



## Spatiotemporal EEG dynamics of the sleep onset process in preadolescence

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### ABSTRACT

**Background:** During preadolescence the sleep electroencephalography undergoes massive qualitative and quantitative modifications. Despite these relevant age-related peculiarities, the specific EEG pattern of the wake-sleep transition in preadolescence has not been exhaustively described.

**Methods:** The aim of the present study is to characterize regional and temporal electrophysiological features of the sleep onset (SO) process in a group of 23 preadolescents (9–14 years) and to compare the topographical pattern of slow wave activity and delta/beta ratio of preadolescents with the EEG pattern of young adults.

**Results:** Results showed in preadolescence the same dynamics known for adults, but with peculiarities in the delta and beta activity, likely associated with developmental cerebral modifications: the delta power showed a widespread increase during the SO with central maxima, and the lower bins of the beta activity showed a power increase after SO. Compared to adults, preadolescents during the SO exhibited higher delta power only in the slowest bins of the band: before SO slow delta activity was higher in prefrontal, frontal and occipital areas in preadolescents, and, after SO the younger group had higher slow delta activity in occipital areas. In preadolescents delta/beta ratio was higher in more posterior areas both before and after the wake-sleep transition and, after SO, preadolescents showed also a lower delta/beta ratio in frontal areas, compared to adults.

**Conclusion:** Results point to a general higher homeostatic drive for the developing areas, consistently with plastic-related maturational modifications, that physiologically occur during preadolescence.

### 1. Introduction

In the last few decades several findings have clearly demonstrated the local nature of sleep [1]. Indeed, different brain areas show specific sleep electroencephalographic (EEG) patterns, and distinctive sleep EEG hallmarks undergo a regional regulation (e.g., Ref. [2–5]). In this view, sleep represents a local and use-dependent phenomenon: considering the sleep-wake cycle as a continuum, it is possible to observe electrophysiological correlates of both sleep and wakefulness simultaneously in different cortical areas [6–9]. Moreover, according to the homeostatic perspective, the local features of sleep depend on the regional activity and plasticity during the previous wakefulness [10,11].

Sleep onset (SO) represents a complex, gradual, and dynamic process of transition between two different states: wakefulness and sleep. It is

accompanied by subjective, behavioral, and physiological changes [12] and it is characterized by frequency-specific regional and temporal electrophysiological modifications [13–16]. The electrophysiology of the wake-sleep transition has been exhaustively investigated in adulthood [12,17]. Scalp recordings showed that the frontal areas are the first to fall asleep, showing the very first signs of synchronization and the higher rate of delta activity increase, compared to the other frequency bands [13–16,18,19]. Similarly, the theta band globally spreads during the transition, mainly in frontocentral areas [15], and the activity in the alpha frequency range grows in anterior areas during the transition to sleep [14,15,20,21]. The sigma activity increases once asleep and the fastest frequencies start to decrease already before the beginning of the sleep period [15]. Studies with intracerebral recordings also found regional asynchronies between cortical and deep cerebral areas during the SO [22,23]. Furthermore, marked changes in brain dynamics

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**Abbreviations**

SO	sleep onset	TST	total sleep time
EEG	electroencephalogram	SWS	slow wave sleep
EMG	electromyogram	REM	rapid eye movement
EOG	electrooculogram	WASO	wake after sleep onset
FDR	false discovery rate	TBT	total bed time
FFT	fast Fourier transform	SEI	sleep efficiency index
NREM	non-rapid eye movements	PreSO	pre sleep onset
PSG	polysomnographic	postSO	post sleep onset
SWA	slow wave activity	SE	standard error
SDSC	sleep disturbance scale for children	LORETA	low resolution electromagnetic tomography
CBCL	child behavior checklist	BOSC	better oscillation detection method
		FNE	first night effect

interactions has been observed during the wake-sleep transition [24–28].

Starting from the evidence of modifications in the sleep EEG pattern in healthy aging [29], we recently investigated the spatiotemporal dynamics of SO in older adults [30], showing age-related peculiarities in the regulation of alpha and sigma band, and a decrease of delta activity and delta/beta ratio compared to younger adults, the latter pointing to a reduced homeostatic drive and higher arousal at SO in the elderly. Such finding suggests that the local electrophysiology of the SO process may be influenced by age.

Sleep EEG frequencies undergo massive changes during typical development [31], and modifications occurring in some EEG rhythm seem involved in brain maturational processes [32,33]. In particular, the delta power shows an inverted “U” shape trajectory [34,35], and a more posterior prevalence during development compared to adulthood [32, 36,37]. These phenomena parallel the maturational modifications in synaptic density [38] and in the grey matter’s volume [39], supporting the view of a relationship between brain maturations and developmental changes in Slow Wave Activity (SWA). The sigma activity also exhibits a pattern that strictly reflects the age-related brain modifications: changes in topography, amplitude, duration, frequency, density, and developmental trajectories are linked to the maturation of thalamocortical structures [40], which are responsible for generation and propagation of the sleep spindles.

Although children and adolescents exhibit different local frequency-specific sleep EEG patterns compared to adults, only two studies have investigated sleep EEG characteristics during the wake-sleep transition in typical development. Spiess and coworkers (2018) studied the slow waves at SO, aiming to investigate if the two distinct processes of synchronization responsible for the generation of Slow Waves Type I and Type II previously described in adulthood [16] do also occur in preadolescence. They found that preadolescents had a linear increase of density, amplitude, and slope in all the considered cortical areas (medial anterior, medial posterior, lateral left/right anterior and lateral left/right posterior), suggesting the absence of the temporal dissociation between the two processes of synchronization in this population [41]. Furthermore, the higher density and amplitude of slow waves observed in central and parietal areas of preadolescents, compared to young adults, point to a faster SO process for the centro-parietal areas, likely representing the expression of a higher local homeostatic need linked to plastic processes [41]. According to de Zambotti and coworkers (2020) the progressive cortical synchronization process during the wake-sleep transition also occurs in adolescence (12–20 years). The authors assessed the EEG pattern of the SO in the frontal region, showing an increase in the delta relative power and decrease in the alpha, sigma, beta1, and beta2 relative power in the transition to sleep. Furthermore, younger subjects expressed higher delta power and lower theta, alpha e sigma in frontal areas, as compared to the older ones.

Overall, the existing data on the EEG correlates of the SO process in

children and adolescents are scarce. The only two available studies are limited to the topography of the slow waves [41] and to the description of the SO in the frontal regions [42]. An exhaustive description of the spatio-temporal EEG dynamics of the SO process during typical development, accounting for the entire spectrum of frequency bands and for the entire scalp, is still missing.

Given the peculiarities of sleep EEG patterns in preadolescence and our preliminary data of different age-related SO dynamics in elderly [30], we aimed to investigate the spatio-temporal EEG correlates of the wake-sleep transition in a population of preadolescents. Since the SWA represents an index of sleep propensity and it changes during lifespan, with the most conspicuous modifications occurring in preadolescence, we directly compared SWA of preadolescents with a group of healthy young adults from a previously acquired dataset.

## 2. Materials and methods

### 2.1. Participants

Thirty-three healthy preadolescents (age range: 9–14 years) were selected from two dataset previously acquired in our laboratory. Ten participants were excluded from the analyses due to technical difficulties during the polysomnographic (PSG) acquisition (N = 3) or problems of other nature (i.e., high number of artifacts in the period preceding the SO, N = 7; see the Quantitative EEG analysis section for details). Hence, the analyses were computed on a sample consisting of 23 experimental subjects (10 F; mean age:  $11.5 \pm 1.66$  years).

Preadolescents with regular sleep-wake cycle, monitored by sleep log, have been included in the study and the parents of the participants filled out the Sleep Disturbance Scale for Children (SDSC) [43] and the Child Behavior Checklist (CBCL) [44] to exclude the presence of sleep disorders and medical and/or psychiatric conditions, respectively. The subjects with an IQ score above 85 were included in the study, as assessed through the Raven’s Matrices [45] -colored or standard based on age- (N = 19) or the Weschsler Intelligence Scale for Children Fourth Edition (WISC-IV [46]) (N = 4). All participants were free of any medication for the week preceding the experimental night.

Participants and their parents were informed about the procedure and the aims of the study and gave their written informed consent. At the end of the session, they received a gift. The study has been approved by the Institutional Review Board of the Department of Psychology (#0001266) and was conducted in accordance with the Declaration of Helsinki.

With respect to the analysis computed on the delta/beta ratio and SWA, we performed a direct comparison between the sample of preadolescents and a group of 40 healthy young adults (20 F; mean age:  $23.8 \pm 2.88$  years) from a dataset previously acquired in our laboratory. The regional and temporal EEG dynamics during the sleep-wake transition in this group have been previously described (for details see

Ref. [15]). For the sample of young adults, the inclusion criteria were regular sleep-wake cycle, no nap habits, absence of excessive daytime sleepiness, absence of sleep, medical, neurologic, or psychiatric disorders assessed by one-week sleep log and clinical evaluation respectively, and no drug intake.

## 2.2. Procedure

Subjects underwent a PSG recording of undisturbed nocturnal sleep at the Sleep Psychophysiology Laboratory of the Department of Psychology (Sapienza, University of Rome).

During the week preceding the experimental night each participant fulfilled a sleep log every morning, within 15 min after the awakening, to control for the regularity of sleep-wake schedule and the avoidance of daily naps in the day of the experimental sessions. Participants and their parents arrived at the laboratory between 17:00 and 19:00 and they had a light dinner after the PSG montage. The recordings started approximately between 21:00 and 23:00, in accordance with the subject's bedtime habits, and ended after 10 h of bedtime or with a spontaneous morning awakening. Participants slept in a soundproof, temperature-controlled room, during weekends or on free-school days.

Recording conditions were similar in the sample of young adults except for the subject's arrival at the Laboratory: they came to the laboratory at 20:00; the recording started at individual sleep habits and ended after the final morning awakening. The PSG recordings of young adults regarded a baseline PSG acquisition subsequent to an adaptation night in the laboratory and preceding a 40-h-sleep-deprivation protocol, followed by a recovery night.

## 2.3. Polysomnographic recording

The signals were acquired through a 32-channel system (Brain Amp MR plus system, Brain Products GmbH, Gilching, Munich, Germany). The 28 unipolar cortical derivations (C3, C4, Cp1, Cp2, Cp5, Cp6, Cz, Fp1, Fp2, F3, F4, F7, F8, Fc1, Fc2, Fc5, Fc6, Fz, O1, O2, Oz, P3, P4, P7, P8, Pz, T7, T8) were placed in accordance with the International 10-10 system. The EEG signals were acquired from scalp electrodes (Ag/AgCl) with averaged mastoid references (A1 and A2), with a sampling rate of 250 Hz and bandpass filtered at 30 Hz. Electrode impedance was kept below 5 k $\Omega$ . The bipolar electrooculogram (EOG) electrodes were placed about 1 cm from the lateral canthi up for the right eye and down for the left eye and were recorded with a time constant of 1 s. Submental electromyogram (EMG) was recorded with a time constant of 0.03 s.

The signals of the young adults' group were recorded by an Esaote Biomedica VEGA 24 polygraph with a sampling rate of 128 Hz. The 19 unipolar derivations (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, O1, O2, T3, T4, T5, T6) were acquired by Ag/AgCl electrodes, placed in accordance with the International 10–20 system and averaged mastoid references (A1, A2). EOG electrodes were placed about 1 cm from the medial and lateral canthi of the dominant eye; EMG electrodes were placed on the submental muscles.

Cortical impedance was kept below 5 k $\Omega$ .

## 2.4. Data analysis

### 2.4.1. PSG measures

Sleep scoring and artifact rejection were carried out manually by an expert sleep researcher, for 20-s epoch, according to Rechtschaffen and Kales' criteria [47]. We decided to maintain this sleep scoring criteria instead of the current American Academy of Sleep Medicine (AASM) criteria [48] because we performed a retrospective analysis and comparison of previously collected data already scored with the Rechtschaffen and Kales' criteria, also considering that our interest was focused on the SO process and not the sleep macrostructure. A visual inspection of each EEG, EOG, and EMG channel was performed for artifact rejection. Specifically, we removed and excluded from the

analysis epochs containing muscular, ocular and electrical interferences that impacted the cortical traces, according to Rechtschaffen and Kales scoring criteria [47]. We considered an artifact a change of pattern on any additional cortical channels [47], i.e., cortical traces obscured by muscle tension, amplifier blocking artifacts associated with movement of the subjects and/or ocular movements. We evaluated the following macrostructural parameters: stage 1 and stage 2 latencies (minutes); Total Sleep Time (TST) resulting from summing the time spent in stage 1, stage 2, SWS and REM sleep; percentage of each stage of sleep (time spent in a stage of sleep/TST X 100); number of awakenings; number of arousals; Wakefulness After Sleep Onset (WASO, in minutes); Total Bed Time (TBT); and Sleep Efficiency Index (SEI = TST/TBT X 100). PSG measures of preadolescents and young adults were compared using unpaired two-tailed t-tests.

### 2.4.2. Quantitative EEG analysis

For the analyses of the EEG spatiotemporal pattern of the wake-sleep transition, 12-s epochs were scored, using the same criteria described in the previous section. Since the PreSO period is characterized by a large number of artifacts, the minimum artifact-free PreSO period necessary to be compared to the PostSO interval and to be included in the dataset was six 12-sec artifact-free epochs. Subjects that did not reach this minimum number of artifact-free epochs were excluded from subsequent analyses. For both PreSO and PostSO periods, power spectra of the 28 cortical derivations were computed by a traditional fast Fourier transform (FFT) routine for 4-s-epochs (Hanning Window) with a custom-built software in LabVIEW environment, performing the same procedures used in our previous studies on the SO process [15,30,49]. We considered the 0.50–25 Hz frequency range. Spectra from three consecutive 4-s-epochs were averaged to allow for alignment with the visual scoring of sleep stages, based on 12-s epochs scoring. The individual SO was determined by the appearance of the first K-complex or sleep spindles [15,30,49]. After the FFT, all data analyses were performed using MATLAB R2011b.

### 2.4.3. Single Hz EEG topography

We assessed the EEG topography during the 5 min PreSO and PostSO. Before carrying out statistical analyses, data were reduced to a 1-Hz bin width by collapsing four adjacent 0.25-Hz bins; the only exception regarded the 0.5–1.00 Hz bin, for which two contiguous 0.25 Hz bins were collapsed.

The EEG power values for each 1-Hz frequency bin were log-transformed and were considered as dependent variables and compared by paired t-tests in the intervals before and after SO, for each cortical derivation. Correction by False Discovery Rate (FDR [50]) was applied.

### 2.4.4. Time course of the EEG frequency bands

Due to the different length of the intervals preceding and succeeding the SO and to allow the comparison between the individual time courses, we adopted the same procedure previously described and used to portray the wake-sleep transition [15,30,49]: a) the individual time courses were aligned as a function of the first spindle and/or K-complex; b) the time series of the two intervals before and after SO were divided into 5 and 20 segments (percentiles), respectively; c) after the rejection of muscular and ocular artifact, the individual time courses were averaged across all subjects. After this procedure, the PreSO and PostSO represented a 5th and a 20th percentile of the global intervals preceding and succeeding the SO. The PreSO interval encompasses the temporal window between lights out and the appearance of the first K-complex and/or sleep spindles and the postSO interval started with the falling asleep and ended with the last epoch of the first NREM cycle. Two subjects were excluded from this analysis due to too many artifacts across the NREM cycle and recording problem during the PSG acquisition, respectively, so we performed the analysis on the time course on a sample of N = 21 experimental subjects.

No SO REM episodes were scored, and only one subject skipped the first REM episode.

The log-transformed EEG power maps were computed for the five intervals before and after SO, for the following frequency bands: delta (0.50–4.75 Hz), theta (5.00–7.75 Hz), alpha (8.00–11.75 Hz), sigma (12.00–15.75 Hz), and beta (16.00–24.75 Hz). For the postSO period, we also calculated the power maps for the 10th, 15th and 20th intervals with the aim of depicting the topographical EEG kinetics across the first NREM sleep cycle.

2.4.5. Comparison between preadolescents and young adults

We performed a direct comparison between preadolescents and healthy young adults from a previously acquired dataset. Since in the adults group the signal was acquired on 19 cortical derivations, for these analyses we reduced and aligned the number of the considered cortical locations of the preadolescents, to make the two groups comparable (i. e., removing the electrodes that were not present in the adults' montage before the statistical analyses). In both groups, the 19 cortical derivations considered for these analyses were: F1, F2, F3, F4, F7, F8, Fz, C3, C4, Cz, O1, O2, P3, P4, Pz, T3, T4, T5, T6. The same FFT procedure used in preadolescents and described in the quantitative EEG analysis section was performed in adults before the statistical analyses.

The between-groups comparison was performed on two EEG measures: SWA and delta/beta ratio. For the analysis on SWA, we computed in both groups the relative EEG power in order to reduce between-group and between-subjects variability. Thus, the raw spectral power of the 0.25 bins of the delta band was expressed as a percentage of the raw total power spectrum of each cortical derivation, and then we averaged the 0.5–2 Hz bins and 2–4 Hz bins in order to obtain the EEG relative power of 'slow delta' (0.5–2 Hz) and 'rapid delta' (2–4 Hz).

The delta/beta ratio is considered an index of arousal level during sleep [51,52]. First, we summed the raw power of the 0.25 Hz bins in the 0.5–4 Hz and 16–24 Hz range to obtain the raw delta and beta band power; then, for each derivation, we computed the ratio between the two bands to obtain the delta/beta ratio.

A two-way mixed ANOVA, with Time (Pre-vs. Post-SO) as the within-subjects factor and Group (Preadolescents vs. Adults) as the between-subjects factor was computed for each scalp electrode, for both relative delta power and delta/beta ratio. With the aim of describing the direction of the ANOVA main effects, the t-value corresponding to each F-value was computed, and the sign of each t-value was defined by the difference between the mean values of the levels of each factor [30,53].

Correction by FDR [50] was applied. In case of significant interactions, we performed t-tests for post-hoc comparisons.

3. Results

3.1. PSG measures

The sleep macrostructural variables (means and standard errors) assessed in the groups of preadolescents and adults are reported in Table 1, as well as the comparison between the two groups. Preadolescents substantially exhibited a normal night of sleep, with values similar to those of our previous studies [54]. The direct comparison between the two groups showed that preadolescents had longer stage 1 and stage 2 latencies, lower percentage of stage 1 and REM sleep, higher percentage of SWS, higher WASO and number of arousals, and higher TST and TBT, compared to adults.

3.2. Scalp topography of the single hz EEG

The power maps reported in Fig. 1 depict the regional patterns of EEG cortical activity before and after SO in preadolescents and the comparison between these two temporal intervals (Post/Pre ratio and t-tests), describing a scenario characterized by clear differences between the intervals preceding and succeeding the wake-sleep transition. After the FDR correction [50], the level of significance was set to  $p \leq 0.036$ .

The differences between cortical activity PreSO and PostSO are significant for all cortical derivations in the frequency range 0.5–6 Hz. In the delta frequency range (0.5–4 Hz) after the SO, the power spectra increased widely, with maximal values in frontocentral areas and maximal differences expressed in the activity below 2 Hz, and a more posterior prevalence of the postSO increase at 4 Hz. The 5–7 Hz activity exhibited a central predominance. The maximal differences between the Pre- and PostSO intervals were widely expressed in the 5 Hz bin, whereas at 6 Hz the increase was more markedly localized in central areas. The significant increase at 7 Hz regarded all cortical areas with the exception of few posterior derivations (P7, P8, O1, O2, Oz).

The alpha activity range (8–11 Hz) switched from a posterior PreSO prevalence to an anterior PostSO predominance. At 8 and 9 Hz, we found a significant postSO increase in frontocentral areas and a decrease in posterior regions. At 10 and 11 Hz the PostSO increase was widespread in all derivation except the posterior ones, for which we observed a significant occipital decrease at 10 Hz.

The sigma activity increased after the wake-sleep transition, with the maximal differences in frontocentral areas. Specifically, at 12 and 13 Hz the differences were significant for all cortical derivations and the power increase was localized more markedly in frontocentral areas. In the rest of the sigma band, we observed maximal differences in central areas: at 14 Hz the increase was significant for all derivations except Oz, while at 15 Hz the increase was lower compared to the other bins of the band and encompassed all derivations except for temporal and occipital locations.

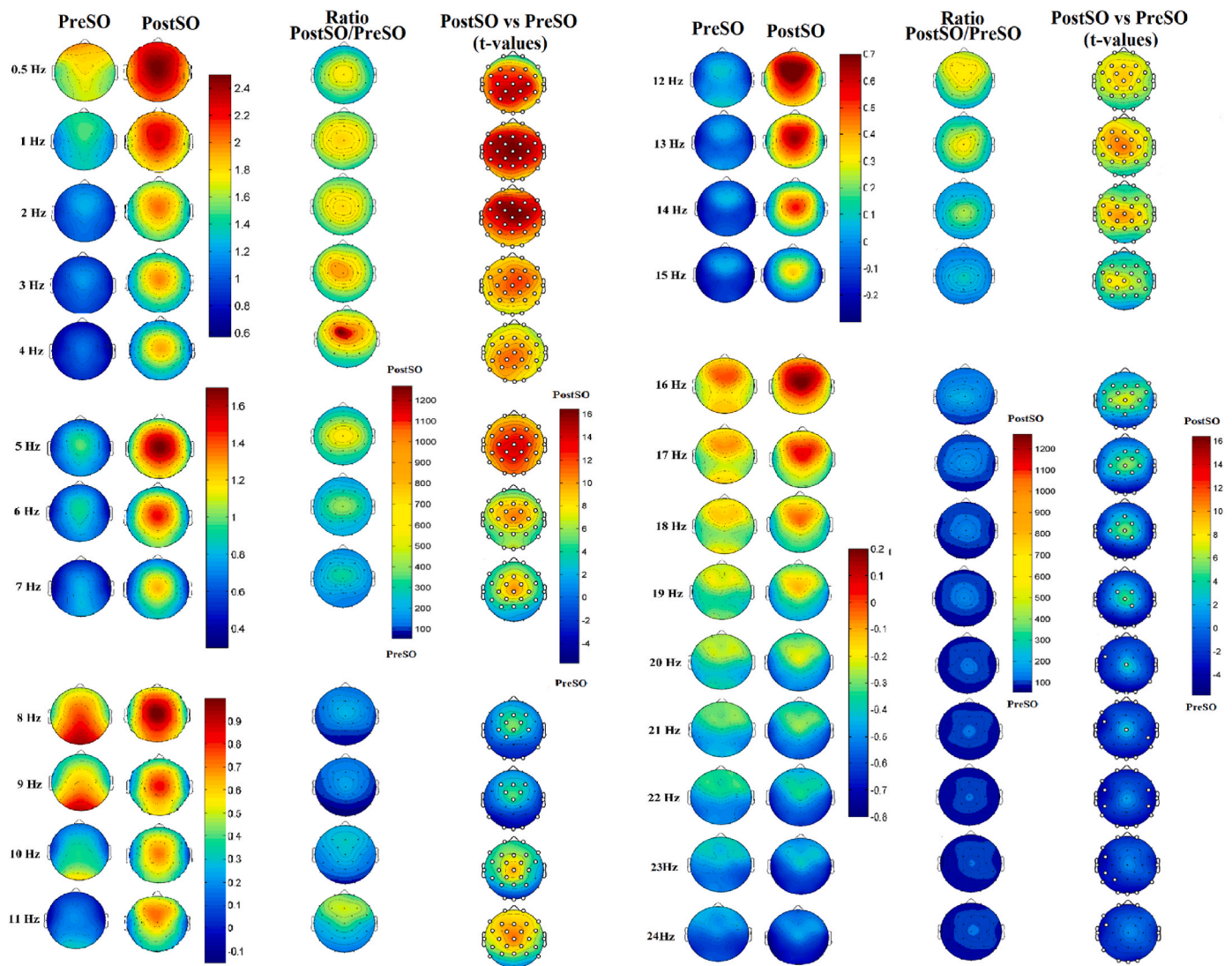
The EEG activity >16 Hz showed a PostSO frontocentral power

Table 1

Polysomnographic (PSG) measures. Means and standard errors of the PSG variables in 21 preadolescents and 40 healthy young adults (first and second column, respectively). Results of the direct comparison (unpaired t-tests) between the two groups are reported in the third and fourth columns (t-values and p-values, respectively). Asterisks stands for significant differences. Abbreviations: SWS= Slow Wave Sleep; REM = Rapid Eye Movement; WASO= Wake After Sleep Onset; TST = Total Sleep Time; TBT = Total Bed Time; SEI= Sleep Efficiency Index.

	Preadolescents Mean ± SE	Young Adults Mean ± SE	t	p
Stage 1 latency (min)	14.3 ± 2.5	6.6 ± 0.9	3.5	* < 0.001
Stage 2 latency (min)	17.5 ± 2.4	11.2 ± 1.8	2.1	*0.042
Stage 1 (%)	3.0 ± 0.5	6.3 ± 0.5	-4.5	* < 0.001
Stage 2 (%)	57.7 ± 1.3	59.3 ± 1.1	-0.9	0.366
SWS (%)	18.2 ± 0.9	10.3 ± 1.0	5.2	* < 0.001
REM (%)	21.1 ± 0.9	24.1 ± 0.8	-2.4	*0.019
WASO (min)	50.8 ± 9	26.1 ± 3.0	3.2	*0.002
Awakenings (#)	35.0 ± 3.4	28.5 ± 1.7	1.9	0.058
Arousals (#)	66.6 ± 5.7	35.4 ± 2.8	5.5	* < 0.001
TST (min)	500.1 ± 14.3	441.4 ± 6.1	4.4	* < 0.001
TBT (min)	567.1 ± 9.2	484.8 ± 10.1	5.3	* < 0.001
SEI % (TST/TBT)	88.1 ± 1.9	91.7 ± 1.1	-1.7	0.086





**Fig. 1.** Topography of EEG changes during the SO at 1 Hz resolution (left side: frequency range 0.5–11 Hz; right side: frequency range 12–25 Hz). In both sides of the figure the first two columns depict the topographical distribution of the log-transformed mean power spectra of the 5 min preceding (PreSO) and succeeding (PostSO) the SO, respectively. The maps were scaled between minimal (min) and maximal (max) values separately for each frequency band, calculated for each derivation in Pre- and Post-SO periods. The third column shows the relative EEG changes expressed as the ratio between Pre- and Post-SO periods (PostSO/PreSO \* 100). The fourth column displays the statistical differences (t-tests) of EEG power between PreSO and PostSO. Values are expressed as t-values. White dots indicate significant differences after the FDR correction ( $p \leq 0.036$ ). Positive values stand for an increase of power spectra in the PostSO over the PreSO.

increase in the slowest bins (16–18 Hz), within a general phenomenon of decrease for the entire frequency range. Specifically, the increase was more widespread and intense at 16 Hz, mainly encompassing frontal and central areas, conjunctively to a reduction in occipital regions. This phenomenon of beta enhancement progressively decreased in the higher frequency bins, pointing to a general PostSO power reduction.

### 3.3. Time course

Fig. 2 describes the temporal features and evolution of the SO process, showing the EEG changes across the transition to sleep and during the first NREM cycle in preadolescents.

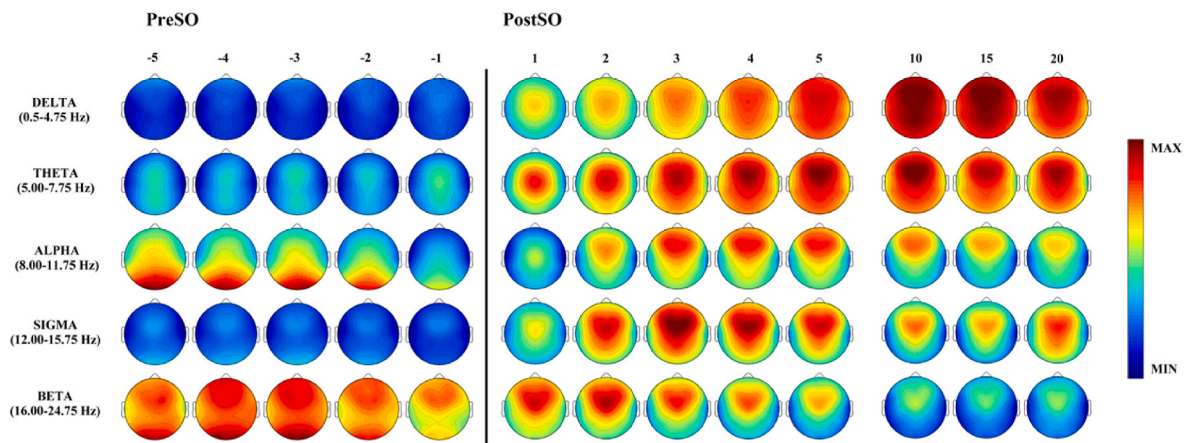
The delta activity exhibited a maximal expression in frontocentral areas throughout the entire transition. After falling asleep, preadolescents exhibited an increased delta power mainly expressed in central areas, that progressively spread in the entire scalp, reaching a peak of activity at the 10th percentile, and then started to decrease as the REM approached. The temporal trend of theta activity paralleled the delta's one, exhibiting a central predominance just after falling asleep

and a frontocentral prevalence through the first NREM cycle. For the alpha activity a phenomenon of anteriorization is observable: before the wake-sleep transition there was an occipital prevalence that decreased gradually approaching the SO, followed by a postSO shift to anterior regions. As a consequence of defining the SO as the first appearance of a K-complex/sleep spindle, it is possible to observe a marked increase of sigma activity after the transition to sleep, with maximum values in frontocentral areas. The beta activity progressively decreased during the PreSO period. Nevertheless, a beta power increase can be observed in frontocentral regions immediately after the SO, accompanied by a reduction in more posterior areas, and followed by broad phenomenon of beta decrease across the first NREM cycle in all cortical derivations.

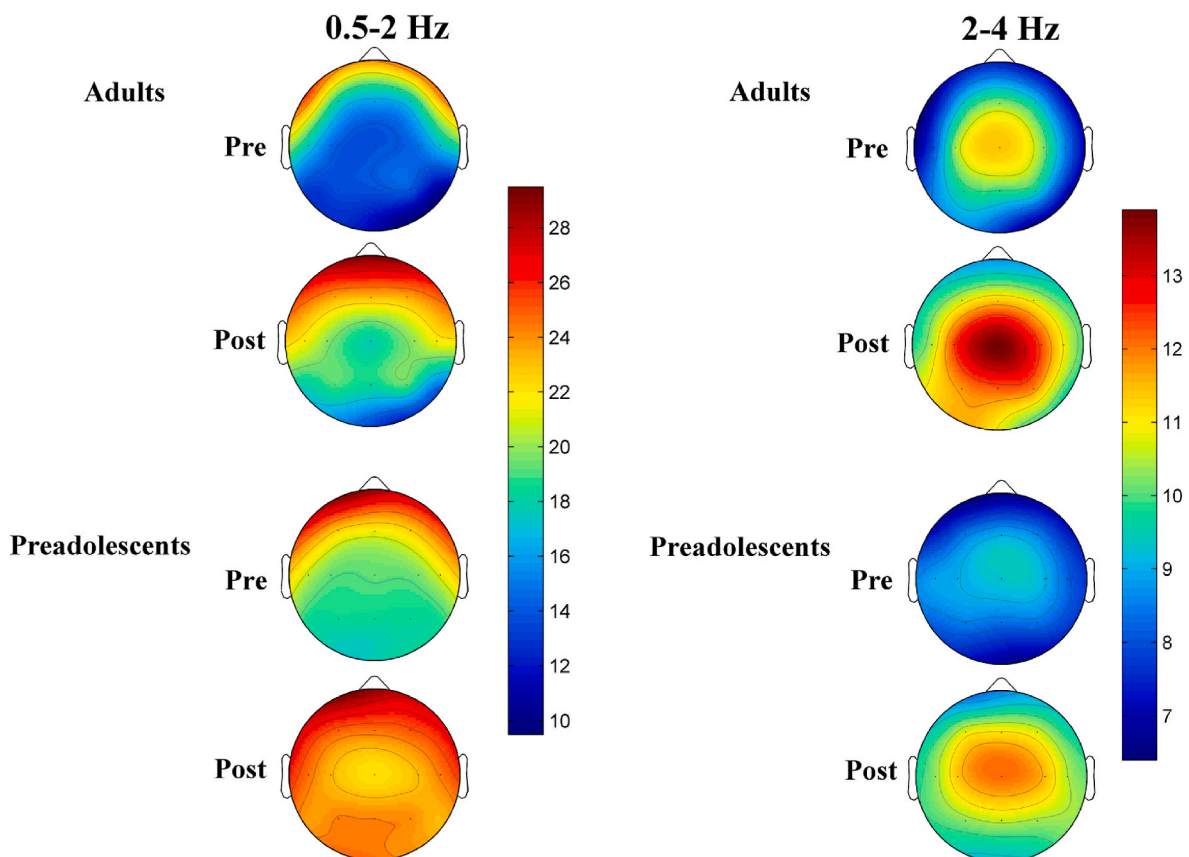
### 3.4. Comparison between preadolescents and young adults

#### 3.4.1. Slow wave activity

The descriptive maps of delta relative power in preadolescents and young adults (Fig. 3) showed in both groups and in both slow and rapid delta a power increase after the falling asleep, with maximal values



**Fig. 2.** Time course of EEG frequency bands during the SO process in preadolescents (log-transformed data). Topographical maps show the means of the 28 cortical derivations for delta, theta, alpha, sigma, and beta bands. In the left side of the picture the topography of the interval that precedes the SO (PreSO) is depicted. Topographical maps were obtained dividing the PreSO in five equal intervals (from -5 to -1). The vertical black line represents the first epoch of stage 2 NREM sleep (first epoch with a spindle and/or K-complex). The right side of the figure depicts the first five intervals (from 1 to 5) succeeding the SO (PostSO) and the last three columns on the right side represent the 10th, the 15th, and the 20th intervals during the first cycle of NREM sleep.

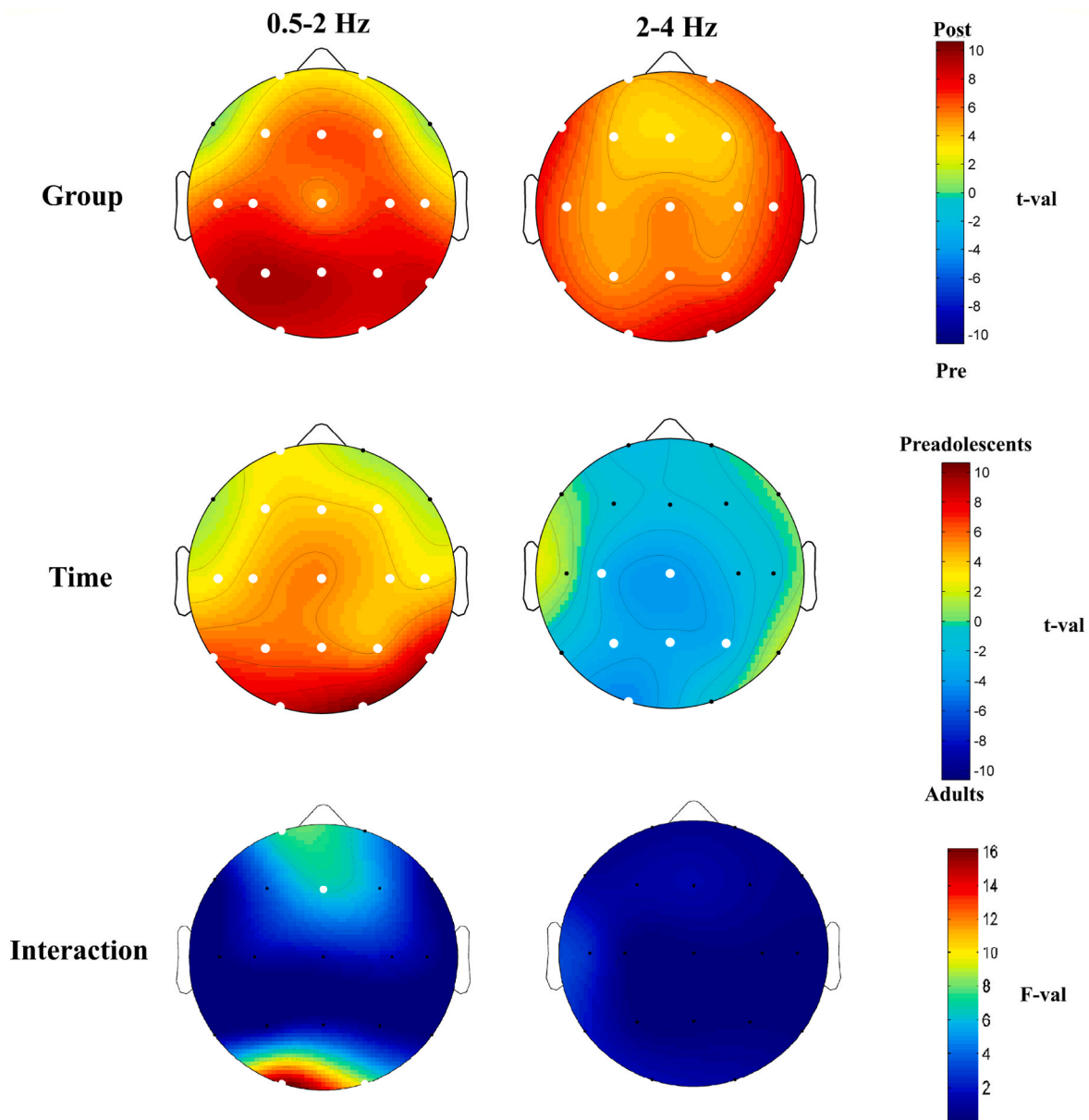


**Fig. 3.** Topographical maps of relative delta power (first column 0.5–2 Hz; second column 2–4 Hz) in the interval preceding (Pre, 5 min) and succeeding (Post, 5 min) the wake-sleep transition, for adults (Adults, first two lines) and preadolescents (Preadolescents, third and fourth lines). The maps were scaled between minimal and maximal values calculated separately for slow and rapid delta in all the derivations in pre- and post-SO periods, in both age groups.

expressed in the 0.5–2 Hz for both groups (first column). Specifically, in young adults the postSO increase in the 0.5–2 Hz range was more prominent in prefrontal areas (second row, first map), whereas preadolescents exhibited a more widespread postSO increase (fourth row, first map).

The results of mixed ANOVA Time X Group (Fig. 4) showed significant (critic p after FDR correction  $\leq 0.021$ ) main effect of Time and

Group for both 0.5–2 Hz and 2–4 Hz range, and significant Interaction only in the 0.5–2 Hz range. Specifically, in the 0.5–2 Hz range, the Time effect pointed to a generalized power increase after falling asleep, with the exception of two frontal derivations (F7 and F8) and with maximal values in posterior areas, while at 2–4 Hz the effect was significant for all cortical derivations. The Group effect showed that preadolescents had more slow delta (0.5–2 Hz) widely in all cortical derivations with the



**Fig. 4.** Results of the two-way mixed ANOVA on relative delta power for each scalp derivations, with Time (Pre vs. Post) as within-subjects factor (first line) and Group (Preadolescents vs. Adults) as between-subjects factor (second line). Results of main effects Time and Group are expressed in t-values corresponding to original F-values, to describe the direction of differences. The sign of t-values is derived from the difference between the mean values of the level of each factor. Results for the Interaction (third line) are expressed as F-values (third line). White dots stand for significant differences after FDR correction (critic  $p \leq 0.021$ ). First and second columns displays respectively the 0.5–2 Hz and 2–4 Hz frequency range.

except of Fp2, F7 and F8, with maximal differences in posterior areas, and lower rapid delta (2–4 Hz) in centro-posterior regions, compared to young adults.

Data showed significant interaction only in the 0.5–2 Hz range for frontopolar (Fp1), frontal (Fz), and occipital (O1, O2) derivations.

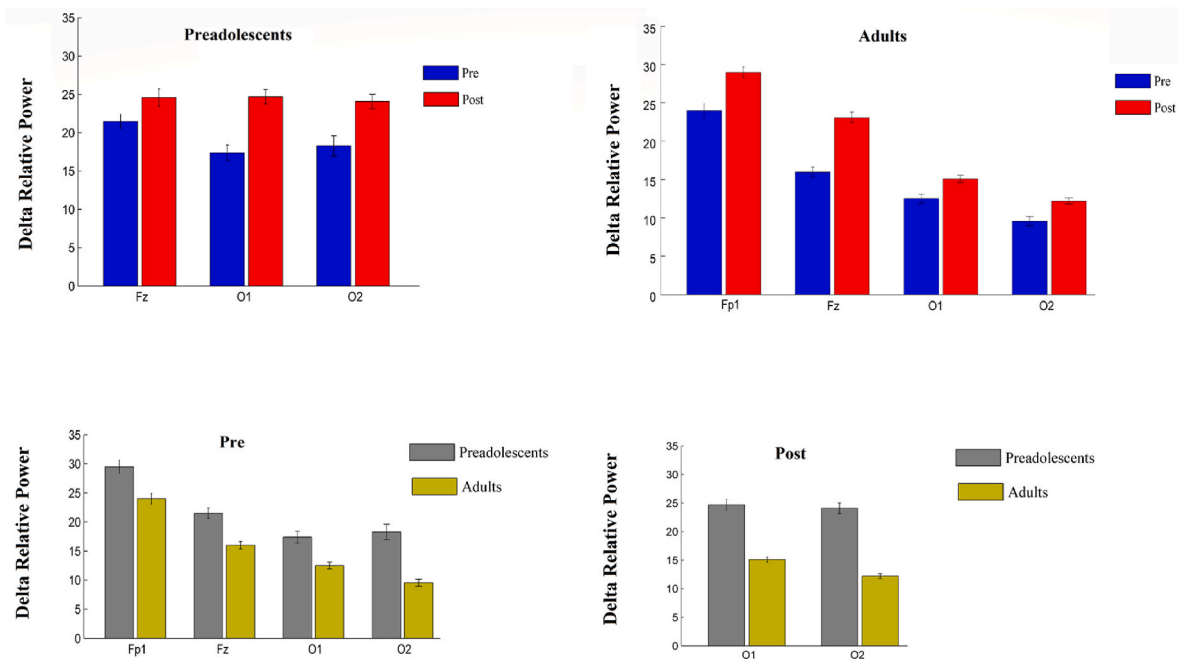
Post-hoc comparisons (Fig. 5, first line) displayed that preadolescents, after falling asleep, exhibit higher slow delta relative power in frontal and occipital derivations, compared to the interval preceding the SO. The group of young adults, once asleep, had higher slow delta in frontopolar, frontal, and occipital derivations compared to the PreSO period. Post hoc comparisons between the two groups in the two time intervals (Fig. 5, second line) showed that before falling asleep preadolescents, compared to young adults, exhibited higher delta power in prefrontal, frontal and occipital derivations; while, once asleep, they displayed higher slow delta activity in occipital areas.

### 3.4.2. Delta/beta ratio

Fig. 6A depicts the descriptive maps of delta/beta ratio in preadolescents and young adults during the wake-sleep transition. After falling asleep, both groups showed a higher delta/beta ratio: in adults, it was markedly predominant in frontopolar areas, whereas in preadolescents the prevalence was more posterior, with maximum values in midline centroparietal areas.

The results of the mixed ANOVA Time X Group (Fig. 6B) showed significant (critic  $p$  after FDR correction  $\leq 0.025$ ) main effects of Time (all cortical derivations), Group (Fp2, F8, Cz, O2, P3, P4, Pz, T6) and significant Interaction (Fp1, Fp2, F8, O2, T6). Specifically, the Time effect showed a diffused increase of delta/beta ratio in the PostSO over the PreSO, while the Group effect pointed to a higher delta/beta ratio in centro-posterior areas and a lower index in the right frontal region in preadolescents, compared to young adults.

The post-hoc comparisons (Fig. 6C, first line) showed an increase of



**Fig. 5.** Post-hoc t-tests for the interaction of the two-way mixed ANOVA performed on slow (0.5–2 Hz) delta relative power with Time (Pre vs. Post) as within-subjects factor and Group as between-subjects factor. Only derivations with significant differences ( $p < 0.05$ ) are depicted. First line: histogram of slow delta relative power (0.5–2 Hz, mean and standard errors) of intervals preceding (Pre, blue) and succeeding (Post, red) the SO, in the two groups (Preadolescents and Adults). Second line: histogram of slow delta relative power (0.5–2 Hz, mean and standard errors) of preadolescents (Preadolescents, grey) and adults (Adults, green), in the interval preceding (Pre) and succeeding (Post) the SO. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

delta/beta ratio for both preadolescents and adults after SO in frontal and right occipito-temporal areas. Moreover, compared to young adults, preadolescents exhibited higher delta/beta ratio posteriorly (O2, T6) in both preSO and postSO, and lower delta/beta ratio in the anterior derivations (Fp1, Fp2, F8) in PostSO (Fig. 6C, second line).

#### 4. Discussion

To the best of our knowledge, this is the first study aimed at describing the electrophysiological correlates of the SO process in a sample of preadolescents, depicting its temporal and regional dynamics, and comparing delta activity and delta/beta ratio of preadolescents to a sample of young adults. The main findings confirmed the electrophysiological pattern of the sleep-wake transition observed in adults [15,49], but highlighting several age-related peculiarities in preadolescents: a) the postSO increase of the slowest frequencies (i.e., delta and theta) did not encompass all derivations in the 7 Hz bin, and b) the lower bin of the beta band showed a postSO increase in fronto-central derivations. Crucially, compared to young adults, preadolescents expressed greater relative delta power in the 0.5–2 Hz in frontopolar, frontal and occipital areas before falling asleep. Once asleep, the relative delta power in the slow delta (0.5–2 Hz) was higher in occipital regions in preadolescents, compared to young adults. Finally, preadolescents exhibited higher delta/beta ratio in posterior derivations both before and after SO and, once asleep, a lower delta/beta ratio occurred in frontal regions, for preadolescents, compared to the older group.

##### 4.1. SWA and delta/beta ratio

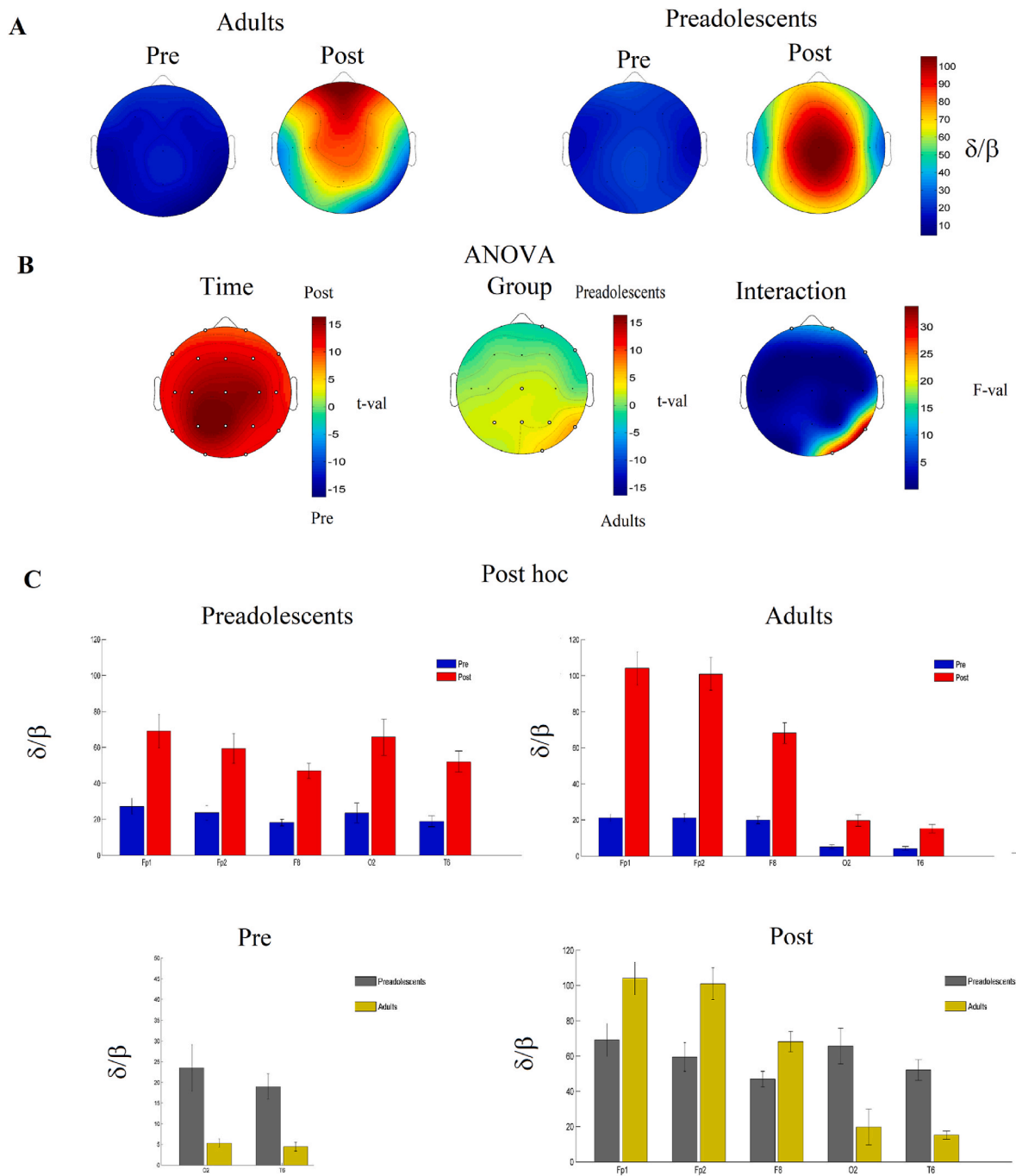
SWA dynamics in preadolescents during the wake-sleep transition substantially mirrored the process described in adults [15,49]. In particular, we observed: a) a postSO frontocentral increase of absolute delta power, with a maximum increase in the lowest bins (0.5–2 Hz) and maximal values in central derivations; b) the postSO maximal values of

delta power in the slowest bins of the band are detectable in both absolute 1-bin powers and relative SWA (i.e., slow delta); c) the prevalence of the delta activity, in some extent observable even before falling asleep, increased centrally, reaching a frontocentral peak towards the midpoint of the first NREM cycle, and started to decrease before the first REM episode.

Considering the delta activity as an undisputed marker of sleep pressure [55,56], the observation of its widespread increase after SO and the presence of some activity even before SO is not surprising. Indeed, literature shows that the maturation of the homeostatic process begins early in the developmental trajectory [57]. Thus, the temporal dynamic of the delta frequency band in preadolescents parallels the process observed in adults [15] consistently showing a certain increase of activity even before the SO and reaching its maximum at the midpoint of the first NREM cycle. This result confirms that the restorative homeostatic process is already active in this population.

According to the role that slow oscillations have in cognitive development and functioning [58], the higher expression of slow delta (0.5–2 Hz) in preadolescence compared to young adults with maximal values in posterior areas is not surprising. A recent study [59] showed that in preadolescents (aged 7–14) frontal areas have a lower propensity to generate slow waves, compared to adults (aged 20–40). Furthermore, our result is consistent with the view of sleep as a local and use-dependent phenomenon and in line with the higher expression of slower frequencies in preadolescence both in sleep and wakefulness [34,59–61]. On the other hand, the overall higher expression of rapid delta (2–4 Hz) in adulthood may appear counterintuitive, considering that preadolescents seem to show a general increased delta power (0.5–4 Hz) compared to adults [59]. Nevertheless, during development, and specifically the period of preadolescence and adolescence, it has been demonstrated the increase of mean delta frequency during sleep with age [34]. Consistently to the modification of both sleep and wake EEG rhythms in the context of massive quantitative and qualitative brain maturation processes, including the reduction of lower and increase of





**Fig. 6.** Delta/Beta Ratio in Adults and Preadolescents. **(A)** Topographical maps of delta/beta ratio index in the interval preceding (5 min PreSO) and succeeding (5 min PostSO) the sleep-wake transition, for adults and preadolescents. The maps were scaled between minimal and maximal values calculated for all the derivations in pre- and post-SO periods in both age groups. **(B)** Results of the two-way mixed ANOVA on the delta/beta ratio for each scalp derivations, with Time (Pre vs. Post) as within-subjects factor and Group (Preadolescents vs. Adults) as between-subjects factor. Results of main effects Time and Group are expressed in t-values corresponding to original F-values, to describe the direction of the differences. The sign of t-values is derived from the difference between the mean values of the level of each factor. Results for the Interaction are expressed as F-values. White dots stand for significant differences after FDR correction (critic  $p \leq 0.025$ ). **(C)** Post-hoc t-tests. Only derivations showing significant differences are depicted. Histogram depicts the delta/beta ratio (mean and standard errors) of intervals preceding (Pre, blue) and succeeding (Post, red) SO in the two groups (Preadolescents and Adults) in the interval preceding SO (Pre) and succeeding (Post) SO. The range of the values is not uniform, with the aim of making differences between cortical locations visible (second line). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

faster frequencies [61,62] and the increase of the peak frequency [63], our findings might reflect the ongoing development of thalamo-cortical and cortico-cortical networks that generate the EEG activity expressed during the SO period. Furthermore, slow and rapid delta seems to behave differently in state of high sleep pressure (e.g., sleep deprivation [64]) and different generators has been proposed for the two different frequency groups [65]. Future studies should replicate and deepen this data, shedding light on source generators (e.g., low-resolution electromagnetic tomography, LORETA [66]) and the underlying oscillatory activity (e.g., better oscillation detection method, BOSCO [67]).

For what concern the delta/beta ratio, considering its role as indirect measure of the arousal level [68], its post-SO increase in both pre-adolescents and young adults, points to the expected arousal reduction while falling asleep in both groups. Nevertheless, the topographical expression was more posterior in preadolescents, compared to adults, both in the pre and postSO intervals. Specifically considering the two age groups in the two intervals, in the PreSO preadolescents exhibited higher slow delta in frontopolar, frontal and occipital areas and a higher posterior delta/beta ratio (i.e., lower arousal level). These findings are consistent with the age-related reduction of the delta activity during wake [61] and, specifically, the wake preceding SO [41,42]. Since previous studies analyzed the SO process only in frontal derivations [42] and the Slow Wave features in the 30 s before SO [41], our results extend the existing evidence of delta dynamics during the wake PreSO with respect to spatial (i.e., beyond frontal derivations) and temporal dynamics (i.e., 5 min). Hence, consistently with previous study [41] it could be hypothesized the occurrence of more signs of local sleep during the PreSO wakefulness in preadolescence, likely due to a faster build-up of homeostatic drive during development [41,69]. The hypothesis of a stronger homeostatic pressure in preadolescence compared to young adults is consistent with previous findings showing a) an age-related reduction of the homeostatic SWA decline during the night from childhood to middle-age [70], and b) a longitudinal decline of delta energy during the first NREM period across adolescence [71].

In the PostSO interval we observed higher slow delta power and delta/beta ratio in posterior areas and lower delta/beta ratio in frontal areas in preadolescents, compared to adults. Our results are in line with the literature of a more posterior expression of SWA during sleep in preadolescence [32,36,37,59] and with the later frontalization of SWA [32,59]. During typical development, posterior areas are the first to undergo cerebral maturation, while the frontal ones start this process later, during adolescence, after 14 years old [32]. Thus, considering the role of SWA in homeostatic regulation and development-related cortical plasticity, we might interpret our data as an expression of higher sleep need for the more mature and day-active areas and a lower activity in areas (i.e., the frontal ones) that have yet to undergo major changes (e.g., cerebral maturation processes, pruning). Hence, since the experimental subjects involved in the present study had a mean age of  $11.5 \pm 1.66$  y, we might speculate that our sample has not yet gone through the delta reduction, whose start is between 11 and 16.5 years, first in posterior regions [35], or, at least, that this phenomenon is only partially started and have not yet involved anterior areas, accounting for the observed 'more posterior' maximal values.

Moreover, the present findings are consistent with results observed through the slow wave detection procedure previously performed during the SO in preadolescents [41]. Beyond showing the absence of the dissociation between the two distinct synchronization processes active in adulthood [16], Spiess and coworkers found respectively a central and posterior faster increase in slow wave amplitude and number during the sleep-wake transition [41]. In this view, our findings support and extend the notion that preadolescents fall asleep more posteriorly (i.e., less frontally) than adults.

#### 4.2. Theta activity

We observed a central prevalence of theta activity, with a PostSO

power increase widely expressed at 5 Hz and with central maxima at 6 and 7 Hz, consistently with the activity that this frequency band exhibits during sleep in preadolescence (i.e., central predominance [35]). Furthermore, since the theta activity is considered a marker of sleepiness and an index of sleep homeostasis, the dynamics showed by the theta activity could be interpreted as an expression of the homeostatic regulation in the context of developmental-related processes.

Compared to the data previously described for young adults [15], we observed a lack of increase at 7 Hz in few posterior derivations; this data is consistent with the expression of maximal values observed in central areas during sleep in preadolescence [35], compared to the occipital maximal changes previously observed in adulthood in the postSO interval [15], allowing to hypothesize that this adult topography is not yet mature. Furthermore, it should be noted that 7 Hz bin is on the alpha bin' border and that 7 and 8 Hz bins showed similar topography, with the 8 Hz bin expressing parietooccipital decrease of power spectra PostSO. Future studies should investigate the underlying genuine oscillations.

The temporal dynamics of the wake-sleep transition showed that, across the first NREM cycle, the theta prevalence from PreSO to PostSO remained stable in central areas spreading anteriorly and posteriorly during the first NREM cycle, reaching its maximal at the midpoint of the first NREM cycle and then starting to decrease, as the REM approached.

#### 4.3. Alpha and sigma activity

The alpha frequency band goes from an occipital topography before falling asleep to a fronto-central prevalence once asleep, and the statistical comparison points to an anterior increase and a posterior decrease of the alpha power in the PostSO compared to the PreSO period. This finding is consistent with the alpha anteriorization phenomenon found in the SO of young adults [15], supporting the hypothesis of a different functional meaning of the alpha rhythm in Pre- and PostSO intervals also in preadolescence. According to this view, the wake state is characterized by the occipital alpha idle rhythm [72], while the frontocentral alpha activity during sleep could be implicated in synchronization processes and involved in sleep maintaining mechanism.

For the sigma activity, as might be expected defining SO at the occurrence of the first K-complex or sleep spindle, the PostSO interval showed an increased power in the sigma frequency range. From a topographical standpoint, the observed pattern substantially replicates the one previously described in young adults [15].

#### 4.4. Beta activity

We found a PostSO power increase in the slowest bins of the beta band with frontocentral predominance, more widespread at 16 Hz, together with a diffuse phenomenon of beta reduction mainly observable in the highest frequency bins. The temporal dynamics of the SO showed that the frontocentral beta increase occurred in the very first intervals after the wake-sleep transition and progressively decreased across the first NREM cycle, replaced by a general trend of decrease. The beta activity is considered an electrophysiological marker of arousal and motor activation [73–76]. In this view, while the reduction of the beta activity replicates the results obtained in young adults [15,49] and elderly individuals [30] suggesting an arousal reduction after the SO, the frontocentral increase may appear surprising. However, it is worth noting that such phenomenon encompassed only the lowest bins of the band and was wider and more intense in the 16-Hz-bin, that is adjacent to the spindles' frequency range. Furthermore, the regional features of the beta enhancement mirror the topography observed for the rapid spindles. Interestingly, several evidence suggest that mature fast spindles emerge during adolescence [31]: both sleep spindles and sigma activity exhibit a frequency increase during typical development [69, 77–80], and the typical centroparietal peak has been observed at 13

years [81] and between 17 and 20 years [32]. In this view, we might hypothesize that, during their maturation, sleep spindles may include phenomena characterized by a faster frequency compared to the classical (adult-like) centro-parietal sleep spindles. Future studies need to deepen this phenomenon through slow and rapid spindles detection procedure or source localizations [82].

## 5. Limits and future directions

Raw data of this study were selected from a previously acquired dataset. For this reason, PSG were not recorded with the aim of investigating SO. To increase our sample, subjects from two different protocols in which participants in the afternoon performed a task (Serial Reaction Time Task or Word Pair Task) were retrieved. It is not possible to exclude an influence of tasks on EEG topography, but it is unlikely that these experimental manipulations had an impact on the wake-sleep transition, as previously assumed in similar protocols investigating the SO process [41].

Considering the specific analyses performed on relative delta power and delta/beta ratio, while young adults' data referred to a baseline recording night, following an adaptation night in the laboratory, preadolescents lacked adaptation night in laboratory. This choice was made according to self- and parents-reported difficulty in changing sleep environment and organizational issues (e.g., school schedule, sport activities) of preadolescents. This might have implied the First Night Effect (FNE), that is a worse sleep quality the first night that the subjects sleep in the lab [83]. Thus, since we cannot exclude that the differences we observed between preadolescents and adults are affected by FNE, future studies should replicate the data considering an adaptation night.

Regarding the lower frequency bands, even though the delta and theta activity showed similar maturational trajectory (i.e., reduction of power spectra) during development, the decrease of the EEG power of the two frequency bands starts at two different timepoint, with the theta reduction beginning at 9 years old and the delta decrease starting later, at 11 years old. Since our sample included preadolescents aged 9–14, further longitudinal investigations with larger experimental sample's groups divided by age according to specific features and temporal trajectory of the spectrum of frequency ranges are needed to shed light on the specific SO age-related features linked to specific maturational trajectories.

## 6. Conclusions

To our knowledge, this is the first study to investigate the whole-scalp spatial, temporal and frequency-specific (1 Hz resolution) EEG features of the SO process in preadolescence, a temporal life window in which sleep shows quantitative and qualitative features that differ from the adult's pattern. While the observed wake-sleep transition in preadolescence mirrors the dynamics of adult's process, we observed specific age-related electrophysiological peculiarities. Higher signs of synchronization in preadolescents in more posterior areas compared to adults may reflect a greater homeostatic drive in these regions, in the perspective of specific local and use-dependent processes during brain development. In other words, we observed a higher homeostatic drive in the more mature and wake-active areas in preadolescence, likely reflecting cortical plasticity phenomena related to the brain maturation processes [33,84]. Furthermore, we hypothesize that the beta postSO increase we observed in preadolescents possibly reflects a not-completely mature spindles, accounting for cerebral ongoing maturation processes reflected in the SO EEG.

Albeit the present results need to be replicated and extended, our findings are likely imputable to cerebral maturation dynamics occurring during preadolescence, depicting the wake-sleep transition phenomenon in preadolescence as affected by the strong maturational changes that physiologically occur in this phase of life. Future studies should provide a further characterization of this electrophysiological pattern

and help to understand its role in homeostatic sleep regulation processes during brain development.

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## CRediT authorship contribution statement

**Ludovica Annarumma:** Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Formal analysis, Data curation. **Flaminia Reda:** Investigation, Formal analysis, Data curation. **Serena Scarpelli:** Validation, Data curation. **Aurora D'Atri:** Methodology, Data curation. **Valentina Alfonsi:** Validation, Software. **Federico Salfi:** Visualization, Investigation. **Lorenzo Viselli:** Visualization, Investigation. **Mariella Pazzaglia:** Writing – review & editing, Visualization, Conceptualization. **Luigi De Gennaro:** Writing – review & editing, Visualization, Resources, Project administration, Conceptualization. **Maurizio Gorgoni:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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