# Normal Sleep EEG

# 10

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## 10.1 Sleep EEG Recordings, Why and When

It is well known that many epileptic discharges may be absent during the waking state and occur only (or at least more easily) in sleep. For this reason, brief sleep recordings during spontaneous sleep or after sleep deprivation are generally performed in regular EEG laboratories to disclose such paroxysms. These recordings are often not longer than 30 min, representing de facto a nap. A nap shows normally the process of falling asleep from the waking state to drowsiness and from drowsiness to light NREM sleep. These stages are usually the most informative stages for the epileptologist who is searching for clinically relevant abnormalities and especially for epileptic discharges not demonstrable in the waking state. However, additional information can be obtained only during deeper and REM sleep.

Nocturnal sleep and daytime nap, besides the difference in circadian phase, differ in multiple important aspects, such as total sleep time, the amount of sleep spindle-rich stage 2 sleep, slow-wave sleep (SWS), and REM sleep [1]. A more complete sleep study can be performed in sleep laboratories, with the aim of recording a whole night sleep or a 24 h time span and analyzing not only EEG but also other physiologic parameters with a complete polysomnography (or video-polysomnography, representing the gold standard for sleep investigation-PSG), in order to get a more complex perspective about the dynamics of patient's sleep, the trend of cardiovascular parameters, and the presence of abnormal movements during sleep.

The principal indications to perform all night PSG study are the following:

1. To differentiate between epileptic and non-epileptic nocturnal events (e.g., parasomnias, syncope due to nocturnal arrhythmias, sleep-related movement disorders)
2. To diagnose electrical status epilepticus during slow-wave sleep (ESES)
3. To demonstrate the absence of REM atonia in patients with REM behavior disorder (RDB)
4. To investigate sleep-related breathing disorders (especially in suspected obstructive sleep apnea syndrome (OSAS) with clinical signs of comorbid sleep disorders and/or significant pulmonary, cardiovascular, neuromuscular diseases)
5. To investigate sleep-related movements disorders (i.e., periodic limb movement (PLM))
6. To investigate, together with other diagnostic tests (multiple sleep latency test-MSLT) daytime sleepiness of unknown origin (e.g., suspected narcolepsy)

## 10.2 General Rules of Sleep Stages Scoring

Normal human sleep comprises two states—rapid eye movement (REM) and non-REM (NREM) sleep—that alternate cyclically across a sleep cycle. State characteristics are well defined: NREM sleep includes synchronous cortical EEG phenomena (sleep spindles, K-complexes, and slow waves) together with low muscle tonus; during the REM sleep, EEG is desynchronized, muscles are atonic, and dreaming occurs. A nightly pattern of sleep in mature humans sleeping on a regular schedule includes reliable features. Sleep begins in NREM and progresses through deeper NREM stages (stages N2 and N3) before the first episode of REM sleep occurs, approximately 80–100 min later. Thereafter, NREM sleep and REM sleep cycle with a period of approximately 90 min. NREM stage N3 concentrate in the early NREM cycles, and REM sleep episodes lengthen across the night (Fig.10.1). In the usual 6.5–8.0 h of sleep of young adults, stage N1 makes up about 5% of total sleep time (TST), stage N2 50–55%, stage N3 20%, and REM sleep 20–25%. Age affects the pattern of sleep stages across the night. In the newborn the sleep cycle is much shorter, approximately 40–45 min, slow-wave sleep (stage N3) more abundant, and REM sleep also much

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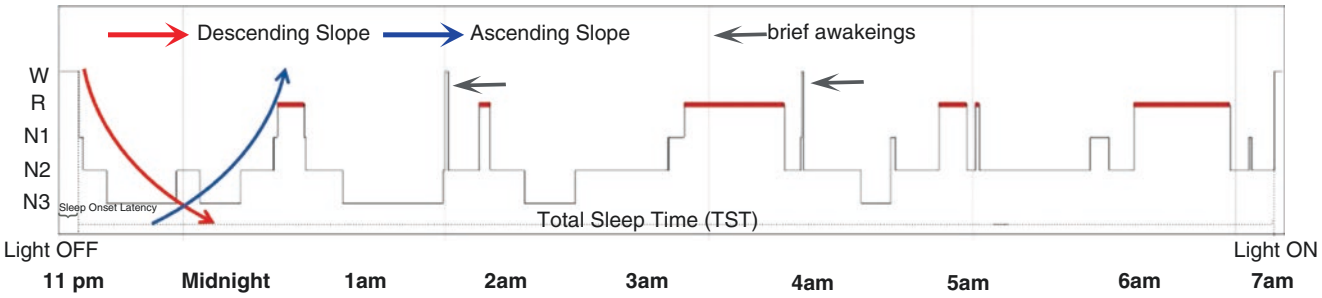


**Fig. 10.1** Sleep pattern from a healthy human. An exemplary hypnogram depicting the different sleep stages over 8 h of nocturnal sleep. *W* wake, *R* REM, *N1* N1 sleep stage, *N2* N2 sleep stage, *N3* N3 sleep stage. The ascending-descending of the sleep cycle are represented by the red and blue arrow, respectively. Note that this pattern is less evident in the second part of the night particularly toward the last cycle

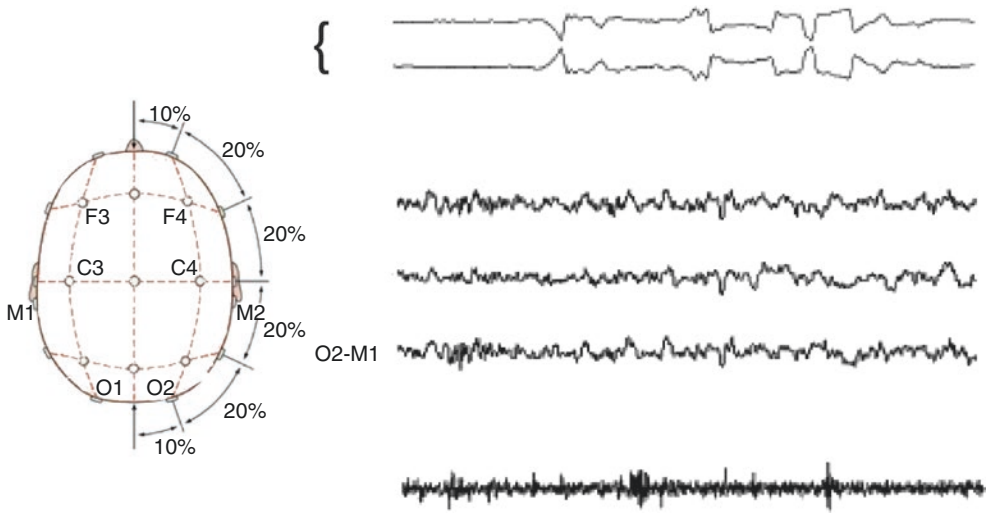


**Fig. 10.2** Minimal recommended derivations for PSG recordings according to the AASM manual: two EOG derivations (E1, left EOG; E2, right EOG); three EEG channels (F4, C4, O2) referred to the contralateral mastoid (M1); one EMG derivation placed over the chin muscle. *F* frontal, *C* central, *O* occipital

higher, about 50% of TST. Moreover, sleep onset directly into the REM state may happen, and sleep is dispersed throughout the 24-h period. In late infancy and childhood, sleep becomes nocturnal with an afternoon nap. NREM sleep always occurs first, the sleep cycle lengthens progressively toward the 85 min of the adult, and slow sleep and REM sleep decrease. In old age there is a marked diminution of stages N3, slight reduction of REM sleep, a decrease of total sleep time, and increasing episodes of wakefulness.

The official rules for sleep stage classification in sleep laboratories were first established during an international expert consensus in 1968, described by Rechtschaffen and Kales [2], and then updated and modified in 2007 by the American Academy of Sleep Medicine (AASM) [3] and subsequent versions.

The AASM manual, despite some intrinsic limitations and weakness, represents the international approved standard for sleep and associated events (arousal, cardiac, respiratory, and movement events) scoring rules. Actually the latest AASM version regarding rules for scoring of sleep dated 2018 [3].

At least three EEG channels, one EOG (electrooculogram) and one chin EMG (electromyography) are necessary to score sleep stages (Fig. 10.2 and Table 10.1). Sleep staging is based on visual analysis of 30-s subsequent epochs, recognizing the main features of each single epoch in order to classify the latter as one of five distinct stages: one stage of wake (W) and four different sleep stages (N1, N2, N3, R) (Fig. 10.3).

The general rules for sleep stage scoring, according to AASM manual [3], are reassumed in the Table 10.2.

## 10.3 Bases of Sleep Regulation

The neurobiological bases of sleep and wake and the regulation of the cyclic alternation of these two states are extremely complexes, and their detailed description goes beyond the objectives of this chapter. This paragraph aims to delineate the principal elementary mechanisms of sleep, but it not constitutes an exhaustive review of this fascinating but complicated topic.

**Table 10.1** Technical specifications for EEG, EOG, and EMG according to AASM manual [3]

| | | |
|---|---|---|
| EEG*:* at minimum 3 EEG channels (frontal, central, and occipital derivations) | Recommended derivations are:<br>(a) F4-M1<br>(b) C4-M1<br>(c) O2-M1<br>(d) Backup electrodes should be placed at F3, C3, O1, and M2 to allow display of F3-M2, C3-M2, and O1-M2 if electrodes malfunction during the study<br>*Note*: M1 and M2 refer to the left and right mastoid processes. M1 is the standard reference electrode for recording EEG | Acceptable EEG derivations are:<br>(a) Fz-Cz<br>(b) Cz-Oz<br>(c) C4-M1<br>(d) Backup electrodes should be placed at Fpz, C3, O1, and M2 to allow substitution of Fpz for Fz, C3 for Cz or C4, O1 for Oz, and M2 for M1 if electrodes malfunction during the study |
| EOG | The recommended EOG derivations and electrode positions are:<br>(a) Derivations: E1-M2 (left) and E2-M2 (right)<br>(b) Electrode positions: E1 is placed 1 cm below the left outer canthus and E2 is placed 1 cm above the right outer canthus | Acceptable EOG derivations and electrode positions are:<br>(a) Derivations: E1-Fpz and E2-Fpz<br>(b) Electrode positions: E1 is placed 1 cm below and 1 cm lateral to the outer canthus of the left eye, and E2 is placed 1 cm below and 1 cm lateral to the outer canthus of the right eye |
| CHIN EMG | Three electrodes should be placed to record chin EMG:<br>(a) One in the midline 1 cm above the inferior edge of the mandible<br>(b) One 2 cm below the inferior edge of the mandible and 2 cm to the right of the midline<br>(c) One 2 cm below the inferior edge of the mandible and 2 cm to the left of the midline | The standard chin EMG derivation consists of both the electrodes below the mandible referred to the electrode above the mandible. The other inferior electrode is a backup electrode to allow for continued display of EMG activity if one of the primary electrodes malfunctions |

*EEG* electroencephalogram, *EMG* electromyography, *EOG* electrooculography, *C* central, *F* frontal, *P* parietal, *O* occipital, *M* mastoid

The balance of sleep (S) and wake (W) states is related to reciprocal interactions between sleep-promoting systems (located in the medial part of brainstem, dorsal reticular substance of the medulla, ventrolateral preoptic nucleus (VLPO), and basal forebrain) and wake-promoting systems (ascending reticular activating system (ARAS) that includes the pontine and midbrain tegmental region, the posterior hypothalamus, and the basal forebrain cholinergic neurons).

Regulation of wakefulness is principally delegated to the neurons of the reticular activating system that modulates the cortical activation throughout two pathways [4]:

- A dorsal path from cholinergic neurons of latero-dorsal and pedunculo-pontine tegmental nuclei that activate glutamatergic thalamocortical projections.
- A ventral path that involves the aminergic arousal system from the brainstem compounded of serotoninergic (dorsal raphe nuclei), noradrenergic (locus coeruleus), histaminergic (tuberomammillary nucleus), and dopaminergic (ventral periaqueductal grey) neurons. This route receives also contributions from orexinergic neurons and melanin-concentrating hormone neurons of lateral hypothalamus and cholinergic neurons from the basal forebrain.

Sleep occurs when the VLPO, anterior hypothalamus, and basal forebrain are activated and inhibit the ARAS principally throughout GABAergic and galaninergic projections.

Transition between W and S represents hence the result of reciprocal inhibition between arousal- and sleep-promoting systems. This relationship can be modelled as a "flip-flop switch" circuit [5] in which the two competing sides inhibit each other generating a bistable feedback loop with two alternative states (W and S) without intermediate patterns. Mathematical models based on physiological data proposed a dynamic sleep-wake cycle regulation that assumes the existence of transitional states depending on the strength of the external (sensory) inputs [6–8] and the intracycle sleep dynamic regulation [9]. Simplifying, the effect of a stimulus during sleep is influenced by the state dominance of sleep- or wake-promoting forces on the descending or ascending slopes of the cycles. [10]. A sleep cycle begins with a descending slope, where the sleep stages follow a deepening tendency (from stage N1 to N3), followed by an ascending slope, characterized by an "ascending" sequence of stages—going from deep to more superficial (from N3 toward stage N1 and then REM sleep) (Fig.10.1). This pattern is less clearly observed in the second half of night sleep. Descending slope carries sleep-promoting tendencies, whereas the ascending one results from wake/rapid eye movement (REM)-promoting force. The dynamic interplay between ascending and descending slope in each sleep cycle is strictly related to the sleep homeostatic regulation, i.e., the accumulation of sleep pressure (propensity) during waking and its dissipation during sleep [11, 12]. When the homeostatic

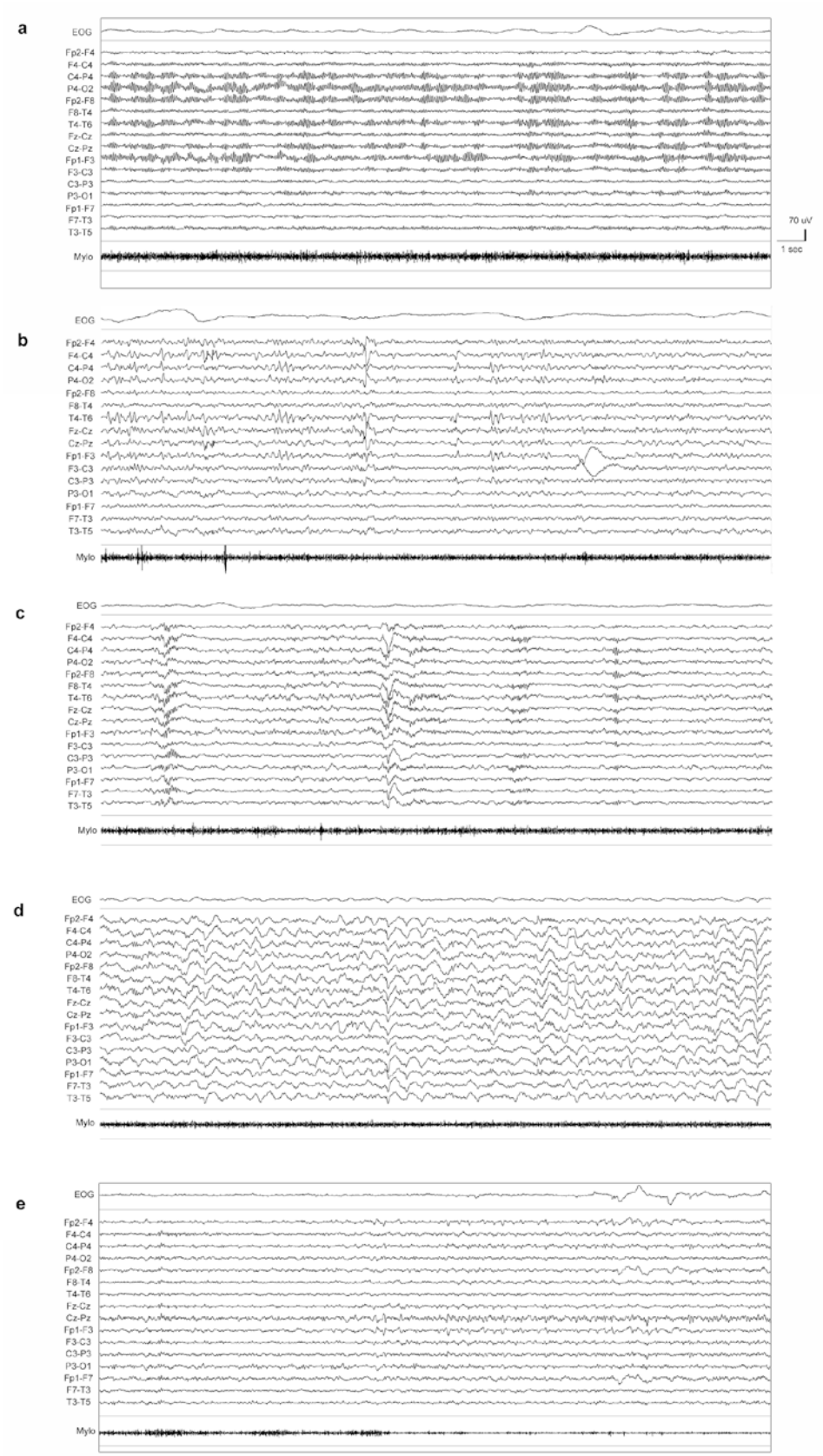


**Fig. 10.3** Sleep stages. (**a**) stage W; (**b**) stage N1; (**c**) stage N2; (**d**) stage N3; (**e**) stage R. The representative EEG pages correspond to a time window of 30 s. EEG traces are displayed in bipolar montage. *EOG* electrooculogram. EMG derivation is represented by the activity of the mylohyoid muscle (mylo)

**Table 10.2** General rules for sleep stages scoring

| | |
|---|---|
| The following terminology should be used for the stages of sleep in adults | (a) Stage W (wakefulness)<br>(b) Stage N1 (NREM1)<br>(c) Stage N2 (NREM2)<br>(d) Stage N3 (NREM3)<br>(e) Stage R (REM) |
| Score epochs using the following parameters | (a) Score sleep stages in 30-s, subsequential epochs commencing at the start of the study<br>(b) Assign a stage to each epoch<br>(c) If two or more stages coexist during a single epoch, assign the stage comprising the greatest portion of the epoch |
| Score in accordance with the following definitions for EEG frequencies | (a) Slow-wave activity: frequency of 0.5–2.0 Hz and minimum amplitude of 75 μV peak to peak in frontal derivations<br>(b) Delta waves are 0–3.99 Hz<br>(c) Theta waves are 4–7.99 Hz<br>(d) Alpha waves are 8–13 Hz<br>(e) Beta waves are greater than 13 Hz |

pressure is high (that is during the descending slope of cycles), it drives the hypothalamic sleep-promoting neurons to high level of firing, which keeps the wake-promoting arousal system inhibited. This allows the thalamic burst-firing system to produce spindling and slow-wave oscillations that protect the continuity of sleep against arousals. When the homeostatic pressure decreases, the firing of the VLPO nucleus declines gradually, accompanying the sleeper to progressively higher levels of arousal along the ascending slopes of the sleep cycle preparing the next REM period [13]. Depending on the level of the homeostatic pressure, the same sensory input can elicit "traditional" arousal-like or sleep-like responses. A sleep-like response may be K-complexes, a series of K-complexes with spindles, or a sudden increase in slow-wave synchronization in deeper sleep [10]. From a functional point of view, the two slopes are essentially different, and apparently identical sleep stages are in fact not the same in descending and ascending slopes. Stage N2 during the descending slope differs from stage N2 sleep during the ascending one, reflecting the balance between sleep- and wake-promoting force at any point of the sleep cycle [10].

## 10.4 EEG Changes During Sleep, General Concepts

EEG changes during sleep might be of long duration (termed "tonic events") or transient (termed "phasic events"). The classical macrostructural dimension of sleep dynamics based on the 30-s epochs analysis mainly relates to the "tonic" events, i.e., the relatively long-lasting backgrounds patterns. Long periods of EEG desynchronization characterized REM sleep as well as wakefulness, while prolonged synchronization pattern occur during deep sleep, like stage N3. The microstructure of sleep refers to transient phenomena that occurs spontaneously or evoked. These events occur during specific parts of wakefulness or REM sleep (such as rapid eye movements) or during various stages of NREM sleep, being the classical hallmarks of sleep stages (as the occurrence of spindles and K-complex (KC) during N2). In addition, the cycling alternating pattern (CAP) framework provides a microcyclicity measure of NREM sleep representing an indicator of physiological and pathological sleep instability and playing a role in gating pathological and physiological sleep events. The CAP phases are built by variously combined EEG phasic events (KC, slow-wave activity). The distribution of transient sleep events across sleep, including CAP, seems to clearly follow the interplay of sleep- and wake/REM-promoting forces both within the individual cycles and through the whole night course, in association with the interactions of reciprocal antagonistic brain stem networks determining cortical responsiveness [14]. The following paragraphs describe in details the macrostructural and microstructural EEG elements of sleep, emphasizing their reciprocal relationships as a continuous evolving process that insures good sleep quality and contributes to a maintain individual brain resilience [13].

## 10.5 Sleep Onset

The onset of sleep under normal circumstances in healthy adults is through NREM sleep. This fundamental principle of normal human sleep reflects a highly reliable finding and is important in considering normal versus pathologic sleep. For example, the abnormal entry into sleep through REM sleep can be a diagnostic sign in adult patients with narcolepsy. According to the AASM manual, sleep onset is defined by the first epoch scored as any stage other than stage W (generally corresponding to the first epoch of stage N1) (Table 10.3). This approach, while is helpful to characterize the macrostructure of a 7–8 h of nocturnal EEG activity, is unsatisfactory for determining the microstructure of the sleep onset process. A common example is the waxing and waning of alpha activity just before and during stage N1. By just checking whether the percentage of alpha activity is over or under 50% (as required to distinguish stage W from N1), the scorer ignores potentially interesting micro-oscillations along the arousal continuum. The available tests that measure sleepiness or vigilance (as MSLT or maintenance of wakefulness test-MWT) are based on calculating the time to sleep onset, that is, according to official guidelines, as the first epoch of any sleep stage. However, this criterion could be too rigid or too permissive, making the test poorly

**Table 10.3** AASM rules for sleep stages [3]

| | |
|---|---|
| W | *Onset*: more del 50% of the epoch contains either one or both:<br>1. Alpha rhythm (posterior dominant rhythm) over the occipital region<br>2. Other findings consistent with stage W (all individuals)<br>(i) Eye blinks (0.5–2 Hz)<br>(ii) Rapid eye movements associated with normal or high chin muscle tone<br>(iii) Reading eye movements<br>*End:* transition to stage N1, N2. The earliest sign of drowsiness is the absence of eye blinks |
| N1 | *Onset:* more del 50% of the epoch contains low-amplitude mixed-frequency EEG (LAMF) and/or the appearance of any of the following phenomena:<br>(a) EEG activity in range of 4–7 Hz with slowing of background frequencies by ≥1 Hz from those of stage W<br>(b) Vertex sharp waves<br>(c) Slow eye movements<br>*End*: transition to stage W, N2, and R |
| N2 | *Onset*: co-occurrence of: (a) delta waves must not exceed the 20% of the epoch (b) either or both the following occur during the first half of that epoch or the last half of the previous epoch:<br>1. One or more K-complexes unassociated with arousals<br>2. One or more sleep spindles<br>*End*: transition to stage W, N3, R, an arousal followed LAMF (stage N1), or a major body movement followed by LAMF and slow eye movement (SEM) |
| N3 | *Onset*: ≥20% of an epoch consists of SWA irrespective of age<br>*End*: transition to stage W, N2, N1, R |
| R | *Onset*: co-occurrence of: (a) low-amplitude LAMF activity without K-complexes or spindles; (b) low chin EMG tone (no higher than in any other sleep stage and usually at the lowest level of the entire recording) for the majority of the epoch; (c) rapid eye movements (REMs) at any position within the epoch<br>*End*: one of the following: (a) transition to stage W or N3; (b) increase in chin EMG tone above the level of stage R for the majority of the epoch and criteria for stage N1 are met; (c) occurrence of an arousal or a major body movement followed by LAMF and SEM (score the epoch as stage N1); (d) one or more non-arousal-associated K-complexes or sleep spindles in the first half of the epoch in the absence of REMs, even if chin EMG tone remains low (score the epoch as stage N2) |
| Arousal | Arousal during sleep stages N1, N2, N3, or R if there is an abrupt shift of EEG frequency, including alpha, theta, and/or frequencies greater than 16 Hz (but not spindles) that lasts at least 3 s, with at least 10 s of stable sleep preceding the change. Scoring of arousal during REM requires a concurrent increase in submental EMG lasting at least 1 s |

sensitive or specific. It can be argued that a brief "microsleep" intruding into wake state cannot be considered as unequivocal sleep; by counterpart, it has been demonstrated that performances, as driving reaction time, may be altered in drowsiness state, before definite sleep onset [15]. Light drowsiness represents a specific brain state. Neurophysiological studies have demonstrated event-related potentials peculiarities during light drowsiness [16], and both altered inter- and intrahemispheric EEG coherence when compared with wakefulness, suggesting that cerebral functional organization changes during light drowsiness [17, 18]. While physiological and behavioral features show large intersubjective variability and ambiguity, analysis of EEG seems to be the most reliable method with respect to detection of sleep onset. In adults, the earliest indication of transition from wakefulness to stage N1 usually consists of a combination of dropout of alpha activity and slow rolling eye movements (Fig. 10.4). The alpha waves are replaced by low-voltage slow activity, mainly in the range of 2–7 Hz. In late infancy and early childhood, drowsiness is characterized by typical diffuse 4–6 Hz rhythmic theta activity (hypnagogic hypersynchrony), while later in childhood and, in many cases, in the declining years of life, the onset of drowsiness is characterized by greater amounts of slow activity mingling with the posterior alpha rhythm. An electroencephalographically defined drowsy state does not exist in the neonate, and, in elderly, abrupt transitions from wakefulness to light sleep are quite common. Deepening of drowsiness is associated with enhancement of slow activity. At this stage, arousing stimuli lead to immediate return of the posterior alpha rhythm, called "paradoxical alpha response" [19]. When alpha rhythm is reactivated in deep drowsiness or in NREM sleep, the maximum is usually frontal rather than occipital named "short microarousals."

## 10.6 Deep Drowsiness (Stage N1 Sleep)

Following the AASM scoring rules (Table 10.3), stage N1 (Fig. 10.3, panel b) is defined by the attenuation of the alpha rhythm and the occurrence of low-amplitude, mixed-frequency activity (defined as low-amplitude, predominantly 4–7 Hz activity) for more than 50% of the epoch. Burst of relatively high-voltage very synchronous theta activity is

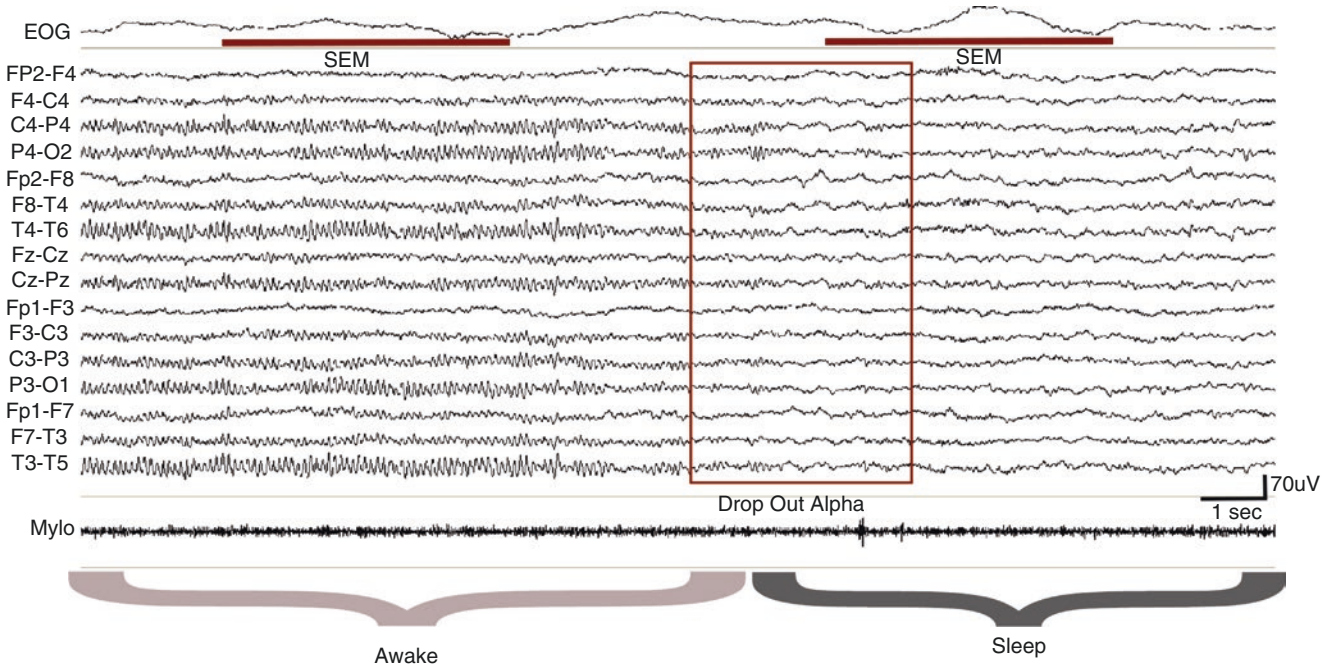


**Fig. 10.4** The sleep onset. Representative EEG showing the combination of the alpha rhythm dropout and SEM, thus indicating the sleep onset. EEG traces are displayed in bipolar montage. *EOG* electrooculogram. EMG derivation is represented by the activity of the mylohyoid muscle (mylo)

common during the onset of N1 in children and young adolescent. Slow eye movements (SEM) commonly precede the EEG transition from W to N1. Although the onset of SEM usually leads the EEG transition by only 1 or 2 min, the lead time may occasionally—particularly during daytime sleep—be as long as 15 min. SEM are very useful to distinguish stage N1 transition occurring during stage N2 or R sleep.

The characteristic neurophysiologic elements of this stage, but not mandatory to N1 scoring, are vertex sharp waves and positive occipital sharp transients of sleep.

### 10.6.1 Vertex Sharp Waves (V Wave)

*V wave (VWs)*: Vertex Sharply contoured waves with duration <0.5 s maximal over the central region and distinguishable from the background activity [3].

Vertex sharp waves (also named "vertex waves," "V waves," "vertex sharp transients," or "vertex spikes") are sharply contoured compounded electroencephalographic potentials characterized by a main negative component, preceded and followed by brief and low-voltage positive components. VWs are 50–200 ms long, with a variable voltage (until 250 μV) and a maximal topographic expression over the central region, often with a phase opposition on median derivations (Fig. 10.5, panel a). They are typically bilateral and symmetric, but they may show also asymmetries, especially in children or in pathological conditions [20, 21]. VWs may appear as isolated events, clearly standing out over the background activity, or they can occur in repetitive salvos firing at a range of about 1/s or faster. VWs usually appear in deep drowsiness/stage N1 and may persist during stage N2.

It is generally accepted that VWs are comparable to different sensory modalities evoked potentials, presenting analogies to evoked acoustic responses in wake state, which have maximum expression on vertex areas. The most common neurophysiological interpretation is that VWs are either a direct response to an external stimulus or a mechanism to maintain sleep (indirect response) after a stimulus [22]. This is similar to the common understanding of the K-complex and is based on the evidence that both VWs and K-complexes may be elicited by sudden stimulation irrespective of the sensory modality. In neurophysiologic studies, VWs have been associated with the N300 and N350 evoked potential responses [22, 23]. MEG and fMRI studies have attempted to determine the sources of these distinct waveforms and have found that the maximum amplitude of vertex waves localized over midline areas of the cortex [24–26]. In particular, VWs represent the activity of integrated functional system mainly involving the sensory-motor cortices

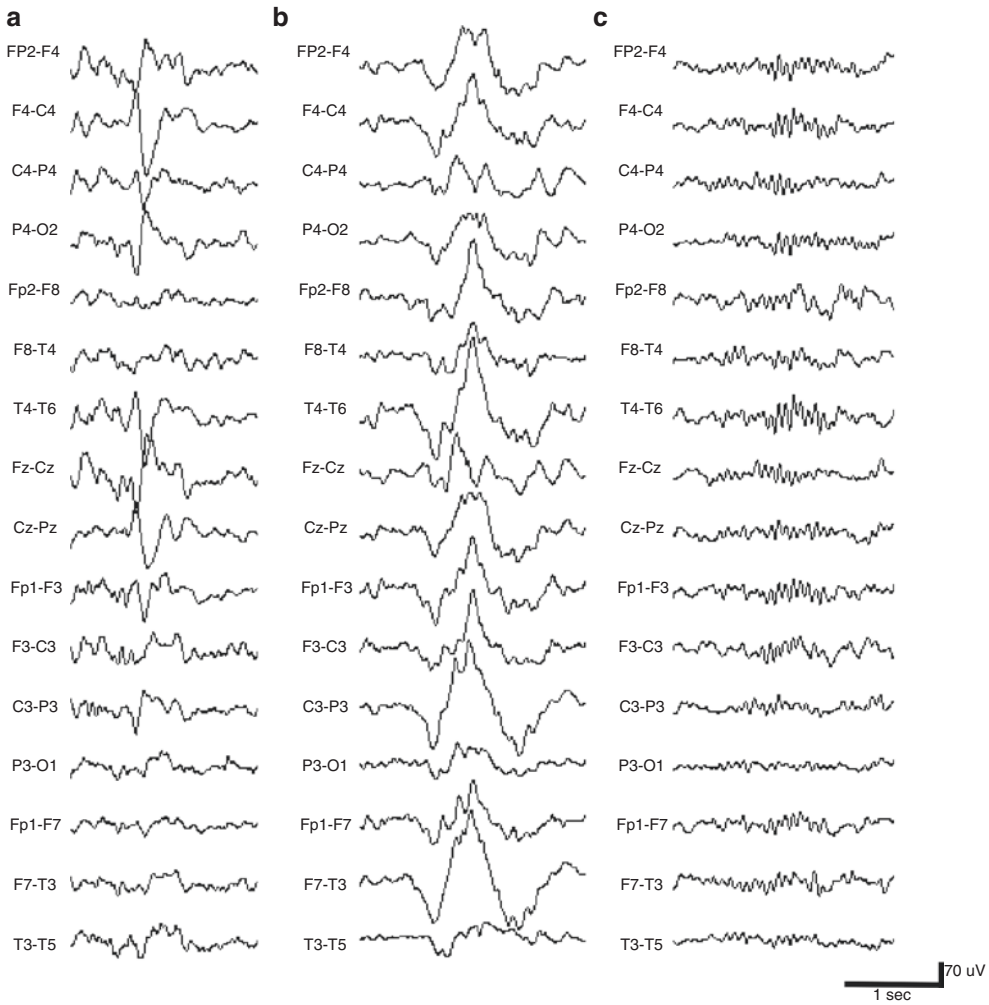


**Fig. 10.5** Representative examples of vertex waves (panel **a**), K-complex (panel **b**), sleep spindles (panel **c**) recorded during sleep. EEG traces are displayed in bipolar montage

(probably the generator) and the posterior medial regions (medial occipital cortices). Interestingly, no thalamic involvement was documented with fMRI [26].

#### 10.6.1.1 Vertex Sharp Waves Across the Life Span

VWs may occur as infrequent broad components by 6 months of age but are seen as prominent elements around 16 months, becoming sharper with a shorter duration by 24 months and repetitive by 30 months [27, 28] (Fig.10.6). VWs expression is maximal between 2 and 12 years, when they show a greater amplitude, longer duration, and a more frontal expression. In school-age children, vertex waves may show moderate amplitude asymmetries with asymmetrical spread into the vicinity. Under these circumstances, the physiologic vertex activity may be confused with cerebral rolandic spikes. Rolandic spikes, usually picked up by electrodes C3 or C4 over central areas, may occasionally arise from the vertex itself. When such a coexistence of vertex potentials exists, the physiologic vertex waves are usually of longer duration and of somewhat higher voltage than the abnormal spikes [21]. Vertex waves may become small and inconspicuous in aged individuals and are often poorly demonstrable in such persons.

### 10.6.2 POSTs (Positive Occipital Sharp Transients of Sleep)

*POSTs* are an EEG activity of deep drowsiness and sleep, characterized by positive spike-like waves localized on occipital areas, mainly in theta range. POSTs are often bilateral and synchronous but may be also asymmetrical [29] (Fig. 10.7).

POSTs are not strictly connected to a specific sleep stage. These elements appear mostly during superficial sleep and may persist during deep sleep, but they are practically absent in REM.

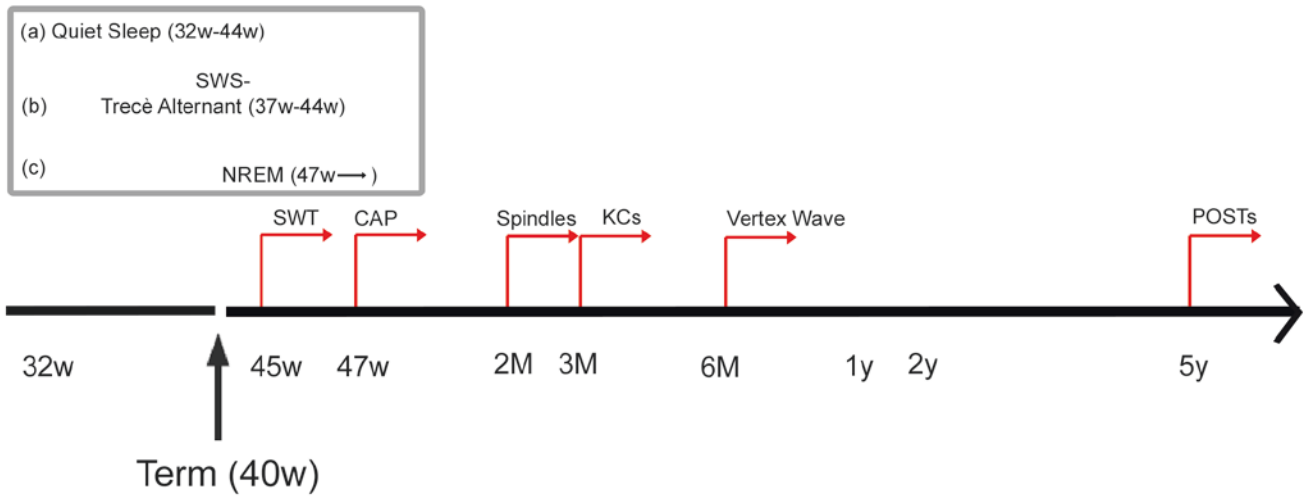


**Fig. 10.6** Schematic diagram of temporal evolution of main neurophysiological features of sleep in infancy. The grey box indicates periods of appearance of main behavioral stages: (**a**) Quiet sleep (QS) is commonly described from 32nd postconceptional weeks until the 44th and is characterized by long-lasting bursts of large amplitude delta activity; (**b**) *Tracé alternant* pattern alternated with high amplitude delta activity starts after the 37th postconceptional age. The *Tracé alternant* is defined as bursts of slow waves, sometimes mixed with sharp waves, alternating with periods of relative quiescence; from the 44th to the 47th postconceptional week, the QS shows important changes that foreshadows to the sleep stages appearance: *tracé alternant* disappears as the proportion of slow waves increases, and the term "slow-wave sleep" (SWS) can be used. Further categorization of sleep states into the stages of sleep becomes possible. (**c**) From the 47th postconceptional age, NREM sleep, similar to the one structured in adults, occurs. The red arrows indicate the age of appearance of the main sleep phasic features. *POSTs* positive occipital sharp transients of sleep, *CAP* cycling alternating pattern, *KCs* K-complexes, *SWS* slow-wave sleep, *w* weeks, *y* year

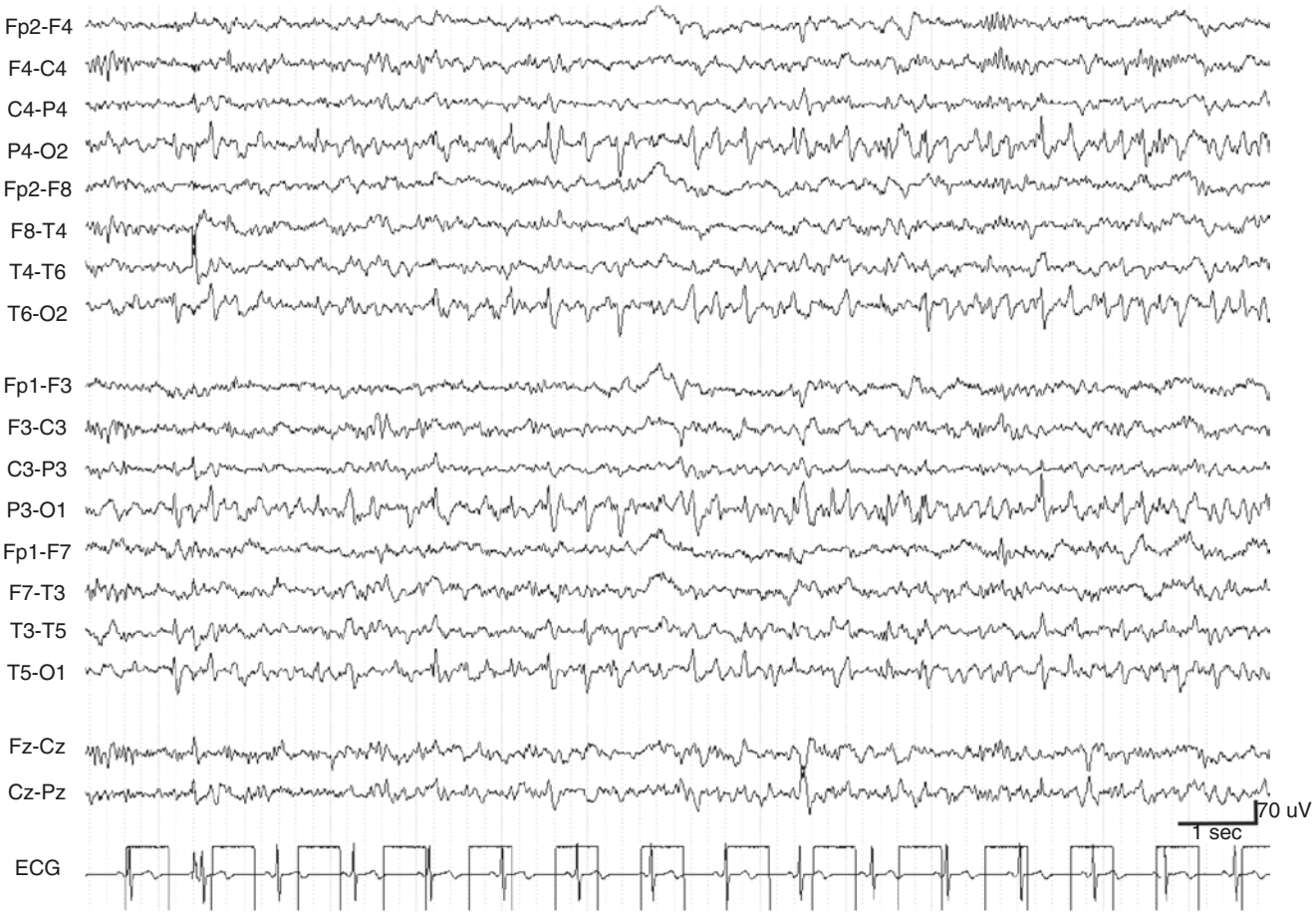


**Fig. 10.7** POSTs. Representative EEG page showing bilateral POSTs in N2. Note the presence of frequent sub-continuous positive spike-like waves and theta activity localized on the parieto-occipital and temporo-occipital areas. EEG is displayed in bipolar montage

POSTs are not consistently established before 5 years of age (Fig. 10.6), although they may be prominent in some children from about 3 years. This pattern is most commonly found in adolescents and young adults, whereas their prevalence declines in elderly, with a slight female prevalence [30].

Although POSTs have anecdotally been correlated to various abnormal conditions [31, 32], they are generally considered as a normal variant of physiological sleep EEG activity, and their real significance remain uncertain. It has been hypnotized that POSTs may be related to visual function, representing a "playback" of visual information collected during the day [33].

The connection to visual activity is also supported by their absence in blind or severely amblyopic people [34] and by the similarities of these potentials to lambda waves, a posterior EEG activity during wakefulness elicited by visual exploration or by looking geometric patterns.

## 10.7 Light Sleep (Stage N2 Sleep)

Stage N2 is characterized by the appearance of peculiar EEG figures (K-complex and spindles) standing over a background activity mainly constituted by medium voltage theta and delta activity (Fig. 10.3, panel c). Beside slow-frequency background activities, fast frequencies are often observed in N2 in the range of 15–30 Hz even in unsedated patients with no history of chronic intake of sedatives. AASM rules for scoring N2 sleep are summarized in the Table 10.3.

### 10.7.1 K-Complexes

*K-complex*: A well-delineated, negative, sharp wave immediately followed by a positive component standing out from the background EEG, with total duration ≥0.5 seconds, usually maximal in amplitude when recorded using frontal derivations. For an arousal to be associated with a K-complex, the arousal must either be concurrent with the K-complex or commence no more than 1 second after termination of the K-complex [3].

K-complexes (KCs) were discovered in the early 1930s by Loomis and colleagues [35], as electric potentials both evoked by auditory stimuli (knocking on the door of the experimental chamber, thus the letter "K" in the name of these elements) and spontaneous. KCs are characterized by an initial biphasic (and not seldom multiphasic) sharp positive component followed by a slow negative wave, often mixed with superimposed final fast components (12–14 Hz sleep spindles) (Fig. 10.5, panel b). The slow component may exceed 1000 ms in duration, and its length and degree of prominence depend on filter setting. KCs are >0.5 s in duration and >75 μV in amplitude and show a frontal prominence, just like the rest of sleep slow-wave activity [36]; they can occur isolated or grouped in series. When KCs are averaged, the peaks of positive and negative waveforms are seen as P200, N550, and P900 components in the averaged event-related potential (ERP), with the N550 and P900 components typically largest over frontal electrode sites. Because the N550 amplitude can be in excess of 100 μV, it is thought to reflect the synchronized activity of a large number of cortical neurons [37] and has been hypothesized to reflect cortical integrity [38].

#### 10.7.1.1 KC Across the Life Span

KCs appear during the same age span of spindles (3–6 months) (Fig. 10.6), becoming larger in older children and in early adolescence and showing a progressive reduction in amplitude and frequency in elderly. The frequency of KCs decreases from cycle to cycle, parallel with the decrease in the depth of sleep [39].

The underlying cellular mechanism of K-complexes is based on a slow (<1 Hz) oscillation of cortical neurons associated with fluctuations of the membrane potential between a depolarized and hyperpolarized level [40] very similar to the up- and downstates of below 1 Hz sleep slow oscillations [10].

The physiological significance of KCs has been the subject of significant debate. On the one side, KCs are arousal-related phenomena being supported by accompanying activation patterns such as an increase of heart rate and phasic increases in muscle tone. However, the fact that KCs activity mirrors other slow waves in NREM sleep supports the idea that KC is a promoter of sleep [10, 13, 41].

#### 10.7.1.2 KC as Arousal Phenomena

KCs can be elicited by sensory stimuli [42], are associated with signs of autonomic activation [43], and are sometimes followed by an EEG arousal. These evidences suggest that they may be functionally related to arousal systems. Several studies have shown that KCs can be elicited by any sensory modality but with different cortical activation patterns, depending on the type of stimulation [37, 42, 44–46]. In 2014, Laurino and colleagues [47] identified the topological/dynamic features of evoked KCs depending on stimulus modality or local cortical properties. The earliest wave (the initial positive element of the K-complex, also called P200) was topographically located on the stimulation-related primary sensory areas; this potential acts as traveling cortical excitation that elicits a bistable cortical response, appearing on the EEG as a biphasic slow wave over fronto-central regions (the giant negative deflection (N550) and the subsequent positive one (P900), respectively, reflecting downstate

and upstate of <1 Hz oscillations), depending on the reactivity of cortex in different NREM sleep levels. In their conclusion the authors confirm the KC's Janus-faced dual properties: on the one hand, they are evoked by an input-related cortical excitation, and on the other hand, they represent an induced, cortical slow wave in the fronto-central region.

#### 10.7.1.3 KC as Slow Wave

Some features of KCs are common with slow waves, the hallmark of sleep homeostasis. As slow-wave sleep (SWS), frequencies of KCs tend to decrease in stage N2 from evening to morning and from cycle to cycle [39] and show a rebound effect elicited by sleep deprivation [48]. The amplitude of KCs is proportional to the depth of the sleep cycle in which it is measured [49]. Furthermore, the decreasing trend of number, amplitude, and density during aging is similar in KCs and in SWS and reflects the progressive reduction of cortical thickness [38, 50, 51].

### 10.7.2 Sleep Spindles

*Sleep spindle*: A train of distinct waves with frequency 11–16 Hz (most commonly 12–14 Hz) with a duration ≥0.5 s, usually maximal in amplitude in the central derivations [3].

Spindles are defined as waxing-and-waning EEG waves oscillating at a frequency of 11–16 Hz and predominant over central EEG derivations; spindles characterize NREM N2 but can also be found during NREM N3 (Fig. 10.5, panel c). Spindles are discrete events, a feature that distinguishes them from spindling activity (i.e., the continuous EEG activity between 11 and 16 Hz, often reported as the EEG power in this frequency band). Minimum spindle's duration is set to 0.5 s, while no maximal duration value has been proposed. The spindle frequency range is typically between 11 and 16 Hz, although some authors report much slower (9–10 Hz [52, 53]) and faster (18 Hz [54]) spindles. Furthermore, (at least) two types of spindles are reported in humans: late slow frontal (9–12 Hz) and early fast centro-parietal (13–15 Hz) spindles (reviewed in [55]). This dichotomy was reported in various EEG and MEG studies [53, 56, 57] but also with functional magnetic resonance imaging (fMRI) [58] and after pharmacological manipulation [59]. This distinction, based on the spindle time onset, frequency, and topography, also corresponds to different relationships with sleep cycling. The first spindle trains show a frequency around 14 Hz, while the 12 Hz spindles appears a little later with deepening sleep although the patient is still in N2. With deepening sleep (at the transition between N2 and N3), an even slower spindle occurs (around 10 Hz) with maximum topography over the frontal leads. This activity is likely to be a forerunner of rhythmic discharges in the 6–10 Hz range, which is commonly observed in N3.

Fast centro-parietal and slow frontal spindles reflect the involvement of different neocortical regions [53]. Fast centro-parietal spindles reflect a more local synchronization mainly constrained to the thalamus, precentral/premotor cortices, and hippocampus, while late slow frontal spindles are the results of a more global brain synchronization [58]. These findings suggest the presence of multiple generator areas for spindles in humans and support the notion that sleep arises from activities of local circuits [53]. On average fast centro-parietal spindles precede slow frontal spindles by 200–500 ms; timing differences among cortical spindles reflect propagation along the thalamic reticural nucleus (RE).

The neurophysiological mechanisms of spindle generation reflect the intrinsic properties and interactions between inhibitory cells in the RE and bursting thalamocortical (TC) relay neurons. According to the model of Steriade [40], sleep spindles rhythm is initiated in GABAergic thalamic reticular neurons, which impose onto thalamocortical neurons rhythmic inhibitory postsynaptic potentials, thus de-inactivating a low-threshold Ca2+ current, which promotes burst firing. These bursts are transferred to the cortex that is responsible of generating rhythmic excitatory postsynaptic potentials at spindles' frequency. Spindle generation involves inhibition of thalamocortical afferents, hence suggesting that they constitute the stones of loss of responsiveness to external stimuli observed during NREM sleep. The "sensory gate" notion assigned to the thalamus and mediated by the spindles confers a useful role of spindling bursts to preserve sleep continuity by inhibiting sensory inputs [13].

#### 10.7.2.1 Sleep Spindles Across the Life Span

Mature sleep spindles usually appear during the second month of life (for review, see [60] [Fig. 10.6]). Before that time, the dominant EEG pattern spindle-like activity is termed "delta brushes" seen in premature infants and in utero. They consist of spindle-like oscillations of 8–20 Hz, riding on top of delta (0.3–1.5 Hz) waves. These oscillations can occur during any stage (sleep or waking); however, as the brain matures, they become restricted to sleep. Spindles are initially seen over central areas of the brain and gradually develop over frontotemporal areas during the first year of life [61]. During adolescence, density reaches a relative maximum with equal distribution across frontal, central, and parietal leads. In aging, there is a return to the same pattern seen earlier in development, with highest density at central leads. Spindles are most impressive in childhood and adolescence; their voltage tends to become smaller throughout adulthood. In old age, spindles of low voltage are very common; this is

probably not due to old age alone but to cerebrovascular disease. Sleep spindles share this decline of voltage with vertex and K-complexes as age advances. Spindles have been reported to be more frequent in women than in men [62].

#### 10.7.2.2 Spindles and Slow-Wave Activity (SWA)

With respect to slow waves, spindles tend to occur preferentially at upstates [40, 63]. Given that slow waves propagate from prefrontal cortex toward posterior regions [64, 65], and spindles occur sooner in posterior regions (see above), the result is that frontal spindles occur later during slow-wave upstates.

In stage N3 when SWA is maximal, spindle density is reduced. In early NREM sleep, when SWA is highest, spindle density and spindle frequency are significantly lower. Moreover, spindle density and frequency are lower in the middle of NREM cycles when SWA is maximal and higher toward the transition to REM sleep when SWA tapers off.

## 10.8 Deep Sleep (Stage N3 Sleep)

Stage N3 (slow-wave sleep or deep sleep) represents the sum of previous stage S3 and stage S4 of Rechtschaffen and Kales (R&K) nomenclature. The hallmark of this stage is the so-called slow-wave activity (SWA), formed by high-voltage slow waves of delta frequency, between 0.5 and 2 Hz measured over the frontal regions (Fig.10.3, panel d). The frequency range of SWA is not universally defined as for different authors it is considered between 0.5 and 4.5 Hz [21, 64, 66]. AASM rules for scoring N3 stage are summarized in the Table 10.3. In previous R&Ks scoring rules, deep sleep was divided in two different stages, depending on the percentage of the epoch dominated by SWA (20–50%, stage S3; ≥50%, stage S4) (Fig.10.8). Sleep spindles may persist during stage N3, but they become less relevant; also KC may be present, whereas eye movements are not usual. Chin EMG is often lower than in light sleep. Small sharp transients may be superimposed on the slope of a slow wave, forming a pattern recalling a mitten, with a "thumb section," represented by the sharp component and a "hand section" formed by the subsequent slow wave. The "Mitten pattern" can only be recorded with a monopolar referential montage during relatively deep sleep stages. This activity is usually prevalent over the frontal and central regions and is considered a normal variant [21]. Another physiological EEG pattern is called "alpha sleep pattern," and it typically reaches its maximum in stage N3. It is characterized by rhythmical 7–11 Hz activity, often combined with slow delta activity, prevalent over the frontal leads. The alpha sleep pattern must be differentiated from alpha-delta sleep, a pattern associated with delta sleep deficit and often noted in patients with fibromyalgia [67], chronic fatigue syndrome [68], and depressive disorders [69]. By contrast, the alpha sleep pattern has been found to be associated with a stable sleep organization [70].

### 10.8.1 Slow-Wave Activity (SWA)

*Slow-wave activity*: Waves of frequency 0.5–2 Hz and peak-topeak amplitude >75 μV, measured over the frontal regions referenced to the contralateral ear or mastoid (F4-M1, F3-M2) [3].

Slow waves are the surface-EEG visible epiphenomenon of slow (<1 Hz) oscillations in membrane potential of cortical neurons, alternating between a hyperpolarization phase (*downstate*), when virtually all cortical neurons remain silent for a few hundred milliseconds, and a subsequent depolarization phase (*upstate*) when neurons fire at high rate, more than in quiet wakefulness [71, 72]. This phenomenon is due to intrinsic currents and intracortical network interactions [73–76] depending on the function of the cerebral cortex alone [71, 73, 77, 78].

The slow oscillations occur during any stage of NREM sleep with an increasing rate as sleep deepens [64]; the sporadic oscillations occurring during light sleep (stages N1–N2) seem to correspond to K-complexes, whereas during deep sleep, they are related to slow waves in the frequency <1 Hz. The spatiotemporal dynamics of these oscillations are the same regardless the sleep stage, supporting the theory about a continuum of reactive sleep EEG elements (i.e., transient phenomena which may occur both spontaneously and evoked by sensory stimuli) like vertex waves, KC, and SWA [10]. During the first phases of light sleep (stages N1 and N2), an acoustic stimulus may evoke vertex waves (comparable to an amplified acoustic evoked potential—N350). From stage N2 the stimulus may elicit a KC, characterized by a first element comparable to a residue of evoked potential (P200) followed by a SW (N550 and P900). In deepening of sleep, the response becomes more complex and nonspecific (as SW activity configuring CAP A1 phases—see below). This theory is consistent with recent EEG-fMRI findings [26, 79, 80] and HdEEG studies [47, 81].

Slow-wave oscillation during sleep thus represents the fundamental stone by which the sleep process builds its proper rhythms. Using high-density electroencephalogram recordings in humans, Massimini and colleagues [64] have shown that each wave originates at a definite site and travels over the scalp at an estimated speed of 1.2–7.0 m/s. Waves originate more frequently in prefrontal- orbitofrontal regions and propagate in an anteroposterior direction. Each slow

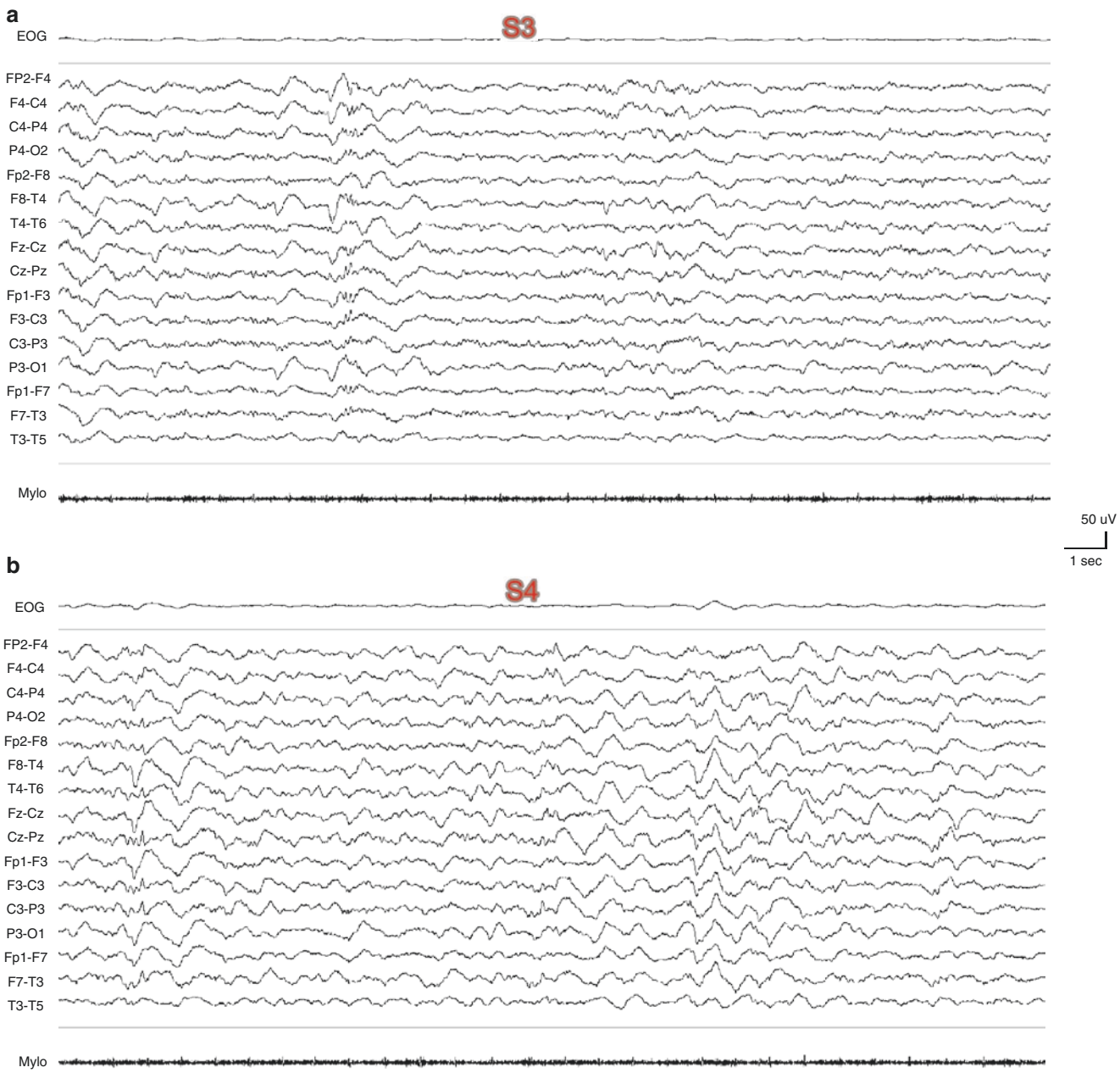


**Fig. 10.8** Representative EEG pages of deep human sleep. According to the Rechtschaffen and Kales scoring rules, deep sleep was divided in two different stages (actually founded in a single stage N3), depending on the percentage of the epoch dominated by SWA (20–50%: stage S3, panel **a**; ≥50%: stage S4, panel **b**). EEGs are displayed in bipolar montage. *EOG* electrooculogram. EMG derivation is represented by the activity of the mylohyoid muscle (mylo)

oscillation starts small and becomes progressively larger and finally dissolves, suggesting that an initial small depolarizing event involves a progressively wider population of neurons through cortico-cortical connections, as it extends through the cortex.

The amount of SWA is related to sleep pressure and homeostatic regulation of sleep, increasing in function of previous wake and returning to baseline during sleep. It has been proposed that, in adults, the homeostatic decline of SWA along consecutive sleep cycles is related to a progressive reduction in synaptic strength, which is thought to increase during wakefulness due to learning processes and decrease during sleep through a sleep-dependent process of synaptic downscaling, leading to restoration of energy and space resources [11, 12, 82]. Computered models [83], studies of LFP rats recordings [84] and of human EEG [81], have been demonstrated that these well-established sleep pressure-related modifications in SWA during the course of sleep are

not limited to a decrease of the total number of SW but they are associated with changes in specific electrophysiologic parameters of the individual slow waves. In particular, compared to a relative small reduction of the density of slow waves (i.e., the total number of SW/hour of sleep), there is a more relevant decrease of high-amplitude SW and of the slope of SW, as well as an increase in waves with multiple peaks [81, 85].

#### 10.8.1.1 SWA Across the Life Span

SWA undergoes remarkable changes during development that parallel the time course of cortical maturation. In studies including children and adolescents, the topographical distribution of SWA was analyzed with scalp and high-density electroencephalography [86, 87]. The results showed age-dependent differences in SWA topography: SWA was highest over posterior regions during early childhood and then shifted over central derivations to the frontal cortex in late adolescence [88]. This trajectory of SWA topography matches the course of cortical gray maturation [86].

The SW delta activity (total SW counts, amplitude, and slope) decreases with aging starting from adolescence [89]. Homeostatic sleep regulation seems however unaffected in adolescence [88]. In adults, significant reduction of SWA prosecutes, and this SWA impairment becomes especially prominent in older adults (for review, see [66]). The maximal age-related decrements in absolute SWA are observed over the prefrontal cortex (PFC) derivations and in the first NREM sleep cycles, with reductions of 75–80% on average relative to young adults.

## 10.9 REM Sleep

REM sleep is the third major physiological state of vigilance, beside wakefulness and NREM sleep. REM sleep is characterized by rapid eye movements associated with a decreased amplitude of EEG activity, similar to that seen during wakefulness and a loss of muscle tone. The co-occurrence of an EEG signal similar to that of the waking state and a behavior of unresponsiveness leaded to the term of "paradoxical sleep." In the course of the decades, REM sleep has also been called "activated sleep" or, for the evidence that subjects awakened from REM sleep reported usually vivid dreams, "dream sleep." REM sleep is defined by the co-occurrence of electroencephalographic, electrooculographic, and electromyographic characteristics. Therefore, REM sleep should be assessed certainly only with polygraphic methods. Whenever the electroencephalographer must search specifically for REM periods, attention must be laid on the use of two channels for electrooculography (two additional canthus electrodes, connected to the ears), one channel for cutaneous electromyography (submental region) and a thermocouple or strain gauge for pneumographic documentation [21]. Nevertheless, even in routinely EEG recordings (without oculographic leads), electroencephalographs can recognize the REM sleep occurrence being the ocular potentials mostly quite impressive and almost always leading to marked eye movement artifacts in frontopolar and anterior temporal leads [90].

Background activity during REM is low-amplitude, polyrhythmic, and mixed-frequency characterized by fast activity and a small amount of 3–7 Hz theta rhythms, usually similar to that seen in stage N1, with trains of "Sawtooth waves" (SWTs) as superimposed rhythm (Table 10.3; Fig. 10.3, panel e). Sequences of alpha activity, 1–2 Hz slower than during wakefulness, are common. The first REM phase of the night is often shorter than those seen in the last part of the sleep time, and it can be characterized by a mixture of REM and sleep spindles and/or K-complexes. The typical hallmarks of REM stage are the occurrence of rapid eye movements (REMs), low chin EMG tone, and sawtooth waves (SWTs) (Fig.10.9).

*REMs*: Conjugate, irregular, sharply peaked eye movements with an initial deflection usually lasting <500 ms.
*Low chin EMG tone*: Baseline EMG activity in the chin derivation no higher than in any other sleep stage and usually at the lowest level of the entire recording.
*SWTs*: Trains of sharply contoured or triangular, often serrated, 2–6 Hz waves maximal in amplitude over the central head regions and often, but not always, preceding a burst of rapid eye movements [3].

### 10.9.1 SWTs (Sawtooth Waves)

STWs were first described by Jouvet et al. [91] and Berger et al. [92] decades ago, but their source and neurophysiologic meaning have not been defined yet. STWs are bursts of sharply contoured or triangular, often serrated, surface positive waves, in the frequency range of 2–6 Hz, with an amplitude comprised between 20 and 100 μV. These waves are bilateral and symmetrical, and widely distributed over the scalp, but maximal in amplitude over the central or frontal areas [93, 94] appearing at about 5 weeks of age [95] (Fig. 10.6). STWs' mean density seem to be lower during the first REM period compared to subsequently sleep cycles [96]. STWs' trains are correlated with other phasic events of REM sleep, usually following transient muscle activities and preceding/occurring in conjunction with bursts of rapid ocular movements [97–99]. Despite the prevalence of STWs over the vertex, animal models sug-

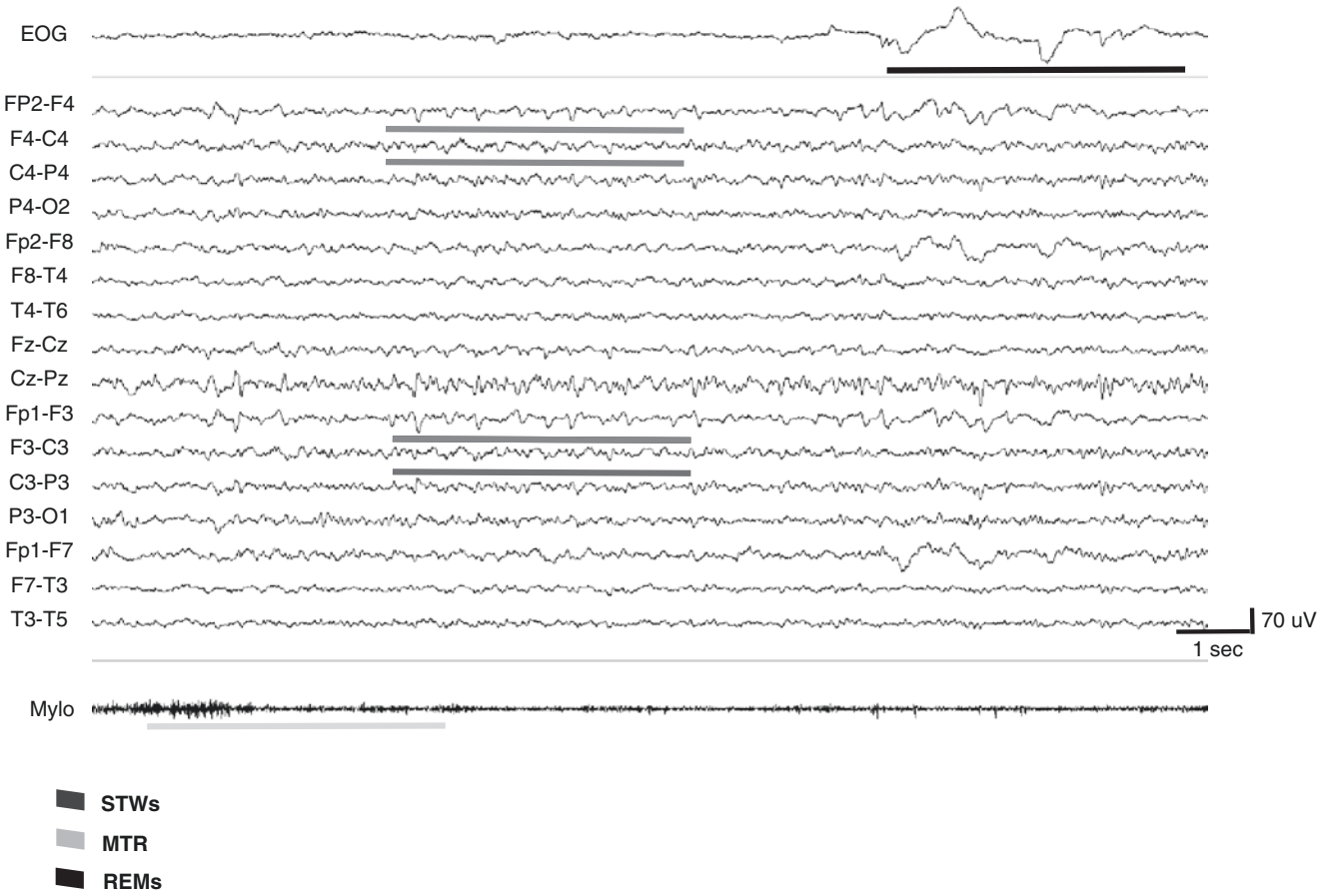


**Fig. 10.9** REM sleep. Note the 2.5 Hz notched waves, prominent in F3-C3, F4-C4, Fp1-F3, Fp2-F4 occurring before REMs. The characteristic sequence of MTR, SWT, and REMs at the onset of stage REM is demonstrated. *MTR* muscle tone reduction, *SWT* sawtooth waves, *REMs* rapid eye movements. EEG is displayed in bipolar montage. *EOG* electrooculogram. EMG derivation is represented by the activity of the mylohyoid muscle (mylo)

gested that STWs are possibly related to ponto-geniculo-occipital spikes, a potential related to REM sleep and documented only in animals, originating in the pons, involving the lateral geniculate nucleus, and terming over the occipital regions [100]. This relationship is consistent with the evidence that in patients affected by brainstem pathologies as post-polio syndrome [101] or vegetative states [102], abnormalities in STWs have been documented. Surprisingly, however, anomalies in STW have been demonstrated also in supratentorial disorders as hemispheric stroke [103] and temporal lobe epilepsy [104].

## 10.10 Microstructure of Sleep and the Cyclic Alternating Pattern (CAP)

The 30 s epoch scoring confers a stepwise outline to the sleep histogram characterized by periods of static configuration (sleep stages) interrupted by rapid shifts (stage changes). This method of scoring neglects short-duration events lasting less than the scoring epoch, although such events also carry important information. Transient EEG phenomena have been described within the sleep recordings allowing identification of what is known as the microstructure of sleep [105, 106]. These brief phenomena are related to the sleep instability and arousals.

According to the AASM definition (Table 10.3), arousal is defined as an abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz (but not spindles). It can be accompanied by an increase of electromyographic activity and of cardiac frequency or by body movements. An arousal must be preceded by at least 10 s of continuous sleep. Nevertheless, this definition may be not complete, as other EEG elements, characterized by slow activity, as K-complexes or delta bursts, are considered arousal-related phenomena but are not scored as arousals unless they are associated with an EEG frequency shift toward theta, alpha, or beta rhythms (Fig. 10.10, panel a). Furthermore, the AASM criteria of arousal does not include the concept of periodicity.

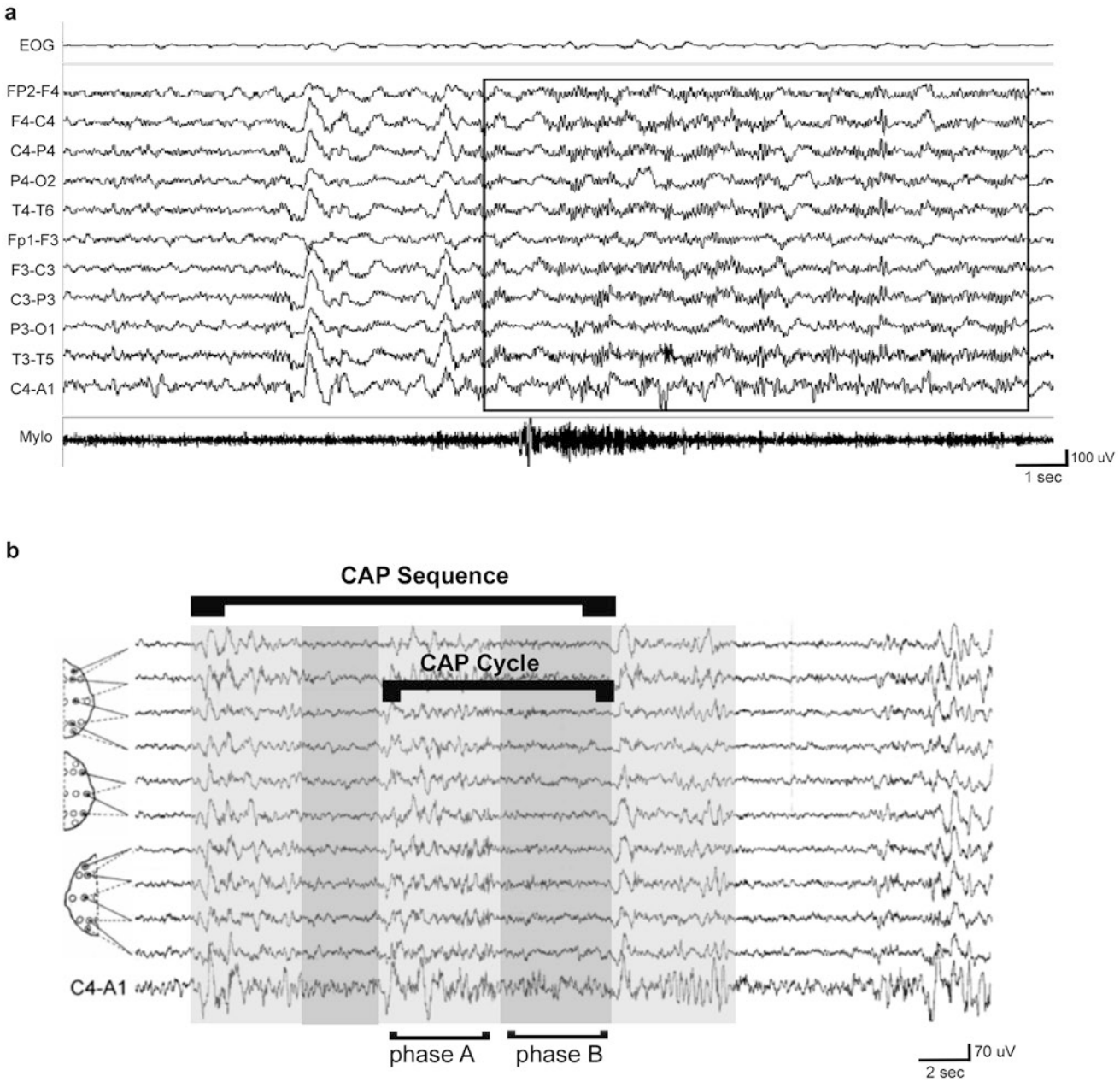


**Fig. 10.10** Panel (**a**) Arousal according to AASM criteria (arousal is described by the black box). Only rapid rhythms are considered. Slow waves preceding the shift toward rapid frequencies are excluded. EEG is displayed in bipolar montage. *EOG* electrooculogram. EMG derivation is represented by the activity of the mylohyoid muscle (mylo). Panel (**b**) A CAP cycle is defined as a sequence of two alternating stereotyped EEG patterns, each lasting more than 2 and less than 60 s, called phase A and phase B, which are the expression of a sustained fluctuation between "greater arousal" level (phase A: usually 8–12 s) and "lesser arousal" level (phase B: usually 16–25 s). At least two full CAP cycles in succession are needed to define a CAP sequence; all CAP sequences begin with a phase A and end with a phase B. The phase A that terminates a CAP sequence is counted as non-CAP

In the middle of the 1980s, Terzano and co-workers [107] recognized a microstructural cyclicity in NREM sleep, named cyclic alternating pattern (CAP). The introduction of the CAP framework provides a substantial departure from the general consensus about arousals during sleep either conceptually and as EEG criteria. The conceptual basis of arousals as proposed by the American Sleep Disorders Association and reported in the AASM manual is that arousals, being a transient cortical activation, are markers of sleep disruption representing a detrimental and harmful feature for sleep [108] and thus excluded from the conventional staging procedures. According to the CAP

theory, arousal is an integral part of sleep texture taking part in the sleep regulation processes [41] and represents a complex phenomenon involving not only cortical areas but also other brain centers and peripheral neural components [13, 41]. The activating pattern occurring within the somato-vegetative systems do not always correspond to a cortical activation, as the arousal definition seems to suggest. The outcome of stimulation can also be a mild cortical activation expressed as a mixed slow-rapid EEG pattern (as for subtypes A2 of CAP) or can evoke a protective reaction of the sleeping brain (as for subtypes A1 of CAP) as described below.

### 10.10.1 Definitions of CAP and Non-CAP

The cyclic alternating pattern (CAP) is a specific type of periodic activity of NREM sleep characterized by phases of EEG activation (**A** phase) and subsequent phases of return to background activity (**B** phase), both ranging between 2 and 60 s, evolving in a cycling pattern.

A phase **A** and the following phase **B** compose a CAP cycle, and a succession of cycles defines a CAP sequence. All CAP sequences begin with a phase **A** and end with a phase **B** (Fig. 10.10, panel b).

The absence of CAP for >60 s is scored as non-CAP, considered as a phase of sustained physiologic stability. An isolated phase **A** and the phase **A** that terminates a CAP sequence is considered as non-CAP (Fig. 10.11). CAP sequences have no upper limits for duration and number of CAP cycles. Each CAP sequence is usually formed by five to six CAP cycles.

CAP sequences usually precede the transition from non-REM to REM sleep. REM sleep is characterized by the lack of EEG synchronization; thus phase **A** in REM sleep consists mainly of desynchronized activities (fast low-amplitude rhythms), which are separated by a mean interval of 3–4 min. Consequently, under physiologic circumstances, CAP is not present in REM sleep. However, pathologic conditions characterized by repetitive **A** phases recurring at intervals <60 s, as periodic REM-related sleep apnea events, can produce CAP sequences in REM sleep. Within non-REM sleep, a CAP sequence is not interrupted by a sleep stage shift if CAP scoring requirements are satisfied. Consequently, because CAP sequences can extend across adjacent sleep stages, a CAP sequence can contain a variety of different phase **A** and phase **B** activities.

#### 10.10.1.1 CAP Phase A Boundaries

##### Amplitude Limits

Phasic activities initiating a phase **A** must be 1/3 higher than the background voltage, calculated during the 2 s before onset and 2 s after offset of a phase **A** itself. However, in some cases, a phase **A** can present ambiguous limits due to inconsistent voltage changes. Onset and termination of a phase **A** are established on the basis of an amplitude/frequency concordance in the majority of EEG leads.

##### Temporal Limits

Each phase **A** or **B** is 2–60 s in duration. If two consecutive phase **A** are separated by an interval <2 s, they are combined as a single phase **A**. If they are separated by a >2 s interval, they are scored as independent events.

#### 10.10.1.2 Phase A EEG Events and Subtypes

Compared to background activity, phase **A** can be composed of slower, higher-voltage rhythms, faster lower-voltage rhythms, or by mixed patterns including both. They may include delta bursts, sequences of vertex sharp transients, K-complex sequences, polyphasic bursts, K-alpha, intermittent alpha, and EEG arousals (Table 10.4).

Based on the reciprocal proportion of EEG synchrony (high-voltage slow waves) and EEG desynchrony (low amplitude rapid activities), phase **A** can be classified into three subtypes (Fig. 10.12):

- *Subtype A1:* EEG synchrony is the predominant activity. If present, EEG desynchrony occupies <20% of the entire phase **A** duration. Examples of **A1** include delta bursts, K-complex or vertex sharp transient sequences, and polyphasic bursts with <20% of EEG desynchrony.
- *Subtype A2:* The EEG activity is a mixture of slow and fast rhythms with 20–50% of phase **A** characterized by EEG desynchrony. Examples of **A2** include polyphasic bursts with more than 20% but less than 50% of EEG desynchrony.
- *Subtype A3:* The EEG activity is predominantly low-voltage fast rhythms with >50% of phase **A** occupied by EEG desynchrony. Examples of **A3** include K-alpha, EEG arousals, and polyphasic bursts with >50% of EEG desynchrony. A movement artefact within a CAP sequence is also classified as subtype **A3**.

Different **A** phases show distinct topographic distribution. **A1** can be considered as frontal lobe arousals, as they prevail in anterior regions, whereas **A3** are localized principally over the posterior areas. **A2** share both spectral and topographic characteristics of A1 and A3. They origin over the anterior regions with an initial slow component, and then they spread toward parieto-occipital areas acquiring the characteristics of **A3** subtypes (fast low-voltage activity) [109]. Subtype **A1** is most common as sleep EEG synchrony increases (from light to deep non-REM sleep) and when synchrony predominates (stage N3). **A1** phases are concentrated during the descending branch of the sleep cycle and follow the homeostatic decay of slow-wave oscillation both within one cycle

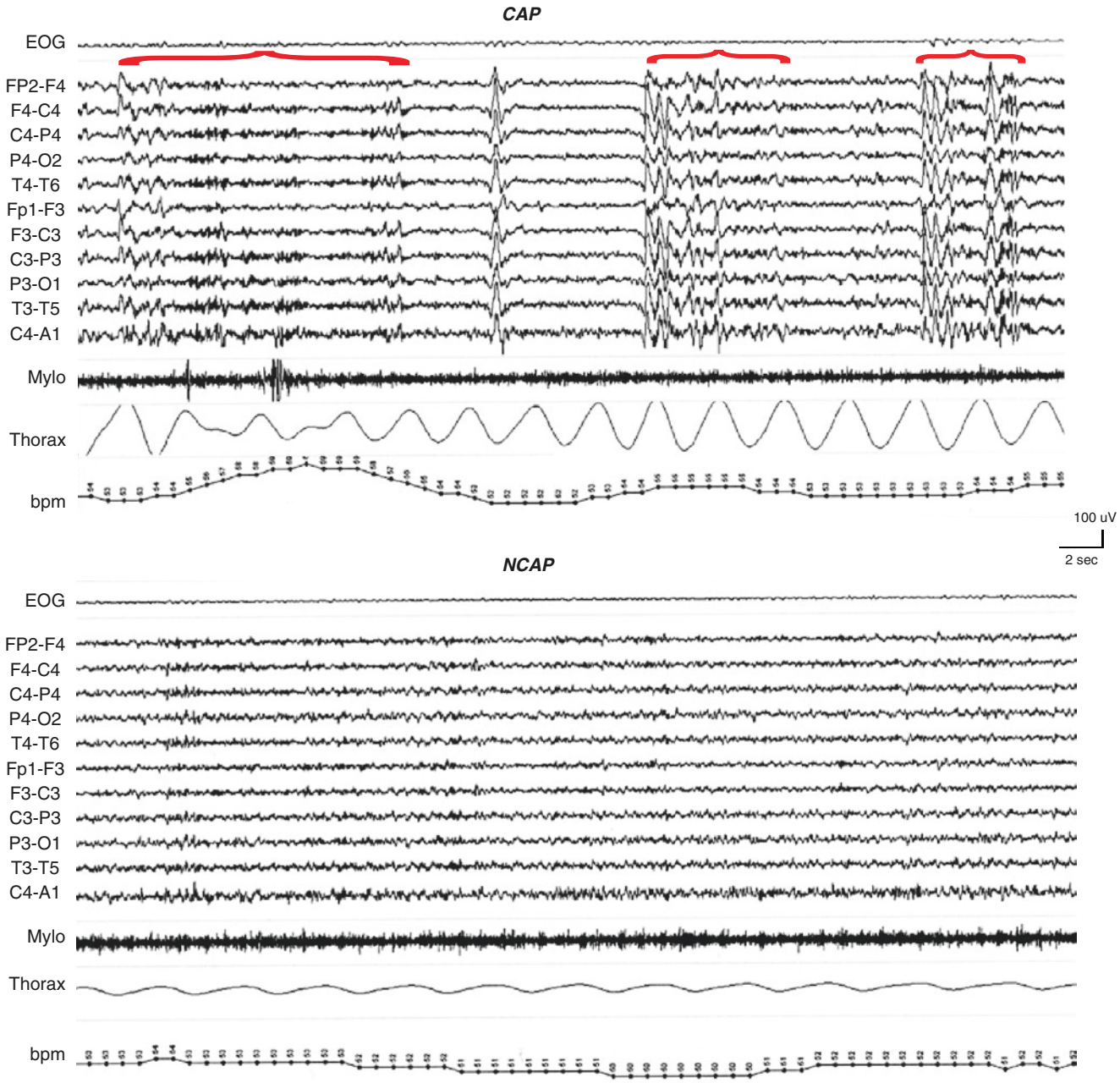


**Fig. 10.11** Examples of CAP and NCAP during N2. *Top image*: CAP during N2. Three A phases are highlighted by red brace brackets. Note the correspondent increase in heart frequency (bpm) during CAP A phases. *Bottom image*: NCAP during N2. Note the absence of EEG, heart frequency, and respiratory fluctuations. EEG is displayed in bipolar montage. *EOG* electrooculogram. EMG derivation is represented by the activity of the mylohyoid muscle (mylo). Thorax: respiratory effort. Bpm: heart rate

**Table 10.4** Example of A phases

| | |
|---|---|
| Delta bursts | Sequence of at least two waves in delta frequency and with an amplitude at least 1/3 higher than the background activity |
| Polyphasic bursts | Clusters of high-voltage delta waves, intermixed with faster rhythms (in the theta, alpha, or beta frequency bandwidth) |
| K-alpha | A K-complex followed immediately by an alpha burst with an overall duration of ≥2 s |
| Intermittent alpha | Intermittent sequences of alpha activity, usually localized more anteriorly and often increased in amplitude and decreased in frequency than during wakefulness. It is normally seen during the first phases of sleep, when stage N1 remerges in the ascendant branch of sleep cycle, or during REM sleep |
| EEG arousals | Abrupt shift of EEG frequency including alpha, theta and/or frequencies greater than 16 Hz (but not spindles) that shortly interrupt the sleep continuity, lasting at least 3 s, with at least 10 s of stable sleep preceding the change and, if scored during REM, with a concurrent increase in submental EMG lasting at least 1 s |

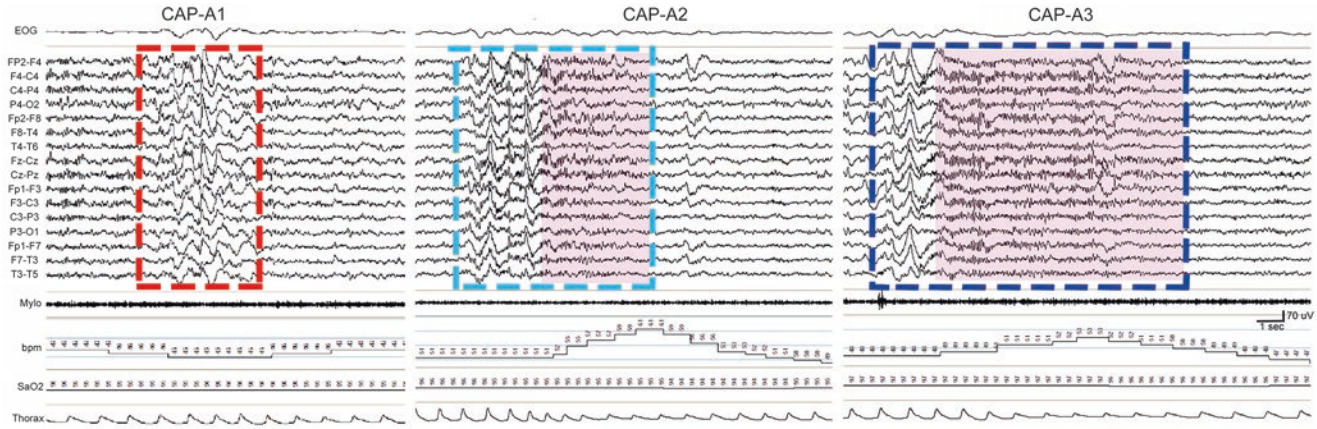


**Fig. 10.12** Examples of CAP-A subtypes. The red box identifies the limits of A1 phase, the light blue one the A2 phase, and the blue box the A3 phase. The pink box shows the amount of EEG desynchronized activity in each A phase: less than 20% in A1 (note that in this example A1 is constituted only by SWA), between 20 and 50% in A2 and >50% in A3. Notably during A2 and A3 subtypes, EEG activity is accompanied by changes in heart rate and respiratory effort. EEG is displayed in bipolar montage. *EOG* electrooculogram. EMG derivation is represented by the activity of the mylohyoid muscle (mylo). Thorax: respiratory effort. Bpm: heart rate. $SaO_2$: oxyhemoglobin saturation

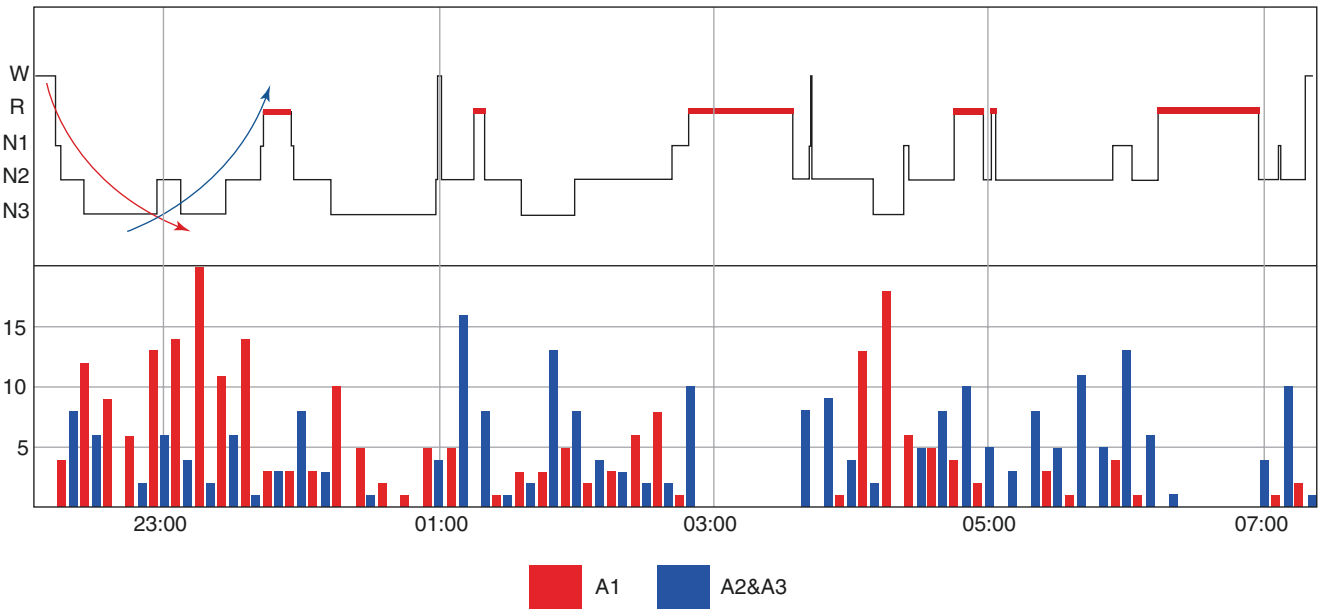


**Fig. 10.13** Distribution of A phases matched with hypnogram. Red bars: number of synchronization phases (A1) each 10 min. Blue bars: number of desynchronization phases (A2 + A3) each 10 min. A1 phases prevail during the descendent branch (identified by the red arrow on the hypnogram) and the plateau of deep sleep, whereas A2 and A3 phases are localized primary during the ascending branch (identified by the blue arrow on the hypnogram), preceding the appearance of REM sleep. The progressive decline of A1 along the night reflect the homeostatic sleep process

and from cycle to cycle. Subtypes **A2** and **A3** are mostly concentrated as sleep-related brain activity progresses from synchrony to greater desynchrony (e.g., in stage N2 preceding the onset of REM sleep), and they prevail during the ascending branch of the sleep cycle [10] (Fig.10.13). The same perturbation can evoke a **A1** or **A2/A3** response depending on the sleep propensity and intracycle dynamic regulation. The elicitation of the CAP **A1** pattern by acoustic stimuli during CAP B phases has proven that a certain amount of (reactive) sleep slow waves are evoked by sensory stimulation [47, 110]. Based on these observations, the CAP system can be viewed as a short range homeostatic process in which the amount of slow-wave activity is buffered instantly (fast homeostatic reaction), therefore preserving sleep continuity: a natural "slow-wave injection," protecting sleep against perturbations.

### 10.10.2 Measures of CAP and CAP trend During Age Span

CAP is a marker of sleep instability, as well as other EEG features, and it highly depends on brain development. Among the various CAP parameters, CAP rate is the most extensively used for clinical purposes. Calculated as the percentage ratio of total CAP time to non-REM sleep time, CAP rate is the measure of arousal instability; it can be enhanced when sleep is disturbed by internal or external factors and its variations correlate with the subjective appreciation of sleep quality with higher values of CAP rate associated with poorer sleep quality.

CAP rate in normal sleepers shows a low intraindividual variability from night-to-night [111]; CAP rate has a complex evolution during development.

In newborns, as soon as the NREM sleep emerges, CAP begins to develop, and the oscillating pattern of the different phasic EEG activities becomes evident. The gradual appearance of an oscillating pattern of slow EEG activities representing the first prototype of CAP appears at 46–55 weeks of conceptional age (Fig.10.6). During infancy, CAP rate shows a gradual increase with a peak in adolescence and then a gradual decrease in adulthood followed by an increase in the elderly [112–116] (Fig.10.14).

These age-related changes of CAP rate reflect the biological growth processes that lead to adolescence, the development maturational consolidation, and finally the process of senescence that is accompanied by the increasing of sleep instability.

The peripubertal peak of CAP rate is associated with the maximum of the A1 subtypes percentage, which shows a bell-shaped course during the life (Fig. 10.15). In contrast, subtypes **A2** and **A3** undergo a linear increase from infants, preschool children to the old age, similar to the arousal evolution across the life span [110, 112, 117]. The ratio between A1 and A2/A3 is higher in school-age children, supporting the notion that sleep in this age range (6–10 years) may be considered as the "gold standard" for sleep quality [118] because of its length, continuity, and restorative features. On the other hand, the increase of the percentage of A2 in preschoolers might represent the higher sleep instability of this age period. In school-aged children, the increased values of CAP rate during N3 and the greater percentage of **A1** subtypes indicate that in this age group, the homeostatic process requires a higher number of oscillations in order to maintain the restorative function of sleep [113, 115, 119].

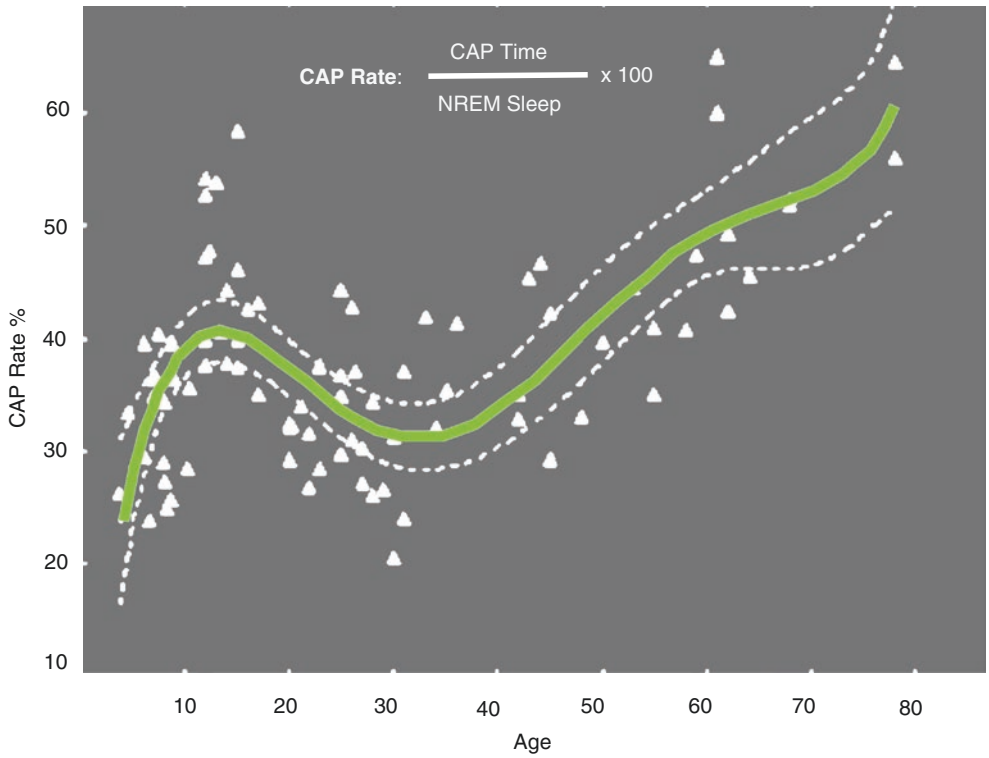


**Fig. 10.14** Age-related modifications of CAP rate along the normal life span. Note a bimodal distribution with a first peak around the puberty followed by a decrease during adult life and a subsequent new increase in senescence. The green line identifies the average physiological distribution of CAP rate across ages, while dotted white lines show the related standard deviations. White triangles refer to the CAP rate of single subjects included in the analysis. The present figure has been extrapolated from the data presented in [110]. Age is expressed in years

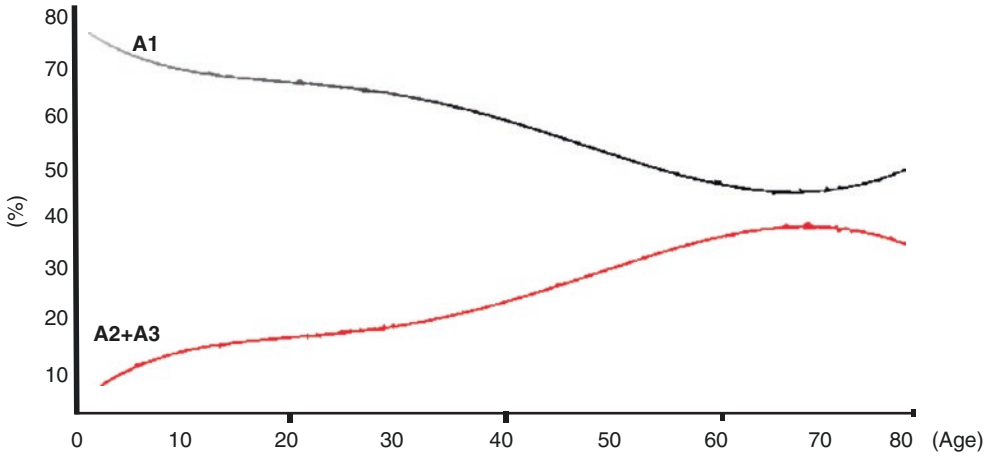


**Fig. 10.15** Normative age-related changes of phase A subtypes. The percentages of subtypes A1 (black line) tend to decrease along the lifespan mirrored by the reciprocal increase of subtypes A2 and A3 (red line). The opposite trends converge approximately at the age of 60–70 years. The present figure has been extrapolated from the data presented in [110]. Age is expressed in years

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