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Video-Polysomnographic Assessment for the Diagnosis of Disorders of Arousal in Children

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Abstract

Objectives

To highlight the slow-wave sleep (SWS) fragmentation and validate the video-polysomnographic (vPSG) criteria and cutoffs for the diagnosis of disorders of arousal (DOA) in children, as already reported in adults.

Methods

One hundred children (66 boys, 11.0 ± 3.3 years) with frequent episodes of DOA and 50 nonparasomniac children (32 boys, 10.9 ± 3.9 years) underwent vPSG recording to quantify SWS characteristics (number of N3 sleep interruptions, fragmentation index, slow/mixed and fast arousal ratios, and indexes per hour) and associated behaviors. We compared SWS characteristics in the 2 groups and defined the optimal cutoff values for the diagnosis of DOA using receiver operating characteristic curves.

Results

Patients with DOA had higher amounts of N3 and REM sleep, number of N3 interruptions, SWS fragmentation, and slow/mixed arousal indexes than controls. The highest area under the curve (AUC) values were obtained for SWS fragmentation and slow/mixed arousal indexes with satisfactory classification performances (AUC 0.80, 95% confidence interval [CI] 0.73–0.87; AUC 0.82, 95% CI 0.75–0.89). SWS fragmentation index cutoff value of 4.1/h reached a sensitivity of 65.0% and a specificity of 84.0%. Slow/mixed arousal index cutoff of 3.8/h reached a sensitivity of 69.0% and a specificity of 82.0%. At least one parasomniac episode was recorded in 63.0% of patients and none of the controls. Combining behavioral component by vPSG increased sensitivity of both biomarkers to 83% and 89%, respectively.

Conclusions

We confirmed that SWS fragmentation and slow/mixed arousal indexes are 2 relevant biomarkers for the diagnosis of DOA in children, with different cutoffs obtained than those validated in adults.

Classification of Evidence

This study provides Class III evidence that SWS fragmentation and slow/mixed arousal indexes on vPSG accurately identify children with DOA.

Glossary

AHI = Apnea Hypopnea Index; AUC = area under the curve; CA = confusional arousal; CAP = cyclic alternating pattern; CI = confidence interval; DOA = disorder of arousal; NREM = non-REM; PLMS = periodic limb movements during sleep; PSG = polysomnographic; ROC = receiver operating characteristic; ST = sleep terror; SWS = slow-wave sleep; SWSFI = slow-wave sleep fragmentation index; vPSG = video-PSG.

Sleepwalking, sleep terrors (STs), and confusional arousals (CAs) are the 3 main clinical manifestations of disorders of arousal (DOAs), a common childhood parasomnia.¹ DOAs are caused by incomplete awakening from non-REM (NREM) sleep, especially slow-wave sleep (SWS), characterized by recurrent inappropriate, often disturbing behaviors associated with partial or complete amnesia of the episodes.^{2,3} DOAs are usually considered as a frequent and benign sleep disorder in children, with more than half of children experiencing at least one episode of ST or CA, and almost 30% of sleepwalking.^{4,5} Frequent episodes are seen in 5.0%–10.0% of children,⁶ and may be associated with substantial consequences such as injuries, sleep disruption, and altered daytime functioning, as observed in adults.⁷

According to the main classification systems, the diagnosis of DOA is based only on clinical criteria, in contrast to other sleep disorders.^{1,8,9} DOAs usually can be diagnosed based on careful history-taking; however, severe or atypical clinical situations, especially in adults, may require additional investigations.¹⁰

Excessive SWS fragmentation and the abnormal persistence of a slow EEG pattern, characterized by predominant diffuse and synchronous slow delta activity during N3 sleep interruptions, appear to represent typical polysomnographic (PSG) patterns in DOA.² We recently validated video-PSG (vPSG) criteria for the diagnosis of DOA in adults, showing a higher SWS fragmentation and slow/mixed SWS arousal indexes in patients compared to controls. We also identified cutoff values for these 2 relevant PSG biomarkers that lead to satisfactory classification performances (with sensitivity and specificity ranging from 80% to 94%).¹¹

The prevalence of DOA is 3 times higher in children than in adults,⁶ and these parasomnias represent a frequent reason for referral at this age in specialized sleep clinics. A validation of these neurophysiologic biomarkers is needed to improve the diagnostic procedure of DOA in the pediatric population. Given that sleep architecture greatly depends on the age,¹² especially relative to SWS amount, distribution, and EEG characteristics (i.e., higher amplitude and lower frequency of the slow wave activity),¹³ we may wonder whether similar criteria and related thresholds can be applied to a pediatric population. The aims of this study were to (1) compare some SWS characteristics in children with DOA and control children without history of DOA, (2) define cutoff values for relevant biomarkers for the diagnosis of DOA, and (3) assess whether SWS alterations are associated with demographic and clinical characteristics in children with DOA.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

All participants and their parents signed informed consent, and this study was conducted in accordance with the Declaration of Helsinki and French Good Clinical Practices.

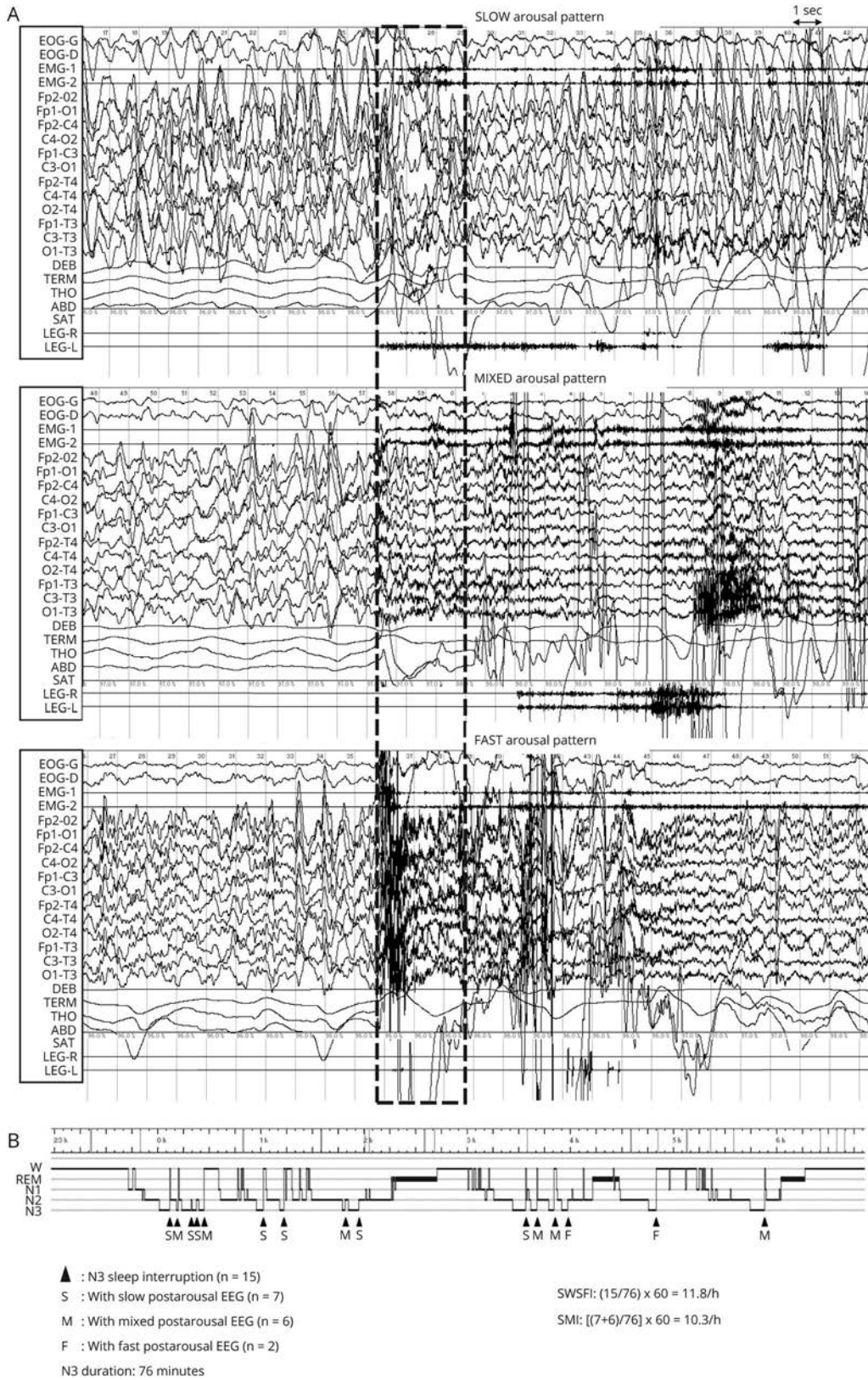
Participants

One hundred children (66 male; median age 10.9 years, range 3.2–17.8) with a diagnosis of DOA were enrolled at the Sleep Disorders Unit of Montpellier, France. Inclusion criteria were (1) typical clinical history of DOA according to the International Classification of Sleep Disorders–3¹; (2) at least 1 parasomniac episode per month; and (3) at least 1 episode during the last month. Exclusion criteria were nonstabilized psychiatric disorder (for instance, severe depressive or anxiety disorder or psychotic disorder), concomitant sleep disorder (restless legs syndrome with symptoms more than twice a week, narcolepsy, or hypersomnolence disorder), past or present history of personal and familial epilepsy of any etiology, sleep deprivation, or drug-induced parasomnias. The clinical subtypes of DOA (sleepwalking, CA, or ST), frequency of parasomniac episodes, age at onset, and first- and second-degree family history of DOA were systematically documented by a clinical interview of parents for young children and by the patients themselves for adolescents. The presence of a history of violent behaviors (self-injuries, hetero-aggressive behaviors), disturbed nighttime sleep (sleep onset insomnia, frequent awakenings), and altered daytime functioning (complaint of fatigue, sleepiness, attentional and behavioral problems) were also reported, assessed by medical interview.

Fifty children (32 male, median age 12.5 years, range 3.7–16.3) without past or present history of nocturnal agitation, parasomnia, or epilepsy, and without formally diagnosed sleep disorders, were also evaluated in our center and constituted the control group. However, children may experience minor sleep disturbances such as fatigue, drowsiness, or snoring, and thus do not constitute a completely healthy control group.

None of the participants was taking any medication known to influence sleep, breathing, or motor activity for at least 2 weeks prior to the sleep recording. They were asked to follow their habitual sleep schedules on weekdays and weekends during the month preceding the vPSG.

Figure 1 EEG and Annotated Hypnogram



(A) EEG characteristics of the first 3 seconds of N3 interruptions categorized in 3 patterns: slow, mixed, and fast. (B) Annotated hypnogram of a child with disorder of arousal, showing the temporal distribution of the N3 interruptions, with calculation of the slow-wave sleep fragmentation index and the slow/mixed index. N3 = non-REM sleep stage 3; SMI = slow/mixed index; SWSFI = slow-wave sleep fragmentation index.

Table 1 Clinical and Polysomnographic Characteristics in Controls and Children with Disorders of Arousal (DOAs)

Variable	Controls (n = 50)		DOA (n = 100)		p Value
	N	%	N	%	
Male sex	32	64.0	66	66.0	0.81
Age, y ^a	10.95 ± 3.87		11.04 ± 3.32		0.89
Polysomnographic characteristics					
Total sleep time, min ^a	454.92 ± 62.07		457.63 ± 51.46		0.78
Sleep efficiency, % ^a	86.63 ± 7.77		86.87 ± 6.84		0.84
Sleep latency, min ^a	20.24 ± 18.15		24.02 ± 20.59		0.28
N1 sleep, % ^a	3.30 ± 1.99		3.53 ± 2.06		0.52
N2 sleep, % ^a	55.40 ± 5.92		48.40 ± 6.59		<0.0001
N3 sleep, % ^a	21.62 ± 5.66		26.17 ± 5.49		<0.0001
N3 sleep duration, min ^a	97.22 ± 23.27		118.97 ± 26.03		<0.0001
N3 sleep latency, min ^a	36.68 ± 25.04		37.70 ± 22.72		0.80
REM, % ^a	19.66 ± 4.53		21.89 ± 4.52		0.007
Microarousal index/h ^a	7.26 ± 3.99		7.95 ± 4.49		0.36
PLMS/h ^a	1.57 ± 2.68		2.28 ± 5.16		0.37
AHI/h ^a	1.29 ± 1.63		0.95 ± 1.59		0.25
Slow-wave sleep microstructure					
N3 interruptions, n	4.84 ± 2.96		10.95 ± 5.63		<0.0001
SWS fragmentation index/h of N3 sleep ^a	2.98 ± 1.71		5.57 ± 2.71		<0.0001
Fast arousal ratio, %	17.03 ± 23.75		4.99 ± 9.52		0.0003
Mixed arousal ratio, %	49.41 ± 30.31		56.61 ± 26.42		0.14
Slow arousal ratio, %	33.56 ± 28.38		38.40 ± 27.31		0.31
Slow/mixed arousal ratio, %	82.97 ± 23.75		95.01 ± 9.52		<0.0001
Fast arousal index/h of N3 sleep ^a	0.46 ± 0.60		0.26 ± 0.49		0.04
Mixed arousal index/h of N3 sleep ^a	1.44 ± 1.15		3.10 ± 2.10		<0.0001
Slow arousal index/h of N3 sleep ^a	1.08 ± 1.07		2.20 ± 1.91		0.0005
Slow/mixed arousal index/h of N3 sleep ^a	2.53 ± 1.71		5.30 ± 2.68		<0.0001

Abbreviations: AHI = Apnea Hypopnea Index; DOA = disorder of arousal; N1 = non-REM sleep stage 1; N2 = non-REM sleep stage 2; N3 = non-REM sleep stage 3; PLMS = periodic leg movements during sleep; SWS = slow-wave sleep.

^a Continuous variables are expressed as mean ± SD.

vPSG Assessment

All participants underwent 1-night vPSG recording in the sleep laboratory. This included EEG leads (C3/A2, Fp1/T3, T3/O1, O1/C3, C4/A1, Fp2/T4, T4/O2, O2/C4), electro-oculogram, chin EMG, and ECG. Respiration was monitored with a nasal cannula/pressure transducer system, mouth thermistor, chest and abdominal bands, and pulse oximeter. Leg movements were assessed with surface EMG electrodes placed on the right and left anterior tibialis muscles. Sleep stages, microarousals, periodic limb movements during sleep (PLMS), and respiratory events (Apnea Hypopnea Index

[AHI]) were manually scored by a single scorer (R.L.) to avoid interscorer variability, according to standard criteria for children.^{14,15}

Specific attention was given to SWS characteristics (i.e., N3 duration, percentage and latency from sleep onset), its fragmentation, and the postarousal EEG patterns recently validated in adults.¹¹ Briefly, SWS interruption events were defined as (1) the occurrence of abrupt EEG frequency shifts with a combination of theta and alpha waves, and frequencies >16 Hz and lasting 3–15 seconds (i.e., microarousals) or (2)

Table 2 Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Area Under the Curve (AUC) of Slow-Wave Sleep (SWS) Microstructure Parameters to Identify the Presence of Disorders of Arousal Among Patients and Controls

	Cutoff values	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
SWS fragmentation index/h of N3 sleep	≥3.8/h	0.80 (0.73–0.87)	0.73 (0.64–0.82)	0.76 (0.64–0.88)
	≥4.1/h		0.65 (0.56–0.74)	0.84 (0.74–0.94)
Slow/mixed arousal index/h of N3 sleep	≥3.3/h	0.82 (0.75–0.89)	0.77 (0.69–0.85)	0.74 (0.62–0.86)
	≥3.8/h		0.69 (0.60–0.78)	0.82 (0.71–0.93)
Mixed arousal index/h of N3 sleep	≥1.9/h	0.76 (0.69–0.84)	0.70 (0.61–0.79)	0.74 (0.62–0.86)
	≥2.5/h		0.55 (0.45–0.65)	0.88 (0.79–0.97)
Slow arousal index/h of N3 sleep	≥2.0/h	0.68 (0.59–0.76)	0.48 (0.38–0.58)	0.80 (0.69–0.91)
	≥2.7/h		0.37 (0.28–0.46)	0.90 (0.82–0.98)
Slow/mixed arousal ratio, %	≥90.9	0.63 (0.54–0.72)	0.81 (0.73–0.89)	0.47 (0.33–0.61)

Abbreviations: CI = confidence interval; N3 = non-REM sleep stage 3.

similar events but lasting >15 seconds (i.e., sleep to wake transitions) or (3) events with persistent delta waves (0.5–3 Hz) associated with increased muscle activity and lasting >3 seconds. The total number of SWS interruptions per hour of N3 sleep was reported and named SWS fragmentation index (SWSFI). Each N3 interruption was categorized by predominant slow, mixed, or fast EEG activity during the first 3 seconds following the increase of EMG activity (figure 1). Analysis of postarousal EEG activity was performed on central and occipital leads to assess sleep to wake transitions and persistent SWS if present. While the slow wave topography generally shows a frontal predominance in adults,¹⁶ large changes were observed during development, with a shift from occipital/central regions during childhood, gradually reaching the frontal regions by the end of adolescence.¹⁷ Three indices were calculated (i.e., slow, mixed, and fast arousal patterns per hour of N3 sleep). Three ratios were also computed by dividing the percentage of SWS interruptions classified as fast, mixed, or slow arousals by the total number of SWS interruptions. All time-synchronized vPSG recordings were analyzed to detail the behavior associated with SWS alterations. Sudden motor behaviors including staring or looking around, raising the head or trunk, any facial or vocal expression of fear or surprise, sitting in bed, standing, or screaming, were qualified as parasomniac episodes, according to the findings of 2 recent studies.^{18,19}

Statistical Analyses

Categorical variables are presented as percentages, quantitative variables as mean with SD. To compare demographic, clinical, and PSG variables between 2 groups (e.g., patients with DOA vs controls), logistic regression models were run. To compare diagnostic performance of the SWS parameters, receiver operating characteristic (ROC) analyses were performed. The best possible threshold was defined by the highest Youden Index ($[\text{specificity} + \text{sensitivity}] - 1$). Comparisons of SWS

parameters with dichotomized characteristics in children with DOA were made using logistic regression models. Significance level was set at $p < 0.05$. Analyses were performed using SAS (version 9.4; SAS Inc., Cary, NC).

Data Availability

Anonymized data not provided in the article because of space limitations will be shared by request from any qualified investigator.

Results

Clinical Characteristics of Children With DOA

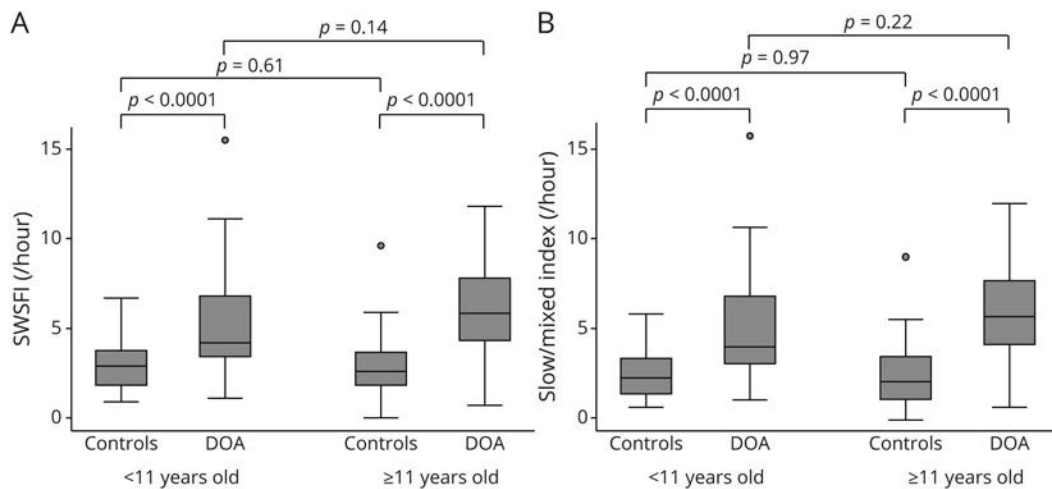
Among the 100 children with DOA, 90 reported sleepwalking episodes, 92 CA, and 73 ST, with 57 patients sharing the 3 clinical subtypes at different time periods; only 4 had 1 isolated subtype (ST only). Eighty-four patients reported at least 1 episode per week, and 36 daily episodes. The median age at onset was 5.0 years (1.0–14.0), with a median disease duration of 5.6 years (0.2–14.8 years). A positive family history of DOA (first- and second-degree) was reported in 62 among 86 patients with available information (72.1%), with 40.6% of relatives having persistent forms in adulthood. Thirty-four children (34.0%) had at least 1 past episode of violent behavior related to parasomniac episodes, 51/71 patients (71.8%) disturbed nighttime sleep, and 57/74 (77.0%) altered daytime functioning. Comorbid neurodevelopmental disorders were reported by 36 patients, mainly learning disorders and attention-deficit/hyperactivity disorder (without intellectual disability, signs of regression, or autism spectrum disorder). Among the 8 patients reporting migraine, none of them had a migraine episode during the week preceding the vPSG recording. Seven patients had concomitant anxiety or mood disorder. Infrequent comorbid restless legs syndrome and sleep enuresis were reported by 8 and 10 patients.

Table 3 Clinical and Polysomnographic Characteristics of Children With and Without Disorder of Arousal (DOA) According to Age Groups

	3-10 years old						11-18 years old						Comparisons, p Values				
	Controls (n = 23)			DOA (n = 52)			Controls (n = 27)			DOA (n = 48)			Controls: 3-10 y vs 11-18 y		DOA: 3-10 y vs 11-18 y	11-18 y: controls vs DOA	
	N	%		N	%		N	%		N	%		N	%			
Clinical characteristics																	
Male	18	78.26	33	63.46	14	51.85	33	68.75	0.05	0.58	0.21	0.15					
Sleepwalking	—	—	45	86.54	—	45	93.75	—	0.32	—	—	—					
Confusional arousals	—	—	45	86.54	—	47	97.92	—	0.06	—	—	—					
Sleep terrors	—	—	39	75.00	—	34	70.83	—	0.64	—	—	—					
All subtypes	—	—	29	55.77	—	30	62.50	—	0.49	—	—	—					
Daily episodes	—	—	17	32.69	—	19	39.58	—	0.47	—	—	—					
Positive family history	—	—	31	70.45	—	31	73.81	—	0.73	—	—	—					
Violent behaviors	—	—	16	30.77	—	18	37.50	—	0.48	—	—	—					
Disturbed nighttime sleep	—	—	22	66.67	—	29	76.32	—	0.37	—	—	—					
Altered daytime functioning	—	—	26	70.27	—	31	83.78	—	0.17	—	—	—					
Polysomnographic characteristics																	
N3, %	22.46 ± 6.33		26.81 ± 5.04		20.90 ± 5.03		25.47 ± 5.92		0.34	0.22	0.002	0.001					
N3 duration, min	106.13 ± 20.59		127.79 ± 25.40		89.63 ± 23.06		109.42 ± 23.40		0.01	0.0003	0.0006	0.0007					
N3 Latency, min	32.70 ± 25.87		35.63 ± 24.04		40.07 ± 24.28		39.94 ± 21.23		0.30	0.35	0.63	0.98					
N3 interruptions, n	5.17 ± 3.17		10.96 ± 6.03		4.56 ± 2.79		10.94 ± 5.24		0.47	0.98	<0.0001	<0.0001					
REM, %	20.37 ± 5.35		23.19 ± 4.03		19.05 ± 3.69		20.48 ± 4.64		0.31	0.002	0.01	0.17					
SWSFI/h of SWS	2.85 ± 1.43		5.18 ± 2.75		3.10 ± 1.93		5.99 ± 2.62		0.61	0.14	<0.0001	<0.0001					
Slow/mixed arousal ratio, %	89.23 ± 18.00		95.93 ± 8.83		77.43 ± 27.02		94.01 ± 10.21		0.08	0.32	0.10	0.005					
Slow/mixed arousal index/h of SWS	2.52 ± 1.35		4.99 ± 2.73		2.53 ± 1.99		5.65 ± 2.62		0.97	0.22	<0.0001	<0.0001					
Parasomniac episode (≥1)	—		27	51.92	—	36	75.00	—	0.02	—	—	—					

Abbreviations: N3 = non-REM sleep stage 3; SWSFI = slow-wave sleep fragmentation index. Continuous values are expressed as mean ± SD.

Figure 2 Bow-Whisker Plots



(A) Slow-wave sleep fragmentation and (B) slow/mixed arousal indexes according to age groups and diagnostic categories. DOA = disorder of arousal; SWSFI = slow-wave sleep fragmentation index.

PSG Characteristics of Children With DOA and Controls

Compared with controls, children with DOA had higher percentage of N3 and REM sleep, and reduced N2, without differences for N3 latency, total sleep time, sleep efficiency, AHI, and PLMS. Patients with DOA had a higher number of N3 interruptions, SWSFI, slow, mixed, and slow/mixed arousal indexes, and slow/mixed ratio (table 1). Sixty-three patients (63%) had at least one episode of parasomnia associated with SWS interruption during the vPSG recording (mostly confusional arousals) vs none of the controls. Sleep-related episodes were not associated with complex, hyperkinetic, stereotypic, or bizarre motor patterns, thus not in favor of hypermotor seizures. Moreover, no epileptiform discharges on surface EEG were found during the vPSG recording.

PSG Criteria for DOA in Children

We first used the thresholds previously validated in the adult population (i.e., $\geq 6.8/h$ for the SWSFI, $\geq 2.5/h$ [to reach excellent sensitivity], and $\geq 6/h$ [to reach excellent specificity] for the slow/mixed index).¹¹ Applying these cutoff values leads to moderate classification performances in our sample of children, with a sensitivity of 34.0%, 87.0%, and 37.0%, and a specificity of 98.0%, 58.0%, and 98.0%, respectively.

ROC analyses were then performed to determine the best cutoff values that discriminate patients with DOA from controls. We found that SWSFI $\geq 4.1/h$ and slow/mixed arousal index $\geq 3.8/h$ had satisfactory classification performances (area under the curve [AUC] 0.80; 95% confidence interval [CI] 0.73–0.87 and AUC 0.82; 95% CI 0.75–0.89, respectively) without differences between them (table 2). For the SWSFI, the sensitivity increased from 65% to 73% and the specificity decreased from 84% to 76% when using the cutoff of 3.8/h instead of 4.1/h. Sensitivity reached 69%–77% with a

slow/mixed arousal index cutoff of 3.3/h, while specificity decreased from 82% to 74%. The slow/mixed arousal ratio offered fair classification performances (table 2).

Combining at least one parasomniac episode recorded by vPSG increased the sensitivity of the SWSFI $\geq 4.1/h$ cutoff from 65% to 83% (95% CI 76.0–90.0) and the slow/mixed index $\geq 3.8/h$ cutoff from 69% to 89% (95% CI 83.0–95.0), respectively, without changing specificity.

We then assessed whether the SWS characteristics may be associated with age in children with DOA. Dividing the population according to the median age (age groups: 3–10 and 11–18 years), we found that the oldest patient group did not differ from the youngest for SWSFI and slow/mixed arousal index, with same results for the controls. In contrast, both patient groups had higher SWSFI and slow/mixed arousal indexes but also increased N3%, N3 duration, and N3 interruptions than their respective age controls (table 3 and figure 2).

Demographic, Clinical, and Neurophysiologic Characteristics in Children With DOA

We found no between age group (according to the median, i.e., 10 years) or sex differences on clinical subtypes, frequency of episodes by clinical history, familial history of DOA, violent behavior, disturbed nighttime sleep, or daytime functioning. However, younger patients less frequently exhibited parasomniac behaviors during the vPSG (51.9% vs 75.0%; $p = 0.02$) (table 3). Compared to patients with nondaily episodes ($n = 64$), patients with daily episodes ($n = 36$) had a higher SWSFI ($6.54/h \pm 2.78$ vs $5.02/h \pm 2.52$, $p < 0.01$) and slow/mixed arousal index ($6.23/h \pm 2.76$ vs $4.78/h \pm 2.51$, $p < 0.01$), without differences for N3 duration, latency, or slow/mixed arousal ratio. No such significant differences were found between sexes, between patients with familial vs sporadic DOA,

with and without complaint of disturbed nighttime sleep, or with and without violent parasomnias. Finally, PSG characteristics did not differ between patients with DOA with and without complaint of disturbed nighttime sleep.

Discussion

Our study validated the vPSG criteria for the diagnosis of DOA in children. A higher SWS fragmentation and slow/mixed SWS arousal indexes were found in patients compared to nonparasomniac controls. These relevant PSG biomarkers, already reported in adults with DOA, also showed satisfactory diagnostic performances applying new cutoffs for children.

We studied a well-characterized population of children with DOA seen in clinic by sleep experts with a vPSG assessment. We confirmed that children with DOA often experienced the 3 clinical subtypes of DOA (sleepwalking, ST, and CA), had frequent positive family history,^{4,20,21} and neurodevelopmental comorbidities,²⁰ sleep enuresis,²¹⁻²³ and migraine,^{24,25} as previously reported. DOA is common and usually considered as a benign disorder in children; however, substantial consequences may be observed, as already reported in adults.^{7,26,27} Indeed, our population of children with DOA reported at least one previous violent parasomnia episode in 34%, nighttime sleep disruption in 72%, and altered daytime functioning in 77%.

Our main objective was to compare the vPSG and related SWS characteristics between children with DOA and nonparasomniac children. We found higher N3, REM, and reduced N2 sleep percentages in patients than controls, in line with results reported in adults with DOA and in sleep-deprived condition.^{11,28-30} These findings may reflect a higher NREM and REM sleep pressure as an endophenotypic feature of pediatric DOA. As sleep changes with age¹² and DOAs frequently improve spontaneously over the years,⁴ we also assessed whether the youngest patients of our sample (≤ 10 years) differed from the older ones (> 10 years) and found a decrease in N3 duration in the latter group, also found in the control group.

We confirmed excessive SWS fragmentation in children with DOA, with higher SWSFI than controls in both age groups. These results are in line with previous studies showing a marked NREM instability in children with DOA, as assessed by the cyclic alternating patterns (CAP) analyses.³¹⁻³³ Although the SWSFI takes into account the duration of N3 sleep, our results indicated a lower SWS fragmentation in children, patients, and controls than previously reported in adults (5.1/h vs 10.1/h in patients, and 2.6/h vs 4.4/h in controls).¹¹ A recent study also reported that the total number of N3 interruptions gave correct performances in diagnosing DOA in adults (AUC 0.77, 95% CI 0.685-0.864).³⁴ However, we recommend the use of the SWSFI instead of the number of N3 interruptions as this last measure largely depends on the duration of N3 sleep, being highly influenced by environmental conditions, medication, and especially age. Applying the adult threshold for

SWSFI (i.e., 6.8/h) in our pediatric population,¹¹ the sensitivity was low and the diagnostic performance limited. Lowering the SWSFI cutoff to 3.8/h improved the sensitivity to 73.0%, together with an acceptable specificity of 76.0%. The subanalyses performed according to age groups were not in favor of an adaptation of the threshold for the youngest children.

We compared the EEG patterns of each arousal from N3 sleep and found higher slow, mixed, and slow/mixed arousal indexes in patients with DOA compared to controls. We defined optimal cutoff for the slow/mixed index ($\geq 3.8/h$) that gave satisfactory classification performances (AUC 0.82). We also observed a higher ratio of slow/mixed arousals in patients compared to controls; however, the difference was significant only in children older than 11 years, as also reported in adults.¹¹ The patterns of slow EEG arousals from N3 sleep may overlap with the CAP A1 subtype, showing a high rate in prepubertal children that gradually decreases with age, in contrast to an increase of the CAP A3 rate, a pattern of fast and desynchronized marker of NREM sleep instability.^{35,36} Slow arousal patterns are suspected to reflect an antiarousal mechanism, being a sleep-related milestone of normal brain development.^{37,38} Altogether, these findings suggested a delay in the maturation of sleep regulation in children with DOA, implying both the sleep homeostasis and the arousal mechanisms from NREM sleep. In this context, both SWSFI and slow/mixed arousal index are relevant biomarkers for DOA in children, as also reported in adults,¹¹ and less the slow/mixed arousal ratio especially in younger children.

Comparing the overall diagnostic classification with the respective optimal cutoff in adults and children, the 2 main biomarkers performed slightly less well in children than in adults. The peculiar characteristics of SWS in children with higher amplitude and lower frequency of slow wave activity than in adults¹³ may contribute to the lower specificity of these diagnostic markers in the pediatric population.

We also categorized parasomniac episodes based on observable behaviors associated with N3 interruptions during vPSG and found that 63% of patients with DOA had at least 1 episode, 75% of children above 10 years of age, 52% of those below 10 years of age, and none of the controls, in line with previous studies.^{11,21} Combining the video-based analysis to the SWSFI and slow/mixed arousal index increased the diagnostic performance in increasing the sensitivity to 83.0% for the SWSFI and 89% for the slow/mixed index. Our results also emphasized that children with daily episodes had a more severe SWS fragmentation characterized by higher SWSFI and slow/mixed arousal index, a finding not previously found in adult patients.¹¹ If confirmed, the quantification of the SWS fragmentation may be a relevant biomarker not only for the diagnosis of DOA in children but also for its severity. The calculation of the SWSFI and the slow/mixed index does not require any specific software, and can be easily implemented in a clinical sleep laboratory. If the scoring of N3 interruptions is rapid and rarely problematic, we may recognize that the postarousal EEG analysis requires more skills and time for scoring. Our previous work conducted in adults has shown excellent interrater

agreement for both SWSFI and slow/mixed index (97.0% and 93.1%, respectively).¹¹ Finally, the 2 indexes offer good performances to be clinically significant with a sensitivity and specificity between 80% and 90%. Our method therefore has the potential to be used easily in clinical routine.

Altogether, our findings favor that objective SWS alterations should be added in the next revised diagnostic criteria for DOA in children, as previously suggested in adults, as already required for the diagnosis of other parasomnias, namely REM sleep behavior disorder.^{1,39}

In interpreting the findings from the present study, some limitations have to be taken into account. Our population of patients and controls was limited on sample size and age groups, which could prevent establishing SWS fragmentation cutoffs according to age. Our study was monocentric, and we did not validate our results in a second independent sample, which could limit the generalization of our findings. As we did for adult patients with DOA, we performed the postarousal EEG analysis during the first 3 seconds of each event, independently of whether the postarousal duration was longer than 3 seconds. The objective of this 3-second assessment was to avoid mixed conditions with potential temporal EEG changes due to long arousals or episodes. Moreover, the quantification of the duration of episode is difficult to define precisely with either EEG (i.e., slow and mixed EEG patterns that characterized also sleep-like activity) or video-based characteristics (i.e., in case of mild motor activation). Given the frequent comorbidity between sleep-related hypermotor epilepsy and DOA, we used strict exclusion criteria and we rigorously ruled out clinical and EEG arguments for an epileptic origin. However, patients were not recorded with a full EEG montage and we cannot formally exclude interictal epileptic EEG activity and that a few episodes were epileptic events.⁴⁰ We did not challenge the validity of SWS alterations and related cutoffs in patients with other sleep disorders, such as sleep-related hypermotor epilepsy and sleep apnea syndrome. In the future, it will be of interest to evaluate the diagnostic performances of the present SWS fragmentation criteria in a sample of children with sleep-related hypermotor epilepsy compared to those with DOA. We did not systematically assess clinical characteristics and comorbidities in the nonparasomniac control group, which is not a formal healthy control group. Complaints of disturbed nighttime sleep and altered daytime functioning were not assessed with standardized psychometric tools, so these findings should be interpreted with caution. Our results may not be generalized to all children with DOA as we included only patients with typical and frequent episodes referred to a tertiary sleep unit for such evaluation. For some children, the frequency of episodes of DOA will improve and resolve over the years,⁴¹ while other children, potentially with a more frequent or severe DOA, will have a persistent phenotype in adulthood. The heterogeneous course of the disease favors a delay in the NREM sleep maturation process in remittent cases, and other pathophysiologic mechanisms to be elucidated in persistent cases. The natural history of children with DOA from this study needs to be further assessed. Although our results did not support adapting the thresholds for the younger

children, we did not compare patients based on their pubertal status. Longitudinal studies have shown that adolescence is associated with major changes in SWS characteristics.¹³ Finally, additional studies are needed to confirm the performance, the validated cutoff, and the time distribution of N3 sleep interruptions in DOA in different age groups, including children, adolescents, young adults, adults, and seniors, compared to other populations with different pathologies and of similar age.

We confirmed that SWS fragmentation is a hallmark of DOA in children. Our study assessed the diagnostic value of vPSG criteria for DOA in children, and found that SWSFI and slow/mixed arousal index are robust biomarkers of DOA and its severity in children, with different cutoffs than those for adults. Our study supports the need to include vPSG-based criteria for the diagnosis of DOA in children.

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Continued

Appendix (continued)

Name	Location	Contributions
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References

- American Academy of Sleep Medicine. International Classification of Sleep Disorders, Third Edition (ICSD-3). Darien, IL: American Academy of Sleep Medicine; 2014.
- Castelnovo A, Lopez R, Proserpio P, Nobili L, Dauvilliers Y. NREM sleep parasomnias as disorders of sleep-state dissociation. *Nat Rev Neurol* 2018;14:470.
- Zadra A, Desautels A, Petit D, Montplaisir J. Somnambulism: clinical aspects and pathophysiological hypotheses. *Lancet Neurol* 2013;12:285–294.
- Petit D, Pennestri M, Paquet J, et al. Childhood sleepwalking and sleep terrors: a longitudinal study of prevalence and familial aggregation. *JAMA Pediatr* 2015;169:653–658.
- Laberge L, Tremblay RE, Vitaro F, Montplaisir J. Development of parasomnias from childhood to early adolescence. *Pediatrics* 2000;106:67–74.
- Stallman H, Kohler M. Prevalence of sleepwalking: a systematic review and meta-analysis. *PLoS One* 2016;11:e0164769.
- Lopez R, Jausset I, Scholz S, Bayard S, Montplaisir J, Dauvilliers Y. Functional impairment in adult sleepwalkers: a case-control study. *Sleep* 2013;36:345–351.
- American Psychiatric Association. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 5th ed. Arlington: American Psychiatric Association; 2013.
- World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization; 1992.
- Loddo G, Lopez R, Cileia R, Dauvilliers Y, Provini F. Disorders of arousal in adults: new diagnostic tools for clinical practice. *Sleep Sci Pract* 2019;3:5.
- Lopez R, Shen Y, Chenini S, et al. Diagnostic criteria for disorders of arousal: a video-polysomnographic assessment. *Ann Neurol* 2018;83:341–351.
- Hayton MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep* 2004;27:1255–1273.
- Campbell IG, Feinberg I. Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation. *Proc Natl Acad Sci USA* 2009;106:5177–5180.
- Iber C, Ancoli-Israel S, Chesson A, Quan S. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, 1st ed. Westchester: American Academy of Sleep Medicine; 2007.
- Ferri R, Fulda S, Allen RP, et al. World Association of Sleep Medicine (WASM) 2016 standards for recording and scoring leg movements in polysomnograms: developed by a joint task force from the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG). *Sleep Med* 2016;26:86–95.
- Finelli LA, Borbély AA, Achermann P. Functional topography of the human nonREM sleep electroencephalogram. *Eur J Neurosci* 2001;13:2282–2290.
- Kurth S, Ringli M, Geiger A, LeBourgeois M, Jenni OG, Huber R. Mapping of cortical activity in the first two decades of life: a high-density sleep electroencephalogram study. *J Neurosci* 2010;30:13211–13219.
- Ledard N, Artru E, Colmenarez Sayago P, et al. Adrenergic reactions during N3 sleep arousals in sleepwalking and sleep terrors: the chicken or the egg? *J Sleep Res Epub* 2019:e12946.
- Loddo G, Sessagesimi E, Mignani F, et al. Specific motor patterns of arousal disorders in adults: a video-polysomnographic analysis of 184 episodes. *Sleep Med* 2018;41:102–109.
- Nevsimalova S, Prihodova I, Kemlink D, Skibova J. Childhood parasomnia: a disorder of sleep maturation? *Eur J Paediatr Neurol* 2013;17:615–619.
- Guilleminault C, Palombini L, Pelayo R, Chervin RD. Sleepwalking and sleep terrors in prepubertal children: what triggers them? *Pediatrics* 2003;111:17–25.
- Mehlenbeck R, Spirito A, Owens J, Boergers J. The clinical presentation of childhood partial arousal parasomnias. *Sleep Med* 2000;1:307–312.
- Soster LA, Alves RC, Fagundes SN, et al. Non-REM sleep instability in children with primary monosymptomatic sleep enuresis. *J Clin Sleep Med* 2017;13:1163–1170.
- Lopez R, Jausset I, Dauvilliers Y. Pain in sleepwalking: a clinical enigma. *Sleep* 2015;38:1693–1698.
- Barabas G, Ferrari M, Matthews W. Childhood migraine and somnambulism. *Neurology* 1983;33:948–949.
- Lopez R, Jausset I, Dauvilliers Y. Objective daytime sleepiness in patients with somnambulism or sleep terrors. *Neurology* 2014;83:2070–2076.
- Stallman HM, Kohler MJ, Biggs SN, Lushington K, Kennedy D. Childhood sleepwalking and its relationship to daytime and sleep related behaviors. *Sleep Hypnosis* 2017;19:61–69.
- Carrillo-Solano M, Leu-Semenescu S, Golmard J, Groos E, Arnulf I. Sleepiness in sleepwalking and sleep terrors: a higher sleep pressure? *Sleep Med* 2016;26:54–59.
- Zadra A, Pilon M, Montplaisir J. Polysomnographic diagnosis of sleepwalking: effects of sleep deprivation. *Ann Neurol* 2008;63:513–519.
- Borbély AA, Baumann F, Brandeis D, Strauch I, Lehmann D. Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroencephalogr Clin Neurophysiol* 1981;51:483–493.
- Zucconi M, Oldani A, Ferini-Strambi L, Smirne S. Arousal fluctuations in non-rapid eye movement parasomnias: the role of cyclic alternating pattern as a measure of sleep instability. *J Clin Neurophysiol* 1995;12:147–154.
- Guilleminault C, Lee J, Chan A, Lopes M, Huang Y, Da Rosa A. Non-REM-sleep instability in recurrent sleepwalking in pre-pubertal children. *Sleep Med* 2005;6:515–521.
- Bruni O, Ferri R, Novelli L, Finotti E, Miano S, Guilleminault C. NREM sleep instability in children with sleep terrors: the role of slow wave activity interruptions. *Clin Neurophysiol* 2008;119:985–992.
- Barros A, Ugucioni G, Salkin-Goux V, Leu-Semenescu S, Dodet P, Arnulf I. Simple behavioral criteria for the diagnosis of disorders of arousal. *J Clin Sleep Med* 2020;16:121–128.
- Terzano M, Mancia D, Salati M, Costani G, Decembrino A, Parrino L. The cyclic alternating pattern as a physiologic component of normal NREM sleep. *Sleep* 1985;8:137–145.
- Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instability. *Sleep Med Rev* 2012;16:27–45.
- Halász P, Terzano M, Parrino L, Bódizs R. The nature of arousal in sleep. *J Sleep Res* 2004;13:1–23.
- Halász P, Parrino L, Szucs A. Reactive slow waves in sleep underlying several physiological and pathological NREM conditions: comments on Flamand, et al. *Sleep* 2019;42.
- Dauvilliers Y, Schenck CH, Postuma RB, et al. REM sleep behaviour disorder. *Nat Rev Dis Primers* 2018;4:19.
- Proserpio P, Loddo G, Zubler F, et al. Polysomnographic features differentiating disorder of arousals from sleep-related hypermotor epilepsy. *Sleep* 2019;42:zsz166.
- Klackenberg G. Somnambulism in childhood: prevalence, course and behavioral correlations: a prospective longitudinal study (6-16 years). *Acta Paediatr Scand* 1982;71:495–499.