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**TITLE:** [**Electrophysiological and micro-architectural features of sleep in children at high risk for depression**](Javascript:viewSubmissionForm('TSP-16-01017','1.0','Electrophysiological%20and%20micro-architectural%20features%20of%20sleep%20in%20children%20at%20high%20risk%20for%20depression','SLEEP','1',%20'null'))

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**Abstract**

**Objective:** This study investigated electrophysiological and micro-architectural features of sleep in 4–18 years old children who were born to depressed mothers.

**Methods:** Thirty-one healthy subjects (15 males, 16 females) participated in the study. Of these, 20 children born to mothers diagnosed with Major Depressive Disorder (MDD) were designated as ‘high-risk’; 11 children born to mothers without a personal history of depression were designated as ‘low-risk’. Polysomnography including three-channel EEG was recorded for one night at the Pediatric Sleep Unit of the University Hospital of Lyon, France. Clinical and demographic data were collected. Sleep macro-structural parameters were analyzed. Sleep micro-structure was assessed with the scoring of Cyclic Alternating Pattern (CAP) and CAP measures were calculated. Spectral analysis was performed and mean EEG band power was computed for each sleep stage. Sleep electrophysiological features (slow waves and sleep spindles) were detected and related parameters were analyzed. Data were compared between high and low-risk groups using Student’s t-tests.

**Results:** A reduction of low-frequency spindle activity and slow spindles spatio-temporal characteristics over frontal and central derivations and an altered distribution of CAP phase A subtypes (reduction of A1 over A2–3 ratio) have been observed in the high-risk group relative to the low-risk group.

**Conclusions:** Limited spindles generation and increased NREM sleep instability have been observed in children born to depressed mothers, thus reflecting functional anomalies in cortical plasticity that could represent a pathogenic factor or an epiphenomenon for MDD.

**Keywords:** Depression; Children; Sleep; Spindles.

**Abbreviations**

BMI: Body-mass index

DSM: Diagnostic and statistical manual of mental disorders

HR: High-risk

LR: Low-risk

MDD: Major depressive disorder.

MINI: Mini-international neuropsychiatric interview

1. **Introduction**

Major depressive disorder (MDD) is very common worldwide with the highest lifetime prevalence of any psychiatric disease. Its clinical importance and public health relevance undeniably reveal the need for a global attention focused at identifying early risk biomarkers of the disorder to reduce the impact of its socioeconomic burden [1]. Among these, sleep has recently emerged as a potential marker of depression and other psychiatric disorders [2]: the importance of sleep in major depression is so essential that some authors [3] suggested that a diagnosis of MDD should be made with caution in the absence of sleep disturbances. Indeed, specific alterations of sleep have been repeatedly associated to major depression [4], both as clinical features and recurrent polysomnographic patterns.

While the macro-architecture of sleep in depressed adults has been characterized in depth [5–7], with a particular focus on the disinhibition of stage R sleep [8–10], its micro-structure, as especially revealed by the delta sleep ratio [11–13], and the electrophysiological features, such as slow waves [14–17] and sleep spindles [18–20], are still under debate. Nonetheless, electrophysiological and micro-architectural biomarkers may help to speculate on anomalies of the neurodevelopment, thus elucidating the underlying pathophysiological mechanisms of the disease. This holds particularly true for young patients with early-onset MDD [21–24] and even more for never-depressed children at high risk for depression [21,25–29].

As for these children, a large body of literature [30–33] has documented the heritability of MDD and familiarity has been shown to be a major, if not dominant, component of the susceptibility to depression. Depression is more likely to occur among the offspring of depressed mothers and more than half of them develop the disease before adulthood [32,33]. Interestingly, maternal depression has been associated to the emergence of cognitive and emotional risk factors for MDD in early childhood, including socio-emotional disturbances and cognitive impairment leading to depressed mood [34–37]. For these reasons, sleep researchers often consider mothers’ mood status to discern children’ risk for depression [21,26,29,33,38].

Moreover, recent literature has shown that a reduced neuroplasticity is linked to depression vulnerability [39–42] and its impairment represents a risk factor for MDD particularly during brain maturation in developmental age [41,43]. In this perspective, sleep emerges compellingly since several studies revealed a strong correlation between sleep and cognitive processes: sleep appears essential for neuroplasticity and memory consolidation [18,44–48], while retaining information can be disrupted by sleep deprivation or reduced sleep quality [49,50].

Among the different mechanisms through which sleep exerts its function in cognitive development, the occurrence of spindles seems to have a beneficial effect on novel memories formation immediately after their acquisition and on retrieval of remote memories in updates, thus being of utmost importance in memory consolidation and learning [44,51–53]. Also, the micro-structure of sleep, as revealed by the analysis of the cyclic alternating pattern (CAP) [54,55], is relevant for neurodevelopment and cognition, particularly during childhood [46,56]: the functional significance of CAP in cognitive performance reveals noteworthy clinical implications that seem essential to better understand the pathophysiological mechanisms underlying neurodevelopmental disturbances.

Unfortunately, sleep in children at high risk for depression has only scarcely been evaluated and research on this topic is still at an early stage with inconsistent and non-systematic findings. Since sleep disturbances are well described in depressed adults and youngsters, they might reveal novel interesting elements in children at high risk that could suggest underlying mechanisms of mood disorders development. The macro-architecture of sleep is altered both in high-risk infants [25,29] and children [26,27], though these studies found contradictory results and findings on similar cohorts were not entirely consistent. These inconsistencies confirm that traditional scoring is not sufficient to identify sleep abnormalities in these children and macro-architectural sleep parameters are highly not specific and rather inaccurately determined.

On the other hand, the microstructure of sleep and its electrophysiological features have been investigated by only few studies. Bat-Pitault et al. 2016 [29] found that SWA and DSR were increased in high-risk infants, whereas, more interestingly, sleep spindles density was reduced, especially in females. A lower spindle activity has been reported also in high-risk children and adolscents [21], along with a reduced temporal coherence [28].

Furthermore, CAP measures have been proposed to provide biomarkers of sleep instability [54], especially in those subjects whose sleep is not affected in terms of traditional scoring measures. As far as now, only three studies [57–59] have evaluated the CAP in depressed adults: an increase of CAP rate and of duration and number of CAP cycles have been reported, along with peculiar disturbances of phase A subtypes. Therefore, CAP analysis allowed to demonstrate a more profound instability of NREM sleep than did conventional scoring, thus providing a useful tool in clinical contexts. Nonetheless, no CAP analysis has been performed in children at high risk for depression.

For these reasons, the aim of the present study was to investigate whether sleep electrophysiological and microstructural anomalies were present in the offspring of depressed mothers. To test this hypothesis, we compared several parameters of slow waves and sleep spindles and the CAP micro-architecture of sleep between a group of twenty children and adolescents born to mothers with MDD and a group of eleven sex- and age-matched controls born to non-depressed mothers.

1. **Material and Methods**
   1. **Recruitment and exclusion criteria**

A cohort of children and their mothers was recruited to evaluate early risk markers for mother–child transmission of depression: children were assessed in the Sleep Center in Lyon (France) from 2006 to 2010. All children were included in the present study, except those who met exclusion criteria: subjects underwent a trial sleep recording with either polysomnography or Holter electroencephalography to evaluate the presence of any exclusion criteria. To reduce neurobiological heterogeneity which could have biased the results, children were excluded if they had any of the following conditions: epilepsy or any other neurological or genetic disease; major obstructive sleep apnea syndrome with a Obstructive Apnea Index > 1 per hour of sleep or an Apnea–Hypopnea Index > 5 per hour of sleep; restless legs syndrome or periodic limb movement disorder; pervasive developmental disorders; if they were still taking daytime naps at the time of the recordings; if they had any current or past psychotropic therapy or medication. To select only never–depressed participants, children underwent psychiatric assessment using the Child Behavior Check List affective problems scale to evaluate depressive symptoms at the time of the recordings. A T–score above the 70th percentile, representing clinically significant depressive symptoms, or the presence of current or past psychotropic therapy or medication were thus used as exclusion criteria. Finally, children were excluded if their mothers had used anti-depressant drugs during pregnancy.

### Subjects and diagnostic procedures

Thirty–one subjects (15 M, age 9.52 ± 3.80) were included in the study. They ranged from 4 to 18 years of age, hence they were divided into two groups according to their age, as previously performed [29]: children aged 4 – 12 years (n = 21), adolescents aged 13 – 18 years (n = 10). Mothers of included subjects underwent psychiatric assessment through phone interviews performed by experienced board certified psychiatrists. The diagnosis of Major Depressive Disorder (MDD) was confirmed by using the validated Mini International Neuropsychiatric Interview (MINI) according to diagnostic and statistical manual of mental disorders (DSM–IV) criteria [60]. Children were then subdivided into two groups according to their mothers’ mood status: 20 children born to mothers diagnosed with present or past MDD were designated as ‘high-risk’ (11 M, age 9.35 ± 4.03); 11 children born to non–MDD mothers were designated as ‘low-risk’ (4 M, age 9.82 ± 3.52). We also collected socio-demographic information concerning participants and their parents, possibly reflecting factors which could have altered the micro-architecture of sleep. Data included children’ weight, height and body mass index, determined as weight over squared height ratio; children’ tobacco exposure due to their parents’ habits; marital status of their parents.

### EEG recording and preprocessing

Children underwent a single night of polysomnography (PSG) with Medatec® system if they were suspected of having parasomnias or disturbed sleep breathing or if they lived far from the Sleep Center. Otherwise, a single night Holter electroencephalographic (EEG) monitoring at home with Micromed® system was used to obtain sleep recordings. For the PSG sessions, children and their parents were received at 7 pm to start recording at 8 pm; parents were asked to supervise their children’ sleeping timetable (e.g. bedtime, lights-out, lights-on) as usual, while recordings were interrupted after awakening maximum at 8 am. For the Holter EEG sessions, scalp connection and disconnection were performed at the Sleep Center, respectively in late afternoon and late morning of the subsequent day; at home, parents were required to note their children’ sleeping timetable (e.g. bedtime, lights-out, awakening maximum at 8 am).

Three EEG unilateral right channels were recorded and then referenced to the auricular left derivation: Fp2–A1, C4–A1, O2–A1. PSG measurements also included bilateral electrooculograms (right and left EOGs), mentalis and bilateral tibial electromyograms (EMGs), an electrocardiogram (ECG) and nasal/oral airflow. For holter EEG monitoring, recordings were the same except for the breathing channel that was excluded since participants who underwent holter EEG had no sleep-related breathing disorder at the first sleep assessment. EEG recordings were band-pass filtered between 0.5 and 30 hertz (Hz) and notch-filtered at 50 Hz.

Artifacts were automatically excluded if power exceeded a threshold calculated as a mean power value in the 0.75 – 4.5 Hz (delta) and 20 – 30 Hz (high frequency) bands: bad epochs were then rejected and spectral power was recalculated to assess the effect of the rejection. Percentages of rejected bad epochs were not significantly different between the two risk groups neither in total sleep time (HR = 7.41 ± 3.38 % ; LR = 7.68 ± 2.75 % ; *p* = 0.8084), nor in stage R (HR = 1.97 ± 1.54 % ; LR = 2.56 ± 2,61 % ; *p* = 0.4970), stage N1 (HR = 7.92 ± 5.61 % ; LR = 7.43 ± 6.64 % ; *p* = 0.8381), stage N2 (HR = 4.15 ± 5.72 % ; LR = 4.51 ± 4.10 % ; *p* = 0.8418) and stage N3 (HR = 17.55 ± 10.09 % ; LR = 16.63 ± 10.52 % ; *p* = 0.8149). Sleep recordings were scored by a trained scorer according to AASM Scoring Manual Version 2.2 standardized criteria [61]: Alice Sleepware® software was used for epoch-by-epoch scoring on 30-second-long segments of PSG channels.

### EEG data analysis

Sleep onset was determined as an epoch of any stage of sleep. General sleep quality was assessed based on visually scored sleep macro-architectural parameters defined as previously reported in Bat-Pitault et al. 2013 [26]: sleep stages percent duration (N1–3%, R%); sleep efficiency; sleep latency; stage R latency; total sleep time (TST); wake after sleep onset (WASO). The microstructure of CAP was previously described by Parrino et al. 2012 [54]. The scoring of CAP was performed on visual EEG inspection by a trained scorer under the supervision of sleep CAP experts, according to published guidelines [55]. Embla® RemLogictm software was utilized for the manual scoring of CAP phases A, whereas phases B were automatically computed based on defined criteria for phase duration [54]. Several CAP measures were automatically calculated by the software and collected for subsequent statistical comparisons: total CAP rate, average CAP cycle duration, number of CAP cycles, percent duration ratio of each phase A subtype (A1%, A2%, A3% and A2–3%), ratio between A1 and A2–3 subtypes (A1/A2–3 ratio), number of A phases per hour for each phase A subtype (A1–3 indexes); each parameter was calculated for night-long sleep.

Spectral power of each of the three EEG channels was calculated for each stage of sleep. The analysis of the power spectrum was performed on consecutive 6-second-long epochs with fast Fourier transform routine (Hamming window) at a frequency resolution of 0.1667 Hz and MatLab® EEGLAB toolbox was used for EEG spectral power analysis. Since the signal amplitude was considerably variable across channels, for each channel thresholds relative to the mean amplitude were used. The 0.5 to 35 Hz spectral power calculated for each sleep stage was compared bin-per-bin between the two risk groups. To further assess spectral differences between the two groups, theta activity, slow wave activity (SWA) and spindle activity (SpA) were calculated as the mean EEG power respectively in the theta (4 – 8 Hz), delta (0.5 – 4 Hz) and sigma (11 – 15 Hz) range, respectively during the total night stage R, N3 and N2 sleep and the first stage R, N3 and N2 sleep episodes. Spindle activity was also computed in the low-sigma (11 – 13 Hz) and high-sigma (13 – 15 Hz) range. Moreover, delta sleep ratio (DSR) was determined as the EEG delta power ratio of the first to the second N3 episode of the night, according to Kupfer et al. 1990 [11].

### Slow waves detection and analysis

Sleep slow waves were automatically detected in N3 stage sleep using a custom MatLab® function, according to the detection algorithm described by Massimini et al. 2004 [62]. The criteria for the detection were applied independently to each average and were as follows: duration from the first negative zero-crossing and the subsequent positive zero-crossing must be longer more than 300 ms; voltage of the negative peak must be less than –80 micro–Volt (µV); amplitude from the maximal negative peak to the maximal positive peak must be greater than 140 µV. Detected slow waves were then plotted to visually assess the reliability of the automatic detection for each subject. For every detected slow oscillation, we collected several single-wave parameters that could be used to compare the two groups: voltage of the maximal positive and negative peaks; negative-to-positive peak-to-peak slow wave amplitude; duration from negative zero-crossing to positive zero-crossing; slow wave up and down-slope. Slopes were computed as the incline of the hypotenuse from the negative zero-crossing to the maximal negative peak (down-slope) and from this one to the maximal positive peak (up-slope). We also calculated each of the previously described parameters as a function of slow wave amplitude. Single slow waves were assigned to 30 µV classes from 140 to 380 µV (eight amplitude classes) in order to compute each parameter for each class. These extremes were assessed after evaluating the distribution of slow waves on 5 µV classes in a larger voltage interval (140 – 1000 µV) and observing that the 140 to 380 µV range included the vast majority (> 95%) of slow waves. Each of the previous parameters and the incidence of slow waves, that is the number of slow oscillations per hour of sleep, were thus computed both for the totality of slow waves and for each amplitude class of slow waves. All these measures were then compared channel-by-channel between the two groups during the total night N3 stage sleep, the first hour of N3 sleep and the last hour of N3 sleep.

### Sleep spindles detection and analysis

Sleep spindles were automatically detected in N2 stage sleep using a custom MatLab® function, according to the detection algorithm described by Ferrarelli et al. 2007 [63]. Electroencephalographic data of all N2 sleep epochs were band-pass filtered between 11 and 15 Hz and band-stop filtered out of 10 and 16 Hz; then, they were normalized using a threshold relative to the mean amplitude for each channel. The local maximum above the threshold was defined as the peak amplitude for each spindle, whereas the time points which immediately preceded and followed this peak, when the time series amplitude dropped below the threshold, were respectively the beginning and the end of each spindle. Detected spindles were then plotted to visually assess the reliability of the automatic detection for each subject. For all detected spindles, the following parameters were evaluated: incidence or spindle density, that is the number of sleep spindles per hour of N2 stage sleep; duration from the beginning time point to the end time point; maximal amplitude at peak; mean frequency, which was supposed to fall in the sigma range (11 – 15 Hz); slope, computed as the incline of the hypotenuse from the beginning time point to the maximal peak; integrated spindle activities (ISAs), calculated by integrating the absolute amplitude values of each spindle divided by N2 sleep duration. We also determined each of the previously described parameters as a function of the spindle frequency. Hence, single sleep spindles were assigned to either one of two frequency classes, i.e. slow spindles (11 – 13 Hz) and fast spindles (13 – 15 Hz), to compute each parameter for each class. Each parameter was thus computed both for the totality of sleep spindles and for each frequency class of spindles. All these measures were then compared channel-by-channel between the two groups during the total night N2 stage sleep, the first hour of N2 sleep and the last hour of N2 sleep.

### Statistical analysis

Statistics was performed using MatLab® software to compare the high-risk group of children born to depressed mothers with the low-risk group of controls. Each comparison was then performed between sex- (males–males and females–females) and age-matched (children–children and adolescents–adolescents) subgroups to assess the specific effect of these demographic variables on sleep. Specific statistical comparisons have been previously reported. A univariate analysis with Student’s t-test was used to detect significant differences (*p* < 0.05) in sleep variables between groups when these variables exhibited a normal distribution: Student’s t-test was performed only after confirming normal distributions through Kolmogorov-Smirnov test; otherwise, the non-parametric Mann-Whitney U-test was used when normality could not be established. Student’s t-test was also used to compare quantitative variables, such as age and Child Behavior Check–List (CBCL) affective problems scale scores. A Fisher’s exact test was used to compare categorical variables, such as sex, obesity, parents’ marital status and tobacco exposure due to parents’ consumption.

1. **Results**
   1. **Socio-demographic data and sleep macro-architecture**

No significant difference was found in socio-demographic data between the two groups (see Table 1), except for the Child Behavior Check–List affective problems (CBCL) scale score that was higher in the high-risk group compared to controls, as previously reported [29]. Also, ten sleep macrostructural parameters have been evaluated; however, no significant differences have been found between the two risk groups (see Table 2).

**Table 1 – Clinical and demographic data**

Clinical and demographic characteristics of the sample by risk of depression and age are here reported. There were no significant differences (*p* > 0.05) in clinical or demographic data between the two risk groups, except for the CBCL Affective Problems Scale score that was significantly (*p* = 0.0024) higher in the high-risk group than the low-risk group. Data are presented as (a) mean ± SD or as (b) number of subjects (%). HR: high risk; LR: low risk; BMI: body mass index; CBCL: child behavior check-list.

|  |  |  |  |
| --- | --- | --- | --- |
|  | HR (*n* = 20) | LR (*n* = 11) | *p*–values |
| Age a | 9.35 ± 4.03 | 9.82 ± 3.52 | 0.7490 |
| *Children* b | 13 (65.0) | 8 (72.7) | 1.000 |
| *Adolescents* b | 7 (36.0) | 3 (27.3) | 1.000 |
| Sex b |  |  |  |
| *Males* | 11 (55.0) | 4 (36.4) | 0.4578 |
| *Females* | 9 (45.0) | 7 (63.6) | 0.4578 |
| Obesity – BMI b |  |  |  |
| *> 95° percentile* | 5 (25.0) | 2 (18.2) | 1.000 |
| *≤ 95° percentile* | 15 (75.0) | 9 (81.8) | 1.000 |
| Marital status b |  |  |  |
| *Married or coupled* | 15 (75.0) | 9 (81.8) | 1.000 |
| *Divorced* | 5 (25.0) | 2 (18.2) | 1.000 |
| Tobacco exposure b | 10 (50.0) | 4 (36.4) | 0.7074 |
| CBCL a | 7.45 ± 3.85 | 3.27 ± 2.05 | **0.0024\*** |

**Table 2 – Sleep macro-architecture parameters**

Sleep macro-architectural parameters are here compared between the two risk groups, with no significant difference (*p* > 0.05). HR: high risk; LR: low risk; SD: standard deviation; TST: total sleep time; WASO: wake after sleep onset.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | HR Mean | HR SD | LR Mean | LR SD | *p*–values |
| N1 [TST ratio] | 0.0700 | 0.0352 | 0.0558 | 0.0301 | 0.2674 |
| N2 [TST ratio] | 0.4768 | 0.0604 | 0.4851 | 0.0718 | 0.7338 |
| N3 [TST ratio] | 0.2774 | 0.0538 | 0.2711 | 0.0710 | 0.7829 |
| Non–REM [TST ratio] | 0.8242 | 0.0727 | 0.8120 | 0.0689 | 0.6520 |
| REM [TST ratio] | 0.1758 | 0.0727 | 0.1880 | 0.0689 | 0.6520 |
| Sleep Efficiency | 0.7667 | 0.1076 | 0.7554 | 0.1090 | 0.2640 |
| Sleep Latency [s] | 3313.5 | 1556.823 | 2926.364 | 1798.868 | 0.5354 |
| REM Latency [s] | 13054.5 | 4838.552 | 11105.45 | 3974.017 | 0.7690 |
| TST [s] | 28354.5 | 4603.692 | 27853.64 | 4296.925 | 0.5542 |
| WASO [s] | 5266.5 | 3565.339 | 6103.091 | 4007.903 | 0.7822 |

* 1. **Spectral power analysis**

No significant differences have been found in the power spectrum during stage R and N3 sleep between the two risk groups. Analogously, no significant differences were found in the theta activity and in the SWA between the two risk groups neither in all-night stage R and N3 sleep nor in the first stage R and N3 sleep episode, respectively. No significant difference was found in the DSR between groups. Finally, no significant sex- and age-related effects have emerged from the analysis.

In sharp contrast, significant differences have been found in the sigma-range spectral power during N2 stage sleep between the two risk groups (see Figure 1): the high-risk group exhibited a lower EEG power both frontally (in the range of 10.33 – 12.83 Hz) and centrally (in the range 11.67 – 12.67 Hz). These differences were found only in all-night N2 sleep. As expected, significant differences were found in the SpA between the two risk groups in all-night N2 stage sleep (see Figure 2A). Particularly, the high-risk group exhibited a lower SpA relative to

controls both frontally (high-risk SpA = 0.1814 ± 0.1271; low-risk SpA = 0.3548 ± 0.2591; *p* = 0.0177\*) and centrally (high-risk SpA = 0.2161 ± 0.1530; low-risk SpA = 0.3695 ± 0.2701; *p* = 0.0501\*). Importantly, this difference was specific for the slow-spindle activity (see Figure 2B). Indeed, the high-risk group exhibited a lower slow-SpA relative to controls both frontally (high-risk SpA = 0.2293 ± 0.1669; low-risk SpA = 0.5031 ± 0.3681; *p* = 0.0077\*\*) and centrally (high-risk SpA = 0.2810 ± 0.2022; low-risk SpA = 0.4862 ± 0.3259; *p* = 0.0383\*).

**Figure 1 – EEG spectral power during N2 stage sleep**

Electroencephalographic spectral power during all-night N2 stage sleep is here compared between high-risk (solid line) and low-risk (dotted line) groups. Power in frontal (A), central (B) and occipital (C) derivations is shown. Spectral power in the low-sigma range was significantly lower frontally (10.33 – 12.83 Hz) and centrally (11.67 – 12.67 Hz) in the high-risk group relative to the low-risk group. \* *p* < 0.05

A B C



Interestingly, these differences were specific for males (see Figure 2C–D) but not for females, with no particular age-related effects. Particularly, the high-risk subgroup of males exhibited a lower frontal SpA relative to controls both in the all-sigma range (high-risk SpA = 0.2243 ± 0.1530; low-risk SpA = 0.4952 ± 0.2743; *p* = 0.0283\*) and in the low-sigma range (high-risk SpA = 0.2893 ± 0.1976; low-risk SpA = 0.6624 ± 0.3177; *p* = 0,0160\*).

**Figure 2** – **SpA during N2 stage sleep**

Electroencephalographic spectral power in the all-sigma (11–15 Hz, A and C) and low-sigma (11–13 Hz, B and D) range, that is the spindle activity and slow-spindle activity, during all-night stage N2 sleep is here compared between high-risk and low-risk groups. SpA and slow–SpA were significantly lower both frontally and centrally in the high-risk group (A–B) and only frontally in the high-risk subgroups of males (C–D) relative to low-risk controls. \* *p* ≤ 0.05 \*\* *p* < 0.01

A B



C D



* 1. **Slow waves analysis**

Incidence, voltage, amplitude, duration and slopes of slow waves were compared between risk groups; however, no significant difference was found neither in all-night N3 stage sleep nor in the first and last hour of N3 sleep. Similarly, no significant difference emerged from comparisons between sex- and age-matched subgroups. Furthermore, the analysis of amplitude-matched slow waves parameters did not reveal significant differences. Nonetheless, an interesting nearly-significant (0.06 > *p* > 0.05) trend emerged in the incidence of low-amplitude slow waves in the last hour of N3 sleep. Particularly, a reduced number of 140 – 230 µV slow waves per hour was found in the high risk group relative to controls, both frontally and centrally (data not shown). No other slow waves parameter demonstrated such a noteworthy tendency, neither sex- and age-matched subgroups comparisons revealed clear effects.

* 1. **Sleep spindles analysis**

Incidence, duration, frequency and slope of sleep spindles revealed no significant differences, though the incidence and duration of spindles were nearly-significantly (0.06 > *p* > 0.05) lower in the high-risk group relative to controls (data not shown). More interestingly, spindles amplitude (*p*frontal = 0.007; *p*central = 0.038) and ISAs (*p*frontal = 0.008; *p*central = 0.047) were significantly lower in the high-risk group, over frontal and central derivations (see Figure 3A–B). This effect was observed in all-night N2 stage sleep, in the first hour and in the last hour; however, since no particular temporal dynamics emerged from the analysis, only all-night comparisons data are shown. Comparisons between age- and sex-matched subgroups revealed different trends of variation. Males (see Figure 3C–D) exhibited a similar pattern as in previous comparisons: spindles amplitude (*p*frontal = 0.001; *p*central = 0.049) and ISAs (*p*frontal = 0.002) were significantly lower in the high-risk group relative to controls both in all-night N2 stage sleep and in early and late N2 sleep. Analogously, high-risk children but not adolescents had lower spindles amplitude and ISAs (data not shown). Finally, high-risk females showed shorter duration (*p*frontal = 0.021; *p*central = 0.036) and faster frequency (*p*frontal = 0.018) both in all-night N2 stage sleep and in early and late N2 sleep.

**Figure 3** – **Sleep spindles parameters**

All-night N2 stage sleep spindles parameters are here compared between the two risk groups (A–B) and between the two sub-groups of males (C–D) and of females (E–F). Significant differences were found frontally and centrally in amplitude and ISAs, both in all subjects and in males. Females reported significant differences in duration and frequency. ISAs: integrated spindle activities. \* *p <* 0.05 \*\* *p <* 0.01

A B

 C D

 E F



The analysis of frequency-matched spindles parameters revealed noteworthy differences between risk groups; the relative distribution of sleep spindles in the two groups is shown in Figure 4. Interestingly, in the first hour of N2 sleep, both frontally and centrally, slow spindles incidence was significantly lower in the high-risk group (see Figure 5A): this effect was specific as it was not observed in the last hour of N2 sleep and fast spindles did not exhibit a similar trend (see Figure 5B). Nonetheless, it is remarkable to note that the incidence of fast spindles is higher over central and occipital regions relative to frontal ones, whereas that of slow spindles is higher over frontal regions, further confirming the previously described topographical distribution of sleep spindles already present at this age [48]. Furthermore, spindles amplitude and ISAs were significantly lower in the high-risk group relative to controls, both for slow and fast spindles (see Figure 5C–F). This effect was observed over frontal, central and occipital derivations, both in the first and last hour of N2 sleep. No significant differences have been detected for spindles duration and slope, though a non-significant trend was observed, with both parameters being lower in the high-risk group in each comparison.

**Figure 4 – Sleep spindles frequency**

Frequency-dependent distribution of sleep spindles incidence is here compared between the high-risk (solid line) and low-risk (dotted line) groups. The global distribution of detected spindles ranged from 10 Hz to 18 Hz. Nonetheless, > 95% of spindles fell into the range 11–15 Hz. The high-risk group exhibited a significantly lower incidence of spindles, especially in the low-frequency range (11–13 Hz).



**Figure 5 – Frequency-matched sleep spindles parameters**

Sleep spindles parameters are here compared between the two risk groups: the high-risk group exhibited a significantly lower incidence of slow (A) but not fast (B) spindles during the first (Early) but not the last (Late) hour of N2 sleep in both frontal and central derivations; a significantly lower amplitude (C–D) and ISAs (E–F) of slow and fast spindles, during both the first (Early) and the last (Late) hours of N2 sleep. ISAs: integrated spindle activities. \* *p <* 0.05 \*\* *p <* 0.01

A B



C D



E F



* 1. **CAP analysis**

Eleven CAP parameters have been evaluated and compared between the two risk groups (see Table 3). Only A1/A2–3 ratio differed significantly (*p* = 0.0147), being lower in the high-risk group (1.7995 ± 0.7955) than in the low-risk group (2.7708 ± 1.2958). Nonetheless, the percent duration of phase A1 subtype was nearly-significantly (*p* = 0.0708) lower in the high-risk group compared to controls, whereas that of A2–3 was nearly-significantly (*p* = 0.0705) higher. Interestingly, these differences were specific for males (see Figure 6A) and adolescents (see Figure 6B) but not for females and children. Moreover, comparisons between these two subgroups emerged significantly also for the percent duration of phase A1 subtype.

**Table 3 – CAP parameters**

CAP sleep micro-architectural parameters are here compared between the two risk groups, with only A1/A2–3 ratio significantly lower in the high-risk group relative to the low-risk group. HR: high risk; LR: low risk; CAP: cyclic alternating pattern. \* *p <* 0.05

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | HR Mean | HR SD | LR Mean | LR SD | *p*–values |
| Total CAP rate [%] | 17.6250 | 13.4328 | 18.2818 | 10.2925 | 0.8891 |
| Cycle duration [s] | 30.7900 | 3.6394 | 31.3091 | 2.8901 | 0.6872 |
| Number of cycles [/h] | 24.9650 | 19.4584 | 24.0455 | 13.3555 | 0.8902 |
| A1 rate [%] | 60.1804 | 16.1009 | 70.3134 | 10.3973 | 0.0708 |
| A2 rate [%] | 27.7668 | 11.3653 | 22.7936 | 6.1318 | 0.1903 |
| A3 rate [%] | 12.0180 | 16.5377 | 6.8772 | 5.9059 | 0.3302 |
| A2–3 rate [%] | 39.7849 | 16.0424 | 29.6709 | 10.4028 | 0.0705 |
| A1/A2–3 ratio | 1.7995 | 0.7955 | 2.7708 | 1.2958 | 0.0147 \* |
| A1 index | 17.3350 | 15.2435 | 17.6909 | 10.8619 | 0.9460 |
| A2 index | 6.1650 | 4.4148 | 5.1364 | 3.2687 | 0.5047 |
| A3 index | 1.4500 | 1.2068 | 1.2091 | 1.3232 | 0.6110 |

**Figure 6 – CAP parameters in males and adolescents**

CAP phase A1 subtype percent durations and A1/A2–3 ratios are here compared between the two risk subgroups of males (A) and adolescents (B). CAP: cyclic alternating pattern. \* *p* ≤ 0.05 \*\* *p* < 0.01

A B



1. **Discussion**

Our study was aimed at evaluating electrophysiological features of sleep and its micro-structure in a cohort of children at high risk for depression as they were born to mothers diagnosed with MDD. To the best of our knowledge, it is the first study that exhaustively and systematically considered all the aspects of the sleep architecture in these subjects, from the traditional scoring macro-structure to a complete assessment of sleep micro-structure, based on the analysis of both EEG spectral power, cyclic alternating pattern and elements of surface electrophysiology, such as slow waves and sleep spindles. We tried to characterize sleep abnormalities in never-depressed but high-risk children while comparing them to a control group of age- and sex-matched children. The sleep anomalies we found in the high-risk group are unlikely due to medications, illness or other confounding factors, since bias effects were avoided as all subjects met exclusion criteria. No significant difference between groups emerged in demographic and clinical data. Moreover, since our sample was composed of never-depressed but high-risk subjects, these defects might be heritable markers of depression predisposition rather than measures of active illness.

Traditional scoring revealed no significant differences between groups in the macro-architecture of sleep, in slight contrast to a similar study [26] conducted on a larger cohort that found a reduced quality of sleep in adolescents but not in children. Nonetheless, as mentioned above, sleep macro-structural parameters should not be considered as reliable markers of vulnerability to depression, since they are highly not specific and inadequately sensitive. Unexpectedly, electrophysiological investigations did not reveal significant results in the spectral power analysis of slow wave activity nor in the evaluation of slow waves parameters. Only one noteworthy trend emerged in the incidence of low-amplitude slow waves, that was lower in the high-risk group compared to controls during the last hour of N3 sleep; however, this finding was rather difficult to interpret and leads no particular clinical or functional implications. Nonetheless, the absence of other differences in slow waves was unexpected since anomalies in the SWA are common in depressed individuals and the spatio-temporal distribution of slow oscillations has already been utilized to trace anomalies in the neurodevelopment at this age [64].

In sharp contrast to slow oscillations, the analysis of sleep spindles revealed intriguing results which were repeatedly confirmed both at spectral and electrophysiological level. Our most relevant finding was a reduction in the activity of slow spindles and related characteristics in children at high risk for depression. Particularly, we demonstrated that high-risk children had a decrease in all-night low-sigma spindle activity over frontal and central regions, where higher densities of slow spindles are usually detected [65]. Underlying this reduction in power was a decrease in several parameters characterizing sleep spindles. Accordingly, the incidence of slow but not fast spindles was lower in the high-risk group during the first but not the last hour of N2 stage sleep. These results were in line with previous findings reported by Lopez et al. 2010 [21]: unfortunately, in that study, sleep spindles were analyzed only in a left frontal electrode, without evaluating the topographical distribution of such elements, and no further analysis was performed on sleep spindles; finally, spindles were not separated according to their frequency (slow and fast spindles), though the frequency range of detection was rather wide (11 – 16 Hz).

Nonetheless, Lopez et al. 2010 [21] observed that such a reduction of spindle density was significant only later in the night (third and fourth N2 sleep episodes) and mostly in females. On the contrary, most of our results were specific for males and children while females and adolescents did not show such a pattern. A similar trend in all-night SpA was found both for females and adolescents, hence we cannot exclude that these findings are not specific for an early stage of development but extend throughout the puberty; thus, we may assert that a small sample size might be the main reason for the lack of significance in these subgroups.

Lopez et al. 2010 [21] attributed the reduction of spindle density, mainly in depressed children but also in those at high risk based on familiar history, to an impaired neuroplasticity at this age, suggesting that it could be considered a vulnerability factor for the development of MDD. The authors also speculated that the dramatic reduction observed in these children would be a compensatory mechanism of the brain to limit the flow of emotionally harmful, persistent and intrusive information from limbic structures to the cortex. Moreover, since the generation of spindles requires inhibitory cells in the reticular nucleus of the thalamus [53], one can hypothesize that thalamo-cortical functional connections might be impaired in individuals at risk for depression, hence a dysfunction in the reticular nucleus and in thalamic circuits may be primarily responsible for spindles deficits in the vulnerability to depression. Within this sophisticate network connecting thalamic and cortical neurons, the occurrence of spindles during sleep is thought to serve as regulator of several aspects of the functional connectivity to the neocortex [53,66]. Indeed, the role of spindles has been implied in many aspects of this widespread communication, including sensory transmission and information processing during sleep, cortical plasticity and synaptic strengthening, memory consolidation and learning [66].

A substantial literature [18,44,45,52] has previously shown that spindles are associated with cognitive functions such as attention and memory and several studies have demonstrated a positive correlation between cognitive performance and spindle activity in adults. Indeed, spindle activity can be reliably regarded as a physiological marker of intellectual ability [52]. Moreover, an efficient generation of sleep spindles appears necessary for the normal intellectual development, being spindle density and sigma power correlated with intelligence quotient (IQ) scores and other cognitive measures also in childhood. Spindles [51,52] are required both for procedural and declarative memory consolidation, though more compelling evidences have emerged for the former type. The duration of N2 sleep, the spectral power within the sigma range and the spindle activity are highly increased after a learning task requiring both types of memory [44]. Also, several parameters of sleep spindles, such as number, density and duration, show a similar trend. Consistently, neuroimaging studies, reviewed in Fogel and Smith 2011 [52], have repeatedly confirmed that neural correlates of spindles include structures that are functionally related to memory retaining and cognition, such as thalamus, anterior cingulate, insula and prefrontal cortex. Interestingly, a consistent body of animal studies, reviewed in Fogel and Smith 2011 [52], reported similar findings, further strengthening these conclusions through referring to neuroplasticity. Indeed, sleep spindles seems to be involved in the long-term potentiation (LTP) which is necessary for memory consolidation; the induction of LTP results in an increased spindles generation and, on the other hand, spindle activity can produce LTP in vitro. Intriguingly, it has been shown that spindles are involved in the hippocampo-neocortical functional communication [67] which takes place during sleep, thus being important mechanisms related to sleep-dependent memory consolidation.

Yet, the specific role of slow and fast spindles has not been clearly defined. However, an increasing number of studies are focusing on this aspect and, recently, a first step into a more precise comprehension of this topic has been done. An increase in low-sigma range activity was observed in frontal regions following procedural and declarative learning, whereas high-sigma range power did not show significant changes [52]. It has been hypothesized that slow spindles may be involved in memory consolidation, whereas fast spindles may support other functions. Nonetheless, findings are not always consistent throughout the existing literature [52] and further studies are required to functionally discriminate between these two kinds of spindles.

Also, we investigated the cyclic alternating pattern of sleep in the same sample of children and we found that an altered distribution of the phase A subtypes was present in the high-risk group relative to controls. Children at high risk for depression had a nearly-significant reduction of A1% and increase of A2–3% subtypes, resulting in a significantly lower ratio of A1 over A2–3 compared to low-risk controls. CAP results were specific for males, further supporting previously reported findings on sleep spindles, and for adolescents, in which NREM instability might have important consequences on sleep quality at this age. Since this was the first study performing CAP analysis in children at high risk for depression, our results were highly innovative, but we did not have a basis for comparison. In any case, our conclusions were based on similar findings reported for other disturbances of the neurodevelopment [46,56].

Intriguingly, CAP analysis appears to be oriented towards similar considerations as spindles deficits. Indeed, CAP findings seem to indicate that high-risk children have increased level of cortical arousability: CAP subtypes A2–3, which were found to be greatly increased with respect to A1, closely correspond to arousals as scored following AASM Scoring Manual Version 2.2 criteria [61]. This might be interpreted as a failure of the central nervous system to control arousals during sleep, thus resulting in a more disturbed quality of restoration. Indeed, the decrease of transient slow EEG oscillations during NREM sleep have been related to poor cognitive functioning in numerous CAP studies [50,68,69]. Genetic syndromes characterized by mental retardation, such as fragile X and Down syndrome, autism and epilepsy with cognitive impairment are all marked by a strong reduction in CAP rate and A1 index [46]. Particularly, it has been repeatedly shown that the degree of mental retardation itself rather than other neurodevelopmental abnormalities affect sleep micro-structure. On the contrary, in children with Asperger syndrome, an autism-spectrum condition characterized by normal-to-high degree of intellectual ability, an increase of slow oscillations has been found, again confirming that it is not the autistic phenotype itself but the degree of cognitive functioning to influence sleep micro-structure, or vice versa. Hence, the reduction of A1 subtype with respect to A2–3 can be reliably regarded as a clinical marker of cognitive impairment and intellectual disability.

The role that sleep plays for consolidating memory during normal development first emerges from the evidence that restriction of sleep in children is associated with impairment in different cognitive functions: its deprivation or fragmentation, particularly during the developmental age, is responsible for a cognitive disruption, while a better quality of sleep is essential for a normal maturation of cortical properties. In this perspective, higher levels of cortical arousability are clearly detrimental. Our hypothesis is focused on an altered development of cognition in depression vulnerable subjects. Indeed, both spindle deficits and CAP findings are likely related to a reduced general cognitive ability in these children and are consistent in indicating an abnormal sleep-related cognition development. Our hypothesis is that the existence of a predisposing heritable programming for depression may trigger the development of a thalamo-cortical circuitry with limited sleep spindles generation, as confirmed by Lopez et al. 2010 [21], and of a neocortical connectivity with increased cerebral arousability. A reduced spindle activity and an increased NREM sleep instability during this age of development, which is highly susceptible of synaptic remodeling [41,43], would in turn produce functional anomalies in brain maturation, thus resulting in an altered cortical plasticity. In this perspective, a reduced neuroplasticity at this age could represent a pathogenic factor or an epiphenomenon for major depression [39–43].

One may wonder whether these anomalies are based on a predisposing environment rather than a genetic programming, thus raising the unresolved issue on the nature-versus-nurture question. Nonetheless, a reduced spindle density has been recently found in high risk 6-month-old infants [29], further strengthening the genetic hypothesis; moreover, spindles are electrophysiological features of sleep that are generated within a preformed circuitry whose development requires a genetic programming for synaptic structuring [53,70]. However, we cannot conclude for certain that environmental predisposing factors are not involved along with genetic susceptibility, hence future studies are required to further evaluate these aspects and finely discern the role of each vulnerability element.

The most questionable limit of our study was the small size of our sample; however, it should be noted that an appropriate statistical approach was used to avoid type 1 errors. Another strong limitation of the study was the absence of a neurocognitive assessment in children, which might have clarified whether our results were correlated to a cognitive dysfunction in the high-risk group; several cognitive functioning tests could have been used to assess the neurocognitive development of these children, such as the Wechsler Intelligence Scale for Children or the Stanford–Binet Intelligence Scales, as previously performed in similar studies [50,71]. Other technical limitations include the use of a small number of EEG electrodes preventing a more precise topographical evaluation of spindles; the use of two different sleep recording systems, though no particular differences emerged from the analysis; and the absence of multiple recording nights to avoid the first-night effect which might have biased our results. Finally, only maternal mood has been considered as a vulnerability factor for the offspring to develop depression, though compelling evidences [32] confirmed the role of paternal and grand-parental depression as susceptibility risk factors as well.

These results, though promising and manifestly significant, should be confirmed by further studies on larger samples in order to verify their reproducibility and stability over time. Neuroimaging studies in humans and electrophysiological studies on animal models are also required to finely explore the possible involvement of thalamo-cortical connections in the vulnerability to depression. Moreover, similar evaluations should be performed on different groups of children, in order to assess whether also other risk factors for depression are marked by the same patterns of sleep, which, then, could reliably be considered as vulnerability traits of depression, irrespective of the etiology. Finally, a long-term follow-up of individuals at high risk for depression, from birth to old age, could indeed reveal intriguing insights in this field of research and, possibly, confirm our hypothesis on the role of sleep in cognitive development as a vulnerability factor for depression.

1. **Conclusions**

Sleep disorders are a frequent manifestation of depression and are likely linked to its vulnerability possibly through an altered neuroplasticity. Our study confirmed the existence of electrophysiological and micro-architectural abnormalities in children and adolescents born to depressed mothers. Particularly, we found a significant reduction in spindle generation and an increased NREM sleep instability in high-risk children compared to matched controls. These findings emphasize the importance of sleep in cognitive and emotional development and may provide useful cues for a better knowledge of the physiopathology underlying depression.

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