

## ASSOCIATION BETWEEN PLMS AND AROUSALS IN RLS

## An Evidence-based Analysis of the Association between Periodic Leg Movements during Sleep and Arousals in Restless Legs Syndrome

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**Study Objectives:** To analyze statistically the association between periodic leg movements during sleep (PLMS) and arousals, in order to eventually support or challenge the current scoring rules and to further understand their reciprocal influence.

**Setting:** Sleep research center.

**Patients:** Twenty untreated consecutive patients with restless legs syndrome (RLS) (13 women and 7 males, mean age 60.9 y).

**Methods:** In each recording, we selected all PLMS/arousal pairs that met the following inclusion criteria: (a) PLMS events that were separated from another PLMS event (preceding or following) by at least 10 s of EMG inactivity; (b) arousal events separated from another arousal event (preceding or following) by at least 10 s of stable EEG baseline activity; (c) PLMS/arousal pairs were then selected among events identified according to the previous two criteria, when PLMS and arousals were separated (offset-to-onset) by no more than 10 s, regardless of which was first.

**Measurements and Results:** We selected a mean of 46.1 (SD 25.55) PLMS/arousal pairs per subject; in these pairs, average PLMS duration was 3.2 s (0.65) and average arousal duration was 6.5 s (0.92). Within these event pairs, the great majority (on average 98.4%, SD 3.88) was separated by less than 0.5 s (i.e., between the end of one event and the onset of the other, regardless of which was first). Arousal onsets preceded PLMS onset in 41.2% of pairs, while the opposite was true for the remaining 58.8% of pairs. A significant correlation between PLMS duration and arousal duration was also found ( $r = 0.447$ ,  $P < 0.000001$ ).

**Conclusion:** The results of this study support the current rule for the definition of the association between periodic leg movements during sleep (PLMS) and arousals. The tight time relationship between PLMS and arousals and their correlated durations seem to indicate that both events might be regulated by a complex mechanism, rather than being connected by a simple reciprocal cause/effect relationship.

**Keywords:** periodic leg movements during sleep, PLMS, arousals, restless legs syndrome, sleep scoring

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## INTRODUCTION

The first polysomnographic (PSG) EMG recordings of periodic leg movements during sleep (PLMS) were carried out in Bologna (Italy) by Lugaresi et al. in 1965,<sup>1,2</sup> but it was only almost 20 years later that duration, amplitude, periodicity, and symmetry of PLMS were defined and manually measured on paper recordings by Coleman in 1982,<sup>3</sup> and constituted reference data for the first scoring criteria introduced by the American Sleep Disorders Association (ASDA) in 1993.<sup>4</sup> These criteria were then used for more than 20 years.

Subsequently, two sets of similar rules for scoring PLMS and periodic leg movements during wakefulness (PLMW) have been established that were based, at least in part, on algorithms proposed for the automatic detection of leg movements (LMs) in PSG, including mathematically defined parameters such as thresholds, intervals, and amplitude.<sup>5,6</sup> The first of these two sets of rules was introduced in 2006 by a task force of the International Restless Legs Syndrome (RLS) Study Group, endorsed by the World Association of Sleep Medicine (WASM/IRLSSG).<sup>7</sup> Subsequently, the majority of these rules

(but not all) were adopted by the American Academy of Sleep Medicine (AASM) in 2007 and confirmed in 2012.<sup>8,9</sup>

Notwithstanding the fact that the current rules are largely based on data-driven measures, they still contain some unchallenged criteria that had been introduced during the “paper era” of sleep medicine and maintained throughout the years, or that had been introduced without a formal assessment of their validity. Among these, the rule to define the association between a PLMS event and an arousal has been established by expert consensus but the statistical properties of this association have not been explored before. The current WASM/IRLSSG<sup>7</sup> and AASM<sup>9</sup> sets of rules both agree that PLMS are considered to be associated with an arousal event when the two events are separated by less than 0.5 s; i.e., between the end of one event and the onset of the other, regardless of which is first. The PLMS arousal index indicates the number of PLMS associated with arousals divided by the number of hours of sleep with PLMS and arousal recording.

The aim of this study was to analyze statistically the association between PLMS and arousals to eventually support or challenge the current scoring rules and to further understand their reciprocal influence.

## METHODS

## Subjects

Twenty untreated, drug-naïve, consecutive patients (13 women, 7 males, mean age 60.9 y) affected by idiopathic RLS

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were included in this study. The patients were recruited at the Sleep Research Centre, Oasi Research Institute, Troina (Italy). In agreement with the International RLS Study Group,<sup>10,11</sup> the minimal criteria accepted for the diagnosis of RLS were: (a) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (b) the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting; (c) the urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching; (d) the urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night; (e) the occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition. Routine blood tests and neurophysiological investigation (EMG and electroneurography of the lower limbs) were also normal. The sleep respiratory pattern of each patient was assessed by means of oral and nasal airflow (thermistor and/or nasal pressure cannula), thoracic and abdominal respiratory effort (strain gauge), and oxygen saturation (pulse oximetry), in a previous recording (within 1 w) or during this study recording; subjects with an apnea-hypopnea index > 5 were not included. Neurological examination resulted unremarkable in all patients. For each patient included, the International RLS Severity Scale (IRLS) score<sup>12</sup> was also obtained.

This study was approved by the local ethics committee and all subjects provided informed consent before entering the study.

### Polysomnographic Sleep Recording

Each subject underwent a polysomnographic full-night recording, after an adaptation night, carried out in a standard sound-attenuated (noise level to a maximum of 30 dB nHL) sleep laboratory. Subjects were not allowed to have beverages containing caffeine during the afternoon preceding the recording and were allowed to sleep until their spontaneous awakening in the morning.

The following parameters were included in the polysomnographic study: EEG ( $\geq 3$  channels, one frontal, one central, and one occipital, referred to the contralateral earlobe); electrooculogram (electrodes placed 1 cm above the right outer canthus and 1 cm below the left outer canthus and referred to A1), electromyogram (EMG) of the submental muscle, EMG of the right and left tibialis anterior muscles (bipolar derivations with 2 electrodes placed 3 cm apart on the belly of the anterior tibialis muscle of each leg, with impedance less than 10 K $\Omega$ ), and ECG (one derivation). EMG signals, in particular, were digitally band-pass filtered at 10–100 Hz, with a notch filter at 50 Hz.

At the beginning of each session and before the start of recording, the sleep technician checked that the amplitude of the EMG signal from the 2 tibialis anterior muscles was < 2  $\mu$ V at rest.

### Sleep and Arousal Scoring and Detection of Leg Movements

Sleep stages were visually scored following standard criteria on 30-s epochs.<sup>13</sup> Arousals were also visually detected during sleep following the standard criteria: an abrupt shift of the electroencephalogram frequency (alpha, theta, and/or

frequencies > 16 Hz, but not spindles) lasting  $\geq 3$  s and preceded by  $\geq 10$  s of stable sleep; in REM sleep, a concurrent increase of the submental EMG lasting  $\geq 1$  s was also required.<sup>9</sup> LMs during sleep were first detected by the sleep analysis software Hypnolab 1.2 (SWS Soft, Italy). With this software, detection is performed by means of a human-supervised automatic approach controlled by the scorer. For this study, one scorer (R.F.) visually edited the detections proposed by the automatic analysis before the computation of the various parameters which were automatically generated by the same software adopting the criteria set by the WASM/IRLSSG.<sup>7</sup> In particular, LMs recorded in the 2 limbs were considered to be a single bilateral LM when they were overlapping or separated (offset-to-onset) by < 0.5 s; in a few cases this resulted in the identification of PLMS > 10 s (but always < 15 s), in agreement with the above cited criteria.<sup>7</sup> The PLMS index was calculated as the number of LMs included in a series  $\geq 4$ , separated by  $\geq 5$  and  $\leq 90$  s, per hour of sleep. Subsequently, the number of intervals included in sequences of  $\geq 3$  (all 10–90 s long) was divided by the total number of intervals. We will refer to this ratio as the periodicity index (PI); this index can vary between 0 (absence of periodicity, with none of the intervals having a length between 10 and 90 s) to 1 (complete periodicity, with all intervals having a length between 10 and 90 s).<sup>14,15</sup>

### Analysis of the PLMS/Arousal Association

In each recording, we selected all PLMS/arousal pairs that met the following inclusion criteria: (a) PLMS events separated from another PLMS event (preceding or following) by  $\geq 10$  s of EMG inactivity; (b) arousal events identified according to the American Academy of Sleep Medicine criteria<sup>9</sup> and separated from another arousal event (preceding or following) by  $\geq 10$  s of stable EEG baseline activity; (c) among the events detected according to the above criteria, PLMS/arousal pairs were included when PLMS and arousal were separated (offset-to-onset) by  $\leq 10$  s, regardless of which was first.

For all PLMS/arousal pairs detected according to the above criteria, 2 main parameters were assessed: (a) minimal distance between the PLMS and the arousal: the distance was set to 0 s when the 2 events overlapped; a positive value was assigned in the case that the arousal occurred after the PLMS and denotes the distance between the end of the PLMS and the onset of the arousal; likewise, a negative value characterizes the cases where the arousal occurred before the PLMS and describes the distance between the end of the arousal and the onset of the following PLMS; (b) the time lag between the onset of the PLMS and the onset of the arousal event (negative values indicated that the arousal onset occurred before the PLMS event onset, positive values indicate the opposite). All the above parameters were obtained automatically by means of a computer program arranged ad hoc for this purpose.

### RESULTS

Table 1 shows the clinical features, sleep architecture, and sleep leg movement activity parameters obtained in the group of patients with RLS. RLS subjects exhibited a moderate-to-severe disease severity (average IRLS score 24.0) and an average PLMS index of 34.6/h.

We detected, on average, 186.6 (SD 97.77) PLMS/patient which were separated from another PLMS event (preceding or following) by  $\geq 10$  s of EMG inactivity. Among these, we identified a mean of 46.1 (SD 25.55) PLMS/arousal pairs per subject (NREM 41.2 [24.28] and REM 4.5 [3.90]) where the events were separated by  $\leq 10$  s. In these pairs, the average PLMS duration was 3.2 s (0.65) and the average arousal duration was 6.5 s (0.92).

On average, in 98.4% (3.88) of pairs/patient (92.3% of all PLMS), PLMS and arousals overlapped or were separated by  $< 0.5$  s, thus fulfilling the criteria of the current scoring rules for the scoring of PLMS associated to arousals (Figure 1A).<sup>7,9</sup>

Figure 2 shows a more detailed analysis of the offset-to-onset difference between the 2 events in each pair. With increasing time difference, the corresponding increase in the percentage of associated pairs increased but with a different slope for lags  $\leq 0.5$  s, compared to lags above this value (4.457 vs. 0.948;  $t = 19.93$ ,  $P < 0.0000001$ ). The 2 regression lines calculated for the 2 slope regions (dashed lines) support this observation and further reinforce the current rules for the scoring of PLMS associated to arousals.<sup>7,9</sup>

Figure 1C depicts the distribution of onset-to-onset intervals between PLMS and arousals in the whole group of patients; in 41.2% of cases, the arousal onset preceded the PLMS onset, while the opposite was true for the remaining 58.8% of pairs. However, in 45.9% of cases, the arousal onset occurred in the second surrounding the PLMS onset (from 0.5 s before to 0.5 s after the PLMS event onset). The overall distribution appeared to be normal; however, it did not pass the Shapiro-Wilk W test of normality ( $W = 0.902$ ,  $P = 0.0001$ ). In particular, it should be noted that the left tail (arousal preceding PLMS) was significantly longer than the right tail.

Finally, Figure 1B shows the time relationship between all pairs of PLMS/arousal events in the lower part, while the upper graph shows the statistical distribution of the time relationship between the 2 events in the pairs. This graphical representation suggested a possible association between the duration of the PLMS and the arousal. We therefore analyzed the correlation between PLMS duration and arousal duration in all pairs of events included in this study. Figure 3 shows this analysis for which a significant correlation coefficient of 0.447 ( $P < 0.000001$ ) was found; this was further confirmed by the same analysis run for each patient which showed a mean correlation coefficient of 0.398 (SD 0.166).

## DISCUSSION

The results of this study show that the great majority of PLMS/arousal pairs not separated by more than 10 s are indeed correctly identified by the current scoring rules that define the association between these two events.<sup>7,9</sup> Even if this was not a physiological study, this finding lends statistical support to the rule and justifies its retention in future revisions of the overall criteria for scoring PLMS.

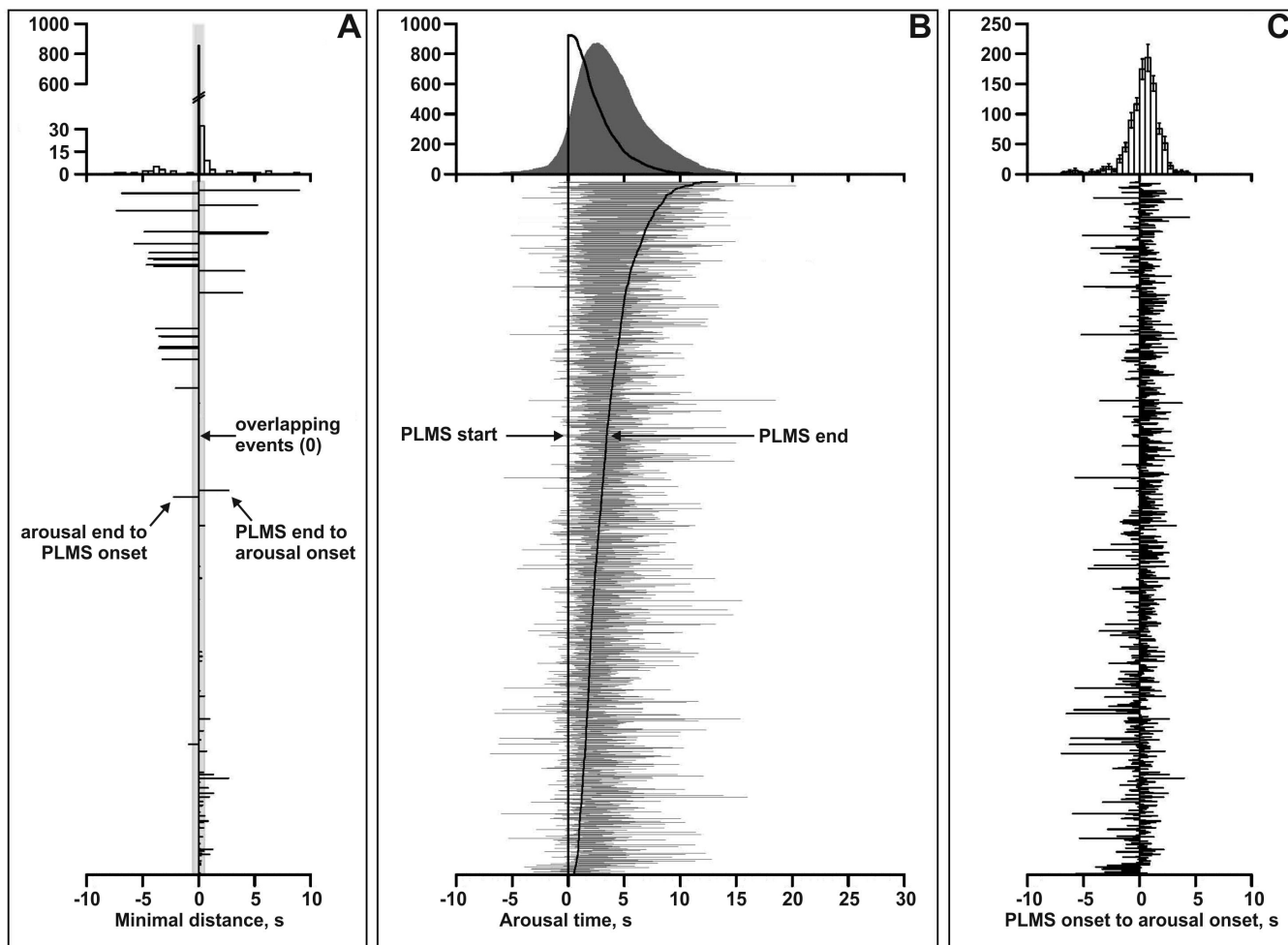
Due to the criteria used in this study for the detection of PLMS/arousal pairs, we analyzed approximately 25% of PLMS contained in the recordings. In RLS, the portion of PLMS accompanied by arousals reported in the literature is consistently below 50% and ranges between 17% and 55%,<sup>16–21</sup> the variability possibly depending on the different rules used

**Table 1**—Clinical features, sleep architecture, and sleep leg movement activity parameters obtained in the group of patients with RLS.

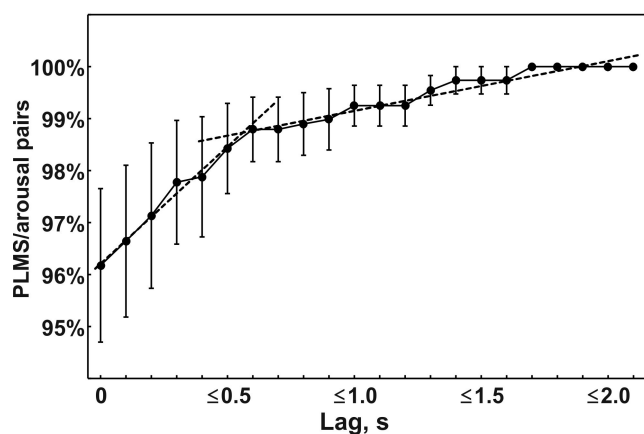
	Mean	SD
Age, years	60.9	10.23
International RLS Severity Scale, score	24.0	6.66
Sleep Architecture		
Time in bed, min	524.1	60.33
Sleep period time, min	489.6	71.25
Total sleep time, min	400.4	61.64
Sleep latency, min	30.0	38.63
REM sleep latency, min	118.5	73.90
Stage shifts/hour	12.0	4.59
Awakenings/hour	5.5	2.57
Sleep efficiency, %	76.9	11.94
Wakefulness after sleep onset, %	17.6	11.10
Sleep stage 1, %	7.7	4.87
Sleep stage 2, %	42.3	10.09
Slow wave sleep, %	17.6	8.33
REM sleep, %	14.9	3.95
Sleep Leg Movement Activity		
Total sleep		
Total LM index, number/h	41.4	18.50
PLMS index, number/h	34.6	18.18
Isolated LM index, number/h	6.7	2.52
NREM sleep		
Total LM index, number/h	46.2	22.14
PLMS index, number/h	40.4	22.27
Isolated LM index, number/h	5.9	2.03
REM sleep		
Total LM index, number/h	20.3	15.89
PLMS index, number/h	10.1	13.64
Isolated LM index, number/h	10.2	6.66
Number of PLMS sequences	11.0	5.49
PLMS sequence duration, s	188.6	194.49
PLMS duration NREM, s	2.6	1.65
PLMS duration REM, s	2.1	0.60
Isolated LM duration NREM, s	2.5	1.08
Isolated LM duration REM, s	2.4	0.77
Periodicity index, total	0.669	0.095

for the definition of the association and on the high interscorer variability in the detection of arousals.<sup>22</sup> Thus, the portion of PLMS analyzed in the present study appears to be within the expected range. This also supports the choice of the time window (10 s) which was based on the need to avoid uncertainties in the assignment of pairs within sequences of repeated events, since it allowed identification of the majority of events of interest.

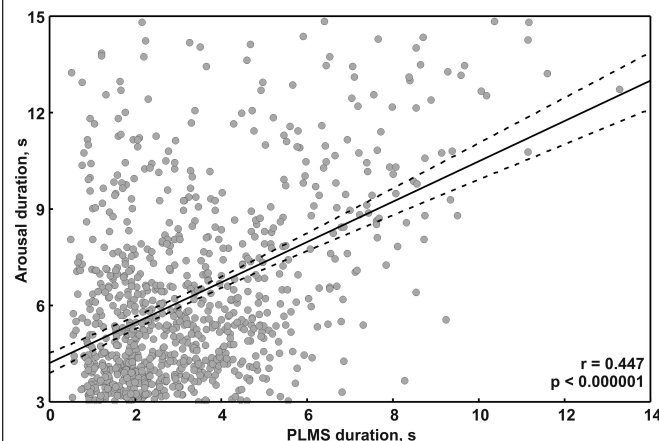
It is interesting to note that, despite the fact that arousals are commonly believed to be caused by PLMS, their onset precedes the onset of PLMS in more than 40% of cases; thus at least in a large percentage of cases, it is difficult to claim a cause/effect relationship. This finding is not surprising and is in agreement with a previous report that analyzed in a less detailed way this relationship<sup>23</sup>; however, it should also be considered



**Figure 1—(A)** Offset-to-onset distance in each pair of events (bottom graph) and their statistical distribution (upper graph). **(B)** Bottom graph – Time relationship between all pairs of PLMS/arousal events; the vertical line indicates the PLMS onset while the “sigmoid” curve over the right side of the figure represents the end of each PLMS event; the horizontal lines represent the extent of the arousal accompanying each PLMS in the pairs. Upper graph – statistical distribution of the time relationship between the two events in the pairs. **(C)** Onset-to-onset distance in each pair of events (bottom graph) and their statistical distribution (upper graph); negative values indicate arousals preceding PLMS, positive values indicate the opposite combination.



**Figure 2—**Analysis of the percentage of event pairs (PLMS/arousal) separated by different time lags. Data are shown as mean (filled circles) and standard error (whiskers). Dotted lines represent the regression lines obtained for lags from 0 to 0.5 s and from 0.6 to > 2 s.



**Figure 3—**Analysis of the correlation between PLMS duration and arousal duration in all event pairs used in this study. The regression line is drawn as a continuous black line. Dotted lines represent the 95% confidence intervals of the regression line.



that arousals, characterized by a shift towards higher frequencies, are often preceded by slow waves that are not considered by the AASM rules for scoring arousals<sup>9</sup> but are integrated in a single and more complex event by the rules coding the so-called cyclic alternating pattern (CAP), and usually indicated as A2 or A3 CAP subtypes.<sup>24,25</sup> Thus, if we consider also slow waves, we would expect that the distribution depicted in the upper graph of Figure 1C should change significantly and shift towards the left side of the graph, similar to the distribution already reported in 1999 by Parrino et al., who analyzed the relationship between CAP events and PLMS in NREM sleep.<sup>25</sup> This was not done in the current study, as there are no rules established regarding the association between PLMS and CAP events. This is further supported by previous studies that analyzed the EEG spectral content surrounding PLMS and where, after a careful synchronization between the motor events and the EEG spectral analysis, an increase in delta waves has been found that precedes the increase in fast activities accompanying PLMS.<sup>26,27</sup>

An interesting (and to our knowledge, new) finding of this study was the significant correlation between PLMS duration and arousal duration. The duration of these events might be interpreted as one feature describing their “intensity.” Currently, there is no definition of “intensity” available; however, it appears sensible to believe that these events have different “intensities” correlated with different degrees of sleep disruption, possibly reflected in differences in associated EEG, motor, and autonomic changes.<sup>26,27</sup> For motor events, a possible candidate for an index of “intensity” might be the area under the curve that integrates both duration and amplitude into a single value<sup>14</sup>; however, since the EMG is an essentially non-calibrated signal, this would be difficult to implement. Moreover, in this study we used the whole duration of the motor event that was determined by the two legs; however, it might be speculated that bilateral movements might produce longer duration than monolateral movements, thus contributing to the correlation found between the length of arousals and PLMS. We did not control for bilaterality or monolaterality of movements in this study; however, it has already been reported that bilateral PLMS are accompanied by larger heart rate and spectral EEG changes than monolateral movements.<sup>27</sup>

The tight time relationship between PLMS and arousals and their correlated durations seem to indicate that both events might be regulated by a complex mechanism including them and other sleep events,<sup>28</sup> such as heart rate and blood pressure,<sup>29–31</sup> rather than being connected by a simple reciprocal cause/effect relationship.

We did not include patients with a significant number of apnea episodes. Nevertheless, some few remaining respiratory events or variations from one polysomnographic study to the next cannot be excluded. Although recent findings show that the association between PLMS and apnea events is temporally much wider than that found in the present study,<sup>32</sup> the contemporary presence of arousal might have introduced a small bias into the results.

In conclusion, this study supports the current definition for the association between PLMS and arousals. In general, there is a need to perform this type of analysis (or more complex analyses if necessary) for all criteria currently used for scoring

PLMS and to incorporate their results into the decision process regarding an eventual improvement of the same criteria. In line with this concept, a recent evidence-based analysis of the association between PLMS and sleep-related breathing events has shown the need to modify the current rules.<sup>32</sup> We also believe that this type of approach would be of benefit in several other fields of sleep scoring, especially those involving the quantification of different transient sleep motor events (chin EMG and other muscles events, bruxism, etc.).

## DISCLOSURE STATEMENT

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