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Age-related changes in sleep spindle characteristics in individuals over 75 years of age: a retrospective and comparative study

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Abstract

Background Sleep and its architecture are affected and changing through the whole lifespan. We know main modifications of the macro-architecture with a shorter sleep, occurring earlier and being more fragmented. We have been studying sleep micro-architecture through its pathological modification in sleep, psychiatric or neurocognitive disorders whereas we are still unable to say if the sleep micro-architecture of an old and very old person is rather normal, under physiological changes, or a concern for a future disorder to appear. We wanted to evaluate age-related changes in sleep spindle characteristics in individuals over 75 years of age compared with younger individuals.

Methods This was an exploratory study based on retrospective and comparative laboratory-based polysomnography data registered in the normal care routine for people over 75 years of age compared to people aged 65–74 years. We were studying their sleep spindle characteristics (localization, density, frequency, amplitude, and duration) in the N2 and N3 sleep stages. ANOVA and ANCOVA using age, sex and OSA were applied.

Results We included 36 participants aged > 75 years and 57 participants aged between 65 and 74 years. An OSA diagnosis was most common in both groups. Older adults receive more medication to modify their sleep. Spindle localization becomes more central after 75 years of age. Changes in the other sleep spindle characteristics between the N2 and N3 sleep stages and between the slow and fast spindles were conformed to literature data, but age was a relevant modifier only for density and duration.

Conclusion We observed the same sleep spindle characteristics in both age groups except for localization. We built our study on a short sample, and participants were not free of all sleep disorders. We could establish normative values through further studies with larger samples of people without any sleep disorders to understand the modifications in normal aging and pathological conditions and to reveal the predictive biomarker function of sleep spindles.

Keywords Polysomnography, Sleep architecture, Spindle, Aging, Oldest old

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Introduction

The global population is increasingly aging. The 2022 world population prospects of the United Nations project population aged 65 and above to increase from 10 to 16% by 2050; 2020 Insee projections announced a doubling of the number of people older than 75 years between 2013 and 2070 [1, 2].

Older people are the most affected by neurocognitive disorders, sleep disorders and polypharmacy [3–6]. Sleep undergoes many age-related changes during normal aging and even more with associated medical conditions [7–12].

We define sleep stages with the help of the micro-architecture and its specific patterns and graphic elements, such as the K-complex and sleep spindle (SS), in the second sleep stage (N2).

Various pathologies, such as cognitive disorders, cause clinical and architecture sleep disorders that can be observed through the study of sleep micro-architecture. Some changes have been described as predictors of subsequent neurocognitive disorders and neurodegenerative pathologies, such as Alzheimer's disease or Dementia with Lewy bodies [13–15].

However, sleep macro- and micro-architectures have no precise definition for normality or abnormality in the oldest populations, even though many authors have conducted small trials or extensive cohort studies on age-related changes in sleep.

To our knowledge, no study has focused on the modifications of the sleep micro-architecture in very old people, although this population is mainly concerned with the accumulation of sleep pathologies, neurodegenerative pathologies, polymedication, and the entanglement of these points.

This exploratory study aimed to verify whether we could identify statistically significant age-related changes in sleep spindle characteristics using laboratory-based polysomnography data from a population sample of elderly (65–74 years) and oldest people (75 and older) registered through normal care routines.

We focused on changes in sleep spindle (SS) characteristics, including localization, density, frequency, amplitude, and duration.

We hypothesized that even a short monocentric retrospective study could reveal such changes in SS characteristics. Light modifications should be observed as they are when studying younger people: density, amplitude, and duration decrease with age, whereas frequency and localization are not affected.

Methods

Overview

The analysis was based on data collected from laboratory-based polysomnography of patients registered between August 2012 and May 2021 at the Sleep Laboratory of the University Hospital of Besançon.

Participants

We selected people aged over 75 years at the time of polysomnography to constitute our research group (further named "75+") and created a control group of people aged between 65 and 74 years (further named "65+").

Polysomnography was recorded as part of the normal care routine of the participants, and we assumed that they all had a sleep complaint, a sleep disorder or both.

To obtain comparable sleep data, we excluded participants with neurological pathologies that could have substantially changed their sleep records (Parkinson's disease, stroke, epilepsy, multiple system atrophy, and meningioma) or who had a mental illness (bipolar disorder). We also excluded patients treated with benzodiazepines or related or antipsychotic drugs.

We compiled the date of birth, age, and date of polysomnography to create both groups and then anonymized participants, giving each record a consecutive number when added to a group.

We listed their treatments to identify those that could modify sleep without having a systematic effect (including opioids, pregabalin, methylphenidate, pramipexole, and rotigotine) and manually reviewed their medical files to check their cognitive status at the time of polysomnography: no disorder, minor (mND) or major (MND) neurocognitive disorder.

The study has been registered by the Clinical Research and Innovation Delegation of the University Hospital of Besançon under the number 2021/643. Data were collected and treated in respect with the European General Data Protection Regulation, in accordance with the French Data Protection Authority (CNIL) reference methodology #004 (Research not involving the human being, studies and evaluations in the health field). According to these national regulations, this study does not require the authorization and approval from an ethics committee, neither an informed consent to participate from all of the participants. Instead, they received a written information form with a non-opposition notice, and had sufficient time for reflection to allow them to stipulate their opposition to the collection and processing of their data, if necessary.

Polysomnography

All polysomnography data were recorded as part of the usual care procedure. The data used in this study were retrospectively collected, and the care procedures were not changed.

Each participant underwent single-night laboratory-based polysomnography, with strictly the same hardware, software and the following montage for every record: nine electroencephalography electrodes (C3, C4, Cz, F3, F4, T3, T4, O1, O2) with a 35 Hz high-pass filter, 0.35 Hz low-pass filter, and 500 Hz sampling frequency. Left and right electrooculogram, bilateral chin and shins electromyogram, single bipolar electrocardiogram, finger pulse oximetry, chest and abdominal excursion, airflow, and body position.

The signals were analyzed using BrainRT™ analysis software (Onafhankelijke Software Groep, Kontich, Belgium) and digitally stored, and sleep staging was performed according to standardized AASM criteria [16].

We manually reviewed the polysomnography data to exclude those with too many artifacts, unstable sleep, or insufficient sleep time. We then selected the most stable 10-min extracts of the N2 sleep stage and sleep stage 3 (further called N3) of the first three sleep cycles; older people rarely reach a fourth cycle, especially when sleeping in the laboratory.

We added to each individual dataset the following items extracted from the polysomnography: obstructive sleep apnea diagnosis (OSA) and its severity based on the apnea–hypopnea index (AHI) following the AASM Scoring Manual Version 2.2, central sleep apnea, prior use of mandibular advancement device or continuous positive airway pressure therapy, and other sleep disorders such as periodic limb movements or nocturnal hypoxemia.

Sleep spindles

Polysomnography data were restricted to electroencephalogram data only and registered in the European Data Format (EDF) using EDF browser version 1.93 64-bit.

Python was used through Anaconda Navigator 2.1.2 to upload the dataset, and spindle detection was assessed through YASA (Yet Another Spindle Algorithm) version 0.6.0 developed by Raphael Vallat [17].

We used the following main criteria to detect and record spindles: a frequency between 9 and 12.5 Hz (the "Slow" Sleep Spindle group, called SS-S), 12.5 and 16 Hz (the "Fast" Sleep Spindle group, called SS-F), and a duration between 0.5 and 2 s. SS had to be detected on two or more electrodes to be counted.

Individual data were analyzed and pooled into large datasets for statistical analysis at the group level and between groups.

Analysis

After visual verification and validation, the collected data were registered in Microsoft Excel using a unique code for each item. Finally, the results were analyzed with descriptive statistics using SPSS software for Windows (version 18.0; SPSS, Inc., Chicago, IL, USA).

Qualitative variables were described in terms of effective and percentage.

We performed a Pearson chi2 test to evaluate the links between SS localization regarding sleep stage and SS type in both population groups (75 + and 65 +), applying Cramer's V correlation test.

Quantitative variables are described as the mean, median, standard deviation, and range. Sociodemographic data were also compared using Pearson chi2 test and either Phi or Cramer's V correlation tests.

For the main sleep spindle characteristics, we applied ANOVA to compare both age groups; two models of ANCOVA were used to adjust the results: Model 1 used exact age and global OSA as covariates; Model 2 used group age, sex and global OSA as covariates.

The significance level was set at 5% for all the statistical analyses.

Results

Between August 2012 and May 2021, 96 participants were identified in the 75 + group. Ninety-one were screened after applying the exclusion criteria for polysomnography records, and 38 patients were excluded because of pathology or treatment. After the polysomnography review, we excluded 17 additional records, leading to 36 participants in the 75 + group being included in the analysis.

The same procedure was performed for the 65 + group, and 274 participants were identified. Two participants in this group refused their data to be used. Excluding duplicates, pathologies and treatments led to a sample of 143 participants. Eighty-six more participants were excluded after the polysomnography review, resulting in 57 participants in the control group.

These data are presented in the flow chart (Fig. 1).

Population

The 36 participants in the 75 + group had a mean age of 79.5 years (± 3.5 years) and were divided into 18 participants aged between 75 and 79 years, 14 between 80 and 84 years and only 4 between 85 and 89 years.

The 57 participants of the 65 + group had a mean age of 68.2 years (± 2.23) and were divided into 42 participants aged between 65 and 69 years and 15 participants aged between 70 and 74 years.

There was no significant difference between the 75 + and 65 + groups regarding sex ratio (1.25 and 0.5;

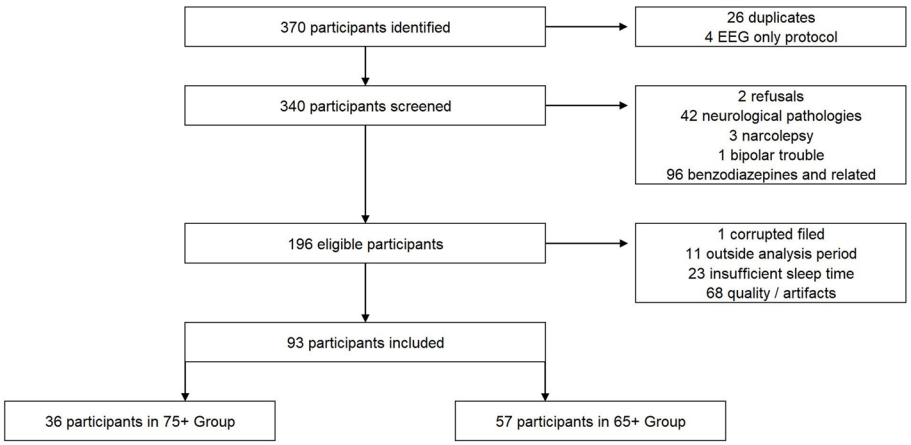

Fig. 1 Flow chart. We identified 370 participants recorded between August 2012 and May 2021 who were 65 years old or more. We excluded 30 records because of duplicated and wrong protocol; 144 because they weren't fitting with medical file inclusion criteria. Finally 103 participants because of the polysomnography themselve. At the end, 36 patients were included in 75 + group and 57 in 65 + control group

$p=0.052$), global (97.2% and 89.5%, $p=0.105$) or stratified OSA diagnosis (mild 16.7% and 12.3%, $p=0.556$; moderate 22.2% and 40.4%, $p=0.077$; severe 58.3% and 36.8%, $p=0.055$).

The groups were also comparable in terms of associated sleep disorder diagnosis (49.1% and 55.6%, $p=0.671$) and neurocognitive disorder (ND) frequency: no ND for 31 and 55 participants ($p=0.104$); mND for five and two participants ($p=0.104$). No participant had MND.

Only 7.5% of the participants were diagnosed with central sleep apnea syndrome, all of whom were in the 75 + group ($p=0.001$). Five patients had continuous positive airway pressure therapy because of known OSA but did not use it during polysomnography.

We found a significant difference in the "Other" treatment category: 16 participants from the 75 + group compared with only 4 from the 65 + group ($p<0.001$) were treated with drugs that could modify their sleep while treating some pain (opioids), restless leg syndrome (pramipexole, ropinirole), or excessive daytime sleepiness (methylphenidate). All the data are presented in Table 1.

Qualitative characteristic: localization

We analyzed the localization source by grouping the electrodes to construct a variable with four values: central (C: C3, C4, and Cz), frontal (F: F3 and F4), temporal (T: T3 and T4), and occipital (O: O1 and O2).

Between the groups, SS-S localization was significantly different in stage N2, revealing a predominant C in the 75 + group and a greater difference between C and F in the 65 + group, with a strong correlation (chi2 10.443 (3), $p=0.015$, Cramer's V 0.389). For SS-F (chi2 3.279 (3), $p=0.351$, Cramer's V = 0.225), predominant C localization was found in both groups; there was no significant difference, and the correlation was moderate between group appurtenance and localization (Table 2 and Fig. 2A).

There was no significant difference in N3 between the groups, with C localization being predominant for both types of SS in both groups (Fig. 2B).

Quantitative characteristics: density, frequency, amplitude, and duration

For the subsequent analysis of sleep spindle characteristics between N2 and N3, our statistical model included three main covariates: age (75 + or 65 +), sex (female or male) and global OSA diagnosis (Table 3).

SS density was greater in N2 than in N3 for SS-S ($p<0.001$) and SS-F ($p<0.001$), with a significant influence from the age group (p 0.05) on slow spindles, with density being greater in the 75 + group.

We observed a significantly greater mean frequency of SS-S ($p<0.001$) and SS-F ($p=0.004$) in N2 than in N3, with no statistically significant influence from the covariates.

Amplitudes were lower in N2 than in N3 for SS-S ($p<0.001$) and greater in N2 for SS-F ($p<0.001$) in the covariate model, with gender influencing the SS-F: females had spindles with greater amplitudes.

The duration of SS was longer in N2 for SS-S ($p=0.001$) and SS-F without reaching a significant level ($p=0.222$), with no clear influence from the covariates, but the age group almost reached significance (longer spindles in the 75 +).

We compared the SS-S and SS-F characteristics in both age groups in a multivariate model using global OSA and exact age as covariates. The Model 1 results are presented in Table 4.

Table 1 Main socio-medical characteristics of the participants of both groups, presented as effective (percentage)

	Group	65 +	75 +	*p*
Effective	N	57 (61.3%)	36 (38.7%)	
Gender	Women	19 (33.3%)	20 (55.6%)	
	Men	38 (66.7%)	16 (44.4%)	
Sex ratio	W/M	0.5	1.25	0.052
Age	Mean (SD)	68.2 (± 2.23)	79.5 (± 3.5)	
OSA	Mild	7 (12.3%)	6 (16.7%)	0.556
	Moderate	23 (40.4%)	8 (22.2%)	0.077
	Severe	21 (36.8%)	21 (58.3%)	0.055
	Global	51 (89.5%)	35 (97.2%)	0.105
CSA		0	7 (19.4%)	**0.001**
Sleep apnea treatment	MAD	0	0	
	CPAP	4 (7%)	1 (2.8%)	0.645
Other diagnosis	N	28 (49.1%)	20 (55.6%)	0.671
Neurocognitive Disorders	None	55 (96.5%)	31 (86.1%)	0.104
	Minor	2 (3.5%)	5 (13.9%)	0.104
	Major	0	0	
Treatments	Anti-depressants	7 (12.3%)	7 (19.4%)	0.383
	Melatonin	3 (5.3%)	1 (2.8%)	1
	Other	4 (7%)	16 (44.4%)	**< 0.001**

Groups were comparable in terms of gender, OSA, sleep apnea treatment, other diagnosis, neurocognitive disorder, anti-depressants and melatonin. There was a significant difference in CSA frequency (none in 65 + group) and in other treatments frequency (a lot more in the 75 + group)

OSA Obstructive Sleep Apnea. Mild for AHI 5–15/hour. Moderate for AHI 15–30/hour. Severe for AHI > 30/hour. *CSA* Central Sleep Apnea, *MAD* Mandibular Advancement Device, *CPAP* Continuous Positive Airway Pressure therapy

Table 2 Sleep Spindles Localization in both sleep stages, comparing age groups

	Sleep Stage N2				Sleep Stage N3			
	SS-S		SS-F		SS-S		SS-F	
	65 + (%)	75 + (%)	65 + (%)	75 + (%)	65 + (%)	75 + (%)	65 + (%)	75 + (%)
Frontal	45.7	11.8	20.6	19.4	23.9	22.6	13.8	20
Central	31.4	47.1	67.6	74.2	39.1	35.5	75.9	80
Temporal	20	29.4	8.8	0	23.9	19.4	10.3	0
Occipital	2.9	11.8	2.9	6.5	13	22.6	0	0
Pearson	*10.443*		*3.279*		*1.251*		*1.813*	
df	*3*		*3*		*3*		*2*	
p	***0.015***		*0.351*		*0.741*		*0.404*	
Cramer	*0.389*		*0.225*		*0.127*		*0.203*	

Grouping electrodes into 4 localizations: Central (C3, C4, and Cz), Frontal (F3 and F4), Temporal (T3 and T4), and Occipital (O1 and O2). The main localization is always Central except for SS-S in N2 where the distribution is more balanced between Central and Frontal in the 65 + group

In the 75 + group, considering exact age and global OSA as covariates, SS density was not significantly different between S and F in stage 2 (p 0.409) or in stage 3 (p 0.319). SS frequency was not different (p 0.206 in N2 and p 0.109 in N3) between SS-S and SS-F. Amplitude changed between SS-S and SS-F in both stages, with SS-S being greater than SS-F in both sleep stages ($p < 0.001$) with no significant influence of covariates. Duration was significantly different in N2 (p 0.001) but not in N3 (p 0.74), being longer in SS-S than in SS-F.

In the 65 + group, the SS-S density was significantly greater in N2 ($p < 0.001$) but not in N3 ($p = 0.797$). Frequencies were not different in N2 ($p = 0.395$) or in N3 ($p = 0.983$) between SS-S and SS-F.

Amplitudes were greater in SS-S in N2 ($p < 0.001$), with a significant influence of global OSA ($p = 0.010$), leading

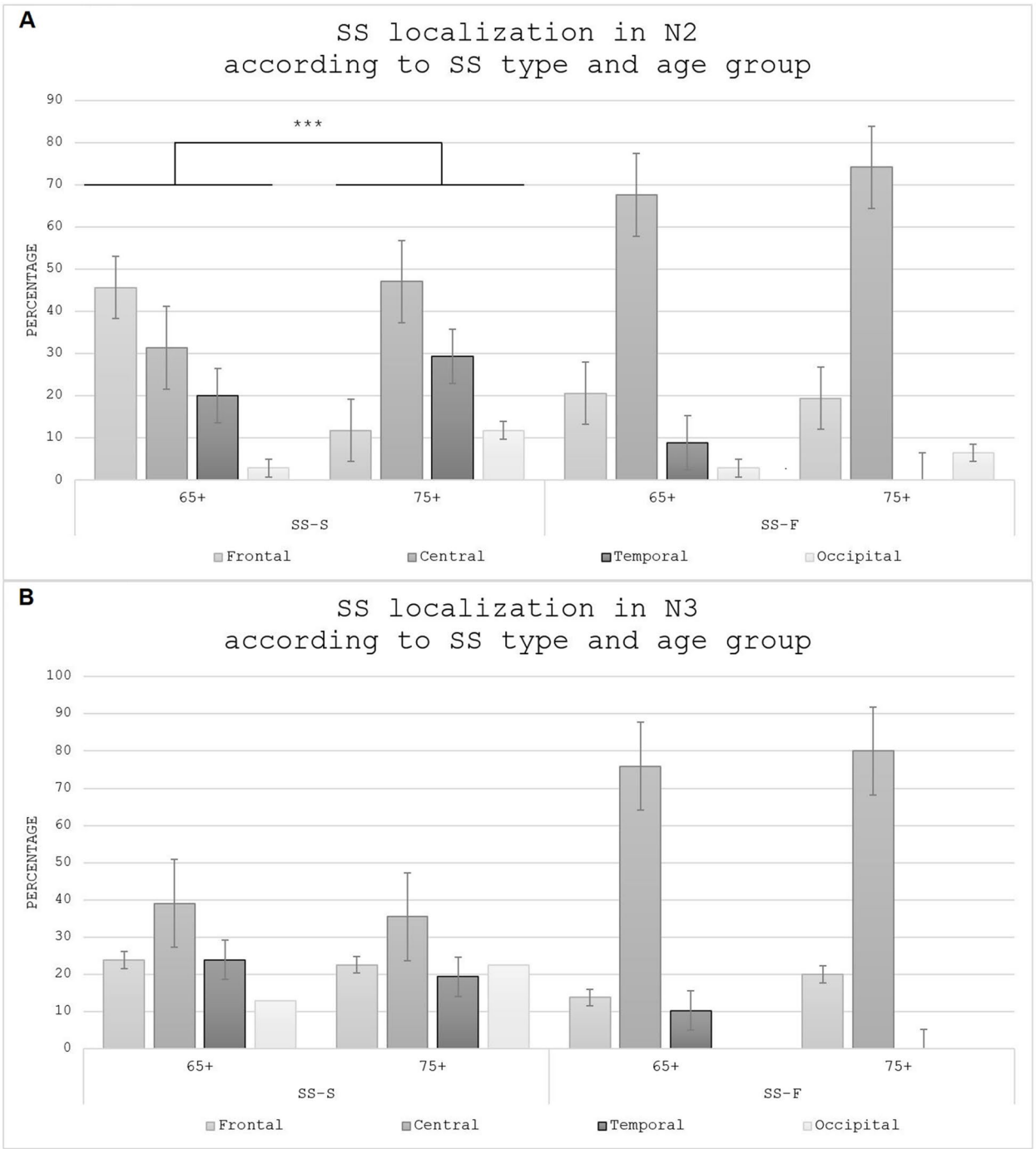

Fig. 2 **A** SS localization in N2 according to SS type and age group. Values are presented as percentage of each localization class for one type of SS per group. Central localization is highly predominant in all SS type in the 75 + group while it is only predominant for SS-F in the 65 + group. **B** SS localization in N3 according to SS type and age group. Values are presented as percentage of each localization class for one type of SS per group. Central localization is predominant for every SS type and there is no significant difference between groups. S: Slow; F: Fast. Error bars show standard error. ***: Statistically significant difference with $p < 0.005$

to greater values; they were also greater in SS-S in N3 ($p=0.039$), with no clear influence of the two covariates.

SS-S duration increased in N2 ($p<0.001$) with increasing age ($p=0.012$) but did not change in N3 ($p=0.606$). All these results are presented as Model 1 in Table 4.

Finally, ANCOVA with a multivariate model was applied to compare S/F spindle characteristics with age group, global OSA and sex as covariates in Model 2 (Table 5).

For density, the N2 SS-S was significantly greater than the SS-F ($p=0.007$), with no clear influence from

Table 3 Sleep stages comparison of the sleep spindles characteristics

		N2		N3		Global	Covariates influence (p)		
		65 +	75 +	65 +	75 +	*p*	age group	sex	OSA
Density	**SS-S**	2.952	3.317	1.748	1.842	**< 0.001**	**0.05**	0.505	1
	SS-F	1.991	1.228	0.293	0.402	**< 0.001**	0.671	0.896	0.504
Frequency	**SS-S**	10.82	10.419	10.763	10.579	**< 0.001**	0.177	0.2	0.598
	SS-F	13.407	13.702	13.189	13.51	**0.004**	0.571	0.503	0.524
Amplitude	**SS-S**	34.959	37.134	36.072	37.816	**< 0.001**	0.506	0.197	0.762
	SS-F	31.409	33.219	28.975	31.432	**< 0.001**	0.148	**0.022**	0.191
Duration	**SS-S**	0.836	0.874	0.793	0.795	**0.001**	0.065	0.158	0.339
	SS-F	0.787	0.791	0.667	0.722	0.222	0.28	0.901	0.941

Values are presented as Mean. We present the mean values of each age group for both Slow and Fast Sleep Spindles. ANCOVA include the age group (75 + or 65 +), OSA diagnosis (yes or no) and gender (female or male) for calculation of statistical difference

Table 4 Spindle types comparison of the sleep spindles characteristics in both groups, with ANCOVA – model 1

		75 +		Global	Covariates influence (p)		65 +		Global	Covariates influence (p)	
		S	F	*p*	exact age	OSA	S	F	*p*	exact age	OSA
Density	**N2**	3.317	1.228	0.409	0.525	0.975	2.952	1.991	**< 0.001**	**0.144**	0.763
	N3	1.842	0.402	0.319	0.24	0.089	1.748	0.293	0.797	0.704	0.508
Frequency	**N2**	10.419	13.702	0.206	0.54	0.692	10.82	13.407	0.395	0.594	0.798
	N3	10.579	13.51	0.109	0.944	0.122	10.763	13.189	0.983	0.883	0.592
Amplitude	**N2**	37.134	33.219	**< 0.001**	0.72	0.985	34.959	31.409	**< 0.001**	0.231	**0.01**
	N3	37.816	31.432	**< 0.001**	0.201	0.195	36.072	28.975	**0.039**	0.763	0.827
Duration	**N2**	0.874	0.791	**0.001**	0.571	0.933	0.836	0.787	**< 0.001**	**0.012**	0.069
	N3	0.795	0.7212	0.74	0.567	**0.009**	0.793	0.667	0.606	0.517	0.814

Model 1 includes exact age and OSA diagnosis as covariates. We see amplitude and duration are different between slow and fast spindles in both age groups

OSA Obstructive Sleep Apnea

Table 5 Spindle types comparison of the sleep spindles characteristics with ANCOVA—model 2

		75 +		65 +		Global	Covariates influence (p)		
		S	F	S	F	p	age group	sex	OSA
Density	**N2**	3.317	1.228	2.952	1.991	**0.007**	0.104	0.879	0.824
	N3	1.842	0.402	1.748	0.293	0.965	0.694	0.331	0.341
Frequency	**N2**	10.419	13.702	10.82	13.407	0.55	0.199	0.364	0.2
	N3	10.579	13.51	10.763	13.189	0.422	0.677	0.266	0.546
Amplitude	**N2**	37.134	33.219	34.959	31.409	**< 0.001**	0.176	0.736	0.184
	N3	37.816	31.432	36.072	28.975	**< 0.001**	0.138	**0.042**	0.933
Duration	**N2**	0.874	0.791	0.836	0.787	**< 0.001**	0.37	0.423	0.065
	N3	0.795	0.7212	0.793	0.667	0.93	0.411	0.476	0.251

Model 2 includes age group (75 + or 65 +), OSA (yes or no) and gender (female or male). In multivariate model, age does not affect any of the modifications we saw in the model 1; while gender affects amplitude variation in N3

OSA Obstructive Sleep Apnea

the covariates, while the density did not differ in N3 ($p=0.965$).

For frequencies, N2 values did not differ between SS-S and SS-F ($p=0.55$), and the N3 values did not differ ($p=0.422$).

For amplitudes, the SS-S amplitude was greater than the SS-F amplitude ($p<0.001$) in both stages, with the influence of sex in stage 3 ($p=0.042$), with females reaching greater amplitudes.

For duration, the SS-S was longer than the SS-F for N2, and the global OSA tended to be the most explanatory factor ($p=0.065$); there was no difference for N3. These results are shown in Table 5 as Model 2.

Discussion

Population data

The medical data of our participants could be considered concerning because of the high percentage of sleep pathology diagnoses in older people and the high rate of sleep-modifying drug consumption.

The *Haute Autorité de Santé* (the first independent French public scientific authority) report on OSA and its treatments showed similar results. OSA is found in approximately 20 to 50% of people after 60 years of age, while only moderate and severe OSA are considered, where we decided to consider mild OSA as well, leading to higher values [18].

In addition, we studied participants using laboratory-based polysomnography as part of their medical care and did not recruit them for our research. This means that they all had a sleep complaint, some sleep symptoms, or comorbidities and risk factors, leading them to undergo polysomnography. We tried to lower this bias by including OSA diagnosis as a cofactor in the analysis.

We excluded participants treated with benzodiazepines and related because of their clinical effects on sleep and their effects on sleep spindles [19, 20]. However, these treatments were used by 96 of the 340 participants screened (28.24%). This was not biased because of the care course of the participants. In a 2017 report on benzodiazepine consumption in France, the Agence Nationale de Sécurité du Médicament et des produits de santé (the French public agency that allows access to health products and ensures their security) presented a growth in consumption with age, with maximal use in women older than 80 years (38.3%). Nevertheless, there are encouraging data about the global consumption of benzodiazepines, with the annual consumption rate decreasing between 2012 and 2015 [21]. We may suppose that the rate we observed in our study reflects a continuous decrease since 2015. However, there is still a very high rate of benzodiazepine consumption in older people at high risk of comorbidities and polymedication.

Sleep spindle characteristics

The first SS topography studies described results from young people in the N2 sleep stage, with a slow frequency peak (< 12.5 Hz) of frontal and central distribution or centro-parietal distribution (depending on the EEG montage), while fast spindles (> 12.5 Hz) were found on every derivation (frontal, central, parietal, occipital) [22, 23].

More recently, but still in healthy young population samples (mean age 29.7 ± 6), an SS topography study revealed a central distribution for the SS-F and a centrofrontal distribution for the SS-S in N2 and a central distribution for the SS-F and a frontal distribution for the SS-S in N3 [24].

Our results are consistent with prior studies, with a predominant central distribution for all types of SS in both groups in sleep stage N3, N2 for SS-F in both groups, and a central distribution for SS-S in N2 in the 75 + group. Simultaneously, it was centrofrontal in the 65 + group.

Some specific SS-S originating from the frontal area seemed to be lost between the 65 + and 75 + participants.

This could be due to alterations in the frontal area observed in older people, according to recent studies showing a negative association between age and cortical thickness, or a correlation between cortical thickness and EEG alterations, especially for sigma power in NREM sleep [25, 26].

Fjell et al. also found a brain size reduction with large interindividual variability, predominantly in the frontal area, which could be due to changes in the synaptic network, leading to a worse detection of SS through frontal external electrodes [27].

According to the studies by Münch et al. and Mander et al., it could also be linked to memory loss. One study showed frontal aging with worse adaptation of the frontal area to sleep deprivation compared to younger people when specifically studying EEG power density in the delta and theta ranges [28].

The other study revealed a regionally selective deficit in fast sleep spindle density with the greatest impairment over the prefrontal area, without a significant link with gray matter volume [29].

Our results support the same hypothesis that age differences in spindle topographic distribution might be the consequence of differences in spindle generation rather than differences in the detection limit.

In 2021, McConnel et al. developed a new concept. SS-F split between the early ones in the N2 sleep stage, with a frequency range between 14.5 and 17.5 Hz, and the late SS-F in the N3 sleep stage, with a frequency between 10–14 Hz [30]. Again, our results are consistent, and we found a significant difference, with a greater mean frequency for SS-F in N2 than in N3 in both the 65 + group and the 75 + group. Many differences between these studies and ours must be considered, mainly in terms of the participants' age. To the best of our knowledge, this is the first study to specifically examine the sleep spindle characteristics of participants aged 75 + years.

The SS density is defined by significant interindividual variability and high sensitivity to perturbations. Through decades of studies, SS mean density has been described by many researchers and trials to define a norm: from 2.7 ± 2.1 SS per minute on a single participant using electromagnetic tomography in 2001 by Anderer et al. to 3.3 per minute for good sleepers and 3.51 per minute for people living with psychophysiological insomnia by Normand et al.; always over young participants; through SS mean densities of 2.54 per minute before and 2.4 per minute after treatment by cognitive behavioral therapy in a 2017 study by Dang-Vu et al. led on insomniac people [31–33]. A review by Espiritu et al. in 2008 showed a large range of SS mean densities obtained between studies, and they could only conclude a decrease in sleep spindle number and density with aging [34–36]. In 2021, Guadagni et al. described SS densities more precisely in the oldest sample population (68.2 ± 5.6 years old) [37]. They found a mean density of 2.4–2.46 SS per minute in central and frontal electrodes in N2 and lower values in N3: 1.46–1.62 in central and 1.66–1.8 in frontal electrodes. SS were recorded in a 10–16 Hz frequency range or 12–16 Hz for eight participants.

Here, by studying older people and more participants, we wanted to determine whether the mean densities would be around the same range for younger people or in another field. Our results are similar to those of Guadagni et al. but with slightly greater mean densities of both N2 and N3 in both age groups. The most important point is that we reached a known significant difference between the N2 and N3 values, and we added the influence of age, with lower values in the oldest group for both sleep stages and both sleep spindle types, at a statistically significant level for the N2/N3 slow spindle comparison.

This difference was not observed in the study by Fillmore et al., who studied SS characteristics through a different protocol, namely, a frequency range of 10–16 Hz, a frontal area only, a young group (18–29 years old) and an older but larger group (50–84 years old) [38].

Here, we decided to study two successive age groups for more accurate comparisons instead of young versus old or only a senior sample population. Moreover, our inclusion criteria were not as strict as those reported in the literature. Indeed, patients receiving benzodiazepines were excluded, but those receiving restless leg syndrome treatments or opioids were not excluded, which may have biased the results because our age groups were not comparable.

It seems that SS characteristics are even more sensitive to study protocols and inclusion criteria than they are susceptible to aging. For another example, Martin et al. studied SS characteristics in a 60–73-year-old population without neurological pathology and no treatment that could have modified sleep, with an AHI < 10, and this time split the SS between slow (11–13 Hz) and fast (13–15 Hz). These results differed from our findings and those of other studies: the mean density was between 2.4 (SS-S) and 2.6 (SS-F)/minute, the mean frequency was between 12.8 and 13 Hz, the mean amplitude was < 25 μv, and the mean duration was < 0.68 s [39].

To limit these variations, Djonlagic et al. based their study on sleep macro- and micro-architectures of polysomnography registered through two large cohorts (MESA and MrOS) [40].

They found that both the SS-S (center frequency, 11 Hz) and SS-F (center frequency, 15 Hz) mean densities decreased for every successive age group (decades) in both cohorts between 50 and 80 years of age, which is concordant with our results. They observed the same type of age-related decrease for SS amplitude and duration, whereas the SS frequency increased for each age group. Our results are not consistent about these points, with increased SS amplitude for both types and very slightly increased durations as developed earlier, while we registered an increase in frequencies.

Again, the means suffered a high interindividual variation, and they found a sex difference in the MESA sample concerning SS-F density, while the only gender effects we observed were amplitudes.

Lam et al. studied a sample population with mild cognitive impairment (MCI) and a mean age of 69.1 years compared to a control group without neurocognitive disorders or treatment and a mean age of 64.8 years [15]. Considering SS-S (11–13 Hz) and SS-F (13–16 Hz), the densities were very low for every type of SS: 0.36 SS-S/minute for the control group and 0.43 for the MCI group; 0.41 and 0.22 SS-F/minute for the control and MCI groups. The durations were closer to our results, with 0.74 s in the control group and 0.75 s in the MCI group, considering NREM sleep overall (N2 + N3).

Recently, in a review to synthesize age-related sleep modification tendencies, Campos et al. reported that SS density and amplitude decrease in elderly people,

duration decreases throughout life, and topography is increasingly reduced to the central area [41].

In another review study, Taillard et al. agreed with density and amplitude reduction with age but added the precision that this decrease was most important in the frontal area, while duration decrease could be better seen in posterior cerebral areas. They also brought the notion that not all spindle type suffers the same modifications through age, as SS-F main characteristics undergo more modifications than slow ones. Finally, they found that sleep spindles modifications through age were more significant in the latest sleep cycle in comparison to first sleep cycle of a night of polysomnogaphy [42].

These points could explain some of the differences we observed in the results; as in older studies, we have not focused on specific SS localizations to perform the calculations. In addition, our data were obtained from fragments of the polysomnography night, most of which were from the first or second sleep cycles. In regular practice, older people undergoing polysomnography as part of normal care rarely reach a third cycle at these ages, particularly after having one or more sleep pathologies and sleep-modifying treatments.

Forces and limitations

Due to the retrospective design of the study, we could not collect specific medical data by questioning the participants. We had to check their computerized medical records to find pieces of information we needed, which were not always well informed. We used the same methodology and collected the same data in every medical file from both groups to avoid any information bias.

Second, the two groups were not comparable in terms of every sociomedical characteristic, and there was a significant difference in CSA diagnosis and other treatments. Diagnosis was still infrequent. To limit the risk of selection bias, we visually selected only the clearest, artifact-free, extracts of N2 and N3 sleep stages from the first, second and third cycles, that clearly met casual identification criteria of sleep staging. Indeed, we assumed that a sleep period affected by a high apnea index for example, would have been less qualitative on the EEG signal and therefore not visually selected and included in the analysis. Still, CSA may have modified the whole night sleep micro-architecture even then.

The use of limited sleep fragments may have affected the results. However, the use of the same methodology for both groups did not lead to measurement bias. This may have artificially increased the mean density values of sleep spindles because they were the key signals used to score the N2 sleep stage and to manually select the sleep fragments used for analysis. This could also increase the mean duration when carefully manually checking for artifacts because a longer spindle is more susceptible to visualization and counting by the human eye.

Third, confounding bias is inherent to observational studies, and there may be some confounding factors that were not considered in this study. However, we limited this risk by collecting the same data on the primary medical status of all the participants, which could have changed the results. For example, the exclusion of patients with neurological pathology or verification of an OSA diagnosis was as prominent in both groups.

This study had several strengths, starting with polysomnography being recorded in a single sleep study laboratory, working only with trained nurses and technicians to perform polysomnography. Two experienced sleep physicians checked the medical files and sleep records for exclusion criteria and record quality.

SS detection was realized by powerful software that was continuously updated based on older algorithms that all proved to be accurate and efficient. In addition, the initial selection of the most stable sleep fragments and manual rejection of artifacts ensured that we registered and used only quality data for the statistical analysis.

Finally, our study sample was quite large owing to the extended registration period, while it was a monocentric study. Therefore, we added a control group to compare our data with the literature and to make direct comparisons between the age groups. This is visible through the statistical power that we reached with multiple significant results, even for calculations performed over a single group.

Conclusion

This retrospective monocentric study was able to verify changes in sleep spindle characteristics between sleep stages and between sleep spindle types (slow or fast).

There were few slight age-related changes in the number of sleep spindles between the over 65 age group and the over 75 age group. It seems that density and duration were the most affected characteristics through age when looking at the exact age, but the differences were lost when strictly comparing the age groups.

Most of our results were consistent with those in the literature, as the localization of the sleep spindles was mostly central. However, the values and means of the main characteristics of sleep spindles changed significantly among all studies, including the most recent and extensive studies.

It is still necessary to conduct wider longitudinal studies with old and oldest participants to analyze their sleep micro-architecture and its evolution over several decades. Therefore, we could finally define typical values and abnormal patterns linked to one or another diagnosis, revealing the role of micro sleep architecture as a

predictive biomarker of neurodegenerative pathologies and their evolution and gravity.

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Authors' contributions
BP have made the design of the work, the acquisition and analysis, the interpretation of data and drafted the work. PV have made substantial contributions to the conception and substantively revised it. HB have made substantial contributions to the conception, helped with the acquisition and interpretation. SG have made substantial contributions to the conception, took part to the acquisition, analysis and interpretation, substantially revised the work.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study has been registered by the Clinical Research and Innovation Delegation of the University Hospital of Besançon under the number 2021/643. Data were collected and treated by a team of the University Hospital in respect with the European General Data Protection Regulation, in accordance with the French Data Protection Authority (CNIL) reference methodology #004 (MR-004: Research not involving the human being, studies and evaluations in the health field). The university hospital center of Besançon has signed a commitment to comply with the CNIL's reference methodologies. According to these national regulations and commitment, this study does not require the authorization and approval from an ethics committee, neither an informed consent to participate from all of the participants. Instead, they received a written information form with a non-opposition notice, and had sufficient time for reflection to allow them to stipulate their opposition to the collection and processing of their data, if necessary.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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