A neurophysiological perspective on sleep and its maturation

Review

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Neurophysiological studies of sleep have increasingly focused on underlying dynamic processes. This would appear particularly relevant to the developmental aspects of sleep. Involvement of sleep-dependent mechanisms in emotional processing, as well as perceptual-sensory, perceptual-motor, and cognitive learning, mostly studied in adults, may play major roles in development. Rapid eye movement (REM) sleep, which is generated by complex neuronal interactions within the pontine reticular formation, and non-REM sleep, which arises from activities in the thalamocortical network, are specifically implicated in different aspects of long-term memory systems. They evolve from previous physiological and behavioural states which can be traced back to the fetal period. Further studies are needed to identify clearly functions reflected by hallmarks of sleep stages, such as spindles and K complexes. A better understanding of the maturational aspects of sleep should provide important insights into physiological development. Assessment approaches taking dynamic characteristics of sleep into account may contribute to the design of better targeted management of sleep-related problems in neurodevelopmental conditions.

In the last 50 years, theories of human development have increasingly focused on the child's interaction with the environment, moving away from earlier, purely maturational models. In this regard, little attention has been paid to sleep, which would appear as periods of disengagement from that interaction. The dramatic changes in skill development observed in the first months of life and the following few years might seem to parallel the increase in total time that the child spends awake: from 6 to 7 hours per day at term to 9 hours at 1 year of age, 12 hours at age 4, and 14 to 16 hours by 10 years of age. However, lack of sleep at that age (i.e. 10y) results in impairments of learning and other cognitive functions.[1] Recent evidence points directly to the close involvement of sleep in adult learning and memory processes.[2] In particular, some processes involved in consolidation of memory required for automation of simple procedural learning seem to occur essentially during sleep.[3] Therefore, sleep might play a similar role during early development.[4]

Systematic studies of the physiology of sleep, mostly conducted in adults and animals, have provided invaluable insights into its organization and biological regulation in health and disease.[5] In children, collection of normative data on sleep has long been limited by technical issues concerning the simultaneous recording of a number of physiological parameters.[6] These include electroencephalogram (EEG), respiration, electromyogram (EMG), electro-oculogram (EOG), heart rate, and behaviour. Lack of concordance between such parameters during sleep appears to be significantly higher in children, to such an extent that the archetypical vision of sleep stages widely used in adults[7] may in fact represent a convenient summing up of more complex processes. Furthermore, although it has long been assumed that the cyclic, physiological modifications of sleep and wakefulness are consistent and fixed, more recent views, which seem to be particularly relevant to young infants and children, envisage them as steady states emerging from dynamic processes.

Until the late 1940s, it was held that sleep resulted from a decrease in sensory stimulation related to fatigue. This concept

See end of paper for list of abbreviations.

was disproved by the demonstration of the critical dependence of the sleep-wake cycle on the activity of the ascending reticular activating system.[8] Many authors then suggested that changes in the infant's relationship with the environment are determined by tuning of neuronal excitation.[9,10] In this regard, motor, respiratory, and EEG characteristics seen in sleep and wakefulness can ultimately be reduced to a few fundamental interactions that follow linear deterministic laws. Therefore, at any given point in development, all children should show the same patterns of sleep and wakefulness. Recordings of sleep patterns would, therefore, allow evaluation of gestational age in infants.[11] Study of these patterns led to the characterization of two types of sleep; this framework of behavioural states (which includes wakefulness) allowed the grouping of physiological parameters into definable entities.

However, in early development, the stability and congruence of physiological characteristics are marginal. In particular, concordance between behavioural and EEG variables is poor.[12] Transition between states occurs discontinuously, relatively frequently over short intervals, and can sometimes be provoked by stimulation at some moments but not at others. This may continue up to the age of 6 months.[13] Therefore, it has appeared more appropriate to envisage behavioural states of (at least) young infants in a dynamic perspective. While these states would represent collections of functional patterns that can be found with high consistency both within and across healthy infants, they would essentially reflect the outcome of spontaneous interaction between dynamic subsystems. Despite this complexity, detailed knowledge of the subsystems is not required for studying 'macroscopic' dynamic stability and critical instability of states.[14] Behavioural states of human infants have been categorized into discrete stable conditions of the infants that are easily recognizable clinically.[15] Associated postural patterns have also been described.[16]

The emergence of behavioural states in early life has been used as an indicator of physiological development and a predictor of good neurological outcome following early insults.[17] The behavioural states were formulated in the context of observation of healthy, term newborns.[15] While they cannot be appreciated in fetal life, for obvious technical reasons, cyclic activities have been described in utero. These mostly concern motor behaviour. Spontaneous movements can be identified by ultrasonography from about 10 weeks of gestation. Although it may appear futile to question to what extent they reflect wakefulness, as this notion cannot be tested in fetal life, some authors have suggested that certain early fetal movements are reminiscent of postnatal movement patterns seen during wakefulness.[18] Clearly rhythmical cycling of motor activity appears between 20 and 28 weeks of gestation[12,19] (Fig. 1). 'Rest'–activity cycles last between 40 and 60 minutes.[19] The resting pattern is characterized by motionless periods including absence of respiratory movements that last minutes to hours.[20] The periods of quiescence are also characterized by reduced responsiveness to environmental stimuli and arousal from sleep. They amount to 53% in infants born at 30 weeks' conceptional age and increase to 60% near term. At 40 weeks' gestational age, there is no significant difference between infants born preterm and term neonates,[21] except for a higher respiratory rate in the former.[22]

Quiet sleep/non-REM sleep

Prechtl's behavioural state 1, recognized by eyelid closure, deep breathing, and absence of general movements, is often referred to as 'quiet sleep' (QS). As noted by Prechtl and Beintema,[15] 'spontaneous startles' may occur. These are sudden, generalized movements that occur irregularly. They become rare after the newborn period. In preterm infants, regularity of breathing becomes informative about sleep states from about 31 weeks' gestation.[22] QS is commonly described from 32 weeks,[11] though recent studies using EEG criteria have suggested that it may be identifiable from around 28 weeks.[23] The EEG during QS shows reliable characteristics from around 31 to 32 weeks, with diminishing proportions of discontinuity. EEG recordings based on elimination of low frequency filtering ('direct current' recordings) revealed prominent, long-lasting bursts of large amplitude delta activity during QS in infants aged 33 to 37 weeks' post conceptional

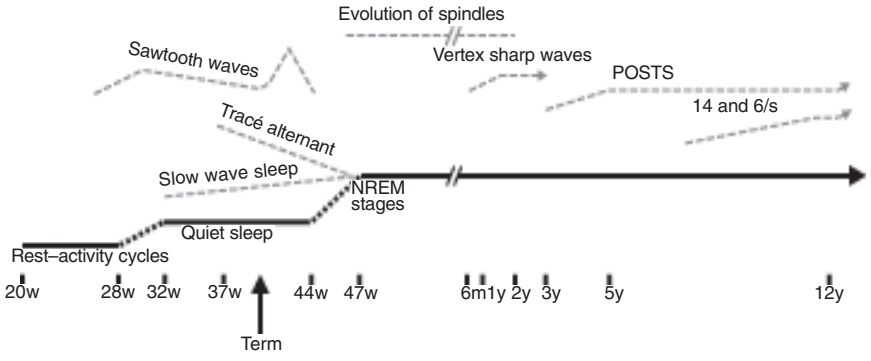

Figure 1: *Schematic diagram of temporal evolution of main neurophysiological features of sleep in infancy and early childhood. Black lines indicate periods of appearance of main behavioural stages. Periods of transition between stages are indicated by ascending dotted lines. Grey dashed lines indicate occurrence and maturational trends of distinctive electroencephalographic features (ascending lines represent increase in occurrence, descending ones decrease, horizontal lines stability, and arrows continuation). POSTS, positive occipital sharp transients of sleep; NREM, non-rapid eye movement.*

age that are not seen on conventional EEG.[24] From around 37 weeks, QS is characterized by at least two different conventional EEG patterns, namely high amplitude delta activity and *tracé alternant* (Fig. 1). The latter is defined as bursts of slow waves, sometimes mixed with sharp waves, alternating with periods of relative quiescence. Higher levels of interhemispheric coherence are noted during the bursts, particularly over the frontal, occipital, and temporal regions, while interhemispheric coherence appears low over the central regions.[25] Studies of direct current coupling show significant relationships between specific cortical areas (notably occipital and frontal phase locking). In addition, spectral approaches of *tracé alternant* in term neonates have found consistent quadratic phase coupling that was generated by a pattern-spanning time-variant phase-locking process.[26] These neurophysiological findings suggest that significant information processing takes place between specific neuronal populations during QS in neonates.

Whereas sleep does not usually commence with QS before the age of 44 weeks, sleep onset is consistently in QS thereafter. This maturational change may be due to a shift from excitation of pedunculopontine nucleus neurons by N-methyl-D-aspartic acid to kainic acid, as well as an increase in inhibitory responses to serotonergic type 1 agonists.[27] Anatomical studies have shown that cholinergic afferents to the thalamic nuclei become active around the same time,[28] and further development of cholinergic neurons is occurring during this period.[29]

From 44 to around 47 weeks' gestational age, the EEG patterns of QS change dramatically. *Tracé alternant* disappears as the proportion of slow waves increases, and the term 'slow-wave sleep' can be used. Further categorization of sleep states into the stages of sleep described in adults[7] becomes possible.[30] Conventionally, stages are thus defined on the basis of standardized criteria using EEG, EOG, and EMG features. Non-rapid eye movement (NREM) sleep includes four stages, stages 3 and 4 commonly being referred to as slow wave sleep (or 'delta' or 'deep' sleep) because of the predominating slow EEG activities. The temporal succession of these different stages during a single period of sleep constitutes the sleep architecture.[6]

As sleep stages emerge, different EEG features appear. 'Sleep spindles' are one of the most striking of these features, so-called because they show this configuration in adults. They consist of rhythmic bursts of 14 per second activity seen over the fronto-central regions, particularly at the onset of sleep. They have been shown to arise from synchronized activities in functionally important neuronal networks linking the thalamus and the cortex.[31] Spindles result from rhythmic spike bursts in inhibitory (GABAergic) thalamic reticular neurons that induce rhythmic rebound bursting in cortical neurons. This process has been shown to result in effective deafferentation of the cerebral cortex.[32] Despite thalamic gating, cortical neurons show enhanced responsiveness and properties of synaptic plasticity.[33] These might have a role in memory and learning processes.[34] The changed role of GABA in the neonatal brain[35] might account for the appearance of spindles from the end of the neonatal period. Spindles show a marked developmental evolution over the first 18 months to 2 years of life[36] (Fig. 1). Interhemispheric synchrony of the spindles is not constant until nearly the infant is 2 years. Spindles appear as prolonged runs (up to 10–15s) between the ages of 3 and 6 months. The frequency of the spindles also changes, with 12/s components becoming more prominent around 12 months of age.

Another EEG feature, which is also prominent from around 48 weeks' gestation, is characterized by large amplitude, often biphasic (positive-negative) slow waves, known as K complexes (the origin of the term is obscure, though 'K' might refer to the knocking noise originally used to evoke them in the laboratory).[37] They are frequently seen in association with the spindles. They are often associated with a small increase in heart rate, reflecting peripheral sympathetic activation. They occur without an obvious trigger but may also appear in response to auditory or tactile stimulation. Prominent evoked potential components are seen at 500ms (N550) and 900ms (P900).[38] While some authors regard K complexes as aborted arousals, others emphasize their role in maintaining sleep. In contrast with this view of K complexes as resulting from an active process, some authors regard them as emerging spontaneously during deep sleep. Neurophysiologically, the K complex reflects a sequence of depolarization and hyperpolarization in cortical neurons. These changes may trigger spindles through corticothalamic connections. The shape and duration of K complexes form the basis, at least partially, of the slow waves seen in 'slow wave sleep'.[39] This is different from another corticocortical mechanism of slow rhythmicity known as the slow oscillation (0.9Hz), whose maturational aspects are yet to be documented. Other, even slower oscillations of brainstem origin lasting around 15 minutes have been proposed,[40] but not yet confirmed in adults, and any developmental significance is not established.

Vertex transients, sometimes termed 'vertex sharp waves', are a third EEG feature associated with the earlier stages of sleep. These may occur as infrequent broad components by 6 months of age, but are seen as prominent elements around 16 months, becoming sharper with a shorter duration by 24 months and repetitive by 30 months[41] (Fig. 1). Vertex transients are thought to correspond to auditory and respiratory-related evoked potentials, with a latency around 300ms.[42]

Other characteristic EEG waveforms have been described in sleep, including occipital 'cone' waves (O waves), positive occipital sharp transients of sleep (POSTS),[43] and surface positive spikes at 14/s and 6/s (Fig. 1). Cone waves peak between 6 months and 3 years of age, decrease thereafter, and disappear during adolescence. POSTS are not consistently established before 5 years of age,[44] although they may be prominent in some children from about 3 years. Fourteen and six per second positive spikes appear later in childhood and are uncommon before puberty. They arise from the mesial aspect of the posterior temporal lobe and their functional significance is unknown, although it is not related to epilepsy.[45]

In QS/NREM sleep, only slow or no eye movements are evident. QS contains all the sleep stages usually summarized as NREM sleep from around 48 weeks, though further maturation continues until around at least 6 years of age.[6] Although sleep stages are defined by their polygraphic appearances, the contribution of EOG and EMG to NREM sleep staging is limited, stages 1 to 4 being mostly defined on the basis of EEG features. Stage 1 sleep can be differentiated from marked drowsiness in adults and older children by slowing of the alpha rhythm and the appearance of theta activity, but this transitional stage is often difficult to identify precisely in young infants. Vertex (sharp) waves can be seen at this stage, though they persist into deeper sleep stages. Slow eye rolling

movements can be seen but they are not specific to this stage. Stage 2 sleep is easier to identify, with the appearance of distinctive sleep spindles and K complexes. The background EEG activity contains variable amounts of delta activity. Stages 3 and 4 are characterized by high amplitude slow-wave activity (<50% of the scored epoch in stage 3; >50% in stage 4). The background EEG activity may be indistinguishable from that of stage 2 as seen in young children. This leads to discrepancies in scoring, as an epoch with high-voltage slow wave activity and a spindle and/or a K complex would not be regarded as stage 2 in adults.

In addition to the main stages of sleep described above, there is now evidence of 'microstates' mostly detected during periods of NREM sleep.[46,47] These reflect depth of sleep, corresponding to the level of stimulation required to awaken the subject. Depth of sleep has been shown to be regulated by the activity of sleep-promoting neurons located in the ventrolateral preoptic area of the hypothalamus mirrored by decreased activity of wake-promoting neurons in various arousal centres including the brainstem-thalamic activating system.[48] When excitatory input to the thalamus diminishes, thalamocortical neurons gradually become more hyperpolarized leading first to light sleep with spindle oscillation. At higher levels of hyperpolarization, delta waves are produced. However, these changes do not appear as a linear process, but rather as a continuum of coalescing low and high frequency oscillations under the slow oscillation.[49]

One EEG manifestation of the slow oscillation is the so-called 'cyclic alternating pattern' (CAP). This consists of transient arousal complexes (phase A) that periodically interrupt the tonic theta/delta activities of NREM sleep (phase B).[47] The different phases of the CAP can be linked to the UP and DOWN cortical states[50] under the influence of the slow cortical sleep oscillation, and of the interplay of this and the thalamocortical and corticothalamic networks. The most common subtype of CAP is the A1, associated with mild or trivial polygraphic variations and activation of somatic and autonomic systems.[47,51] This subtype accounts for up to 90% of all CAP A phases during normal sleep, occurring approximately 200 to 400 times per night.[52,53] The developmental aspects of CAP are yet to be fully documented.[54]

Active sleep/REM sleep

Prechtl's behavioural state 2 is operationally equated to 'active sleep' (AS). In preterm infants, AS can be recognized clinically by irregular heart rate and respiratory movements, together with brisk body movements and REM. There is also muscle atonia,[55] which determines posture.[16] Similar eye movements have also been observed in fetuses,[56] but they are particularly prominent in the first weeks following term. Various types of REM have been documented in newborn infants.[57] They show developmental changes during early infancy.[58] Historically, REM sleep was first discovered in infants.[59] Sleep onset in young infants is often in REM sleep or with a very short REM latency compared with older children and adults. This tendency changes over the first months of life, as QS becomes predominant in the early phases of sleep. Systematic identification of a young infant's sleep epoch as either AS or QS is not always possible. In preterm infants, a large proportion of sleep is thus referred to as 'indeterminate sleep'. The proportion of indeterminate sleep decreases as that of QS increases from 32 to 40 weeks' gestation, while the amount of AS remains constant.[60] In term infants, REM sleep accounts for around 50% of total sleep time (i.e. 8–9h/day spent in REM sleep) and, by some accounts declines from around birth until the end of puberty, when it reaches the 15 to 25% proportion of sleep time seen in adults.[61]

REM sleep has also been described as 'dream' sleep following observations mostly performed in adults[59] and confirmed in children, that although some degree of mental activity can occur in NREM sleep, most vivid dreams occur during REM sleep. In a study of smiling during sleep in term neonates, more than 98% of smiles were found to occur during REM sleep.[4] A body of evidence suggests that REM sleep may be involved in emotional regulation and localized recuperative processes,[62] although its presumed role in memory consolidation has not been confirmed.[63]

The temporal association of REMs with continuous EEG becomes consistent by 30 to 31 weeks' gestational age.[64,65] In infants younger than 36 weeks' gestational age, the association between REMs and continuous EEG is closer than with other features of AS, such as heart or respiratory rate variability, change in body temperature, or motility.[66]

REM sleep is sometimes referred to as 'paradoxical sleep' because its EEG features have been likened to those of wakefulness. Indeed, the discharge patterns of many neurons during REM sleep resemble those seen in wakefulness. Background EEG activity consists of mixed frequencies, usually of relatively low amplitude, although in young infants, differences between EEG in AS and QS are not as clear as in older children. In the former, bursts of sharp theta activity ('sawtooth' waves) may be seen over the temporal regions from a very early age (approx. 27wks' gestation). In older children, occipital sharp waves appear in correlation with the bursts of REMs. These transient EEG waves reflect intense firing in the pontine reticular formation that propagate through the lateral geniculate nucleus to the occipital cortex, hence the term 'ponto-geniculo-occipital waves' or 'PGO waves'. A similar activity can be evoked by abrupt stimuli that provoke a startle response in alert infants. Current views of the mechanisms of REM production and termination focus upon reciprocal interactions between cholinergic REM-on and aminergic REM-off neurons in the pontine reticular formation.[67,68] Although there are extensive interconnections between these structures and the thalamic circuits related to slow-wave sleep, they are considered to be discrete entities.

Transitions

Circadian rhythms (i.e. self-sustaining nearly 24-hour rhythms), not only contribute to the sleep–wake cycle, but also to the propensity to initiate NREM or REM sleep. Circadian rhythms responsive to light signals emerge in primates at a developmental age considered equivalent to 24 weeks' gestation in humans.[69] However, newborn infants produce little or no melatonin. After birth, there is progressive maturation of the circadian system with day/night rhythms of activity and hormone secretion developing between 1 and 3 months of age.[70] Thereafter, melatonin production increases for the next 9 or 10 months and remains stable until just before puberty, when it declines to reach adult values.[71] Human evidence suggests that in fetal life, the mother can entrain the developing circadian rhythm of the fetus to the light/dark cycle.[72] However, although sleep and circadian rhythms are coupled, they are generated by different neuronal mechanisms and their time course of

development is not consistently comparable.[73] Ultradian cycles of NREM-REM sleep can be recognized from 4 to 6 weeks of age, lasting about 60 minutes, reaching 90 minutes by around 1 year of age.

The mechanisms underlying transitions between behavioural states are currently poorly understood. This may be due to the fact that the assignment of discrete states, while providing a widely-used classification tool for clinical practice, does not take into account essentially continuous characteristics in the progression of sleep. This even applies to wake–sleep transitions. Studying the EEG during this transition, Hori et al.[74] identified nine EEG stages that lead from wake to sleep onset in adults, thus subdividing Rechtschaffen and Kale's standard stages wake, stage 1 and stage 2[7]. Direct current shifts, recorded at the transitions between drowsiness, stage 1, and stage 2 sleep in adults, are also found at the transition between slow-wave and REM sleep. It is currently unclear if these represent gradual changes in calcium signalling or the effects of neuromodulatory systems controlling these transitions.[75]

Clinical implications

Despite increasing understanding of the processes that underlie the generation of sleep stages, the functions of sleep remain unclear. Studies of the roles of sleep in brain plasticity have provided important insights into the different processes of long-term memory, including motor, perceptual-motor, sensory-perceptual, and cognitive skill learning. These studies have mostly been performed in adults (whether humans or animals), using various paradigms such as post-training modifications of sleep architecture or sleep deprivation. They showed that both REM sleep and NREM sleep are involved in long-term memory systems, the former being more implicated in implicit and the latter in explicit learning.[76] In children, there is also mounting clinical evidence of the importance of sleep for cognitive and behavioural functioning. Studies of this relationship have mostly focussed on apnoeas and sleep fragmentation.[77] In a recent study, school-age children with obstructive apnoeas related to tonsillar hypertrophy showed subtle impairment of attention, language, memory, and sensorimotor perception.[78] Obstructive sleep apnoeas have also been implicated in the pathophysiology of sudden infant death syndrome. This condition is caused by a deficit in maturational processes that enable infants to arouse when exposed to a life-threatening situation, such as a severe obstructive apnoea, oesophageal reflux, cardiac arrhythmia, or external suffocation.[79] The mechanisms of 'sudden unexpected death in epilepsy' are much debated, but sleep has been clearly implicated as an important independent factor.[80]

More studies are needed to characterize the role of sleep and, in particular, of the maturation of sleep processes in younger children, in relation to development. Such studies might clarify the complex interplay between abnormal sleep patterns and intellectual disability in neurodevelopmental conditions such as autism, Down, Rett, or Angelman syndromes. Some findings seem to vary between these different conditions, confounded by numerous factors that influence sleep, including structural brain abnormalities, seizure disorders, behavioural problems, and environmental factors. In Down syndrome, some authors have stressed the correlation they found between the reduction in REM frequency and percentage, and IQ.[81] Similar alterations of REM episodes, with an increase in indeterminate sleep, were also found in children with autism and Rett syndrome and also in those with Angelman syndrome,[82] but this deteriorated with increasing age only in Rett syndrome.[83] The relationship between abnormal sleep patterns and intellectual disability is likely to be particularly intricate. It is possible, but not demonstrated, that alterations of particular sleep stages may interfere with cognitive processes and behaviour. In addition, a proportion of the neurodevelopmental impairments and of the sleep problems arise as independent manifestations of underlying brain abnormality.

The broader implications of the complex and multifaceted relationships between sleep and seizure disorders in children have been highlighted recently.[84] Some associations between specific epileptic seizure types and particular stages of sleep are well recognized. This is found notably in epileptic spasms and sleep onset/offset, and juvenile myoclonic epilepsy and arousal. Epileptiform activities are distributed unequally across different stages of sleep, varying according to the underlying aetiology and, to some extent, seizure type.[85] Focal spiking related to benign epilepsy with centrotemporal spikes increases to a maximum during stage 2 NREM sleep, while some idiopathic generalized epilepsies show more spiking during REM. A better understanding of the role of stage 2 sleep in learning and memory, discussed above, helps to explain the cognitive difficulties some children experience when spiking continues throughout NREM sleep – continuous spike-waves in slow wave sleep/electrical status epilepticus in sleep,[85] and the predilection of early thalamic injury to produce this EEG picture.[86] However, the epilepsies appear to exert significant effects on sleep, even where spikes are much less evident. Epilepsy disrupts sleep architecture and alters REM sleep in particular.[87] The effects of antiepileptic medication are also varied and complex.[88] Current interest has focused on the effects of different epileptic syndromes on sleep microstructure and in particular on the finding of increased CAP rate and likelihood of seizures in the 'A phase'.[89–91] The same thalamocortical network mechanisms that produce spindles and K complexes, prevalent in this 'A phase', have also been implicated in the onset of epileptic seizures.[92]

Conclusion

Increased insights into the various maturational processes and circuits involved in sleep are currently leading to the development and improvement of clinical interventions for children with neurodevelopmental disorders. The developmental profiles of sleep phenomena, such as those occurring in thalamocortical networks in NREM sleep and in the very different pathways of REM sleep, are striking and clearly occur in relation to maturation of these systems. The clearer understanding of these, which now seems in prospect, will allow more rational assessment of abnormal sleep related phenomena, such as the significance of EEG spikes in children with autism or of sleep disorders in the wider sense. Better appreciation of the role of sleep spindles in learning processes involving long-term potentiation in cortical neurons will help to clarify their implication both in cognitive development and in learning disabilities.* If more robust dynamic methods of assessing sleep in young children can be validated, perhaps based on the notion of microstates, this might allow therapeutic interventions to be targeted more appropriately.

*US usage: mental retardation.

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List of abbreviations

AS	Active sleep
CAP	Cyclic alternating pattern
NREM	Non-rapid eye movement
QS	Quiet sleep
REM	Rapid eye movement