Sleep Medicine 109 (2023) 197–201

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Periodic leg movements during sleep and cognitive functioning in the older general population

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ARTICLE INFO

Keywords:
Periodic leg movements during sleep
Polysomnography
General population
Aging
Cognitive decline
Dementia

ABSTRACT

Objective: The current evidence of a relationship between periodic leg movements during sleep (PLMS) and cognitive functioning is limited and inconsistent. This cross-sectional study assessed associations between PLMS and cognitive functioning among community-dwelling older adults.

Methods: We included community-dwelling older adults who underwent a polysomnography and a cognitive assessment. The PLMS index (PLMI) and PLMS arousal index (PLMAI) were categorized into tertiles: PLMI <5/h (reference), 5–29.9/h, ≥30/h; and PLMAI <1/h (reference), 1–4.9/h, ≥5/h. The cognitive assessment consisted of ten scores covering the main cognitive domains: global cognition, processing speed, executive function, language, episodic verbal memory, and visuospatial function. Associations between PLMI, PLMAI, and cognitive scores were assessed using regression unadjusted and adjusted models.

Results: A total of 579 individuals without dementia were included (mean age: 71.5 ± 4.4 years; men 45.4%). The number of participants in the high-PLMI categories, 5–29.9/h and ≥30/h, was 185 (32.0%) and 171 (29.5%), respectively. Participants in the high-PLMI categories showed no significant difference compared to the reference group regarding their cognitive performance according to the unadjusted and adjusted models. Similarly, we found no association between PLMAI severity and cognitive functioning.

Conclusions: This study shows no cross-sectional association between PLMS severity and cognitive functioning among community-dwelling older adults. However, given the paucity of data in this field, further studies are needed to clarify the relationship between PLMS and cognitive functioning.

1. Introduction

Periodic leg movements during sleep (PLMS) are repetitive and stereotyped muscular contractions in the legs during sleep. PLMS may be associated with clinically significant sleep disturbances or impaired daytime functioning [1]. However, increased PLMS is commonly observed in asymptomatic individuals [2]. Whether PLMS can lead to functional impairment or long-term health consequences remains a

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https://doi.org/10.1016/j.sleep.2023.07.011
Received 4 May 2023; Received in revised form 30 June 2023; Accepted 12 July 2023
Available online 15 July 2023

matter of debate.

PLMS are often time-related with arousals [3], autonomic activations (increased heart rate [4] and blood pressure [5]), and cerebral hemodynamic fluctuations [6], which may potentially affect brain health. An increase in PLMS severity is often observed in sleep and neurological diseases (such as restless legs syndrome [RLS], narcolepsy, and alpha-synucleinopathies) [7], suggesting that PLMS may also represent a marker of central nervous system dysfunction. However, little research has been conducted on the relationship between PLMS and cognitive functioning [8–10]. Two studies have been carried out in patients with Parkinson's disease [8,9]. To our knowledge, the longitudinal study by Leng et al. is the only one to have been conducted in the general population, including 2636 community-dwelling older men with an average age of 76 years [10]. Gaps remain in the literature, such as the fact that there are no data about the cross-sectional association between PLMS and cognitive functioning in the older general population.

The present cross-sectional study tested for potential associations between PLMS severity and cognitive functioning among community-dwelling older adults. We hypothesized that higher PLMS severity would be associated with poorer cognitive functioning, especially in executive function [8,10].

2. Methods

2.1. Study population

Data stemmed from CoLaus|PsyCoLaus, a prospective cohort study on community-dwelling adults [11]. The sample of the present study consisted of 579 participants who accepted both cognitive assessment (performed only in participants aged ≥65 years) and polysomnography (PSG; HypnoLaus subsample [1,2]) during the first follow-up of the study between 2009 and 2013 (Fig. S1). None of the included participants met the criteria for dementia (defined by a Clinical Dementia Rating score ≥1). The institutional Ethics Committee of the University of Lausanne approved the CoLaus|PsyCoLaus study, and all participants provided written informed consent.

2.2. Sleep assessment

Participants underwent PSG 0.8 ± 0.9 years after cognitive assessment. Sleep stages and arousals were scored according to the AASM 2007 criteria [12], and respiratory events according to the AASM 2012 criteria [13]. PLMS were scored according to the World Association of Sleep Medicine/International Restless Legs Syndrome Study Group (WASM/IRLSSG) 2006 recommendations [14] (**Supplemental methods**). We examined PLMS index (PLMI) and PLMS arousal index (PLMAI) using the following categories (roughly tertiles) [10]: PLMI <5/h (reference), 5–29.9/h, ≥30/h; and PLMAI <1/h (reference), 1–4.9/h, ≥5/h. RLS was retained if the participant reported an urge to move the legs that (i) worse during periods of rest or inactivity, (ii) was partially or totally relieved by movement, and (iii) worse in the evening or night than during the day or only occur in the evening or night. IRLSSG rating scale was administered to participants who met criteria for RLS.

2.3. Cognitive assessment

The cognitive assessment included the Mini-Mental State Examination (MMSE; global cognition), Stroop test Victoria version dot condition and word condition (processing speed), Stroop test Victoria version color-word condition (executive function), phonemic and semantic fluency (executive control and verbal ability), Free and Cued Selective Reminding Test (FCSRT) free recall and total recall (episodic verbal memory), DO-40 naming test (language), and constructional praxis task from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; visuospatial function). Cognitive scores were analyzed as continuous variables, except for the scores with a skewed distribution (MMSE, FCSRT total recall, DO-40 naming test, and CERAD constructional praxis task), which were dichotomized according to the lowest 10th percentile (**Supplemental methods** and Table S1) [15].

2.4. Clinical assessment

Education was dichotomized into ≥ high school (high school or university) vs. <high school (mandatory or apprenticeship). Body mass index (BMI) was calculated as weight/height [2]. Diabetes was defined as fasting blood glucose ≥7 mmol/L and/or antidiabetics use. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or antihypertensive drug use. Smoking status was dichotomized into current or former smoker vs. never smoked. Excessive alcohol consumption was defined as ≥14 units/week. Depression was defined as a remitted or current major depressive disorder according to the DSM-IV criteria. Psychotropic medication was defined as using hypnotics, benzodiazepines or derivates, antidepressants, or neuroleptics. Participants were dichotomized into ApoE4 carriers vs. non-carriers (**Supplemental methods**).

2.5. Statistical analysis

Participant characteristics were compared between PLMI categories using independent T-test, Mann-Whitney test, or chi-squared test. Cross-sectional associations between PLMI and cognitive scores were tested using multivariate linear or logistic regression models. Models were unadjusted and then minimally adjusted for age, sex, and education. The fully adjusted models were additionally adjusted for other variables potentially affecting cognitive functioning: BMI, diabetes, hypertension, smoking, alcohol consumption, depression, psychotropic medication, and apnea-hypopnea index. Sensitivity analyses tested: (i) associations between PLMAI and cognitive scores, as well as associations between PLMI, PLMAI and cognitive scores (ii) after excluding 73 participants without ApoE genotype and including ApoE4 status as a confounder in the models, given its association with poorer cognitive functioning, even in older adults without dementia [16], and (iii) after further exclusion of 22 participants using antidepressants (because this medication class affects both PLMS severity and cognitive functioning). A description of how missing data were handled is provided in the **Supplemental methods**. The significance level was set at two-sided $p < 0.05$. Analyses were performed with SPSS version 26 (IBM Corp., Armonk, USA).

3. Results

3.1. Sample characteristics

The sample consisted of 579 participants aged 71.5 ± 4.4 years (range: 65–83 years), of whom 263 (45.4%) were men (Table 1). Compared with participants with PLMI <5/h, those in the high-PLMI categories were more likely to be men, less likely to be current or former smokers, had higher total sleep time, stage N2, arousal index, PLMI in the different sleep stages, and PLMAI, as well as lower rapid eye movement (REM) sleep.

3.2. Associations between PLMI and cognitive functioning

There were no significant associations between PLMI severity and cognitive scores (Table 2).

3.3. Sensitivity analyses

We found no significant association between PLMAI severity and cognitive scores (Table S2). All results were unchanged when excluding participants without ApoE genotype and including ApoE4 status in the models (Tables S3–S4) and after further exclusion of participants using

Table 1
Characteristics of the sample.

	Whole sample	PLMI <5/h	PLMI 5–29.9/h	PLMI ≥30/h	Test	*p*
Participants, n (%)	579 (100)	223 (38.5)	185 (32.0)	171 (29.5)		
Sociodemographic characteristics						
Age, years	71.5 ± 4.4	71.4 ± 4.5	71.1 ± 4.1	71.9 ± 4.5	F = 1.7	0.172
Men, n (%)	263 (45.4)	95 (42.6)	69 (37.3)	99 (57.9)[a,b]	χ^2 = 16.4	**<0.001**
Education (≥high school), n (%)	243 (42.0)	82 (36.8)	81 (43.8)	80 (46.8)	χ^2 = 4.3	0.114
Clinical characteristics						
ApoE4 carriers, n (%)[†]	115 (19.9)	46 (20.6)	34 (18.4)	35 (20.5)	χ^2 = 0.3	0.840
BMI, kg/m^2	26.9 ± 4.6	26.6 ± 4.7	27.0 ± 4.3	27.2 ± 4.8	F = 23.6	0.329
Diabetes, n (%)	105 (18.1)	36 (16.1)	35 (18.9)	34 (19.9)	χ^2 = 1.0	0.599
Hypertension, n (%)	393 (67.9)	145 (65.0)	127 (68.6)	121 (70.8)	χ^2 = 1.5	0.464
Smoking, n (%)	334 (57.7)	142 (63.7)	94 (50.8)[a]	98 (57.3)	χ^2 = 6.8	**0.032**
Alcohol (≥14 units/week), n (%)	99 (17.7)	34 (15.2)	27 (14.6)	38 (22.2)	χ^2 = 4.5	0.104
Depression, n (%)	202 (34.9)	84 (27.7)	61 (33.0)	57 (33.3)	χ^2 = 1.2	0.538
Psychotropic medication, n (%)	124 (21.4)	50 (22.4)	37 (20.0)	37 (21.6)	χ^2 = 0.4	0.836
RLS, n (%)	94 (16.2)	30 (13.5)	30 (16.2)	34 (19.9)	χ^2 = 2.9	0.230
IRLSSG rating scale ≥11, n (%)	67 (11.6)	20 (9.0)	21 (11.4)	26 (15.2)	χ^2 = 3.6	0.158
Sleep characteristics						
Total sleep time, min	386.4 ± 75.4	375.0 ± 80.1	399.1 ± 67.3[a]	387.7 ± 75.3	F = 5.2	**0.005**
Stage N1, %	14.0 ± 9.0	14.4 ± 10.9	12.9 ± 6.9	14.5 ± 8.5	F = 1.8	0.170
Stage N2, %	49.6 ± 12.1	47.8 ± 12.6	49.8 ± 11.4	51.6 ± 11.9[a]	F = 4.8	**0.009**
Stage N3, %	16.8 ± 8.7	17.6 ± 9.6	17.0 ± 7.5	15.6 ± 8.6	F = 2.7	0.065
REM sleep, %	19.6 ± 6.9	20.1 ± 7.1	20.2 ± 6.4	18.3 ± 6.9[a,b]	F = 4.5	**0.011**
Arousal index, events/h	22.7 [16.2, 31.7]	19.8 [14.3, 26.1]	22.5 [17.4, 29.3][a]	27.0 [19.9, 39.3][a,b]	H = 42.2	**<0.001**
AHI, events/h	15.7 [7.4, 28.9]	16.5 [7.8, 31.1]	14.4 [7.2, 26.6]	18.9 [7.2, 29.8]	H = 0.9	0.642
PLMI, events/h	12.3 [0.0, 36.9]	0.0 [0.0, 0.8]	15.9 [9.8, 21.3]	54.4 [41.0, 78.3]		
PLMI (stage N1), event/h	11.6 [0.0, 38.3]	0.0 [0.0, 0.0]	17.3 [7.7, 28.6][a]	53.3 [33.7, 84.3][a,b]	H = 446.0	**<0.001**
PLMI (stage N2), event/h	14.3 [0.0, 43.1]	0.0 [0.0, 0.3]	18.6 [10.7, 27.3][a]	64.1 [47.3, 91.5][a,b]	H = 508.6	**<0.001**
PLMI (stage N3), event/h	0.6 [0.0, 42.8]	0.0 [0.0, 0.0]	9.7 [0.0, 28.7][a]	74.6 [37.8, 120.0][a,b]	H = 369.0	**<0.001**
PLMI (REM sleep), event/h	0.0 [0.0, 5.6]	0.0 [0.0, 0.0]	0.0 [0.0, 4.2][a]	9.2 [1.8, 30.3][a,b]	H = 223.1	**<0.001**
PLMAI, events/h	1.3 [0.0, 5.2]	0.0 [0.0, 0.0]	2.9 [1.1, 5.0][a]	7.5 [2.7, 13.5][a,b]	H = 320.5	**<0.001**

Data are presented as mean ± standard deviation, median [interquartile range] or number of participants (%). Data were analyzed using analysis of variance (F), Kruskal-Wallis test (H), or chi-squared test (χ^2). [†]Missing data (whole sample: n = 73; PLMI <5/h: n = 27; PLMI 5–29.9/h: n = 24; PLMI ≥30/h: n = 22). [a]Significant difference compared with PLMI <5/h. [b]Significant difference compared with PLMI 5–29.9/h. Significant p-values are highlighted in bold (<0.05). Abbreviations: AHI = apnea-hypopnea index; ApoE4 = apolipoprotein E4; BMI = body mass index; IRLSSG = International Restless Legs Syndrome Study Group; PLMI = periodic leg movement index; PLMAI = periodic leg movement arousal index; REM = rapid eye movement; RLS = restless legs syndrome.

antidepressants (Tables S5–S6).

4. Discussion

To our knowledge, this is the first study assessing the cross-sectional association between PLMS and cognitive functioning in the older general population. We found no association between PLMS severity and cognitive performance, suggesting that PLMS may be unrelated to cross-sectional cognitive functioning in the older general population.

Although pathophysiological arguments suggest that PLMS may be related to consequences on brain health [3–6], limited research on the relationship between PLMS and cognitive functioning exists [8–10] and results are conflicting. In the study by Scullin et al., a higher PLMI was associated with lower executive function among 34 Parkinson's disease patients (age: 62.4 ± 8.5 years) [8]. However, the longitudinal study by Bugalho et al., which included 25 Parkinson's disease patients (age: 66.6 ± 9.4 years) failed to find an association between PLMI and changes in the Montreal Cognitive Assessment score [9]. The study by Leng et al., conducted among 2636 community-dwelling older men (age: 76.0 ± 5.0 years), examined associations between PLMI, PLMAI, and longitudinal changes in the Trail Making Test Part B and Modified Mini-Mental State examination [10]. Compared with participants in the reference group (PLMI <5/h), those with a PLMI ≥30/h showed a greater decline in the Trail Making Test Part B[10].

It is challenging to compare our study with previous works [8–10], given the differences in sample characteristics, study design, and cognitive measures. The study by Leng et al. is partly comparable to our study given that it was conducted in a sample from the general population; however, substantial differences exist and may explain the contrasting results, such as the sample characteristics (only men [10] vs. men and women), study design (longitudinal [10] vs. cross-sectional), PLMS scoring (using piezoelectric sensor [10] vs. EMG), and cognitive outcomes.

The present study has some strengths, including analyses performed on a large sample of community-dwelling older adults, scoring of PLMS based on the gold standard PSG/EMG, analysis of an extensive cognitive test battery, and adjustment of analyses for multiple confounders. Limitations were the single assessment of sleep, as studies have reported a certain night-to-night variability in the assessment of PLMS [17]. The inability to determine the time of PLMS occurrence could also be indicated as a limitation, given that disease duration may play a role on the association between sleep disorders and brain health [18]. Although there was a delay between PSG and cognitive assessment, which could also be considered a limitation of the study, we believe that this does not represent a major problem in the present analysis, given that PLMS is a chronic condition that is unlikely to disappear or show major changes within a few months [19]. Finally, other parameters, such as periodicity or time distribution of PLMS throughout the night should be explored in future studies [20].

In conclusion, this study suggests that PLMS are unrelated to cross-sectional cognitive functioning in the older general population. However, given the paucity of data in this field, further studies are needed to clarify the relationship between PLMS and brain health.

Table 2
Associations between periodic leg movement index (PLMI) severity and cognitive functioning.

	Unadjusted		Minimally adjusted		Fully adjusted	
	B (95% CI)	p	*B* (95% CI)	p	*B* (95% CI)	p
Phonemic fluency						
PLMI 5–29.9/h	0.03 (−1.59, 1.66)	0.968	−0.33 (−1.87, 1.22)	0.678	−0.40 (−1.95, 1.15)	0.609
PLMI ≥30/h	0.02 (−1.59, 1.64)	0.980	−0.04 (−1.62, 1.53)	0.959	−0.09 (−1.66, 1.49)	0.915
Semantic fluency						
PLMI 5–29.9/h	0.17 (−1.57, 1.85)	0.840	−0.19 (−1.81, 1.42)	0.814	−0.22 (−1.85, 1.40)	0.788
PLMI ≥30/h	0.14 (−1.52, 1.87)	0.870	−0.05 (−1.70, 1.59)	0.951	−0.05 (−1.69, 1.61)	0.957
FCSRT free recall						
PLMI 5–29.9/h	0.01 (−1.32, 1.33)	0.992	−0.34 (−1.56, 0.88)	0.583	−0.46 (−1.68, 0.77)	0.464
PLMI ≥30/h	−0.45 (−1.77, 0.90)	0.522	−0.19 (−1.44. 1.06)	0.764	−0.30 (−1.56, 0.95)	0.635
Stroop dot condition						
PLMI 5–29.9/h	−1.15 (−3.62, 1.33)	0.365	−0.89 (−3.36, 1.58)	0.480	−1.09 (−3.59, 1.39)	0.388
PLMI ≥30/h	2.08 (−0.45, 4.61)	0.107	1.89 (−0.65, 4.43)	0.144	1.60 (−0.95, 4.16)	0.220
Stroop word condition						
PLMI 5–29.9/h	−1.32 (−4.97, 2.32)	0.478	−0.87 (−4.49, 2.74)	0.636	−1.41 (−5.06, 2.24)	0.450
PLMI ≥30/h	2.61 (−1.10, 6.33)	0.168	2.45 (−1.25, 6.17)	0.195	1.95 (−1.78, 5.69)	0.306
Stroop color-word condition						
PLMI 5–29.9/h	−2.44 (−7.60, 2.72)	0.355	−1.79 (−6.91, 3.32)	0.491	−2.32 (−7.49, 2.84)	0.379
PLMI ≥30/h	2.21 (−3.04, 7.47)	0.410	2.15 (−3.10, 7.41)	0.422	1.67 (−3.62, 6.98)	0.535
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
MMSE ≤27 points						
PLMI 5–29.9/h	0.88 (0.44, 1.77)	0.730	1.04 (0.51, 2.11)	0.923	0.95 (0.45, 1.96)	0.885
PLMI ≥30/h	1.01 (0.51, 1.99)	0.983	1.01 (0.50, 2.04)	0.980	0.90 (0.44, 1.87)	0.787
FCSRT total recall ≤42 points						
PLMI 5–29.9/h	0.63 (0.32, 1.25)	0.187	0.67 (0.33, 1.35)	0.269	0.68 (0.33, 1.39)	0.294
PLMI ≥30/h	0.61 (0.30, 1.22)	0.166	0.54 (0.26, 1.12)	0.100	0.55 (0.26, 1.16)	0.118
DO-40 naming test ≤39 points						
PLMI 5–29.9/h	1.15 (0.66, 1.98)	0.627	1.19 (0.69, 2.08)	0.525	1.14 (0.64, 2.01)	0.655
PLMI ≥30/h	0.60 (0.32, 1.13)	0.115	0.59 (0.31, 1.13)	0.113	0.57 (0.29, 1.08)	0.095
CERAD constructional praxis task ≤9 points						
PLMI 5–29.9/h	0.86 (0.47, 1.56)	0.612	0.90 (0.49, 1.66)	0.748	0.84 (0.45, 1.75)	0.592
PLMI ≥30/h	0.89 (0.48, 1.62)	0.697	0.97 (0.52, 1.80)	0.927	0.92 (0.48, 1.75)	0.798

Data are presented as unstandardized beta coefficient (*B*) or odds ratio (OR) with respective 95% confidence interval (CI) against the reference group (PLMI <5/h). Data were analyzed by linear or logistic regression models using cognitive scores as dependent variable and PLMI as independent variable. Minimally adjusted: adjusted for age (continuous), sex (men vs. women), and education (≥high school vs. <high school). Fully adjusted: additionally adjusted for body mass index (continuous), diabetes (presence vs. absence), hypertension (presence vs. absence), smoking (current or former vs. never), alcohol (≥14 vs. <14 units/week), depression (presence vs. absence), psychotropic medication (presence vs. absence), and apnea-hypopnea index (continuous). Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

Funding

The CoLaus|PsyCoLaus and HypnoLaus studies were supported by GlaxoSmithKline, Faculty of Biology and Medicine of the University of Lausanne, Swiss National Science Foundation (grants 3200B0-105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468, 33CS30-148401, 33CS30-177535, and 3247730_204523), Swiss Personalized Health Network (grant 2018DRI01), Leenaards Foundation, and Vaud Pulmonary League (Ligue Pulmonaire Vaudoise). Nicola Andrea Marchi is supported by Swiss National Science Foundation (Postdoc.Mobility Fellowship) and Faculty of Biology and Medicine of the University of Lausanne. Bogdan Draganski is supported by Swiss National Science Foundation (grants 32003B_212466, 324730_192755, and CRSII5-3_209510), ERA_NET iSEE project (grant 32NE30_198552), Swiss Personalized Health Network, Faculty of Biology and Medicine of the University of Lausanne (Precision medicine and interdisciplinary grants), and Leenaards Foundation.

CRediT authorship contribution statement

Nicola Andrea Marchi: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Arton Peci:** Conceptualization, Methodology, Formal analysis, Writing – original draft. **José Haba-Rubio:** Conceptualization, Data curation, Writing – review & editing. **Geoffroy Solelhac:** Writing – review & editing. **Virginie Bayon:** Writing – review & editing. **Mathieu Berger:** Writing – review & editing. **Peter Vollenweider:** Data curation, Writing – review & editing. **Pedro Marques-Vidal:** Data curation, Writing – review & editing. **Armin von Gunten:** Data curation, Writing – review & editing. **Marie-Pierre Françoise Strippoli:** Data curation, Writing – review & editing. **Martin Preisig:** Data curation, Writing – review & editing. **Bogdan Draganski:** Data curation, Writing – review & editing. **Raphael Heinzer:** Conceptualization, Data curation, Writing – review & editing, Supervision.

Declaration of competing interest

No conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2023.07.011.

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