Sleep Medicine Reviews 16 (2012) 27–45

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Cyclic alternating pattern (CAP): The marker of sleep instability

Liborio Parrino [a], Raffaele Ferri [b], Oliviero Bruni [c], Mario G. Terzano [a,*]

[a] Sleep Disorders Center, Department of Neurosciences, University of Parma, Italy
[b] Sleep Research Center, Department of Neurology I.C., Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy
[c] Department of Developmental Neurology and Psychiatry, Center for Pediatric Sleep Disorders, Sapienza University, Rome, Italy

ARTICLE INFO

Article history:
Received 8 December 2010
Received in revised form
21 February 2011
Accepted 21 February 2011
Available online 26 May 2011

Keywords:
Sleep
Polysomnography
Arousals
Cyclic alternating pattern
Sleep disorders

SUMMARY

Cyclic alternating pattern CAP is the EEG marker of unstable sleep, a concept which is poorly appreciated among the metrics of sleep physiology. Besides, duration, depth and continuity, sleep restorative properties depend on the capacity of the brain to create periods of sustained stable sleep. This issue is not confined only to the EEG activities but reverberates upon the ongoing autonomic activity and behavioral functions, which are mutually entrained in a synchronized oscillation. CAP can be identified both in adult and children sleep and therefore represents a sensitive tool for the investigation of sleep disorders across the lifespan. The present review illustrates the story of CAP in the last 25 years, the standardized scoring criteria, the basic physiological properties and how the dimension of sleep instability has provided new insight into pathophysiolology and management of sleep disorders.

Introduction

"The cyclic alternating pattern (CAP) as a physiological component of normal NREM sleep" was published in the journal Sleep in 1985.[1] Those were years of growing interest in the diagnosis and treatment of obstructive sleep apnea syndrome (OSAS) that collected most of the energy and financial resources dedicated to the field. In addition, the Rechtschaffen and Kales (R&K) manual[2] was recognized as a consistent and mandatory tool for sleep staging worldwide. Scattered contributions on electroencephalographic (EEG) phasic events had been published but an organized group of experts was still lacking. Riding the CAP wave, a number of European sleep researchers headed by Peter Halasz and Gus Declerck organized a workshop on phasic events during the May 1987 International Congress of Clinical Neurophysiology in Amsterdam. The success of the initiative allowed to include sleep microstructure as a topic of the European Concerted Action on Sleep Analysis and a new workshop was held in 1989 in Salsomaggiore (Italy). The entire set of contributions was published in the Raven Press volume Phasic Events and Dynamic Organization of Sleep edited by Terzano, Halasz and Declerck.[3] In the same year, a workshop on sleep microstructure was included in the official programme of the Founding Congress of the World Federation of Sleep Research Societies held in Cannes, France.[4] The '90s were characterized by an increasing number of papers dedicated to the clinical applications of CAP in periodic limb movements, epileptic disorders, sleep apnea syndrome and insomnia.[5] In particular, the variations of CAP in a model of disturbed sleep using continuous white noise throughout the night in normal sleepers became a standardized procedure not only to understand the pathophysiological bases of insomnia but also as a homogeneous setting for testing and comparing new and old hypnotic agents.[6] However, since 1985 most of the papers on CAP had been published by the discovering Parma group and this was both an advantageous and a limiting factor. A favorable situation because the scoring rules and cultural philosophy of CAP were well defined and established by a restricted number of persons who used the new tool daily in both research and clinical practice. The limitation was related to the fact that the procedure was applied by a restricted number of sleep clinicians. In 2000 the journal Sleep Medicine Reviews published the article "Origin and significance of the cyclic alternating pattern",[7] which has become a referential contribution on the physiological and clinical applications of CAP. In November 2000 an audit was organized in Parma involving a group of North American sleep experts (Ronald Chervin, Sudhansu Chokroverty, Christian Guilleminault, Max Hirshkowitz, Mark Mahowald, Harvey Moldofsky, Robert Thomas, Arthur Walters) to evaluate the physiological bases of CAP and discuss the modalities for a more

* Corresponding author. Centro di Medicina del Sonno, Sezione di Neurologia, Dipartimento di Neuroscienze, Azienda Ospedaliera Universitaria, Via Gramsci 14, 43100 Parma, Italy. Tel.: +39 521 704107; fax: +39 521 702693.
E-mail address: mterzano@unipr.it (M.G. Terzano).

1087-0792/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.smrv.2011.02.003

Abbreviations

AASM	American Academy of Sleep Medicine
CNS	central nervous system
CPAP	continuous positive airway pressure
EEG	electroencephalographic
EMG	electromyographic
FFT	fast Fourier transform
GABA	gamma-aminobutyric acid
GH	growth hormone
IQ	intellectual quotient
NREM	normal rapid eye movement
OSAS	obstructive sleep apnea syndrome
PSG	Polysomnographic
REM	rapid eye movement
SWS	slowwave sleep
UARS	upper airway resistance syndrome
WASO	wake after sleep onset

effective diffusion of the methodology. After a lively three-day debate, full agreement was reached on the preparation of an atlas detailing the technical procedures and the scoring rules of CAP parameters in human sleep. The consensus report was published in the journal Sleep Medicine,[8] reinforcing attention on CAP and encouraging further studies based on the shared criteria. Innovative approaches were exploited, including studies on automatic analysis[9–12] and new actors were involved making CAP investigation a real international interest. After the introduction of the 2007 American Academy of Sleep Medicine (AASM) scoring rules,[13] which simplify excessively sleep staging,[14] the necessity to explore the utility of CAP has become a growing request.[15] The present review updates the physiological significance of CAP, outlines the scoring principles, revisits the clinical domains of application and offers a number of perspective studies which can further implement the use of CAP in both clinical and research frameworks.

CAP in states of reduced vigilance

In clinical practice, CAP was initially considered as an electroencephalographic (EEG) sign of cerebral disturbance associated with a reduced vigilance level. Prolonged cyclic alternation of high-voltage slow waves (phase A) and low-voltage irregular activity (phase B) can be recorded in comatose patients and correlates with the clinical outcome.[16–19] In lighter stages of coma, the A phases are closely related to hyperventilation and increased pulse rate and can be associated with greater muscle activity, restlessness and pressure variations of the cerebrospinal fluid.[20] In contrast, autonomic and muscle activities are attenuated during the B phases. This two-fold behavior indicates that during CAP the comatose patient shifts repeatedly between more aroused (during phase A) and less aroused (during phase B) states that entrain also autonomic and motor functions under a common oscillatory process.[21]

As the clinical condition improves and a normal sleep structure is recovered, the cyclic EEG features are progressively replaced by periodic sequences of K-complexes indicating that CAP is the expression of a basic arousal modulator, which survives in conditions of severely impaired vigilance, but that essentially belongs to physiological sleep.[22]

According to these findings CAP appears as a well-defined marker of cerebral activity occurring under conditions of reduced vigilance (sleep, coma), translating a state of instability and involving muscle, behavioral and autonomic functions. The absence of CAP coincides with a condition of sustained arousal stability and is defined as non-CAP. CAP and non-CAP can be consistently manipulated by sensorial inputs.

Reactivity of CAP

The role of EEG reactivity in comatose patients is highly informative. In deep coma without CAP, responsiveness is abolished even under repetitive and powerful stimulation. In light coma, parts of the arousal system are still functioning and stimulation delivered during the low-voltage period of CAP elicits immediately a high-voltage slow activity, i.e., "réaction paradoxale".[23]

This behavior is observed also in non-rapid eye movement (NREM) sleep. Applying separately the same arousing stimulus during the two EEG components of CAP, phase B is the one that immediately assumes the morphology of the other component, whereas the inverse transformation never occurs when the stimulus is delivered during phase A. This stereotyped reactivity persists throughout the successive phases of CAP with lack of habituation. In contrast, when the same stimulus is presented during non-CAP, the EEG responses are generally brief, hypersynchronized and proceed toward progressive habituation.[24] However, a robust or sustained stimulus delivered during non-CAP induces the immediate appearance of repetitive CAP cycles that display the same morphology and reactive behavior of spontaneous CAP sequences. The evoked CAP sequence may herald a lightening of sleep depth or continue as a damping oscillation before the complete recovery of non-CAP.[25]

The EEG features of CAP

In natural sleep the EEG features of CAP are more complex and polymorphic compared to coma and vary in the different stages. In NREM sleep, CAP appears throughout stages 1–4,[8] where phase A is identified by transient events which clearly stand out from the background rhythm (phase B). Compared to phase B, phase A can be composed of slower higher-voltage rhythms, faster lower voltage rhythms, or by mixed patterns including both. Although EEG patterns of phase A are not strictly stereotyped, they generally include one of the phasic events,[26] which are described in Table 1.

Technical and methodological requirements for scoring a CAP sequence

The identification of CAP should be preceded by the definition of sleep stages according to the conventional criteria.[2,13]

Onset and termination of a CAP sequence

A CAP sequence is composed of a succession of CAP cycles. A CAP cycle is composed of a phase A and the following phase B. All CAP sequences begin with a phase A and end with a phase B. Each phase of CAP is 2–60 s in duration. This cut-off relies on the consideration that the great majority (about 90%) of A phases occurring during sleep are separated by an interval <60 s[24].

Non-CAP

The absence of CAP for >60 s is scored as non-CAP. An isolated phase A (that is, preceded or followed by another phase A but separated by more than 60 s), is classified as non-CAP. The phase A that terminates a CAP sequence is counted as non-CAP.

Minimal criteria for the detection of a CAP sequence

CAP sequences have no upper limits on overall duration and on the number of CAP cycles. In young adults, 2 min and 30 s is the

Table 1
Phasic events, EEG characteristics and neurophysiological significance.

- Intermittent typical pattern of alpha fragmentation during light stage 1: characterized by the intermittent alpha rhythm replacement by low-voltage slow activity in the range of 2–7 Hz. Arousing stimulation applied during the intermittent stretches of alpha dropout leads to immediate return of the alpha rhythm
- Vertex sharp. EEG potential of cuspidate morphology, of 50–200 ms duration, of variable voltage (up to 250 mV), waves with a maximum topographic expression on the central areas, particularly the median region (Cz). It occurs in isolation or repetitively, bilaterally and symmetrically, in stages 1 and 2. From the neurophysiological perspective, they are considered as evoked potentials, like K-complexes, and present similarities with evoked acoustic responses in waking which have their maximum expression on the vertex regions. It is thought that they have an excitatory significance and that they are related to a lowering of the threshold of cortical excitability. They can accompany myoclonic hypnic jerks and, according to some authors, are related to startle reactions
- K-complex. Widespread cortical phenomenon. Spontaneous or evoked arousal response associated with or followed by vasoconstriction, an increase of sympathetic activity and a rise in arterial pressure. A component of stage 2 but also of stages 3 and 4 not present (neither spontaneously nor elicited) in REM sleep.
- K-alpha. Alpha activity 8–12 Hz, 0.5–5 s duration which follows a K-complex, a stronger arousal signal of a non-refreshing sleep
- Delta burst. Of cortical origin, with thalamic (reticular nucleus) influence and modulation. It can be elicited by sensory stimuli (acoustic, tactile, etc.). Arousal significance in synchronization during NREM sleep, prevalently in the slow-wave stages. Often heralds body movements, which emerge from deep sleep (stages 3 and 4). It corresponds to a weak variation of the arousal level (activation) often associated with modest polygraphic variations. It can precede signs of EEG desynchronization (see arousal).
- American Academy of Sleep Medicine (AASM) arousal. Frequency shift to theta, alpha or beta rhythms but not spindles. Longer than 3 s. High level of internal activation. Closely related to strong exogenous or endogenous stimulation. Spontaneous arousals are characterized by an age-related nocturnal increase and by an age-related stability in SWS and in REM sleep
- Arousal with slow-wave synchronization: EEG arousal preceded by K-complexes or delta bursts (Fig. 1).

Abbreviations: NREM - normal rapid eye movement; EEG - electroencephalographic; REM - rapid eye movement; SWS - slowwave sleep.

approximate mean duration of a CAP sequence, which contains an average of 6 CAP cycles.[27] At least two consecutive CAP cycles are required to define a CAP sequence (Fig. 2). Consequently, three or more consecutive A phases must be identified with each of the first two A phases followed by a phase B (interval <60 s) and the last phase A followed by a >60 s non-CAP interval.

General rule

A phase A is scored within a CAP sequence only if it precedes and/or follows another phase A in the 2–60 s temporal range. CAP sequence onset must be preceded by non-CAP (a continuous non-REM sleep EEG pattern for >60 s), with the following three exceptions. There is no temporal limitation: 1) before the first CAP sequence arising in non-REM sleep; 2) after a wake to sleep transition; 3) after a REM to non-REM sleep transition.

Stage shifts

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.[28]

REM sleep

CAP sequences commonly precede the transition from non-REM to rapid eye movement (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 sleep consist mainly of desynchronized patterns (fast low-amplitude rhythms), which are separated by a mean interval of 3–4 min.[29] Consequently, under normal circumstances, CAP does not occur in REM sleep. However, pathophysiologies 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.[30]

Movement artifacts

Body movements can trigger or interrupt a CAP sequence. Body movements linked to one or more A phases in the temporal range of 2–60 s, can be included within the CAP sequence if other scoring criteria are met.[28]

Recording techniques and montages

CAP is a global EEG phenomenon involving extensive cortical areas. Therefore, A phases should be visible on all EEG leads. Bipolar

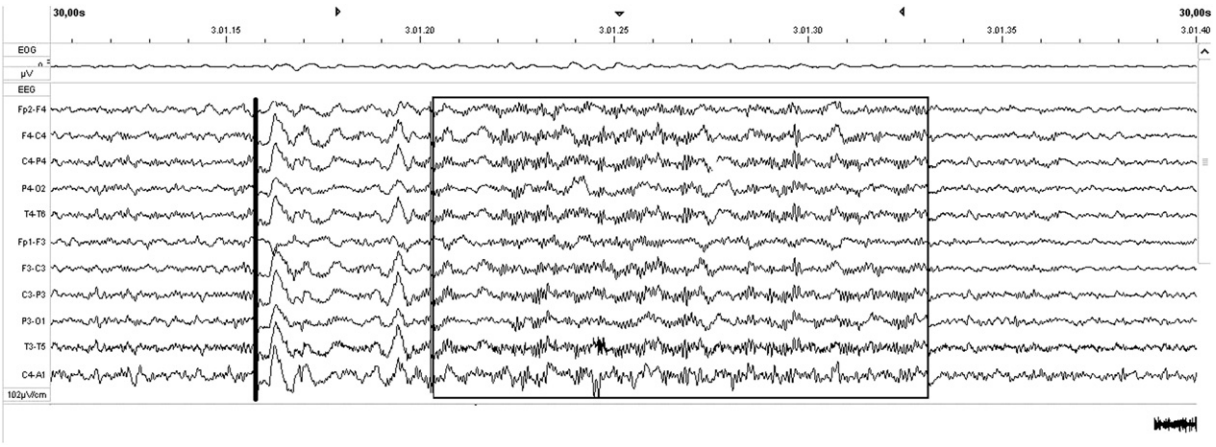

Fig. 1. In the box an EEG arousal during NREM sleep according to the AASM scoring rules. Notice, however, the occurrence of k-complexes (confined between the vertical black line and the box) that herald the onset of the conventional arousal.

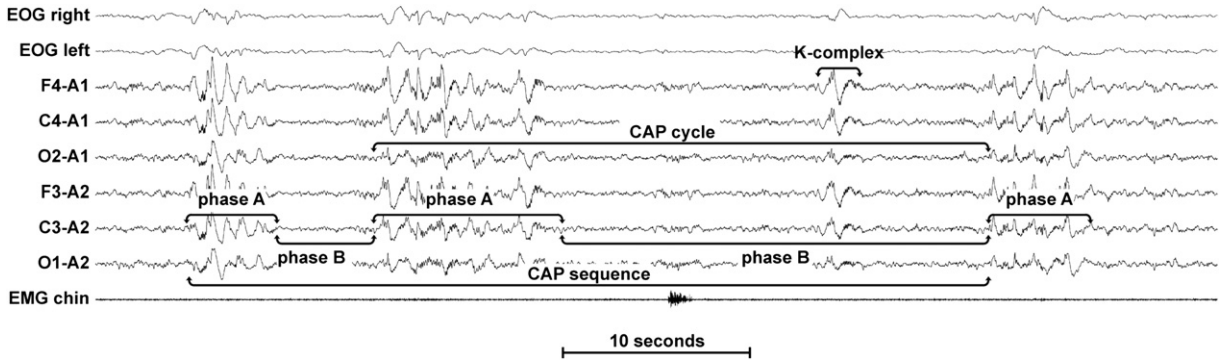

Fig. 2. A CAP cycle is defined as a sequence of 2 alternating stereotyped EEG patterns, each lasting more than 2 and less than 60 s, called phase A and phase B, which are the expression of a sustained fluctuation between "greater arousal" level (phase A: usually 8–12 s) and "lesser arousal" level (phase B: usually 16–25 s). At least 2 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. Note that single K-complexes do not identify a CAP phase A.

derivations such as Fp1–F3, F3–C3, C3–P3, P3–O1 or Fp2–F4, F4–C4, C4–P4, P4–O2 guarantee a favorable detection of the phenomenon. A calibration of 50 mV/7 mm with a time constant of 0.1 s and a high-frequency filter in the 30 Hz range is recommended for the EEG channels. Monopolar EEG derivations (C3–A2 or C4–A1 and O1–A2 or O2–A1), eye movement channels and submentalis electromyographic (EMG), currently used for the conventional sleep staging and arousal scoring, are also essential for scoring CAP. For clinical studies, airflow and respiratory effort, cardiac rhythm, oxygen saturation, and leg movements should be included as part of standard polysomnographic technique.

Amplitude limits

Changes in EEG amplitude are crucial for scoring CAP. Phasic activities initiating a phase A must be a third higher than the background voltage (calculated during the 2 s before onset and 2 s after offset of a phase A). 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. The monopolar derivation is mostly indicated when scoring is carried out on a single derivation. All EEG events which do not meet clearly the phase A characteristics cannot be scored as part of phase A.

Time limits

The minimal duration of a phase A or a phase B is 2 s. If two consecutive A phases 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.

The A phases of CAP

Phase A activities can be classified into three subtypes (Fig. 3). Subtype classification is based on the reciprocal proportion of

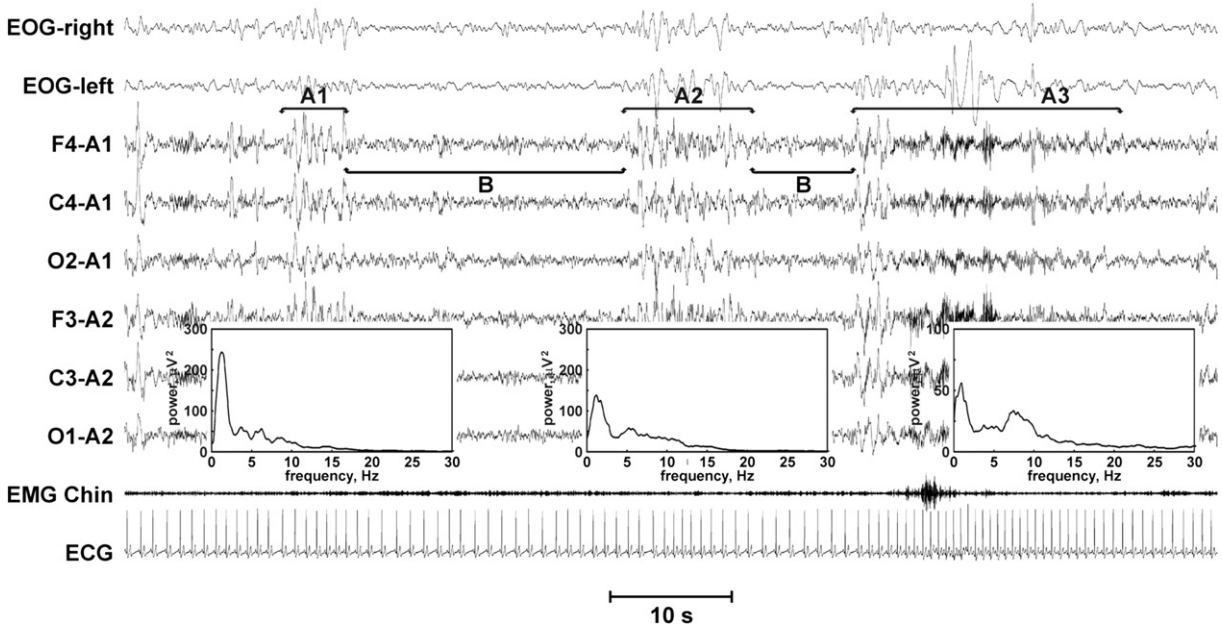

Fig. 3. Short CAP sequence composed by 3 A phases (A1, A2, and A3). Below each A phase, the corresponding power spectrum is shown, computed from the F4-A1 lead. Note the different reciprocal amplitude of the two main frequency components of CAP; on the left, the spectrum of the CAP A1 subtype is dominated by the slow component in the delta frequency range, in the middle, the CAP A2 subtype shows a clearly smaller delta peak with an emergency of a peak in the frequencies above 5 Hz, finally, on the right, the CAP A3 subtype shows a further reduction of the delta peak and a clear peak in the alpha frequency range.

high-voltage slow waves (EEG synchrony) and low-amplitude fast rhythms (EEG desynchrony) throughout the entire phase A duration. The three phase A subtypes are described below.

Subtype A1

EEG synchrony is the predominant activity. If present, EEG desynchrony occupies <20% of the entire phase A duration. Subtype A1 specimens include delta bursts, K-complex sequences, vertex sharp transients, 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 occupied by EEG desynchrony. Subtype A2 specimens include polyphasic bursts with more than 20% but less than 50% of EEG desynchrony.

Subtype A3

The EEG activity is predominantly rapid low-voltage rhythms with >50% of phase A occupied by EEG desynchrony. Subtype A3 specimens include K-alpha, EEG arousals and polyphasic bursts with >50% of EEG desynchrony. A movement artifact within a CAP sequence is also classified as subtype A3.

CAP sequences include different phase A subtypes. The majority of arousals occurring in NREM (87%) are inserted within the CAP sequences, and basically coincide with a phase A2 or A3. In particular, 95% of subtypes A3 and 62% of subtypes A2 meet the AASM criteria for arousals.[31,32] The broad overlap between arousals and subtypes A2 and A3 is further supported by their similar evolution in relation to age and to their positive correlation with the amount of light NREM sleep and negative correlation with the amount of deep NREM sleep.[32]

The concept of cortical, subcortical and autonomic arousal

The conventional definition of arousal includes a cluster of physiologic manifestations expressed by an activation of electrocorticographic rhythms, an increase of blood pressure and muscle tone and a variation of heart rate. During sleep, arousals provide an excitation drive to vital processes whenever respiratory and cardiovascular failure occurs. However, somatosensory and auditory stimulation during sleep may result in cardiac, respiratory and somatic modifications without the EEG features of conventional arousals.[33] This observation implies that there is a range of partial arousal responses with EEG manifestations different from conventional arousals and even without any EEG response. The different arousal responses rely on the different combinations of the central and peripheral components, on the intensity scale of their manifestation, and on the morphological variations of the cortical reactions.[34] Different expressions of arousal can be identified:

1) Behavioral arousal: reported in the R&K manual[2] as movement arousal. Described as any increase in electromyographic activity that is accompanied by a change in any other EEG channel.
2) Cortical arousal: defined by the AASM committee[35] as EEG arousal, it is characterized by transient desynchronized EEG patterns interrupting sleep. It reflects a brief awakening of the cerebral cortex regardless of any concomitant participation of the autonomic system or behavioral components.
3) Subcortical arousal: identified when autonomic activation is associated with a transient EEG pattern different from a conventional AASM arousal.[36–38]

Behavioral arousals and subcortical arousals represent the two extremes of a gradual scale of cerebral activation. However, they are not separated by rigid boundaries. The temporal overlap between cortical, somatomotor and autonomic events within the same arousal episode does not necessarily imply synchrony and the order of activation of the single compartments can vary in the different physiological or pathological circumstances.

In arousal phenomena during sleep there is no mandatory chronological and etiologic subordination. The phenomenon takes place within interactive loops in which the cerebral cortex can be the starting or the ending point but anyway a source of control. The origin of arousal should be defined by the subsystem primarily activated or perturbed. The arousal can be generated directly by the cortex under the impulse of the physiologic evolution of sleep, e.g., the transition from NREM to REM sleep, or in response to a sensorial perturbation, such as respiratory interruption, noisy environment, alteration of blood pressure or heart rate, or a movement. In any case, it is the involvement of the brain that makes arousal a unitary phenomenon[39] in which activation is modulated through a hierarchy of phasic responses ranging from slow high-amplitude EEG patterns (CAP subtypes A1) to fast low-voltage (CAP subtypes A3).

CAP and the gating mechanisms of sleep

If the AASM arousal is a sign of transient sleep discontinuity, the finding of phasic EEG delta activities during enhancement of autonomic functions indicates the possibility of physiological activation without sleep disruption. In effect, non-visible sleep fragmentation induced by acoustic tones has been seen to be associated with increased daytime sleepiness, indicating that the processes of sleep consolidation may be impaired – in this case by sensorial stimulation – without evidence of sleep discontinuity.[40] In other words, slow EEG events (K-complexes and delta bursts) and AASM arousals (fast rhythms) share functional properties, and, despite their EEG differences, they may be included within the comprehensive term of activating complexes. Such a variety of EEG manifestations relies on specific gates which control the flow of internal and external inputs. The thalamic-basal forebrain gate is an ultimate step of resistance against arousing impulses. Initially the cortex tries to preserve sleep continuity with reinforcement of its gates that are indicated by the occurrence of K-complexes and delta bursts in the sleep EEG. However, when the thalamic gate cannot control the afferent inputs a cortical change is seen translated by an alpha mixed or an alpha/beta frequency burst.[41] Anyway, the initial reaction of the cerebral cortex is a sleep-protective response as the majority of transient rapid activities are preceded by a slow high-amplitude EEG burst.[42]

Power spectral analysis of CAP shows that the different phase A subtypes in NREM sleep are variants of a continuous two-fold process: an initial high-voltage slow-wave component, which predisposes the cerebral cortex to a greater readiness and opens the way to the more rapid activity, correlated with strong activating effects.[43,44]

What distinguishes the single arousal event is the build-up and reciprocal distribution of the EEG components. In the A1 phases of CAP, which host exclusively K-complexes and equivalent slow-wave activities (vertex potentials and delta bursts), the starting delta power increase is maintained and prevails throughout the entire activation process. A balanced representation of slow and fast EEG frequency bands is the main characteristic of the A2 phases, while rapid EEG activities are the dominant feature of the A3 subtypes and of arousals. This does not mean that all activating complexes exert equivalent effects on sleep structure and on autonomic functions. A hierarchical activation from the slower EEG patterns (moderate autonomic activation without sleep

disruption) to the faster EEG patterns (robust autonomic activation associated with visible sleep fragmentation) has been described in different studies.[38,45–48]

CAP and the <1 Hz oscillation

Besides CAP, the other major EEG activity in the frequency range below 1 Hz is the so-called slow oscillation.[49] This 0.5–0.9 Hz EEG rhythm, which characterizes states of reduced tonic arousal, was outlined during anesthesia and NREM sleep in both animals (cats and rats) and human subjects. The slow oscillation is generated in cortical neurons, and consists of phases of depolarization, characterized by intensive neural firing, followed by long-lasting hyperpolarization. Hence the two phases of the slow oscillation are characterized by opposite neural phenomena: cortical excitation made up of synaptic potentials and cortical inhibition mainly due to disfacilitation in the network. The excitatory component of the slow oscillation is effective in grouping the K-complexes and delta waves, which do not occur in isolation but are grouped into complex wave sequences. The coalescence of slow rhythms is especially visible during NREM sleep. In particular, during slow wave sleep (SWS) high-voltage slow waves rarely appear as isolated features, but in most cases they converge into collectives resulting in the phase A1 subtypes of CAP. The main frequency of slow oscillation occurrence during deep sleep is 0.8 Hz.[50] Accordingly, the mean interval between K-complexes and delta waves within A1 phases hosting large portions of EEG synchronization actually ranges between 0.8 Hz and 0.9 Hz.

As NREM sleep progresses from stage 1 to stage 4, the differences in morphology and voltage between phase A (clusters of K-complexes and delta bursts) and the successive phase B (sleep stage background) become gradually less evident until the EEG is dominated by the uniform pattern of non-CAP[9] with the high-amplitude slow waves recurring in the frequency range of the <1 Hz oscillation. Neurophysiological investigation has ascertained that the slow cortical oscillation (<1 Hz) is absent at sleep onset but begins to organize in small territories, thereafter recruiting larger ones through coupling mechanisms as sleep deepens. Consolidated SWS is characterized by a sustained <1 Hz oscillation,[51] which reflects a stable non-CAP condition.

CAP and the structure of sleep

Sleep architecture is based on the cyclic alternation of two major neurophysiological states: NREM and REM sleep. NREM sleep is composed of three[13] or four[2] stages in which EEG synchrony grows with the increasing depth of sleep. In contrast, EEG desynchrony is the dominant feature of REM sleep. The alternation of NREM and REM sleep constitutes the sleep cycle and its recurrence during the night determines the classical stepwise sleep profile (macrostructure). The NREM portion of the sleep cycle starts with a slow descending branch sloping from the more superficial to the deeper NREM stages, continues with a central trough that represents the deepest stages of the sleep cycle, and ends with a rapid reverse ascending branch, expressed by the more superficial NREM stages that precede REM sleep. Accordingly, the NREM sleep architecture delineates a continuous pattern of build-up (descending branch), maintenance (trough) and resolution (ascending branch) of EEG synchrony. A detailed investigation has ascertained that the spontaneous EEG fluctuations centered on the 20–40 s periodicity of CAP are implicated in the subtle mechanisms that regulate the production and attenuation of slow-wave activities during sleep.[52] In particular, there is evidence that the different components of CAP have a sculpturing effect on the profile of the sleep cycle.[53] Comparing spectral assessment and EEG visual scoring of NREM sleep in normal healthy subjects, 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.[9] The regular EEG oscillations that accompany the transition from light sleep to deep stable sleep are basically expressed by the A1 subtypes. 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 subtypes A1, while 64% of the A phases identified in the ascending branches are subtypes A2 (45%) or A3 (19%). These findings indicate that both slow and rapid EEG activating complexes are involved in the structural organization of sleep.[53] In particular, the build-up and maintenance of deep sleep is achieved through a process of periodic EEG instability accompanied by mild neuroautonomic swings that accompany the downward shift from wakefulness. In contrast, the breakdown of SWS and the introduction of REM sleep are mostly associated with desynchronized EEG patterns and powerful activation of muscle and autonomic functions. The abundance of A1 subtypes in the descending branches and troughs can be the EEG expression of the cerebral mechanisms involved in the REM-off activity, while the predominance of subtypes A2 and A3 (and arousals) in the ascending branches reflects the REM-on drive. Therefore, besides their manifold EEG features, activating complexes are also characterized by a non-random distribution across the night, which assumes a clear-cut periodicity during NREM sleep within the framework of CAP.[24] For this reason CAP is considered as the main expression of sleep microstructure.

The dynamical organization of the EEG during CAP

The dynamical complex organization of the EEG signal structure has been the focus of a number of papers in the past which have shown a decrease in correlation dimension (D_2) as sleep moves toward slow-wave stages. The nonlinear structure of the sleep EEG has mostly been investigated by means of the widely known algorithm by Grassberger and Procaccia.[54] This approach assumes stationarity of data and needs relatively large time series in order to provide reliable results.[55] It appears rather difficult to satisfy these criteria for at least a large proportion of the sleep EEG which contains a great amount of nonstationarities, such as sleep spindles, K-complexes, vertex waves, short-lasting arousals, etc. However, CAP includes all of these transient events and accordingly, the nonlinear aspects of sleep EEG have been re-evaluated taking into account the peculiar organization of these phasic events. In particular, the dynamical properties of the EEG were assessed by means of the Nonlinear Cross Prediction Test (NLCP) test, introduced by Stam et al.[56] This test uses 3 different "model" time series in order to predict nonlinearly the original data set.

Based on the results of this analysis, Ferri et al.[57] concluded that sleep might be considered as a dynamically evolving sequence of different high/low-dimensional states of the EEG, which can be tracked by detecting nonlinearity mostly in correspondence with CAP sequences. CAP might be considered as a state with short periods of low-dimensional nonlinearity which interrupt a baseline EEG not distinguishable from high-dimensional noise (non-CAP). The decrease in dimensionality of the EEG structure, especially evident during the A1 CAP subtypes, indicates a decreased complexity which can be reached by means of an increased brain synchronization. Thus, the dynamics of spatial synchronization of the slow-wave activity recorded from different scalp electrodes during sleep in healthy normal controls were investigated. The different levels of EEG synchronization during sleep (in the

0.25–2.5 Hz band) were characterized by means of the synchronization likelihood (SL) algorithm and its long-range temporal correlations were analyzed by means of the detrended fluctuation analysis (DFA). Higher levels of interregional synchronization during CAP sleep than during non-CAP were found with a small but significant difference between the A and B phases. SL during CAP showed fluctuations probably corresponding to the single EEG slow-wave elements. DFA indicated the presence of significant long-range time connections in the EEG time series with period 1.5–24.0 s. All these results indicate a different role for each CAP condition in the EEG synchronization processes of sleep which show a complex time structure correlated with its neurophysiological mechanisms. Moreover, very slow oscillations in spatial EEG synchronization might play a critical role in the long-range temporal EEG correlations during sleep which might be the chain of events responsible for the maintenance and correct complex development of sleep structure during the night.

The different EEG frequency components of CAP, however, are not uniformly distributed over the scalp. First of all, two main different frequency bands can be detected, characterizing CAP subtypes A1 (0.25–2.5 Hz) and A3 (7–12 Hz); these 2 components coexist in CAP A2 subtypes.[58,59] The topography of these two components also shows a clear prevalence over the anterior frontal regions for the 0.25–2.5 Hz band and over the parietal–occipital areas for the 7–12 Hz band. The use of the low resolution brain electromagnetic tomography (LORETA) functional imaging also allows us to indicate that the generators of the low-frequency component of CAP seems to be localized mostly over the frontal midline cortex. In contrast, those of the high-frequency band involve both midline and hemispheric areas within the parietal and occipital areas. Finally, the non-random association between the two different frequency components of CAP, the generators of which are located in clearly separate structures, seem to indicate that these areas might be in functional intercoupling allowing them to organize the occurrence of the two different frequency components of CAP in a coordinated way. This intercoupling is likely to be subserved by long-range longitudinal intrahemispheric pathways, such as the superior longitudinal (arcuate) fasciculus and the uncinate and fronto-occipital fasciculi that constitute the longitudinal association fiber system that connects each frontal lobe with its respective hemisphere.

To analyze in detail the regional coupling of different brain areas during CAP the levels of EEG synchronization, in the 0.25–2.5 Hz band, during the A1 subtypes of CAP in healthy subjects were analyzed by means of the SL algorithm. SL was averaged for 7 electrode pairs (F4–F3, C4–C3, P4–P3 for the analysis of interhemispheric SL and F4–C4, C4–P4, F3–C3, and C3–P3, for the analysis of intrahemispheric SL). During the A1 CAP subtypes, SL tended to be highest between pairs of electrodes situated over different hemispheres; in particular, SL obtained from F4–F3 was the highest, followed by that of P4–P3. These results indicate that during the sleep A1 CAP subtypes the transient high level of synchronization in the slow-wave EEG range is a phenomenon involving mostly the anterior parts of the brain and is probably based on interhemispheric interactions, possibly mediated by transcallosal connections. Thus, CAP events imply the involvement of a complex pattern of synchronization/desynchonization including both longitudinal intrahemispheric pathways and transversal interhemispheric connections.

In order to explore the large-scale integration, Ferri et al.[60,61] analyzed the functional connectivity patterns of the different EEG frequency bands during the different sleep stages and CAP conditions, using concepts derived from Graph Theory. A graph is a basic representation of a network, which is essentially reduced to nodes (vertices) and connections (edges). In our case, each recording electrode can be seen as a node. Graphs are characterized by a cluster coefficient (Cp) and a characteristic path length (Lp). Cp is a measure of the local interconnectedness of the graph, whereas Lp is an indicator of its overall connectedness. In 1998, Watts and Strogatz[62] showed that graphs with many local connections and a few random long distance connections are characterized by a high cluster coefficient (like ordered networks) and a short path length (like random networks); such near-optimal networks, which are intermediate between ordered and random networks, are designated as "small-world" networks. Since then, many types of real networks have been shown to have small-world features.[63,64]

In 2007, Ferri et al.[60] focused their attention on the slow-wave EEG activity only and reported that Cp increased significantly from wakefulness to sleep while Lp did not show changes. Cp was higher for A1 phases, compared to B phases of CAP. Thus, the network organization of the EEG slow-wave synchronization during sleep seems to show features characteristic of small-world networks (high Cp combined with low Lp); this type of organization is slightly but significantly more evident during the CAP A1 subtypes. In a second study, Ferri et al.[61] included in their analysis additional EEG frequency bands and found values of Cp and Lp compatible with a small-world network organization in all sleep stages and for all EEG bands. All bands below 15 Hz showed an increase of these features during sleep (and during CAP A phases in particular), compared to wakefulness, confirming the initial hypothesis that during sleep there is a clear trend for the functional connectivity of the EEG to move forward to an organization more similar to that of a small-world network (at least for the frequency bands lower than 15 Hz). Sleep network "reconfiguration" might be one of the key mechanisms for the understanding of the "global" and "local" neural plasticity taking place during sleep, with an important role for CAP.

The measures of CAP: ontogenetic aspects

EEG features are highly sensitive markers of brain development. Accordingly, sleep reflects the physiological changes that accompany the different ages of the lifespan. In particular, SWS dominates in the younger decades in contrast to superficial NREM sleep which increases with the aging process. As well as conventional measures, CAP parameters (Table 2) undergo dynamic changes across the maturational phases of life. The age-related values of CAP have been measured and defined in order to establish the physiological ranges of normal sleep.

CAP rate

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.[65]

CAP rate shows a complex evolution during development (Table 3). It is very low in the first months and then shows a gradual

Table 2
The main measures of CAP.

CAP time: the total duration of all CAP sequences
CAP rate: the percentage ratio of CAP time to total NREM sleep time
Phase A1 index: the number of phase A1 subtypes per hour of sleep
Phase A2 index: the number of phase A2 subtypes per hour of sleep
Phase A3 index: the number of phase A3 subtypes per hour of sleep

Table 3
Age-related changes of the main CAP parameters during development.

Age	CAP rate%	A1%	A2%	A3%	A1 index	A2 Index	A3 Index
1–4 months	12.9	85.2	10.3	4.4	19.8	2.8	0.5
Pre-school-age	25.9	63.2	21.5	15.3	24.8	6.5	4
School-age	33.4	84.4	6.4	9.1	39.5	2.7	3.3
Peripubertal	62.1	85.5	9.1	3.2	–	–	–
Adolescence	43.4	71.3	19.7	9.0	45	12.4	5.7
Young adults	31.9	61.4	27.9	10.7	25.5	11.6	4.4
Middle age	37.5	62.0	26.2	11.8	33.3	14.1	6.4
Elderly	55.3	46.6	35.3	18.1	30.0	22.7	11.6

increase with a peak in adolescence, then a gradual decrease in adulthood followed by an increase in the elderly.[66–70]

The similarities between CAP and EEG tracé alternant (TA) described in quiet sleep of neonates have suggested overlapping mechanisms. The data obtained from 3 to 4-month-old infants indicate that the TA is not a precursor of CAP in newborns.[70,71] TA usually disappears between 3 and 4 weeks after birth and the emergence of the first transient EEG activities, such as sleep spindles, lead to the build-up of the NREM sleep.[72,73] Soon after, the appearance of K-complexes and delta bursts allows to define slow-wave sleep (SWS) at 4–4.5 months post-term.[73]

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 (different from that of TA), representing the first prototype of CAP, appears at 46–55 weeks conceptional age. CAP rate in infants of 3–4 months of age increases from 6.83 ± 3.58% to 12.9 ± 2.21%, depending on the level of maturation of sleep patterns. Normative data on CAP for the age range between 12 and 24 months have been recently measured.[74]

Starting at 3 years of age, there is a gradual increase of CAP rate which peaks at the peripubertal age and then decreases to the lowest values of young adults (25.9% in pre-school children aged 3–6 years and 33.4% in school children aged 6–10 years; 62.1% in peripubertal children aged 8–12 years; 43.4% in teenagers; 31.9% in young adults: 37.5% in middle aged and 55.3% in elderly).

These age-related changes of CAP rate reflect the biological growth processes that accompany the preparation and onset of adolescence, the maturational consolidation of development and finally the process of senescence that increases the instability of sleep (Fig. 4).

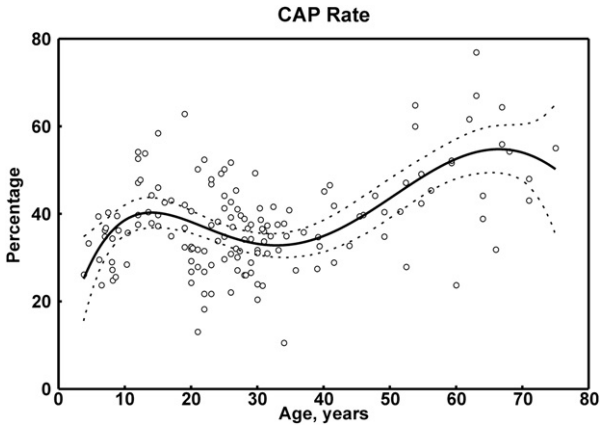

Fig. 4. Age-related modifications of CAP rate along the normal life span. Notice the bimodal distribution with two peaks during adolescence and senescence, respectively.

A phases

The percentage of A1 subtypes shows a bell-shaped course from infants (69.7%) to pre-school (63.2%), school children (84.4%), peripubertal children (85.5%) and in teenagers (71.3%). The percentage of A1 subtypes tends to slightly decrease between 30 and 60 years (young adults: 61.4%; middle age 62.0%) and then declines after the age of 60 (46.6%). In contrast, subtypes A2 and A3 undergo a linear increase from infants, pre-school children to the old age, similar to the arousal evolution across the life span.[66,75] The age-related percentages of the phase A subtypes are detailed in Fig. 5.

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) can be considered as the "gold standard" for sleep quality[76] because of its length, continuity and restorative features. On the other hand the increase of the percentage of A2 in pre-schoolers might represent the higher sleep instability of this age period.

In school-aged children, the increased values of CAP rate during SWS 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.[67,68,77]

CAP cycles

The number of CAP cycles tends to vary during development following the value of CAP rate. In pre-school children the mean number of CAP cycles is 320, in school children 363, in peripubertal 567, in adolescents 366 and in adults ranges between 233 (20–39 years of age) and 343 (>60 years of age).

The mean duration of CAP cycles is somewhat stable during development, with a dominant phase B portion (65%–80% of the entire CAP cycle length). In infants, the CAP cycle mean duration is approximately 30 s, in pre-school children 32.4 s; in school children 30.5 s, in adolescents 25.2 s, in young adults 28 s and in elderly 31 s. The very similar length of CAP cycles indicates the steadiness of CAP oscillation across the lifespan.[27]

Time structure of CAP

The time structure of CAP has been evaluated by plotting the statistical distribution of intervals between the onset of consecutive A phases.[78] Analysis of the A1 interval distribution shows a clear-cut periodicity, with a peak for intervals of about 25 s, while no clear peak emerges for CAP subtypes A2 and A3 phases. Periodicity and time interval distribution of A1 subtypes are similar in different ages, indicating that the periodicity of CAP components can be considered very stable throughout development.

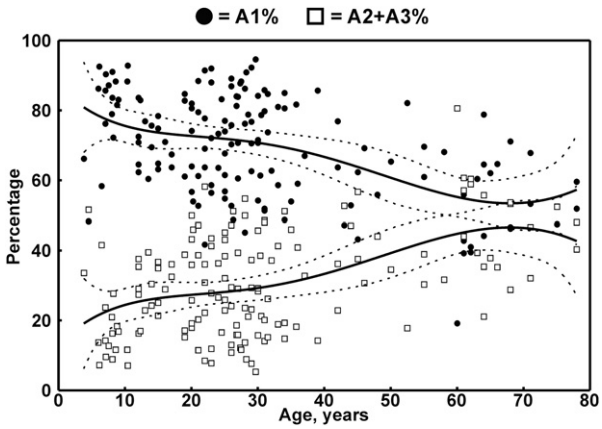

Fig. 5. Normative age-related changes of phase A subtypes. The percentages of subtypes A1 tend to decrease along the lifespan mirrored by the reciprocal increase of subtypes A2 and A3. The opposite trends converge approximately at the age of 60 years.

Clinical applications of CAP

CAP as a marker of non-restorative sleep

There is a great body of evidence that sleep fragmentation – punctuation of sleep with frequent, brief arousals – reduces its restorative properties. This statement is valid even when arousals do not alter the standard 30-s epoch sleep stage scoring. Correlation between the number of arousals and daytime sleepiness in OSAS patients has been reported, but phasic delta activities during sleep (with diurnal consequences) can also exert activating effects. Airway opening may occur in upper airway resistance syndrome (UARS) subjects with a predominant increase in delta power.[79] In other words, reopening of the airway at wakefulness and disappearance of abnormal UARS are not necessarily associated with an arousal. Termination of respiratory events induced by an EEG pattern of delta waves has been also observed in OSAS patients.[33] Involvement of either slow or fast EEG responses depends on the regulation of upper airway patency. Respiratory patterns that need correction activate the central nervous system (CNS). This activation varies, depending on the sensory recruitment and the adequacy of the response. A respiratory challenge can be resolved by CNS activation without involving a cortical arousal. The latter is triggered only when thalamo-cortical structures fail to modulate breathing or when ascending reticular volleys are required to restore respiration. According to the amount of recruitment and numbers of neural structures involved, the CNS activation will be variable. The autonomic nervous system is enhanced when an arousal occurs, which explains the greater increase in heart rate with EEG arousal than without EEG arousal.[80] Anyway, the problem is quantitative not qualitative in the sense that also delta bursts can determine heart rate acceleration and autonomic activation. Generally, the slow and the fast components of EEG activation have different latencies, with the delta portion preceding the rapid activities. This probably determines a graduated impact on the autonomic system. The slow waves determine a softer autonomic reaction, which in certain pathological conditions may be strong enough to overcome a disturbing factor, e.g., an obstructive event. Otherwise, the slow rhythms are immediately replaced by faster EEG activities, which guarantee a more powerful activation of autonomic functions. Probably the effects on daytime function are not linked to a single phase A subtype but to the reciprocal amount and distribution of the single subtypes (Tables 4 and 5). In severe OSAS, CAP analysis shows increased values of CAP rate accompanied by enhanced percentages of subtypes A3 and reduced percentages of subtypes A1. When OSAS patients 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 recovery of the A1 percentage.[81] In primary insomnia, high values of CAP rate are associated with a higher arousal index and increased percentages of all phase A subtypes. Compared to placebo active medication significantly reduces CAP rate, subtypes A1 and A2, but exerts only marginal effects on subtypes A3 and on EEG arousals.[82]

Table 4
Changes of the main CAP parameters (vs. age-matched normal controls) in the different pathologies studied in children and adolescence.

	CAP rate%	A1%	A2%	A3%	A1 index	A2 Index	A3 Index
Autism	=	↓	↑	↑	↓	=	↑
Down syndrome	=	↓	↑	↑	=	–	–
FraX syndrome	↓	↓	↑	↑	↓	–	–
Prader–Willi syndrome	↓	↑	↓	↓	↓	↓	↓
Dyslexia	=	=	↑	=	=	↑	=
Asperger syndrome	↓	↑	↓	=	↓	↓	↓
OSAS	↓	↓	=	=	↓	=	=
ADHD	↓	=	=	=	↓	=	=
Sleep terror	↑	=	=	=	↑	=	=
BERS	↓	=	=	↑	↓	↓	=
Narcolepsy	↓	=	=	↓	↓	↓	=

FraX = Fragile-X; ADHD = Attention deficit hyperactivity disorder; OSAS = Obstructive sleep apnea syndrome; BERS = benign epilepsy with rolandic spikes.

Table 5
Changes of the main CAP parameters (vs. age-matched normal controls) in the different pathologies studied in adults.

	CAP rate%	A1%	A2%	A3%
Noise	↑	↑	↑	↑
Narcolepsy	↓	↓	↑	=
OSAS	↑	↓	=	↑
UARS	↑			
Insomnia	↑	↑	↑	↑
Hypnotics (vs. placebo)	↓	↓	↓	=/↓
First night effect[162]	↑	↓	↑	↑
PLM	↑	↓	↑	↑
Bruxism	=	↓	↑	↑
NFLE	↑	↑	↑	↑
PGE	↑	↑	↑	↓
Depression	↑	↑	↑	↑
Eating disorders	↑	–	–	–
MSA	↓	–	–	–

OSAS: obstructive sleep apnea syndrome. UARS: upper airway resistance syndrome. PLM: periodic limb movements. RLS: restless legs syndrome, NFLE: nocturnal frontal lobe epilepsy. PGE: primary generalized epilepsy. MSA: multiple system atrophy.

CAP and sleep disorders in adults

The cyclic oscillations of CAP are physiological components of the sleep structure[1] in which they act as dynamic segments, pacing the state transition between different NREM sleep stages according to homeostatic and ultradian processes.[83] However, CAP sequences can occur also in response to external stimuli of different sensorial modality (tactile, thermal, acoustic, painful, etc.). Accordingly, the amount of CAP increases when sleep is achieved under conditions of noise stimulation,[25] or in situations of sleep disruption, such as insomnia,[84,85] depression,[86] eating disorders,[87] upper airway resistance syndrome,[88] sleep apnea syndrome,[30] periodic limb movements,[89] nocturnal frontal lobe epilepsy,[39,90–92] primary generalized,[93] and focal lesional epilepsy,[94] Prader–Willi syndrome in adults,[95] while it is lowered by sleep-promoting conditions such as narcolepsy,[96,97] multiple system atrophy,[98] drug administration,[6,82,84,85,99] CPAP treatment in obstructive sleep apnea,[81,100] and night-time recovery sleep after prolonged sleep deprivation.[101] An overview of CAP rate variations in sleep disorders is detailed in Tables 4 and 5.

CAP is not only influenced by sleep disorders but, in turn, modulates the occurrence and distribution of sleep-related events. In particular, the phase A of CAP triggers and paces the allocation of bruxism,[102,103] sleepwalking,[104,105] epileptic events,[106–108] periodic limb jerks,[89] and rhythmic movements during NREM sleep.[109] In contrast, the phase B of CAP is closely related to the repetitive respiratory events of sleep disordered breathing, and only the powerful autonomic activation during the following CAP-A phase can restore post-apnea breathing[30]. Like an alternatively opening (phase A) and closing (phase B) gate, CAP phases act as periodic permissive windows in NREM sleep. These findings indicate that both spontaneous and elicited phasic arousals have a cyclic nature following the multisecond oscillation. As a translation of fluctuating arousal, CAP offers a favorable background for phasic and/or repetitive sleep-related manifestations, i.e., periodic limb movements (Fig. 6), epileptic seizures (Fig. 7), obstructive (Fig. 8) and central sleep apneas (Fig. 9), which are related to a condition of

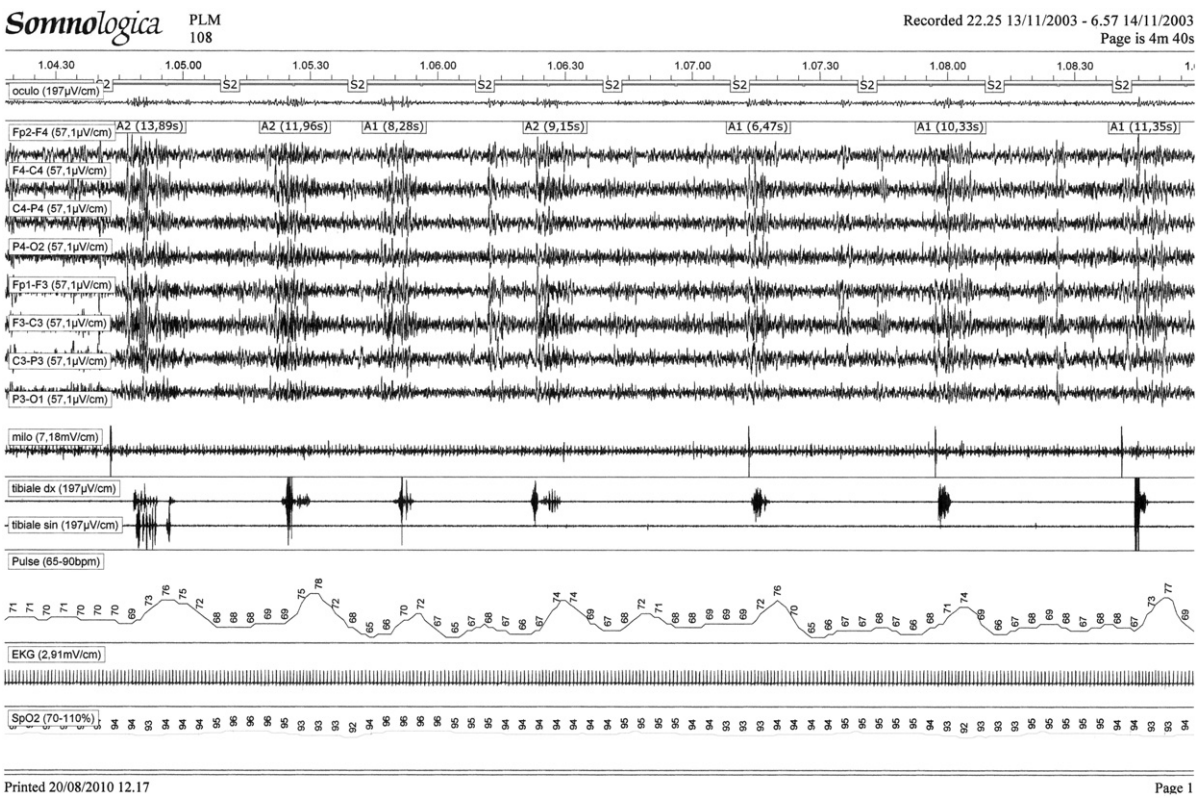

Fig. 6. Specimen of stage 2 sleep with a CAP sequence modulating a series of periodic leg jerks. Notice the concomitant occurrence between the CAP A phases and the limb movements, accompanied by a simultaneous increase of heart rate.

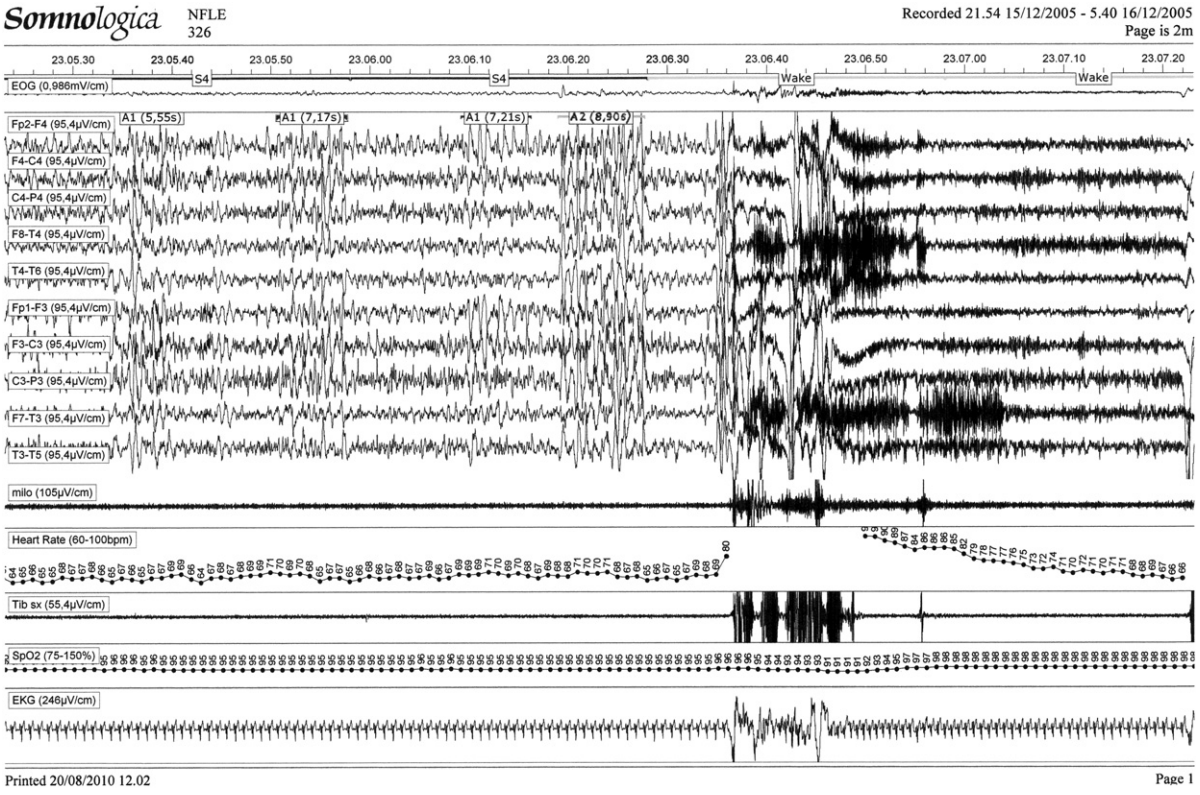

Fig. 7. A paroxysmal arousal in NREM sleep (right side of the recording) preceded by a CAP sequence in a patient with nocturnal frontal lobe epilepsy.

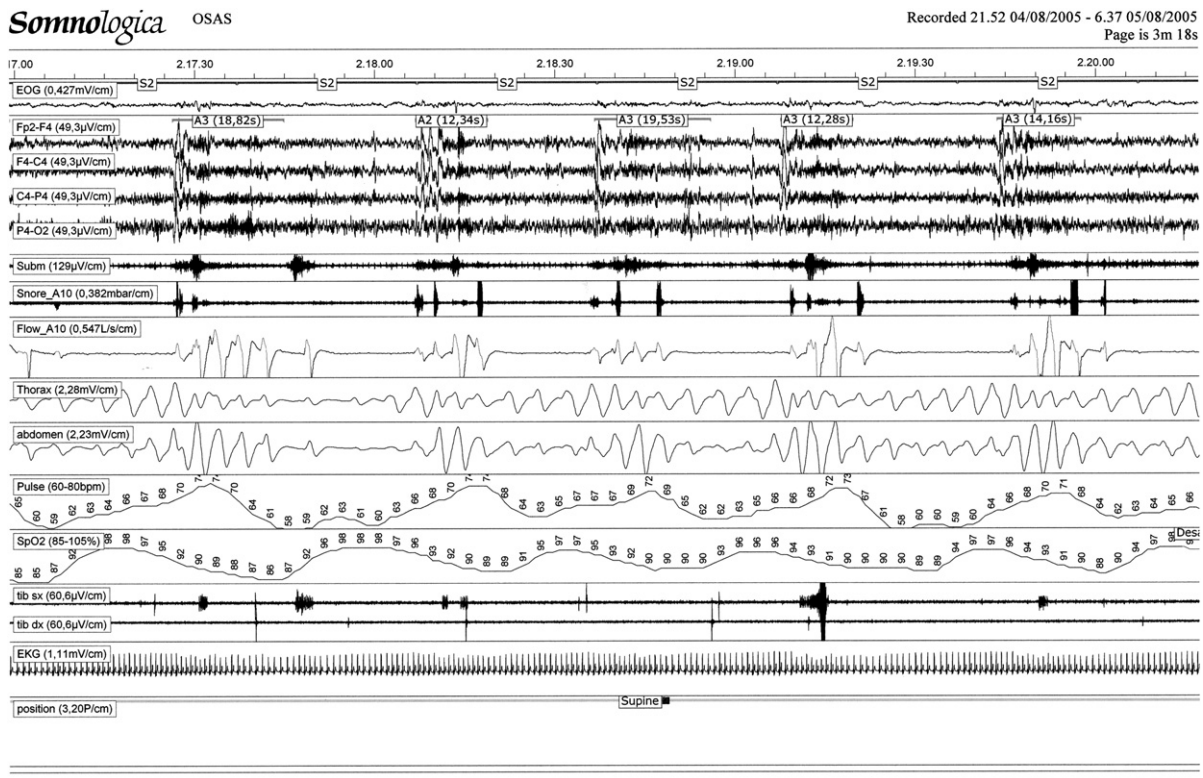

Fig. 8. A CAP sequence induced by repetitive obstructive sleep apneas. The respiratory events appear during the B phases of CAP, while the A phases coincide with the recovery of effective breathing, heart rate acceleration and limb jerks.

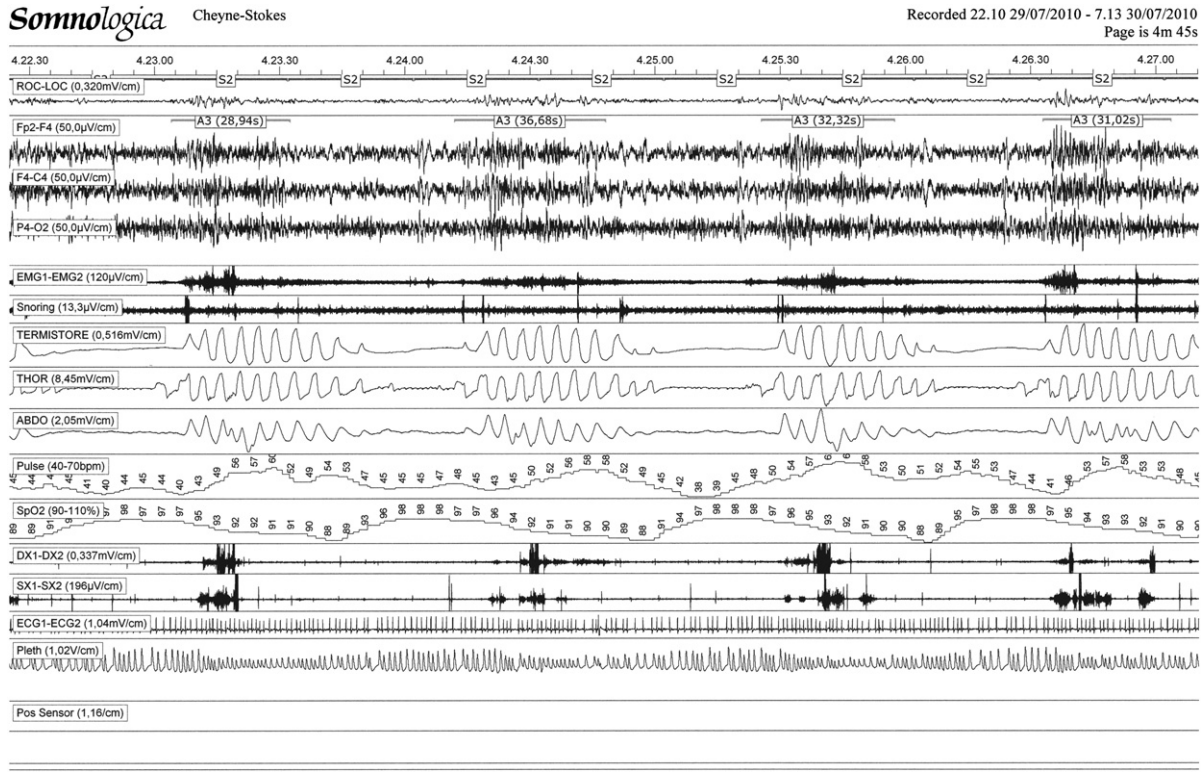

Fig. 9. A CAP sequence associated with central sleep apneas in a patient with atrial fibrillation. Compared to obstructive events the A phases of CAP show a longer length and are not triggered by mechanoceptor stimulation. Still myoclonic manifestations and heart rate rise accompany the hyperventilation pattern driven by the CAP A phases.

unstable sleep during which CAP cycles play a promoting (phase A) or an inhibitory (phase B) gating action on the single EEG, behavioral and autonomic events. Accordingly, a number of sleep disorders can be classified pathophysiologically on the basis of their relationship with CAP and non-CAP. In particular, PLM, sleep bruxism and epileptic manifestations can be considered as phase A-related disorders, while sleep apneas are a typical expression of a phase B related disturbance.

The role of CAP in primary insomnia

Primary insomnia appears to be the exaggeration of a physiological rhythm ordinarily involved in the sleep process. Previous studies have ascertained that acoustic stimuli enhance the physiological amount of CAP rate and determine poor sleep and daytime dysfunction even without an increase of sleep fragmentation. In this perspective, CAP operates as a 'double-edged sword'. While limited quantities of CAP mediate physiological effects, larger quantities reflect the brain difficulties to consolidate and preserve sleep and therefore may be associated with detrimental consequences. Because primary insomnia is not supported by any other sleep, medical, psychiatric or substance-induced problem there is no evidence of an organ disorder. In any case, whatever the nature of disturbance, the outcome is the amplification of an otherwise physiological process. Polysomnographic (PSG) investigation based on an extensive sample of Caucasian patients affected by primary insomnia have demonstrated that CAP parameters reflect consistently the reduced quality of sleep in insomnia complainers and can substantiate the efficacy of hypnotic medication.[82] Discriminant analysis indicates that CAP rate is the most sensitive sleep measure of effective drug treatment, while correlation analysis shows that CAP rate is the PSG parameter that better reflects subjective sleep quality.[110] Similar findings have been confirmed in non-Caucasian subjects. In Japanese patients with psychophysiological insomnia, a randomized crossover comparative study with placebo showed that hypnotic treatment (zolpidem) increased sleep stability by significantly improving the overnight CAP rate as well as subjective sleep quality.[111]

CAP parameters are also useful tools to monitor the effects of intermittent hypnotic treatment. In a double-blind study carried out on adults with primary sleep maintenance insomnia longer than 1 month, PSG measures and perception of sleep quality were assessed at baseline and during the following 6 consecutive nights of alternating treatment with zolpidem (10 mg) or placebo. Compared to baseline values, CAP rate, CAP time, subtype A2, and AI were significantly reduced with zolpidem treatment and correlated with sleep quality, whereas with placebo they did not rebound above baseline.[112]

An intriguing aspect of insomnia is the established finding that people with this disorder often overestimate the time they take to get to sleep and underestimate the total amount of time they actually sleep. To investigate this mismatching phenomenon, a PSG study was carried out in 20 patients with a diagnosis of sleep state misperception or paradoxical insomnia.[113] Recruitment of misperceptors without coexisting neurological, medical or psychiatric disorders was based on objective total sleep time (TST) of at least 6.5 h, objective sleep latency shorter than 30 min, underestimated difference between objective and subjective TST of at least 120 min and subjective estimation of sleep latency >20% of objective sleep latency. PSG data of misperceptors were compared with those of 20 normal gender- and age-matched subjects (controls). Patients and controls presented non significant differences in the amounts of objective sleep time (464 min vs. 447 min) and objective sleep latency (9 min vs. 8 min). However, compared to controls, misperceptors reported a significantly shorter time of perceived sleep (285 min vs. 461 min; $p < 0.0001$), and a significantly longer duration of perceived sleep latency (51 min vs. 22 min; $p < 0.0001$). Arousal index (32/hour vs. 19/hour; $p < 0.0001$) and total CAP rate (58% vs. 35%; $p < 0.0001$) were significantly higher in insomniacs. In the sleep period between objective and subjective sleep onset, CAP rate was 64.4% in misperceptors and 45.1% in controls ($p < 0.002$). Insomniacs showed significantly higher amounts of CAP rate in stage 1 (62.7% vs. 37.5%; $p < 0.0001$) and in stage 2 (53.3% vs. 33.2%; $p < 0.0001$), but not in SWS. The percentage of subtypes A2, which include both sleep-promoting and wake-promoting EEG features, was significantly higher ($p < 0.001$) in mispercetpors (31%) compared to controls (24%). Interestingly, misperceptors reported a limited amount of subjective awakenings (mean: 4) in contrast to objective findings (mean: 11). The mismatch could be in part explained by the high amounts of CAP between successive awakenings which were merged together in a single experience. In other words, if sleep between two successive awakenings is superficial (expressed by sleep stages 1 and 2), unstable (as reflected by increased amounts of CAP), and fragmented (increased arousal index), time separating the two events is perceived as continuous wake. These findings suggest that in misperceptors difficulty to maintain consolidated sleep is interpreted as wakefulness.

Sleep is a dynamic process with a self-regulating character. The nightly recurring sleep process is organized into consecutive cycles in which the sequence of NREM stages and the alternation between NREM and REM sleep show a quite stable tendency and a largely predictable pattern. These constraints produce the macrostructural development of sleep. However, transient EEG changes can interact with the expected development of sleep and ensure adaptation to both internal and external conditions. CAP and arousals represent rapid adaptive adjustments of vigilance during sleep. Failure of these compensatory processes conducts to non-restorative sleep. Therefore, assessment of sleep quality relies on a variety of PSG measures including sleep duration (quantified by total sleep time and sleep efficiency), sleep intensity (reflected by stages 3 and 4), sleep continuity (altered by nocturnal awakenings and arousals) and sleep stability (impaired by excessive amounts of CAP).

These PSG measures are susceptible to deterioration in varying ways and proportions in accordance to the manifold clinical manifestations of insomnia. In the hierarchy of PSG measures, CAP variables appear to be the most sensitive to any source of internal or external perturbation during sleep. Anyway, regardless of the specific characteristics of sleep alteration, insomnia ceases to be an indefinite mental disorder but emerges as a subjective disturbance supported by measurable neurophysiological changes.

CAP and sleep disorders in children

In recent years, several studies in children have shown specific changes of CAP parameters in different sleep disorders, neuropsychological disabilities and mental retardation (Table 4). An overview on CAP in children sleep has been recently published by Bruni et al.[114]

Parasomnias/disorders of arousal (DOA)

It is known that DOA show a typical EEG pattern defined as hypersynchronous delta activity (HSD),[104,115–119] which is similar to the high-voltage delta bursts characterizing CAP A1 subtypes in SWS. Guilleminault et al.[120] reported that chronic sleepwalkers have instability of NREM sleep detectable by CAP analysis, even during nights without sleepwalking episodes. In children, this has been related to the presence of associated sleep disorders, such as upper airway resistance syndrome[118] or other sleep disorders (periodic limb movements). In general the studies on CAP in subjects with sleepwalking or sleep terrors showed an increase of

CAP rate, of A1% and of A1 index in SWS and a decrease in phase B and CAP cycle duration.[104,118,120,121] This shorter duration of CAP cycle and phase B determines an abnormally fast oscillatory pattern of the amplitude of EEG slow components in SWS (defined as HSD, SWS arousals or CAP A1) leading to recurrent arousals from SWS and SWS fragmentation that, as a result, contributes to trigger SWS parasomnias.[120]

Pediatric sleep disordered breathing

In children with sleep disordered breathing (SDB), sleep architecture is commonly preserved and no sleep disruption can be disclosed with the usual sleep scoring. The studies on CAP in SDB children have shown partially contradictory results, which could be related to the different age groups analyzed and to their different degree of respiratory disturbance.

Children with chronic snoring showed a normal sleep architecture but a slight increase of CAP rate, of A2% and A3%, and a slight decrease of A1%, compared to control subjects.[122] Moreover, CAP rate shows positive correlations with behavioral complaints. In contrast, in children with OSAS (aged 5–8 years) a decrease of CAP rate, mainly during SWS, of A1 percentage, and of A1 index was found, compared to normal controls.[123] The apparently conflicting results might be related to the milder SDB of snoring children and to the older age of children in the Lopes et al.' study (6–17 years).[122] Two other two studies in children with upper airway resistance syndrome or OSAS showed an increase of CAP rate, mainly during SWS.[118,124] Interestingly, after orthodontic treatment or after nasal continuous positive airway pressure therapy, children with OSAS showed a compensatory increase of CAP rate and of A1 index, during SWS, compared to controls.[124,125]

Although some discrepancies can be observed in these different studies, a constant decrease in A1 subtypes (mainly during SWS) was found with a corresponding increase of A2 and A3, that represent the negative consequences of SDB on sleep microstructure and lead to an increase in SWS instability, which may trigger other sleep events such as parasomnias or seizures.[126] In fact, the treatment of OSAS determined an increase in A1 percentage and a decrease of SWS instability.

Childhood narcolepsy

In children with narcolepsy the most important finding was a reduced amount of CAP with a decrease of CAP rate and of A1 and A2 indexes in all NREM sleep stages coupled with an increase of A3 index similarly and even more evident than reported in adults.[127] The alterations of CAP in narcoleptic children suggest the presence of an impaired modulation of the arousal-level fluctuations during NREM sleep.

These NREM sleep alterations are very similar to those found in children affected by attention-deficit/hyperactivity disorder (ADHD)[123] who also show clinical similarities represented by restlessness and motor hyperactivity evident in young narcoleptic children, probably needed to overcome drowsiness.

CAP in neuropsychological disabilities

Neuropsychological disabilities with mental retardation. Recent studies on the relationship between CAP and cognitive and memory performances[128–130] support the idea that CAP slow components (A1) play a role in sleep-related cognitive processes and highlight the importance of evaluating CAP in children with mental retardation and learning disabilities with or without mental retardation.

In 2 groups of children with mental retardation, i.e., fragile-X (fraX) and Down syndrome, CAP analysys showed a decrease of CAP rate in SWS and of A1 index in stage 2 and SWS and an increase of A2 and A3 percentages in both groups, compared to normal controls.[131] The lower values of CAP rate and of A1 index in stage 2 and SWS in the FraX group was probably related to the higher degree of mental retardation. Similar results were found in children with autistic spectrum disorder and mental retardation[132] who showed a decrease of CAP rate more evident during SWS and mainly due to a reduction of A1 CAP subtypes. Similarly, in children with Prader–Willi syndrome (PWS), another genetic syndrome commonly associated with mental retardation, CAP analysis[133] revealed a reduction of CAP rate in all sleep stages and of all A subtypes suggesting a decreased NREM sleep instability. Growth hormone (GH) therapy determined an increase of CAP rate and A1 index in SWS.

Considering all the above mentioned studies we suggest that the decrease of CAP rate and of A1 mainly in SWS (associated with the reduction in REM sleep), represents a sleep microstructural pattern typical of intellectual disability.

Neuropsychological disabilities without mental retardation. Recent CAP studies have been carried out in children with cognitive-behavioral disorders (dyslexia, ADHD) and in high-functioning autism like Asperger syndrome (AS).

In dyslexic children the increase of CAP rate and of A1 index in stage 3 compared to controls is probably related to the over-activation of the frontal areas that represent the generators of the sleep EEG low-frequency band (0.25–2.5 Hz) of CAP A1 subtypes.[134] Moreover, cognitive performances (verbal and full-scale intellectual quotient (IQ)) are positively correlated with this increase of A1 index and of CAP rate in stage 3.

In ADHD children the main aspect of sleep microstructure is represented by a decrease of CAP rate during NREM sleep stage 2[135] mediated by a selective decrease of the total number of A1 subtypes. Interestingly, CAP changes in ADHD seem to be similar to those found in narcolepsy[127] and the CAP similarities reinforce the hypothesis of a deficit of the arousal-level fluctuations in ADHD.

AS is a high-functioning autism characterized by normal intelligence, social deficits, rigid ritualistic behaviors, interests, or activities, and communication problems, but without clinically significant cognitive or language delay. In these subjects, CAP analysis reveals an increased percentage of A1 and a decreased percentage of A2 subtypes. Interestingly, CAP rate in SWS and A1 index in SWS are positively correlated with IQ.[77]

CAP in benign epilepsy with rolandic spikes (BERS)

In general, in all the benign forms of epilepsy of childhood, focal spike discharges seem to show no significant relationship with CAP[94]; specifically, in children with BERS no significant differences in spike distribution throughout CAP and NCAP modalities has been found, leading to the conclusion that, despite the high burst frequency during NREM, interictal discharges of BERS are not modulated by the arousal-related mechanisms of CAP. A recent study in 10 children with BERS vs. controls revealed mainly a decrease of NREM instability in sleep stage 2 (in particular, a reduced total CAP rate and A1 and A2 indexes in stage 2 and an increase of A3 index in stage 3). Since there is a spindle-related spike activation in BERS, we speculate that the decrease of NREM sleep instability in stage 2 might be linked to the inhibitory action of spindling activity and spikes on EEG slow oscillations and on arousals. Therefore, spike activity and CAP A1 subtypes seem to be mutually exclusive probably because centro-temporal spikes disturb the physiological synchronization mechanisms needed for the generation of slow-wave components of CAP.[136]

The role of CAP in sleep-related neurocognitive processes

Starting from some theoretical premises,[137,138] a growing body of evidence has been produced on the possible role of sleep slow-

wave activity in sleep-related cognitive processing.[139,140] Moreover, Marshall et al.[141] have shown that transcranial application of intermittent trains of slow (0.75 Hz) oscillating potentials during the initial phase of the sleep cycle can induce significant improvements in memory. These intermittent trains of slow-wave oscillations closely mimic CAP A1 subtypes observed during natural sleep.

As seen above, CAP A1 subtypes are almost exclusively composed by slow waves, map over the frontal regions of the scalp and correspond to periods in which the functional organization of the EEG network shows enhanced small-world network characteristics, a condition favorable for cognitive processing. These features make CAP A1 subtypes reliable candidates for a significant role in sleep-related cognitive processes.

Based on the hypothesis that CAP slow components may be beneficial for cognitive processing, Ferri and coworkers have undertaken a number of studies. Based on the report by Huber et al.[139] that a motor learning task performed during the day was followed by an increase in EEG slow-wave activity (SWA) during the night and that SWA correlated with an improvement in subsequent performance, Ferri et al.[129] examined their original recordings and found that the night after the task, the CAP A1 subtypes were significantly increased in number and this increase correlated with improvements in task performance. Furthermore, in subjects with AS, significant correlations between verbal and nonverbal performance and CAP were found, with a general positive correlation with the A1 subtypes and a negative correlation with A2 and A3 subtypes.[77] Also, dyslexic children have been reported to show a significant positive correlation between A1 subtypes and verbal and full-scale IQ, while CAP rate in NREM sleep stage 3 is positively correlated with verbal IQ[134]. Thus, there is accumulating evidence implicating CAP as an important intermediate in cognitive processing.

In a more recent publication, Aricò et al.[142] reported that CAP rate and A1 subtypes influence cognitive function in healthy subjects. The study illustrates the significant positive correlation between A1 subtypes and neurocognitive tests that characterize frontal lobe cognitive functions (e.g., verbal fluency, working memory, verbal learning). Furthermore, cognitive performance appears to be negatively correlated with A2 subtypes, whereas A3 subtypes are negatively correlated with planning and motor sequencing. These results provide additional support for the hypothesis that the A1 subtypes are associated with higher cognitive functioning, whereas the A2 and A3 subtypes are associated with impaired neurocognitive functioning.

Another recent experimental study has been published by Ferri et al.[130] with the primary objective to explore the association between CAP and neurocognitive performance in a group of normal subjects before and after two nights of experimentally induced sleep fragmentation. The results of this study confirm the results reported by Aricò et al.[142] on the correlations between CAP and daytime performance after undisturbed sleep in a larger group of subjects. After sleep fragmentation, even if the percentage of SWS was dramatically reduced, there was a two-fold increase in total CAP rate across all NREM sleep stages, and all phase A indexes were significantly increased. Also this study supports that CAP A1 subtypes are associated with higher cognitive functioning, whereas CAP A3 subtypes are associated with lower cognitive functioning in young healthy subjects. The lack of cognitive functioning impairment after sleep fragmentation may be due to persistence and even enhancement of transient slow-wave activity contained in CAP A1 subtypes which also caused a significant enhancement of the EEG power spectrum in the lower frequencies. Finally, as an extension of these studies, Drago et al. have analyzed the correlation between sleep and creativity and have recently reported that CAP rate, which in young people reflects primarily the A1 subtype, correlates with originality and conclude that A1 CAP subtypes reflect frontal activity, and the frontal lobes are important for divergent thinking, also a critical aspect of creativity.[143]

In conclusion, several lines of convergent evidence now suggest a correlation between CAP and cognitive processing; however, more studies are needed on larger groups of subjects and with exhaustive neuropsychological testing sets, in order to achieve a more detailed picture of this correlation. Also the experimental manipulation of CAP, whenever possible, might prove to be an interesting approach for a better understanding of this issue.

Automatic analysis of CAP

There is consolidated evidence that CAP parameters provide more detailed information and are significantly more sensitive than conventional sleep measures. However, the visual scoring of CAP is time-consuming and this can compromise an extensive utilization of the method. In other words, only the availability of an adequate system for the automatic detection of CAP can really make it an easily exploitable tool.

To date, various software tools have been carried out with different degrees of development. Jobert et al.[144] suggested the application of the wavelet transform to the analysis of transient events and supported this idea with significant preliminary results. The method introduced by De Carli et al.[145] was based on the application of the wavelet transform to two bipolar EEG traces and one EMG derivation. For the purposes of arousal detection, six frequency bands were considered: slow delta, delta, theta, alpha, sigma and beta. Subsequently, De Carli et al.[43] added a comparison between the mean power values during: a) each entire arousal as automatically recognized, b) the 3.5 s immediately preceding the arousal and c) the 20 s which preceded the 3.5 s pre-arousal epoch.

Rosa et al.[11] proposed an automatic system for the detection of the CAP sequences consisting of three parts: a model based maximum likelihood estimator, a variable length template matched filter and a state machine rule-based decision subsystem. Huupponen et al.[146] identified, via a mean frequency measure and fast Fourier transform (FFT), sleep oscillations with period times of 50–150 s having a relatively large amplitude.

Barcaro et al.[10] and Navona et al.[147] proposed a method based on the computation of five band-related descriptors, which give a measure of how much the amplitude in a band activity is "instantaneously" different from the background activity. These can be viewed as "continuous" descriptors, although no significant information is lost if they are calculated every half second. Mathematically, they are given by the normalized difference between the average band activity amplitude over a "short" interval (2 s) centered on the instant considered and the average amplitude over a "long" interval, i.e., in the order of the minute. Of course, the latter average depends mainly on the background signal. The basic idea is the following: any microstructure phenomenon can be traced back to the fact that at least one descriptor provides values remarkably higher (i.e., above a certain threshold, called the "existence threshold") than the background value. After the recognition of an event, the length of the corresponding epoch can be simply recognized by applying a second threshold, called the "length threshold". The various events are then discriminated according to the bands involved.

Ferri et al.[12] proposed a new method, included in a more complete software for sleep analysis, based on the analysis of the amplitude of the two main EEG frequency bands identified in their specific studies on the spectral content of CAP and representing the slow-wave component typical of the A1 phases and the high-frequency component most evident during the A3 subtypes.[12,44,148] This study reports, so far, the most complete and careful statistical

analysis of the performance of the automatic scoring of CAP. The most important global parameters of CAP, including total CAP rate and CAP time, scored by the automatic analysis showed a significant concordance with those obtained by four human raters. The agreement between the automatic analysis and the consensus scoring for the assignment of the CAP A phase subtype was not distinguishable from that expected from a human scorer. However, the automatic analysis provided a number of false positives and false negatives significantly higher than that of the visual scoring of CAP. An additional objective of this study was to assess the inter-rater reliability between different scorers, from different qualified sleep research groups, in scoring visually CAP; the inter-rater reliability of CAP parameters quantified by the Kendall W coefficient of concordance between the 4 different scorers was high for all the parameters considered and showed values above 0.9 for total CAP time, CAP time in sleep stage 2 and percentage of A phases in sequence; also CAP rate showed a high value. Thus, it is possible to conclude that CAP scoring shows good inter-rater reliability and might be compared between different laboratories the results of which might also be pooled; however, caution should always be taken because of the variability which can be expected in the classical sleep staging. On the contrary, the automatic detection of CAP needs supervision and correction and should be limited to large studies when only general parameters such as CAP rate are considered; more editing is necessary for the correct use of the other results.

The role of sleep instability

Objection could be raised on the usefulness of CAP in the routine clinical practice.[15] Besides the consideration that the authors apply CAP in their daily activities, attention should be focused on the philosophy that lies behind the CAP scoring methodology. The main assumption of CAP is that we must consider that during certain periods of the night the arousal level is unstable. The concept of instability is a basic issue of all complex systems and supports the dynamics of biological variability. Within certain ranges, instability warrants flexible and adaptive features to the complex system. In normal sleep CAP accompanies the stage transitions maintaining in-phase both the EEG and autonomic functions through regular fluctuations. This means that what we observe on the peripheral sensors (respiratory events, heart rate variations, blood pressure shifts, myoclonic jerks) has a consistent and synchronous expression on the EEG and vice versa. In other words, CAP allows to read sleep as a musical score where all the instruments play a coordinated harmony. This means that even without the EEG leads the detection of an unstable cardiorespiratory pattern is certainly associated with an oscillatory behavior of the cerebral activities. To guarantee survival during prolonged unconsciousness (i.e., sleep) a strong interaction among all the biological subsytems is mandatory.

Accordingly, life-threatening events, e.g., repetitive apneas, enhance the brain's necessity to increase the number of protective arousals determining a metronomic setting of oscillations expressed by prolonged CAP sequences. CAP scoring incorporates all the conventional EEG arousals in NREM sleep and provides additional information supplied by the frontal EEG arousals (subtypes A1) which are omitted by the official classification. All this remains unexplored using only the stepwise description of sleep stages. In particular, the new AASM rules have oversimplified the sleep process merging stages 3 and 4 in stage N3 and overemphasizing the role of single arousals in stage scoring.[14] The authors understand that the new AAMS rules are simply tools offered to accelerate the scoring procedures in the routine practice.[149] However, it is a common experience that a number of patients remain inadequately diagnosed and treated in spite of an apparent normal sleep structure. A recent study carried out in patients with restless legs syndrome and periodic limb movements during sleep demonstrates that dopamine-agonist medication reduces the amount of leg jerks but maintains high levels of CAP with persistence of non-restorative sleep. Similar controversies happen daily in sleep labs that ascertain maintenance of excessive sleepiness in OSAS patients even when CPAP restores normal AHI measures. An exploratory approach using the CAP framework would probably shed light on these controversial cases. It is known that CPAP titration detached from the concomitant assessment of CAP can jeopardize the effectiveness of ventilatory treatment.[150,151] The persistence of CAP and arousals even when respiratory events are controlled by an autoadjust equipment indicates an inadequate titration procedure.[152]

Finally, the sensitivity of CAP to medication in insomniac patients could be exploited in the evaluation of new sleep-promoting drugs. So far, hypnotic compounds have based their effectiveness on the paradigm of sleep onset promotion, sleep time enhancement and wake after sleep onset (WASO) reduction. All the available hypnotic agents, especially those belonging to the gamma-aminobutyric acid (GABA) family, share these features which paradoxically offer a flat undifferentiated therapeutic scenario. The new sleep drugs in the pipeline, acting on alternative targets (melatonin, orexin, serotonin), need a new cultural framework which cannot be limited to sleep latency and sleep duration but needs to incorporate also the issue of sleep and autonomic stability. So far, these objectives have been neglected by most clinical trials for drug approval. Comparing gaboxadol and zolpidem in a model of situational insomnia, CAP parameters showed a significant independence from other electrophysiological measures (including spectral analysis), disclosed a strong association with subjective sleep quality and allowed discrimination between the administered drugs.[99] Zolpidem has been used also in a non-insomnia setting. In a recent trial, most patients with idiopathic central sleep apnea experienced a decrease in central apnea/hypopneas with zolpidem. They also had improved sleep continuity, reduced total number of arousals and decreased subjective daytime sleepiness, without worsening of oxygenation or obstructive events.[153] In obstructive sleep apnea, trazodone, increased respiratory effort-related arousal threshold in response to hypercapnia and allowed patients to tolerate a higher CO_2 level.[154] According to Younes[155] "the percentage of time spent in instability is related to how far removed from stability the system is, relative to how much changes in the stability factors can occur spontaneously during the night. Some of the factors that determine stability change from time to time during sleep. Chief among these is arousal threshold". In a recent editorial, Casey[156] stated that "instability of sleep may underlie the generation of central apnea events… it is reasonable to speculate that in many circumstances Cheyne-Stokes respiration-central sleep apnea (CSR CSA) appears to be "arousal-driven" …when reviewing polysomnography tracings perhaps one should wonder if "disrupted breathing is causing unstable sleep (as appears to be true with OSA) or is unstable sleep producing disordered breathing?" These findings suggest that quantification of sleep instability as measured by CAP variables, may serve as valuable endpoints in future research not only in insomnia but also in the management of other sleep disorders.

CAP and cardiopulmonary coupling (CPC) during sleep

During sleep, the coupling of EEG–CAP with modulations in respiratory and autonomic functions, have raised the possibility of utilizing a continuous electrocardiographic (ECG) signal alone to quantify sleep stability.[157]

This novel method, termed cardiopulmonary coupling (CPC) analysis, is based on a continuous ECG signal and employs

Fourier-based techniques to analyze 2 features of the signal: 1) the variability of the cardiac interbeat (RR) interval series and 2) the fluctuations in QRS amplitude induced by respiration-the ECG-derived respiration (EDR) signal. These signals have 2 basic patterns: a high-frequency component due to physiological sinus arrhythmia that reflects breath-to-breath fluctuations, and a low-frequency component that reflects cyclic variation across multiple breaths. These fluctuations in the mean cardiac electrical axis correlate with phasic changes in the respiratory cycle.

PSG data using cardiopulmonary coupling spectrograms indicate that the low and high-frequency coupling regimes has only weak correlation with standard sleep staging but do follow CAP scoring, where low-frequency coupling is associated with CAP and high-frequency coupling with non-CAP.

In patients with sleep apnea, elevated power in the low-frequency coupling region coincides with periods of scored respiratory events. Accordingly, CPC has been developed to measure sleep quality and to detect and phenotype sleep apnea based solely on the continuous ECG signal.[157,158] Improved sleep stability has also been quantified by CPC analysis in patients with heart failure undergoing a Tai Chi exercise program.[159]

However, since increased CAP rate is a dominant feature of impaired sleep quality, CPC analysis can be applied also in studies that investigate poor sleep even in the absence of respiratory events. In a case-control design, continuous ECG recordings collected during PSG from 14 patients with fibromyalgia and 13 matched controls revealed no differences in conventional PSG measures. However, elevated-low-frequency coupling was significantly increased in fibromyalgia patients. Two-week pain diary scores completed by the subjects correlated in expected directions with both high and elevated-low-frequency coupling.[160]

Similar findings were confirmed in a study carried out in patients with major depression. Relative to controls, unmedicated depressed patients showed an increase in low-frequency coupling, an index of unstable sleep. The medicated depressed group showed a restoration of high-frequency coupling, an index of stable sleep, to a level comparable with that of the control group. The CPC indices were associated with subjective sleep quality and the severity of depression.[161]

Conclusions

The present review suggests that a certain amount of information remains uncovered if we limit our assessment to macrostructural events. As a marker of sleep instability, CAP rate may be enhanced by a number of internal or external factors. CAP rate is a highly sensitive poorly specific index as it cannot reveal the nature of perturbation. However, it certainly indicates that one or more factors are interfering with the processes of sleep consolidation and quantifies the magnitude of perturbation. Specificity is mainly supplied by the phase A subtypes which are significantly modified by the sleep disorders and medication (Table 1). In contrast, the presence of non-CAP is closely related to a global condition of stability when all the subsystems that control and influence the sleep mechanisms have achieved a reciprocally balanced interaction.

In the CAP/non-CAP perspective, analysis of sleep microstructure is not limited to the finding of a single event (for example an isolated arousal) but to the identification of a pattern (presence or absence of a CAP sequence) which translates a physiological state that involves cerebral activities, autonomic functions and behavioral features. In other words, what happens upstairs (brain) is reflected at the lower levels (autonomic and muscle parameters) and vice versa. Once we attribute an activation relevance to all CAP A phases, (including also K-complexes and delta bursts) we overcome the barren contrast between visible and non-visible arousals which for years has frozen the possibility to understand the flexible capacity of the brain to use different EEG features in different neurophysiological situations. Conventional EEG arousals are the peak of an iceberg composed of other more subtle but equally powerful activating events. Investigating patients with sleep disordered breathing, Thomas[33] found that in NREM sleep 28% of apneas and 61% of hypopneas are interrupted by a delta burst or K-complexes, i.e., a phase A1 subtype. In normal sleep, subtypes A1 prevail in almost all CAP sequences indicating their topical involvement in the dynamic tailoring of sleep structure.[27] These findings also confirm the sculpturing role of CAP in the basic mechanisms of sleep and open new perspectives on the exploitation of CAP in the pathophysiology of sleep disorders.

Practice points

1) The measure of unstable sleep, expressed by CAP parameters, offers topical information that conventional sleep metrics are unable to provide.
2) CAP methodology requires a solid background in EEG analysis.
3) CAP scoring is certainly time-consuming but can be extremely valuable in certain cases of clinical routine and should be systematically applied in sleep research protocols.
4) The clinical applications of CAP range from diagnostic procedures to treatment adequacy.
5) CAP is a mandatory tool to investigate children sleep and explore sleep-related cognitive processes.

Research agenda

In adults

1) Drug manipulations of CAP: all new drugs introduced on the market with effects on sleep and daytime vigilance should be also explored according to their action on CAP parameters. This can be extended to older agents.
2) Cardiopulmonary coupling: portable devices quantifying CAP (on a single EEG channel) and some autonomic measures may provide a simple, cost-efficient and reliable method to quantify sleep stability, assess night-to-night variability and track treatment effects.
3) Cognitive performances and CAP: a number of studies are in progress to explore the role of CAP in learning processes and memory consolidation.
4) Neuroimaging and CAP: the relation between CAP and brain connectivity during sleep needs to be explored.
5) International Classification of Sleep Disorders and CAP: define the PSG microstructural features of sleep disorders
6) CAP and elderly: in the past century the term elderly was attributed to adults over 60 or 65 years of age. With increased life expectation the concept of elderly has been extended to over 70 and 75 years of age. So far, most studies on CAP parameters have been conducted on infancy and young adults while limited information is available on sleep in elderly individuals. This gap needs to be covered.
7) CAP and daytime sleepiness: extensive investigation has supplied evidence that CAP rate correlates with

subjective sleep quality. In contrast, few studies have explored the relation between CAP parameters and daytime sleepiness. This issue requires further effort.
8) Automatic analysis: new algorithms and neural networks to detect the activation patterns of CAP need to be developed.
9) Scoring criteria: some arbitrary aspects of CAP (e.g., amplitude rules for the detection of A phases) can be revisited exploiting the feedback provided by automatic analysis.

In children
1) Normative studies in children in the age range between 6 months and 3 years.
2) Studies on larger samples of normal children.
3) Longitudinal studies of CAP changes during development.
4) Adaptation of CAP rules to infancy sleep.
5) CAP in children with insomnia.
6) Relationships between CAP and cognitive functioning in children.
7) CAP night-to-night variability.
8) Effect of sleep deprivation on CAP in children.
9) CAP in children with different forms of epilepsy.

References

*1. Terzano MG, Mancia D, Salati MR, Costani G, Decembrino A, Parrino L. The cyclic alternating pattern as a physiologic component of normal NREM sleep. *Sleep* 1985;**8**:137–45.
2. Rechtschaffen A, Kales A, editors. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Brain information service/brain research institute*. Los Angeles: University of California at Los Angeles; 1968.
3. Terzano MG, Halasz P, Declerck AC, editors. *Phasic events and dynamic organization of sleep*. New York: Raven Press; 1991. p. 1–317.
4. Terzano MG, Parrino L. Meeting report. Microstructure of sleep. Founding Congress of the world Federation of sleep research Societies. *Physiol Behav* 1993;**54**:777.
5. Terzano MG, Parrino L. Clinical applications of cyclic alternating pattern. *Physiol Behav* 1993;**54**:807–13.
6. Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG. Multidrug comparison (lorazepam, triazolam, zolpidem, zopiclone) in situational insomnia: polysomnographic analysis by means of the cyclic alternating pattern (CAP). *Clin Neuropharmacol* 1997;**20**:253–63.
*7. Terzano MG, Parrino L. Origin and significance of the cyclic alternating pattern (CAP). *Sleep Med Rev* 2000;**4**:101–23.
*8. Terzano MG, Parrino L, Smerieri A, Chervin R, Chokroverty S, Guilleminault C, et al. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. *Sleep Med* 2001;**2**:537–53.
9. Ferrillo F, Gabarra M, Nobili L, Parrino L, Schiavi G, Stubinski B, et al. Comparison between visual scoring of cyclic alternating pattern (CAP) and computerized assessment of slow EEG oscillations in the transition from light to deep non-REM sleep. *J Clin Neurophysiol* 1997;**14**:210–6.
10. Barcaro U, Navona C, Belloli S, Bonanni E, Gneri C, Murri L. A simple method for the quantitative description of sleep microstructure. *Electroencephalogr Clin Neurophysiol* 1998;**106**:429–32.
11. Rosa AC, Parrino L, Terzano MG. Automatic detection of cyclic alternating pattern (CAP) sequences in sleep: preliminary results. *Clin Neurophysiol* 1999;**110**:585–92.
12. Ferri R, Bruni O, Miano S, Smerieri A, Spruyt K, Terzano MG. Inter-rater reliability of sleep cyclic alternating pattern (CAP) scoring and validation of a new computer-assisted CAP scoring method. *Clin Neurophysiol* 2005;**116**:696–707.
13. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. *The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications*. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
*14. Parrino L, Ferri R, Zucconi M, Fanfulla F. Commentary from the Italian Association of Sleep Medicine on the AASM manual for the scoring of sleep and associated events: for debate and discussion. *Sleep Med* 2009;**10**:799–808.
15. Thomas RJ. Cyclic alternating pattern in the electroencephalogram: what is its clinical utility? *Sleep* 2007;**30**:553–5.
16. Bergamasco B, Bergamini L, Doriguzzi T, Fabiani D. EEG sleep patterns as a prognostic criterion in post-traumatic coma. *Electroencephalogr Clin Neurophysiol* 1968;**24**:374–7.
17. Mancia D, Lechi A, Terzano MG, Gemignani F, Vigouroux PR, Naquet R. Electrophysiological criteria in prolonged post-traumatic coma. Joint study of 150 cases. *Riv Neurol* 1975;**45**:44–59.
18. Bricolo A, Faccioli F, Turazzi S. EEG in posttraumatic coma. Diagnostic and prognostic values. *Rev Electroencephalogr Neurophysiol Clin* 1979;**9**:116–30.
19. Valente M, Placidi F, Oliveira AJ, Bigagli A, Morghen I, Proietti R, et al. Sleep organization pattern as a prognostic marker at the subacute stage of post-traumatic coma. *Clin Neurophysiol* 2002;**113**:1798–805.
20. Lundberg N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. *Acta Psychiatr Scand* 1960;**36**:1–153.
21. Evans BM. Periodic activity in cerebral arousal mechanisms – the relationship to sleep and brain damage. *Electroencephalogr Clin Neurophysiol* 1992;**83**:130–7.
22. Steriade M, Amzica F, Contreras D. Cortical and thalamic cellular correlates of electroencephalographic burst-suppression. *Electroencephalogr Clin Neurophysiol* 1994;**90**:1–16.
23. Fischgold H, Mathis P. Obnubilations, comas et stupeurs. *Electroencephalogr Clin Neurophysiol* 1959;(Suppl. 11):2–125.
24. Terzano MG, Parrino L. Functional relationship between micro- and macrostructure of sleep. In: Terzano MG, Halasz P, Declerck AC, editors. *Phasic events and dynamic organization of sleep*. New York: Raven Press; 1991. p. 101–19.
25. Terzano MG, Parrino L, Fioriti G, Farolfi A, Orofiamma B, Sauvanet JP. Modifications of sleep structure induced by increasing levels of acoustic perturbation in normal subjects. *Electroencephalogr Clin Neurophysiol* 1990;**76**:29–38.
26. Phasic events and microstructure of sleep. In: Terzano MG, Parrino L, Mennuni GF, editors. *Consensus conference, Italian association of sleep Medicine (AIMS)*. Lecce: Martano Editore; 1997. p. 1–161.
27. Smerieri A, Parrino L, Agosti M, Ferri R, Terzano MG. Cyclic alternating pattern sequences and non-cyclic alternating pattern periods in human sleep. *Clin Neurophysiol* 2007;**118**:2305–13.
28. Terzano MG, Parrino L, Spaggiari MC, Barusi R, Simeoni S. Mutual cooperation between cyclic alternating pattern and major dynamic events of sleep. In: Barthouil P, editor. *Insomnie et Imidazopyridines*. Amsterdam: Excerpta Medica; 1990. p. 262–70.
29. Schieber JP, Muzet A, Ferriere PJR. Les phases d'activation transitoire spontanées au cours du sommeil chez l'homme. *Arch Sci Physiol* 1971;**25**:443–65.
30. Terzano MG, Parrino L, Boselli M, Spaggiari MC, Di Giovanni G. Polysomnographic analysis of arousal responses in obstructive sleep apnea syndrome by means of the cyclic alternating pattern (CAP). *J Clin Neurophysiol* 1996;**13**:145–55.
31. Parrino L, Smerieri A, Rossi M, Terzano MG. Relationship of slow and rapid EEG components of CAP to ASDA arousals in normal sleep. *Sleep* 2001;**24**:881–5.
32. Terzano MG, Parrino L, Rosa A, Palomba V, Smerieri A. CAP and arousals in the structural development of sleep: an integrative perspective. *Sleep Med* 2002;**3**:221–9.
33. Thomas RJ. Arousals in sleep-disordered breathing: patterns and implications. *Sleep* 2003;**26**:1042–7.
*34. Halasz P, Terzano MG, Parrino L, Bodisz R. The nature of arousal in sleep. *J Sleep Res* 2004;**13**:1–23.
35. ASDA (American Sleep Disorders Association). EEG arousals: scoring rules and examples. *Sleep* 1992;**15**:173–84.
36. Rees K, Spence DP, Earis JE, Calverley PM. Arousal responses from apneic events during non-rapid eye movement sleep. *Am J Respir Crit Care Med* 1995;**152**:1016–21.
37. McNamara F, Lijowaska AS, Thach BT. Spontaneous arousal activity in infants during NREM and REM sleep. *J Physiol* 2002;**538**:263–9.
38. Togo F, Cherniack NS, Natelson BH. Electroencephalogram characteristics of autonomic arousals during sleep in healthy men. *Clin Neurophysiol* 2006;**117**:2597–603.
39. Parrino L, Halasz P, Tassinari CA, Terzano MG. CAP, epilepsy and motor events during sleep: the unifying role of arousal. *Sleep Med Rev* 2006;**10**:267–85.
40. Martin SE, Wraith PK, Deary IJ, Douglas NJ. The effect of nonvisible sleep fragmentation on daytime function. *Am J Respir Crit Care Med* 1997;**155**:1596–601.
41. Hirshkowitz M. Arousals and anti-arousals. *Sleep Med* 2002;**3**:203–4.
42. Halasz P. Arousals without awakening. Dynamic aspect of sleep. *Physiol Behav* 1993;**54**:795–802.
43. De Carli F, Nobili L, Beelke M, Watanabe T, Smerieri A, Parrino L, et al. Quantitative analysis of sleep EEG microstructure in the time-frequency domain. *Brain Res Bull* 2004;**63**:399–405.
44. Ferri R, Rundo F, Bruni O, Terzano MG, Stam CJ. Dynamics of the EEG slow-wave synchronization during sleep. *Clin Neurophysiol* 2005;**116**:2783–95.

* The most important references are denoted by an asterisk.

45. Guilleminault C, Stoohs R. Arousal, increased respiratory efforts, blood pressure and obstructive sleep apnoea. *J Sleep Res* 1995;**4**:117–24.
46. Halasz P. Hierarchy of micro-arousals and the microstructure of sleep. *Neurophysiol Clin* 1998;**28**:461–75.
47. Ferri R, Parrino L, Smerieri A, Terzano MG, Elia M, Musumeci SA, et al. Cyclic alternating pattern and spectral analysis of heart rate variability during normal sleep. *J Sleep Res* 2000;**9**:13–8.
48. Sforza E, Jouny C, Ibanez V. Cardiac activation during arousal in humans: further evidence for hierarchy in the arousal response. *Clin Neurophysiol* 2000;**111**:1611–9.
49. Steriade M, Nunez A, Amzica F. A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *J Neurosci* 1993;**13**:3252–65.
50. Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G. The sleep slow oscillation as a traveling wave. *J Neurosci* 2004;**24**:6862–70.
51. Steriade M. The corticothalamic system in sleep. *Front Biosci* 2003;**8**:878–99.
52. Achermann P, Borbely AA. Low-frequency (<1 Hz) oscillations in the human sleep electroencephalogram. *Neuroscience* 1997;**81**:213–22.
53. Terzano MG, Parrino L, Boselli M, Smerieri A, Spaggiari MC. CAP components and EEG synchronization in the first three sleep cycles. *Clin Neurophysiol* 2000;**111**:283–90.
54. Grassberger P, Procaccia I. Characterization of strange attractors. *Phys Rev Lett* 1983;**50**:346–9.
55. Theiler J. Spurious dimension from correlation algorithms applied to limited time-series data. *Phys Rev A* 1986;**34**:2427–32.
56. Stam CJ, Nicolai J, Keunen RW. Nonlinear dynamical analysis of periodic lateralized epileptiform discharges. *Clin Electroencephalogr* 1998;**29**:101–5.
57. Ferri R, Parrino L, Smerieri A, Terzano MG, Elia M, Musumeci SA, et al. Nonlinear EEG measures during sleep: effects of the different sleep stages and cyclic alternating pattern. *Int J Psychophysiol* 2002;**43**:273–86.
58. Ferri R, Bruni O, Miano S, Terzano MG. Scalp topography and cortical generators of the spectral components of the cyclic alternating pattern (CAP). In: Guilleminault C, editor. *Clinical neurophysiology of sleep disorders*. Edinburgh: Elsevier Ltd.; 2005. p. 95–101.
59. Ferri R, Bruni O, Miano S, Terzano MG. Topographic mapping of the spectral components of the cyclic alternating pattern (CAP). *Sleep Med* 2005;**6**:29–36.
60. Ferri R, Rundo F, Bruni O, Terzano MG, Stam CJ. Small-world network organization of functional connectivity of EEG slow-wave activity during sleep. *Clin Neurophysiol* 2007;**118**:449–56.
61. Ferri R, Rundo F, Bruni O, Terzano MG, Stam CJ. The functional connectivity of different EEG bands moves towards small-world network organization during sleep. *Clin Neurophysiol* 2008;**119**:2026–36.
62. Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. *Nature* 1998;**393**:440–2.
63. Amaral L, Ottino JM. Complex networks – augmenting the framework for the study of complex systems. *Eur Phys* 2004;**39**:147–62.
64. Strogatz SH. Exploring complex networks. *Nature* 2001;**410**:268–76.
65. Terzano MG, Parrino L, Fioriti G, Spaggiari MC, Piroli A. Morphologic and functional features of cyclic alternating pattern (CAP) sequences in normal NREM sleep. *Funct Neurol* 1986;**1**:29–41.
*66. Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG. Cyclic alternating pattern (CAP) in normal sleep: polysomnographic parameters in different age groups. *Electroencephalogr Clin Neurophysiol* 1998;**107**:439–50.
67. Bruni O, Ferri R, Miano S, Verrillo E, Vittori E, Della Marca G, Farina B, Mennuni G. Sleep cyclic alternating pattern in normal school-age children. *Clin Neurophysiol* 2002;**113**:1806–14.
68. Bruni O, Ferri R, Miano S, Verrillo E, Vittori E, Farina B, et al. Sleep cyclic alternating pattern in normal preschool-aged children. *Sleep* 2005;**28**:220–30.
69. Lopes MC, Rosa A, Roizenblatt S, Guilleminault C, Passarelli C, Tufik S, et al. Cyclic alternating pattern in peripubertal children. *Sleep* 2005;**28**:215–9.
70. Miano S, Villa MP, Blanco D, Zamora E, Rodriguez R, Ferri R, et al. Development of NREM sleep instability–continuity (cyclic alternating pattern) in healthy term infants aged 1 to 4 months. *Sleep* 2009;**32**:83–90.
71. Ferri R, Chiaramonti R, Elia M, Musumeci SA, Ragazzoni A, Stam CJ. Nonlinear EEG analysis during sleep in premature and full-term newborns. *Clin Neurophysiol* 2003;**114**:1176–80.
72. Louis J. Sleep maturation in the first two years of life: quantitative aspects, structural and circadian. *Neurophysiol Clin* 1998;**28**:477–91.
73. Grigg-Damberger M, Gozal D, Marcus CL, Quan SF, Rosen CL, Chervin RD, et al. The visual scoring of sleep and arousal in infants and children. *J Clin Sleep Med* 2007;**3**:201–40.
74. Alves GR, Rosa A, Brito M, Pradella-Halinan M, Tufik S. Cyclic alternating pattern in normal children aged 12 to 24 months. *Arq Neuropsiquiatr* 2010;**68**:689–93.
75. Boselli M, Parrino L, Smerieri A, Terzano MG. Effect of age on EEG arousals in normal sleep. *Sleep* 1998;**21**:351–7.
76. Carskadon M, Keenan S, Dement WC. Nighttime sleep and daytime sleep tendency in preadolescents. In: Guilleminault C, editor. *Sleep and its disorders in children*. New York: Raven Press; 1987. p. 43–52.
77. Bruni O, Ferri R, Vittori E, Novelli L, Vignati M, Porfirio MC, et al. Sleep architecture and NREM alterations in children and adolescents with Asperger syndrome. *Sleep* 2007;**30**:1577–85.
78. Ferri R, Bruni O, Miano S, Plazzi G, Spruyt K, Gozal D, et al. The time structure of the cyclic alternating pattern during sleep. *Sleep* 2006;**29**:693–9.
79. Poyares D, Guilleminault C, Rosa A, Ohayon M, Koester U. Arousal, EEG spectral power and pulse transit time in UARS and mild OSAS subjects. *Clin Neurophysiol* 2002;**113**:1598–606.
80. Black JE, Guilleminault C, Colrain IM, Carrillo O. Upper airway resistance syndrome. Central electroencephalographic power and changes in breathing effort. *Am J Respir Crit Care Med* 2000;**162**:406–11.
81. Parrino L, Smerieri A, Boselli M, Spaggiari MC, Terzano MG. Sleep reactivity during acute nasal CPAP in obstructive sleep apnea syndrome. *Neurology* 2000;**54**:1633–40.
82. Terzano MG, Parrino L, Spaggiari MC, Palomba V, Rossi M, Smerieri A. CAP variables and arousals as sleep electroencephalogram markers for primary insomnia. *Clin Neurophysiol* 2003;**114**:1715–23.
*83. Terzano MG, Parrino L, Smerieri A, De Carli F, Nobili L, Donadio S, et al. CAP and arousals are involved in the homeostatic and ultradian sleep processes. *J Sleep Res* 2005;**4**:359–68.
84. Terzano MG, Parrino L. Evaluation of EEG cyclic alternating pattern during sleep in insomniacs and controls under placebo and acute treatment with zolpidem. *Sleep* 1992;**15**:64–70.
85. Parrino L, Spaggiari MC, Boselli M, Di Giovanni G, Terzano MG. Clinical and polysomnographic effects of trazodone CR in chronic insomnia associated with dysthymia. *Psychopharmacology* 1994;**116**:389–95.
86. Farina B, Della Marca G, Grochocinski VJ, Mazza M, Buysse DJ, Di Giannantonio M, et al. Microstructure of sleep in depressed patients according to the cyclic alternating pattern. *J Affect Disord* 2003;**77**:227–35.
87. Dalla Marca G, Farina B, Mennuni GF, Mazza S, Di Giannantonio M, Spadini V, et al. Microstructure of sleep in eating disorders: preliminary results. *Eat Weight Disord* 2004;**9**:77–80.
88. Guilleminault C, Lopes MC, Hagen CC, da Rosa A. The cyclic alternating pattern demonstrates increased sleep instability and correlates with fatigue and sleepiness in adults with upper airway resistance syndrome. *Sleep* 2007;**30**:641–7.
89. Parrino L, Boselli M, Buccino GP, Spaggiari MC, Di Giovanni G, Terzano MG. The cyclic alternating pattern plays a gate-control on periodic limb movements during non-rapid eye movement sleep. *J Clin Neurophysiol* 1996;**13**:314–23.
90. Zucconi M, Oldani A, Smirne S, Ferini-Strambi L. The macrostructure and microstructure of sleep in patients with autosomal dominant nocturnal frontal lobe epilepsy. *J Clin Neurophysiol* 2000;**17**:77–86.
91. Nobili L, Sartori I, Terzaghi M, Francione S, Mai R, Tassi L, et al. Relationship of epileptic discharges to arousal instability and periodic leg movements in a case of nocturnal frontal lobe epilepsy: a stereo-EEG study. *Sleep* 2006;**29**:701–4.
92. Terzaghi M, Sartori I, Mai R, Francione S, Cardinale F, Costana L, et al. Coupling of minor motor events and epileptiform discharges with arousal fluctuations in NFLE. *Epilepsia* 2008;**49**:670–6.
93. Terzano MG, Parrino L, Anelli S, Halasz P. Modulation of generalized spike-and-wave discharges during sleep by cyclic alternating pattern. *Epilepsia* 1989;**30**:772–81.
94. Terzano MG, Parrino L, Spaggiari MC, Barusi R, Simeoni S. Discriminatory effect of cyclic alternating pattern in focal lesional and benign rolandic interictal spikes during sleep. *Epilepsia* 1991;**10**:616–28.
95. Priano L, Grugni G, Miscio G, Guastamacchia G, Toffolet L, Sartorio A, et al. Sleep cycling alternating pattern (CAP) expression is associated with hypersomnia and GH secretory pattern in Prader–Willi syndrome. *Sleep Med* 2006;**7**:627–33.
96. Ferri R, Miano S, Bruni O, Vankova J, Nevsimalova S, Vandi S, et al. NREM sleep alterations in narcolepsy/cataplexy. *Clin Neurophysiol* 2005;**116**:2675–84.
97. Terzano MG, Smerieri A, Del Felice A, Giglia F, Palomba V, Parrino L. Cyclic alternating pattern (CAP) alterations in narcolepsy. *Sleep Med* 2006;**7**:619–26.
98. Vetrugno R, D'Angelo R, Cortelli P, Plazzi G, Vignatelli L, Montagna P. Impaired cortical and autonomic arousal during sleep in multiple system atrophy. *Clin Neurophysiol* 2007;**118**:2512–8.
99. Svetnik V, Ferri R, Shubhankar R, Junshui M, Walsh JK, Snyder E, et al. Alterations in cyclic alternating pattern associated with phase advanced sleep are differentially modulated by gaboxadol and zolpidem. *Sleep* 2010;**33**:1562–70.
100. Parrino L, Thomas RJ, Smerieri A, Spaggiari MC, Del Felice A, Terzano MG. Reorganization of sleep patterns in severe OSAS under prolonged CPAP treatment. *Clin Neurophysiol* 2005;**116**:2228–39.
101. Parrino L, Spaggiari MC, Boselli M, Barusi R, Terzano MG. Effects of prolonged wakefulness on cyclic alternating pattern (CAP) during sleep recovery at different circadian phases. *J Sleep Res* 1993;**2**:91–5.
102. Macaluso GM, Guerra P, Di Giovanni G, Boselli M, Parrino L, Terzano MG. Sleep bruxism is a disorder related to periodic arousals during sleep. *J Dent Res* 1998;**77**:565–73.
103. Lavigne GJ, Khoury S, Abe S, Yamaguchi T, Raphael K. Bruxism physiology and pathololgy: an overview for clinicians. *J Oral Rehabil* 2008;**35**:476–94.
104. Zucconi M, Oldani A, Ferini-Strambi L, Smirne S. Arousal fluctuations in non-rapid eye movement parasomnias: the role of cyclic alternating pattern as a measure of sleep instability. *J Clin Neurophysiol* 1995;**12**:147–54.
105. Guilleminault C. Hypersynchronous slow delta, cyclic alternating pattern and sleepwalking. *Sleep* 2006;**29**:14–5.
106. Parrino L, Smerieri A, Spaggiari MC, Terzano MG. Cyclic alternating pattern (CAP) and epilepsy during sleep: how a physiological rhythm modulates a pathological event. *Clin Neurophysiol* 2000;**111**(Suppl. 2):S39–46.

107. Halasz P, Terzano MG, Parrino L. Spike-wave discharge and the microstructure of sleep-wake continuum in idiopathic generalised epilepsy. *Neurophysiol Clin* 2002;**32**:38–53.
108. Manni R, Zambrelli E, Bellazzi R, Terzaghi M. The relationship between focal seizures and sleep: an analysis of the cyclic alternating pattern. *Epilepsy Res* 2005;**67**:73–80.
109. Manni R, Terzaghi M, Sartori I, Veggiotti P, Parrino L. Rhythmic movement disorder and cyclic alternating pattern during sleep: a video-polysomnographic study in a 9-year-old boy. *Mov Disord* 2004;**19**:1186–90.
110. Parrino L, Ferrillo F, Smerieri A, Spaggiari MC, Palomba V, Rossi M, et al. Is insomnia a neurophysiological disorder? The role of sleep EEG microstructure. *Brain Res Bull* 2004;**63**:377–83.
111. Ozone M, Yagi T, Itoh H, Tamura Y, Inoue Y, Uchimura N, et al. Effects of zolpidem on cyclic alternating pattern, an objective marker of sleep instability, in Japanese patients with psychophysiological insomnia: a randomized crossover comparative study with placebo. *Pharmacopsychiatry* 2008;**41**:106–14.
112. Parrino L, Smerieri A, Giglia F, Milioli G, De Paolis F, Terzano MG. Polysomnographic study of intermittent zolpidem treatment in primary sleep maintenance insomnia. *Clin Neuropharmacol* 2008;**31**:40–50.
113. Parrino L, Milioli G, De Paolis F, Grassi A, Terzano MG. Paradoxical insomnia; the role of CAP and arousals in sleep misperception. *Sleep Med* 2009;**10**:1139–45.
*114. Bruni O, Novelli L, Miano S, Parrino L, Terzano MG, Ferri R. Cyclic alternating pattern: a window into pediatric sleep. *Sleep Med* 2010;**11**:628–36.
115. Espa F, Ondze B, Deglise P, Billiard M, Besset A. Sleep architecture, slow wave activity, and sleep spindles in adult patients with sleepwalking and sleep terrors. *Clin Neurophysiol* 2000;**111**:929–39.
116. Gaudreau H, Joncas S, Zadra A, Montplaisir J. Dynamics of slow-wave activity during the NREM sleep of sleepwalkers and control subjects. *Sleep* 2000;**23**:755–60.
117. Pressman MR. Hypersynchronous delta sleep EEG activity and sudden arousals from slow-wave sleep in adults without a history of parasomnias: clinical and forensic implications. *Sleep* 2004;**27**:706–10.
118. Guilleminault C, Lee JH, Chan A, Lopes MC, Huang YS, da Rosa A. Non-REM-sleep instability in recurrent sleepwalking in pre-pubertal children. *Sleep Med* 2005;**6**:515–21.
119. Pilon M, Zadra A, Joncas S, Montplaisir J. Hypersynchronous delta waves and somnambulism: brain topography and effect of sleep deprivation. *Sleep* 2006;**29**:77–84.
120. Guilleminault C, Kirisoglu C, da Rosa AC, Lopes C, Chan A. Sleepwalking, a disorder of NREM sleep instability. *Sleep Med* 2006;**7**:163–70.
121. Bruni O, Ferri R, Novelli L, Finotti E, Miano S, Guilleminault C. NREM sleep instability in children with sleep terrors: the role of slow wave activity interruptions. *Clin Neurophysiol* 2008;**119**:985–92.
122. Lopes MC, Guilleminault C. Chronic snoring and sleep in children: a demonstration of sleep disruption. *Pediatrics* 2006;**118**:e741–6.
123. Kheirandish-Gozal L, Miano S, Bruni O, Ferri R, Pagani J, Villa MP, et al. Reduced NREM sleep instability in children with sleep disordered breathing. *Sleep* 2007;**30**:450–7.
124. Miano S, Rizzoli A, Evangelisti M, Bruni O, Ferri R, Pagani J, et al. NREM sleep instability changes following rapid maxillary expansion in children with obstructive apnea sleep syndrome. *Sleep Med* 2009;**10**:471–8.
125. Miano S, Pelliccia A, Evangelisti M, Pagani J, Villa MP. Role of continuous positive airway pressure therapy on the pathogenesis of sleep-related frontal lobe epilepsy in a child with obstructive sleep apnea syndrome. *J Child Neurol* 2008;**23**:124–8.
126. Miano S, Paolino MC, Peraita-Adrados R, Montesano M, Barberi S, Villa MP. Prevalence of EEG paroxysmal activity in a population of children with obstructive sleep apnea syndrome. *Sleep* 2009;**32**:522–9.
127. Ferri R, Franceschini C, Zucconi M, Drago V, Manconi M, Vandi S, et al. Sleep polygraphic study of children and adolescents with narcolepsy/cataplexy. *Dev Neuropsychol* 2009;**34**:523–38.
128. Ferini-Strambi L, Ortelli P, Castronovo V, Cappa S. Increased periodic arousal fluctuations during non-REM sleep are associated to superior memory. *Brain Res Bull* 2004;**63**:439–42.
*129. Ferri R, Huber R, Aricò D, Drago V, Rundo F, Massimini M, et al. The slow-wave components of the cyclic alternating pattern (CAP) have a role in sleep-related learning processes. *Neurosci Lett* 2008;**432**:228–31.
130. Ferri R, Drago V, Aricò D, Bruni O, Remington RW, Stamatakis K, et al. The effects of experimental sleep fragmentation on cognitive processing. *Sleep Med* 2010;**11**:378–85.
131. Miano S, Bruni O, Elia M, Scifo L, Smerieri A, Trovato A, et al. Sleep phenotypes of intellectual disability: a polysomnographic evaluation in subjects with Down syndrome and Fragile-X syndrome. *Clin Neurophysiol* 2008;**119**:1242–7.
132. Miano S, Bruni O, Elia M, Trovato A, Smerieri A, Verrillo E, et al. Sleep in children with autistic spectrum disorder: a questionnaire and polysomnographic study. *Sleep Med* 2007;**9**:64–70.
133. Verrillo E, Bruni O, Franco P, Ferri R, Thiriez G, Pavone M, et al. Analysis of NREM sleep in children with Prader–Willi syndrome and the effect of growth hormone treatment. *Sleep Med* 2009;**10**:646–50.
134. Bruni O, Ferri R, Novelli L, Finotti E, Terribili M, Troianiello M, et al. Slow EEG amplitude oscillations during NREM sleep and reading disabilities in children with dyslexia. *Dev Neuropsychol* 2009;**34**:539–51.
135. Miano S, Donfrancesco R, Bruni O, Ferri R, Galiffa S, Pagani J, et al. NREM sleep instability is reduced in children with attention-deficit/hyperactivity disorder. *Sleep* 2006;**29**:797–803.
136. Bruni O, Novelli L, Luchetti A, Zarowski M, Meloni M, Cecili M, et al. Reduced NREM sleep instability in benign childhood epilepsy with centrotemporal spikes. *Clin Neurophysiol* 2010;**121**:665–71.
137. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull* 2003;**62**:143–50.
138. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev* 2006;**10**:49–62.
139. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. *Nature* 2004;**430**:78–81.
140. Maatta S, Landsness E, Sarasso S, Ferrarelli F, Ferreri F, Ghilardi MF, et al. The effects of morning training on night sleep: a behavioral and EEG study. *Brain Res Bull* 2010;**82**:118–23.
141. Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. *Nature* 2006;**444**:610–3.
142. Aricò D, Drago V, Foster PS, Heilman KM, Williamson J, Ferri R. Effects of NREM sleep instability on cognitive processing. *Sleep Med* 2010;**11**:791–8.
143. Drago V, Foster PS, Heilman KM, Aricò D, Williamson J, Montagna P, et al. Cyclic alternating pattern in sleep and its relationship to creativity. Sleep Med 2011, in press.
144. Jobert MM, Tismer C, Poiseau E, Schulz H. Wavelets – a new tool in sleep bio-signal analysis. *J Sleep Res* 1994;**3**:223–32.
145. De Carli F, Nobili L, Gelcich, Ferrillo F. A method for the automatic detection of arousals during sleep. *Sleep* 1999;**22**:561–72.
146. Huupponen E, Himanen SL, Hasan J, Varri A. Sleep depth oscillations: an aspect to consider in automatic sleep analysis. *J Med Syst* 2003;**27**:337–45.
147. Navona C, Barcaro U, Bonanni E, Di Martino F, Maestri M, Murri L. An automatic method for the recognition and classification of the A-phases of the cycling alternating pattern. *Clin Neurophysiol* 2002;**111**:1826–31.
148. Bruni O, Novelli L, Finotti E, Lucchetti A, Uggeri G, Aricò D, et al. All-night EEG power spectral analysis of the cyclic alternating pattern at different ages. *Clin Neurophysiol* 2009;**120**:248–56.
149. Hirshkowitz M. AASM PSG manual: the R&K update? *Sleep Med* 2009;**10**:693.
150. Thomas RJ. Cyclic alternating pattern and positive airway pressure titration. *Sleep Med* 2002;**3**:31–322.
151. Thomas RJ, Terzano MG, Parrino L, Weiss JW. CAP-dominant obstructive sleep disordered breathing – a recognisable polysomnographic variant with practical clinical implications. *Sleep* 2004;**27**:229–34.
152. Marrone O, Insalaco G, Bonsignore MR, Romano S, Salvaggio A, Bonsignore G. Sleep structure correlates of continuous positive airway pressure variations during application of an autotitrating continuous positive airway pressure machine in patients with obstructive sleep apnea syndrome. *Chest* 2002;**121**:759–67.
153. Quadri S, Drake C, Hudgel DW. Improvement of idiopathic central sleep apnea with zolpidem. *J Clin Sleep Med* 2009;**5**:122–9.
154. Heinzer RC, White DP, Jordan AS, Lo YL, Dover L, Stevenson K, et al. Trazodone increases arousal threshold in obstructive sleep apnoea. *Eur Respir J* 2008;**31**:1308–12.
155. Younes M. Role of respiratory control mechanisms in the pathogenesis of obstructive sleep disorders. *J Appl Physiol* 2008;**105**:1389–405.
156. Casey KR. Heart failure, central sleep apnea, CPAP, and arousals: another piece of the puzzle. *Sleep* 2009;**32**:13–4.
*157. Thomas RJ, Mietus JE, Peng CK, Goldberger AL. An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. *Sleep* 2005;**28**:1151–61.
158. Thomas RJ, Mietus JE, Peng CK, Gilmartin G, Daly RW, Goldberger AL, et al. Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. *Sleep* 2007;**30**:1756–69.
159. Yeh GY, Mietus JE, Peng CK, Phillips RS, Davis RB, Wayne PM, et al. Enhancement of sleep stability with Tai Chi exercise in chronic heart failure: preliminary findings using an ECG-based spectrogram method. *Sleep Med* 2008;**9**:527–36.
160. Thomas RJ, Mietus JE, Peng CK, Goldberger AL, Crofford LJ, Chervin RD. Impaired sleep quality in fibromyalgia: detection and quantification with ECG-based cardiopulmonary coupling spectrograms. *Sleep Med* 2010;**11**:497–8.
161. Yang AC, Yang CH, Hong CJ, Tsai SJ, Kuo CH, Peng CK, et al. Sleep state instabilities in major depressive disorder: detection and quantification with electrocardiogram-based cardiopulmonary coupling analysis. *Psychophysiology* 2011;**48**:285–91.
162. Moser D, Kloesch G, Fischmeister FP, Bauer H, Zeithofer J. Cyclic alternating pattern and sleep quality in healthy subjects: is there a first night effect on different approaches of sleep quality? *Biol Psychol* 2010;**83**:20–6.