

# Effect of Age on EEG Arousals in Normal Sleep

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**Summary:** EEG arousals were quantified in 40 nocturnal polysomnographic recordings belonging to four age groups (teenagers: 10 to 19 years; young adults: 20 to 39 years; middle-aged: 40 to 59 years; elderly:  $\geq 60$  years). Ten subjects (five males and five females) participated in each group. The subjects were healthy and sound sleepers. All sleep recordings were preceded by an adaptation night which aimed at excluding the presence of sleep-related disorders. The recordings were carried out in a partially soundproof recording chamber and in a standard laboratory setting. Arousal indices (AI), defined as the number of arousals per hour of sleep, were calculated for total sleep time (AI/TST) and for all the sleep stages. AI/TST increased linearly with age ( $r=0.852$ ;  $p<0.00001$ ): teenagers (13.8), young adults (14.7), middle-aged (17.8), elderly (27.1). An age-related positive linear correlation was found also for the arousal indices referred to NREM sleep ( $r=0.811$ ;  $p<0.00001$ ) and to stages 1 and 2 ( $r=0.712$ ;  $p<0.00001$ ), while in stages 3 and 4 and in REM sleep, arousal indices showed stable values across the ages. Overall, arousals lasted  $14.9\pm 2.3$  seconds, with arousal duration stable across the ages (range of means: 13.3-16.6 seconds) and no relevant differences between NREM sleep ( $14.6\pm 2.5$  seconds) and REM sleep ( $16.2\pm 5$  seconds). The paper discusses the impact of age on arousals, the similarities between arousals and the *phases d'activation transitoire*, and the consideration that arousals are physiological components of sleep.

**Key words:** Normal sleep; arousals; aging; sleep microstructure; *phases d'activation transitoire*

THERE IS INCREASING AGREEMENT on the issue that the essence of disturbed sleep is fragmentation, frequent interruptions, and lack of continuity. Unfortunately, the conventional sleep-scoring system is insufficient to tabulate sleep fragmentation. The Rechtschaffen and Kales manual was actually developed to provide guidelines for staging sleep in normal human adults,<sup>1</sup> and not for producing microanalysis of brief arousals. The standard procedure assigns a single stage score to the single 20-second or 30-second epoch, even when polygraphic features of different stages are present in the same epoch. If a transient arousal occupies  $<50\%$  of the epoch, the epoch is scored according to the polygraphic activities that take up its greatest portion. If the transient arousal covers the majority of the epoch length, the epoch is scored as wakefulness. In both cases, transient arousals are overlooked using standard procedure

scoring. In the Rechtschaffen and Kales manual, the only clear reference to arousals is applied to movement arousals, related to muscle activity during sleep, and defined as an increase in EMG on any channel which is accompanied by a change in pattern on any additional channel. Even though movement arousals can have some importance in the scoring of stages, the manual explicitly states that they are not used as epoch scores.

With the development of clinical sleep medicine, there has been growing attention to EEG arousals and to their possible relation with inadequate sleep. In the light of this, the need for microanalysis integrating the standard scoring procedures has become a cogent issue. In 1992, the American Sleep Disorders Association (ASDA) published a set of rules for scoring EEG arousals independent of the Rechtschaffen and Kales system.<sup>2</sup> So far, arousals have been basically investigated in conditions of disturbed sleep (especially sleep-related breathing disorders), but agreement on a quantitative definition of boundary conditions has never been reached. All subjects appear to have a certain number of spontaneous arousals, which are an intrinsic component of physiological sleep.<sup>3,4</sup> However, the mini-

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mal number of interruptions that may characterize disturbed sleep, or—conversely—the maximal number of interruptions that may be allowed as undisturbed sleep, remain to be established. Until normative data on EEG arousals in healthy subjects without complaints about sleep are defined, the validity of their clinical application should be considered precarious.

The present study reports the number, distribution, and duration of EEG arousals quantified under standardized recording conditions in normal sleepers of different age groups.

## MATERIAL AND METHODS

The data were collected from 40 nocturnal polysomnographic recordings belonging to four age groups: teenagers, 10-19 years; young adults, 20-39 years; middle-aged, 40-59 years; and elderly,  $\geq 60$  years.

Participants were paid volunteers, recruited for previous normative studies carried out at the Parma University Sleep Disorders Center. A total of 57 subjects aged between 10 and 80 years who provided informed consent were the candidates. Selection proceeded according to a number of requirements. Candidates had to be non-complaining healthy individuals with regular life habits, good sleep quality, and no daytime complaints. Moderate smoking (less than 10 cigarettes per day) was allowed. Not more than two cups of coffee and two glasses of wine or beer could be taken daily. Candidates had to be free from medical and neurological disorders. Exclusion of psychiatric disturbances was based on the DSM-III-R (before 1994) or DSM-IV criteria (since 1994). The accustomed time to go to bed had to range between 22:00 and 24:00 hours. Most nights, subjects were required to fall asleep in less than 30 minutes, to sleep more than 6½ hours, and to have fewer than three nocturnal awakenings (never prolonged). All candidates were monitored at home for 10 consecutive days.

Every morning, each candidate completed a multisection questionnaire providing information about sleep quality.<sup>5</sup> Subjects were required to be fairly or completely satisfied with their sleep, with little variability across the nights. Daytime vigilance was evaluated subjectively at regular intervals. Napping had to be absent, as well as excessive diurnal sleepiness. The subjects that met these requirements were asked to maintain their habitual sleep-wake schedule, which was controlled by sleep logs in the days immediately before the recording sessions. In the 3 weeks prior to and during laboratory investigation, participants were not allowed to use CNS drugs or any other medication interfering with sleep.

A video-controlled adaptation night at the sleep laboratory allowed the selected subjects to familiarize themselves

with the sleep laboratory, and was meant to assess the absence of sleep disorders. In order to investigate periodic limb movement syndrome (PLMS), polysomnography of all subjects included bilateral EMG of the anterior tibialis muscles. Exclusion was determined by a PLMS index  $\geq 5$  per hour of sleep. Sleep-related breathing disorders (SRBD) were monitored in all subjects by means of oronasal airflow and respiratory belts. Additionally, oxygen saturation, snoring, and body position were monitored in all individuals over the age of 30. Exclusion was determined by a respiratory disturbance index  $\geq 5$  per hour of sleep. When snoring was reported as a frequent characteristic of sleep, esophageal pressure was measured to exclude upper-airway resistance syndrome. Across all the age groups, BMI never exceeded 25 kg/m<sup>2</sup> in males and 23 kg/m<sup>2</sup> in females. On the basis of subjective assessment and polysomnographic findings, 10 individuals (5 males and 5 females) were selected for each age group.

Participants went to bed at their usual time, and they were asked to refrain from drinking beverages containing caffeine or alcohol during the previous afternoon and evening hours. The recordings were accomplished in a partially soundproof recording chamber (sound pressure level below 30 dB Leq) under video-controlled supervision in a standard laboratory setting in order to avoid the occurrence of arousals induced by perturbing environmental stimuli. EEG was obtained from C3/A2 derivation integrated by bipolar montages (Fp1-F3, F3-C3, C3-P3, P3-O1 or Fp2-F4, F4-C4, C4-P4, P4-O2). Sleep stages and arousals were scored from the central EEG derivation. Polysomnographic investigation was limited to standard montages in order to minimize sleep disturbance. Eye movements, submental electromyogram (EMG), and heart rate were recorded bipolarly. A calibration of 50 mV/cm was used for all the EEG channels with a time constant of 0.1 second and a high-frequency filter in the 30 Hz range. The total recording time for all recordings was 500 minutes. Sleep quality and daytime sleepiness were assessed upon awakening and the day after the recording.

The analysis of conventional sleep parameters (macrostructure) was based on the standard guidelines using 30-second epochs,<sup>1</sup> while arousal parameters were scored according to the ASDA's rules<sup>2</sup>: arousals are characterized by abrupt changes in EEG frequency, which may include theta, alpha and/or frequencies greater than 16 Hz but not spindles. At least 10 seconds of continuous sleep must precede the EEG arousal, and a minimum of 10 seconds of intervening sleep is necessary to score a second arousal. Arousals in NREM sleep may occur without concurrent increases in submental EMG amplitude, while they are scored in REM sleep only when accompanied by concurrent increases in submental EMG amplitude. The EEG frequency shift must be 3 seconds or longer in duration.

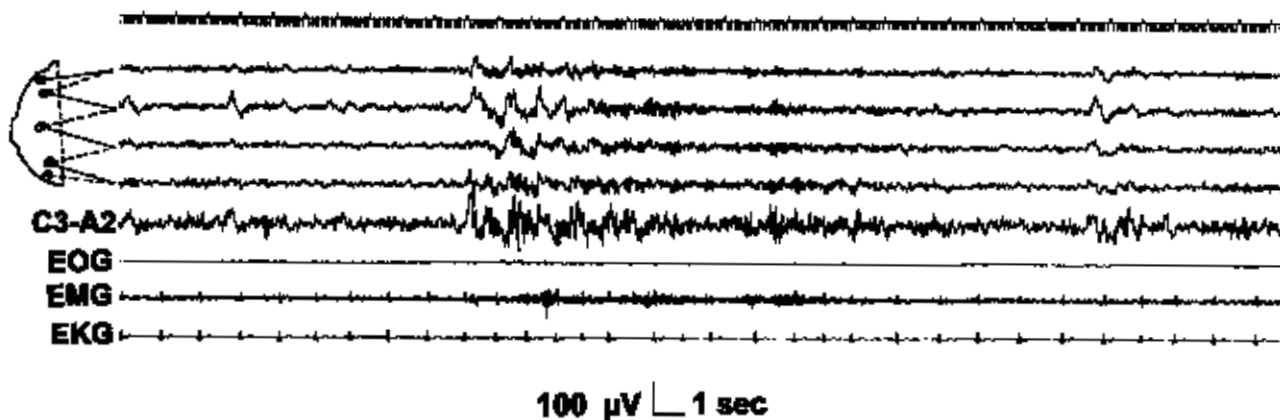


Figure 1.—EEG arousal in stage 2 sleep preceded by a sequence of K-complexes.

Table 1.—Independent identification of arousals by the two raters (MGT and LP)

		MGT		
		identified arousals	missed arousals	total arousals
LP	identified arousals	5394	482	5876
	missed arousals	337		337
	total arousals	5731	482	6213

Arousal scoring is independent of Rechtschaffen and Kales scoring procedures. Subject to specific conditions, K-complexes and delta waves accompanied by an EEG frequency shift can be scored as arousals (Fig. 1).

For each group the following sleep parameters were scored:

**Sleep macrostructure**—Sleep latency (SL): the interval between lights-out and the first appearance of stage 1 subsequently progressing into stage 2; total sleep time (TST): the time from sleep onset to the end of final sleep epoch minus time awake; wake after sleep onset (WASO): the time spent awake between sleep onset and end of sleep; total duration of stage 1 (S1), stage 2 (S2), stage 3 (S3), stage 4 (S4), NREM sleep and REM sleep.

**EEG arousals**—Total number of arousals in the Rechtschaffen and Kales stages; arousal indices (AI), defined as the number of arousals per hour of sleep, calculated for total sleep time (AI/TST), stages 1 and 2 (AI/S1+S2), stages 3 and 4 (AI/S3+S4), NREM sleep (AI/NREM), REM sleep (AI/REM), and mean duration of arousals.

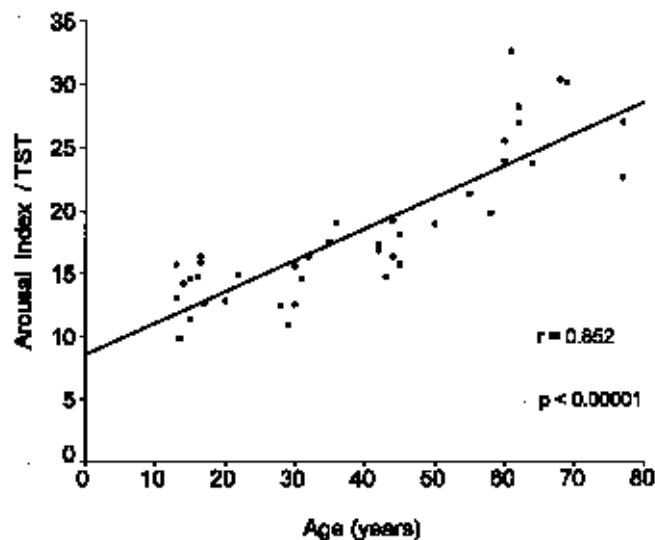


Figure 2.—Evolution with age of arousal frequency during total sleep time (TST).

### Statistical Analysis

All recordings were scored separately by two “blind” EEG readers (MGT and LP). The inter-rater agreement was 0.92 for the macrostructure and 0.87 for arousals.

The agreement between MGT and LP for macrostructural data was defined in a previous experimental set, in which a number of sleep recordings were scored independently by pairs of Italian sleep experts from different laboratories, in order to establish the intra- and inter-group concordance<sup>6</sup> and match the results with those of an automatic sleep-stager.<sup>7</sup>

For the present study, the inter-rater agreement for arousals was assessed on the global values of the 40 recordings. Under independent scoring conditions for

**Table 2.**—Age-related macrostructural variations

	subjects				p F (3, 36)	statistical differences
	10 teenagers (TA)	10 young adults (YA)	10 middle aged (MA)	10 elderly (ED)		
SL	9 (5)	16 (14)	6 (5)	12 (7)	NS	
TST	465 (26)	455 (33)	464 (28)	406 (42)	0.0001	ED < others
SE	93 (5)	91 (7)	93 (6)	81 (8)	0.0001	ED < others
WASO	10 (11)	12 (8)	17 (17)	68 (45)	0.0001	ED > others
S1	11 (5)	21 (12)	12 (7)	32 (16)	0.0001	ED > TA = MA
S2	225 (33)	219 (37)	235 (47)	234 (31)	NS	
S3	40 (11)	36 (13)	59 (22)	33 (11)	0.002	MA > others
S4	73 (17)	61 (16)	43 (23)	21 (13)	0.0001	ED < TA = YA ; MA < TA
S3+S4	113 (23)	97 (24)	102 (30)	54 (16)	0.0001	ED < others
REM	116 (25)	118 (19)	115 (24)	86 (23)	0.009	ED < others
REML	81 (30)	76 (20)	79 (16)	82 (32)	NS	

SL: sleep latency. TST: total sleep time. SE: sleep efficiency. WASO: wake after sleep onset. S1: stage 1. S2: stage 2. S3: stage 3. S4: stage 4. REM: REM sleep. REML: REM sleep latency. Standard deviations in parentheses. Apart from SE (expressed in %), all variables are expressed in minutes.

**Table 3.**—Distribution of EEG arousals throughout the Rechtschaffen and Kales stages

	subjects				p F (3,36)	statistical differences
	10 teenagers (TA)	10 young adults (YA)	10 middle aged (MA)	10 elderly (ED)		
Total	107 (17)	112 (22)	137 (15)	184 (38)	0.0001	ED > others
S1	7 (4)	8 (5)	11 (8)	24 (17)	0.002	ED > others
S2	68 (19)	70 (27)	85 (17)	134 (34)	0.0001	ED > others
S3	6 (5)	3 (4)	7 (6)	6 (8)	NS	
S4	7 (4)	3 (2)	3 (4)	1 (1)	0.0001	TA > others
S3 + S4	13 (6)	6 (5)	10 (8)	7 (8)	NS	
NREM	88 (15)	84 (3)	106 (20)	165 (30)	0.0001	ED > others
REM	18 (14)	26 (5)	29 (16)	17 (13)	NS	

Variables are expressed in absolute values. Total: sleep period time. S1-S4: stages 1, 2, 3, 4. NREM: NREM sleep. REM: REM sleep. WASO: wake after sleep onset. Standard deviations in parentheses.

every sleep recording, each rater marked on a personal sheet the exact time and epoch in which an arousal occurred. Data comparison was made when the scoring procedure was completed. As illustrated in Table 1, a total of 6213 arousals were identified by at least one of the two raters. LP missed 337 of the 5731 arousals identified by MGT, while the latter missed 482 of the 5876 arousals detected by LP. The number of arousals on which both

raters agreed was 5394 (86.8% of 6213). Quantification and measurement was carried out only on the arousals recognized by both scorers. With respect to duration, the beginning and end of each agreed arousal was established concomitantly by the two raters.

Across the ages, overall differences between macrostructural parameters, number of arousals, and AI were analyzed by a one-way ANOVA. Where the null

**Table 4.**—Arousal indices in the different portions of sleep

	subjects				p F (3, 36)	statistical differences
	10 teenagers (TA)	10 young adults (YA)	10 middle aged (MA)	10 elderly (ED)		
AI/TST	13.8 (2.2)	14.7 (2.6)	17.8 (2)	27.1 (3.3)	0.00001	TA < MA ; ED > others
AI/ S1+S2	18.4 (3.7)	19.3 (3.4)	25.5 (7.4)	37.9 (8.8)	0.00001	ED > others
AI/S3+S4	6.9 (2.9)	3.7 (3.1)	5.7 (4.8)	7.1 (6.1)	NS	
AI/NREM	15 (3)	14.8 (3.5)	18.2 (4.2)	30.7 (3.3)	0.00001	ED > others
AI/REM	9 (5.6)	13.3 (3.4)	14.7 (6.4)	11.3 (6.9)	NS	

AI: arousal index (number of arousals per hour of sleep) referred to: TST (total sleep time); S1+S2: stages 1 and 2; S3+S4 (stages 3 and 4); NREM: NREM sleep; REM: REM sleep. Standard deviations in parentheses.

hypothesis could be rejected (significance cut-off:  $p < 0.05$ ), comparisons between the different ages were made by means of post-hoc tests (Bonferroni). Correlation coefficients were measured for estimation of AI versus age.

## RESULTS

In the subjective morning report, all participants defined the quality of the previous night's sleep as basically satisfactory and not far from their habitual nocturnal experience. There was no evidence of excessive daytime sleepiness. The main macrostructural data are presented in Table 2.

Sleep latency did not differ significantly across the ages, in which young adults presented the longest time to fall asleep (16 minutes) and the widest variability (standard deviation 14 minutes). Teenagers, young adults, and middle-aged subjects slept significantly more (sleep efficiency average range: 91% to 93%) than the elderly (sleep efficiency 81%). Accordingly, the intra-sleep wake time found in the older subjects was significantly longer (mean 68 minutes) than in the other age groups. The amount of stage 1 was significantly higher in the elderly (32 minutes) when compared to teenagers (11 minutes) and middle aged subjects (12 minutes), while stage 2 showed no significant differences among the four age groups. Slow-wave sleep (ie, stages 3 and 4) and REM sleep were significantly shorter in the older subjects when compared to teenagers, and young and middle-aged adults. No age-related differences emerged from REM latency. The distribution of EEG arousals is illustrated in Table 3.

Compared to the other age groups, the elderly presented significantly higher amounts of arousals throughout total sleep time (mean: 184), within stage 1 (mean: 24), stage 2 (mean: 134), and NREM sleep (mean: 165). In stage 4, the number of arousals was significantly higher in teenagers (mean: 7) when compared to the other age

groups. No age-related differences emerged from stage 3 and from REM sleep. Table 4 presents the arousal index (AI) data.

An age-related increase was found for AI/TST, AI/S1+S2 and AI/NREM sleep. AI/TST differed significantly across the ages ( $p < 0.00001$ ), with clear-cut discrimination between teenagers (13.8) and middle-aged subjects (17.8), and between the elderly (27.1) and all the other groups. AI/S1+S2 ( $p < 0.00001$ ) and AI/NREM ( $p < 0.00001$ ) presented significant differences between the elderly and the other age groups, while AI/S3+S4 and AI/REM showed stable values across the ages. AI/TST ( $r = 0.852$ ) (Fig. 2), AI/NREM sleep ( $r = 0.811$ ), and AI/S1+S2 ( $r = 0.712$ ) fitted a linear increase with age (all correlations:  $p < 0.00001$ ).

Arousal indices provided information on the recurrence of arousals. In particular, during NREM sleep, the mean interval between successive arousals ranged between 2 minutes in the elderly (AI/NREM: 30.7), and 4 minutes in teenagers and in young adults (AI/NREM:  $\leq 15$ ). Table 5 describes the duration of arousals.

The average length of arousals was substantially unmodified across the different ages (Table 5). Overall, arousals during TST lasted  $14.9 \pm 2.3$  seconds, with arousal duration stable across the ages (range of means: 13.3 seconds-16.6 seconds) and limited differences between NREM sleep ( $14.6 \pm 2.5$  seconds) and REM sleep ( $16.2 \pm 5$  seconds). No gender-related differences were detected for all the investigated parameters.

## DISCUSSION

Despite a fair constancy among normal subjects of a given age group, sleep varies from night to night in the same individual. The brain can never be completely isolated from the outside world, and even when environmental conditions are strictly under control, some internal unex-

pected factor (mental, motor, sensitive, vegetative) can have possible influences on sleep. In order to minimize sleep perturbation, the recording procedures used for the present investigation were limited to montages that allowed scoring of sleep stages and arousals. Thus, we could not quantify the number of arousals possibly associated with occasional PLMS, respiratory events, or other intercurrent phenomena.

The subjects at risk for PLMS and SRBD were controlled and withdrawn on the basis of anamnestic information and polygraphic cut-offs, although it is known that the clinical expression of certain sleep disorders, eg PLMS, can fluctuate from night to night. Upper-airway resistance syndrome was excluded in most snorers, although it is known that the syndrome can be present in non-snorers.<sup>8</sup> It is important to notice, however, that sleep macrostructure was compatible with age-matched standard findings,<sup>9</sup> that sleep quality was rated as satisfactory by all participants, and that there was no evidence of daytime sleepiness, a complaint strictly related to these disorders.

Our aim was to achieve a standardized setting in order to reduce the impact of internal and external perturbing events. Actually, we could not establish in all cases whether a given arousal occurred spontaneously or as a stereotyped evoked reaction. There is, however, consistent evidence that a given healthy individual expresses all nights a fairly constant number of arousals, which are hardly manipulated even when the sleeper undergoes sensorial disturbance.<sup>10,11</sup> What instead seems to have a strong repercussion on arousals is the age factor.<sup>12,13</sup>

The progressive increase of EEG arousals from the younger to the senior groups met the well-established issue that aging is physiologically associated with sleep fragmentation.<sup>4,14</sup> The frequency of arousals was lowest in teenagers (AI/TST: 13.8) and in young adults (AI/TST: 14.7), followed by a moderate increase in middle-aged subjects (AI/TST: 17.8), and by a drastic enhancement in the senior group (AI/TST: 27.1). The positive correlation between age and the number of arousals per hour of sleep has been already described by Mathur and Douglas in 55 subjects with a mean age of 37 and an interval of 20-70 years.<sup>13</sup> In that study, however, sleep was recorded from both normal subjects and patients with sleep-related breathing disorders (ie, snoring, apneas), and there was no acclimatization to or control of the environmental conditions in which the recordings were accomplished. Still, arousal frequency clustered around 15 per hour in the younger subjects and around 30 per hour in the elderly. In a further study carried out on a group of normal subjects aged 35.8±8 years, Bonnet and Arand reported a mean baseline arousal index of 13.7.<sup>15</sup>

Compared to previous investigation, in which the frequency of arousals was referred exclusively to TST, in the present study EEG arousals were also quantified during

Table 5.—Mean duration of EEG arousals in sleep

	subjects				
	10	10	10	10	40
	teenagers	young adults	middle aged	elderly	all ages
TST	13.9 (1.8)	16.6 (2.2)	13.3 (1.6)	15.7 (2)	14.9 (2.3)
NREM	13.9 (2)	16.4 (2.4)	12.7 (1.8)	15.4 (2.2)	14.6 (2.5)
REM	13 (1.8)	16 (2.3)	16.3 (6.8)	19.3 (5.8)	16.2 (5)

The mean values and standard deviations (in parentheses) are expressed in seconds and are referred to total sleep time (TST), NREM sleep (NREM) and REM sleep (REM), respectively.

superficial sleep (stages 1 and 2), deep sleep (stages 3 and 4), NREM sleep, and REM sleep. Overall, our data were in tune with the findings of the Strasbourg's school on the *phases d'activation transitoire*,<sup>3</sup> arousal patterns of sleep that share striking polygraphic similarities with the ASDA's arousals. Together with other phasic events, the *phases d'activation transitoire* are representative features of sleep microstructure, the clinical relevance of which remains to be completely explored.<sup>16</sup> The consolidated literature of the Strasbourg school indicates that the *phases d'activation transitoire* are under strong endogenous control.<sup>10</sup> Across the natural life span, the *phases d'activation transitoire* are characterized by an age-related increase in TST and by an age-related stability in deep sleep and in REM sleep.<sup>12</sup> Within each age group of the present investigation, the increase of AI/TST was mainly charged to NREM sleep and particularly to stages 1 and 2, whereas the arousal indices in deep sleep and in REM sleep showed trivial variations across the different ages.

The arousal index issue is closely related to the interval between successive EEG arousals. According to the ASDA report, EEG arousals occur in some conditions with a periodicity of about 1 minute.<sup>2</sup> This consideration is probably addressed to particular sleep disorders characterized by repetitive arousal intrusions (as occurs in obstructive sleep apnea syndrome), but it seems to be unsuitable for physiological conditions. Actually, in no age group and in no sleep stage did our data show a sustained 60-second periodicity. Accordingly, most of the *phases d'activation transitoire* identified in a group of normal subjects aged 19 to 23 years had a mean interval of 4.9 minutes.<sup>3</sup>

It is known, however, that in certain portions of sleep, arousals can appear grouped together in time, as occurs in the proximity of REM sleep,<sup>17</sup> where they may even reach approximate rates of one or more arousals per minute.<sup>18</sup> The existence of an endogenous arousal oscillation with a 20- to 40-second periodicity has been established in all

NREM stages, including the time between sleep onset and slow-wave sleep.<sup>18-20</sup> This natural arousal rhythm, expressed by standardized EEG features,<sup>21</sup> is arranged in the sequences of the cyclic alternating pattern known as CAP.<sup>18,22,23</sup> The ASDA arousals, at least those that occur in NREM sleep, appear to be components of the CAP phenomenon.<sup>24,25</sup>

According to the ASDA rules, only the EEG arousals lasting at least 3 seconds are considered for scoring, but no indication is supplied on their mean or maximal duration. Altogether, in our normal subjects, EEG arousals had an average length of about 15 seconds throughout TST, with minor differences between the ages and between NREM and REM sleep.

In conclusion, normal aging increases the number of EEG arousals throughout sleep, but has limited impact on their mean duration. Although increasing attention is addressed to the clinical relevance of sleep fragmentation, EEG arousal responses basically represent a general physiological phenomenon of cortical activation during sleep.<sup>3,26</sup> The consistency of our findings within the different age groups and the agreement with the historical literature indicate that EEG arousals are “expected guests” of physiological sleep rather than exclusive correlates of sleep disturbance. What remains to be determined is the threshold between normal and pathological values. The present study offers a set of normative data for evaluating the clinical validity of EEG arousals at representative ages across the life span.

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