



PHYSIOLOGICAL REVIEW

State transitions between wake and sleep, and within the ultradian cycle, with focus on the link to neuronal activity

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KEYWORDS

Neuronal activity;
Spectral power
time-courses;
Reciprocal interaction
model;
Neuronal transition
probability model;
Sleep onset;
Sleep inertia;
Frequency bands

Summary The structure of sleep across the night as expressed by the hypnogram, is characterised by repeated transitions between the different states of vigilance: wake, light and deep non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. This review is concerned with current knowledge on these state transitions, focusing primarily on those findings that allow the integration of data at cellular level with spectral time-course data at the encephalographic (EEG) level. At the cellular level it has been proposed that, under the influence of circadian and homeostatic factors, transitions between wake and sleep may be determined by mutually inhibitory interaction between sleep-active neurons in the hypothalamic preoptic area and wake-active neurons in multiple arousal centres. These two fundamentally different behavioural states are separated by the sleep onset and the sleep inertia periods each characterised by gradual changes in which neither true wake nor true sleep patterns are present. The results of sequential spectral analysis of EEG data on moves towards and away from deep sleep are related to findings at the cellular level on the generating mechanisms giving rise to the various NREM oscillatory modes under the neuromodulatory control of brainstem-thalamic activating systems. And there is substantial evidence at cellular level that transition to and from REM sleep is governed by the reciprocal interaction between cholinergic REM-on neurons and aminergic REM-off neurons located in the brainstem. Similarity between the time-course of the REM-on neuronal activity and that of EEG power in the high beta range (~18-30 Hz) allows a tentative parallelism to be drawn between the two. This review emphasises the importance of the thalamically projecting brainstem activating systems in the orchestration of the transitions that give rise to state progression across the sleep-wake cycle.

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Introduction

Sleep within each ultradian cycle is a dynamic process where EEG-defined states of vigilance

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succeed each other in an apparently simple and well-defined manner: wake to light (stage 2) sleep to deep slow wave sleep then back to light (stage 2) sleep before entry into REM sleep or wake. As indicated later, this simplicity holds only when the data are averaged over many subjects, but it does give an overall view of the cycle structure and provides an essential reference framework for research at cellular level. While the hypnogram provides a convenient means to visualise sleep structure, and remains a useful classificatory tool in clinical practice, it has been superseded in EEG research work by more quantitative measures that bring out the essential continuity characterising the temporal progression—a continuity obscured by the assignment of discrete stages. Spectral analysis for example shows that slow waves, spindles and fast frequency oscillations co-exist at all times in sleep, in varying proportion. They take turn to predominate and it is this predominance sequence that defines stage assignment within the hypnogram. It is the detailed continuity obtained by such quantitative methods that enables conclusions to be drawn on the cellular origin of the overall structure of the ultradian cycle as seen in the spectral power time-courses.

This review is concerned with state transitions, be they in the sleep-wake cycle, within the ultradian cycle or within the NREM episode. This covers a vast field especially since over the past two decades the issue of state transition has been intensely investigated from a number of different angles, incorporating cellular, electrophysiological, physiological and behavioural studies. We therefore propose to focus primarily on those findings that enable the integration of neurophysiological data at the cellular level with time-course data at the EEG level, leaving other aspects of state transition to a brief summary and referring the reader to recent reviews where possible. This integration, made possible by the explosion in recent years of basic findings on key nuclei and neuronal circuitry implicated in the control of sleep and on the cellular basis of the different sleep rhythms,¹⁻³ is a very challenging aspect of sleep research today. Together, these findings have provided the elements necessary for the establishment of tenable hypotheses relating the temporal progression of activity at the EEG level to that at sub-cortical level.^{4,5}

Transition from wake to sleep

The wake-sleep transition is anything but clear-cut, with a sleep latency period between the start of

the polysomnography and spindle-defined sleep onset that often involves an alternation between stage 1 'sleep' and wake before the occurrence of the stage 1 episode that ends with sleep onset. This episode, often referred to as the sleep onset period, marks a period of gradual change operating at every level of biological organisation and involving a progressive reduction in the arousal level until the instalment of definite sleep. In parallel with marked changes in the EEG⁶⁻¹⁰ there are physiological,¹¹⁻¹⁸ cognitive,¹⁹ subjective^{20,21} and behavioural^{11,22} changes that take place gradually during this transitional period, indicating that falling asleep is a continuous and complex process. (See Ogilvie²³ for a comprehensive review). So at what point on the arousal continuum can a subject be said to be really asleep, or in other words what is the moment of sleep onset? On this point there is no clear consensus among sleep EEG workers some of whom go along with Dement and Kleitman⁷ and Rechtschaffen and Kales⁸ who define sleep onset in stage 1 based on criteria of alpha reduction. The most frequently used definition, however, situates it at the first appearance of sleep spindles or K-complexes (stage 2),^{6,9,10,24-26} probably because this can be more precisely pinpointed. We shall imply this second definition when we refer to sleep onset.

The two fundamentally different behavioural states, wake and sleep, are thus separated by a "no man's land" extending over several minutes composed essentially of stage 1 'sleep' during which the electrical activity of the brain gradually changes from wake to sleep mode. Using a 5-s resolution, Hori et al.¹⁰ traced the sequence of change in the EEG that leads from wake to sleep onset, by subdividing the standard stages wake, stage 1 and stage 2, into nine sub-stages. In this subdivision, two concern wake, six stage 1 and one stage 2 sleep. The sequence of change in the six-stage correlates of stage 1 indicates that this stage is a period of continuous transition. The start of this period is more wake-like in character with the presence of intermittent alpha waves, whilst the end is more sleep-like with the appearance of vertex sharp waves, first alone then in bursts. It has been suggested²⁷ that the vertex sharp wave could be an incipient K-complex and therefore the beginning of the cortically generated slow (<1 Hz) oscillation that characterises NREM sleep.^{28,29} Although instructive in its description of the sleep onset period, the Hori scoring system has the same limitation as the more classical ones: the inability to examine quantitatively the temporal interrelationship between the spectral constituents of the signal.

Sequential spectral analysis, on the other hand, lends itself particularly well to the study of dynamic changes in the EEG, providing time-course data that have proved to be useful for exploring the temporal correlation between cortical EEG and sub-cortical neuronal activities.^{4,5} Most of the studies reviewed here are based on spectral power time-courses averaged over several subjects. Although this approach effectively conceals the detailed structure of the time-courses that constitute the average, it is sufficient to bring out the general behaviour of the time-courses and allows conclusions to be drawn on the relationship between the concurrent power time-courses in the different frequency bands. To enable the averaging of individual subject data, time-course data are often normalised prior to analyses, both on the time and on the power axes. These transformations do not affect time-course results since they preserve the shape and relationships of the individual curves as well as the sequence of events over time.

Using sequential spectral analysis Merica et al.^{30,31} have shown that the sleep onset period is marked by smooth changes where activity in the beta band (15-30 Hz) decreases and in the delta band (0.5-4 Hz) increases (Fig. 1). Interestingly, there is a significant positive correlation between the duration of the sleep onset period and beta intensity therein but no significant correlation with delta intensity.³⁰ This would suggest that

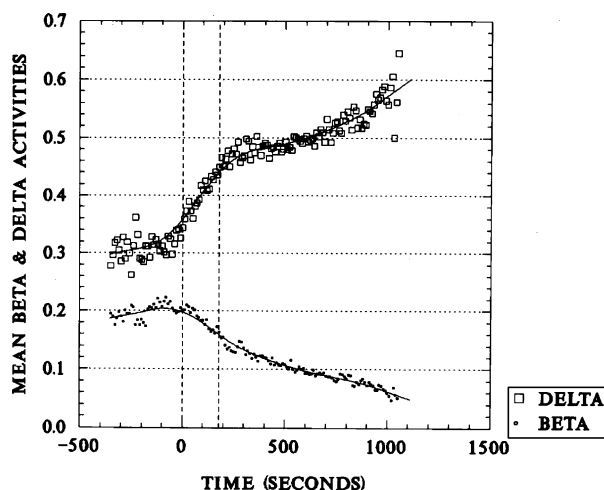


Figure 1 The time-courses of beta and delta power, expressed as the relative proportion of their amplitudes in the total signal, across the wake-sleep transition. Data are averaged over 28 healthy subjects. The average sleep onset period (~ 3 min) lies between the vertical broken lines. The sleep onset period is defined as the stage 1 episode that immediately precedes definite sleep. Reprinted from *Physiology and Behaviour*, vol. 52, Merica and Gaillard³¹ with permission from Elsevier.

the process of falling asleep is more one of withdrawal from the waking state rather than of invasion of the sleeping state. These initial studies, however, are limited in that they consider only the beta and delta constituents of the EEG signal. Moreover, the delta band limits adopted in these and other studies carried out before the discovery (1993) of the cortically generated slow oscillation, do not allow a distinction between thalamically generated clock-like delta (1-4 Hz) and the cortically generated slow oscillation (<1 Hz). More recently, De Gennaro et al.,²⁶ using single Hz resolution, extended the range of frequencies studied, to cover a continuous range (1-28 Hz). Time-course results show that power in all frequencies change across the sleep onset period: slow frequencies below 7 Hz (delta and theta) gradually increase, as do frequencies in the 12-16 Hz range (sigma), whilst fast frequencies above 17 Hz (beta) gradually decrease. These patterns of change continue in the same direction after sleep onset. Power in the 8-11 Hz (alpha) range, on the other hand, displays a strikingly different temporal compartment in the sleep onset period compared to that observed after sleep onset. Like beta power it declines gradually across the sleep onset period, but unlike beta it reaches its minimum at sleep onset and adopts a time-course similar to that of power in the slower frequencies thereafter, namely it progressively goes up. This result suggests that alpha prior to sleep onset is wake related whilst alpha after sleep onset is sleep related. This interpretation is substantiated by a number of studies: De Gennaro et al.³² report that during the sleep onset period, the declining time-course of power in the alpha range is highest in the occipital region, a region known to indicate relaxed wakefulness.²⁷ Also, at sleep onset the process of synchronisation marked by the appearance of spindles involves a generalised increase in EEG activity over all slow and middle frequencies, including those in the alpha range. During the transition from wake to sleep, the observed occipital prevalence of alpha activity ends as it spreads to more anterior regions. In line with findings reported by Pivik and Harman,³³ these results suggest that the alpha activity after sleep onset is an expression of the generalised process of synchronisation rather than a sign of persisting arousal. Moreover, on the basis of coherence analysis, Hori et al.³⁴ report two different patterns of coherence in alpha activity in the transition from wake to sleep: a posterior coherence associated with wake EEG and an anterior one associated with sleep EEG. Finally, there is a slowing in responsiveness to external stimuli as alpha activity decreases in the sleep

onset period, yet this behavioural responsiveness ceases entirely when alpha reappears at sleep onset,²² indicating again that alpha prior to sleep onset differs from alpha activity in sleep. Taken together, these data all point to the fact the transition from wake to sleep is a gradual process involving both the turning off of the waking state and the turning on of the sleep state.

Cellular neurophysiology provides evidence pointing in a similar direction: inhibition of wake promoting neurons concurrent with activation of sleep promoting neurons. The role of the hypothalamus in the regulation of sleep and wake states has been recognised as early as 1930,^{35,36} but it is only in recent years that a population of sleep promoting neurons localised in the ventrolateral preoptic (VLPO) area of the hypothalamus has been identified.^{37,38} Gallopin et al.³⁹ have shown that these GABAergic neurons are inhibited by wake-promoting monoaminergic and cholinergic neurotransmitters and have postulated that there exists a reciprocal inhibitory interaction between these neurons and wake-promoting neurons to which they project, localised in multiple arousal centres in the upper brainstem and diencephalon. Thus under the influence of circadian factors input from the retina⁴⁰ and the suprachiasmatic nucleus⁴¹ as well as homeostatic factors,⁴² the sleep-promoting neurons in the VLPO appear to increase their firing rate and in so doing inhibit the wake-promoting neurons. The progressive decrease in the firing rate in the arousal systems would in turn remove inhibition from the VLPO neurons, further increasing their activity. Neurons in the VLPO, however, are not the only population to increase activity with decreasing activity in the arousal system. Suntsova et al.⁴³ have shown that a population of neurons in the median preoptic nucleus (MnPN) presents a similar sleep-wake discharge profile and appears to have similar anatomic and neurochemical properties. Hence these authors postulate that the population of MnPN neurons, together with that of the VLPO neurons exert inhibitory control over the arousal system, probably acting preferentially on those systems that are not strongly inhibited by the VLPO sleep-promoting neurons. Although the signal to go to sleep or to wake appears to act as an on-off switch, the process of going from one state to the other is a progressive one involving a transitional period. Fig. 2 shows at the cellular level a gradual decline in the sequential mean firing rate in neurons recorded from cholinergic brainstem-thalamic activating nuclei across wake and a wake-sleep transitional period⁴⁴ that parallels the time-course of the fast frequency EEG activity observed in Fig. 1. The somewhat irregular pattern of change observed in

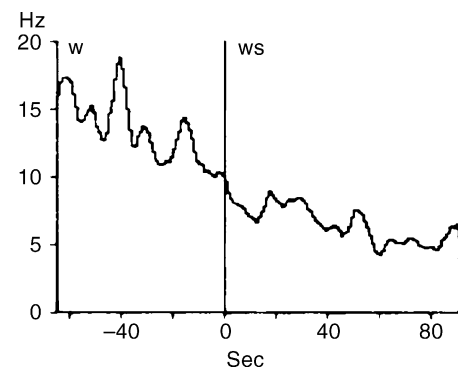


Figure 2 Sequential mean firing rates in a group of five neurons recorded in the peribrachial area of the pedunculopontine nucleus across wake (W) and the transitional epoch from wake to sleep (WS). Time 0 indicates the onset of WS. Reproduced from Steriade et al.⁴⁴ with the kind permission of the publisher.

the period of wake that precedes the wake-sleep transitional period in Fig. 2 (also suggested in Fig. 1) probably reflects the repeated alternation between stage 1 'sleep' and wake that is frequently encountered during the sleep latency period. However, the sleep onset or transitional period is characterised by a definite downward trend in activity both in the fast frequency EEG and in the cholinergic brainstem-thalamic activating nuclei at the cellular level. Thus it is important to distinguish between the sleep latency and the sleep onset periods when studying the transition from wake to sleep.

Transitions within NREM

These transitions concern the move towards deep sleep followed by a move away from deep sleep. The two together constitute the basic building block of the NREM episode, and on the average there are in the early episodes about 4 or 5 of them.⁴ The compartment averaged over many subjects is, however, much simpler: a single excursion to deep sleep and back (Fig. 3) and it is this simple picture that gives a reference frame for work at cellular level. At this level, Szymusiak et al. showed that the initial increase in activity of the VLPO sleep-promoting neurons initiated by the wake-sleep switch continues to increase proportionally with sleep depth.³⁸ This progressive increase is mirrored by a progressive decrease in the firing rates of the wake-promoting neurons in the various arousal centres including those in the brainstem-thalamic activating system. As a result of the diminished excitatory input to the thalamus, thalamocortical neurons gradually become more hyperpolarised leading first to light sleep (spindle oscillatory mode) then at a more hyperpolarised

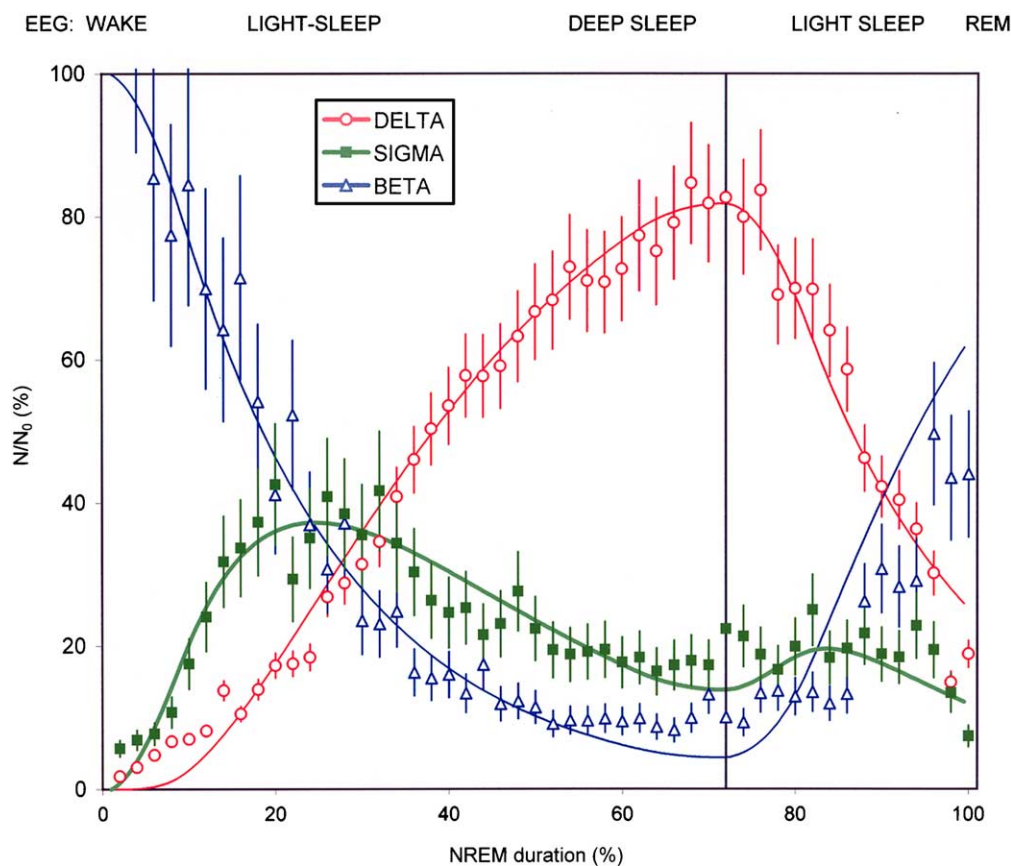


Figure 3 Simultaneous power time-courses for the beta, sigma and clock-like delta frequency bands in the first NREM episode. Data are averaged over six healthy subjects and fitted using the NTP model. The number of neurons (N) in each mode beta, sigma and delta, is expressed as a percentage of the number of neurons in beta mode (N_0) at the start of the NREM episode. N_0 is the fixed size of the NTP model generating population at the brainstem. Note that beta drops to $1/e$ of its initial value when sigma reaches its first maximum: this is one of the principal characteristics of a three-stage cascade process involving stochastic transitions. Others are the S-shaped rise of delta in the sleep-deepening phase of the episode, and the exponential fall of delta accompanied by a second sigma peak, in the sleep-lightening phase. The vertical line at about 72% indicates the separation between the sleep-deepening (hyperpolarising) and the sleep-lightening (depolarising) phases.

level to deep slow wave sleep (clock-like delta mode). Increased excitatory input, on the other hand, depolarises the thalamocortical cells producing a transition to wake or REM sleep.⁴⁵ Moreover, decreased activity in the ascending activating systems leads to a progressive deafferentation of the forebrain initiating at sleep onset the cortically generated slow (<1 Hz) oscillation, which reaches full development as sleep deepens and which is obliterated by brain activated states.⁴⁶ The depolarising component of this slow oscillation has a major role in triggering, shaping and synchronising thalamically generated rhythms (spindles and the clock-like component of delta waves) as well as fast oscillations, forming at the cortex the complex wave sequences observed on the EEG.^{3, 47, 48} Thus under the modulatory control of the brainstem activating system a permanent dialogue is established between cortex and thala-

mus that allows the orderly appearance over the entire cortex of the various rhythms characterising NREM sleep progression. These basic findings established essentially on the basis of state-dependent EEG characteristics and on events of the order of milliseconds to several seconds in duration, shed light on the general pattern of state progression operating across NREM. Can these be linked to the continuous dynamic changes of the EEG as expressed by the spectral power time-courses? To address this question we focus on research carried out at the EEG level.

Findings on the generating mechanisms that give rise to the various sleep EEG rhythms, in particular the existence of different modes of oscillation of thalamocortical neurons depending on their membrane potential^{49,50} has incited a number of groups to analyse the relationship between these rhythms at the EEG level. Most of these studies report an

overall reciprocal relationship between both the sigma-delta⁵¹⁻⁵³ and the beta-delta⁵⁴⁻⁵⁶ power time-courses within NREM as measured by a single correlation coefficient. This overall measurement, however, does not take account of the dynamic changes in the relationship across the NREM episode and as such is misleading. This is particularly true for the sigma-delta relationship, which is not uniform over time:^{56,57} power in both the sigma and delta bands rise at the start and fall at the end of the episode, while the reciprocal relationship is confined to the central time zone. Both Aeschbach and Borbély⁵² and Dijk et al.⁵³ have pointed out this pattern of change. Moreover the same pattern is observed at the thalamus.⁵⁸ On the basis of cellular data, a reciprocal relationship between sigma and delta could have been expected throughout the entire NREM episode given the intrinsic nature of each thalamocortical cell where sigma and delta oscillation modes are mutually exclusive. Merica and Fortune^{4,59} examined the simultaneous time-courses of power in the major frequency bands beta, sigma and delta looking for a mechanism that would reconcile EEG time-course data with data at cellular level. The three curves (Fig. 3) show a set of quite distinctive characteristics in the sleep deepening phase: beta power drops exponentially while delta exhibits an S-shaped monotonic rise (more or less mirroring beta) and sigma increases rapidly and goes through a maximum while delta is still rising. The sigma maximum coincides exactly with the moment when beta has dropped to $1/e$ of its initial value. In the sleep-lightening phase the inverse is observed: a rapid exponential drop in delta is mirrored by a rise in beta and sigma goes through a secondary maximum of lesser intensity while delta is dropping. This very particular relationship between the time-courses of power in the different bands, referred to in⁵ as the 'pattern', is explained by the neuronal transition probability (NTP) model, which fits the data well. Briefly, the model postulates that this pattern is the result of stochastic transitions of the firing-rate frequencies of the brainstem-thalamic activating neurons: first a cascade of transitions towards then a cascade of transitions away from deep sleep. (Fig. 4 gives an example of the direct parallelism between brainstem firing-rate change and the move at the EEG from fast to spindle rhythm). The time-courses of the firing rates corresponding to each sleep state form a template that modulates both thalamic and cortical output.⁵ At the thalamus the modulation results in identical cascades for thalamocortical neurons: from beta to sigma to clock-like delta oscillation in the sleep deepening phase

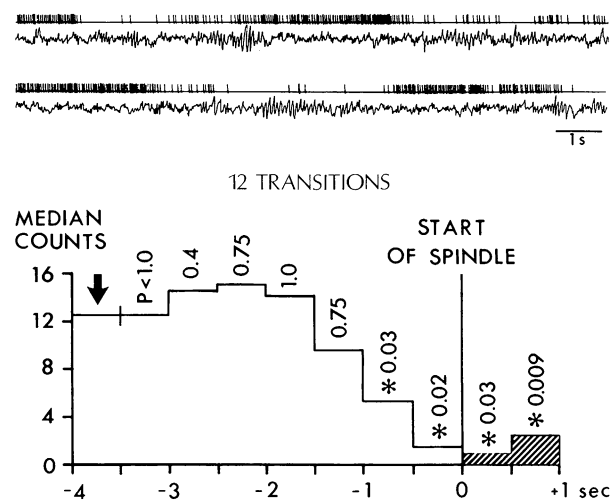


Figure 4 Firing rate in a midbrain reticular neuron of the cat during repeated EEG desynchronisation-synchronisation transitions (top 2 traces). The graph depicts results from 12 such transitions and shows that unit firing decreases prior to spindle onset at the EEG (time=0). Adapted from Steriade et al.⁸⁶ with the kind permission of the publisher.

followed by the inverse cascade in the sleep-lightening phase. Due to the integrating networks comprising cortical, reticular thalamic and thalamocortical neurons, the thalamically generated cascades form at the cortex the complex wave sequences observed on the EEG from which the time-courses of power are extracted. The single-unit cellular study of the firing rate time-courses depicted in Fig. 4, however, shows that a single neuron in the brainstem takes about 1.5 s to slow down from wake (fast) to sleep (spindle) mode. Whereas EEG spectral power time-course measurements (e.g. Fig. 3) show that spindle oscillation mode takes about 10-20 min to reach maximum power. What brings about this delay? In our view, the answer lies in the difference between single unit and neuronal population aspects of what transpires at the brainstem. Although a single unit may well jump rapidly to spindle mode, it is the stochastic compartment of the entire brainstem population of the involved neurones that will determine the power going into spindle activity. This concept of stochastic delay, inherent in the NTP model⁴ is sufficient to explain the observed shape of the EEG spindle power evolution in time. Thus, the NTP model provides a mechanism by which the very particular relationship between the power time-course shapes can be physiologically explained, and thereby links EEG activity to findings at the cellular level. In addition, and confirming an inherent implication of the model, the shape and timing of these time-courses are

found to be practically identical at different cortical sites⁵ despite the regional differences in their average power levels reported by a number of workers.

As stated earlier the overall structure of the ultradian cycle is often described by the progression, wake to light sleep to deep slow wave sleep then back to light sleep before entry into REM sleep or wake, in other words a single excursion to deep sleep and back. However, perusal of NREM structure in individual subject data shows that this simple progression is seldom met with in practice despite the fact that it is implied in much of the research referred to in this review. It is an oversimplification resulting from the common use of averaged data and it conceals an important reality: the episode exhibits repeated alternations towards and away from deep sleep, manifested as multiple delta processes, i.e. delta peaks accompanied by corresponding changes in beta and sigma component.⁴ Sinha et al.⁶⁰ and Feinberg and March⁶¹ were the first to see multiple delta peaks as a basic feature of the NREM episode. The NTP model was used to study the detailed structure of the spectral power time-courses over the typical NREM episode of individual subject data⁴ where delta processes are seen to

replicate the 3-band pattern seen in averaged data.⁵⁹ This revealed that NTP theory can fit the systematic oscillatory or alternating character of these time-courses well. It also revealed that, as in the case of overnight sleep having an average of about four NREM-REM cycles, the early NREM episode has an average of about four delta processes. One of the questions posed by this observation concerns the origin of the state-change command signals that alternate the system to go towards or away from deep sleep within NREM. Preliminary results on a correlation between these alternations and the occurrence within the episode of independently defined arousal events (Fig. 5) suggest that this behaviour may be controlled via the arousal system, in particular the brainstem-thalamic activating system.⁶² The figure shows that transitory activation phases (TAPs) together with ASDA defined microarousals⁶³ appear to trigger shifts away from deep sleep, while K-bursts and delta-bursts occur preferentially on the rising limb of the power curves, and appear to encourage deep sleep. Despite the clear temporal relation, no firm conclusion of causation can be drawn at this stage. This preliminary result is in line with similar findings reported by Terzano and Parrino⁶⁴ on the sculpturing of the NREM episode by the different

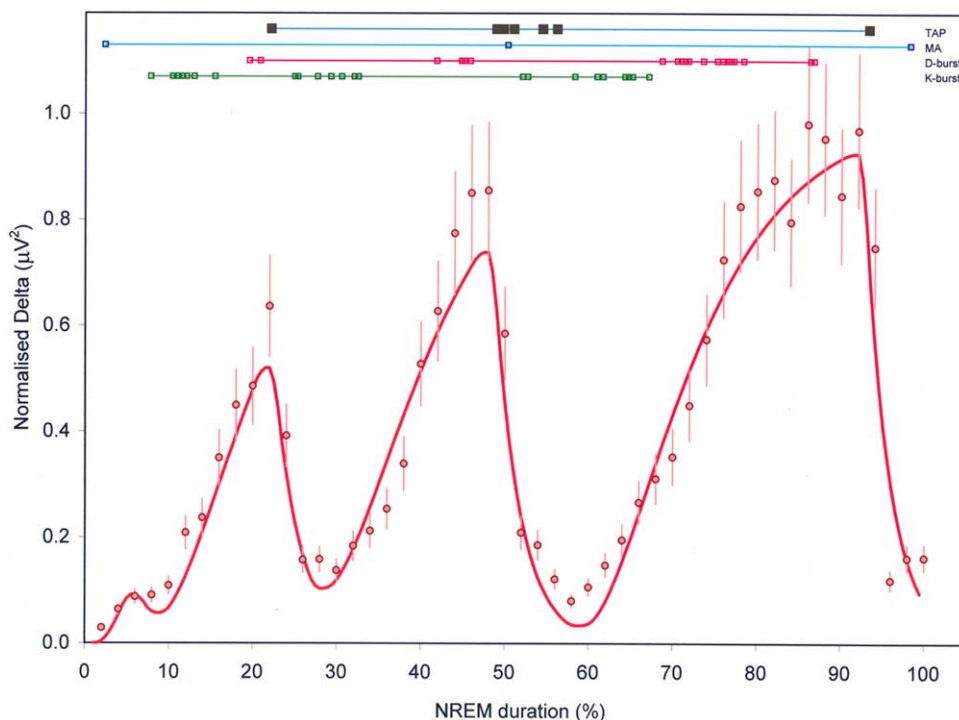


Figure 5 Time course of delta power within the first NREM episode, for a typical healthy subject, together with the times of occurrence of the various types of EEG arousal events: transitory activation phases (TAPs), ASDA defined micrarousals (MA), K-bursts (K-burst) and delta-bursts (D-burst). This dual display provides a visual appraisal of the temporal relation between arousal events and the detailed structure of the NREM episode. The NTP model fits the data well as indicated by the goodness of fit criterion given by the coefficient of determination $R^2=0.94$.

components of the cyclic alternating pattern that overlap with well defined arousal events. Thus the interaction between the sleep promoting and the wake promoting neurons, with their alternating predominance, would appear to be decisive not only at sleep and wake onset but appears to operate throughout each NREM episode.

NREM-REM-NREM transitions

NREM and REM sleep are two very different states identified by characteristic electrophysiological signatures that are detected using a combination of EEG, EOG and EMG signals. These two distinct sleep states alternate regularly across the night giving rise to about four or five ultradian cycles. It is the transitions from the synchronised NREM to the activated REM state (REM onset) and from the REM to the NREM state (REM offset) that interests us here.

Over the past decade cellular neurophysiology has provided numerous findings that have considerably enhanced knowledge on the brain structures and the mechanisms involved in the generation of REM sleep (See Reinoso-Suárez et al.⁶⁵ for a comprehensive review). In contrast, there is a relative paucity of research conducted at the EEG level and aimed at analysing the physiological changes that occur in the transitions to and from human REM sleep. This is perhaps due in part to the fact that the fast frequency low amplitude EEG characterising activated sleep is subject to larger measurement error than are the slower high amplitude frequencies, and therefore, more difficult to analyse. However, there are clear pointers to a possible link between data from the cellular and EEG levels of investigation.

At the cellular level, based on anatomical and physiological data, McCarley and Hobson proposed the reciprocal interaction model⁶⁶ to explain the generation of the NREM-REM cycle. The model postulates that transition into and out of REM sleep is produced by the reciprocal interaction between cholinergic and aminergic neuronal populations located in the brainstem. More recently, the model was revised to incorporate new anatomical and neuromodulatory data,⁶⁷ but the major tenets of the original model, namely cholinergic facilitation and aminergic inhibition of REM sleep, were retained. According to the revised model, transition from NREM to REM sleep occurs when activity in the aminergic REM-off neurons located in the locus coeruleus (LC) and the dorsal raphe nucleus (DRN) ceases. These neurons, active during wake, decrease their firing rate at sleep onset, a gradual

reduction that continues throughout the NREM episode causing the REM-on neurons in the cholinergic mesopontine nuclei (Laterodorsal tegmental nucleus, LdT and pedunculopontine nucleus, PPT) to become disinhibited. As the LdT/PPT neurons become active, minutes before entry into REM sleep,⁴⁴ they activate reticular formation neurons in positive feedback which in turn generates the occurrence of REM sleep events (rapid eye movements, muscle atonia) and finally produces the onset of REM. Transition from REM to NREM sleep occurs when activity in the cholinergic REM-on neurons ceases: during REM sleep, the excitatory input from the REM-on neurons to the LC and DRN leads to a gradual increase in activity of the REM-off neurons which in turn inhibits REM-on neurons until cessation of their discharge and the REM episode ends. When active, the REM-on neurons furnish excitatory input to the thalamus causing thalamocortical cells to depolarise and hence give rise to periodic EEG activation. Establishing EEG spectral correlates whose time-courses parallel those of the REM-on neurons illustrated in Fig. 6, would provide a means to link subcortical activity to activity at the EEG level and thus further reinforce the reciprocal interaction model by fitting it to actual EEG data. Such a link would also facilitate the exploration of transitions into and out of REM sleep in man.

Although not directly addressing the issue of EEG spectral power changes that characterise NREM-REM and REM-NREM transitions per se, power time-course data measured in the different frequency bands across the night^{52,54-56} provide a general overall view of these changes as the two major sleep states alternate. These data show that the time-course of beta power across both the NREM and REM sleep states differs from that of the slower frequencies. In terms of the average state compartment within the NREM episode (light sleep, deep sleep, light sleep), the slower frequencies delta, theta, alpha and sigma show a roughly arch-shaped time-course, while beta is roughly U-shaped (Fig. 3). A reciprocal pattern also exists in the REM episode, where beta power rises and asymptotes to a high plateau level and power in the lower frequencies fall and asymptote to a low plateau level. Thus the REM onset transition is marked by a gradual change in the spectral constituents, initiated before the end of the preceding NREM episode and continuing into the initial part of the REM episode. Moreover, Hadjiyannakis et al.⁶⁸ showed that the three physiological markers of REM sleep onset (decrease in muscle tone, appearance of saw tooth waves and of rapid eye movements) identified in the pre-REM phase of NREM sleep coincide with the decline of delta, theta and sigma power. In contrast to the continuity of the REM onset

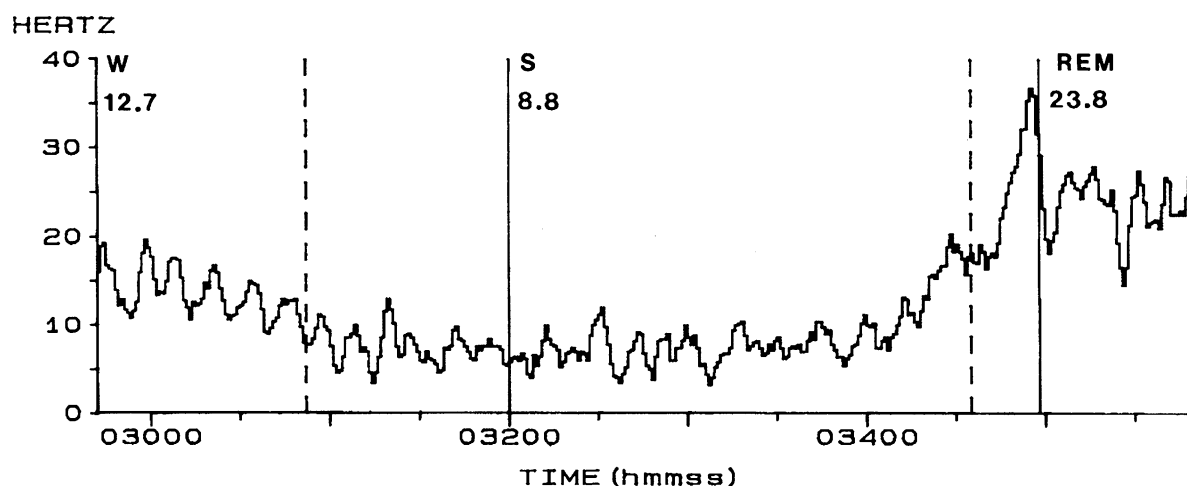


Figure 6 Sequential mean firing rate of a thalamically projecting peribrachial neuron, during the progression wake (W) to NREM sleep (S) to REM sleep. Transitional epochs from W to S and from S to REM are indicated by vertical interrupted lines at 0:30:53 and 0:43:34, respectively. Reproduced from Steriade et al.⁴⁴ with the kind permission of the publisher.

transition, REM offset appears to be marked by abrupt changes: in beta with a rapid fall and sigma with a rapid rise, from their plateau levels in REM. These are accompanied by the gradual increases of power in the delta, theta and alpha bands marking the start of the following NREM episode, with no visible change taking place in the latter part of the preceding REM episode.

The three studies that have directly addressed the issue of frequency-specific changes across NREM-REM and REM-NREM transitions⁶⁸⁻⁷⁰ corroborate the above observations for the slower frequency bands, but not for the fast frequency beta band. In order to obtain a more coherent picture that agrees with neurophysiological data for the fast frequency compartment across REM-onset and REM-offset transitions, Ferri et al.⁶⁹ resorted to the use of ratios. This approach was dictated by their earlier all-night study⁷¹ that showed no significant change in beta activity between NREM and REM sleep. Ratios, however, are difficult to interpret. They conceal the original time-courses and as such obscure the link between EEG and neuronal activity. The discrepancies for the fast frequencies may well be due to the definition of the beta band used in these studies: 15-30, 15-25 and 16-25.75 Hz, respectively. Uchida et al.⁵⁴ stressed the importance of the beta band limit definition in such time-course analyses. These authors showed that activity in the traditional beta band range (15-35 Hz) is non-uniform in its relationship with delta activity with only the 20-28 Hz portion of the band displaying a consistent inverse relationship across both NREM and REM sleep. Moreover, Merica and Fortune⁷² reported that the shape of the time-course curves in the range

15-18 Hz differs significantly from that in the range 18-30 Hz both in NREM and REM sleep. Combining the two curve types in a single band can therefore lead to ambiguous results that could render difficult the study of sleep state transitions. Taken together, these data suggest it is the high beta band (18-30 Hz) that may reflect the REM-on neuronal activity, since it displays a time-course similar to that reported for the sequential firing rate of brainstem-thalamic activating neurons (Fig. 6).

In addition to the frequency-specific changes at NREM-REM-NREM transitions described above, De Gennaro et al.⁷⁰ showed that these transitions are accompanied by topographic shifts in relative power. Interestingly, the most topography-specific change concerns the alpha range (7-10.75 Hz). During NREM sleep this EEG activity predominates in the anterior regions, but after the onset of REM sleep predominance shifts to the posterior region where it remains throughout the entire episode, an observation also reported by Roth et al.⁷³ Transition out of REM is accompanied by an anterior diffusion of alpha activity. A similar shift was observed at sleep onset. This result strengthens the supposition that there may exist two different alpha rhythms: one associated with a cortically activated state and the other with a cortically synchronised state.

Sleep to wake transition

Just as there exists a sleep onset period preceding definite sleep, there also exists a sleep offset

period following definite sleep, often referred to as the sleep inertia period. Sleep inertia denotes a state of hypovigilance, confusion and impaired cognitive and behavioural performance, immediately after awakening from sleep. Although the sleep inertia period has received less attention than the sleep onset period, there are sufficient data to support the view that the process leading from sleep to full waking alertness, is gradual and lasts anything from a few minutes (e.g.^{74,75}) up to a few hours (e.g.⁷⁶). The time taken for sleep inertia to dissipate depends on the complexity of the task undertaken on awakening, with cognitive performance accuracy taking longer than performance speed.⁷⁷ Moreover, it would appear that the intensity of sleep inertia depends on the stage from which sleep emerges, with awakening from slow wave sleep producing more negative effects on subsequent performance than awakening from REM sleep (e.g.⁷⁸⁻⁸⁰). Increased sleep depth caused by sleep deprivation also appears to exacerbate sleep inertia on awakening from recovery sleep.⁸¹ These observations suggest that, as could be expected, less time is required to reverse the sleep-state when the brain is already in an activated state as it is in REM sleep. It remains, nevertheless unclear to what extent circadian influences on performance affect the reported results, since these are not taken into account. Studies that have measured the time-course of sleep inertia dissipation show that it subsides in an exponential manner for both subjective alertness and objective performance, thus establishing the continuous nature of the sleep-wake transition.^{82,83,76}

The studies referred to above have focussed on measures of alertness and performance upon awakening, with no measurement of EEG spectral changes that may characterise the sleep inertia period. The one study that examined EEG power spectra during spontaneous awakening from sleep showed a gradual and continued drop in power in both the theta and delta bands, extending well into the first few minutes of behaviourally identified wake.⁸⁴ Similar studies, extended to cover the entire spectral range and including time-course data are needed for a better understanding of the sleep inertia phenomenon and its possible link to findings at the cellular level. Since our principal aim here is to relate cellular to EEG research, we have given only a succinct review of the literature on the sleep-wake transition and direct the reader to an extensive review on the subject by Ferrara and De Gennaro.⁸⁵

Practice points

1. There exist two alpha rhythms: one associated with a brain-activated state with posterior predominance and the other with the synchronised state and an anterior predominance.
2. The inverse relationship between sigma and delta activity during the NREM episode is confined to the central portion of the episode only.
3. The early NREM episodes show repeated alternations towards and away from deep slow wave sleep, an observation concealed in data averaged over several subjects.
4. Only the upper beta band (above ~18 Hz) shows a consistent reciprocal relationship with delta activity across both NREM and REM and this could reflect REM-on neuronal activity.
5. The intensity of sleep inertia depends on the stage from which sleep emerges, with less time required to reach full alertness when the brain is already in an activated state (REM or stage 1).

Research agenda

1. Determine the sites of origin and the cellular basis of the two different alpha rhythms: one associated with a brain-activated state and the other with synchronised sleep.
2. Determine on a neurophysiological basis the optimal definitions for fast-frequency (beta) band limits, so as to approach some kind of standardisation.
3. Make a sequential spectral power analysis of the final ultradian cycle and the following sleep inertia period.
4. Attempt to Integrate the Reciprocal Interaction and the Neuronal Transition Probability models.
5. Make a frequency analysis over the NREM episode of the spike train from brainstem neurons as they slow down from the beta-equivalent to the spindle-equivalent firing rate.⁸⁶—and then to the delta-equivalent firing rate—in order to confirm overall parallelism with the pattern of the EEG spectral power time-courses.

Acknowledgements

The Swiss National Science Foundation supported a part of the author's research. Sleep staging and signal analysis were done using the ERA software package (Phitools, Grenoble, France).

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