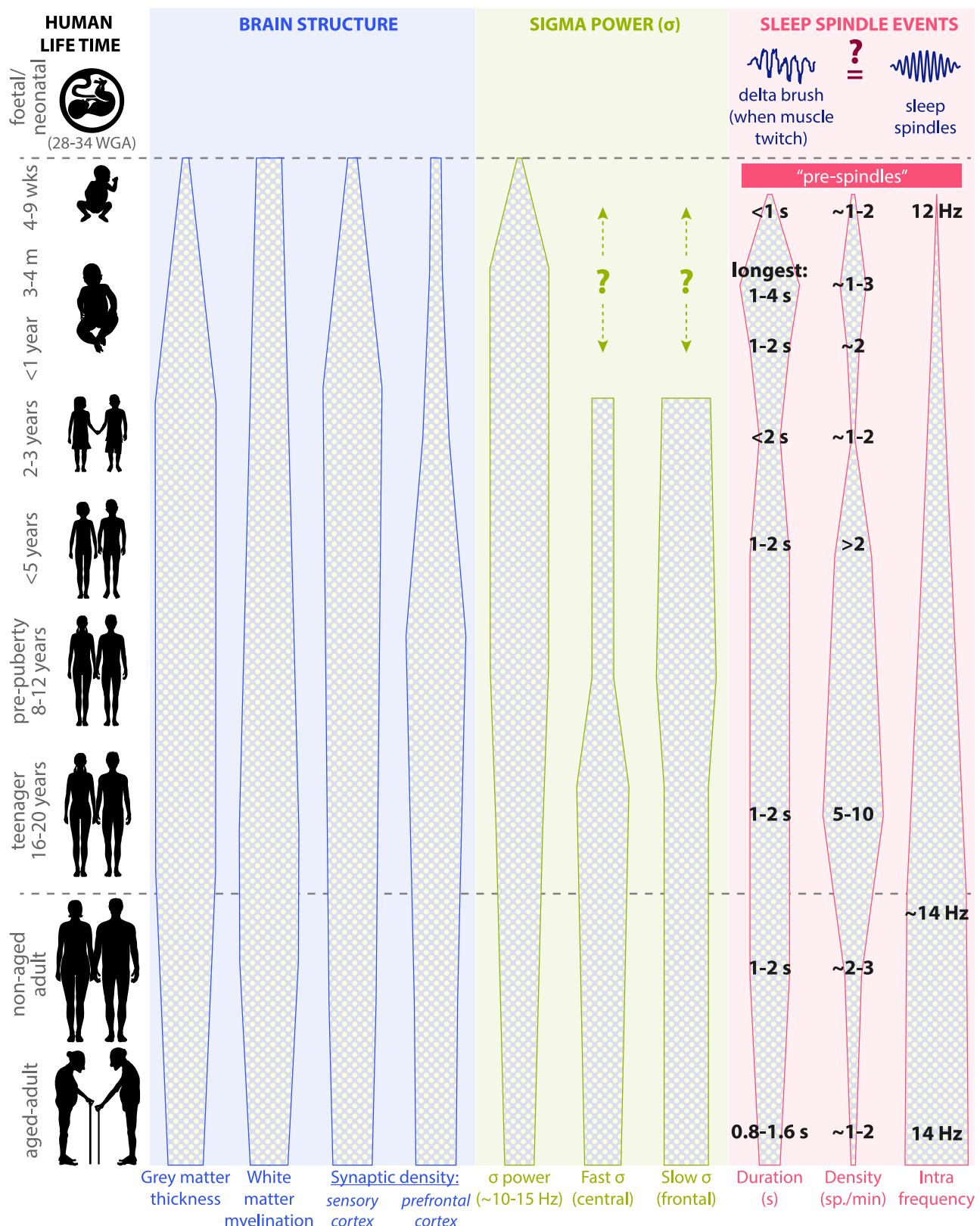


FIGURE 11. Sleep spindles across the lifespan. Parallel evolution of structural parameters of the brain, of sigma power, and of discrete sleep spindle events is shown, with age ranges indicated on the left and type of parameter given on the bottom. Thickness of the dot-patterned bands indicates changes in a semiquantitative manner. Real numbers are only given for sleep spindle events according to the references cited in the text. Density and duration are given for combined fast and slow spindles. The mechanistic and functional relation between delta brushes and sleep spindles still needs to be established. [Cartoons are adapted and modified from Servier Medical Art [CC BY 3.0].]

sitions C3 and C4 (298, 424, 514a) and that show bilateral synchrony after 6–9 mo (192). A clear sigma power peak in the NREMS EEG spectrum also appears at 2 mo in intermediate frequency ranges (12–14 Hz) (301). Sigma power becomes elevated in all NREMS episodes after 2 mo, but the U-shaped dynamics of sigma power within NREMS bouts and the power increase over consecutive bouts are not evident during this period, indicating that the homeostatic regulation of sleep has not yet matured (301). Infant sleep spindles are large until the end of the first year of age at intermediate frequencies (298, 385, 424, 514a). There is also a report on “ultrafast” spindles around 14–17 Hz in 2- to 3-yr-old children that were largely gone at 5 yr (468). Spindles appear from 2 to 4 mo until ~1 yr over frontal and parietal areas as long (~1–4 s) events with intermediate to high density (several spindles/min), followed by a decline to low densities (<1 spindle/min) of short spindles until ~2 yr of age.

2. Developmental time course until adolescence

Once the sigma peak has appeared, NREMS power spectra show a comparatively broad but shallow peak in the lower range of frequencies that overall remains relatively stable until adolescence except for a decrease initiating before puberty (93, 339, 412, 468). This stability obscures that fast and slow sigma power components develop in opposite manners. A fast spindle peak is not clearly distinguishable from frontal spindle activity, which is already present in toddlers and continues to be dominant until prepuberty (93, 277, 550). The fast spindle peak of the mean N2 power spectra increases strongly at adolescence (339, 550). Regarding discrete sleep spindles, there is a marked increase in the density of frontal spindles, until 5 yr of age, to >2 up to 6 spindles/min (367, 385, 539, 585) that continues until around preadolescence, during which density levels reach 5 up to >10 spindles/min (262, 539), whereas central areas show comparatively few spindles (262, 277). Mean peak levels for spindle density (2–3 / min), amplitude (~30 nV²), and duration (~1 s) are reached around young adulthood in both males and females (501). This indicates that puberty is the life period of maximal spindle activity during which mature spindle topography also develops. Slow spindles also show an abrupt increase in frequency by ~1 Hz at prepubertal ages, whereas fast spindles change little from toddler to adolescent ages (550). Globally, mean frequency of spindles increases linearly until adolescence (93) and young adulthood (501, 550), consistent with a relative increase of fast over slow spindles (501). Mean frequencies remain relatively stable during adulthood and aging (501).

3. Correlation between brain and sleep spindle maturation

It is important to note that all major frequency bands of NREMS show marked alterations from preschool age to

adolescence (339). The developmental trajectory of sleep spindles closely follows early postnatal periods of overall brain maturation, as do all other frequency bands as well, and is probably further constrained by the maturation of excitability at the level of the thalamus, as suggested by the presence of early long-duration spindles. The postero-anterior maturational process was also reported for SWA and is particularly evident here in an opposing developmental profile of fast and slow sigma power activity and in a relative dominance of frontally generated spindles. The developmental sleep spindle patterns correlated with reaction time in young children (181) and in longitudinal studies of brain maturation (262), showing that they are informative about the neurobiological correlates of healthy cognitive development. Abrupt alterations, such as the ones described for frontal spindle frequency, could be particularly interesting in relation to prefrontal maturation (550). The strong increase in spindle density and the late increase in fast spindles are phenomena for which the structural basis is not clear. There have also been suggestions for sex differences at the adolescent level (212). Interactions with additional maturation processes, such as that of slow-wave activity and of homeostatic and circadian systems, remain to be elaborated. For example, in adolescents, overnight spindle characteristics depend on chronotypes (sect. IVC).

C. Aging

All aspects of sleep, from its efficiency and consolidation to its regulation and spectral composition, show reduced functionality with aging (99, 175, 201, 540). There is notably an overall attenuation of absolute power density levels across all frequency bands to levels ~60% of those seen in young male, including a weakened sigma power shoulder in mean NREMS power spectra (353). Over successive NREMS episodes, the U-shaped time course of sigma power within episodes is preserved, but the increase across NREMS episodes becomes markedly attenuated for all frequencies <14 Hz (353). Attenuated sleep efficiency and changes in SWA dynamics are likely causally interrelated (171, 353). Discrete spindle events detected by visual scoring or automated methods also show decreases in density and amplitude by ~50% and duration by ~20% (255, 311a, 450), as also documented in large-scale longitudinal studies (501) **[FIGURE 11]**. A majority of these studies report an overall slight increase in mean spindle frequency. The overall decline in spindle parameters with aging is attenuated by 10–15% in females (99, 501).

There have been efforts to correlate these changes with age-dependent structural, functional, and cognitive modifications of the TC system. Both grey matter and white matter integrity decline gradually during the normal aging process (199, 375). The overall decline in spindle activity could be related to the fact that aging goes along with volume changes. Thus spindle amplitude negatively correlated with

sulcal atrophy (255). Frontal-predominant aging processes could relate to a more pronounced decline of sigma power density levels (352) and sleep spindle properties (409) in anterior derivations. However, it is important to remember that alterations in SWA, including in the waveform of SOs, are also powerful indicators of brain aging (e.g., Ref. 604). The circadian regulation of sigma power is also attenuated (330, 636), possibly due to the decline in circulating melatonin (353). Age-related modification of sleep spindle activity did not correlate with alterations in sleep efficiency (501), sleep consolidation (255, 330), and recovery sleep after a 25-h sleep deprivation (517). Interestingly, however, an impairment in motor sequence learning (the finger-tapping task, see sect. VIIIC) correlated with a reduced hemodynamic activity in corticostratial networks at moments of high spindle density in old compared with young individuals (211). Moreover, the decline in prefrontal cortical spindle density, together with decreased hippocampal activation, correlated with a decline in episodic learning (401). Parallels are further observed in disorders of aging (sect. XD). This is in line with the idea that sleep spindles may be required for the reactivation of brain areas specifically involved in learning (sect. VIIIA). This process becomes halted with aging, as the density of sleep spindles seems no longer high enough to enable reactivation.

VIII. MEMORY CONSOLIDATION

Of particular interest has been an involvement of sleep spindles in memory formation. Memory formation begins with the creation of a memory trace that needs to be consolidated to generate a lasting memory. A memory trace involves ensembles of neurons, in which the information is encoded at multiple levels, such as alterations in gene expression, electrical excitability, and/or synaptic connectivity. Memory traces are then retrieved and transmitted to one or several circuits capable of storing these in an enduring and retrievable format, also called a “memory engram” (592). Memory is thought to be enabled via preferential connections between engrams that are established through mechanisms involving synaptic plasticity (494).

In general terms, sleep probably provides conditions that support the transformation of memory traces into memory engrams, thus supporting the consolidation of memory (504). There are several theoretical accounts about the neural bases of these conditions. These range from sleep as a state of reduced interference that passively facilitates consolidation (418), to NREMS serving to homeostatically regulate synaptic strength and spine numbers (326, 593), to active and cooperative roles of NREMS- and REMS-specific rhythms in consolidation of memory traces (504). Experimental evidence supports a role for all these theories. The theory of “active systems consolidation” is the currently best supported hypothesis in terms of an active role

played by NREMS. It is also the sole theory implicating spindles in the consolidation of declarative and nondeclarative procedural forms of memory (504). Critical for its influential role have been experimental studies showing that, during NREMS, 1) there is a reactivation of neural activity patterns acquired during learning, a first step in transforming memory traces into more enduring formats; 2) there is an enhanced functional connectivity between brain areas implied in learning, brain areas thus cooperate during the transfer of memory-related information; and 3) cueing stimuli during NREMS support memory consolidation, which indicates that sensory experience linked to learning promotes memory trace re-activation. The central postulate to the transfer and transformation of an initial labile memory trace thus implies the existence of a carrier mechanism that specifically routes these memory traces through mechanisms involving synaptic plasticity (504).

Sleep spindles are proposed as prime candidates in this process because they promote synaptic plasticity (sect. VIIIA), they change themselves upon learning (sect. VIII, C and D) (**FIGURE 12A**), and they are time-locked to hippocampal ripples and SOs (sect. VIE). Moreover, their refractoriness (sect. VD) and their clustering on the infraslow time scale (sect. IVE) define time windows during which various processes relevant for synaptic plasticity and for reactivation of memory traces can be sequentially executed, while being protected from sensory interference (**FIGURE 12B**). To critically review this proposal, we first summarize available data on the implication of sleep spindles in synaptic plasticity. A major gap here are the mechanisms by which sleep spindles themselves are plastic, such that they can become more frequent or larger upon a learning experience. Here we propose possible scenarios that should stimulate further experimentation. We then summarize results from memory tasks in humans and rodents that show correlative evidence for a role of sleep spindles, and we highlight recent approaches that bring in the causal perspective.

A. Synaptic Plasticity Associated with Sleep Spindles

Sleep spindles are associated with rhythmic, synchronized neuronal activity between pre- and postsynaptic neurons and provoke activation of Ca^{2+} -dependent signaling pathways (sect. V, B–D). Such events favor the induction of associative forms of long-term synaptic plasticity. Thalamic circuits themselves show rapid forms of plasticity in response to sensory experience during wakefulness. This could modify sleep spindles during subsequent sleep.

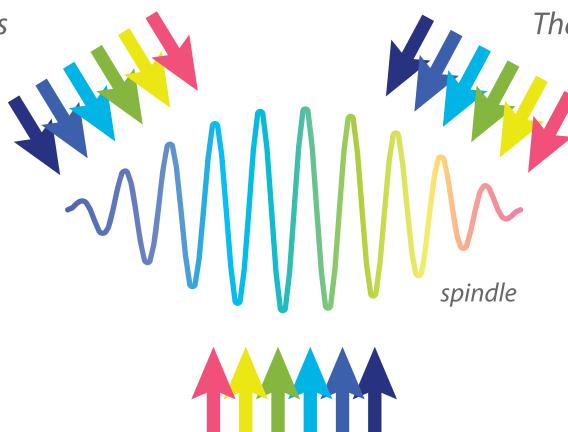
1. *Sleep spindles promote plasticity*

In vitro studies tested whether repetitive low-threshold burst discharges, such as those found during sleep spindle generation in thalamus, promote plasticity (for review, see

A

SYNAPTIC PLASTICITY

Plasticity of
electrical (gap junctions)
and chemical synapses

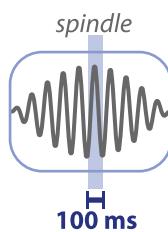
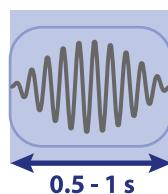
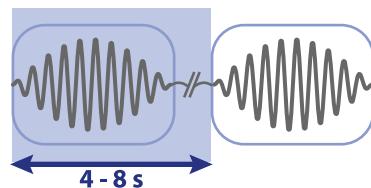
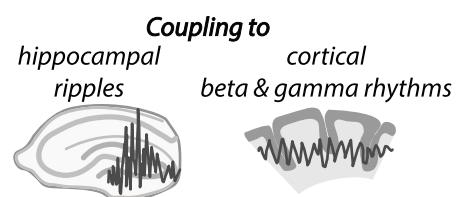
**TOP-DOWN PLASTICITY**

Attentional-related
plasticity of
Thalamic Reticular Nucleus
subcircuits

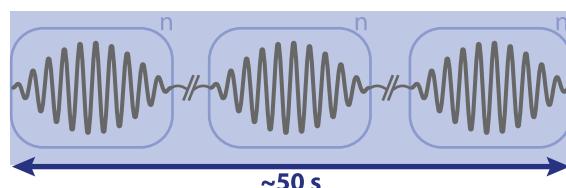
BOTTOM-UP PLASTICITY

Use- and experience-dependent plasticity
of thalamic sensory circuits

B

**INTRASPINDEL INTERVAL****COUPLING TO CORTICAL SLOW OSCILLATION****SPINDEL REFRACTORY PERIOD**

- Re-activation of thalamocortical loops engaged during waking
- Decoding of memory traces

**0.02 Hz -OSCILLATION**

- Internal processing
- Repeated reinstatement of memory traces

Continuity period of
mammalian NREMS

FIGURE 12. Schemes summarizing sleep spindle plasticity and temporal windows set by sleep spindles that are relevant for memory consolidation. **A:** three proposed mechanisms by which sleep spindles can become modified as a result of synaptic plasticity and wake-related experience. Rainbow colors illustrate a variety of mechanisms and possible effects on sleep spindles. **B:** temporal windows over which sleep spindles are relevant for memory consolidation. Multiple spindle occurrence within the 0.02-Hz oscillation is illustrated by the *n* above the spindle oscillation box.

Ref. 368). Excitatory synapses between TC and TRN neurons in the somatosensory thalamic nucleus show associative, burst-dependent long-term potentiation that depended on GluN2B-containing NMDARs located on TRN cells (33, 368). TRN-TC synaptic projections express a burst-dependent long-term depression that depended on metabotropic glutamate receptors (488). A non-Hebbian long-term potentiation of these inhibitory synapses has also been described (554). These mechanisms may strengthen thalamocortical circuits, but they all required relatively long sequences of low-threshold bursts for induction of plasticity that do not typically occur during natural spindles. Cortical afferent stimulation more closely reproducing sleep spindle-related activity identified a long-term potentiation of EPSP-burst coupling in TRN cells through a GluN2C-dependent mechanism involving $\text{Ca}_v3.2$ channels (205). Gap junctional coupling between TRN cells also turned out to be plastic (257, 350). Furthermore, when layer 2/3-layer 5 projections were activated with spindle-derived spike trains in rat brain slices, associative forms of plasticity were observed (516). Spindle-like rhythmic neuronal activity can thus in principle trigger several forms of long-term plasticity. To explore whether a link between synaptic plasticity and spindles could be found in natural sleep, one study paired primary motor cortex transcranial and hand muscle electrical stimulation to induce changes in muscle-evoked potentials. These persisted over a night of sleep and correlated best with alterations in the density of slow spindles measured over sensorimotor areas.

2. Experience-dependent plasticity modifies sleep-spindle-generating circuits

Use- and experience-dependent forms of plasticity during wakefulness affect subsequent sleep, as well documented for SWA (284, 623). In comparison, consequences on sleep spindles are less known, although there is evidence for changes in learning tasks (sect. VIII, C and D) and in response to the extent of sensorimotor activity during the day (61, 284, 308). Furthermore, the receptive field properties of visual and auditory thalamus are altered by sensory experience (189, 190). To address consequences on sleep spindles, one study evaluated a rapid form of plasticity in orientation tuning within 1 h after visual stimulation (35). Notably, in subsequent NREMS, visual thalamic neurons that showed the greatest plasticity also displaced increased coherence with SWA and sleep spindles. Expression of plasticity required corticothalamic synaptic activity feedback. These landmark findings demonstrate that rapid receptive field plasticity in thalamus during wakefulness leaves a lasting trace that guides the subsequent engagement of neurons in sleep spindles and coordinated interactions with cortex.

3. Cellular and synaptic mechanisms underlying sleep spindles may be modified by attentional mechanisms

In tasks demanding selective attention to one of two presented stimuli, TRN activity is strongly regulated within

sectors corresponding to the attended sensory modality (265) through a prefrontal-basal ganglia circuit (444). It will be important to test whether this excitatory input induces plasticity that modifies sites and strength of subsequent sleep spindles.

B. Active Systems Consolidation

The theory of active systems consolidation proposes that a triple time-locking of sleep-related rhythms between cortex, thalamus, and hippocampus provides a temporal window and optimal neuronal conditions for memory traces to be consolidated. The reactivation of memory traces is thought to depend on hippocampal ripples that, when coinciding with the occurrence of SO-sleep spindle events, enable consolidation (sect. VIE). Supportive evidence comes from human and rodent studies, such as odor-reward associative learning in rats and declarative learning in humans, during both of which a higher number of coordinated discrete hippocampal ripple and prefrontal spindle events coincided with the SOs (433). Spindle-ripple coordination was also described over infraslow time scales defined by the 0.02-Hz oscillation (362) and by default-mode networks (316). This could give rise to 25-s epochs with favorable conditions for hippocampus-dependent memory consolidation. Furthermore, closed-loop feedback stimulation of prefrontal cortex to increase the number of ripple-coupled SO-spindle events improved spatial memory (398). Based on hippocampus-dependent learning in humans, it was even proposed that spindles directly affect hippocampal representations, thereby facilitating in particular the recall of learned material with the lowest similarity to that of the pre-sleep exposure (270).

A so far unresolved aspect is a better understanding of the conditions under which this triple coupling is relevant during NREMS. Both N2 and N3 are implied in memory consolidation processes, but they differ in the quality and extent of this coupling (sects. IVA and VIE). Through functional connectivity measures using fMRI, a preferential strengthening between hippocampus and cortex was observed during N2, in particular during a sleep spindle (22). Moreover, targeted memory reactivation was more successful in triggering spindles on the upstate of the SOs (K-complexes) during N2 (241). However, memory-relevant roles were also found for sleep spindles during N3 (60). Even without explicit learning during wakefulness, local cortical electrical activity patterns observed during wakefulness reappeared during NREMS, preferentially in conjunction with hippocampal ripples and sleep spindles (305).

It is clear that first steps towards a causal role of the triple coupling between SOs, spindles, and ripples in active systems consolidation are made (241, 354, 398). Next steps would ideally combine monitoring of sleep stages with targeted interference of SO-spindle-ripple coupling, for example, through targeted memory reactivation (241) to further

strengthen causality (sect. XIB). It is plausible that fast and slow spindles, together with different SO generators during N2 and N3 (sect. IVA), and heterogeneities across TC circuits, will ultimately yield a highly differentiated picture of the role of SO-spindle couplings in different forms of memory reactivation.

C. Nondeclarative Forms of Memory

Numerous studies identified a role for N2 in the learning of diverse motor tasks that can be broadly classified into several categories of increasing complexity (for review, see also Refs. 4, 325). Of relevance here are implicit motor learning tasks designed to refine a basic human motor skill in terms of precision or velocity. To these belong the rotor pursuit task or the serial reaction time task that guide movement with external cues (such as a circle on the screen that is to be pursued with the cursor). A second category are motor sequence learning tasks that are cognitively more demanding because learning occurs explicitly through executing a previously communicated sequence of movements. Well-known is the finger-tapping task in which fingers need to be moved rapidly and precisely according to a prescribed sequence. A third category involves tasks that are cognitively complex and for which strategies need to be elaborated in the course of the task. A relevance for N2 in tasks of the first two categories was supported by sleep deprivation in the second half of the night, which compromised learning the next day (557), or through correlating the overnight skill improvement with the amount of time spent in N2 across a night (77, 216, 625) or during a nap (456). In contrast, nightly disruption of N3 sleep or of REMS interfered little with this kind of memory (235). Still, the details of how N2 is involved vary in some studies (47, 438), and SWA has also been implied in an implicit motor memory task (285), and other studies question the role of sleep in implicit motor learning as a whole (325, 469, 621). Very revealing about the complexity of the interaction between sleep and implicit motor learning are studies with mice, for which improving on the accelerating rotarod task involved both NREMS and REMS (371, 653).

Motor learning tasks in human are typically executed on the evening of a test night, and retesting occurs at variable intervals, such as after a nap (456), the next morning (77, 358, 438, 582), after one additional night (506), or a week later (212, 215). Sleep measures are done in the night post-learning, as sleep spent shortly after learning is relevant for performance improvements. The improvement in motor execution correlated with an increase in various characteristics of spindles in the post-learning night (quantified using thresholding or Wavelet methods in N2 NREMS), such as sigma power (598), density (47, 77, 212, 215, 358, 419, 438, 456, 506), duration (438), or amplitude (582). The implication of sleep spindles has been most robustly documented for motor refinement tasks of the second category,

which suggests that they favor some degree of explicit recall in memory formation. Instead, both sleep spindles and SWA, as well as REMS, are involved in tasks that are cognitively more complex such as the mirror tracing task (212, 216, 279, 506, 582, 583), a visuomotor learning task (213, 285), or the tower of Hanoi task (213, 216). An interesting case is the tower of Hanoi task that is learned over several days and where both refinement of motor skills and learning of optimal strategies are required. In this case, increases in fast sleep spindle density and frequency were observed at early learning stages, whereas REMS duration was greater when performance was close to optimal (213). Increases seemed to be mostly related to fast spindles (47, 216, 358, 438, 456) and best for the hemisphere contralateral to the hand used for the task (77, 456). Initial skill level of individuals may facilitate the correlation with spindle density during the night (480). Jointly, these studies highlight that even seemingly simple tasks engage different mnemonic processes that range from refinement of motor control to the internal planning of movements or the elaboration of appropriate strategies. Spindles appear best associated with tasks where learning is explicit and during early stages of learning during which motor activation patterns and sensorimotor integration need to be put in place. In support of this role, enhanced functional connectivity between thalamus, putamen, and hippocampus during sleep spindle occurrence after a finger tapping task was reported (77). Moreover, reactivation and strengthening of memory traces observed in BOLD signals occurs during NREMS following learning of this same task (613). There is also support for the idea that closed-loop transcranial electrical stimulation in the spindle-frequency range to boost ongoing spindle activity is beneficial for motor skill learning (sect. XIB). In contrast, spindle-dependent reactivation of brain areas in the finger-tapping task is attenuated in aging (211) (sect. VIIB). In schizophrenic patients, a decreased spindle density correlated with the decreased learning capabilities in the finger-tapping task (628).

D. Declarative Forms of Memory

Sleep's implication in declarative memory is particularly fascinating because of its broad actions that range from facilitating recall of simple learned materials to inspiring insight and creative ideas (504). Changes in sleep spindle characteristics have been found for this broad range of beneficial actions. Starting from the observation that spatial exploration preferentially alters sleep spindle occurrence during N2 (422), spindles have been linked to verbal memory retention, facilitation of the competition of novel knowledge with existing one, and promoting insight into hidden rules (214, 504). Word-pair or word-image association tasks have been used most frequently to correlate sleep spindles with overnight recall performance. Subjects are asked before a test night to remember lists of word pairs that are shown to them for a limited period of time (typically ~30–60 min of total learning time). After overnight

sleep or a nap, they are asked the next morning or a few days later to recall the second word once they are presented with the first word or image. Controls are variably exposed to the word pairs without a learning request or to an alternative declarative task (e.g., passive visual recognition). Across studies, many details of the task vary in terms of number of word pairs to remember, the semantic relation between word pairs, instruction on how to remember the pairs, and the exact learning procedure (e.g., availability of corrective feedback). Moreover, most available studies are based on correlations between various spindle parameters and recall performance. Spindle measures are taken from variable sites, broadly assuming that this form of learning involves sensory and associative cortical areas in addition to its dependence on hippocampus. One aspect that emerges from these studies is that intense learning with >100 word pairs leads to increases in diverse measures of spindle activity and/or sigma power in central derivations of young adults in the initial periods of N2 NREMS in the majority of studies (228, 279, 433, 527, 529, 537); but see Ref. 212, 216), whereas weaker or negative correlations were found for less intense memory tasks (110, 235, 278, 279, 391, 392). Correlations were reported to be best for early NREMS (235), but correlations later in the night particular regarding general cognitive abilities were also found (216). An interesting alternative to word-pair tasks are visual recognition tasks, which produced changes in spindle-related parameters over parietal areas involved in visual functions (110, 111). Here, the increase in spindles and/or time spent in spindle-enriched sleep seemed too specific for the brain areas used for learning the task. Similar observations were also obtained in studies using memory recall from movie watching after a nap (132). The contribution of fast or slow spindles was studied in a few cases for the word-pair task (228, 393, 528, 537). Intriguingly, slow spindles (<13 Hz) in frontal derivations overall showed a more consistent relation to recall performance (228, 393, 529, 537), suggesting that spindle activity in prefrontal, attention-related rather than in sensory cortex is important in these tasks. Intense learning tasks also promoted an enhanced coupling of spindles over central derivations to the SO (433) or a preferential correlation with C3 and C4 spindles during N3 sleep (132). Pharmacological boosting of sleep spindle density promoted various declarative forms of memory (sect. XIA).

A very important aspect identified in some studies was that learning-related changes in sleep spindles varied with the general cognitive abilities of the subjects measured before the test night (393, 528, 529, 598) that correlate themselves with baseline spindle density (sect. IX). Assessing learning-induced changes in sleep spindles needs thus to take cognitive abilities of the study subjects as a covariate.

Few rodent studies have addressed modifications in sleep spindles upon hippocampus-dependent learning tasks, but optogenetics now opens powerful opportunities to causally

link sleep rhythms to learning in a temporally and spatially controlled manner. For both SWA (429) and REMS (78), enforcing sleep rhythms through optogenetically driving the circuits involved in their generation is beneficial for hippocampus-dependent learning. Similarly, a first effort to causally implying spindles in hippocampus-dependent learning was achieved through optogenetically promoting thalamic synchronization during the active state of the SO, which facilitated contextual fear memory in mice (354). Prior correlative studies showed that odor-reward associating tasks generated an increase in power in the sigma band and in the number of spindles in prefrontal EEG recordings at 30 and 60 min post-learning (195), and an increased coupling to the up-state of the SO (433), with no reported difference in the mean power in the delta frequency band (195). There is also some evidence that declarative learning might change the amount of spindle-rich intermediate sleep (533).

In addition to declarative memory tasks in humans, there is correlative evidence for a contribution of spindle-related activity to episodic memory details (615). Furthermore, cueing of emotional stimuli boosted sleep spindle oscillations better than neutral ones (366). A series of studies indicate that sleep spindles might benefit the integration of new information into existing knowledge. Such evidence was shown for novel words with no lexical meaning but that were reminiscent of known words (584), or for the ability to classify visual objects based on whether or not they were already presented (270). The amount of increase in fast sleep spindles was widespread in a task where insight into hidden rules of a serial reaction time task was quantified. Subjects that showed most insight had elevated fast spindle activity not only in motor areas engaged in the task, but also in contralateral frontal-central areas possibly related to the gradual awareness of possible rules behind the task (656).

E. Outlook

Sleep spindles are integral to some of the most influential theoretical concepts and experimental designs in the field of sleep and memory consolidation in both human and rodent. They generate a set of neuronal conditions that enable a selective activation and routing of memory traces deposited during wakefulness for long-term storage. Although sleep affects memory formation through many complementary mechanisms, sleep spindle-guided insights have been particularly fruitful because of converging evidence at many levels, from promotion of synaptic plasticity, to temporal coupling with other rhythms, to favoring/interacting with hippocampal replay, to sensory protection, to correlational evidence between memory performance and sleep spindle activity. Still, many basic questions remain to be addressed. What makes sleep spindles malleable by wake-related experience? Do different forms of experience trigger spindles that vary in their site of origin and their strength? Does the sectorial organization of TRN come in here critically, such

that sleep spindles can be generated locally, or across sectors, according to wake-related modifications in thalamic circuits? Which are the synaptic pathways that link them to extrathalamic areas such as hippocampus? Which are the mechanisms that enable sleep spindle recruitment at the right time in the right place, such that certain memory traces can be specifically re-activated? Do they encode information or are they merely creating the right neuronal conditions for the cortical-hippocampal dialogue? Rodent experimentation seems ideal at this time to bring answers. Sleep spindles are now well described in rodent, they can be optogenetically controlled with high spatiotemporal resolution, and many memory tasks are available for which critical sites of neuronal plasticity were identified. Therefore, the set of wake-related experiences that augment sleep spindle occurrence can be systematically explored and causally related to the TRN sector engaged, the cortical location of changes, and the behavioral outcome. As we move to better understand what a cortical spindle is in terms of its subcortical origins, we will come to appreciate the intricate anatomical organization of TRN-thalamic circuits and perhaps their powerful capacity to rapidly undergo plastic changes that guide later spindle generation.

IX. COGNITIVE ABILITIES AND INTELLIGENCE

Studies of the biological bases of cognitive abilities, in particular intelligence, commonly involve structural measures of the brain, such as its total size or grey matter volumes (250). EEG signals are also related to alterations in brain structure, both during maturation (85) and aging (sect. VIIIC). Sleep spindles depend on the reciprocal interaction between thalamus and cortex that are central to cognition. Sleep spindles have thus been probed regarding correlations to wake-related cognitive abilities. A remarkable observation that motivates pursuing such correlations is that genes implied in attentional disorders are expressed in sleep-spindle generating circuits (335).

A. Relation to White Matter Integrity

Spindle power correlated with markers of white matter integrity around the thalamus, corpus callosum, and forceps minor in young adult subjects (231, 486). In contrast, grey matter volume changes correlated best with SWA (85). Furthermore, in young adults, the rate by which sleep spindle activity showed increased coherence between the hemispheres correlated with the improvement in attentional tasks (586).

B. Relation to Attentional Capabilities

A link between sleep spindles and attention has been identified through genetic association studies for neurodevelop-

mental disorders, such as in autism-spectrum disorders or attention-deficit hyperactivity disorders. Several risk genes for these disorders are highly expressed in TRN, and their mutation leads to gross alterations in cellular electrophysiology (335). A recently documented case is the gene *PTCHD1* (Patched domain-containing protein 1) that leads to broad intellectual disabilities in humans when mutated. When deleted in the TRN of mouse, behavioral correlates of the disorders, such as deficits in attentional tasks and learning, were also observed, together with deficits in TRN bursting, synaptic output, and spindle generation (640). A further very interesting case is the gene *Erbb4*, which encodes a receptor tyrosine kinase that contributes to the development of corticoreticular projections and for which genetic studies indicate a link to schizophrenia and mental disorders (13). Animals with mutations in the *Erbb4* gene show an impaired switching of attention between different sensory cues. These are overcome through antagonizing the excessive cortical drive onto somatostatin-positive TRN neurons. Although in this case sleep spindle deficits were not yet pursued, these correlations open roadways to link the genetic basis of inherited intellectual disabilities to dysfunctions of TRN circuits.

C. Relation to Intelligence Quotients

First attention in relation to intelligence quotients (IQs) stems from observations on mentally retarded children <5–8 yr who showed various alterations in sleep spindles, with occasionally extreme, almost continuous manifestations (236, 547). Abnormal spindle densities were also observed in older (14–19 yr) subjects with intellectual disorders (63). Within the healthy population, sleep spindle density over central and frontal derivations repeatedly correlated with an individual's ability to learn a given task (110, 228, 393, 528, 529, 598). These observations were summarized in a proposition of an inverted U-shaped relation between sleep spindles and cognitive ability, whereby both too few or excessive spindles compromise mental ability (214).

There are efforts to circumscribe the cognitive domains influenced by spindle activity. Concerning intelligence assessments, fast spindle density during N2 at the right frontal derivation, but not time spent in N2, correlated with general intelligence in mixed-sex test groups (67). Similar results were obtained for spindle activity and the counts of fast and slow spindles over central derivations, although the correlation was best for high-IQ participants (528). In a study involving mostly female participants, sigma power and the total number of sleep spindles in N2 correlated with performance IQ, whereas verbal IQ correlated with REMS parameters (216). Again, the participants in the top third of IQ levels gave the best result. Concerning learning potential in declarative or procedural memory tasks, spindle activity correlated positively irrespective of whether it was mea-

sured during a night with or without learning (228, 391, 393, 528). Individual spindle activity also predicted the success of cognitive-behavioral therapy in treating insomnia (147). There is also strong evidence from a well-powered study for an important role of sex (603). Fast spindle density over the majority of derivations correlated positively with general IQ in females, but negatively in males in parietal and occipital derivations. There were also positive correlations with slow spindle duration in females. This sex specificity is in agreement with observations of stronger links between neuroanatomical characteristics and intelligence measures in females (603).

Do spindle characteristics correlate with periods of growing or declining cognitive abilities, such as during youth or aging? A recent longitudinal study finds that the maturation

of fast spindles from preadolescence to adolescence correlates with overnight learning abilities, whereas general cognitive abilities correlated better with slow spindle maturation, implying a role for prefrontal maturation (262). Most cross-sectional studies vary in the choice of age range, sex, cognitive category, and spindle parameters measured (513). Correlations relating spindle activity measures to aspects of IQ in young to mid-age children exist, but are not consistently positive (105, 232, 277). A meta-analysis indicates that spindles overall associate positively with cognition, but effects vary according to the cognitive domain tested (513). For example, spindle activity correlated positively with fluid IQ, working memory, and speed/accuracy but negatively with immediate word recall or with sensorimotor skills. An additional observation that seems specific at prepubertal and adolescent stages is that the relation between

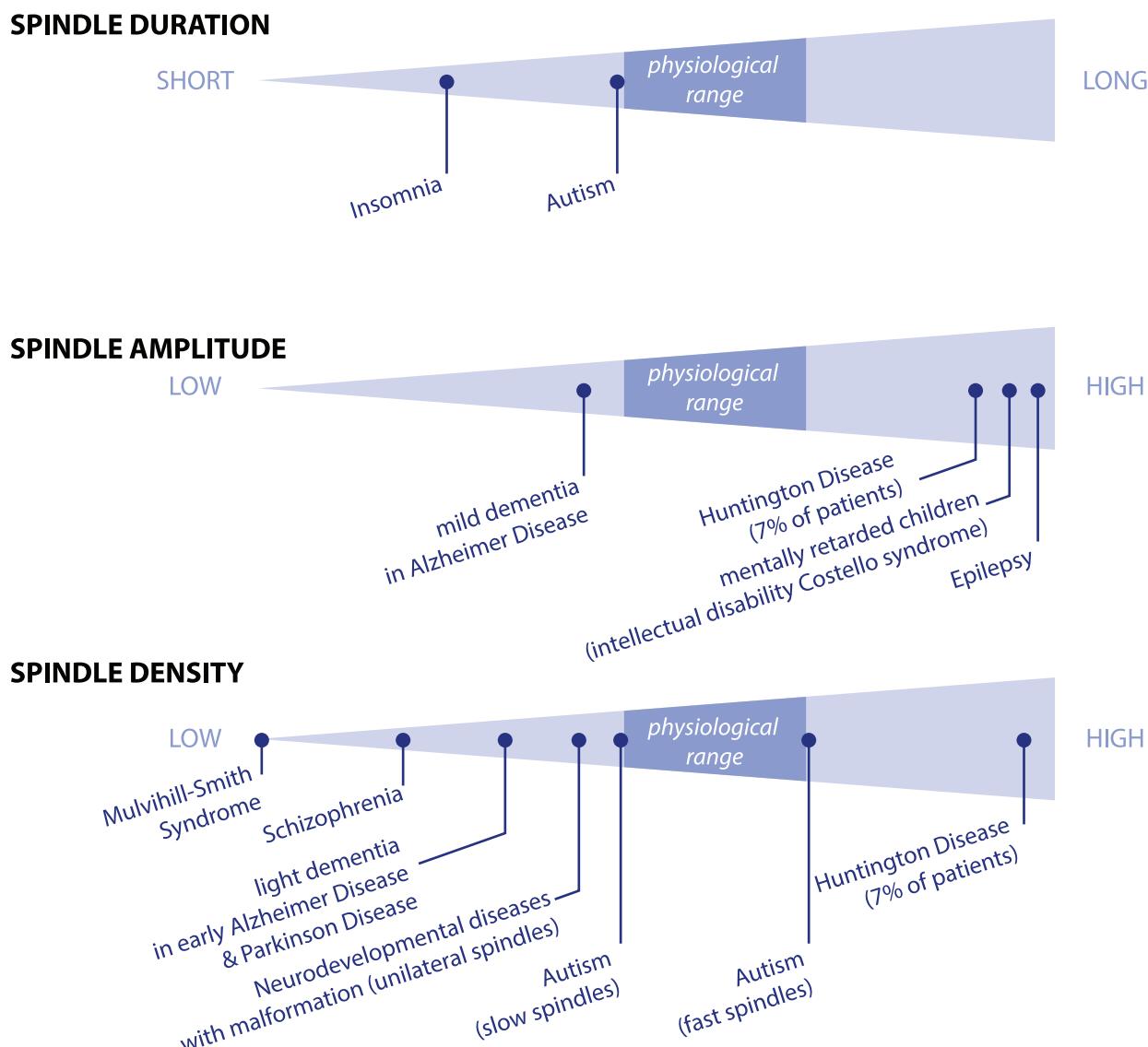


FIGURE 13. Overview of sleep spindle modifications with disease. Only effects on discrete sleep spindle events are considered according to the references cited in section X. Alterations are indicated relative to a physiological range that is centered within a range of possible alterations in the weaker (left) and stronger (right) direction. Points connected to lines refer to semiquantitative changes relative to the physiological range.

sleep spindles and cognitive function is occasionally negative, as found for procedural memory (31), for immediate recall in a hippocampal task (338), and for the execution of fine motor tasks (105). This could be due to a dominance of slow spindle activity over central derivations in N2 of preschool children (181, 277). Fast spindle density was a reliable marker of cognitive function in middle-aged adults (342). In older (50–70 yr) subjects, spindle measures no longer correlated with the structural integrity of the white matter (231). Moreover, deficits in the formation of new memories in both motor (211) and declarative tasks (401) correlated with impaired or altered reactivation of brain areas during spindle occurrence. Parallels were also found in cognitive decline found in age-related pathologies (sect. XD).

X. SLEEP DISORDERS AND NEUROLOGICAL DISEASE

The relation between sleep spindles and sleep stability (sect. IV) suggests that aberrant sleep spindle function may accompany if not causally underlie sleep disturbances. Furthermore, the dependence of sleep spindles on intact TC circuits (sects. V and VI) indicates that altered sleep spindles may sensitively report on diseases with perturbed TC function, such as epilepsy, age-related pathologies, and neuropsychiatric disorders. Novel studies emphasize a link between sleep spindles and neurodevelopmental disorders (254, 647), which substantiates their dependence on brain maturation (sect. VII). Additional reported alterations of sleep spindles in mood and anxiety disorders document that sleep spindles may provide insights into cognitive impairments on a broad scale of TC dysfunctions (455, 647). There are also noteworthy studies on traumatic head insult (198), coma (608), and pediatric cardiac arrest (184), which report that recovery of N2 and the re-appearance of sleep spindles correlate positively with the restoration of cognitive ability. While there is thus a broad potential for sleep spindles as causal factors or as biomarkers for disease, it is also clear that altered sleep spindle parameters need to be more finely resolved to move towards a diagnostically more useful level (FIGURE 13). Here, we focus on disorders for which links to sleep spindle dysfunctions are comparatively well-documented. Furthermore, for several types of generalized epilepsy, animal studies have contributed importantly to elucidate some of the genetic and ionic dysfunctions in sleep-spindle generating circuits and to promote the use of effective medications (439).

A. Sleep Disorders

1. Primary insomnia

Primary insomnia patients perceive difficulties falling or staying asleep, or waking up early in the morning, without

obvious symptoms of physiological or psychological illness (57). Behavioral, neuroimaging, peripheral, and stress hormone measurements jointly point to insomnias as resulting from “hyperarousal” states that manifest at many physiological levels and interfere with sleep, delaying its onset or causing frequent arousals. Causes for insomnia are multiple: predisposing genetic or environmental factors, precipitating life events, but also a vulnerability towards developing an insomnia that is chronic. Currently, few studies have investigated at what point deficits in sleep spindles, commonly considered sleep-protective elements (sect. VIF), are implied in insomnias. A small study on college students indicated that low sleep spindle density may be a predisposing factor for insomnia in response to the stress in examination periods (149). In contrast, sleep spindle density in chronic insomnia patients, assessed visually in only a single derivation, was overall not different (49). Here, discrepancies between studies in terms of patient selection, EEG derivations, and sleep spindle parameters are probably major reasons for an inconclusive picture. Among the 14 studies selected in a meta-analysis (638), 6 found no group differences, whereas 8 reported variable results. One study found a group-by-sex interaction with higher absolute sigma power in female primary insomniacs (88). Another study found shorter sleep spindles in a subgroup of insomnia patients that misperceived their own sleep, but not in patients without such misperception (459). It is thus likely that sleep spindle deficits may be characteristic for a specific subgroup of insomnia patients. The 0.02-Hz oscillation, a measure of sleep fragility, should also be considered in these patients, because insufficient deactivation of the default mode networks, a putative BOLD correlate of infraslow fluctuations, was reported in insomniacs (406). Additionally, a group of insomniac patients without secondary comorbidities showed greater heartbeat-evoked late component potentials, suggesting abnormal interoceptive sensitivity (637). Identifying pathways of brain hyperarousal and their link to infraslow manifestations in the sleeping brain is an important next challenge that also needs to be addressed in animal research.

2. Sleep-related movement disorders

Of particular interest at the intersection between sleep disorders and sleep spindles are sleep-related movement disorders, in which one observes stereotyped and often repetitive spontaneous activation of different sets of muscles that cause involuntary limb movements, tooth grinding, or abnormal breathing (474). These motor events occur periodically, with a preference over 20- to 40-s intervals, which has prompted the view that NREMS might be particularly vulnerable to arousal-promoting events over the infraslow time scale (FIGURE 6). Indeed, in the case of restless leg syndrome, periodic leg movements occur synchronized with signs of arousal at the level of the EEG and of autonomic symptoms (208). Although the relation to infraslow periodicities found in full-band EEG or band-limited sigma

power measurements needs to be established, these patients show an increased number of CAPs (sect. IVE), which are considered signs of sleep instability in humans. Moreover, a large-scale study quantifying periodic leg movements across the healthy populations correlated with an increased time spent in N2 (259). Sleep-related movement disorders, but also widespread signs of motor arousal in the healthy population, are the currently strongest pathological correlate of arousal modulations identified on the infraslow time scale.

B. Epilepsy

Sleep spindle-generating mechanisms may, when pathologically perturbed, lead to epileptiform activity that shares characteristic EEG waveforms in human and rodent. Typical representatives of these perturbed spindles are spike-and-wave discharges (SWDs). These are sudden-onset, bilaterally synchronous, 3–4 Hz phasic and large-amplitude electrographic events that are typical for several forms of idiopathic generalized epilepsies in children. One of these is absence epilepsy in children, which gives rise to nonconvulsive loss of consciousness for a few seconds, occasionally hundreds of times a day, with severe consequences for daytime cognitive functioning (for review, see Refs. 52, 217, 369). Causal links to spindle generation are derived from amply available rodent and carnivore models of absence seizures. Another example of childhood epilepsy is Dravet syndrome, an epileptic encephalopathy that involves both cortical and thalamic hyperexcitability (514). Thalamic hyperexcitability associated with excessive sleep spindle generation may also be involved in loss of consciousness in temporal lobe epilepsy (203).

SWDs in absence epilepsy typically occur during quiet wakefulness and early sleep across all scalp electrodes (369, 541). Furthermore, many pharmacological or genetic rodent models, complemented by the experimental induction of SWD-like activity in brain slices, suggest that sleep-spindle-generating corticothalamic networks are key for the generation of SWDs (52, 217). Within these networks, there are many sites at risk for excessive synchronization. To these belong 1) abnormally elevated cortical input (66, 420), 2) loss of GABA_A-receptor-mediated lateral synaptic inhibition within the TRN (288), and 3) loss of the GluA4 receptor on TRN cells (475). Cellular studies show that hypersynchronous activity in TRN will lead to excessive GABA release around TC cells, in turn activating not only synaptic GABA_A but also extrasynaptic GABA receptors, such as delta-containing GABA_A or GABA_B receptors (124, 323). The importance of GABAergic mechanisms in TC cells in the susceptibility to generate SWDs is amply documented (52). Prolonged and strong GABA-mediated hyperpolarizations delay rebound discharge in TC cells, yet once it occurs, it is more robust and synchronized than in response to normal GABA_A-only IPSPs. The ensuing more synchronous burst discharge of TC cells is key for triggering

cortical SWDs, as also shown conclusively through inhibitory opsins to force clustered repetitive bursting in TC neurons or to switch them from phasically bursting to tonic discharge (560). The former powerfully induced SWDs even when applied unilaterally; the latter interrupted SWDs in established animal models of SWDs. Apparently contradicting this interpretation, unit recordings from rat models of SWDs found only ~15% of TC neurons discharging a burst per spike-wave event in a SWD (411). However, this study focused on the very densely interconnected whisker-to-barrel system; therefore, comparatively few synchronized TC cells may have a large impact. This TC circuit also projects to higher-order and associative thalamic nuclei via bifurcations in the corticothalamic and the TC-TRN circuitry (sect. VE), which would facilitate synchronization beyond one cortical column. Indeed, combined imaging and EEG studies highlight that different thalamic nuclei play different roles in the functional consequences of seizures, notably in relation to seizure generation and loss of consciousness (203).

C. Age-Related Neurodegenerative Disorders

In age-related neurodegenerative disorders, cognitive decline is exacerbated compared with healthy aging, and sleep disturbances are common. At the same time, these patients present with a diversity of structural and functional alterations in brain stem, thalamus, and cortex, raising the possibility that EEG hallmarks such as spindles correlate with the severity of the disease or might have predictive potential for disease progression. A group of mixed-sex Alzheimer's patients with light dementia and with largely preserved sleep architecture showed a decrease in the number of fast spindles during N2 in central derivations that was twice as strong compared with age-, sex-, and education-matched normal aging controls (507). In spite of this decline, sleep spindle density still correlated with cognitive performance (245, 507). In another case of amnestic mild cognitive decline that can precede Alzheimer's disease, however, many architectural and spectral alterations in sleep and cognitive decline correlated best with changes in SWA and not with the reduction in fast spindle density in frontal derivations (645). With progression of the disease, reductions become so severe that it is difficult to separate the N2 stage from N1. Reductions in sleep spindles are also found in Parkinson's disease patients. Here, subjects with lower fast spindle densities and amplitudes in posterior cortical areas were more likely to develop dementia than patients with comparatively high levels of sleep spindles (356). Although these patients also had smaller SO amplitudes, these were not predictive for dementia. In the most extreme case of premature aging in the Mulvihill-Smith syndrome, a single case study reports an overall absence of sleep spindles and K-complexes (651). These studies indicate that sleep spindle properties could be predictive markers for cognitive decline over a heteroge-

neous range of neurodegenerative processes. Contrary to other neurodegenerative disorders, some Huntington's disease patients show a higher density of sleep spindles (194) or even giant spindles (447, 481).

D. Neurodevelopmental and Neuropsychiatric Disorders

Retarded or perturbed brain growth or maturation underlies a large variety of neurodevelopmental disorders that affect an individual's capacities throughout its life. Some of the best known disorders that globally compromise intellectual, emotional, and social abilities also show disrupted sleep from early infancy on. Sleep and brain maturation are interdependent; causal relationships are thus not clear. Still, the focus on sleep spindles has illuminated some of the relationships between sleep and cognitive development when brain maturation is perturbed (254) (sect. IX). Disorders with rare cortical malformations and seizures often showed unilateral events and/or a lack of bilateral synchrony, although overall spindle counts could be relatively normal (544). Mental retardation of various types, including also the relatively mildly retarded Costello syndrome patients, was accompanied by unusually large spindles at normal frequencies and no seizures (163, 547, 548). Autism spectrum disorders and attentional deficit hyperactivity disorders have in common that they often go with prolonged latency to sleep onset and frequent awakenings. Here, various alterations in spindle-related properties were observed, but an imbalance in fast and slow spindles was common (254), with a tendency for relatively greater slow spindle power in preadolescent autistic infants (519).

Studies on deficits in sleep spindles have accumulated for schizophrenia, a severely debilitating disorder arising out of various combinations of genetic predisposition and environmental stressors. As the disorder combines sleep disturbances with sensory misperceptions, depressive symptoms and memory decline, sleep spindles may help to identify the pathological link between the sleep disruptions and the TC deficiencies that could underlie the cognitive deficits.

Among the many sleep disturbances in drug-naïve or medicated schizophrenia patients (101, 104, 403), a decreased spindle density in N2 or whole NREMS is a most consistent common denominator across patient categories, ranging from early-stage psychosis to chronically medicated groups. A trend for decreased sleep spindle density in first-degree relatives is also reported, independently of whether or not these suffered from neuropsychiatric symptoms (402, 534). In contrast, a compromised generation of sleep spindles is absent in psychotic patients not suffering from schizophrenia. This indicates that spindle deficits are not a general feature of psychosis (101, 403); instead, they highlight a potential vulnerability to develop schizophrenia out of psychosis.

In chronically medicated schizophrenia, there are observations on a decreased ipsilateral coherence (628) and on changes in spindle amplitude and duration (534). Other spindle parameters, notably their coupling to the SO, remain relatively unaffected in human (164) but are altered in neurodevelopmental rodent models of schizophrenia (484). Whether or not fast and slow spindles in human are similarly affected is currently open, with equal decreases in spindle density in frontal and centroparietal derivations (207) or specific decreases in fast spindles reported (534). Reduced sleep spindle density correlated with positive symptoms in early course patients (402) and with overnight consolidation of motor memory (164).

In spite of the heterogeneity of the schizophrenia in terms of structural, neuromodulatory, and functional alterations, thalamus and TRN recur as sites of deficits in various measures. The volume of thalamic nuclei, notably of the mediadorsal one, was smaller (238), and the number of parvalbumin-expressing TRN cells was reduced in post mortem tissue of patients and in animal models (575). Decreased expression of NMDAR subunits, notably of the GluN2C subunit that is strongly expressed at cortical synapses made onto TRN, may result secondarily from the decreased number of TRN cells (293). Schizotypic traits in otherwise healthy subjects correlate with elevated thalamic glutamine and glutamate levels and diminished sleep spindle density (392). Altered thalamic functions may thus be graduated among the population and turn into disease only once a threshold is reached. Furthermore, lists of genetic risk factors obtained in genome-wide association studies encode postsynaptic and voltage-gated Ca^{2+} channels that are central to key elements of spindle-generating circuits (sect. VB). Among the identified genes, two missense mutations were identified in the *CACNA1i* gene encoding the $\text{Ca}_v3.3$ Ca^{2+} channel that reduce the membrane expression levels of the ion channel (21), which is crucial for TRN's function in spindle generation (sect. VB). These are indications of a critical role for the integrity of thalamic functioning as both predisposing and causal agent in schizophrenia.

E. Outlook

Establishing sleep spindles as biomarkers, if not causative factors, in disease is a major goal in the sleep spindle field, in which basic knowledge is substantial and first correlative evidence for potential diagnostic usefulness is available. The current picture is, however, incomplete and blurred by ambiguity between many different pathologies and spindle parameters. Still, the fact that density of sleep spindles is similarly altered in very different diseases indicates that the recruitment of sleep-spindle-generating circuits has many different points of vulnerability. This is consistent with the multiple steps involved from their initiation until their appearance at the cortical surface. Amplitude changes are less frequent and best associated with an excessive synchroniza-

tion, as observed in epilepsy. These are the first steps in a field in which genetic approaches, circuit endophenotypes, and animal models are rapidly coming together to replicate aspects of a human disease. Hopefully, sleep data from well-classified patient subgroups will inspire such approaches to the ultimate benefit of rendering sleep spindles to diagnostic, and possibly therapeutic, tools.

XI. PHARMACOLOGICAL AND TARGETED INTERFERENCE WITH SLEEP SPINDLES

Interference with sleep spindles has a long record in the pharmacological therapy of a broad array of sleep disturbances (410). Well-known hypnotic agents, such as benzodiazepines and the non-benzodiazepine derivatives (also called Z-drugs), increase sigma power at the expense of SWA (9) to promote sleep maintenance. These drugs act allosterically to enhance GABAergic transmission that is key for sleep spindle generation (sect. V, B and C). The Z-drugs show some specificity for sleep spindle modulation and have thus been used to probe sleep spindle function through pharmacological interference.

Interference with high temporal control is now possible with closed-loop feedback strategies that detect spindles in real time and can be coupled with strategies for sleep spindle suppression or boosting. Such targeted interference bears unprecedented possibilities to probe sleep spindles at any moment with respect to a hypothesized function.

A. Pharmacological Interference

Sleep spindle activity is augmented through the hypnotic agents of the non-benzodiazepine drugs (also called Z-drugs), such as zolpidem (class of imidazopyridines), zopiclone and eszopiclone (class of cyclopentenolones, the latter being one stereoisomer of the former), and zaleplon (class of pyrazolopyrimidines) (9, 82, 210, 595, 627). Z-drugs act through positive allosteric mechanisms on synaptically located GABA_A receptors containing the α 1-subunit (sect. V, B and C). Zolpidem and eszopiclone potentiate intrathalamic synaptic inhibition (303) and increase relative sigma power density in all-night power spectra in humans (9, 82, 595). Drug effects are greatest for power >13 Hz (9, 595) and correlated in nap studies with increases in the density of fast and slow spindles by ~ 1 spindle/(min of N2) over central derivations, with minor actions on their amplitude (419). Zolpidem also enhanced the coupling of sleep spindles to the SO together with a facilitating effect on verbal memory (452). The usefulness of zolpidem to pharmacologically boost spindles is further motivated by a good preservation of sleep architecture, although N2 is typically prolonged at the expense of REMS (9, 82, 419, 595) and N3 prolongation was observed during naps (314, 419). Mem-

ory-facilitating actions of zolpidem were found in morning nap studies, where zolpidem treatment enhanced verbal memory recall but did not improve the finger-tapping task (419). In extension of correlational studies, this suggested that N2 spindles could be rate-limiting in declarative memory formation but less so in simple motor skill learning. A nap study using visual memory for pictures found that zolpidem biased memory to negative, high-arousing pictures, as opposed to positive ones (314), thus opening questions into a possible spindle dependence of emotional effects in memory formation. Eszopiclone applied to schizophrenic patients augmented sleep spindle density by ~ 0.2 spindles/min. Memory improvement for the finger-tapping task correlated similarly with spindle density before and after drug treatment, suggesting that the additional spindles contribute to memory formation (627).

In addition to Z-drugs, a variety of other pharmacological treatments support correlations between sleep spindle density increases and memory formation. In a study using serotonin or norepinephrine uptake inhibitors, there was an improved consolidation of the finger tapping tasks in humans that was proportional to the increase in spindle density in N2 and N3 (506). Such pharmacological treatment compromised instead hippocampal-dependent spatial learning in a manner that correlated with the suppression of intermediate sleep (635). Sodium oxybate is a precursor for a GABA_B receptor agonist that strengthens low-frequency power at the expense of sigma power during NREMS. Sodium oxybate reduced fast spindle density by ~ 1 spindle/min without affecting their amplitude (419). However, no effects on declarative or emotional memories were observed (314, 419).

A novel pharmaceutical avenue is opened by the observation that not only synaptic but also nonsynaptic GABA_A receptors are important for sleep spindle generation (sect. VB). This has stimulated efforts in developing drugs targeting these nonsynaptic receptors (197, 626). The need for further drug development is also clear given that Z-drugs act inconsistently between species. In rodents, there is a depression rather than a potentiation of sigma power (15), and there are hypnotic effects through mechanisms involving not α 1- but α 2-receptors (334). There are also compounds, such as E-6199, which greatly increase sleep continuity in mice but which have a minor effect on sigma power (15). In this context, it is interesting to note that zolpidem suppresses CAPs (sect. IVE). Zolpidem also boosts ripple occurrence in rodents (333), suggesting that some of the memory effects observed are unrelated to sleep spindles.

B. Targeted Interference

Targeted interference is used in essentially two different ways.

The first is based on the idea that the brain behaves as a resonator that can be boosted through periodic sensory stimuli or transcranial stimulation techniques (54, 407). For instance, boosting SOs has positive effects on memory formation when using transcranial direct current stimulation (408) or in-phase auditory stimulation (448). Analogously, sleep-spindle-like rhythmicity can be entrained through stimulation in the sigma frequency range. So far, this was done in humans using auditory or alternating current stimulation. In animals, optogenetic strategies were used.

The second way relies on sleep spindles as reactive elements (sect. VIF). The idea is to evoke sleep spindles as a way to promote memory trace reactivation (sect. VIII). This approach, referred to as targeted memory reactivation (505), triggers sleep spindles by re-exposing the sensory cues that were used for initial memory encoding. This approach promises to be more modality-specific and to favor internal memory-consolidating processes.

1. Boosting sleep spindles through resonance

The density of both fast and slow spindles could be increased in parietal derivations with 1- to 2-s-long, 12- or 15-Hz white-noise stimuli, respectively, suggesting that generators for both slow and fast spindles respond independently to resonance (27). These additional spindles showed properties close to spontaneous fast and slow spindles, and they also appeared more frequently on the active state of SOs.

Transcranial current stimulation techniques have also been applied in the context of boosting spindles (26). The most spindle-specific approach is a study on transcranial alternating current stimulation over frontal-parietal areas. This stimulation was used in a closed-loop feedback such that a 12-Hz, 1.5-s-long stimulation started only once a spontaneous spindle was generated (390). When applied during N2, this resulted in an increase in the high-frequency sigma band for a period of up to several seconds after stimulation in a subgroup of subjects. Stimulation electrodes were positioned such that spindle generation was preferentially enhanced around centro-parietal sites, where spontaneous spindles are also dominant. A causal role of fast sleep spindle activity in motor skill learning could be demonstrated, whereas stimulation was inefficient for declarative learning. Transcranial direct current stimulations involving sleep spindle modifications have been described in clinical settings (159).

Optogenetic enforcement of TRN-related synchronized activity was achieved in animals through repetitive 8-Hz stimulation of parvalbumin-expressing TRN neurons in anterior TRN (354). Such stimulation time-locked to the active phase of the SO improved hippocampal-dependent memory, whereas stimulation outside the active phase did not.

Spindle-like activity was generated in prefrontal cortex and hippocampus, pointing to a role of anterior TRN in hippocampal sleep spindle generation and consolidation of declarative memory. This landmark study shows that exploiting regionally specific TRN-dependent synchronous activity helps boost memory. Approaches used in this study can now be refined in terms of optogenetic stimulation protocols and stimulation sites to better mimic physiological sleep spindles and their effects on memory.

2. Targeted memory reactivation involving sleep spindles

Both auditory or olfactory cues used during encoding of memory traces evoked sigma power increases that were greater than those evoked by control cues not used for learning (91, 131). Interestingly, the EEG signal during the sleep spindle elicited by the learned cue could be used to obtain information about the learned material (91). Cues also elicited K-complexes that preceded spindles, but these did not distinguish between cue types (91). In a similar approach, cued responses that successfully elicited sleep spindles also predicted the quality of later memory retrieval. Furthermore, the greater the associated sigma power increase, the better was the later performance (630). Cueing was also successfully used to probe potential different roles in SO-spindle coupling during N2 and N3 sleep in humans (241). These studies represent the so far best evidence that sleep spindles provide neuronal conditions favorable for memory reactivation.

Results from these cueing experiments further support the existence of temporal windows set by slow periodicities of spindles due to refractory processes (sect. VD) and by their organization on the 0.02-Hz time scale (28). Thus cues presented outside of the refractory period of sleep spindles produced a better memory effect than when cues were presented during the refractory period, when spindles were unlikely to be generated.

XII. UNIFYING VIEWS

Sleep spindles are prominent electrical characteristics of the sleep EEG and its modifications by the circadian and homeostatic systems, by experience and learning, and by disease. Beyond these phenomenological characterizations, the cellular and synaptic origins of sleep spindles are well described. Modern research moves closer to interfacing between the circuit basis of sleep spindles and their system-relevant manifestations. Further crosstalk between animal and human research, as repeatedly illustrated in this review, will make it clear that sleep spindles have a much broader impact than expected based on their phenomenological appearance as brief sinusoidal waves. Instead, they transform neural, circuit, and long-range connectivity in the sleeping brain to accommodate core sleep functions. In the authors'

belief, future progress will mainly proceed along the following grand lines (**FIGURE 13**).

A. From Phenomenological Markers to Timers of NREMS Core Functions

Sleep spindles are part of a broader temporal organization of NREMS that touches on fundamental sleep needs. This organization is indicated by a clustering of sleep spindles on the infraslow time scale together with hippocampal ripples and parameters of the autonomic nervous system. These coordinated oscillations render NREMS a continuum of substates with probably different roles, such as the control of behavioral arousability and internal information processing. A more complete assessment of the physiological, behavioral, and pathological implications of these internal dynamics will require the identification of the brain areas involved in the coordination between brain and periphery. The full palette of oscillating elements, from autonomic targets, to hemodynamic states, to Ca^{2+} levels in cortical dendrites, will unravel a pervasiveness of NREMS in generating and coordinating a brain-bodily state. This will ensure a reciprocal crosstalk between brain and periphery to the best benefit of the sleeping organism.

B. From Sinusoidal Waves to Determinants of the Cortical State

A major advance is the recognition that sleep spindles transform excitatory and inhibitory activity across cortical layers. Elucidation of the roles of this spindle-generated cortical state for the external and internal processing during NREMS will undoubtedly provide major insights. For one part, given its inhibitory impact on deep layers, it likely contributes to the spindle-dependent protection of NREMS from external influence. For the other part, given its disinhibitory impact on upper layers, cortico-cortical information transfer and mechanisms of local sensory plasticity may take place. Elucidating spindle-generated cortical states in terms of their particular cellular, dendritic, and synaptic activity is undoubtedly one of the best approaches to reveal the significance of sleep spindles for NREMS.

C. From Memory Correlates to Time Frames for Active Systems Consolidation

Originally supporting correlative evidence for a role of NREMS in memory consolidation, sleep spindles actively generate the neural conditions required for active systems consolidation. Their role involves first their timing. Through the phasic organization of sleep spindles on various time scales, memory-promoting processes are discretized and kept separate from other processes. This involves next their involvement in reactivation of memory

traces and their likely presence in hippocampus to promote particular states of excitability. Research in animals will help to define the pathways along which sleep spindle activity acts in active systems consolidation.

D. From Correlates of Neuropsychiatric Illness to Biomarkers for Cognitive Deficits

Sleep disturbances are widespread in neuropsychiatric disorders, with the pathophysiological links often incompletely defined. Sleep spindles promise to provide some degree of specificity in the diagnostic assessment of TC integrity. Once we understand better the structural and functional determinants of sleep spindle densities, amplitudes, and properties, further diagnostic refinement will be possible. The molecular understanding of sleep spindles may further guide investigations into the genetic and acquired deficits leading to wake-related cognitive deficits. This could bring novel opportunities to exploit sleep as a readout for wake-related cognitive disabilities and to use targeted interference to possibly alleviate symptoms of the disorders.

XIII. THE EPILOGUE

Sleep spindles are one of several major sleep rhythms, but they have singularly contributed to develop a neuroscientific view of what makes NREMS a major vigilance state. This concerns in particular the well-known characteristics of NREMS as a state of behavioral quiescence with preserved sensory reactivity, and as a state of internal replay of recently acquired memory traces. Sleep spindles additionally show that NREMS is formed along a sleep-wake continuum with different degrees of arousal for which neuronal, hemodynamic, and peripheral activities need to be coordinated. The combination of sleep- and neuro-centered aspects of sleep spindles points to a hierarchical organization of sleep rhythms in space and time to accommodate these fundamental needs and benefits. Sleep spindles turn out to be versatile elements for interareal communication and propagation, for plasticity promotion, and for the control of sensory gating. Through these multiple assets, sleep spindles are an integral part of a brain-body organization of NREMS that will move us closer to resolve the enigmas of sleep functions.

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