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### Summary

Sleep measurement is based on conventional rules, which simplify the complex architecture of this mandatory physiological activity. The dynamic development of sleep shows a regular cyclic nature, which is reflected also in the microstructural organization of phasic EEG events. In NREM sleep, arousals rarely appear in isolation but are most commonly arranged in sequences recognized as the cyclic alternating pattern (CAP). Composed of EEG features endowed with properties of activation (phase A) and deactivation (phase B), CAP translates a condition of sustained arousal instability. Due to the close temporal relation between CAP, autonomic functions and behavioral activities, CAP operates as a master clock that entrains different rhythms in a common temporal pattern. Crucially participating in the build-up, maintenance and attenuation of slow wave sleep, CAP represents a fundamental pillar of sleep processes together with the homeostatic drive, the ultradian cyclicality and the circadian oscillation. The pivotal role of CAP in the basic sleep mechanisms justifies its involvement in the pathophysiology of most sleep disorders and offers new perspectives in clinical management strategies. The absence of CAP (defined as non-CAP) corresponds to a sustained condition of stability extended to both brain and body. CAP and non-CAP metrics overcome the rigid limitations of conventional stage scoring and provide a more flexible and genuine neurophysiological substrate to shed light upon the brain-body coupling during sleep.

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**Key words:** Cyclic alternating pattern, sleep, EEG, arousals

### „Cyclic alternating pattern“ und „Brain-Body-Coupling“ im Schlaf

Die Beurteilung des Schlafes erfolgt gemäss konventioneller Kriterien, die die komplexe Architektur dieser essenziellen physiologischen Aktivität vereinfachen sollen. Physiologischer Schlaf folgt in periodi-

schen Zyklen, was sich im EEG in der Mikrostruktur der Schlafphasen widerspiegelt. Im NREM Schlaf kommen isolierte Arousals nur sehr selten vor, meist kommt es zu Sequenzen, die als „cyclic alternating pattern“ (CAP) bezeichnet werden. Mit Sequenzen transienter elektrokortikaler Ereignisse von Aktivierung (Phase A) und Deaktivierung (Phase B) repräsentiert CAP eine Schlafinstabilität und ein relativ niedriges Arousal-Niveau. Auf Grund des engen zeitlichen Zusammenhangs zwischen CAP, autonomer Funktionen und Verhalten funktioniert CAP als ein übergeordneter Zeitgeber zu Koordinierung verschiedener Rhythmen in einer gemeinsamen zeitlichen Periodizität. Gemeinsam mit ultradianen Zyklen und zirkadianen Oszillationen wirkt CAP als zentraler Pfeiler des Schlafes im Aufbau, in der Aufrechterhaltung und Vertiefung des Delta-Schlafes mit. CAP spielt in diesen grundlegenden Schlafmechanismen eine zentrale Rolle, daher versteht sich auch die wichtige pathophysiologische Bedeutung von CAP in den meisten Schlafstörungen, wodurch sich neue klinische Perspektiven für Behandlungsstrategien eröffnen. Fehlen von CAP (definiert als non-CAP) ist assoziiert mit einem anhaltenden Zustand von Stabilität, übertragen auf Hirn und Körper. Mittels CAP und Non-CAP gelingt es, starre Limitationen der konventionellen Schlaf-Stadien-Einteilung zu überwinden, was eine flexiblere, authentischere und neurophysiologischere Sicht auf das Brain-Body-Coupling während des Schlafes erlaubt.

**Schlüsselwörter:** Cyclic alternating pattern, Schlaf, EEG, Arousal

### Le tracé alternant cyclique et le couplage du cerveau et du corps durant le sommeil

L'analyse conventionnelle du sommeil repose sur des règles rigides, qui tendent à simplifier l'architecture complexe de cette activité physiologique essentielle. Le sommeil est cyclique par nature, entre autre dans l'organisation des événements EEG phasiques observés sur une courte échelle de temps (microstructure du sommeil). Au cours du sommeil non-REM, ces événements phasiques („arousals“) apparaissent rarement de manière isolée, mais sont le plus souvent organisés en

séquences appelées tracé alternant cyclique (“cyclic alternating pattern”, CAP). Composé d’éléments EEG suggérant l’activation (phase A) et la désactivation (phase B), le CAP est l’expression d’une instabilité prolongée du sommeil. En raison de la concomitance entre CAP, fonction autonome et mouvement, le CAP peut être vu comme le chef d’orchestre qui régule les différents rythmes les uns par rapport aux autres. En participant de manière cruciale dans l’événement, le maintien et l’atténuation du sommeil à ondes lentes, le CAP représente – avec le processus homéostatique, le rythme ultradien et le rythme circadien – l’un des piliers fondamentaux du processus sommeil. Le rôle majeur du CAP dans les mécanismes fondamentaux du sommeil explique son implication dans la pathophysiologie de la plupart des troubles du sommeil, et offre de nouvelles perspectives de traitement en clinique. L’absence de CAP correspond quant à elle à une stabilité prolongée du cerveau, comme du reste du corps. Quantifier les phases de CAP et d’absence de CAP permet de contourner les limitations rigides du scoring des phases de sommeil, et offre un cadre flexible, correspondant plus à la réalité neurophysiologique, pour étudier les relations cerveau-corps pendant le sommeil.

**Mots clés :** Tracé alternant cyclique, sommeil, EEG, micro-éveils

## Introduction

The current method of sleep analysis, according to the AASM system, is centered on sleep macrostructure that identifies rapid-eye movement sleep (REM) and non-REM with its different stages (NREM1, NREM2, NREM3) based on 30-second scoring epochs [1].

Under physiological conditions, sleep macrostructure presents an operational framework based on the following principles and rules:

1. Falling asleep always occurs in non-REM sleep,
2. the brain takes about 25 minutes to reach deep sleep,
3. the first REM sleep episode appears approximately 10 minutes after the end of deep sleep,
4. NREM3 prevails in the first part of the night, while REM sleep dominates in the second half.

This asymmetry reflects the gradual attenuation of the intensity of slow wave sleep during the night, like a spring loaded during the waking hours and progressively discharged across the night. Because it increases after sleep deprivation and drops when the waking period is short, deep sleep is considered an important marker of sleep homeostasis.

The alternation of NREM and REM sleep constitutes the sleep cycle. Each sleep cycle has a duration of approximately 90 minutes. Sleep macrostructure

resembles a 5-wagon train, each coach lasting about an hour and a half. The first three wagons, which constitute the core sleep, are controlled predominantly by the acid gamma-aminobutyric acid (GABA), a sedative neurotransmitter. The last two coaches compose the so-called optional sleep and are modulated by an activating neurotransmitter, acetylcholine, which prepares the brain to the morning awakening. The turning point between the two types of sleep, in particular between the third and the fourth wagon, coincides with a delicate phase of sleep continuity and is often the time of awakening for many insomniacs.

However, the quality of sleep is not only based on its duration, depth and continuity as arousals are also involved in the restorative properties of sleep. Although scored as single features, arousals rarely appear in isolation, while they are mostly organized in sequences like a swarm of flying birds. The regular organization of arousals, known as CAP (cyclic alternating pattern), defines the microstructure of sleep and measures the amount of unstable sleep.

Accordingly, the quality of sleep is based on 4 pillars:

- Duration (total sleep time)
- Intensity (amount of deep sleep)
- Continuity (nocturnal awakenings)
- Stability (CAP parameters).

## The rules of CAP and non-CAP

CAP is the most comprehensive method for the detection and measurement of sleep microstructure. CAP spans across long periods of NREM sleep, it overcomes the boundaries of standard rigid epochs and offers a dynamic contribution to the static framework of conventional scoring. CAP reveals the presence of a complex scaffold, hidden but perfectly integrated beneath the surface of conventional sleep stages [2].

CAP is defined as a periodic EEG activity occurring under conditions of reduced vigilance (sleep, coma). It is characterized by sequences of CAP cycles defined by an A phase (transient electrocortical events that are distinct from background EEG activity) and by the following B phase (return to background EEG activity).

A CAP sequence is composed of at least two consecutive CAP cycles (Figure 1).

The absence of CAP for more than 60 s is scored as non-CAP (NCAP) and coincides with a condition of sustained physiological stability [3]. Isolated A phases are classified as NCAP (Figure 2).

The last A phase that closes a CAP sequence is not included in the scoring of CAP and is scored as NCAP.

Therefore every CAP sequence begins with an A phase and ends with a B phase. The amplitude of phasic activities initiating a phase A must be 1/3 higher than the background voltage.

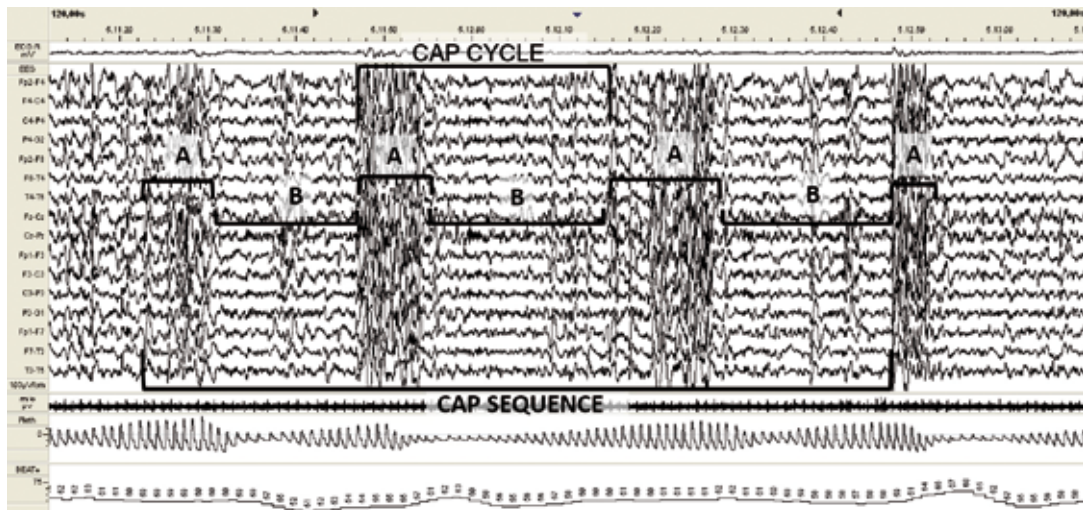


Figure 1: Cyclic alternating pattern (CAP) during NREM sleep. A CAP cycle is defined as a sequence of A phase and B phase. At least two full CAP cycles in succession are needed to define a CAP sequence; thus, the minimum content of a sequence is A-B-A-B-A. Montage, from top to bottom: right electrooculogram (EOG-R); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2-F4, F4-C4, C4-P4, P4-O2, Fp2-F8, F8-T4, T4-T6, Fz-Cz, Cz-Pz, Fp1-F3, F3-C3, C3-P3, P3-O1, Fp1-F7, F7-T3, T3-T5); chin electromyogram (milo); finger photoplethysmogram (Pleth); heart rate (BEAT).

Each CAP phase, both A and B, is 2 - 60 s in duration. This cutoff relies on the consideration that the great majority (about 90%) of A phases occurring during sleep are separated by an interval of less than 60 s [4]. If two consecutive phases A are separated by an interval < 2 s they are counted as a single phase A. CAP sequences are not interrupted by a sleep stage shift if CAP scoring

requirements are satisfied. Therefore, a CAP sequence can contain a variety of different phasic activities and extend across adjacent sleep stages.

CAP sequences commonly precede the transition from non-REM to REM sleep and end just before REM sleep onset. REM sleep is characterized by the lack of EEG synchronization; thus phase A features in REM

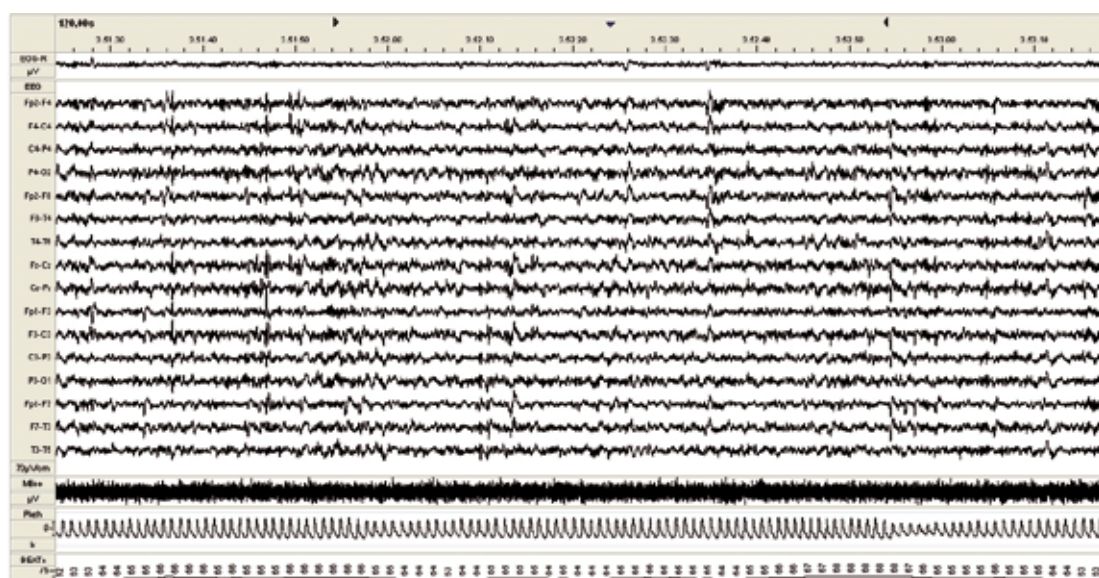


Figure 2: Absence of cyclic alternating pattern (NCAP) during NREM sleep. Montage, from top to bottom: Right electrooculogram (EOG-R); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2-F4, F4-C4, C4-P4, P4-O2, Fp2-F8, F8-T4, T4-T6, Fz-Cz, Cz-Pz, Fp1-F3, F3-C3, C3-P3, P3-O1, Fp1-F7, F7-T3, T3-T5); chin electromyogram (milo); finger photoplethysmogram (Pleth); heart rate (BEAT).



sleep consist mainly of desynchronized patterns (fast low-amplitude rhythms), which are separated by a mean interval of 3 - 4 min [5]. Consequently, under normal circumstances, CAP sequences do not occur in REM sleep.

However, sleep disorders characterized by repetitive A phases recurring at intervals < 60 s (for example, periodic REM-related sleep apnea events), can produce CAP sequences in REM sleep.

### Phase A subtypes

Phase A activities can be classified into three subtypes, referring to the reciprocal proportion of EEG synchrony and EEG desynchrony, as follows:

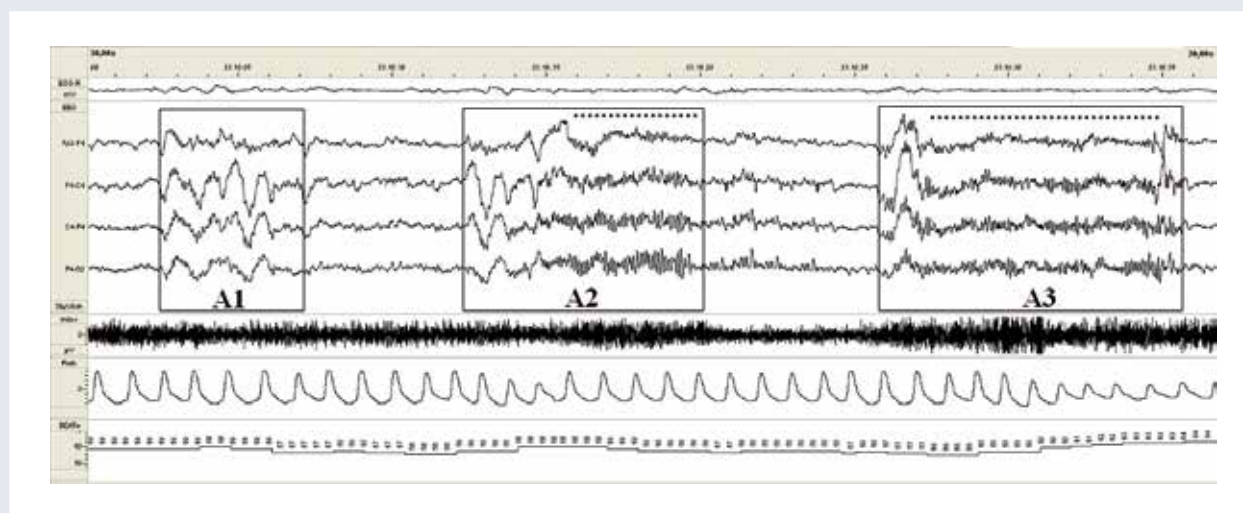
1. Subtype A1. EEG synchrony (high-amplitude slow waves) is the predominant activity. If present, EEG desynchrony (low-amplitude fast waves) occupies < 20% of the entire phase duration.
2. Subtype A2. The EEG activity is a mixture of slow and fast rhythms with 20 - 50% of phase A occupied by EEG desynchrony.
3. Subtype A3. The EEG activity is dominated by rapid low-voltage rhythms with more than 50% of phase A occupied by EEG desynchrony.

Different subtypes of phase A can occur within the same CAP sequence (Figure 3).

The majority of EEG arousals occurring in NREM sleep (87%) is included within the CAP sequences and basically coincide with a phase A2 or A3 [6]. In particular, 95% of subtype A3 events and 62% of subtype A2 events meet the AASM criteria for arousals [7].

### The significance of CAP

CAP sequences and NCAP periods physiologically appear during the night with a nonstochastic distribution. A detailed investigation showed that the non-triggered EEG fluctuations centered on the 20 - 40 s periodicity of CAP are involved in the subtle mechanisms that control the production and attenuation of sleep slow-wave activities [8]. Comparing spectral assessment [9, 10] and EEG visual scoring of NREM sleep in healthy individuals, the amount of slow rhythmic oscillations (spectral analysis) parallels the number of CAP cycles (visual detection), with a striking agreement between spectral power gatherings and visually scored A phases [11]. Within the sleep cycle, 90% of the A phases detected in the descending branches and 92% of the A phases detected in the troughs are subtype A1. In contrast, 64% of the A phases identified in the ascending branches are subtypes A2 (45%) and A3 (19%). These findings indicate that both slow and rapid EEG activating complexes are involved in sleep architecture [12]. Build-up and maintenance of deep sleep are guaranteed by a process of periodic EEG instability accompanied by mild neurovegetative fluctuations that accompany the downward shift from wakefulness (A1 subtypes). Conversely, the breakdown of slow-wave sleep and the introduction of REM sleep are mostly associated with desynchronized EEG activities and powerful activation of muscle and autonomic functions (A2 and A3 subtypes). Therefore, in addition to their manifold EEG features, the A phases are characterized by a non-random distribution across the night, which assumes a clear-cut periodicity during NREM sleep within the framework of CAP. For this reason, CAP is a “master clock” that determines the pace within which temporal patterns can be generated and implemented [13, 14].



**Figure 3: Three CAP A phase subtypes. The phase A subtypes delimited by the boxes.**

The dotted lines indicate the fast low-amplitude portion of the A phase.

Montage, from top to bottom: right electrooculogram (EOG-R); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2-F4, F4-C4, C4-P4, P4-O2); chin electromyogram (milo); finger photoplethysmogram (Pleth); heart rate (BEAT).

## Measuring CAP

EEG features are highly sensitive markers of brain development. Accordingly, during a person's life-span physiological changes can be determined by sleep analysis at different ages. CAP parameters undergo dynamic variations across natural maturation and they can be used to establish the normal ranges of sleep. Studies conducted in childhood sleep disorders, neuro-psychological disabilities, and cognitive retardation have revealed specific alterations of CAP parameters in the different pathological conditions [15, 16].

## A phases

A bell-shaped curve describes the normal percentages of A1 subtypes in different age groups, conversely, a linear increase is observable in subtypes A2 and A3 from infancy to advanced age, similar to the arousal patterns during a life span [17] (Table 1).

## CAP rate

CAP rate is the most widely exploited microstructural parameter for clinical purposes. CAP rate quantifies sleep instability and it is defined by the ratio of total CAP time in NREM sleep to total NREM sleep time. CAP rate increases when sleep is disturbed by internal or external factors, and its variations reflect the perception of sleep quality, with higher values of CAP rate related with poorer sleep quality.

In normal subjects, CAP rate is characterized by a low night-to-night intraindividual variability. Across development CAP rate undergoes complex variations (Table 1).

## CAP and the autonomic nervous system

CAP represents an integrative tool to enhance knowledge on the interaction between EEG activity and autonomic functions during sleep. CAP translates a state of instability [18] which is not only confined to the cerebral activities but reverberates upon behavioral and autonomic functions in a mutually entrained synchronized oscillation. Indeed, the CAP phenomenon provides a fluctuating web of agreement and order among EEG rhythms, blood pressure, muscle tone and heart rate [19]. On the contrary, during NCAP both arousal and autonomic functions interact in a condition of sustained stability [20]. The relation between sleep microstructure and autonomic functions has been investigated in healthy subjects by means of spectral analysis of heart rate variability during sleep [21]. A significant difference was found between CAP and NCAP conditions in the low frequency (LF) and high frequency

**Table 1:** The age-related values of cyclic alternating pattern (CAP) rate and percentages of CAP A phases subtypes in healthy subjects.

Age	CAP rate (%)	A1 (%)	A2-A3 (%)
Infant	12.9	69.7	30.3
Preschool-aged children	25.9	63.2	36.8
School-aged children	33.4	84.4	15.6
Peripubertal children	62.1	85.5	14.5
Teenagers	43.4	71.3	28.7
Young adults	31.9	61.4	38.6
Middle aged subjects	37.5	62.0	38.0
Elderly persons	55.3	46.6	53.4

(HF) components, which increased and decreased during CAP, respectively. Similar results were described in healthy children and adolescents [22]. By means of the product of the coherence and cross-power of the HRV and the corresponding ECG-derived respiration signal, Thomas et al. [23] showed spontaneous abrupt transitions between high- and low-frequency cardiopulmonary coupling regimes in NREM sleep. The two distinct regimes demonstrated a closer relationship with CAP compared to the standard sleep stages.

EEG arousals commonly produce autonomic nervous system activation, with extensive and rapid parasympathetic withdrawal, consistently with the increased sympathetic modulation of systemic vascular resistance and cardiac contractility [24, 25]. Although with lower intensities, even K-complexes and delta-bursts, which are not scored as conventional EEG arousals, are associated with significant changes in heart rate, consisting of tachycardia followed by bradycardia [26]. These findings indicate a reciprocal interaction between what happens upstairs (brain) and downstairs (body). Endowed with different activation properties the phase A subtypes of CAP (from A1 to A3) allow during sleep a variety of adaptive adjustments to both internal and external inputs. The relation between the different types of A phases and cardiovascular system (heart rate) have been studied in normal and pathological conditions [27, 28].

## CAP in sleep disorders

Physiologic, paraphysiologic and pathologic movements during NREM sleep are always organized around a basic, stereotyped, transient activation of the brain regulated by the arousal system [29]. In addition to

being a physiological component of sleep, CAP can be triggered by different external stimuli (tactile, thermal, acoustic, painful, etc.). It has been noticed that applying separately the same arousing stimulus during the phase B of the CAP cycle, this immediately assumes the morphology of the other component; when the stimulus is delivered during phase A the inverse transformation never occurs. This stereotyped reactivity persists throughout the successive CAP phases with lack of habituation. Conversely, the same stimulus presented during NCAP causes an electrocortical response characterized by brief, high-voltage slow waves, with tendency toward progressive habituation [4, 30]. However, a strong or prolonged stimulus delivered during NCAP induces the sudden appearance of repetitive CAP cycles with the same morphology and reactive behaviour of spontaneous CAP sequences that may lead to a lighter stage shift or continue until NCAP is completely recovered.

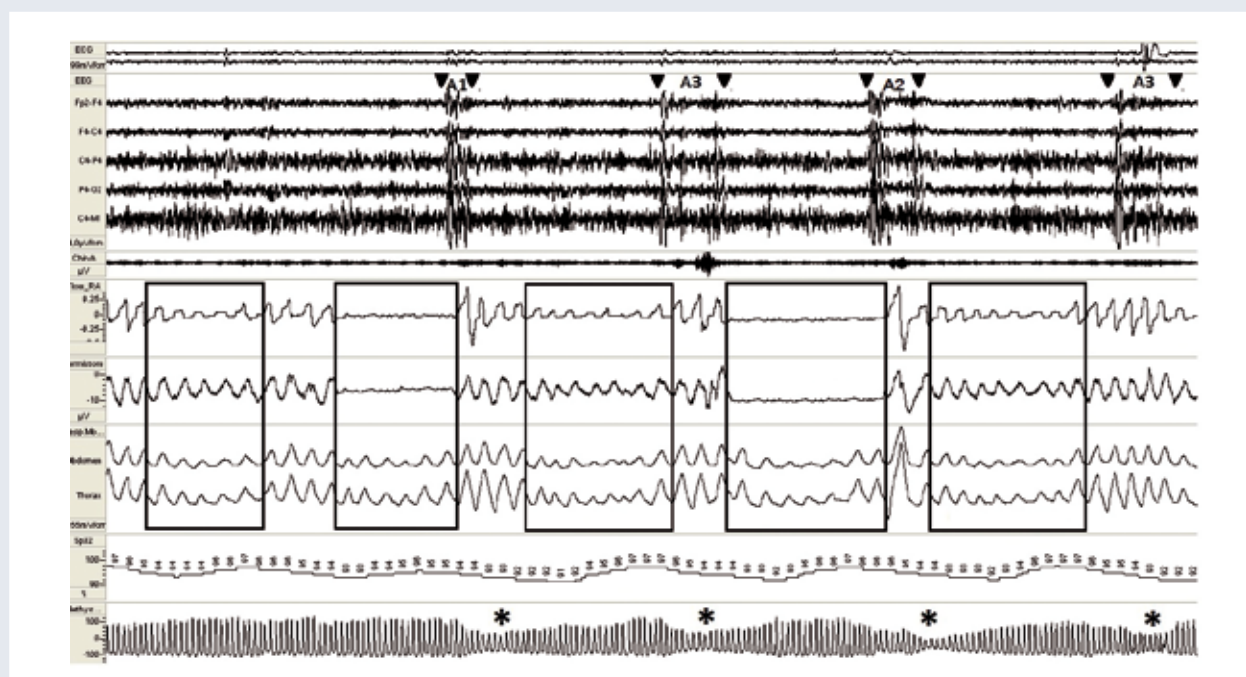
Coherently, CAP rate increases under noise stimulation [30] or in conditions of sleep disruption such as insomnia [31 - 33], depression [34], eating disorders [35], upper airway resistance syndrome (UARS) [36], obstructive sleep apnea syndrome (OSAS) [37], periodic limb movements [38], sleep related hypermotor epilepsy (former nocturnal frontal lobe epilepsy) [29, 39 - 43], primary generalized [44] and focal lesional epilepsy

[45]. In contrast, CAP rate decreases during sleep-promoting conditions such as narcolepsy [46, 47], administration of hypnotic drugs [31, 32, 48 - 50], continuous positive airway pressure (CPAP) treatment in OSAS [15, 16], and night-time recovery sleep after prolonged sleep deprivation [51]. Neurodegenerative disorders, e.g. multiple system atrophy [52], mild cognitive impairment and Alzheimer disease [53], characterized by an interrupted interaction between brain and body, are also associated with low amounts of CAP rate.

CAP is not only influenced by sleep disorders, but in turn it modulates the frequency and distribution of sleep-related events. In particular, phase A triggers bruxism [54, 55], sleepwalking [56, 57], epileptic events [58, 59], periodic limb jerks [38], and rhythmic movements during NREM sleep [60]. Conversely, phase B is associated to the repetitive respiratory events of sleep-disordered breathing, followed by the robust autonomic activation during the following phase A that restores post-apnea breathing [37].

### Sleep-disordered breathing

CAP offers a favorable background for phasic and repetitive sleep-related manifestations (Figure 4).



**Figure 4. Modulation of EEG response to respiratory events.** The figure reports examples of respiratory events (boxes) in which airway re-openings occur with different EEG patterns (delimited by black triangles). The asterisks show the pulse wave amplitude drops. From the left to the right, a hypopnea without EEG response, an apnea with phasic delta activity (A1 subtype of CAP), a hypopnea with EEG arousal (A3 subtype of CAP), an apnea with a mixture of slow and fast rhythms (A2 subtype of CAP) and a hypopnea with EEG arousal (A3 subtype of CAP). Montage, from top to bottom: electrooculogram (EOG); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2-F4, F4-C4, C4-P4, P4-O2 and monopolar derivation C4-M1); chin electromyogram (ChinA); nasal pressure airflow (flow-RA), oronasal thermal sensor (termistore), rib cage (thorax) and abdominal (abdomen) movements, and oxymetry (SpO2) finger photoplethysmogram (Pleth).

It is known that increased amounts of arousals are a regular finding in OSAS [37, 61, 62].

However, typical manifestations of secondary cortical events are also the respiratory effort-related arousals (RERAs). More specifically, RERAs are defined by obstructive upper airway flow reductions (which do not meet the criteria of apnea or hypopnea) associated with progressive negative esophageal pressure lasting at least 10 s and culminating in an arousal [63].

In the estimation of cerebral impact of respiratory events in NREM sleep, the CAP metrics offer more extensive information than AASM rules. While the arousal index was statistically similar in mild and moderate-severe OSAS patients, sleep instability, expressed by CAP time, showed a progressive enhancement from normal subjects to mild and moderate-severe OSAS patients. The moderate-severe OSAS showed a significant increase of CAP rate and A3 phases, while a normal CAP rate coexisted with a higher amount of A3 subtypes in the mild group [64].

The sleeping brain can solve respiratory challenges even without involving a cortical arousal. Conventional EEG arousals are elicited only if thalamo-cortical structures are unsuccessful in modulating breathing or when ascending reticular volleys are necessary to re-establish respiration [65]. EEG activation also enhances the autonomic nervous function as reflected by a greater increase of heart rate during arousals. However, heart rate acceleration can be elicited also by delta bursts and autonomic activation can occur without a simultaneous EEG arousal [21, 26].

When patients with OSAS are treated effectively with nasal continuous positive airway pressure (CPAP), the ventilatory-induced reduction of CAP rate, which correlates significantly with daytime sleepiness, is associated with a robust curtailment of subtypes A3 and a progressive recovery of the A1 percentages [15, 16].

## Insomnia

Patients with chronic insomnia and normal blood pressure values lack physiological nocturnal dipping of both systolic and diastolic values. The missing reduction of blood pressure dipping is linked to brain cortical activation during sleep even without arousal rate variations [66]. These findings suggest a pivotal role of hyperarousal and increased CAP in the missed modulation of autonomic functions during sleep.

The enhancement of CAP time and CAP rate in insomniac patients is a universal feature, independent of cultural or genetic constraints. A study on a large sample of Caucasian patients with primary insomnia showed that CAP parameters consistently correlate with a poor quality of sleep and can be useful to value the effectiveness of hypnotic drugs [49]. Japanese patients affected by psychophysiologic insomnia showed similar results in a randomized crossover comparative

study with placebo which demonstrated that hypnotic medication (with zolpidem) increases sleep stability with a reduction of CAP rate and improves subjective sleep perception [67].

Wavelet energy and entropy of CAP parameters allowed to quantify objective differences between insomniac patients and normal controls. In particular, insomnia sleep recordings present a longer duration and a higher EEG complexity of B phases between successive A1 subtypes during the build-up phases of slow wave sleep. Moreover, A3 subtypes show an increased duration and a more irregular structure [68].

CAP analysis can be a useful tool also to understand and manage sleep state misperception in insomniac patients. Misperceptors have normal CAP rate in slow wave sleep but considerably higher amounts of CAP rate in stage 1 and 2. Compared with objective polysomnographic findings, misperceptors report lower amounts of subjective awakenings (average: 4 vs 11) separated by longer intervals. Objective awakenings are always separated by periods of superficial sleep (stages 1 and 2) endowed by high amounts of CAP. A shallow and unstable sleep between two separate objective awakenings is perceived as an experience of continuous wakefulness, creating a mismatch between PSG data and subjective interpretation [33].

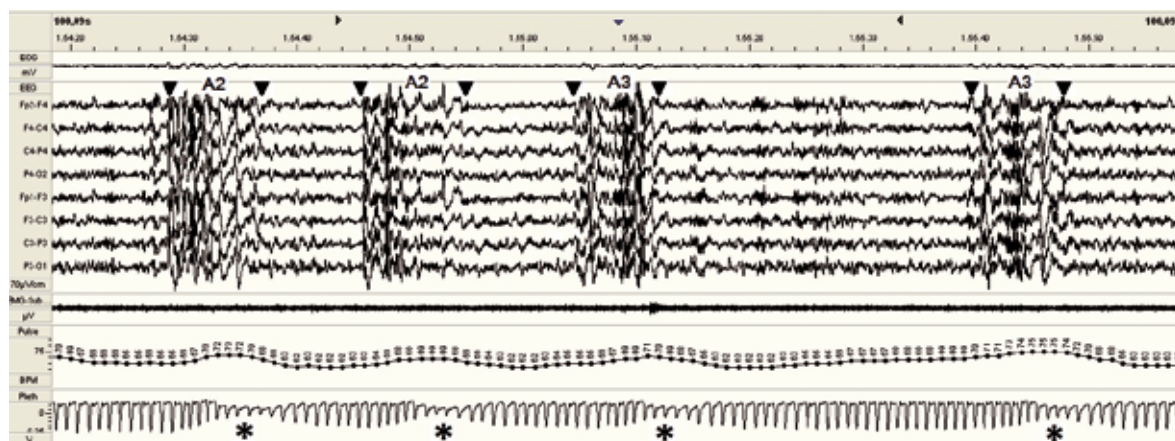
## Nocturnal Frontal Lobe Epilepsy

Nocturnal Frontal Lobe Epilepsy (NFLE) is characterized by a clinical spectrum of paroxysmal motor manifestations ranging from major seizures to paroxysmal arousals and minor motor events. A common feature is the onset of all episodes during NREM sleep, with different distribution with the sleep stages. Major attacks prevail in NREM3 leading abruptly to a wake condition as paroxysmal arousals and minor motor events may recur every night, sometimes several times per night, arising mainly from CAP in stage NREM2 [69]. These nocturnal manifestations cause enhanced sleep fragmentation and higher percentages of wakefulness, as well as increased amounts of CAP time, CAP rate, CAP cycles, and mean duration of CAP sequences [40, 42].

In NFLE patients, the robust enhancement of CAP is associated with a balanced enhancement of all phase A subtypes (especially phases A1), but without relevant changes of respective percentages [42]. This feature differs from other sleep disorders with high values of CAP rates, such as OSAS, where an increase of subtypes A2 and A3 and a significant reduction of phase A1, are observed [15, 16].

Antiepileptic medication reduces the amount of objectively recorded seizures and most conventional sleep measures (i.e. REM latency, wake after sleep onset, sleep efficiency) recover normal values [43]. Nevertheless, NREM sleep instability remains pathologically high (CAP rate +26% compared to controls), and is associated with





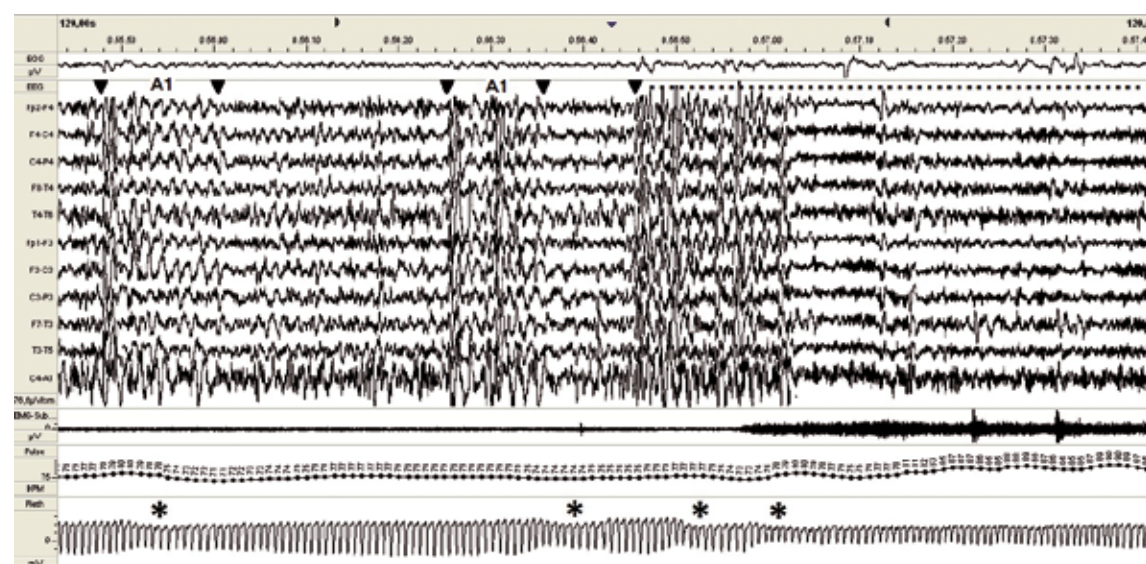
**Figure 5: Vegetative instability during inter-ictal EEG abnormalities in NFLE patient.**

The phase A subtypes delimited by the black triangles. The asterisks show the pulse wave amplitude drops (markers of autonomic activation). Montage, from top to bottom: electrooculogram (EOG); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2–F4, F4–C4, C4–P4, P4–O2, Fp1–F3, F3–C3, C3–P3, P3–O1); chin electromyogram (EMG-Sub); heart rate (pulse); finger photoplethysmogram (Pleth).

persistence of daytime sleepiness. The residual high NREM sleep instability is probably related to the persistence of epileptic discharges that act as internal triggers of subcontinuous arousal fluctuations during NREM sleep [43]. In turn, these arousal swings promote a gait effect on the occurrence of nocturnal motor events, especially in the form of minor motor events that could be

the expression of stereotyped innate motor sequences triggered by arousal facilitation and codified by central pattern generators [70, 71].

In patients with NFLE the electrocardiographic RR interval decreases in the post epochs of all A phases suggesting an involvement of sympathetic pathways. Although the decrease in RR interval signal and the in-



**Figure 6: Paroxysmal arousals arising from cyclic alternating pattern (CAP) in stage NREM3.**

The phase A subtypes delimited by the black triangles. The asterisks show the pulse wave amplitude drops (markers of autonomic activation). The dotted lines indicate the paroxysmal arousal event.

Montage, from top to bottom: electrooculogram (EOG); electroencephalogram (EEG; bipolar EEG derivations using international electrode placement Fp2–F4, F4–C4, C4–P4, P4–O2, Fp2–F8, F8–T4, T4–T6, Fp1–F3, F3–C3, C3–P3, P3–O1, Fp1–F7, F7–T3, T3–T5 and monopolar derivation C4–A1); chin electromyogram (EMG-Sub); heart rate (Pulse); finger photoplethysmogram (Pleth).



crease in LF power during post epochs is more evident during A3 subtypes, all the phase A subtypes present a similar latency of 4 seconds in the minimum of the RR series. These findings suggest that the CAP phenomenon exerts an influence on the autonomic response, which is independent from the type of activation and from the time of sleep.

Analyzing the pulse wave amplitude (PWA) drops as a marker of autonomic activation [27], it can be observed that the persistence of inter-ictal EEG abnormalities, determines a sustained condition of vegetative instability characterized by a periodic activation of the sympathetic tone (Figure 5).

This means that clinical management of NFLE cannot be considered complete and satisfactory whenever intensive EEG paroxysms fuel high amounts of CAP rate.

A recently published article updates the definition of the disorder and establishes new diagnostic criteria. NFLE is now changed into SHE (Sleep-related Hypermotor Epilepsy), reflecting the evidence that the attacks are associated with sleep, that seizures may arise from extra-frontal sites and that the motor features of the seizures are highly characteristic [72]. The paper confirms that an increase of sleep instability is very common in SHE, particularly when multiple events occur in NREM sleep (Figure 6) [40, 42, 69].

## Conclusions

Sleep is not an organ and therefore cannot be touched or physically quantified. We cannot taste, smell or take a picture of sleep because sleep is a function. A daily mandatory activity that reflects the need to rest and allows brain and body to carry out specific and non-negotiable performances.

The rules of sleep architecture demand that all parts of the apartment (brain and body) participate in a democratic interaction and reciprocal support in order to warrant survival in a condition of prolonged unconsciousness.

During CAP, sleep microstructure embraces parallel layers of EEG, motor and autonomic functions in coherent columns of activation (phase A of CAP) and deactivation (phase B of CAP) in a cyclic polyphonic image of arousal instability.

During NCAP, the entire apartment reaches a stable multi-voice configuration both upstairs (brain) and downstairs (body).

This approach overcomes the rigid limitations of conventional stage scoring and provides a more flexible neurophysiological substrate to investigate and shed light upon the brain-body coupling during sleep.

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