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Opinion

Aperiodic sleep networks promote memory consolidation

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Hierarchical synchronization of sleep oscillations establishes communication pathways to support memory reactivation, transfer, and consolidation. From an information-theoretical perspective, oscillations constitute highly structured network states that provide limited information-coding capacity. Recent findings indicate that sleep oscillations occur in transient bursts that are interleaved with aperiodic network states, which were previously considered to be random noise. We argue that aperiodic activity exhibits unique and variable spatiotemporal patterns, providing an ideal information-rich neurophysiological substrate for imprinting new mnemonic patterns onto existing circuits. We discuss novel avenues in conceptualizing and quantifying aperiodic network states during sleep to further understand their relevance and interplay with sleep oscillations in support of memory consolidation.

Multiscale rhythms support memory reactivation, transformation, and consolidation during sleep

How does the human brain turn novel experiences into long-lasting stable memories? Over the past four decades a large body of work has established that sleep plays a key role in memory formation [1,2]. The influential active systems memory consolidation hypothesis suggests a two-stage process in which novel information is initially encoded in the hippocampus and the neocortex, and subsequently becomes neocortex-dependent as new information is consolidated [1,3–5]. The sleeping brain exhibits rich temporal dynamics which are thought to subserve this transformation of mnemonic representations [6–9]. During sleep, prominent neuronal oscillations emerge which serve as an intrinsic clocking mechanism for self-organized timed reorganization. Specifically, non-rapid eye movement (NREM) sleep is characterized by slow oscillations [<1.25 Hz; sometimes also including delta activity <4 Hz], sleep spindles (~12–16 Hz), and ripple oscillations (~100–200 Hz)]. Importantly, these cardinal sleep oscillations are thought to emerge from different neural circuits: slow oscillations are most prominent in prefrontal cortex, spindles are thought to emerge in thalamocortical loops, and ripples are most prevalent within the hippocampus [1,7,8,10–12]]. The selective synchronization of these oscillations, which span several spatial and temporal scales, has been suggested to trigger a processing cascade [8,10,13]. Specifically, the occurrence of hippocampal ripples has been associated with the selective reactivation and **replay** (see Glossary) of spiking sequences which reflect novel mnemonic content [7,14,15]. The repeated activation is thought to trigger plasticity, thus imprinting a permanent mnemonic trace (also termed the **engram**).

In this perspective we first review recent evidence supporting and extending the active systems consolidation theory. We discuss evidence that temporally precise **cross-frequency coupling** indexes the integrity of memory pathways but might not convey only memory-specific information. We then review evidence that sleep oscillations constitute discrete **oscillatory bursts** that are interleaved with episodes that are not characterized by prominent spectral signatures

Highlights

The quality of cortical slow oscillation–spindle coupling shapes hippocampal ripple expression and indexes the integrity of memory pathways.

Synchronized and desynchronized network states alternate on a slow timescale to temporally segregate reactivation and subsequent information processing.

Temporally specific disruption of bidirectional network interactions impairs information transfer and leads to increased forgetting.

Desynchronized network states are characterized by broadband electrophysiological signatures potentially reflecting rapid shifts in population excitation–inhibition balance.

Novel methods to conceptualize and analyze aperiodic network states are required.

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and that are often considered to reflect quiescence or noise [16]. The physiologic origins of these non-oscillatory episodes are not fully understood [17]. We utilize the terms **desynchronized**, **aperiodic**, and non-oscillatory network state interchangeably to describe episodes in which prominent oscillations are absent. This encompasses timepoints before and after an oscillatory (e.g., spindle) burst, where the network switches from a synchronized to a desynchronized (or vice versa) state, as well as prolonged episodes that lack a defining periodicity [such as during rapid eye movement (REM) sleep] where no clear oscillatory peak in the power spectrum is discernible and are therefore referred to as aperiodic [18,19].

The prevalence of oscillatory and aperiodic states in the sleeping brain

Although oscillations constitute the most salient feature of electrophysiological sleep recordings, one cannot assume that this also reflects their degree of functional significance. During a typical night of 8 h of sleep, we spend ~25% (2 h) in REM sleep, which in humans is not characterized by continuous oscillations, unlike the very prominent ongoing theta (3–8 Hz) activity observed in rodent REM sleep [20]. Furthermore, we spend ~50% (4 h) in NREM2 and another 25% (2 h) in deep slow wave (NREM3) sleep [21]. NREM2 is characterized by spindle bursts 1–2 s in length which periodically reoccur approximately every 3–6 s [9,13,22]. Hence, one can assume a ratio of ~3:1 of time spent in an aperiodic versus a synchronized state in NREM2 sleep. Likewise, sleep slow oscillations constitute the hallmark of NREM3, but are by definition only present ~50% of the time on average. Taken together, using a conservative estimate, one must conclude that ~50% of total sleep is spent in an asynchronous network state. Note, several definitions for the detection of oscillatory events have been utilized, which might yield varying duration estimates. It is now considered best practice to employ algorithms that establish the presence of oscillations based on relative and not on absolute amplitude criteria, thus resulting in more comparable estimates across different cohorts [21,23].

Collectively, these considerations raise a question: do these non-oscillatory time periods have a functional relevance, or can we discard them as sleep intermissions reflecting random noise? Given that information encoding typically takes place during wakefulness, which is characterized by predominately aperiodic states, it is conceivable that desynchronization during sleep might play a similar role in benefiting further processing of newly encoded events [19,24].

We discuss here these aperiodic network states and argue that episodes without prominent oscillations reflect a less-ordered neural state. From an information-theoretical perspective, random neural activity provides more unique patterns and increased **complexity**, thus constituting the optimal milieu to imprint new information onto existing circuits. By contrast, during oscillatory bursts, the underlying population is firing in synchrony, thus limiting their information-processing capacity. This consideration implies that optimal information processing necessarily needs to occur after discrete oscillatory bursts. We discuss recent empirical evidence in support of this consideration and conclude by discussing how aperiodic activity can be conceptualized and how it might relate to the underlying circuit architecture, specifically with respect to the **excitation–inhibition (E/I) balance**. Given the high degree of interspecies similarity of sleep oscillations, we speculate that aperiodic activity might reflect a suitable level of abstraction to understand the increased coding capacity in the human brain. Jointly, this will provide a perspective on how oscillations in concert with broadband aperiodic activity provide the necessary substrate for plasticity and imprinting of novel information onto existing circuits.

Recent trends in understanding systems memory consolidation

The conceptualization of the two-stage process of memory formation typically takes a hippocampus-centric perspective [6,7,25]. Specifically, the hippocampal ripple is proposed to serve as a

conductor that orchestrates the network organization supporting sleep-dependent memory formation [7,26]. For instance, electrical or optogenetic manipulation of hippocampal ripple expression has a profound impact on cortical slow oscillation–spindle timing and subsequent memory formation [10,27]. Similarly to work in rodents, replay of novel mnemonic information constitutes a ripple-triggered process in humans [15]. In line with these considerations, evidence suggested that longer ripples exert a stronger influence on neocortical circuits and subsequent behavior [28,29]. In the same vein, low-frequency activity also exhibits multiple distinct facets. It has been reported that slow oscillations (<1.25 Hz) and delta activity (~1–4 Hz) constitute two distinguishable phenomena which also subserve distinct functions [30]. Optogenetic manipulation of spiking that was coupled to slow oscillations strengthened the hierarchical oscillatory coupling and improved mnemonic performance. By contrast, optogenetic manipulation of delta activity weakened memory consolidation, indicating that slow oscillations and delta activity have dissociable roles in memory formation and opposite effects on behavior [30].

Taken together, these findings have further refined our perspective on systems memory consolidation by highlighting previously underappreciated nuances. Crucially, at first sight several recent findings seem to contradict the classic theory. For instance, ripples were thought to constitute a uniquely hippocampal feature, but have now also been observed in adjacent regions in the medial temporal lobe [7,13,31] as well as in neocortical association areas [32,33]. To date, the role of neocortical ripples is insufficiently understood, but the preliminary evidence suggests that tight temporal coordination with their hippocampal counterparts is necessary for memory formation during wakefulness and sleep [32,33]. Crucially, these findings also indicate that the neocortex might be more involved in encoding novel information than was previously thought. These considerations are nicely paralleled by a recent set of imaging findings collectively suggesting that the neocortex is in fact a rapid learner and does not necessarily require hippocampal input [34]. In a related set of studies, several groups have demonstrated a reversed directionality for the hippocampal–neocortical dialogue and reported that neocortical activations in fact trigger and shape the hippocampal ripple expression and associated replay. For instance, activity in the prefrontal cortex [13,29,35], anterior cingulate [36], or temporal cortex [37] has been shown to modulate hippocampal reactivations, which in turn again modulate neocortical areas, thus constituting bidirectional interactions.

Currently, less is known about the role of REM sleep in memory consolidation. Although there is growing evidence that REM sleep is also involved in memory formation [20,38], the precise mechanisms are unknown. A particular focus has been on the hippocampal theta rhythm (~3–8 Hz), which is less pronounced in humans than in rodents [39], and to date it is unclear if these constitute functional homologs. In a related line of inquiry, it had been argued that REM might play a key function in maintaining network hemostasis by adjusting the balance of excitation and inhibition [40,41], which will be discussed in detail below.

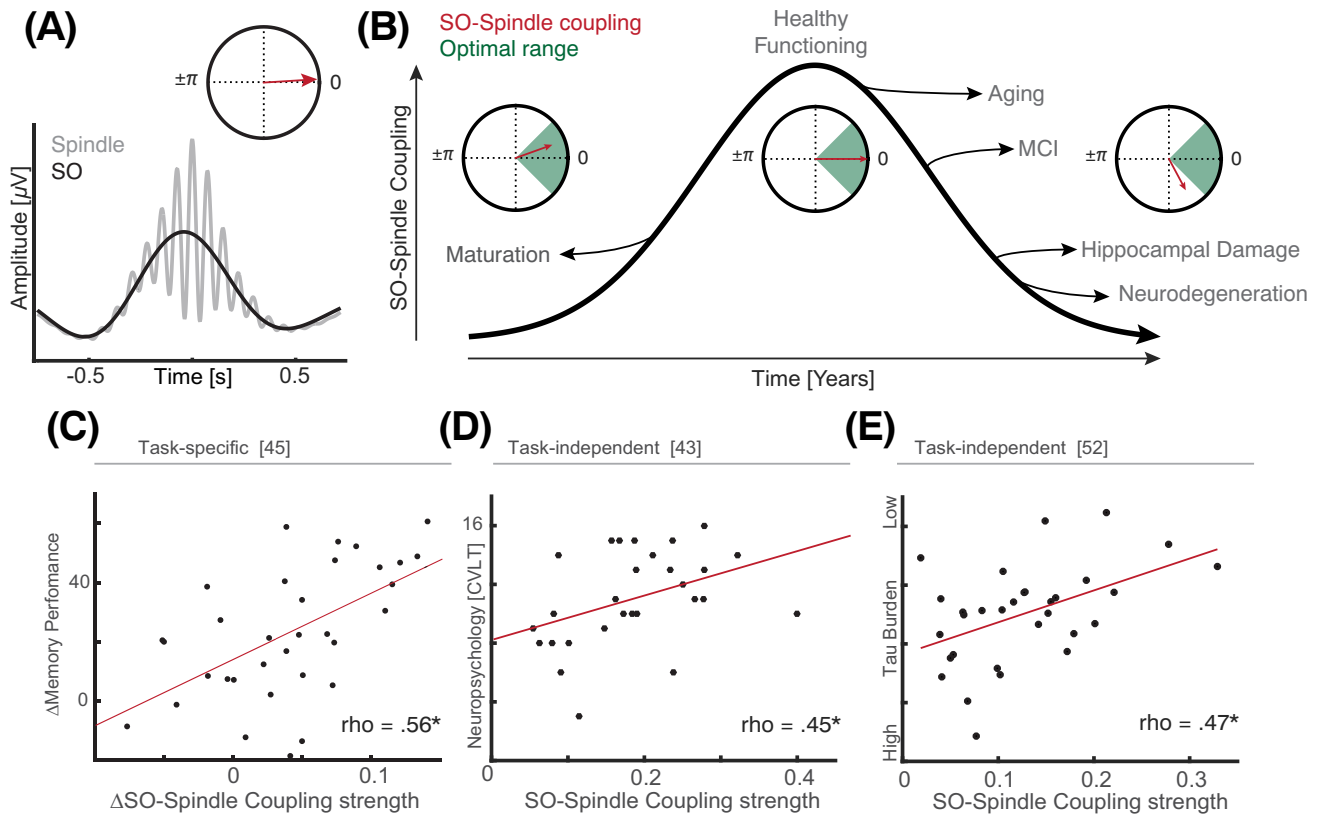### Out of sync, out of memory: integrity of memory pathways is indexed by precision of the temporal coordination

Sleep oscillations do not occur in isolation, but often emerge sequentially on a rapid timescale [1,8]. Crucially, cardinal sleep signatures do not merely coincide in time, but are synchronized to each other through phase–amplitude cross-frequency coupling (PAC) where the oscillatory phase of the slower frequency modulates the amplitude of the faster component [1,8,13,42]. For instance, it has repeatedly been shown that the slow oscillation phase predicts the spindle amplitude (Figure 1A) [8,43–45]. Likewise, the slow oscillation phase also modulates ripple amplitude, which in turn is also comodulated by the spindle phase [8,13]. Most commonly, the coupling strength (the magnitude of how strongly these events are coupled to each other, as

Power law: one parameter scales as a function of the power of a second parameter. Amplitude in the brain typically scales as a function of $1/f^x$, where x denotes an exponent ranging between –2 and –4.

Replay: periodic reoccurrence of neuronal firing patterns, which first occurred during initial encoding and are now repeated, predominantly during non-rapid eye movement (NREM) sleep, and that are thought to strengthen mnemonic representations. Replay can be time-compressed and/or forward and backwards.

Shannon entropy and information theory: a quantification of signal variability that effectively assesses the uncertainty about a signal or the probability of observing a distinct state. Information theory builds on the entropy framework and quantifies information as the degree to which uncertainty about a signal can be reduced given a known input signal.

Two-photon calcium imaging: a modified type of fluorescence microscopy. Different cell types can be labeled *in vivo*. Laser light is then used to excite molecules of a fluorescent dye, and local calcium concentrations can be inferred from fluorescence intensity changes.

Figure 1. Slow oscillation (SO)–spindle coupling across the lifespan tracks the integrity of memory pathways. (A) Spindle activity (grey) is nested in the SO (black), preferably in the up-state (close to the SO peak or, as shown in the inset, close to 0°). (B) Coupling between SOs and spindles can be quantified by their coupling strength (length of the vector in red) as well as by their coupling direction (where the vector is pointing). Several studies have suggested that there is a narrow (<90°, in green) optimal window to successfully initiate the hippocampal–neocortical dialogue in support of memory formation. Crucially, SOs and spindle first grow into synchrony during maturation, whereas temporal dispersion can be observed later in life as a function of age- or disease-related cognitive decline. Examples include age-related prefrontal atrophy [43,44], mild cognitive impairment (MCI) [53], hippocampal damage after autoimmune encephalitis [51], and precursors of neurodegenerative disease [52,55]. (C–E) SO–spindle coupling has been found to track both task-specific behavioral performance (C) and task-independent metrics such as neuropsychological test scores (D) or the burden of precursors of imminent cognitive decline (E). Jointly, these findings suggest that SO–spindle coupling indexes the integrity of memory pathways, which constitute the foundation for information transfer in the prefrontal cortex (PFC)–medial temporal lobe (MTL) network. The graphs in (C–E) are adapted from data reported in [43,45,52].

determined by correlation) was quantified and linked to metrics of behavioral performance [42,46]. It recently became apparent that the precise timing is crucial [43,44]: it does not only matter that a spindle always peaks at a consistent slow oscillation phase, but the spindle must occur at a specific phase angle within the slow oscillation cycle (Figure 1B). The subsequent processing cascade in the hippocampus is only triggered if the spindle hits this narrow 'sweet-spot' [13]. In recent years it has been demonstrated that multiple age- as well as disease-related deficiencies impair this coupling, which in turns predicts mnemonic deficits and cognitive decline (Figure 1C–E).

The brain generates slow oscillations and spindles from early childhood, but these only become strongly coupled during the maturation and development of the memory system (Figure 1C) [45,47,48]. By contrast, during healthy aging, these oscillations undergo temporal dispersion and become increasingly uncoupled and less precise in their timing [21,43,44,49,50], thus leading to increased forgetting. Crucially, pathological insults at multiple network nodes can impair the

coupling. For instance, age-related atrophy in the medial prefrontal cortex (PFC) diminishes slow oscillation–spindle interactions and cognitive efficacy (Figure 1D) [43]. Similar effects can be observed after autoimmune-mediated encephalitis affecting hippocampal functioning [51] or deposition of precursors of neurodegenerative disease [52], and coupling precision errors increase as degeneration commences [53–55].

Importantly, slow oscillation–spindle coupling has repeatedly been linked to mnemonic performance. Depending on the task, both coupling strength and coupling direction are predictive of either declarative or procedural memory tasks, respectively [43–45,56,57]. Crucially, most studies have ruled out confounding factors such as oscillatory amplitude, number of events, or broadband changes. Despite these careful controls, slow oscillation–spindle coupling correlates with performance, mostly irrespective of the task. Furthermore, there are several related reports that coupling metrics also correlated with overall neuropsychological test scores (Figure 1D) [43] or metrics of structural integrity (Figure 1E) [52]. Given that correlations can be seen for both task-specific (performance in a given task or reactivation of specific mnemonic traces [45,58,59]) as well as task-unspecific variables (trait-like characteristics such as overall neuropsychological test scores or metrics of structural integrity – i.e., grey matter density) [43,52]), one might conclude that coupling metrics do not necessarily index specific mnemonic content, but more likely non-specifically index the overall functionality of memory pathways. This consideration is in line with the observation that transient electrical volleys in the form of either direct brain stimulation [60] or endogenous epileptic activity [61] may engage these circuits, as indicated by spindles that exhibit physiologic waveform shapes. It is currently unknown whether these events constitute pathologic pseudo-spindles that lack function or whether this phenomenon is the result of network resonance in response to the electrical volley [61–63].

This consideration is paralleled by a set of recent findings that revealed a variable memory response following hippocampal ripples [64]. Variability here reflects the fact that a single ripple oscillation can trigger multiple responses depending on the state of the receiving region, reflecting either reactivation of specific mnemonic trace or a variable, unspecific and potentially 'content-free' response. This lack of specificity could imply that an oscillatory burst conveys unspecific information and mainly indexes the network engagement.

Information processing in the sleeping brain: stable representations in a dynamic system

Sleep oscillations are not a continuous phenomenon, but appear in bursts. At every occurrence, the precise manifestation is variable and depends on the present network state. For instance, it has recently been shown that hippocampal ripple expression is dynamically shaped by the precision of cortical slow oscillation–spindle coupling. Specifically, if the spindle failed to peak within a narrow phase range, hippocampal ripple expression was diminished [13].

Furthermore, several lines of inquiry converge on the notion that spindle bursts do not occur at random timepoints, but follow a rhythm on a slower timescale [9,13,22]. Rhythmic spindle bursts relative to hippocampal ripples were first described in rodents [9], albeit on a slower timescale (approximately every 12 s). Recently, similar observations were made in humans (~3–6 s; Figure 2A). This set of findings implies that this slower rhythm delineates episodes of high synchrony (oscillations) from aperiodic states (absence of oscillations) because, for example, ripple expression is intricately linked to spindles [7,8,10]. Notably, spindles might also occur in isolation, and it is currently unknown whether spindle trains differ in their function from isolated spindles [65].
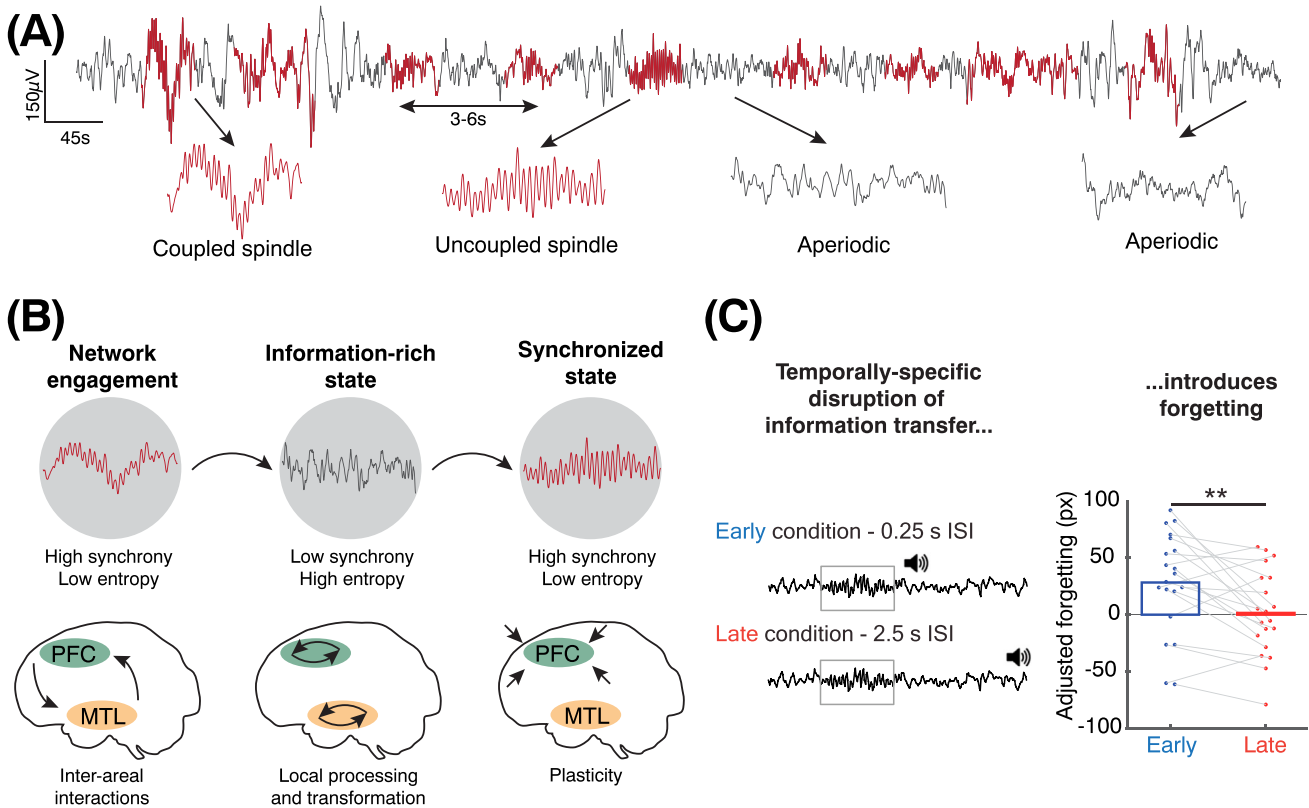
Figure 2. Spindle timing and information transfer. (A) 45 s of non-rapid eye movement (NREM) sleep (electrode Cz, black) with superimposed spindle oscillations (in red). Arrows highlight distinct signatures of NREM sleep, including (left to right) spindles nested in slow oscillations (SOs), uncoupled spindles, and two examples of aperiodic states. Note, spindles exhibit a second-order temporal structure and recur rhythmically every ~3–6 s. (B) Schematic of how the different NREM states might contribute to memory consolidation. Note, it is currently unclear whether coupled and uncoupled spindles are functionally distinct, and it is unknown in which sequence oscillatory and aperiodic states alternate. (Left) Coupled SO–spindles trigger bidirectional hippocampal–neocortical interactions (as indicated by the arrows). (Center) During aperiodic states, networks might switch to local processing to enable transformation of mnemonic content (arrows indicate local processing loops). (Right) Highly synchronized population activity is necessary to mediate synaptic plasticity to enable long-term neocortical storage. (C) (Left) Auditory-triggered disruption of information transfer. A sound was presented directly after an oscillatory (grey box) event (0.25 s, early) or with a longer temporal delay (2.5 s, late). (Right) Only early sound presentation selectively disrupted information transfer, as indicated by an increased forgetting rate. (C) Reproduced, with permission, from [22]. Abbreviations: ISI, inter-spindle interval; MTL, medial temporal lobe; PFC, prefrontal cortex.

It remains puzzling how a dynamic system, which exhibits constant waxing and waning of activity patterns, can implement the formation of stable and long-lasting mnemonic representations. Several approaches were recently introduced to trace mnemonic representations during sleep. For instance, methodologies such as **decoding**/classification or similarity analyses have all been applied to sleep recordings (Box 1) [66,67]. Crucially, most methods implicitly assume that the underlying pattern remains mostly stable with a fixed succession of, for example, firing cells [68]. Although the majority of evidence for replay was obtained from single-cell firing, similar approaches have been utilized at the level of field potentials [58,59]. To date, it remains unclear what level of abstraction is necessary to successfully track a memory trace throughout consolidation [69]. Importantly, recent advances show that population activity provides an information content comparable to the underlying single-unit firing patterns [70]. Specifically, intracranial recordings in humans provide high explanatory power because it has been shown that decoding in sensory and frontal areas based on high-frequency activity (HFA, ~70–150 Hz) [71,72] contains more decodable information than single-unit firing or scalp electroencephalography (EEG) activity [73]. Furthermore, this HFA signal does not solely

> **Box 1. Tools to estimate information content in the sleeping brain**
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> Sleep is thought to subserve the processing of mnemonic information. However, it is non-trivial to study endogenous information processing during sleep in the absence of external input. Several studies circumvented this issue by presenting auditory or olfactory cues during sleep [91–93], which enabled event-related analysis. However, this technique does not allow the study of truly intrinsic processing of memory traces during sleep. Several approaches recently moved away from an activation-based framework and adopted an information- or representation-based framework [94,95], which can also be applied to continuous recordings where no external events are present. Using either multivariate classification (sometimes also termed decoding or discrimination [67]) or representational similarity correlation [96]) analyses, several groups have started to assess whether neural patterns that were present during encoding are spontaneously recapitulated during sleep. These techniques assume a relatively stable representation during sleep, despite dramatically different electrophysiological features (see Figure 3B in main text). An algorithm is trained on a specific pattern that was present during learning or awake retrieval. Next, sleep recordings are searched for evidence that a similar pattern reoccurs, which, based on likelihood estimations (e.g., correlation with behavior or permutation statistics), is then considered as evidence for reactivation. The mutual information framework constitutes a related approach to detect similarities between encoding, retrieval, and sleep patterns [13]. Recently, reactivation and decoding approaches have also been combined to study sleep-dependent learning [97]. The authors demonstrated that periods of memory reactivation span several seconds, encompassing both oscillatory as well as aperiodic states. Furthermore, the results indicated that the duration of memory reactivation exceeded the typical duration of sleep spindles, further supporting the notion that processing entails aperiodic states. One shortcoming that applies to all these techniques is that it is currently unclear what the most informative features are. In other words, there is no consensus on which level of abstraction is necessary to extract memory-specific information from neural recordings [98]. As an example, is it sufficient to quantify a spatial pattern, or do we need to incorporate precise temporal information?

reflect population-spiking activity, but captures additional afferent inputs, thus further increasing its information content [74].

Collectively, oscillations reflect highly temporally and often also spatially, structured sequences that can be captured by a few parameters. In the **Shannon entropy and information theory** framework [75,76], oscillations reflect states of high order and consequently of low Shannon entropy [77,78]. Crucially, low entropy states reflect limited information capacities and are suboptimal for imprinting novel information [79]. By contrast, aperiodic states reflect higher levels of entropy, thus providing additional capacity to encode new information [24,77]. In line with this consideration, several recent studies showed that inter-areal information flow is actually enhanced after an oscillation and not during the oscillation itself [13,22,59]. These findings contribute to the notion that oscillations serve as a messenger signal, but that information transformation might occur during a desynchronized state where synchrony and shared information cycle in antiphase (Figure 2A,B). After a hippocampal ripple, the directed influence from hippocampus to neocortex does not peak immediately, but ramps up only after 1–2 s, preceded by information flow from PFC to hippocampus [13]. Crucially, it has been observed that, if a sound is presented directly following an oscillatory event (<1 s), the processing cascade is disrupted, resulting in less information flow and leading to increased forgetting (Figure 2C). One testable hypothesis that emerges from these considerations is that oscillation-locked decoding should peak after, and not during, the spindle or ripple event [58,59]. Moreover, recent evidence revealed that replay signatures at the level of brain-wide networks exhibit broadband and not narrow-band signatures [80], further substantiating the notion that information processing is maximized during asynchronous network states (Figure 3A).

Collectively, this set of findings suggests that the neocortical interplay of slow oscillations and spindles triggers hippocampal reactivations. Thereafter, the cortex goes from a synchronized into a desynchronized state to maximize processing capacities when reactivating mnemonic information. Similar considerations might apply to episodic memory formation during wakefulness [77,81], but is currently unknown whether the outlined principles are generalizable between wakefulness and sleep.
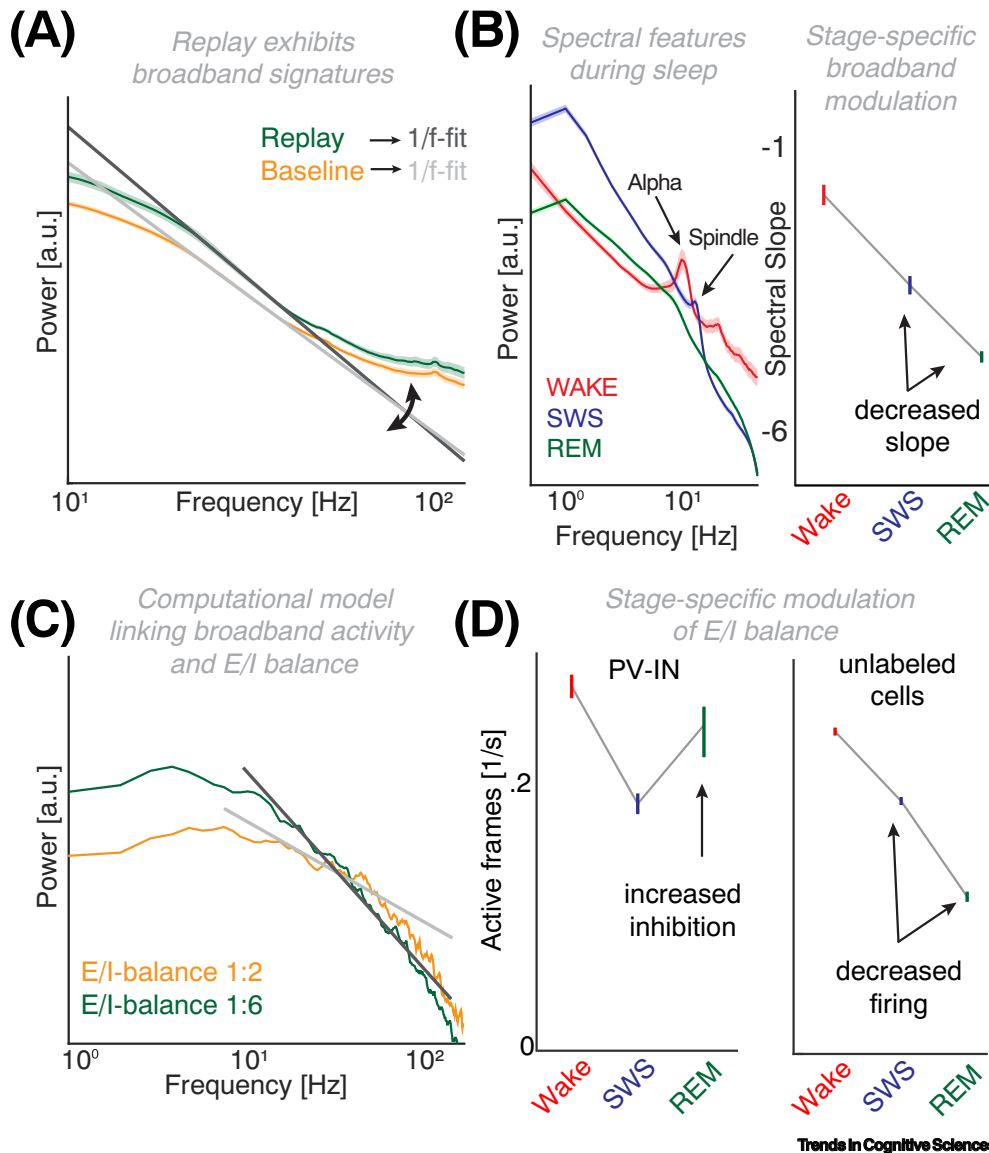
Figure 3. Non-oscillatory electrophysiological features track excitability during sleep. (A) Replay of information (green; baseline in orange) is not frequency-specific but exhibits broadband spectral signatures. Superimposed (dark and light grey) spectral slope estimates that show a shift along the *y* axis and imply a rotation of the power spectrum. (B) (Left) Electrophysiological power spectra during sleep. During wakefulness alpha oscillations at ~11 Hz are prominent (red), whereas slow-wave sleep (SWS, blue) is characterized by increased delta (<4 Hz) and spindle power (~16 Hz). Note that rapid eye movement (REM) sleep (green) does not exhibit any prominent oscillations, as indicated by the absence of a characteristic bump exceeding the 1/*f* drop-off. (Right) Quantification of the slope of the 1/*f* drop-off reliably distinguishes between sleep stages. (C) Computational model linking the shape of the power spectrum to the balance between excitation and inhibition (E/I balance). Increasing the level of inhibition from 1:2 (orange) to 1:6 (green) resulted in a steepening of the power spectrum slope. (D) Two-photon calcium imaging demonstrated a relative increase in inhibition. (Left) Inhibitory parvalbumin[+] interneuron (PV-IN) activity was increased during REM sleep. (Right) Overall firing rates were reduced during SWS and REM sleep. This effect was highly significant for unlabeled cells, including pyramidal cells as well as somatostatin interneurons, thus nicely mimicking the distribution observed for human slope estimates at the population level [*cf* (B), right side]. In summary, this set of findings indicates that a relative increase in inhibition is mediated by a decrease in overall firing as well as by an increase in inhibitory drive. (A) Modified, with permission, under the Creative Commons CC-BY license from [80]; (B) was published under the CC-BY license and was adapted, with permission, from [18]; (C) adapted, with permission, from [87]; and (D) adapted, with permission, from [88]. Abbreviation: a.u., arbitrary units.

The physiologic basis of non-oscillatory brain activity during sleep

Neuronal oscillations are thought to emerge from the synchronized firing of multiple neurons within a population [82,83]. Conversely, it could be assumed that desynchronized electrophysiological field patterns should also be the result of asynchronous neuronal firing [84]. However, to date it is not established how the collective firing of different neuron types gives rise to the local field potential [82]. Several lines of research suggest that there might be a region- and state-specific transfer function between spiking activity and field potentials [85].

Traditionally, spectral analyses have been used to determine neuronal oscillations, and similar methods have been adopted to quantify the absence of oscillations (Box 2) [86]. It is also evident that spectral transformations of sleep data exhibit rich state-dependent signatures (Figure 3B) [18]. Although oscillations can be identified as bumps that exceed the $1/f$ drop-off in the power spectrum, several recent attempts have parameterized the $1/f$ decay and linked it to physiology [19]. When displayed in log–log space, the power spectrum can be estimated by a linear fit in which both the offset on the y axis and the slope have been linked to population firing [84,87]. One model proposes that the steepness of the slope of the power spectrum is linked to the balance of excitation and inhibition in the underlying population (Figure 3C). Although the model only accounted for ~24% of the variance in the empirical data, it provided an additional perspective into both monkey and human recordings. Inhibition was boosted by the administration of the GABAergic anesthetic propofol. In both species, the slope became steeper when inhibition increased [18,87]. When applied to sleep data, it was found that the slope distinguished between different sleep stages and specifically delineated REM from both wakefulness and NREM sleep, solely based on the electrophysiological recordings (Figure 3B) [18]. Crucially, the slope during REM was found to be more negative than during NREM, indicating an increased level of inhibition. This consideration was paralleled by a recent **two-photon calcium imaging** study which revealed a comparable pattern at the level of population firing [88]: First, overall firing activity was decreased during REM sleep, but firing of inhibitory cells was selectively increased, thus constituting a relative shift of the E/I balance towards inhibition (Figure 3D). Moreover, a recent study employing magnetic resonance spectroscopy provided complementary results by demonstrating a learning-specific shift towards inhibition during REM sleep [89]. A functional and behavioral dissociation in NREM sleep was observed in which excitability and overall performance were increased, irrespective of pre-sleep learning. It had previously been observed that REM sleep subserves downscaling of excitability in cortical networks, which was accompanied by changes

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Box 2. How to quantify non-oscillatory brain activity

Time-series analysis in neuroscience often utilizes spectral analyses, such as Fourier, Hilbert, or wavelet transforms, to study the activity in distinct frequency bands [86]. For instance, in sleep EEG, the Fourier transform is commonly used to obtain a power spectrum where individual peaks can be detected (e.g., in the spindle band [99]). Subsequently, activity in this frequency band can be extracted using band-pass filtering combined with a Hilbert transform to extract amplitude- and phase-specific information. However, it is less common to study timepoints in sleep electrophysiology where no prominent spectral signatures are present [100]. This raises the question of how to quantify network states where strong oscillations are absent. One approach that has been motivated by physics is the analysis of $1/f$ characteristics, which have often been interpreted as a **power law** [17]. Several tools have been introduced in recent years to disentangle oscillatory activity (which exhibits a defining temporal scale with a fixed period) from non-oscillatory or aperiodic activity [18,19,87,101,102] which lacks defining temporal characteristics (and is therefore sometimes termed 'scale-free'). These approaches include polynomial fitting of the power spectrum, Gaussian modeling [19], and irregular resampling [101] of the time series. What all approaches have in common is that they enable the extraction of parameters that describe the statistical regularities of the background activity and are well suited for quantifying states that lack prominent oscillations. Crucially, these tools still require a spectral transformation at some point in the process. Currently, only a few approaches solely operate in the time- and not frequency-domain [103,104]. Future developments will need to take techniques into account that can quantify temporal regularities, for instance based on waveform shape [105], which are not obvious to the naked eye, but might contain complementary information to more established algorithms.

in both firing as well as spectral power [40,41]. Crucially, this effect spanned almost all frequency bands, which implied a change in the aperiodic background activity.

Collectively, although we are at the beginning of understanding how unit firing, population activity, and network oscillations are related, several recent empirical findings have provided a perspective on how to conceptualize both oscillatory as well non-oscillatory brain states in relationship to network homeostasis between excitation and inhibition.

Concluding remarks

The mechanisms that support the self-organization of the sleeping brain to optimally support information reactivation, processing, transfer, and consolidation remain elusive. Converging evidence suggests that sleep oscillations may provide key messengers to coordinate memory consolidation in space and time. These oscillations likely constitute an endogenous timing mechanism that provides distinct windows of opportunity for information processing, as exemplified by the spindle pulsing every 3–6 s, which might segregate reactivation, transfer, and consolidation. Importantly, selective synchronization within narrow time-windows might serve as a tuning mechanism – similar to a radio dial – to selectively engage communication channels [13,90], as indicated by slow oscillation–spindle coupling that precisely indexes hippocampal ripple expression and subsequent reactivation [8,10,13,30,58].

Crucially, we argue that aperiodic states, which are interleaved with oscillatory states, provide an information-rich state to transform, consolidate, and eventually imprint new information onto neuronal circuits. However, our understanding of aperiodic episodes is limited and many questions remain (see Outstanding questions). We have reviewed evidence suggesting that the absence of temporal structure might actually be beneficial for information coding. This concept will also require the development of novel tools to quantify non-oscillatory activity.

Finally, it is important to highlight that this theory is fully compatible with previous considerations because it implies that oscillations, in concert with broadband activity, jointly support information coding. Collectively, we propose an oscillation-mediated dynamic process with rapid cycling between synchronized and desynchronized states that each subserve distinct elements of sleep-dependent memory formation, namely triggered reactivation and subsequent processing for consolidation.

Declaration of interests

No interests are declared.

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Outstanding questions

How does the sleeping brain achieve specific reactivations? Does slow oscillation–spindle ripple coupling precision serve as a temporal code to selectively retrieve information?

What are the functional roles of short- and long-duration ripples? At which point in the processing hierarchy is the duration of the oscillatory burst read out and used for subsequent computations? Likewise, do the same principles extend to slow oscillations and spindles?

What are the precise functional differences between slow oscillation-coupled and -uncoupled spindles? Do spindles that occur in trains differ in their function from spindles that occur in isolation? What is their relationship with aperiodic activity, and what are the organizing principles of their interplay?

Why are sleep oscillations highly similar in different species, despite dramatically different cognitive capacities? Which neural markers reflect the increased information-coding capacity in the human brain?

How can time-varying, ever-changing neural activity support the emergence of stable and long-lasting mnemonic representations?

Are aperiodic network states a brain-wide phenomenon, or do they also occur locally? What is the interplay of aperiodic activity in different network nodes, such as the hippocampus and PFC?

Are aperiodic states as observed during wakefulness, NREM, and REM sleep related? Do different aperiodic episodes exhibit similar functional properties, or do they reflect a multiplexed signal? Does the duration of aperiodicity play a functional role in memory consolidation?

How does aperiodicity relate to plasticity, which typically requires highly synchronized inputs? Alternatively, is plasticity only mediated by oscillations?

What is the spatial structure of aperiodic network states? Do co-occurring desynchronized states delineate distinct large-scale networks? How are

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oscillatory and aperiodic networks related?

Do spindle timing and inter-spindle intervals correlate with mnemonic capacities?

Do ripples in humans and rodents support the same functions, despite pronounced differences in their peak frequency?

What is the functional significance of 1/f-scaled background activity? How is population firing linked to spectral parameters? Do distinct spectral parameters (slope, offset, autocorrelation function, band-limited features) index homeostasis?

What is the appropriate level of abstraction to study memory reactivation and its relationship to aperiodic activity: neural firing, field potentials, local circuit activity, or large-scale population activity as measured at the network level?

Do the principles of the interplay between synchronization and desynchronization during sleep generalize to wakefulness?

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