Chapter 4

Sleep Spindles – As a Biomarker of Brain Function and Plasticity

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1. Introduction

1.1. Overview of spindles as thalamocortical (TC) oscillations

Spindles appear in the EEG as sinusoidal waves with frequency in the range 11 to 16 Hz. Together with K-complexes they are the hallmarks of NREM sleep and their appearance is taken as evidence of the onset of light sleep. Their specific distribution and exact frequency, changes in early and late sleep during the night. Sleep spindles are also known as "sigma waves" a term initially recommended (1961) but later discouraged by the International Fenderation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN), and redefined as a "group of rhythmic waves characterized by progressively increasing, then gradually decreasing amplitude"[1].

Spindles are one of the basic TC EEG rhythms appearing in sleep, these include the slower rhythms in the 0.05–1 Hz (slow rhythm), the 1-4 Hz (delta rhythm), and the 8–12 Hz (alpha and mu rhythms) .On the other side of the spindle frequency range we encounter the higher rhythms in the 16 to 25 (beta band), the 26 to 90 Hz (gamma band), the 100-200Hz bursts (hippocampal ripples that are associated with spindles) and the 300–600 Hz (ultrahigh-frequency oscillations) [2]. Although spindles have been the most thoroughly studied of these rhythms, in experimental animals as well as humans, with electrophysiological, metabolic, brain imaging and pathology, molecular genetic and computational modeling methods, their nature is still elusive. Their role has been debated for a long time but it is now believed that their contribution includes sleep promotion and maintenance associated to sensory gating, motor representation development, and cognition and memory consolidation.

The existence of two types of spindles were first described by Gibbs and Gibbs (1964), which differed in frequency by approximately 2-Hz; fast spindles, with a frequency of 14-Hz in the centro-parietal region; and slow spindles with a frequency of around 12 Hz, which are more

pronounced in frontal region [3]. Recent studies using simultaneous EEG and MEG recordings have clarified multiple simultaneously activating cortical sources of two types of spindles in the centro-parietal areas [4-6], involving motor and sensory-motor cortex.

In this chapter we will review the basic mechanisms of sleep spindles and consider their possible uses as biomarkers for the state of the brain, focusing specifically on recent work on changes in sleep spindle activity during recovery from stroke.

2. Neural mechanism of sleep spindles during NREM sleep

2.1. Neural mechanisms underlying spindle generation

The existing fragmented views of the spindles' underlying mechanisms constitute a formidable puzzle. The main questions addressed so far will be covered in the following subsections.

Spindles and the neuronal mechanisms underlying their generation have been extensively studied in experimental animals [2,7] It is important to distinguish the mechanisms underlying the spindle rhythm generation, those producing the electrical sources of spindles recorded on EEG/MEG and those responsible for triggering, spread, synchronization and stopping this rhythm.

The **spindle rhythm** is considered to be paced from thalamus since it disappears after destruction of thalamus and survives in decorticated animals and even in thalamic slices [8]. The spindle frequency is basically determined by an interplay between the mutually interconnected GABAergic inhibitory neurons of the reticular nucleus of thalamus (RT) and the TC neurons (Figure 1), their intrinsic properties and their influence by cortical as well as brainstem ascending inputs. RT neurons impose hyperpolarization on TC neurons. This activates a nonspecific cation current, Ih, which depolarizes TC neurons and thus leads to activation of low threshold Ca++ currents (LTC) and bursting. The latter feeds back excitation on RT neurons, thus closing the loop and preparing for the next cycle. Each TC bursting besides feedback to RT imposes on pyramidal neurons an EPSP, which underlies each EEG spindle wave. The degree/duration of IPSPs imposed by RT on TC determines the intra-spindle frequency, but corticothalamic inputs have a decisive role on this pacing mechanism. This mechanism explained the old observation of two modes of TC activity, a rhythmical bursting and a tonic activity, the former prevailing (in the form of spindles or delta EEG waves) during quiescent NREM sleep and the latter in wakefulness. A simple common path for initiating the bursting mode is the hyperpolarization of potentially bursting neurons, so that Ih would be de-inactivated. Brainstem, hypothalamic, basal forebrain and the quantitatively most prominent cortical afferents to nRT neurons gate through this hyperpolarization the involvement of TC neurons in this cyclical interaction with nRT. This leads to the swich of TC neurons from tonic to bursting mode. Since the bursting mode is incompatible with faithful relay of sensory information to the cortex, spindles assume a gating role of dynamic sensory deafferentation during sleep.

Regarding the **electrical generators** of spindles, depth EEG recordings in humans have demonstrated superficial as well as deeper frontal cortical sources as well as sources in ventrobasal thalamus, which are usually but not necessarily synchronous to those on scalp EEG [1]. Animal experiments using depth profiles and intracellular recordings in thalamus and cortex have demonstrated that individual EEG spindle waves are scalp reflections of currents generated in cortex by EPSPs of cortical neurons. The elementary dipoles are considered to be generated primarily on the long apical dendrites of single pyramidal neurons; their extracellular current return branch contributing to EEG. These EPSPs are usually subthreshold depolarizations of apical dendrites and so give rise to smooth surface negative waves (type I spindle waves resembling recruiting responses). Only a few of the TC EPSPs progress from apical dendritic depolarization to deep soma and basal dendritic depolarization leading to cell firing and are shown on EEG as negative –positive sharper spindle waves (type II resembling augmenting responses). A spindle is usually a mixture of these two types of spindle waves [9]. These elementary dipoles will generate EEG spindles to the degree that they occur synchronously in a large number of neurons and in accordance to the rules of volume conduction in brain.

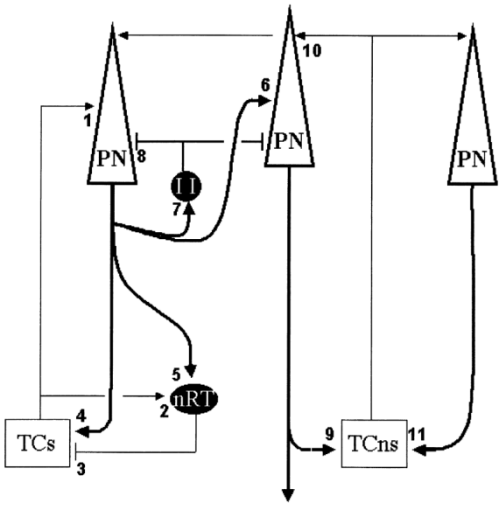

Figure 1. Main TC (TC) circuits relevant to spindles generation (simplified diagram based on Guillery et al., and Jones [10-11]). Excitatory connections are shown terminating with arrows and inhibitory connections are shown with bars. TCs and TCns are TC-specific and non-specific projections to pyramidal neurons (PN) in cortex. They are subject to feedback inhibition by nucleus reticularis (RT) and cortical inhibitory interneurons (II), respectively, shown as filled circles. TCs, considered as `core', 'first order' or `specific', excite PN of cortical layer 6 of the same TC sector (1) and RT neurons (2) and are inhibited by the latter (3). PN feed back to thalamus (4,5) and have a rich recurrent collateral network exciting other PN (6) as well as local inhibitory interneurons (7). TCns, considered as `matrix', `high order' or `non-specific', have similar connections with RT and PN of the same sector (not shown here), except for their rather non-discriminatory efferents to the upper cortical layers (10) rather than the fourth cortical layer. The PN of layer 5 (middle) constituting the main output of cortex can excite the latter type of TC neurons of remote sectors (9).

Several factors appear to **allow or instigate the appearance of spindles**. In the former one may include influences from brainstem, hypothalamic and basal forebrain to both TC and cortex, but the instigation role is attributed to cortical activation of RT neurons. This appears to occur in phase with a slow cortical oscillation (~0.75 Hz) [12] sporadically and during the A1 phase of the cyclic alternating pattern [13].

Cortical excitation of RT neurons is also found instrumental in the **spreading and synchronizing** spindles through TC and cortico-cortical excitation (Figure 1). It is noteworthy that the two function-related modes of firing characterize not only relay (specific) TC neurons but also the `non-specific' intralaminar nuclei. Cortical activation of the latter as well as of recurrent cortico-cortical excitation spread the spindle rhythm to wide cortical areas. The initially **waxing** amplitude of the EEG waves is grossly correlated to the amplitude of neuronal EPSPs and reflects gradual recruitment of more and more neurons in analogy to the augmenting and recruiting responses which are experimentally induced by activation of TC neurons in sensory-motor and intralaminar nuclei respectively, i.e. an initial specific activation of cortex leads to feedback excitation of nonspecific TC which will in turn project back to a much larger cortical area. This will then lead to the large amplitude EEG and hence the maximum amplitude in the middle of the spindle The **waning** is attributed to deterioration of synchronization of more and more extensive TC sectors, their asynchronous feedback to thalamus rendering RT neurons out of phase to each other, while also the recruitment eventually reaches a large enough number of cortical neurons whose feedback to the thalamus depolarizes TC neurons and thus terminates the rhythm.

Ascending arousal influences **disallow** spindles. For example cholinergic afferents from brainstem excite TC and inhibit RT neurons during awake and REM states, thus inhibiting the rhythm generation that prevails in NREM sleep i.e. spindles and deltas.

The **incidence** of spindles is reported to peak at a frequency of 0.2-0.3 Hz [14]. In longer time terms, spindles are under both circadian and homeostatic control [15]. Spindles density is decreased in early sleep stages (in inverse homeostatic relationship to slow waves). The same is observed after sleep deprivation, when there is also an increase in spindle amplitude and a reduction in intra-spindle frequency variability, which indicates a higher level of synchronization in TC cells under conditions of increased sleep pressure.

The incidence of spindles has considerable variance (1±40 s inter-spindle intervals in humans). Also variable is their topographic prevalence in the brain, their time of appearance in sleep stages, their association to other EEG landmarks (like K-complexes) and their dependence on drugs. All these suggest that spindles do not constitute a unique and/or uniform phenomenon.

2.2. Association/dissociation of spindles with other EEG waves of NREM sleep

The association of spindles the slow cortical oscillation (~0.75 Hz) [12] is proposed to be causative in the sense that this oscillation which is supposedly generated within neocortical

networks, synchronizes neuronal activity into generalized down-states (hyperpolarization) of global neuronal silence and subsequent up-states (depolarization) of increased wake-like neuronal firing. With the beginning of the latter cortico-thalamic volleys are proposed to drive the generation of spindle activity.

During the A1 phase of the cyclic alternating pattern [13] spindles gather together with K-complexes. It is interesting that spindles are associated to K-complexes but are mutually exclusive with delta. The latter may be explained by the afore mentioned involvement of voltage-gated channels Ih and LTC, since the membrane can be only at one voltage level at a time. During sleep spindles the membrane potentials of TC neurons are between –55 and –65 millivolts, whereas delta oscillations occur in the range –68 and –90 millivolts. The progressive hyperpolarization of TC neurons during the course of sleep may explain the prevalence of spindles in early stages and delta dominance in stage 4 sleep [16]. K-complexes (the descending phase of their prominent negative wave) are associated with a population burst discharge of cortical neurons, including layer 5 and 6 pyramidal cells projecting to the thalamus. Such a strong and synchronous input may discharge reticular cells directly or indirectly and thus could serve as the initiator of sleep spindles [2]). In a recent study the incidence of spindles immediately following K-complexes was between 65-70% [17]. However in this study neither the probability of appearance nor the power of spindles correlated to the amplitude or any other feature of the K-complexes that preceded them. When K-complexes appeared spontaneously after the start of a sporadic spindle, the spindles were invariably shut down for the duration of the K-complex, usually being replaced by a short lived oscillation in the high theta frequency band. Also the spindles appearing immediately after a K-complex had invariably faster spectral frequency than the sporadic spindles. Such findings suggest that the association of K-complexes with spindles is strong but may be due to a common trigger rather than a causative interaction.

2.3. Spectral spindles frequency. Whence the appearance of two spatiotemporally distinguished types of spindles?

The observations of Gibbs and Gibbs (1950) [3] that the frequency of frontally recorded spindles is slower (about 12 per second) than that of spindles above the centroparietal cortex (about 14 per second), later confirmed in animals, suggest that several seeds of synchrony can emerge within the thalamus that are temporally coordinated by their corresponding neocortical networks. The different spectra of the two types are proposed to depend on anatomical differences (different thalamic rhythm generators and different distance from the cortical electrical generators). A possible explanation has been based on the fact that TC neurons in anteroventral and anteromedial nuclei, which connect limbic structures with cingulate and prefrontal areas, do not receive inhibition from RT but from zona incerta and other areas and so do not fire in coherence to other TC neurons during spindles [18-19]. The two types of spindle activity show different maturational courses [20] suggesting some fundamental difference.

Observing the actual intervals between individual waves of fast and slow spindles peaks on EEG we do not see a continuous spectrum with two peaks but rather a step like transition between two stable spectral frequencies even in cases the two types follow each other. More generally EEG spindles have been shown to display high intra- and inter-night robustness and stability of spectral frequency in individual subjects in spite of larger differences between subjects. This unique profile of spindles was suggested to be one of the most heritable human traits (heritability of 96%, not influenced by sleep need and intensity). Consistent with this suggestion is the demonstration that several diseases with strong genetic background are associated with changes in spindles, like Asperger syndrome, developmental dyslexia, Williams syndrome or malformations of cortical development ([21] and references therein). So, EEG studies propose for each of the two types of spindles a stable spectral frequency determined probably by the degree of hyperpolarization of TC neurons; determined in turn by intrinsic properties of these neurons. The latter as well as neuroanatomical differences are hypothesized to reflect genetically determined traits rather than sleep-dependent mechanisms. However the thalamic neurons membrane properties contributing to spindles rhythm display diurnal variation when recorded in vitro (more depolarization, bursting, LTC and Ih when recorded at night compared to the day [22]).

3. Electroencephalographic (EEG) and magneto encephalographic (MEG) findings, and other neurodiagnostic method of spindles

Sleep research is enjoying its second renaissance. Just like the first renascence in the late 50s and 60s the new one is driven by advances in accessing directly the correlates of electrical activity in the brain. The first renascence of sleep research was founded on the new capability of using EEG to extract a direct correlate of mass electrical activity of the sleeping brain. The pioneers sensed that something new was in the air with the advent of the new neuroimaging methods of PET and fMRI and remarkable progress in electrophysiology (EEG and MEG). This sentiment of great expectations is nicely captured in Jouvet's words: ".. so the majority of researchers are waiting with bated breath for the results of studies combining PET scanning, "functional' magnetic resonance imaging (fMRI), magnetoencephalography and tomographic electroencephalography …" [23].

We are now living this much awaited new era of sleep research, its second renaissance with the spotlight falling to the study of spindles for the reasons already outlined in the earlier sections. To appreciate the results obtained so far and even more importantly to sense the promise of things yet to come, it is important to understand what the new techniques can deliver and what they cannot and contrast this with what has been done so far. We will therefore describe snippets of new research obtained from different methods and point out in each case how these results add to earlier studies thanks to the new capabilities, but also how they are constrained by the limitations of the method. We will group the results in terms of the major categories of measurements in roughly the chronological order that each became available.

3.1. Non-invasive mass early mass-electrophysiology

The foundation of the modern neuroscientific study of sleep was laid by the questions posed by Henri Pieron [24] and Nathaniel Kleitman [25] about the physiological basis of sleep and the nature of regulation of sleep and wakefulness and of circadian rhythms. It took many decades though and critically the improvement in electrophysiological measurements that allowed the critical categories of sleep stages and sleep processes to be documented in an objective way. The key finding was of course the discovery of rapid eye movement (REM) sleep and its reproducible identification in any well designed study with polysomnography [26]. The cascade of discoveries that followed by the same pioneers together with William C. Dement, Michel Jouvet and many others continues for over a decade but by the 70's the field appeared to be running out of steam. In retrospect the big picture is easier to see and it can be summarized as the inability to connect the view of electrical events revealed by non-invasive mass electrophysiology mostly in humans and the detailed description of sleep control provided by highly invasive animal electrophysiology.

The source electrical activity is greatly distorted as it crosses the highly resistive skull, and as a result the EEG signal generated lacks spatial specificity. The EEG record at any one electrode is a crude average of real electrical events; at any one instance the signal could be due to any one or more generators spread over wide range of brain areas. The reader of sleep literature is used to EEG records that appear smooth with regular oscillatory patterns that cover wide parts of the scalp. This smoothness of the EEG signal is often interpreted as a consequence of uniformity in activity of the sleeping brain. In reality much of this apparent smoothness is a byproduct of EEG technical limitation and the efforts to limit them (e.g. through filtering).

A fine spatial and temporal detail in the pattern of activations would be smoothed by the passage through the highly resistive skull and in any case it would not survive the pre-processing of the signal. The absence of high spatial and temporal variability should not therefore be interpreted as evidence of absence. Spatial uniformity was however exactly what was implicit in the descriptions of brain activity within each of the major subdivision of sleep. This interpretation was of course at odds with the identification of fine spatial differentiation of mutually interacting nuclei at the brainstem and hypothalamus revealed by exquisite animal experiments of the pioneers. The reality of invasive neurophysiology was not of course inconsistent with the signal recorded by EEG but the interpretation of the latter was.

As is often the case in science, the animal neurophysiologists and the EEG researchers continue developing their own studies and terminology and practically ignored the inconsistencies between the implicit frameworks each society of researchers constructed. The unrecognized impact of this impasse probably contributed to the relative stagnation of sleep research that followed in the seventies and eighties as new methods were needed to bridge the results produced by the refined electrophysiology of animal sleep research and the gross electrophysiology of human sleep EEG.

In the early 1970s and through the 1980's mass electrophysiology was changing in fundamentals ways. First the advent of superconductivity and other technological innovations allowed measurements of the magnetic field generated by the human brain [27]. Magnetoencephalography (MEG) had some clear technical advantages over EEG, but the inertia of sticking largely to analysis techniques developed for EEG and the heavy pre-processing of the very noisy and limited data that early MEG hardware with only one or very few MEG sensors meant that the new capabilities were not exploited for almost a decade [28]. The advances in MEG, especially in terms of localization of cortical activity at the peaks of evoked response, spur a revitalization of EEG technology. In terms of instrumentation it eventually lead to computerized (paperless) EEG; which allowed long term recordings; in terms of analysis it lead to attempts to extract spatial information about the brain generators – it was not adequate anymore to describe the topology of the EEG signal on the scalp.

These advances augmented the effectiveness of standardization of sleep recording protocols. A proper sleep study had to provide enough electrophysiological records to produce a hypnogram, i.e. to divide a night's sleep into stages according to well-defined standards [29]. This classification essentially used the dominant frequency components and the big graphoelements to define each sleep stage. Sleep spindle activity is the highest during NREM 2 sleep stage and together with the K-complex are the two defining graphoelement for this sleep stage.

The contribution of MEG to the study of spindles has been limited in the 70s and 80s, partly because sleep studies with MEG are difficult and partly because partly because there is no timelocking mechanism for averaging and partly because there is little one can do that cannot be done with EEG with instruments offering limited coverage of the head with one or at most few sensors. Inability to identify spindles using a particular instrument and protocol was sometimes interpreted as inability to detect spindles with MEG [30] and different models were proposed to explain the apparent discrepancy between EEG and MEG spindle detection [31]. Eventually researchers recognized that when only few sensors were available the placement of the sensors is a critical determinant whether or not correlates of focal events in the brain will be captured in the measurements [32].

The advent of multichannel arrays covering a wider area, and especially the ones using planar gradiometer meant that events from at least part of the brain could be identified from the area below the sensor array. Indeed for the first time a concordance was reported for gross signal properties using such 24-channel array of MEG sensors and the EEG for simultaneous recordings from the scalp midline. However using the current dipole model for the generators no focal generators could be identified for spindles and slow waves [33]. The use of multichannel MEG hardware covering the entire head demonstrated that spindles involved activation of wide areas of the cortex. However, with modelling restricted to equivalent current dipoles all that could be done was to compare the relative occurrence of spindle-like activity in different parts of the cortex [34-36].

The EEG and MEG studies until the first few years of the new millennium have provided valuable information about the distribution of spindles in early and late sleep and the relation between spindle frequency and the phase of the slow cortical oscillations as described in section 2. In particular regularities in topography and timing were described in more detail than the original description of Gibbs, as already described in the previous section.

Defining cortical sources of spindles using simultaneous EEG and MEG recordings can provide valuable information on the role of the cortex and the underling neural basis and mechanism of generation of spindles [37] (Figure 2). Cortical activation centered in four areas, the precentral and postcentral areas in frontal motor cortex and parietal cortex of each hemisphere. Fast spindles were associated with more frequent activation of postcentral areas with stronger activation strengths, whereas slow spindles were associated with more frequent activation of precentral areas with stronger activation strengths. The differences in cortical activation patterns and activation strengths between the two types of spindles suggest that two distinct forms of spindle bursts propagate to cortex through different underlying neuronal circuits.

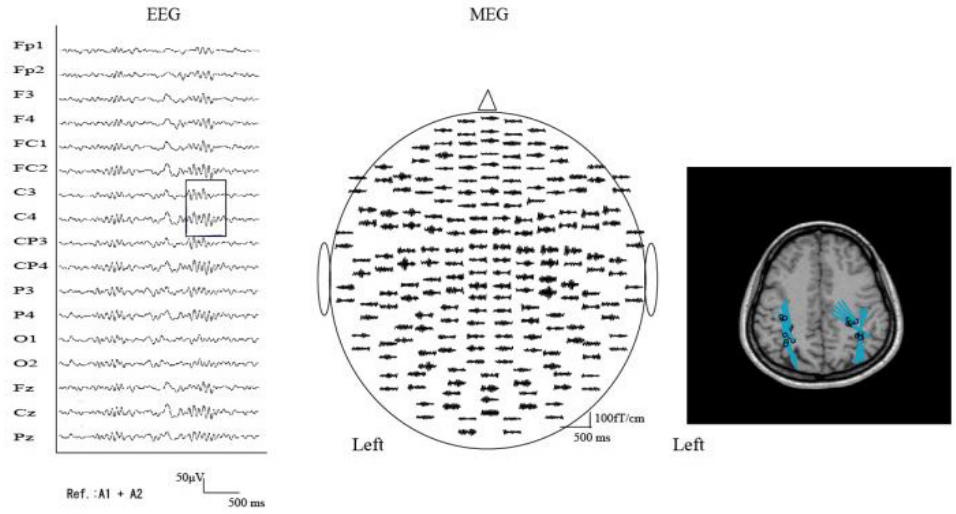

Figure 2. Symmetric distribution of 14-Hz fast spindles recorded with simultaneous electroencephalogram(EEG) and magnetoencephalogram (MEG). EEG shows spindles with a frequency of 14 Hz and amplitude of 30μV in the centro-parietal areas with the highest amplitudes in the central midline(Cz) and parietal midline(Pz) (Left) . Simultaneous MEG shows spindles with a frequency of 14 Hz and amplitude of 100.0 fT/cm distributed symmetrically in the MEG middle channels. The head is viewed from above (middle). The cortical sources of the same spindle were estimated as ECDs (equivalent current dipoles) with MEG clustered around the central sulcus of both hemispheres (right). Four locations consisting of the precentral and postcentral areas, in precentral areas of the posterior part of frontal cortex of each hemisphere and the postcentral areas of the parietal cortex activated. These cortical sources constituted the cortical distribution of spindles.

3.2. Hemodynamic studies (including combined EEG/fMRI)

PET does not have sufficient temporal resolution to probe in detail the evolution of activity correlated with large sleep graphoelements, so early studies have mostly focused on changes between sleep stages and awake state [38] with some attempts to characterize activity in spindles [39]. Advances in PET and particularly the simultaneous recording of the EEG allowed changes in PET signal to be correlated with changes in spindle activity, showing mostly CBF decrease in the human thalamus during stage 2 and SWS sleep, in proportion to the power density in the spindle-related sigma frequency range. A more recent study provided evidence for positive correlations in the thalamus and right hippocampus with sleep spindle activity [40]. Despite heroic efforts by PET researchers and some useful information obtained, it is difficult to draw firm conclusions about spindles from the PET data because the duration of the unit of measurements in PET is so much longer than the duration of spindles (< second) and even the periods of high and slow spindle activity (few seconds).

The advent of fMRI and its rapid development has revolutionized neuroscience and it has produced images of the sleeping brain that surpass even the most optimistic expectations of sleep researchers. The fMRI technology still relies on hemodynamic processes, but it has some clear advantages compared to PET. First, it allows much finer temporal and spatial resolution – its basic temporal unit is in the order of seconds rather than minutes; the spatial resolution is better and it can cover the entire brain, cerebellum and brainstem. It is also less invasive as it uses no radiation, although it still exposes the subjects to magnetic fields much higher than what humans are usually exposed to in their natural environment. Despite these advances, the use of fMRI in sleep research was limited for a long time because the rapid changes in the magnetic field create huge EEG artifacts. Without EEG it is difficult to do serious sleep research because sleep stages and the characterization of sleep events can only be done using EEG. This serious drawback has been removed with the development of methods that allow (nearly) simultaneous EEG and fMRI [41]. This new capability has lead to an avalanche of EEG gated fMRI sleep studies with important new insights about the nature and role of spindles coming with each new study. We focus on a couple of recent studies that arrive at significant conclusions and also point out the direction that research is following today.

Maquet and colleagues having done pioneering research on sleep with PET have recently moved to fMRI studies of sleep. The collaboration of Maquet's team with Schabus who has done some pioneering work on spindles with EEG has produced an excellent study where EEG gated fMRI allowed a detailed characterization of fast and slow spindles in terms of generators that are commonly active for both types of spindles and distinct neural networks that are activated for each one [42]. They reported an activation pattern common to both spindle types involving the thalami, paralimbic areas (anterior cingulated and insular cortices), and superior temporal gyri. No thalamic difference was detected in the direct comparison between slow and fast spindles but at a lower statistical threshold slow spindles showed increased activity in both thalami. Fast spindles showed thalamic activation in the common areas, but restricted to the lateral and posterior part of both thalami. At the cortical level identified significant common increases in activity were detected in paralimbic areas:

the left insula and the anterior cingulate cortex, bilateral superior temporal gyri (auditory cortex). The differences between slow and fast spindles were clear-cut. For slow spindles activity in the superior frontal gyrus was the only addition to the common activation pattern. The absence of additional frontal activity for slow spindles, what distinguishes slow from fast spindles with EEG, was attributed to a non-systematic participation to each slow spindle occurrence by any one frontal region. Fast spindles were correlated with activity in a number of areas in addition to the common activation pattern. These activations include areas around the sensorimotor strip, mid cingulated cortex and the SMA – all areas showing sensorimotor (μ) rhythm activity in relaxed wakefulness. Direct contrast between the two spindle types showed a larger recruitment of mesial-prefrontal and hippocampal areas during fast, relative to slow, spindles, a result consistent with the notion that fast but not slow spindles are related to learning (see below).

The complex relationship between spindles and specific activations was further explored in another recent study using EEG gated fMRI. In this study, 30 minutes of simultaneous whole brain fMRI data at 1.5 Tesla and polysomnographic EEG were collected while subjects were falling asleep in the MR scanner. From these data, 5 minute epochs were extracted each from a single sleep stage for more than 85% of the time. All in all, 93 epochs of a single sleep stage were extracted. 27 epochs during wakefulness, 24 during sleep stage 1, 24 during stage 2 and 18 in SWS were used for the final analysis. In addition to comparisons between stages and identification of regional changes of activity the researchers compared the connectivity network of timeseries extracted from timeseries of regional activations. Specifically the connectivity of the hippocampal formation with the rest of the brain was examined at different sleep stages and during spindles. The analysis failed to show increased hippocampal BOLD signal during fast spindles; instead, it was functional connectivity between the hippocampal formation and neocortical areas that increased during the appearance of fast spindles [43].

3.3. Invasive electrophysiology

Reviewing the development of our understanding of sleep spindles, it is becoming clear that important new insights were obtained when new tools became available that allowed a qualitatively new view of either local or global brain activity related to spindles or how local and global spindle-related brain activity relate to each other. While the foundations for the important developments in electrophysiology and neuroimaging were laid in late eighties, the mechanisms underlying sleep spindles (and TC rhythms in general) were seen in a new light thanks to pioneering work of Rodolpho Llinas and Mirca Steriade. Llinas and colleagues employed in vitro preparations to show that the membrane ionic channels endowed pacemaker properties to thalamic neurons. Steriade and colleagues employed in vivo experiments to demonstrate the importance of the nucleus reticularis thalami and its activation by the cortex in the generation and spread of the spindles rhythm, reviewed together in Steriade and Llinas [44]. This concept was refined as the "thalamic clock" theory [45]. The historical irony is that in spite of this revolutionary advance in understanding spindles made possible only by the synthesis of in vitro and in vivo studies, Steriade himself remained an outspoken critic of data collected in vitro [46].

Invasive electrophysiology in normal humans is of course not justified, but implantation of the brain for clinical reasons provides unique opportunities to access the brain directly. An important recent study has provided valuable insights by characterizing sleep spindles in humans by pooling together simultaneous recordings of intracranial depth EEG and unit spiking activities in multiple brain regions in the hippocampus and cortex of 13 individuals undergoing presurgical localization of pharmacologically resistant epilepsy [47-48]. The authors of these studies report that spindles occur across multiple neocortical regions, and less frequently also in the parahippocampal gyrus and hippocampus. Most spindles are spatially restricted to specific brain regions with topographically organized spindle frequency with a sharp transition around the supplementary motor area between fast (13–15 Hz) centroparietal spindles and slow (9 –12 Hz) frontal spindles occurring 200 ms later on average, consistent with earlier reports. They further report that fast spindles often occur with slow-wave up-states and that spindle variability across regions may reflect the underlying TC projections. They do not find a consistent modulation of neuronal firing rates during spindles [47]. They also report that most sleep slow waves and spindles are predominantly local inferring therefore that the underlying active and inactive neuronal states also occur locally [48].

3.4. Tomographic MEG and EEG studies

The results described above showed that spindle-related activity involves widespread activity in multiple cortical and subcortical areas. It involves characteristic times that are a fraction of the typical spindle period and the ones that characterize sleep periodicity as this is reflected in the sleep stages or the cyclic alternating pattern (CAP) [49] with characteristic phases of quiet activity and groupings of the large graphoelements that characterize each sleep stage. In short the study of spindles, like the study of much else about the brain, requires techniques that can look at the whole of the brain with time resolution from a few milliseconds to many minutes. The solutions described above were the ones that satisfied, at least partly, this need by combining more than one technique. As we will see below a more direct approach is provided by tomographic analysis of MEG and EEG data. The key transition came in the late 1980s and early 1990s for MEG with the introduction of truly tomographic analysis of multichannel MEG data [50] and a few years later for EEG [51]. Tomographic analysis of minimally pre-processed MEG data revealed a dynamic view of brain function [28, 52] that was very different to the smooth version of reality that was the consensus of decades of studies using equivalent current dipole analysis of highly pre-processed (filtered and averaged) MEG and EEG signals. The EEG and MEG community remained skeptical of tomographic analysis for a long time, despite convincing evidence converging from many directions: the agreement between results obtained with the analysis of the standard average and heavily filtered MEG signal with the results obtained after the same average and filtering operations were applied to the tomographic single trial solutions [52], the more consistent picture obtained with single trial analysis of MEG data with the variability encountered in animal invasive electrophysiology and the detailed justification of the methodology in terms of mathematical properties of the lead fields [53]

The change in heart came slowly and moved primarily by the demonstration of high variability with the advent of single-trial fMRI studies. Tomographic analysis of sleep data

offers some great advantages, but the difficulty of sleep studies and the skepticism of the community posed great obstacles. The first such study with MEG focused on eye movements [54]. Attempts to characterize the graphoelements of NREM 2, K-complexes and spindles produced results showing activity in widespread areas as previously reported, but without much order to be useful for clarifying the role of different sleep stages. It was therefore decided instead to compare the quiet periods across different sleep stages with each other and with the state of wakefulness with eyes closed just before sleep [55]. These comparisons produced clear cut differences and notably a gradual increase in gamma band activity in the left dorso-medial prefrontal cortex from awake state through the four NREM sleep stages, culminating in the highest gamma band activity during REM sleep. It is tantalizing that this area or frontomedial areas close to it are implicated in memory consolidation in animals and in EEG-gated fMRI studies and shows increased connectivity with the hippocampal formation during fast spindles [43]. A meta-analysis of a group of 192 patients with focal brain lesions found the highest association between insomnia and left dorso-medialprefrontal damage [56]. Recent work from our team showed that this area is activated in the spindle range of frequencies during the core periods of NREM2 [57]. Specifically a direct comparison between activity during NREM 2 and awake state showed that the activity in posterior brain areas is substantially reduced compared to the awake state, while in the left dorso-medial prefrontal cortex – the centre of the area identified in the gamma band in the comparison between core states in REM and awake state – the activity is higher in the spindle range of frequencies (Figure 3A). A direct comparison between the activity during core states of NREM 2 and NREM1 showed increase in the spindle range of frequencies in the same left dorso-medial prefrontal cortex and in the thalamus (Figure 3B). The implication of this same area in the spindle range of frequencies during the quiet periods of NREM 2 stage provides yet another tantalizing clue hinting of some involvement of this area in the process of memory consolidation.

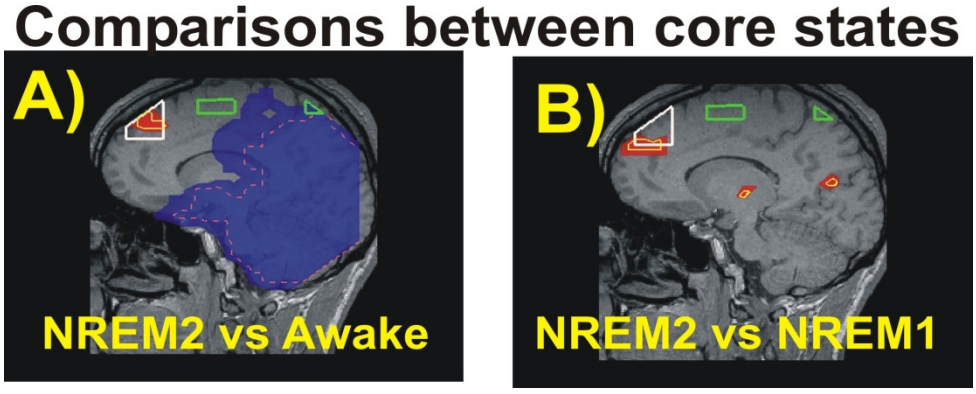

Figure 3. Comparisons between MEG recorded acticationsin the spindle frequency range (12-16 Hz) in core states of NREM2 and awake (A) and NREM1 (B) states. The thin yellow contour bounds the area that shows statistically significant increase in activity for all three subjects studied with $p < 0.0001$. In each case the areas identified in the comparison between REM and awake state in the gamma band are also shown by heavy outlines: the left dorso-medial prefrontal cortex (L-DPFC) in white and the pre SMA and precuneus in green.

The ability of EEG to be recorded simultaneously with fMRI and PET is an important advantage that has not yet been fully explored, at least not for sleep studies. It is nowadays possible to obtain some information about source generators from just the EEG signal [58-59]. Simultaneous EEG/MEG studies, notably from the team of Halgren and colleagues [60-62] are not only valuable in the richer information they capture, but they can also guide us how to reliably obtain information from more widely available EEG measurements, that are also more suitable for clinical applications as we will describe next. Finally, in closing this section it is worth noting that the increase sophistication in EEG measurements and experiment design are producing new information not just about the nature of sleep spindles but also about their role [63-64].

4. Stable sleep profiles in clinical and other conditions

4.1. Consciousness and spindles

As we gradually fall asleep spindles appear in the EEG at stage 2 NREM, when consciousness has evidently been lost. Their rate appears to correlate with the sleeper's tolerance to noise and sleep maintenance. The futility of correlating a physical to a psychological phenomenon withstanding, one may therefore ascribe to spindles a role of marker or neural correlate of the loss of consciousness. However, we are still searching for possible roles of spindles in the several and complex aspects of consciousness, its neurological levels, its variable memory contents and its physiologically or pathologically altered states.

Animal and human studies show that spindles are sleep maintaining events [65-66] that block the transfer of sensory information to the cerebral cortex during sleep [64], thus preventing sleep-interrupting arousals. The frequency of the spindles decreases with deepening of sleep and increases as sleep becomes lighter in each consecutive sleep cycle [68]. Teleologically speaking, in order to sleep, consciousness for all but the most relevant of stimuli must be prevented and a host of studies convince us that this is accomplished at the level of TC circuits [69]. TC neurons upon a decrease of ascending from brainstem mostly cholinergic afferents shift to a bursting mode of firing dictated by their hyperpolarization by RT inhibitory neurons the duration of which determines the frequency of their oscillation subsequently transmitted to and augmented by the cortex as spindles rhythm of 11-15 Hz (see 2.1.). While TC neurons are hyperpolarized and engaged in this bursting mode, sensory afferents are expectedly prevented from reaching the cortex, resulting in almost complete deafferentation, except for very strong or alarming stimuli [65]. In consistency to these observations, thalamic metabolic activity was shown to decline in association to increased spindle-frequency [70]. The recent observation (described in 2.2.) that spindles are invariably shut down for the duration of the K-complex and they appear right after at increased spectral frequency [71] support a role of spindles in preventing stimuli (which triggered the K-complex) to reach consciousness.

The definition of ‘‘Consciousness as information integrated’’ [72] leads to the question: Has our unconscious sleeping brain lost its dynamic complexity or its capacity to integrate the enormously diverse patterns of its activity into a unique consciously perceived whole?[73]. Among the arguments supporting the second of the two explanations is that spindles

prevent integration of brain activity. Furthermore, their spatiotemporal dynamics and relationship to K-complexes as well as their involvement with hippocampus into a memory consolidating "dialogue" contribute to a very complex image of the sleeping brain [55]. During the whole of sleep, and especially in the second stage of NREM sleep, a dynamic confrontation of arousing and anti-arousing mechanisms is evident in the macro- and microstructure of the EEG. Loss and regaining of consciousness is continuously debated by hundreds of K-complexes and tens of microarousals each night, which are normally too short to fully awaken us, but constitute an opening of a dynamic window of information-processing, allowing some monitoring of possible threats. If the stimuli represent a lack of threat, sleep is maintained or protected partly with the help of spindles.

Anesthetics lead also to loss of consciousness - in the sense of turning the subjects oblivious to their environment - with different mechanisms depending on the drug used. One mechanism they partly share with natural sleep is apparently the production of spindles in a similar way, as several anesthetics hyperpolarize TC neurons (by activating 2PK channels and/or by potentiating GABA receptors) and halothane induced spindles are antagonized when carbachol is injected into the pontine reticular formation [74]. Spindling then causes a decorrelation between sensory input to TC neurons and these neurons' output to the cortex, thus contributing to the loss of consciousness.

4.2. Spindle-coma

Coma can be considered as a deregulation of the brain's arousal system caused by diffuse brain damage or by focal brainstem lesions. The arousal systems are 1) an upper level encompassing cerebral cortex and white matter 2) a middle level encompassing thalamus and upper brainstem and 3) a lower level encompassing lower midbrain and pons [75].

In coma the EEG shows a various patterns, a generalized slowing in the delta or theta range, alpha-coma, spindle-coma, burst-suppresion and epileptiform activity. In coma, regardless of pathology, a normal sleep-wake cycle is mostly disrupted or completely absent. However, the coma tracing may resemble normal wakefulness [76] or normal sleep [77]. The occurrence of spindles in comatose patients is refereed as spindle-coma is often caused by Central Nervous System (CNS) trauma, infection, and metabolic encephalopathy. The mechanism of abnormal spindling has been considered as midbrain involvement with sparing thalamic structures [77-79]. Silverman (1963) suggested that the spindle-coma in supratentorial lesions suggests relatively intact cortical function and a good prognosis [80].

Spindle-coma is considered as a benign form of coma, with EEG reactivity to stimuli heralding a favorable outcome. Spindles in comatose patients are best demonstrated during first few days [81] after trauma. They observed spindle activity in 91% of patients of post-traumatic coma, and 30% of these went to prolonged coma. Symmetrical occurrence of spindles was found to be of good prognosis, asymmetry and decrease of spindles showed a rather poor prognosis [81].

The presence of spindle activity after hypoxic or anoxic injury does not always indicate a good outcome. A more recent works supports these findings in comatose children and

concludes that the reappearance of sleep patterns and sleep spindles is sign of good prognosis. In traumatic coma, these sleep elements are more frequently observed. Spindle coma represents a combination of physiological sleep and coma, the latter accounting for the failure of arousal. The neurophysiological mechanism of spindle coma is the preservation of pontine raphe nuclei and TC circuits subserving sleep spindle activity, with the impairment of ascending reticular activating pathways at the midbrain level that maintain wakefulness [82-84]. The presence of sleep-like patterns was shown to be indicative of a better outcome. NREM sleep elements, K-complexes and sleep spindles as well as rapid eye movements (REM) sleep elements alternating with NREM sleep elements were also indicators of a better outcome. Only monophasic EEG or a cyclic alternating pattern with absence of sleep elements indicates a poor outcome.

4.3. Spindles and epilepsy

Epilepsy and sleep disorders are considered by many to be common bedfellows. Sleep can affect seizure occurrence, threshold, and spread, while epilepsy can have a profound effect on the sleep/wake cycle and sleep architecture [85-87]. NREM sleep differentially activates interictal epileptiform discharges (IED) during slow wave (N3) sleep, while ictal seizure events occur more frequently during light NREM stages N1 and N2. Some types of seizures preferentially occur during NREM stage-2 sleep with spindles, and association between sleep and activation of epileptiform activity on EEG has been of interest to investigators for years. Medial temporal spindles are present in some children with focal epilepsy.and the frequency of spindles may be slower in patients with epilepsy, probably as an effect of antiepileptic drugs. Longer spindle duration has been observed just prior to seizures of nocturnal frontal lobe epilepsy. Overall IED rate may be increased during sleep with spindles, but the spatial distribution of spike frequency appears similar during wakefulness and sleep in children with intractable focal seizures. Thus sleep with spindles may decrease the threshold of emergence of IED activity diffusely rather than focally [88]. These EEG clinical observations are consistent with spindles representing a series of depolarizations of lower (type I) or higher (type II) firing capacity (riding on top of a DC negativity) and so constitute a state of relatively higher cortical excitability (see chapter 2.1.). The effect is rather non specific in the sense that the slow (<1 Hz) oscillation of NREM sleep, and in particular spindles, K-complexes and delta waves, share some features that may contribute to the aggravation of epileptic phenomena (see also clinical studies at the end of this chapter). These effects may be related to the dynamic bistability of neuronal membrane potentials and neuronal readiness for bursting and widespread synchronization [86].

Spike and wave discharges (SWDs), the electrographic hallmark of typical absence seizures, which are an integral component of several idiopathic generalized epilepsies [89], have been reported to occur preferentially during the light stages of NREM sleep, where the majority of sleep spindles are observed and in a reverse relationship to their rate throughout the night [90]. Gloor in 1978 [91] proposed that the same TC circuit producing sleep spindles would generate SWDs in states of cortical hyperexcitability [91]. The hypothesis was based in experiments in the animal model of feline generalized epilepsy with penicillin (FGPE)

and developed further on the basis of in vitro and in vivo experiments, especially using rodent genetic models of absence seizures [92-95].

A more recent report [96] concludes that "the hypothesis that sleep spindles are transformed in SWDs now appears highly doubtful" based mainly on the arguments that (a) SWDs occur also during the day (during quiet awake state), (b) a compromised thalamic GABA receptors' function as a necessary condition for SWDs generation are not defensible and (c) spindles are initiated in thalamus while SWDs in the cortex. In our opinion SWDs do not develop from spindles (any more than humans developed from apes); they develop from the same TC circuit under different conditions - a thesis with solid experimental support to which the above paper subscribes to. The transition from spindles to SWD was just what was observed in the particular FGPE model (awake cats under fentanyl and curare successively injected with pentobarbital and penicillin [97]) and gave major support to the hypothesis that SWDs develop from the same TC circuits as spindles. Further more it was these experiments in FGPE, which first argued in favor of above (b - not compromised GABA inhibition) and (c - primacy of cortical mechanisms) [9, 69, 91, 92, 93, 99, 100]. One of the first robust observations, pivotal to the suggestion of this hypothesis, but not adequately followed up since, is that the spectral frequencies of spindles and SWD model co-varied in different cats displaying an impressively accurate for EEG almost 2:1 or 3:1 relationship [98] and most importantly that the transition from one to the other in FGPE was not continuous but step-like. This observation suggested that SWD may result from an increased cortical excitability which enhances the firing of pyramidal neurons to thalamic volleys of each spindle wave and thus activates recurrent cortical inhibition annulling the effect of the next one or two thalamic volley, i.e. it conferred to cortex the mechanism of SWD elaboration (as demonstrated and explained later in other animal models), through cortical recurrent GABAergic inhibition. This slower cortical rhythm was proposed to be transferred to the thalamus to gradually grow as a cortico-thalamo-cortical SWD rhythm. The experiments in the FGPE model that followed and supported this hypothesis have been reviewed [92-93, 100]. Further testing of this hypothesis was made possible when in vivo and in vitro studies revealed the exact mechanism of spindles generation in thalamus [44] (see chapter 2.1) and when this knowledge was applied to experiments on rodent genetic models of absence seizures [94-95].

In a general view, EEG alpha rhythm presents itself in awake state, when visual and other environmental stimuli cease; sleep spindles reflect the bursting mode of TC neurons which raise awakening threshold by blocking the weak sensory inputs, an effect further aggravated during delta waves in NREM N3; and finally SWD almost totally incapacitate awareness of and reaction to the environment either in awake or sleep condition and especially in the transition between the two. There is evidence suggesting that this may depend more on a top-down effect rather than merely being allowed by a decrease in arousal inputs from the brainstem [69,93]. There is little doubt however that all these rhythms - alpha, spindles, delta and SWD - (and not only) appear to cardinally involve cortico-thalamo-cortical circuits and bursting of TC and cortical neurons, albeit at distinct frequencies. The task is to understand why the frequency spectrum of TC rhythms is distinct rather than continuous and what is the role of internal (membrane and circuit) properties as

well as external influences on this reentrant TC system in setting the frequency constrains, but also allowing, triggering, augmenting, spreading and stopping each of these rhythms.

The elegant experiments of Steriade and his colleagues identified the cortex as responsible for instigation, augmentation and generalization of spindles (ch. 2.1.) and this may be truer for SWDs [65], as explained above [9, 69, 91, 92, 93, 99, 100]. In spite of the long held view of a brain-wide synchronous start of SWDs out of a normal background, one of the most important recent discoveries in the field has been the identification of a cortical 'initiation site' of SWDs. A consistent cortical site of initiation of SWDs within the perioral region of the somatosensory cortex was demonstrated in rodent absence seizures. High density EEG as well as MEG and fMRI studies in patients with different types of idiopathic generalized epilepsy (IGE) has shown SWDs in discrete, mainly frontal and parietal cortical regions before they appear over the rest of the cortex [101-106]. These studies strongly suggest that the frontal lobe is important for the generation of the 3Hz corticothalamic oscillations Do spindles play a role in this new view of IGE?

In a study aiming to investigate the relationship between IED and phasic sleep phenomena in patients with juvenile myoclonic epilepsy, only 2.7% of IED emerged specifically through sleep spindles as opposed to 65% from K-complexes, while IEDs were both facilitated by increased vigilance (CAP - A phase) and promoted the appearance of such periods [107]. In a further study of childhood absence epilepsy [108] focal SWDs occurred mainly during non-CAP and CAP-B periods (periods of reduced vigilance) of NREM sleep, whereas generalized SWDs occurred during the CAP-A of NREM sleep and especially at the transition from reduced to enhanced vigilance of NREM sleep. Regarding the efforts to understand the relationship between spindles and epilepsy, these studies emphasize the importance of (a) mutual interaction between the two, (b) recognizing that different types of epilepsy may have different mechanisms and (c) the importance of observing the "bigger picture" in both time (i.e. CAP periods) and brain space, since both sleep and epilepsy by definition involve large brain circuits.

4.4. Spindles in dyslexia

Much of the interest in sleep spindles arises from their putative role in learning through memory consolidation. An early comparison of sleep architecture of children with reading difficulties with normal children of the same age (8 – 10 years old) showed differences but no special emphasis was placed in spindle activity [109]. A very recent study however comparing Dyslexic and normal children (ages 8 to 16) identified important differences in sleep architecture including an increase in spindle density during NREM 2 [110]. More importantly only the sigma band power in NREM2 was positively correlated with the Word Reading test and in a Memory and Learning Transfer reading test while no significant correlations were found with the Non-Word Reading test; also, a positive significant correlation was found between spindle density and the Word Reading. Although these findings seem to implicate non-rapid eye movement (NREM) sleep and specifically sleep spindles in learning the relation is far from clear and more research is needed.

4.5. Spindles in schizophrenia

Recent studies using high-density electroencephalography have revealed a marked reduction in sleep spindles in Schizophrenia. Ferrarelli et al reported using whole-night high-density EEG recordings in 49-schizophrenia patients [111]. They had whole-night deficits in spindle power (12-16Hz) and in slow (12-14 Hz) and fast (14-16 Hz) spindles amplitude, duration, number and integrated spindle activity in prefrontal, centroparietal a d temporal regions. These results indicate that spindle deficits can be reliably established in schizophrenia, are stable across the night, are unlikely to be due to antipsychotic medications, and point to deficit in the thalamic reticular circuits. The reticular thalamic nucleus (TRN) consists of a gamma amino butyric acid (GABA) ergic neurons, which receive excitatory afferents from both cortical and thalamic neurons and sends inhibitory projections to all nuclei of dorsal thalamus.

TRN-thalamus circuits are involved in bottom-up activities, including sensory gating and the transfer to the cortex of sleep spindles. The TRN is implicated in the neurobiology of schizophrenia, the reduction of sleep spindles revealed in schizophrenias, and deficits in attention and sensory gating have been consistently found in Schizophrenia [112]. Schizophrenic patients failed to demonstrate normal sleep-dependent improvement in motor procedural learning. In normal subjects, overnight improvement on the finger tapping motor sequence test (MST) and other simple motor skill tasks specifically correlates with the amount of Stage 2 sleep in the last quartile of the night [113-114]. MST improvement also correlates with number and density of fast spindles [115]. The MST is performed with the left hand, and right>left asymmetry of spindle density and power in the motor cortex observed [114]. Sleep spindles are hypothesized to mediate the consolidation of procedural memory on the MST [114-116] and other motor tasks [64]. However, spindle activity of schizophrenic patients has reduced [117], and s positive relation between stage 2 spindle density and verbal declarative memory performance was observed [118]. In the context of intact practice-dependent learning, chronic medicated schizophrenic patients failed to demonstrate significant overnight improvement of motor procedural memory. They differed significantly from healthy controls, which did show significant improvement. The amount of sleep in the last quartile of the night significantly predicted initial overnight improvement in schizophrenia. The reduction of sleep-dependent consolidation of procedural memory in schizophrenia and sleep makes an important contribution to cognitive deficits [119] and now link variation in the expression of this deficit to specific sleep stages.

5. Clinical use of dynamic sleep spindle profiles in organic brain injuries

5.1. Sleep, the distribution of spindles, recovery after stroke

The sleep of stroke patients during night time has reported both insomnia and hypersomnia [120]. In the acute stage of hemispheric stroke, poor sleep efficiency [121-122], augmented wakefulness after sleep onset (WASO) [122], increased numbers of awakenings have been reported [123].

Poor sleep efficiency and wakefulness after sleep onset will reduce cognitive function in the acute phase after stroke [124]. Sleep is described as restless, light, or poor-quality sleep, although its duration appears normal.

Spindle distribution may be locally depressed by various types of cortical, subcritical pathology, including the generation of ascending reticular formation and thalamo-cortical pathways. The ipsilateral spindle depression following unilateral frontal leucotomy was first observed [125-126].Cress and Gibbs (1948) observed spindle asymmetries (ipsilateral depression) in 98 % of patients with hemispheric cerebrovascular accidents, whereas only 48% had focal abnormalities in the waking EEG [127].

Many investigations have reported sleep EEG changes following thalamic lesions [128-130].

Such studies may clarify the neuroanatomical circuitry that underlies sleep spindle rhythm generation, and may reveal clinically useful information such as for prognostic purpose or as an objective assessment of recovery from stroke.

Paramedian thalamic stroke (PTS) is an occasional cause of organic hypersomnia, which in the absence of sleep-wake cycle, and has been attributed to disruption of ascending activating impulses and considered a “dearoused “state, the disruption of both arousal and NREM sleep.

A decrease of sleep spindles, slow wave sleep, and REM sleep occurs in patients with the syndrome of fatal thalamic insomnia (FTI), in which neuronal loss is restricted to the anterior and dorsomedial nuclei of the thalamus. Bassetti et al. (1996), reported in 12 patients showed nocturnal polysomnographic findings paralleled the severity of hypersomnia [128]. Hypersomnia following PTS is accompanied by deficient arousal during the day and insufficient spindling and slow wave production at night, The center of the ischemic lesion was the inferior region of dorsomedial nucleus(DM) and the medial anterior part of the CM(centromedian neucles), confirming the autopsy study of Castaine et al [131]. The DM nucleus plays a important role in sleep regulation, and the reduction of spindles and slow-sleep-wave (SWS) was observed, these oscillatory activities are the expressions at neuronal level of different degrees of a same TC neuronal networks. However, an increase of spindles not of SWS suggests that the transition from spindling to SWS depends on the hyper polarization of a critical number of TC neurons.

PET scans showed bilateral thalamic hypometabolism with additional basal ganglia or mesiolateral frontal and cingular hypometabolism in patients with paramedian thalamic calcifications [132]. Wake-sleep studies showed abnormal sleep organization and in the case with frontal and limbic PET hypometabolism ,pre-sleep behaviour associated with “subwakefulness” EEG activities, lack of EEG and spindles and K-complexes, and features of status dissociates. Paramedian thalamic stuructures and interconnected, especially frontal and cingular, areas play a part in the organization of the wake-sleep cycle.

Hermann et al., demonstrated the neurological, neuropsychological, and sleep-wake deficits of 46 paramedian thalamic stroke patients [133]. Oculomotor palsy (76%), mild gait ataxia (67%), deficits of attention (63%), fluency and error control (59%), learning and memory

(67%), and behavior (67%) were common in the acute stroke phase. Outcome was excellent with right-sided infarcts but mostly incomplete with bilateral and left-sided lesions. Long-term recovery after paramedical thalamic stroke is significantly better in right-sided than in bilateral and left-sided. Bilateral and left-sided strokes regularly present with deficits in executive functions and memory, which may persist and will be the unfavorable outcome. Initially, hypersomnia was present in all patients associated with increased stage 1 sleep, reduced stage 2 sleep, and reduced sleep spindles. Post-stroke hypersomnia improves within months, a moderate improvement in sleep spindle activity may occur at the same time, whereas sleep EEG changes may remain unchanged for years.

Further studies are needed to confirm the specificity of these findings for hypersomnia following PTS and to confirm the hypothesis of relationship between spindles, NREM sleep, and cognition.

However there have been few prior studies of the effects of extrathalamic hemispheric lesions on the human sleep EEG. the role of the cerebral hemispheres (cortical, subcortical regions) in the regulation of sleep-wake functions and the modulation of the sleep EEG remains unclear[134]. Physiological experiments with an encephalae isole cat preparation (transected between caudal medulla and spinal cord) established that cortical activation facilitates waking EEG activity due to the presence of corticoreticular projections [135]. The cerebral hemispheres have also been found to contribute to the generation of sleep EEG patterns. The corticothalamic feedback could to support large-scale synchronization of spindle oscillatory activity [136]. Gottselg et al., demonstrated a significant reduction in the power and coherence of sleep spindle activity in EEG recorded over that hemisphere ipsilateral to the lesion during the acute stage of stroke [137]. The cerebral hemispheres are crucially involved in generating synchronous sleep spindles. And they demonstrated that a significant increase in the power and coherence of sleep spindle frequency activity from the acute to the chronic phase of stroke. The plastic mechanism allowed the possibility of recovery to spindle frequency, power and coherence. The stronger ipsilateral effects of cerebral lesions on spindle oscillations indicated reduction of amplitude of sleep spindles in the ipsilateral hemisphere, as well as reduction of cortical activation of spindle oscillations and underling corticothalamic projections [138].

5.2. Sleep and the distribution of spindles after traumatic brain injury

Electroencephalographic approach to the clinical assessment of consciousness has been tried in clinical situations with the anticipation that will support the diagnosis and prognosis. Electrical activities of brain tissue to immediately and secondary brain damage have been considered of good prognostic value for brain injury. Many neuroimaging techniques have shown the alterations in the brain parenchyma following severe traumatic brain injury, such as DAI (Diffuse axonal injury), which at the neuronal level, rapid acceleration and deceleration and the consequent rotational forces damage the axons in the cerebral and brain stem white matter, cerebellum. The magnetic resonance imaging (MRI) can show white matter degenerations or small penetrate hemorrhages that normal appearance on CT.

Urakami demonstrated spindle alterations following DAI using simultaneous EEG and MEG recordings [139].

In the postacute stage (mean 80 days) of DAI patients, frequency, amplitude, cortical activation source strength of spindle activities was significantly decreased compared with normal subjects. In the chronic stage (mean 151 days), spindles significantly increased, and no significant difference was found between normal subjects. DAI patients' cognitive functions also improved, with favorable 1-year outcome. Spindle activities may reflect recovery of consciousness, cognitive functions following a DAI [139].

The wide spectrum of sleep disorders in patients with chronic traumatic brain injuries occur, hypersomnia, insomnia, and parasomnia (such as acting out dream, nightmares, sleep paralysis, sleep walking and so on) [140]. Sixty adult patients with TBI, who presented with sleep-related complaints 3 months to 2 years following TBI were analyzed. Sleep disorders are a common finding after the acute phase of TBI. Daytime somnolence may lead to poor daytime performance, altered sleep-wake schedule, heightened anxiety, and poor sense of well being, insomnia and depression. Noticeably, sleep changes and deranged sleep architecture are common in chronic TBI patients. The same as stroke patients, regarding for TBI patients, spindles improve during subacute to chronic stage, while a wide spectrum of sleep disorders remains in chronic stage. Sleep disturbance can compromise the rehabilitation process and the ability to return to work. A diagnosis and subsequent treatment of these disorders may facilitate physical and cognitive rehabilitation of TBI patients.

6. Sleep and motor learning

6.1. The sleep cycle, memory systems, and memory stages

The human sleep cycle across the night, NREM and REM sleep cycle every 90 min, while the ratio of NREM to REM sleep shifts. During the first half of the night, stages 3 and 4 NREM (SWS) dominate, while stage 2 NREM and REM sleep succeed in the latter half of the night. EEG patterns shows in the different sleep stages, K complexes and sleep spindles occurring during stage 2 NREM, slow (0.5-4 Hz) delta waves developing in slow wave sleep (SWS), and theta waves seen during REM.

Sleep plays an important role in learning process and memory consolidation.

Human memory is divided into declarative forms, with subdivisions into episodic and semantic; and non- declarative forms, subdivided into procedural skill memory [141]. Following the initial encoding of a memory, several ensuring stages are proposed, developing stages of memory, beginning with consolidation, as well as integration of the memory representation, translocation of the representation, during the periods of erasure of the memory. Following later recall, the memory representation is believed to become unstable once again. Memory consolidation refers to a process whereby a memory become increasingly resistant to interference from competing or disrupting factors in absence of further practice [142].

All stages of sleep except sleep onset stage 1 NREM sleep have been implicated in one or more aspects of memory consolidation [143].

Regarding for which stage of sleep is important for the consolidation of a certain memory types, there is some agreement among researchers, however, two different theories exist which explain the role of the various sleep stages on the consolidation of different memory traces [144]. The dual-process theory explains a single sleep stage (REM sleep or SWS) acts and is necessary to form distinct memory traces (procedural or declarative), depending on which memory system that traces is form. The sequential hypothesis, memories are consolidated through the ordered sequence of non-REM sleep followed by REM sleep, so that both stages of sleep are necessary for consolidation. Both non-REM and REM sleep stages, the repeated pattern of non-REM sleep followed by REM sleep are important for memory consolidation. Some memory traces may require more SWS (declarative memory), whereas other memory traces may require more stage 2 non-REM or REM sleep (procedural memory). Rapid eye movement (REM) sleep may be important in processing memory traces and previously learned motor and sensory task. Non-REM (NREM) sleep, particularly slow wave sleep (SWS), its maximal expression in the frontal brain areas, relate to sleep homeostasis and frontal cognitive functions. SWS may increase neuronal plasticity enhancing attention, consolidating procedural and declarative memory [145]. The variability's of the emotional content of the memory, the cognitive weight of the task, and the initial skill level of the learner affect the stage of sleep which concerned the declarative and procedural memory consolidation.

6.2. Sleep –dependent memory consolidation

Sleep consolidates new memories by strengthening and integrating them with existing memories. Differentiating sleep-stage specific contributions to neural plasticity as proposed in sleep-dependent memory consolidation. Interest in relationship between mamory consolidation and sleep spindles is comparatively recent. The theories of memory consolidation suggest that storage is initially hippocampally mediated, but gradually gains neocortical representation through dialogue between two structures [146]. Slow oscillations (<1 Hz) allow synchronization between neocortical activity and hippocampal ripples, which are crucial to memory consolidation. Spindles increase during the up-state of slow oscillations [147] and are temporally aligned with hippocampal ripples[148-149],implicating them in the plasticity of hippocampal-neocortical consoridation process. Spindle activity is associated with improvements in procedural and declarative memory [150-152]. Word-pair learning before sleep induced higher sleep spindle activity than a nonlearning task, and spindle activity correlated positively with recall after sleep [153]. Further, Tamminen et al (2010) showed the role of spindles in the integration of newly learned information with existing knowledge, contrasting this with explicit recall of the new information [154]. Spindle activity was associated with overnight lexical integration in the sleep group, but not with gains in recall rate or recognition speed of the novel words themselves. Spindle activity appears to be particularly important for overnight integration of new memories with existing neocortical knowledge.

The strongest functional connectivity between the HF (Hippocampal Formation) (cornu ammonis, dentate gyrus, subiculum)and neocortex was observed in sleep stage 2(compared with both slow-wave sleep) [155]. A strong interaction of sleep spindle occurrence and HF connectivity in sleep stage 2 with increased HF/neocortical connectivity during spindles.

An increase of acetylcholine and a decrease in serotonin during REM sleep in rodents facilitate protein synthesis and long-term potentiation (LTP) in the hippocampus [156]. Both REM sleep and non-REM sleep play a role in long-term synaptic potentiation. Sleep spindles play an important role in sleep-dependent memory improvement. Sleep spindles may depolarize the postsynaptic membrane, resulting in a large influx of calcium ions that leads to cascade of cellular events. These events result in gene expression and protein synthesis necessary for LTP of the postsynaptic membrane.

6.3. Sleep promotes motor learning

Sleep following motor skill practice has been demonstrated to enhance motor skill learning off-line (continued overnight improvements in motor skill that are not associated with additional physical practice) for young people who are healthy. However, older adults who are healthy do not benefit from sleep to promote off-line skill enhancement. Patients with chronic stroke demonstrate sleep-dependent off-line motor learning of both implicit and explicit versions of a continuous sequencing task. Sleep enhances both spatial and temporal movement components of a continuous tracking task after stroke. This effect is unique to stroke, age and sex- matched controls that are healthy did not experience sleep- or time-dependent of-line motor learning on either version of the spatial or temporal movement component of task. During the chronic stage of stroke, sleep should be positive between therapy sessions to promote off-line learning of the skill practiced during therapy.

The motor system comprises a network of cortical and subcortical areas interacting by excitatory and inhibitory circuits.

The motor network will be disturbed after stroke when the lesion either directly affects any of these areas or damaged-related white matter tracts. Also abnormal interactions among cortical regions remote from the ischemic lesion might also contribute to the motor impairment after stroke. Pathological intra-and inter-hemispheric interactions among key motor regions constitute an important path pathophysiological aspect of motor impairment after subcortical stroke. Much of the neurobiological mechanisms leading to changes to the changes in cortical connectivity after stroke remain to be elucidated [157].

6.4. Sleep-dependent off-line learning in older adults who are healthy

Evidence suggests that stage 2 non-REM sleep, REM sleep or both are associated with consolidation of simple motor task off-line for young people who are healthy. In particular, sleep spindles are an important mechanism of sleep-dependent off-line memory improvement. Sleep-dependent off-line performance enhancement has been conducted using young people who are healthy, and older people are considered not benefit from sleep

to enhance motor learning. One hypothesis that older adults fail to demonstrate sleep-dependent off-line motor learning because they experience a reduction in both the time spent in REM sleep and the number of sleep spindles. If older adults who are healthy do not demonstrate sleep-dependent off-line motor learning due to changes in their sleep characteristics, it would follow that altering the sleep characteristics of older adults may enable these individuals to benefit from sleep to enhance off-line motor learning. Increased time spent in REM sleep, greater REM density, and decreased REM latency through the use of sleep-aid medication were correlated with enhanced performance of older adults on a word-recall task [158]. If REM sleep is important for promoting off-line motor learning, older individuals may benefit from sleep to enhance off-line learning if underlying changes in sleep architecture are addressed. Further attempts are required to relate sleep stages and sleep spindles with performance improvement for older people, and potential benefits of modifying these sleep parameters via medication or other means remain to determined.

6.5. Sleep-dependent off-line learning after stroke, brain injury

Recent evidence has demonstrated that people with brain injury benefit from sleep to enhance off-line motor learning. Damage to the prefrontal cortex due to stroke, tumor, or trauma demonstrated sleep-dependent off-line learning of a finger sequencing task [159].People with chronic stroke benefit from sleep to enhance motor skill learning of both implicit and explicit versions of a continuous tracking task [160-161]. Sleep also promote off-line motor learning through both improved spatial tracking accuracy and anticipation of upcoming movements in people with chronic stroke [162].A few studies to date have demonstrated the importance of sleep in promoting off-line motor skill learning suggest that stroke or brain injured patients benefit from sleep to enhance off-line learning of motor tasks. Patients with chronic stroke spent about the same amount of time in REM sleep but more time in stage 2 non-REM sleep compared with published norms. The number of sleep spindles increases from acute to chronic stroke. The alterations in sleep architecture demonstrated by chronic stroke patients (maintenance adequate amounts of REM sleep, increase stage 2 non-REM sleep, and increase spindle activity) enable them to demonstrate sleep-dependent skill enhancement. Further works utilizing sleep laboratories is needed to evaluate EEG data and understanding of alterations of sleep architecture and off-line learning of chronic stroke patients.

7. Conclusion

7.1. Spindles: Outlook and open questions

OQ-1: What is the role of sleep spindles in general and more specifically how do they relate to learning and memory consolidation mechanisms.

OQ-2: What mechanism keeps spindle spectral frequency within so narrow limits, which are stable through the night for a given individual?

OQ-3 related to OQ-2: Why do we observe a step like transition of TC neurons membrane hyperpolarization, which leads from spindles to delta TC rhythm, without appreciable intermediate rhythm frequencies?

QQ-4: How can spindle properties be used as biomarkers for the normal brain function and specific pathological conditions?

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