

노년기 수면장애의 신경생리학적 지표

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Contents

- Sleep disorders commonly seen in the elderly
 - Insomnia
 - Sleep Apnea Syndrome
 - Restless Legs Syndrome (RLS) and Periodic Limb Movements during Sleep (PLMS)
 - REM Sleep Behavior Disorder (RBD)

Insomnia

Introduction

- Age-related sleep changes

Box 1: Typical sleep changes with aging

- Decreased total nocturnal sleep time
- Delayed onset of sleep
- Advanced circadian phase: early to bed, early to rise
- Reduced slow-wave sleep
- Reduced rapid-eye-movement (REM) sleep
- Reduced threshold for arousal from sleep
- Fragmented sleep with multiple arousals
- Daytime napping

(Wolkove, CMAJ 2007:176:1299–304)

Actigraphy suggests age-related differences in napping and nocturnal sleep

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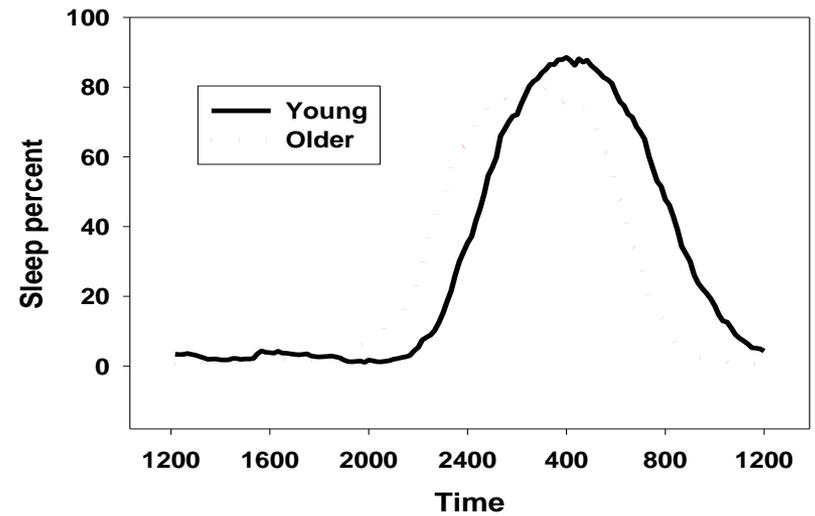
SUMMARY The aim of this study was to contrast the time distribution of out-of-bed napping in young and older adults through recordings of wrist activity, and to evaluate the correlates of napping with nocturnal sleep. Seventy-three young adults between 18 and 32 years and 60 older adults between 60 and 75 years of age participated in the study. Subjects were selected for good general health and had few sleep complaints. They wore wrist-activity monitors and kept daily sleep logs for 1 week. Automatic sleep scoring was edited by the authors, supplemented by sleep logs and illumination data as well as activity data. Napping episodes were modestly increased in older adults, but there was no difference in the daily duration of napping. Older adults napped more in the evening (especially within 2 h before bedtime), whereas young adults napped more in the afternoon. The older adults with evening naps ($n = 31$) showed earlier nocturnal wake-up times and decreased nocturnal sleep duration compared with the older adults without evening naps ($n = 29$). There was no difference in nocturnal sleep between young adults with afternoon naps ($n = 32$) and without afternoon naps ($n = 41$). In determining the effects of napping on nocturnal sleep, timing of napping and age are important. Maintaining alertness during the evening (e.g. by bright light exposure or moderate exercise) would be a possible approach to delay wake-up times in older adults.

KEYWORDS aging, circadian, naps, sleep, wrist activity

Table 1 Nocturnal sleep parameters of young and older adults

<i>Sleep parameters</i>	<i>Young (n = 73)</i>	<i>Older (n = 60)</i>	<i>P-value</i>
Bedtime	00:17 ± 1:11	22:39 ± 1:20	<0.001
Wake-up time	08:11 ± 1:23	06:35 ± 1:04	<0.001
Sleep-onset time	00:24 ± 1:11	22:50 ± 1:20	<0.001
Sleep-offset time	08:10 ± 1:23	06:30 ± 1:05	<0.001
TIB (min)	474.5 ± 54.5	475.9 ± 64.3	0.894
SL (min)	7.4 ± 2.9	10.6 ± 5.6	<0.001
SPT (min)	465.5 ± 55.4	460.2 ± 62.9	0.600
TST (min)	420.8 ± 48.2	366.1 ± 53.2	<0.001
SE (%)	88.8 ± 3.9	77.4 ± 9.4	<0.001
WASO (min)	44.7 ± 19.8	94.1 ± 54.3	<0.001

Values are mean ± SD; TIB, time in bed; SL, sleep latency; SPT, sleep period time; TST, total sleep time; SE, sleep efficiency; WASO, wake-up time after sleep onset.



24-hr Sleep distribution

(Yoon, J Sleep Res 2003;12:87–93)

Circadian Rhythms in Aging (1)

- 1) Age-dependent impairment in phase shifting: Shift work adaptation ↓
- 2) Flattening of the diurnal sleep-wake rhythm amplitude: ↑ napping
- 3) Phase advance: more larklike

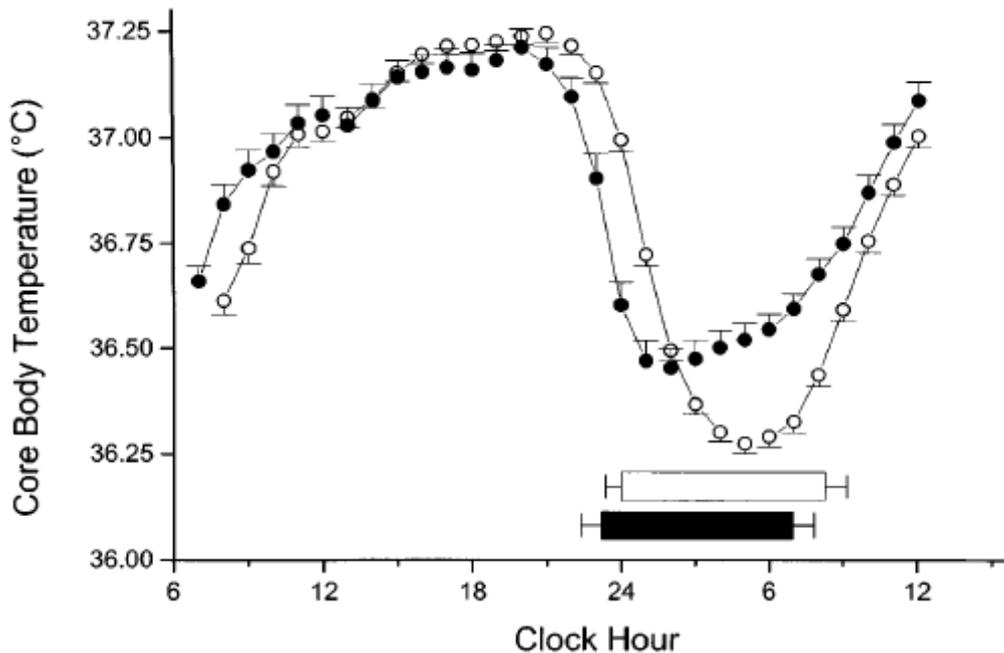


Fig. 3. Core body temperature waveforms averaged with respect to time of day for young and older subjects. ●, Older subjects ($n = 43$); ○, young subjects ($n = 97$); solid bar, usual sleep episode of older subjects (mean ± 1 SD); open bar, usual sleep episode of young subjects (mean ± 1 SD). Shown are data from scheduled *day 3*, the

(Duffy, Am J Physiol
1998;275:1478-87)

Age-Related Changes of Circadian Rhythms and Sleep-Wake Cycles

In-Young Yoon, MD, PhD, Daniel F. Kripke, MD,* Jeffrey A. Elliott, PhD,* Shawn D. Youngstedt, PhD,* Katharine M. Rex, BA,* and Richard L. Hauger, MD†*

OBJECTIVES: To compare relationships between the sleep-wake cycle and endogenous circadian rhythms in young and older adults and to examine correlates between evening naps and circadian rhythms in older adults.

DESIGN: For 1 week of home recording, subjects wore wrist-activity monitors and kept daily sleep logs. After the home monitoring, subjects entered the laboratory on a 90-minute sleep-wake schedule and were monitored on this schedule for at least 30 hours.

SETTING: Community living and laboratory.

PARTICIPANTS: Sixty-seven young adults, aged 18 to 32, and 56 older adults, aged 60 to 75, who were healthy and had few sleep complaints.

MEASUREMENTS: Times of nocturnal sleep, out-of-bed napping, and illumination were obtained at home. Sleep propensity and oral body temperature (OBT) were measured in the laboratory, along with circadian rhythms of cortisol and 6-sulfatoxymelatonin (aMT6s, assayed from urine samples collected every 90 minutes).

RESULTS: Home sleep times and illumination acrophases (fitted peak times) were advanced in older adults. The phase angles (time intervals) between onset of aMT6s and sleep onset were not changed in older adults, but sleep offset was more advanced than acrophase and offset of aMT6s with aging. Acrophases of cortisol and sleep propensity were advanced in older adults to the same extent as sleep times, but OBT was less advanced than sleep times. Older adults who took evening naps showed more advanced sleep offset and circadian rhythms of aMT6s,

but there were no differences in the phase angles of sleep onset and circadian rhythms of aMT6s and cortisol compared with older adults who did not take evening naps.

CONCLUSION: Measuring different circadian markers suggested different phase relationships between the sleep-wake cycle and endogenous circadian rhythms in aging. Early awakening in older adults cannot be explained simply by a relative phase advance of the circadian system. Evening naps and advanced illumination may play a role in the advance of the circadian system in aging. *J Am Geriatr Soc* 51:1085-1091, 2003.

Key words: sleep-wake; circadian; aging; melatonin; naps

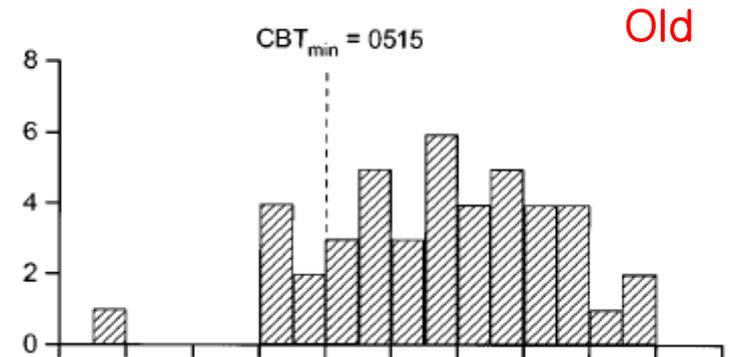
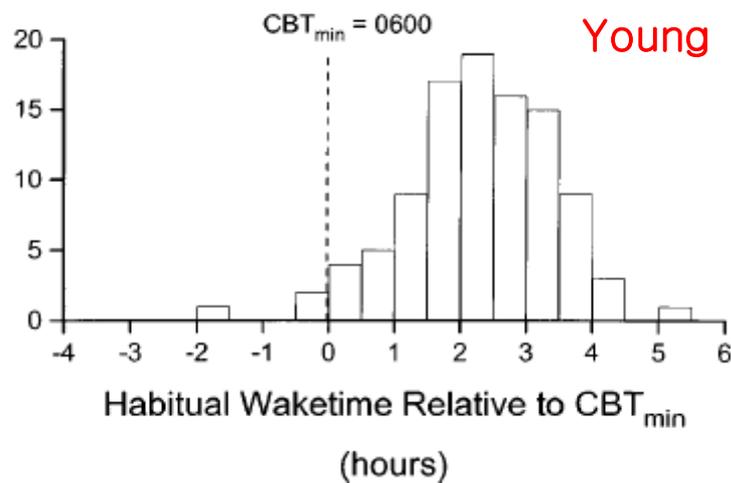
Older people often go to bed early at night and wake up early in the morning.^{1,2} The advance of sleep time in older people has been explored in reference to endogenous circadian rhythms. Although it is generally accepted that older people show a phase advance of circadian rhythms compared with young people,^{3,4} some studies have reported no phase advance of core body temperature (CBT)⁵ or melatonin acrophase⁶ in older people. There has also been some controversy about changes of phase relationships between sleep time and circadian rhythms in older people. In one study,⁷ the interval between the CBT fitted minimum and awakening time was not different between young and older subjects. The interval was 85 minutes for the young group and 95 minutes for the older group. A similar result was replicated in another study, with the awakening time being

Circadian Rhythms in Aging (2)

Table 1. Parameters of Nocturnal Sleep at Home and Circadian Rhythms of 6-Sulphatoxymelatonin (aMT6s) and Cortisol in the Laboratory of Young and Older Adults

Parameter	Young (n = 67)	Older (n = 56)	P-value
	Mean ± Standard Deviation		
Sleep onset time	00:23 ± 1:12	22:51 ± 1:19	<.001
Sleep offset time	08:11 ± 1:22	06:32 ± 1:06	<.001
Total sleep time, minutes	421.7 ± 48.3	367.1 ± 51.6	<.001
Wake time after sleep onset, minutes	45.08 ± 20.29	94.67 ± 54.43	<.001
aMT6s onset	23:10 ± 1:41	22:01 ± 2:14	.002
aMT6s acrophase	03:39 ± 1:30	03:02 ± 1:40	.004
aMT6s offset	8:29 ± 2:04	8:04 ± 1:45	.245

(Yoon, JAGS 2003:51:1085–91)



(Duffy, Am J Physiol 1998:275:1478–87)

Circadian Rhythms in Aging (3)

- Typical sleep period is more advanced than circadian markers in the elderly
 - 1) The earlier bedtimes and wakeup times in the elderly
 - : Changes in the circadian timing system is not the only answer.
 - 2) A weakening of homeostatic processes in the regulation of sleep and waking
 - : Decreased ability to consolidate sleep in the elderly
 - : Earlier exposure to light in the morning and evening nap
 - : Earlier wakeup times

Prevalence of insomnia (1)

TABLE 6. *Prevalences of chronic sleep disturbances within older populations of men and women*

Study (reference)	n	Ages	% DIS ^a	% DMS ^a	% EMA ^a	% INS ^a
Hammond, 1964 (21)	144,514	65+				23.5
Karacan et al., 1976 (22)	215 ^b	60+				23.0
Bixler et al., 1979 (23)	336	51–80	17.3	32.7	17.3	38.4
Karacan et al., 1983 (24)	285	65+	13	27	13	
Lugaresi et al., 1983 (25)	488	65+				38.0
Smirne et al., 1983 (26)	1,070	60+				19.0
Welstein et al., 1983 (27)	831	65–103				26.0
Mellinger et al., 1985 (28)	798	65–79				25.0
Morgan et al., 1988 (29)	1,023	65+				23.0
Ford and Kamerow, 1989 (30)	1,802	65+				19.3
Weyerer and Dilling, 1991 (31)	393	60+				24.9
Gislason et al., 1993 (32)	430	65–84	10.0	33.4	16.7	
EPESE	9,282	65+	19.2	29.7	18.8	28.5

^a DIS = difficulty initiating sleep; DMS = difficulty maintaining sleep; EMA = early morning awakening; INS = Insomnia.

^b Estimated.

EPESE, Established Populations for Epidemiologic Studies of the Elderly

(Foley, Sleep 1995:18:425–32)

c.f.) Prevalence of chronic insomnia among general population – about 10%

Prevalence of insomnia (2)

- Gender effects

TABLE 1. Average sleep complaint score and prevalence of sleep-derived syndromes by sex and community: EPESE 1982

	n	Average age	Average sum of complaints score	Difficulty initiating or maintaining sleep %	Insomnia %	Awakes not rested %	No complaints %
East Boston^a							
Total	3,537	73.3	3.71*†	45.2*	33.7*	15.0	11.0†
Men—all ages	1,343	72.9	3.35	41.7	29.4	14.2	12.4
Women—all ages	2,194	73.4	3.92	47.4	36.4	15.5	10.2
New Haven^{bc}							
Total	2,717	74.5	3.20*†	34.9*†	27.5*	15.0*	16.8*†
Men—all ages	1,128	73.9	2.82	29.1	21.2	13.2	20.5
Women—all ages	1,589	74.9	3.47	38.3	31.1	16.1	14.7
Iowa^d							
Total	3,028	74.4	3.41*†	45.3†	23.2*†	7.4	7.9†
Men—all ages	1,129	73.7	3.21	43.4	19.5	6.3	8.7
Women—all ages	1,899	74.8	3.53	46.4	25.4	8.1	7.5

(Foley, Sleep 1995:18:425–32)

- More sedative/hypnotic use in elderly women than elderly men
- A yearly incidence of insomnia in the elderly: about 5%

Medical diseases and insomnia

- Medical diseases and chronic illness play an important role in much of poor sleep in old age.

Medical Illnesses Associated with Sleep Disruption	
Illnesses	Examples
Acute or chronic pain	Arthritis, chronic lower back pain, chronic headaches, cancer, postoperative pain, fibromyalgia, neuropathy, orofacial pain, burn injury
Cardiac and vascular disease	Nocturnal angina, symptoms of congestive heart failure (e.g., hypoxemia, Cheynes-Stokes/periodic breathing, nocturia), peripheral vascular disease with nocturnal leg pain
Pulmonary disease	COPD, accumulated bronchial secretions, nocturnal bronchospasm, sleep-related laryngospasm, rhinitis/sinusitis
Gastrointestinal disorders	Symptoms of gastro-esophageal reflux disease (e.g., pain, coughing), non-ulcer dyspepsia, ulcer pain
Endocrine disease	Central apnea associated with hypothyroidism, symptoms of diabetes (e.g., nocturnal hypoglycemia or hyperglycemia, nocturia, neuropathic pain), symptoms of menopause (e.g., hot flashes, mood changes)
Renal disease	Uremia
Genitourinary problems	Incontinence
Neurological disorders	Post-CVA (e.g., aspiration, periodic breathing, pain related to inability to change position), dementia, nocturnal seizures, parkinsonism (drug side effects), Parkinson's disease, neuromuscular degenerative disorders

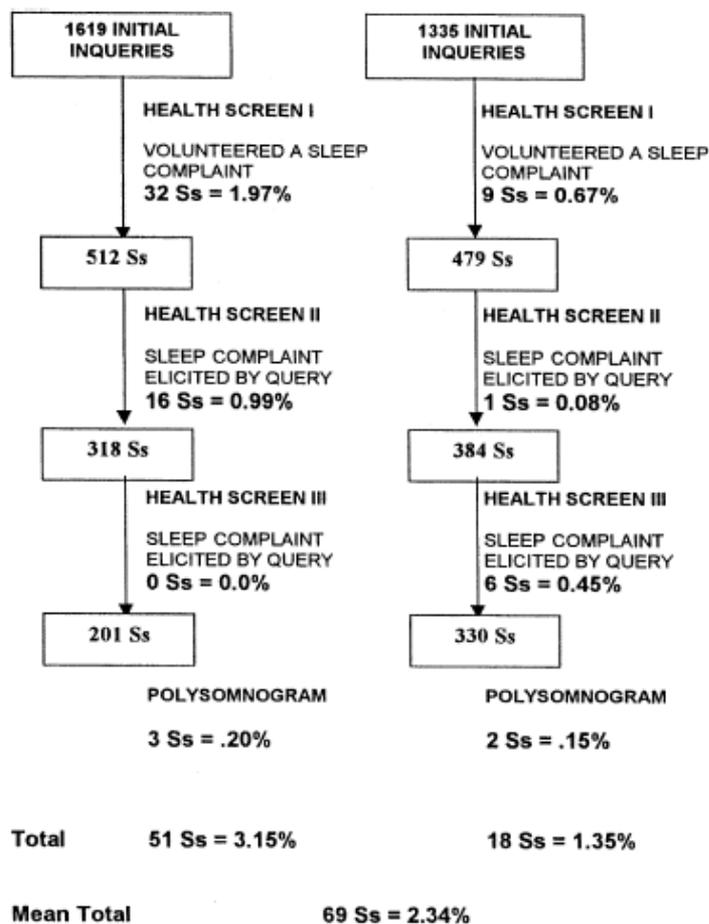
Psychiatric disorders – Depression and anxiety disorders

(Ancoli-Israel, Harv Rev Psychiatry 2008;16:279–86)

Sleep complaints cosegregate with illness in older adults

Clinical research informed by and informing epidemiological studies of sleep

Michael V. Vitiello^{a,*}, Karen E. Moe^a, Patricia N. Prinz^b



When elderly subjects with comorbidities are carefully screened, the resulting insomnia prevalence may be only 1 % to 3%.

Treatments (1)

- Five basic principles in pharmacotherapy in the elderly

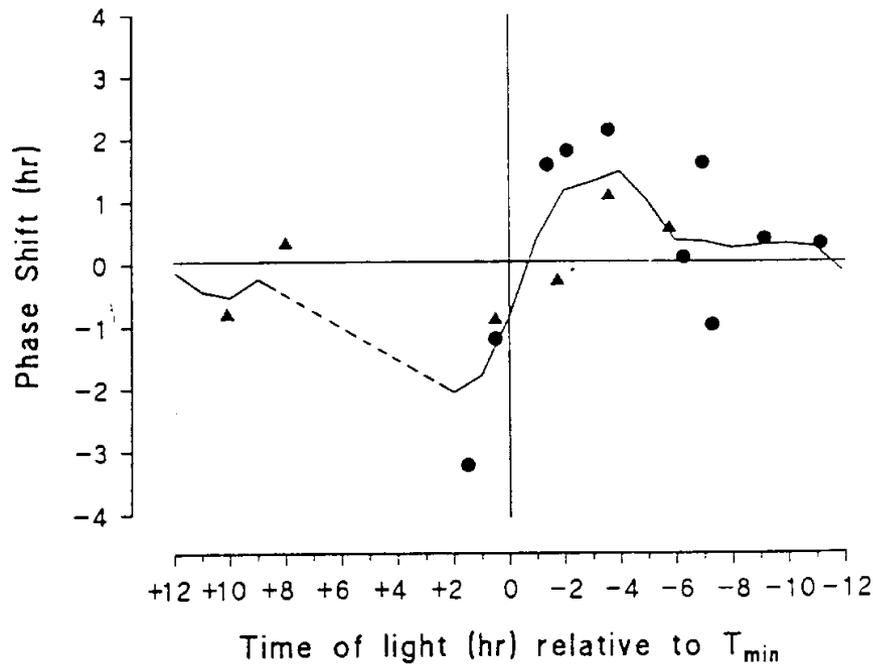
- 1) Use of the lowest effective dose
- 2) Use of intermittent dosing (2 to 4 times weekly) ??
- 3) Short-term medication prescribing (not more than 3 to 4 weeks)
- 4) Gradual medication discontinuation to reduce rebound insomnia
- 5) Preference for medications with shorter elimination half-lives to minimize daytime sedation. ??
 - : Clonazepam should rarely be used. ??
(Half life, clonazepam; longer than 20 hr, mirtazapine; 20–40 hr)

Treatments (2)

- Phase-response curve (PRC) to light

P. advance

P. delay



Treatments (3)

- The effects of light therapy in the elderly

1. Phase-shifting effects of light

- 1) Alleviation of sleep maintenance insomnia with timed exposure to bright light. *Campbell SS, Dawson D, Anderson MW. J Am Geriatr Soc 1993;41(8):829-36.*
- 2) The treatment of early-morning awakening insomnia with 2 evenings of bright light. *Lack L, Wright H, Kemp K, Gibbon S. Sleep 2005;28(5):616-23.*

2. Alerting effects of light

- 1) Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. *Satlin A, Volicer L, Ross V, Herz L, Campbell S. Am J Psychiatry. 1992;149(8):1028-32.*
- 2) Bright-light treatment reduces actigraphic-measured daytime sleep in nursing home patients with dementia: a pilot study. *Fetveit A, Bjorvatn B. Am J Geriatr Psychiatry. 2005;13(5):420-3.*

c.f.) delirious patients

Sleep Apnea Syndrome

Definition of SAS

- International classification of sleep disorders (ICSD, 2005)

1. 1) Apnea-hypopnea index (AHI) ≥ 5 and
 - 2) At least one of the following
 - a) **daytime sleepiness**, unrefreshing sleep or insomnia
 - b) waking with choking
 - c) loud snoring or observed apnea

or

2. Apnea-hypopnea index (AHI) ≥ 15

c.f.) Epidemiological studies vs.
clinical setting / case control studies

Prevalence (1)

Prevalence of the middle-aged: men – 4%, women – 2%

TABLE 7. *Distribution of men and women, by decade, with RDI <10, ≥10, ≥20 and ≥40*

	RDI < 10		RDI ≥ 10		RDI ≥ 20		RDI ≥ 40	
	n	% ^a	n	%	n	%	n	%
Age								
65–69								
Men (n = 75)	19	25	56	75	38	51	21	28
Women (n = 77)	40	52	37	48	28	36	16	21
Total (n = 152)	59	39	93	61	66	43	37	24
70–79								
Men (n = 79)	26	33	53	67	38	48	22	28
Women (n = 102)	42	41	60	59	39	38	16	16
Total (n = 181)	68	38	113	62	77	43	38	21
80–89								
Men (n = 17)	6	35	11	65	11	65	4	24
Women (n = 35)	12	34	23	66	16	46	13	37
Total (n = 52)	18	35	34	65	27	52	17	33
65–99								
Men (n = 171)	51	30	120	70	87	51	47	28
Women (n = 214)	94	44	120	56	83	39	45	21
Total (n = 385)	145	38	240	62	170	44	92	24

^a Percentages = within gender and within age group.

RDI, respiratory disturbance index; apnea + hypopnea

Apnea or hypopnea: based on respiratory effort without airflow measurement

(Ancoli-Israel, Sleep 1991:14:486–495)

Prevalence (2)

Table 1. Sample Characteristics by Sleep-Disordered Breathing Severity*

Characteristic	No. of Participants	Apnea-Hypopnea Index		
		<5	5-14	≥15
Total sample	5615	53	29	18
Sex				
Male	2648	42	33	25
Female	2967	63	26	11
Age, y				
39-49	519	70	19	10
50-59	1648	60	24	16
60-69	1668	49	32	19
70-79	1425	46	33	21
80-99	355	44	36	20

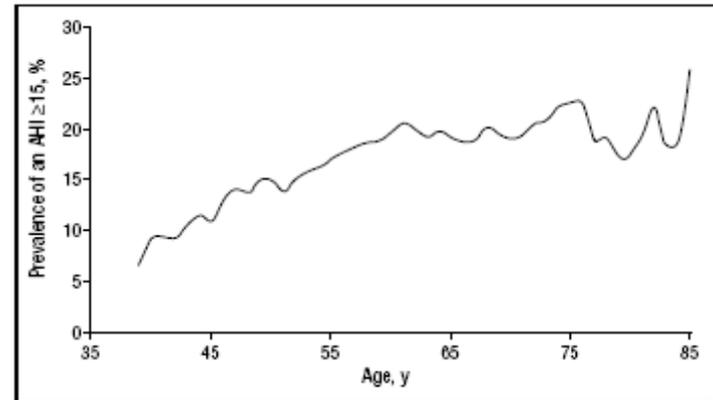


Figure 1. Smoothed plot (5-year moving average) of the prevalence of an apnea-hypopnea index (AHI) of 15 or greater by age.

(Young, Arch Intern Med 2002;162:893–900)

c.f.) Vitoria–Gasteiz, Spain Cohort

: 71–100 years, men: AHI ≥ 5, 81% / AHI ≥ 15, 57%

women: AHI ≥ 5, 80% / AHI ≥ 15, 49%

Mechanisms for the increasing prevalence

1. Upper airway (UA) collapsibility ↑

: UA resistance ↑, pharyngeal wall fat deposit ↑
muscular endurance ↓

2. Sleep fragmentation ↑ and Slow wave sleep ↓

→ respiratory instability characterized by periodic breathing and central apneas

3. Ventilatory control instability

4. Not receiving HRT in women

: The role of sex hormones in UA muscle activity, UA resistance and ventilatory control

→ An amplification of well-established causes of SAS

AGE AND RESPIRATORY DISTURBANCE

Polysomnographic Respiratory Abnormalities in Asymptomatic Individuals

Milena K. Pavlova, MD; Jeanne F. Duffy, MBA, PhD; Steven A. Shea, PhD

(Pavlova and Duffy, Sleep 2008;31:241–248)

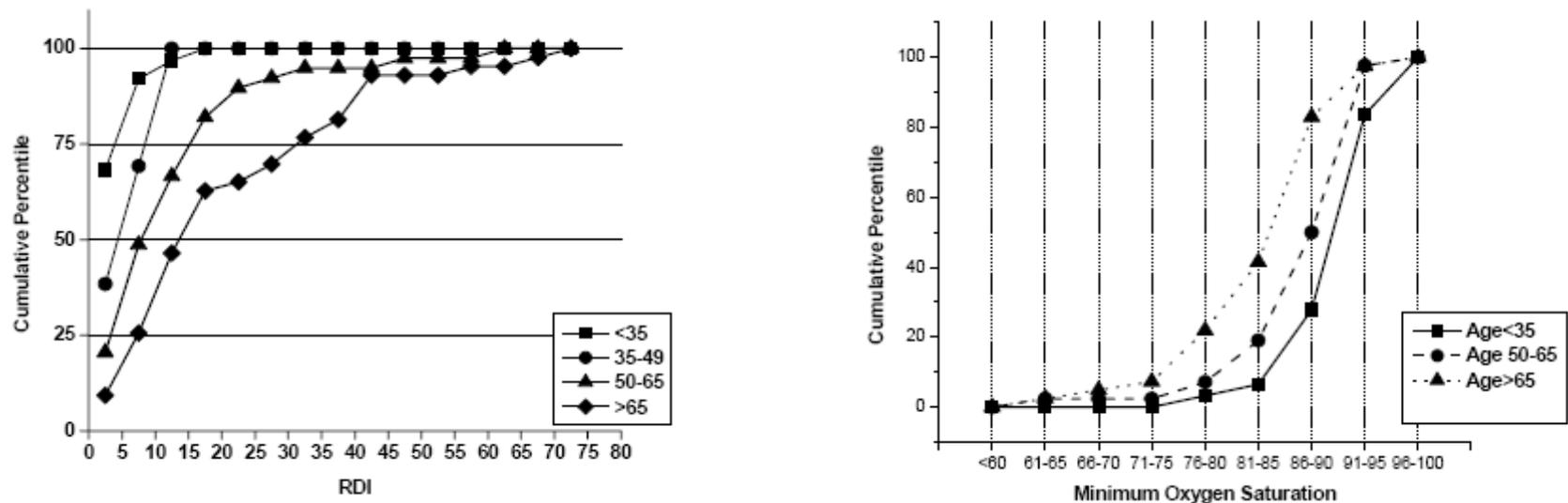


Figure 2—Cumulative relative frequency of respiratory disturbance index (RDI: events per hour of sleep; upper plot) and minimum arterial oxyhemoglobin saturation recorded overnight (%: lower plot) according to age group. More than 95% of the subjects younger than 50 had an RDI < 12.5, whereas fewer than 50% of the subjects older than 65 years had RDI < 12.5. The increasing RDI with age was associated with concomitant lower minimum arterial oxyhemoglobin saturation with age (1 age group was omitted from the arterial oxyhemoglobin saturation plot due to missing or insufficient data).

CV Disease and SAS (1)

1. Weaker or no association between CV risk factors and SAS in the populations ≥ 65 years than the ones < 65 years

- 1) Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. *Newman AB. Am J Epidemiol. 2001;154:50-9.* – *only in women*
- 2) Age-dependent associations between sleep-disordered breathing and hypertension : the Sleep Heart Health Study. *Haas DC, Circulation. 2005;111:614-621.* – *no association in OSA pts ages over 60 years*

2. The relationship between CV disease and SAS is maintained with aging.

- 1) Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *Nieto FJ, JAMA. 2000; 283:1829-36.*
- 2) Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Shahar E. Am J Respir Crit Care Med. 2001;163:19-25.*

CV Disease and SAS (2)

Eur Respir J 2009; 33: 797–803
 DOI: 10.1183/09031936.00023208
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Association between C-reactive protein and unrecognised sleep-disordered breathing in the elderly

F. Roche^{*,#}, J.-M. Gaspoz^{*,#}, V. Pichot^{*,†}, M. Picard-Kossofsky[#], D. Maudoux^{*}, A. Garcin^{*}, S. Celle^{*,†}, E. Sforza^{*} and J.C. Barthélémy^{*,†} on behalf of the PROOF and SYNAPSE Study Groups

TABLE 3 Spearman correlation coefficients relating log C-reactive protein (CRP) with nocturnal parameters

	Log CRP	AHI	ODI	AAI
AHI				
Coefficient	0.060	1		
p-value	0.09			
ODI				
Coefficient	0.121	0.803		
p-value	0.006	<0.0001		
AAI				
Coefficient	0.037	0.799	0.652	1
p-value	0.301	<0.0001	<0.0001	
S_pO₂ <90% time %				
Coefficient	0.078	0.162	0.295	0.074
p-value	0.027	<0.0001	<0.0001	0.036
Minimal S_pO₂				
Coefficient	-0.082	-0.408	-0.571	-0.291
p-value	0.020	<0.0001	<0.0001	<0.0001
Sleep duration				
Coefficient	-0.013	-0.103	-0.023	-0.131
p-value	0.704	0.003	0.519	0.001

AHI: apnoea/hypopnoea index; ODI: oxygen desaturation index; AAI: autonomic arousals index; S_pO₂: arterial oxygen saturation measured by pulse oximetry; AAI: autonomic respiratory-related arousal index.

CV Disease and SAS (3)

Sleep Breath (2009) 13:11–17
DOI 10.1007/s11325-008-0210-x

ORIGINAL ARTICLE

Endothelial dysfunction and inflammatory reactions of elderly and middle-aged men with obstructive sleep apnea syndrome

Seockhoon Chung • In-Young Yoon •
Yoon-Kyung Shin • Chul Hee Lee • Jeong-Whun Kim •
Hee Jeong Ahn

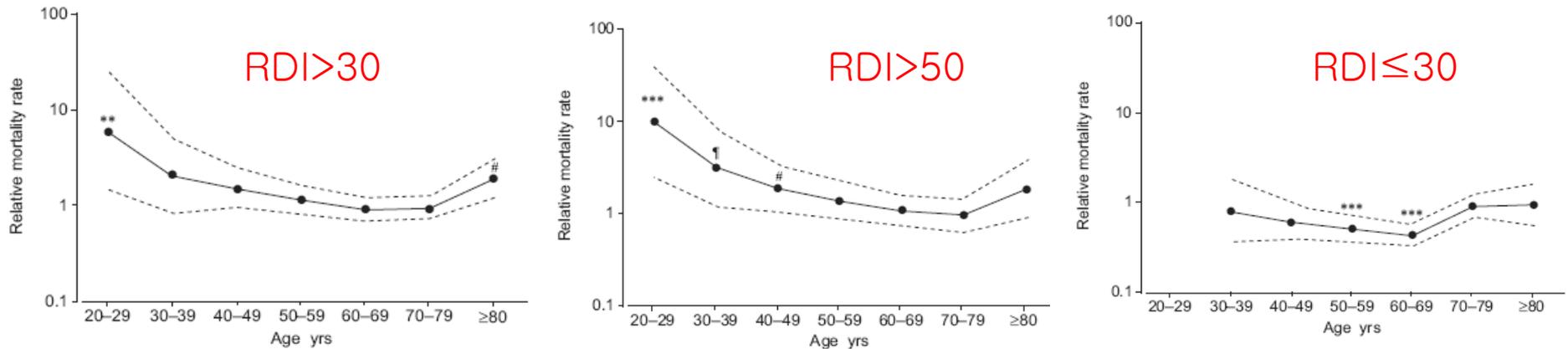
Table 3 Stepwise multiple linear regression model of FMD and Log CRP in middle-aged and elderly OSAS patients

Group	Dependent variable	Included parameters	Beta	Adjusted R^2	<i>p</i> value
Middle-aged	FMD	Lowest O ₂ saturation	0.25	6%	<0.01
	Log CRP	BMI	0.22	11%	<0.01
		Waist-to-hip ratio	0.21		
Elderly	FMD	No variable	–	–	–
	Log CRP	AHI	0.46	19%	<0.01

OSAS Obstructive sleep apnea syndrome, FMD flow-mediated dilatation, CRP C-reactive protein, BMI body mass index, ODI oxygen desaturation index, AHI apnea hypopnea index

Mortality and SAS (4)

- Declining all-cause mortality rates with age



(Lavie, Eur Respir J 2005;25:514–520)

1. Marked CV response in young severe OSA → Early mortality
→ Only patients resistant to SAS seen among elderly patients
2. Pre-conditioning effect due to repeated intermittent hypoxia
→ Promoting some degree of cardiovascular protection

Cognitive Impairment and SAS (1)

Sleep-Disordered Breathing and Cognitive Impairment in Elderly Japanese-American Men

Daniel J Foley, MS¹; Kamal Masaki, MD^{2,3}; Lon White, MD, MPH^{2,3}; Emma K. Larkin, MHS⁴; Andrew Monjan, PHD, MPH⁵; Susan Redline, MD, MPH⁴

Table 2—Sociodemographics, selected risk factors, and medical conditions by severity of sleep-disordered breathing: HAASSA 1999-2000

Characteristics	Sleep-disordered Breathing ¹			
	Total (N=718)	AHI<5 (N=204)	AHI=5-29 (N=376)	AHI ≥30 (N=132)
Age 85 yrs and older	27.2%	30.4%	27.1%	25.0%
Married	77.1	76.0	74.7	83.3
High school education	57.3	54.9	58.0	57.6
Body mass index ≥30	3.6	3.9	2.1	6.8*
Neck size >16 inches	16.1	12.8	16.0	22.0
Habitual Snoring	20.9	13.7	20.7	31.1**
Daytime drowsiness	20.2	16.7	19.4	30.3**
IADL/ADL difficulty	25.4	24.5	24.7	29.6
Depressed mood (CESD-11>8)	9.5	9.8	8.8	12.9
Poor cognition (CASI<74)	12.0	15.7	11.2	18.2
History of:				
Stroke	12.6	11.8	12.5	14.4
CHD	21.4	23.0	19.7	23.5
Hypertension	62.9	59.3	62.2	71.2
Diabetes	25.9	24.5	26.1	28.0

(SLEEP 2003;26:596-599)

Table 3—Mean cognitive functioning scores¹ by severity of sleep-disordered breathing: HAASSA 1999-2000

AHI	CASI	MMSE	Short-term Memory	Attention	Concentration
Range	0-100	0-30	0-12	0-8	0-10
<5 (absent)	83.3	24.1	7.9	6.4	7.7
5-14 (mild)	83.7	24.2	8.0	6.4	7.7
15-29 (moderate)	83.5	24.1	8.0	6.4	7.7
30+ (severe)	83.6	24.2	8.0	6.4	7.7

¹ Mean score is adjusted for age; HAASSA, Honolulu-Asia Aging Study of Sleep Apnea; CASI, Cognitive Abilities Screening Instrument; MMSE, Mini-Mental State Examination; AHI, apnea-hypopnea index

Cogni

ELDERLY WITH SLE

Cognitive Funct Population: the

Emilia Sforza, MD, PhD¹; Fréd
Sébastien Celle, PhD¹; Delphine

Table 3—Scores of cognitive function tests (mean ± SD) of participants according to apnea-hypopnea index (AHI)

	AHI < 15 (n = 382)	AHI 15-30 (n = 278)	AHI > 30 (n = 167)	*P
Subjective cognitive difficulties	29.1 ± 1.9	29.2 ± 1.9	29.1 ± 2.0	ns
MMSE (score)	28.4 ± 1.7	28.7 ± 1.4	28.6 ± 1.2	ns
FCSR				
Total Immediate recall	15.4 ± 0.9	15.4 ± 0.8	15.2 ± 1.1	ns
Total Delayed recall	15.6 ± 0.9	15.6 ± 0.8	15.2 ± 1.3	0.02
Free Delayed recall	12.2 ± 2.2	12.1 ± 2.3	11.7 ± 2.8	0.04
Recognition score	15.9 ± 0.4	15.9 ± 0.4	15.8 ± 0.6	0.06
Visual memory	12.5 ± 1.6	12.4 ± 1.8	12.4 ± 1.8	ns
DST				
Digit span forward	5.5 ± 1.0	5.5 ± 1.1	5.4 ± 1.1	ns
Digit span backward	4.2 ± 1.0	4.2 ± 0.9	4.2 ± 1.0	ns
Baddeley dual task				
Dual task decrement	93.5 ± 10.1	93.0 ± 10.5	92.9 ± 12.2	0.08
Trail Making				
Trail Making Test A (speed)	47.5 ± 15.8	46.5 ± 15.4	47.5 ± 15.4	ns
Trail Making Test A (errors)	0.10 ± 0.3	0.10 ± 0.4	0.13 ± 0.4	ns
Trail Making Test B (speed)	103.5 ± 48.8	104.3 ± 50.6	103.2 ± 48.5	ns
Trail Making Test B (errors)	0.45 ± 0.9	0.47 ± 0.7	0.46 ± 0.9	ns
Semantic memory				
Verbal fluency Phonemic	19.3 ± 6.5	19.2 ± 6.4	19.5 ± 7.2	ns
Verbal fluency Semantic	29.5 ± 7.8	30.0 ± 8.3	30.6 ± 8.5	ns
Stroops				
Word (score)	98.1 ± 13.7	97.9 ± 13.9	96.5 ± 15.2	ns
Color (score)	70.7 ± 10.7	70.6 ± 11.2	68.1 ± 11.5	0.03
Color word (score)	49.3 ± 7.7	49.2 ± 8.3	49.0 ± 8.6	ns
WAIS Similarities test	16.9 ± 5.5	16.9 ± 5.5	17.3 ± 5.5	ns

FCSR, Free and cued selective reminding test; DSST, digit symbol substitution test.

*One-way Anova

AS (2)

Healthy Elderly

Beauchet, MD, PhD³;
MD, PhD¹

:33:515-521)

Cognitive Impairment and SAS (3)

Minimal Cognitive Impairment in the elderly with SAS (in SNUBH)

	Without SAS AHI < 15 (n=23)	With SAS 5 ≤ AHI < 30 (n=21)	With SAS AHI ≥ 30 (n=21)	<i>p</i>
MMSE	26.2±2.6	27.2±1.8	26.1±3.0	.266
Verbal Fluency (semantic)	16.1±3.8	16.7±5.8	16.3±4.4	.917
BNT	12.2±1.8	12.6±1.6	11.4±4.4	.157
WLM _immediate recall	19.3±3.6	19.3±3.2	17.7±3.9	.229
WLRT _delayed recall	7.1±1.6	7.2±1.5	6.0±1.2	.016
WLRcT _recognition	9.1±1.4	9.4±1.4	9.3±1.0	.719
CPT	10.0±1.5	10.2±1.1	9.8±1.1	.539
Visual memory (CR)	7.3±2.6	7.3±3.4	6.8±3.0	.831
TMT_A_error	.39±.65	.43±.68	.43±.81	.980
TMT A time	58.6±20.4	48.9±24.9	68.2±33.8	.072
TMT B error	1.1±1.4	1.2±1.8	2.1±1.7	.111
TMT B time	175.7±77.1	144.3±85.2	175.4±79.4	.352

SAS, Sleep apnea syndrome; MMSE, Mini-Mental State Examination; BNT, Boston naming test; WLM, word list memory-immediate test; WLRT, word list-delayed free recall test; WLRcT, word list-recognition test; CPT, constructional performance; CR, Constructional recall; TMT, trail making test;

Daytime sleepiness and SAS (1)

- Is sleepiness increased with aging ?

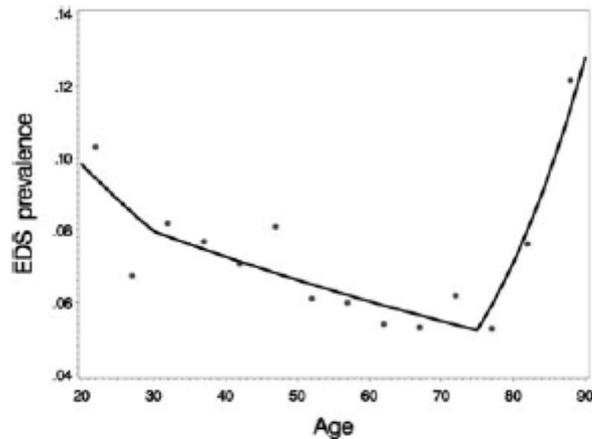


FIG. 1. Age-specific prevalence of EDS.

(Bixler, J Clin Endocrinol Metab 2005;90:4510–15)

Table 4. Prevalence(%) of sleep problems by age and sex.

	Male							Female						
	20-29	30-39	40-49	50-59	60-69	70+	total	20-29	30-39	40-49	50-59	60-69	70+	total
Difficulty initiating sleep	17.4	14.8	13.1	12.5	13.4	14.8	14.2	21.0	18.1	13.8	21.4	23.6	21.8	20.0
Difficulty maintaining sleep	9.5	14.8	16.2	18.6	23.0	29.0	18.1	17.0	21.7	19.5	24.2	26.8	30.7	23.4
Early morning awakening	9.6	16.1	26.0	34.7	40.3	35.2	26.9	11.1	12.3	15.8	22.4	30.1	31.6	20.6
Loss of deep sleep	29.4	30.8	27.5	18.7	13.0	11.0	22.1	33.7	34.8	29.3	23.4	16.3	11.3	24.8
Interruption of sleep by snoring or dyspnea	1.5	3.3	3.3	3.1	2.5	1.8	2.6	0.8	1.0	1.5	2.2	1.7	1.5	1.5
Disagreeable sensations in legs	1.7	2.7	2.7	2.0	2.6	3.2	2.4	3.1	2.8	2.9	3.5	3.7	4.2	3.4
<u>Excessive daytime sleepiness</u>	<u>4.6</u>	<u>3.8</u>	<u>3.5</u>	<u>2.1</u>	<u>1.8</u>	<u>0.9</u>	<u>2.8</u>	<u>4.0</u>	<u>2.8</u>	<u>3.0</u>	<u>1.9</u>	<u>0.9</u>	<u>0.7</u>	<u>2.2</u>
n	2241	2262	2397	2710	2252	1737	13599	2400	2434	2488	2914	2424	2455	15115

(Kaneita, J Epidemiol 2005;15:1–8)

Daytime sleepiness and SAS (2)

Risk Factors for Excessive Sleepiness in Older Adults

Allan I. Pack, MB, ChB, PhD,^{1,2} David F. Dinges, PhD,^{1,3} Philip R. Gehrman, PhD,¹
Bethany Staley, RPSGT,¹ Frances M. Pack, RN,¹ and Greg Maislin, MS, MA^{1,2}

(Ann Neurol 2006;59:893–904)

Table 4. Final Multivariable Model and Sensitivity Analysis for Final Multivariable Model

Variables	Final Multivariable Model ^a		Sensitivity Analysis for the Final Multivariable Model ^b
	OR (95% CI)	<i>p</i>	OR (95% CI)
Apnea–hypopnea index (OR for 20-events/hr increase)	1.4 (1.1–1.9)	0.01	1.4 (1.0–1.9)
PSQI self-report of overall sleep quality (OR for one-point increase)	2.3 (1.6–3.6)	<0.0001	1.8 (1.1–3.0)
% Time in REM sleep (OR for 6.8% increase)	1.4 (1.1–1.9)	0.01	1.4 (1.0–2.0)
Pain or physical discomfort ≥ 3 times/week	5.9 (2.2–19.0)	0.001	19.2 (3.3–370.2)
Any wheezing or whistling from chest at night	3.2 (1.4–8.0)	0.001	5.1 (1.6–18.7)
US Pharmacopoeia more/less common vs rare/none	1.9 (1.1–3.3)	0.02	1.5 (0.8–3.1)
Male sex	1.9 (1.0–3.5)	<0.05	3.7 (1.6–9.0)
>7 alcoholic beverages per week	0.42 (0.20–0.86)	0.02	0.28 (0.10–0.72)

Daytime sleepiness and SAS (3)

Sleep disordered breathing in an elderly community-living population:
Relationship to cardiac function, insomnia symptoms and daytime sleepiness

Peter Johansson ^{a,b,*}, Urban Alehagen ^{a,b}, Eva Svanborg ^{c,d}, Ulf Dahlström ^{a,b}, Anders Broström ^{c,e}

(Sleep Med 2009;10:1005–1011)

Table 1
Characteristics of the population and subjective sleep complaints across the severity of SDB.

Characteristics	AHI				<i>p</i> ¹	<i>p</i> ²
	<5 No SDB (<i>n</i> = 148, 45%)	≥5 Mild SDB (<i>n</i> = 107, 32%)	≥15 Moderate SDB (<i>n</i> = 53, 16%)	≥30 Severe SDB (<i>n</i> = 23, 7%)		
Male, % (<i>n</i>)	43 (64)	53 (57)	55 (29)	61 (14)	0.2	0.035
Age, mean (SD)	78.6 (3.5)	78.1 (2.9)	78.7 (3.2)	78.5 (3)	0.48	0.77
SBP, mean (SD)	148 (18)	149 (19)	148 (23)	146 (17)	0.91	0.64
DBP, mean (SD)	74 (9)	75 (9)	75 (9)	76 (9)	0.81	0.36
BMI, mean (SD)	26.7 (3.6)	28.2 (5)	27.4 (4.3)	29.9 (4.3)	0.001	0.02
<i>Comorbidities</i>						
Diabetes, % (<i>n</i>)	22 (32)	22 (23)	32 (17)	22 (5)	0.43	0.35
HT, % (<i>n</i>)	71 (105)	72 (77)	81 (43)	70 (16)	0.52	0.4
IHD, % (<i>n</i>)	21 (31)	27 (29)	36 (19)	26 (6)	0.2	0.06
RD, % (<i>n</i>)	18 (27)	16 (17)	11 (6)	17 (4)	0.7	0.36
TIA/Stroke, % (<i>n</i>)	5 (8)	8 (9)	15 (8)	17 (4)	0.08	0.02
<i>Medication</i>						
ACEI/ARB, % (<i>n</i>)	21 (31)	34 (36)	32 (17)	26 (6)	0.12	0.06
B-blockers, % (<i>n</i>)	27 (40)	43 (46)	57 (30)	44 (10)	0.001	<0.01
Digoxin, % (<i>n</i>)	4 (6)	7 (8)	6 (3)	4 (1)	0.69	0.52
Diuretics, % (<i>n</i>)	32 (48)	35 (37)	38 (20)	48 (11)	0.52	0.51
Hypnotics, % (<i>n</i>)	15 (23)	13 (14)	13 (7)	22 (5)	0.73	0.97
<i>Insomnia symptoms</i>						
DIS, % (<i>n</i>)	36 (53)	38 (41)	51 (27)	52 (12)	0.15	0.04
DMS, % (<i>n</i>)	65 (96)	63 (67)	66 (35)	61 (14)	0.95	0.84
NRS, % (<i>n</i>)	36 (54)	41 (44)	49 (26)	52 (12)	0.27	0.06
EMA, % (<i>n</i>)	43 (63)	36 (38)	38 (20)	44 (10)	0.68	0.5
<i>Excessive daytime sleepiness</i>						
ESS, mean (SD)	6.5 (3.8)	6.6 (3.8)	6.8 (3.5)	6.7 (4.1)	0.81	0.57
ESS ≥ 10, % (<i>n</i>)	18 (27)	21 (22)	24 (13)	22 (5)	0.8	0.36

Daytime sleepiness and SAS (4)

Effects of Age on the Clinical Features of Men with Obstructive Sleep Apnea Syndrome

Seockhoon Chung^a In-Young Yoon^b Chul Hee Lee^c Jeong-Whun Kim^c

(Respiration 2009;78:23–29)

Table 5. Results of subjective assessment scales and polysomnographic findings related with sleep structures

	Young (n = 254)	Middle-aged (n = 373)	Elderly (n = 130)	p value
Total sleep time, min ^{a-c}	370.9 ± 61.3	354.7 ± 56.2	333.3 ± 57.3	<0.01
Sleep efficiency, % ^{a-c}	86.9 ± 9.3	83.4 ± 10.5	76.3 ± 11.6	<0.01
Wake time during sleep period, min ^{a-c}	48.6 ± 45.3	61.4 ± 43.0	87.3 ± 50.9	<0.01
Wakes, n ^{a,b}	9.5 ± 6.5	12.9 ± 15.4	15.8 ± 23.5	<0.01
Sleep latency, min	15.9 ± 41.9	12.9 ± 26.5	19.7 ± 30.2	0.12
Stage 1, %	14.7 ± 8.2	16.3 ± 9.0	16.9 ± 10.4	0.04
Stage 2, % ^{b,c}	52.5 ± 10.7	51.6 ± 11.0	47.0 ± 14.8	<0.01
Stage 3 and 4, % ^{a,b}	6.3 ± 5.8	2.7 ± 4.1	1.9 ± 5.3	<0.01
REM sleep, %	15.4 ± 5.8	14.7 ± 6.3	13.7 ± 7.4	0.06
Respiratory arousal index	16.2 ± 19.4	16.2 ± 19.1	14.2 ± 18.2	0.56
PSQI ^{b,c}	7.4 ± 3.3	8.0 ± 4.4	10.0 ± 5.1	<0.01
Patients with PSQI > 5, n ¹	167/239 (69.9%)	227/345 (65.8%)	81/106 (76.4%)	0.11
ESS ^{b,c}	10.8 ± 4.7	10.6 ± 5.4	7.8 ± 5.0	<0.01
Patients with ESS > 10, n ^{1,b,c}	126/246 (51.2%)	175/366 (47.8%)	36/114 (31.6%)	<0.01

^a p < 0.05, young versus middle-aged; ^b p < 0.05, young versus elderly; ^c p < 0.05, middle-aged versus elderly.

¹ Estimated in patients who responded to each scale.

Treatments (1)

- **Operation**
: Not usually recommended because of muscular endurance ↓
- **Oral appliances**
: Occasionally used, but limited because of poor dental health or denture use
- **CPAP**
: Standard treatment of moderate to severe SAS
: No difference in the compliance from younger patients ??

Comparison of patients with severe SAS (AHI≥30) according to age in SNUBH

	Middle age (35-64yrs) N=189	Older age (≥65yrs) N=43	<i>p</i>
age	48.07 ± 7.97	70.26 ± 4.31	<.001
BMI	27.61 ± 4.25	26.14 ± 3.70	.037
AHI	51.79 ± 17.53	46.27 ± 11.78	.014
PSQI	6.96 ± 3.60	9.43 ± 4.51	.002
ESS	10.72 ± 4.62	9.42 ± 5.50	.109
CPAP Titration	61 (32%)	21 (49%)	.040

Treatments (2)

Clinical and polysomnographic variables of patients with severe SAS participating in CPAP titration according to age in SNUBH

	Middle age(35–64yrs) N=61	Older age(≥65yrs) N=21	p
age	50.77 ± 7.71	69.81 ± 3.93	<.001
BMI (kg/m ²)	28.88 ± 5.71	26.47 ± 4.16	.079
BDI	7.39 ± 7.11	11.14 ± 8.90	.055
PSQI	7.43 ± 3.86	9.14 ± 4.21	.090
ESS	11.31 ± 4.51	9.71 ± 5.91	.201
AHI (/h)	55.43 ± 19.97	58.53 ± 10.25	.046
Average SaO ₂ (%)	93.18 ± 4.43	92.71 ± 2.40	.646
Lowest SaO ₂ (%)	73.90 ± 9.52	75.47 ± 8.91	.509
Sleep of <SaO ₂ 90% (%)	15.76 ± 19.10	18.16 ± 17.64	.615
ODI	47.31 ± 21.79	41.69 ± 13.01	.163
CPAP pressure (mmH ₂ O)	9.48 ± 2.59	9.24 ± 3.25	.736
CPAP rent	58 (95%)	13(62%)	<.001

Restless Legs Syndrome (RLS)

Diagnostic Criteria

Essential diagnostic criteria for RLS

- 1 An urge to move the legs,
usually accompanied or caused by uncomfortable
and unpleasant sensations in the legs
(Sometimes the urge to move is
present without the uncomfortable sensations and
sometimes the arms or other body
parts are involved in addition to
the legs)
- 2 The urge to move or unpleasant
sensations begin or worsen during periods
of rest or inactivity such as
lying or sitting
- 3 The urge to move or unpleasant
sensations are partially or totally relieved
by movement, such as walking or
stretching, at least as long as
the activity continues
- 4 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 (When symptoms are very
severe, the worsening at night may
not be noticeable but must have
been previously present)

IRLSSG, 1995
→ NIH revision, 2003

(Allen, Sleep Med 2003;4:101–119)

하지 불안 증후군의 진단기준(필수항목)

1. 다리를 움직이고 싶은 강한 충동을 느낀다. 이러한 충동은 다리에 불편한 혹은 불쾌한 감각과 동반되어 나타나는 경우가 흔하다.
2. 움직이고 싶은 충동 혹은 불쾌한 감각이 눕거나 앉아있는 동안, 즉 휴식 중이나 가만히 있는 동안에 발생하거나 악화된다.
3. 움직이고 싶은 충동 혹은 불쾌한 감각이 걷거나 다리를 뺏는 등의 움직임에 의해 부분적으로 혹은 완전히 해소되며, 최소한 움직이는 동안에는 이러한 증상의 해소가 지속된다.
4. 움직이고 싶은 충동 혹은 불쾌한 감각이 낮보다 저녁 혹은 밤에 더 심하거나 저녁 혹은 밤에만 발생한다.

Short Communication

Prevalence of restless legs syndrome and associated factors in the Korean elderly: The Korean Health and Geriatrics Survey

12.1%

Epidemiology of Restless Legs Syndrome in Korean Adults

Yong Won Cho, MD, PhD^{1,6}; Won Chul Shim, MD, PhD^{4,6}; Ju Han Kim, MD, PhD^{5,6}; Richard P. Allen, PhD⁷; Christopher J. Earley, MBBCh, PhD⁷

7.5%

Journal of Sleep Medicine, 2008;11(2):119-124

SLEEP 2008;31(2):219-223.

Restless Legs Syndrome and Its Impact on Quality of Life in Korean Adults: Prevalence, Associated Factors, and Impact on Quality of Life in Korean Adults with Psychiatric Disorders

Seong-Jin Cho, MD, PhD¹; Jin Pyo Hong, MD, PhD²; Maeng Je Cho, MD, PhD³; Hochang B. Lee, MD, PhD⁴; Sung Man Chang, MD, PhD⁵

0.9%

Journal of Sleep Medicine, 2009;12(8):1069-1076

SLEEP 2009;32(8):1069-1076.

J. Sleep Res. (2010) 19, 87–92

doi: 10.1111/j.1365-2869.2009.00733.x

Restless legs syndrome

Prevalence, comorbidity, and quality of life of restless legs syndrome in the elderly – results from the Korean Longitudinal Study on Health and Aging

8.4% in the elderly

KI WOONG KIM^{1,2}, IN-YOUNG YOON^{1,2}, SEOCKHOON CHUNG¹, YOON-KYUNG SHIN³, SEOK BUM LEE¹, EUN AE CHOI⁴, JOON HYUCK PARK¹ and JONG-MIN KIM⁵

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Pathophysiology (1)

- * Central dopamine system dysfunction

- 1) Therapeutic effects of L-dopa and dopamine agonists
- 2) Akathisia – caused by dopamine receptor-blocking agents
- 3) Imaging studies – mixed results

- * Brain Iron Deficiency

- * Genetics – familial aggregation of RLS

- * Opiate system dysfunction

Korean Longitudinal Study on Health and Aging (KLoSHA)

	RLS (N=59)	Non-RLS (N=655)	Significance
Hemoglobin (g/dL)	13.7 ± 1.2	13.9 ± 1.4	0.3
Iron (µg/dL)	105.7 ± 37.8	102.7 ± 36.0	0.55
Ferritin (ng/ml)	119.4 ± 106.0	114.6 ± 121.1	0.77
Ferritin (< 50ng/ml, %)	18.6	22.1	0.36
Transferrin (mg/dL)	236.7 ± 39.9	238.2 ± 44.1	0.8
TIBC (µg/dL)	326.6 ± 51.0	332.0 ± 52.3	0.45

Studies using SPECT or PET

- Nigrostriatal dopamine system

Presynaptic transporter

- 1) No difference between RLS patient and normal controls (SPECT)
- 2) Reduction in RLS patients (PET)

Postsynaptic receptor

- 1) No difference (SPECT)
- 2) Lower D2 receptor binding (PET and SPECT)

- Striatal and extrastriatal postsynaptic system

Cervenka, Brain 2006;129 (Part 8): 2017-2028

D2-Rc availability ↑ in RLS

: Higher Rc density (due to upregulation) or hypoactive DA transmission

Objectives

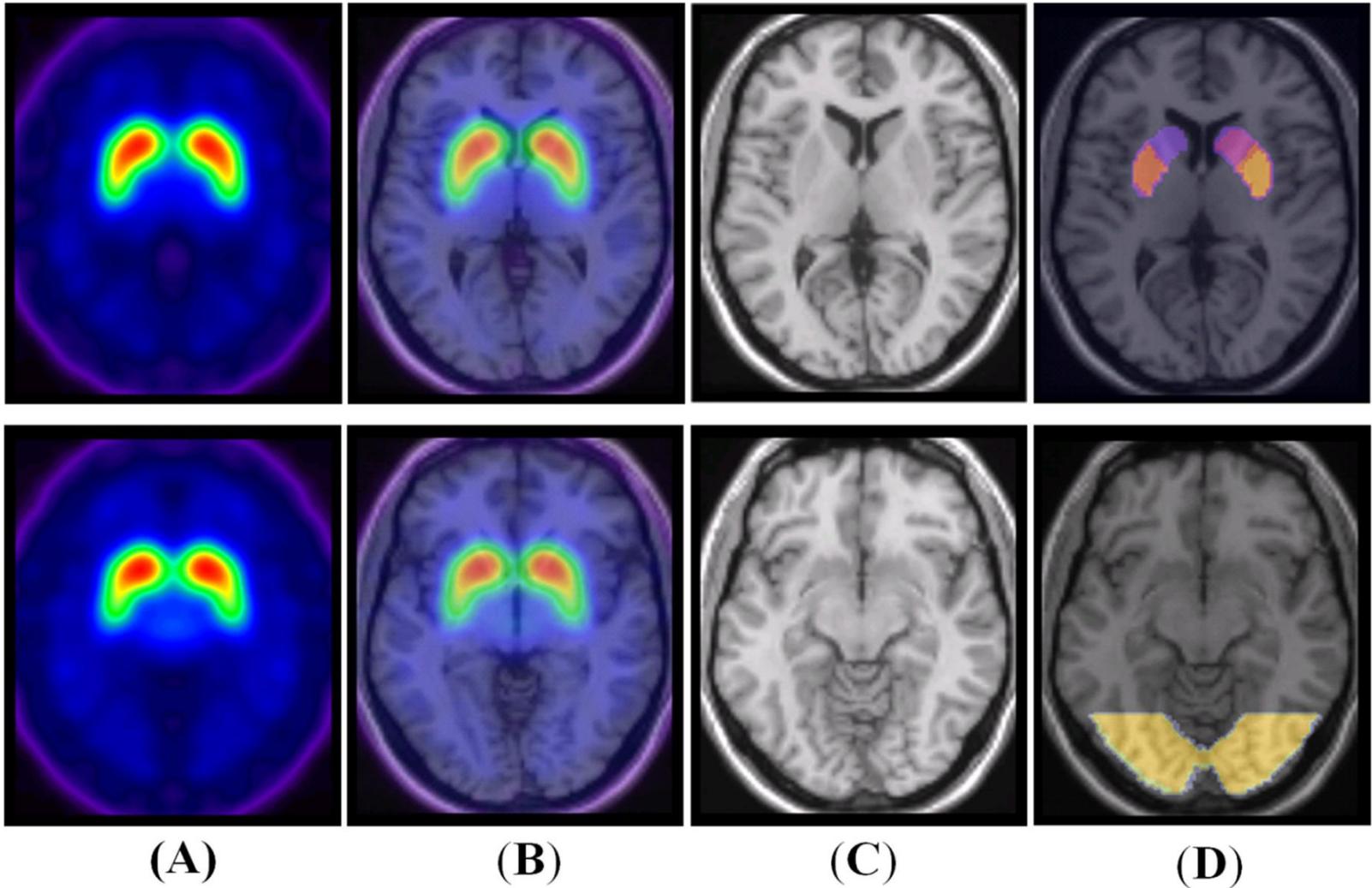
- To investigate striatal presynaptic DA transporters (DAT) and D2 receptors in elderly patients with RLS
- To find the correlation between DA dysfunction and RLS severity in the RLS patients

Subjects

- Thirteen drug-naïve elderly patients with RLS and 12 healthy controls
- Diagnosis of RLS
 - : Face to face interview, four diagnostic criteria by NIH
 - Severity of RLS – IRLSSG Severity Scale
 - Depressive symptoms – Geriatric Depression Scale (GDS)
- Exclusion
 - : Parkinson's disease, Major depressive disorder

SPECT Scans

- A triple-headed rotating γ -camera system equipped with low-energy, high resolution, parallel-hole collimators
- **Data acquisition**
 - 1) ^{123}I - βCIT SPECT
 - : 20-22 hours after injection of 167-185 MBq of ^{123}I - βCIT
(16:30 – 18:30)
 - 2) ^{123}I -IBZM SPECT
 - : 90 min after injection of 167-185 MBq of ^{123}I -IBZM
(19:00 – 21:00)
 - 3) At least 1 week apart between two SPECTs
- **ROI** for entire striatum, caudate and putamen
 - : Manually defined on the SPECT template superimposed on standard MRI



^{123}I - βCIT template superimposed onto the standard MRI (A,B,C). ROIs were manually drawn on the $[^{123}\text{I}] \beta\text{-CIT}$ after overlapping with standard brain MRI, and striatal ROI was divided into the caudate and putamen (D).

Subjects characteristics

	Control (N=12)	RLS (N=13)	<i>P</i> Value
Age, yr	71.8±6.2	81.1±8.7	< 0.01
Sex M/F	8/4	4/9	0.11
RLS severity		17.0±4.4 (range: 9-26)	
GDS	7.3±4.7	7.3±4.2	0.97

DAT and D2 Rc density

	$^{123}\text{I}-\beta\text{CIT}$			$^{123}\text{I}-\text{IBZM}$		
	Control	RLS	<i>P</i> Value	Control	RLS	<i>P</i> Value
Caudate	7.3±1.1	8.4±1.3	0.037	0.73±0.24	0.82±0.15	0.325
Ant. putamen	7.8±1.1	8.8±1.4	0.079	0.98±0.22	1.03±0.21	0.572
Post. putamen	6.5±1.0	7.2±1.1	0.041	0.88±0.20	0.93±0.20	0.533
Striatum	7.2±1.1	8.1±1.2	0.046	0.85±0.21	0.91±0.18	0.448

ANCOVA, covariate - age

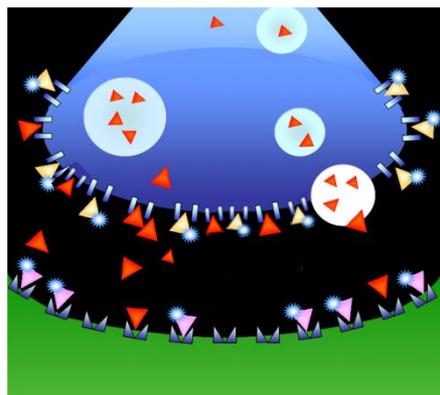
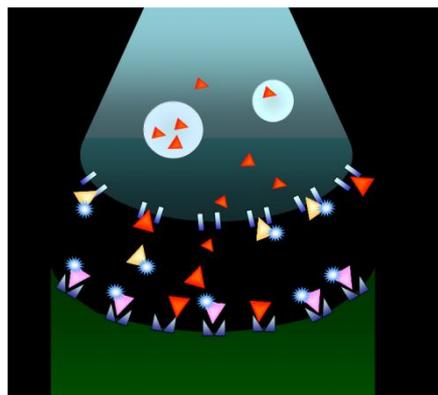
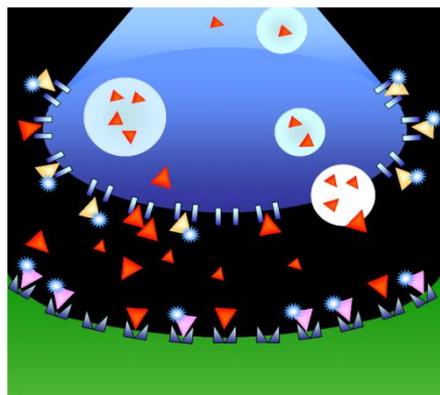
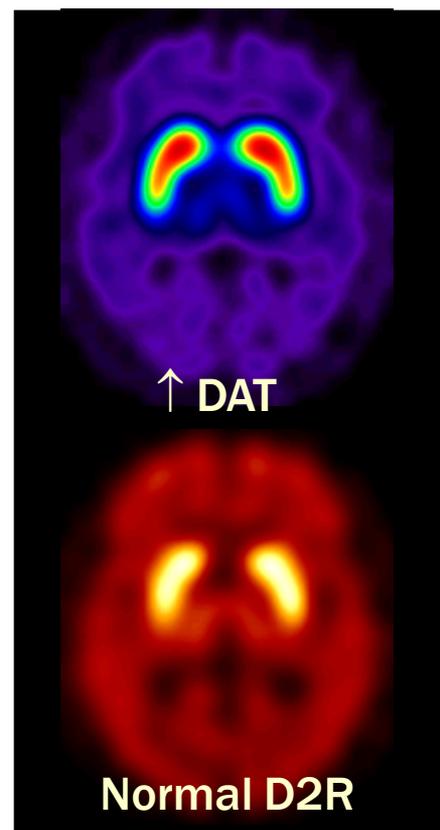
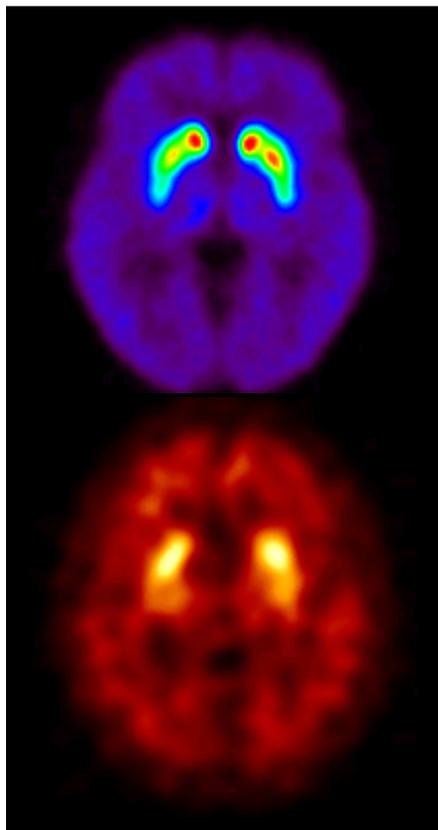
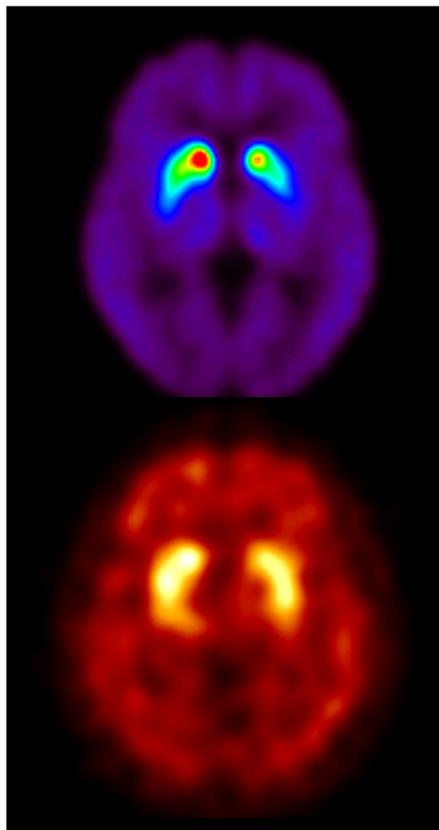
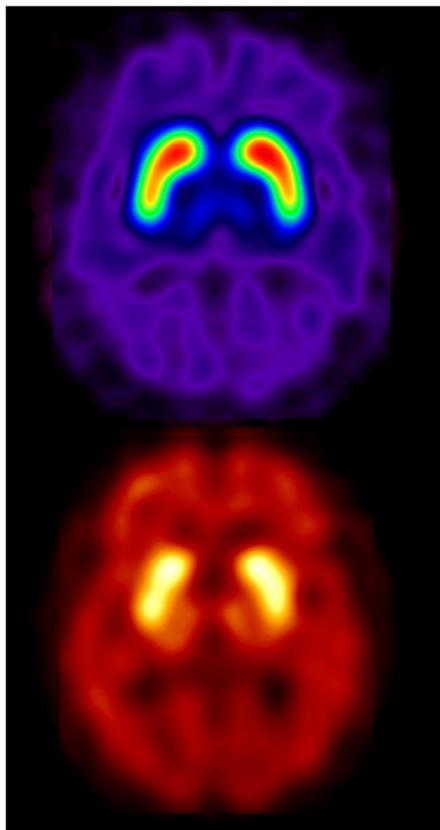
Correlational analysis

^{123}I - βCIT

^{123}I -IBZM

	RLS severity	<i>P</i> Value	RLS severity	<i>P</i> Value
Caudate	-0.366	0.268	0.386	0.241
Ant. putamen	-0.304	0.364	0.431	0.186
Post. putamen	-0.354	0.285	0.229	0.499
Striatum	-0.346	0.297	0.362	0.273

Partial correlation, control variables – age and GDS



Normal

PD

MSA

RLS

Conclusion

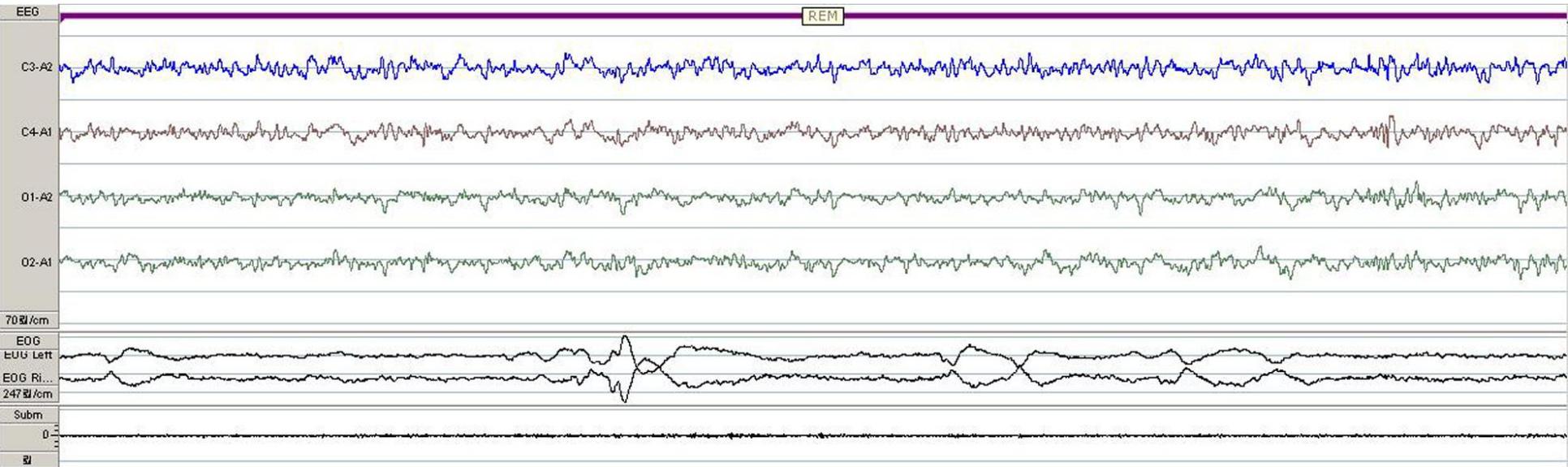
- Nigrostriatal dopamine system in RLS
: Presynaptic transporter ↑, postsynaptic receptor ↔
- 1) A novel finding
 - 2) Suggesting functional change of DA system in RLS
in comparison to structural change of DA system in PD
 - 3) Differences between PD and RLS
 - i) No progression of RLS to PD
 - ii) Fluctuating clinical course
 - iii) Circadian variation of symptoms
 - iv) RLS - More prevalent in female

REM sleep behavior disorder (RBD)

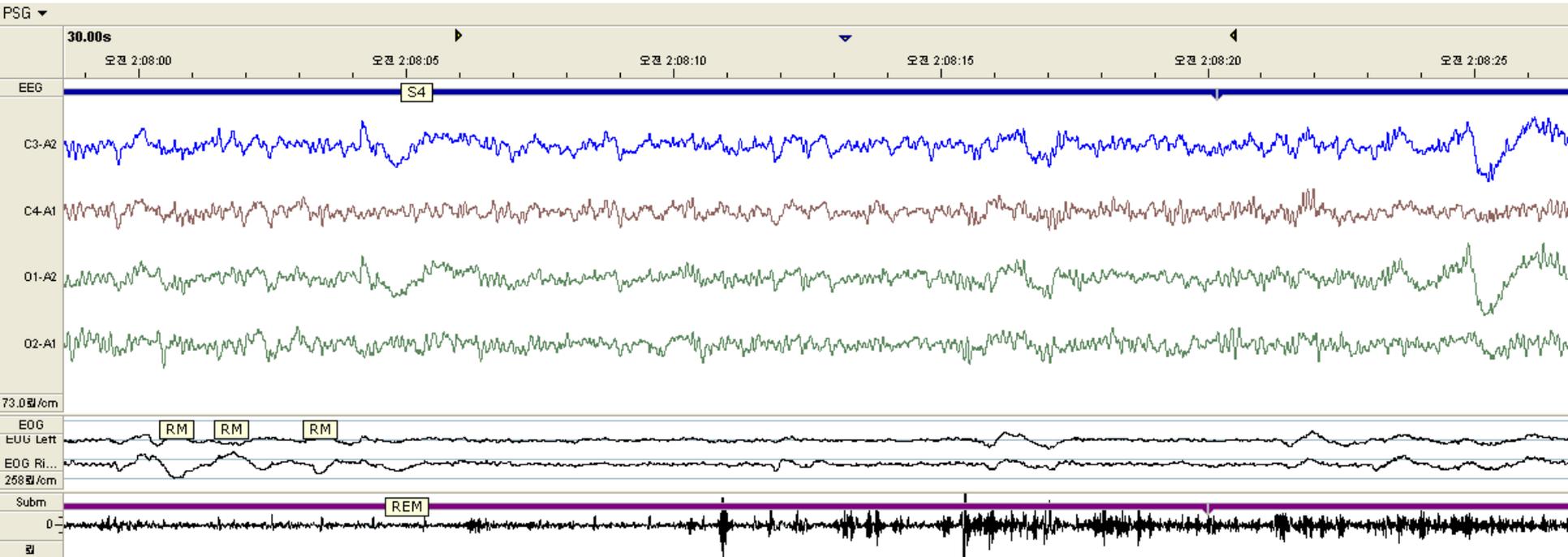
Diagnostic Criteria

- REM Sleep Behavior Disorder (ICSD-2, 2005)
 - A) Presence of REM sleep without atonia (**RSWA**)
 - : the EMG finding of excessive amounts of sustained or intermittent elevation of submental EMG tone
 - : excessive phasic submental or limb EMG twitching
 - B) At least one of the following
 - i) Sleep related injurious or disruptive behaviors by history
 - ii) Abnormal REM sleep behaviors during NPSG
 - C) No EEG epileptiform activity during REM sleep
 - D) No other causes

Normal REM sleep

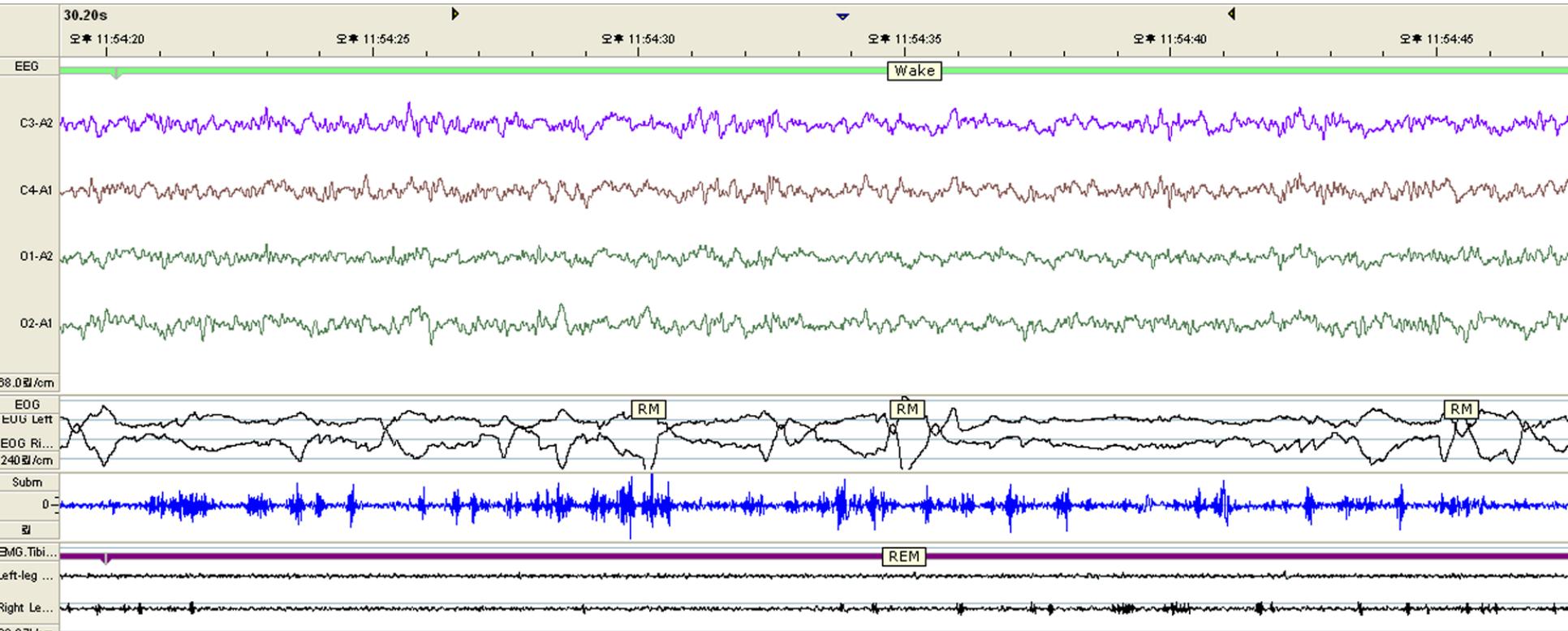


PSG (I)



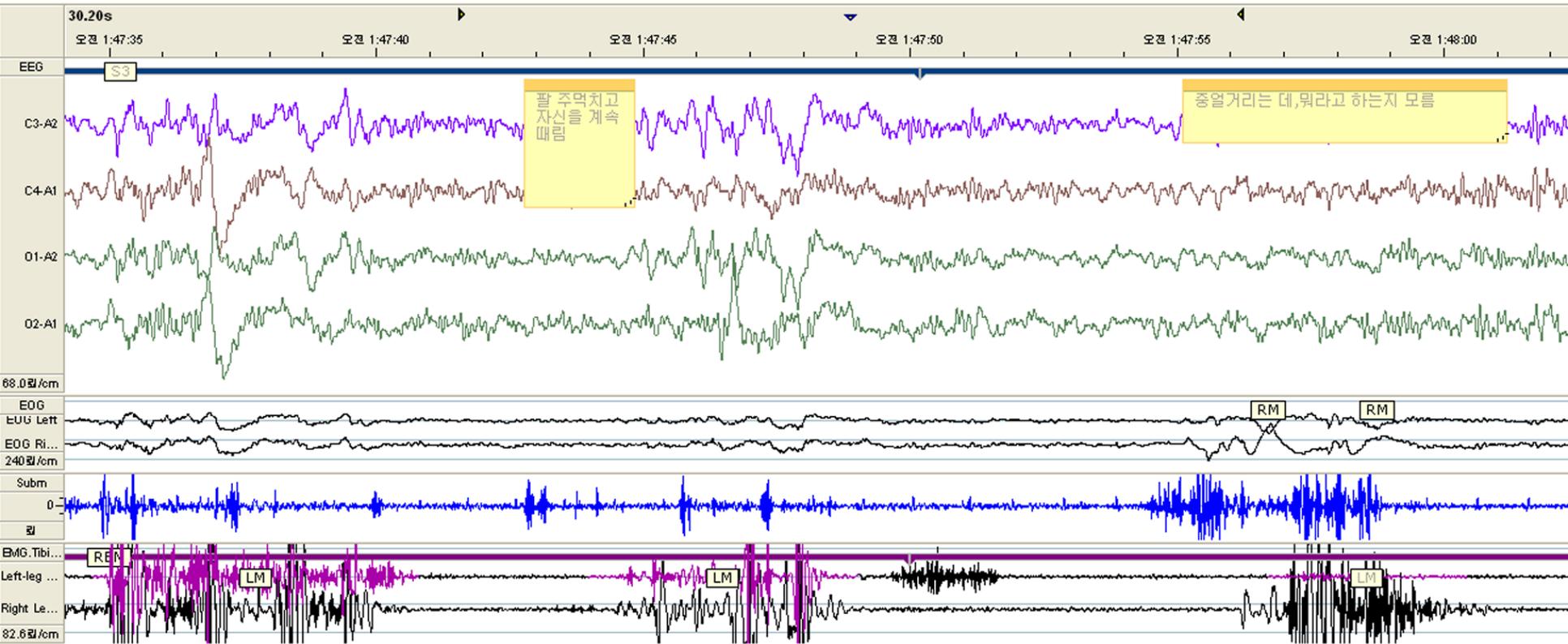
Excessive augmentation of chin EMG tone

PSG (II)



Excessive chin EMG twitching

PSG (III)



1. Excessive limb EMG twitching
2. Vigorous and violent behavior

The implication of nigrostriatal dopaminergic degeneration in the pathogenesis of REM sleep behavior disorder

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Keywords:

dopamine transporter, FP-CIT SPECT, REM sleep behavior disorder

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Background and purpose: The pathogenesis of rapid eye movement (REM) sleep behavior disorder (RBD) is not clear despite its frequent association with Parkinson's disease (PD). We investigated whether the nigrostriatal dopaminergic system is involved in the development of idiopathic RBD.

Methods: Fourteen patients with RBD, 14 patients with PD and 12 normal controls were included in the study. The diagnosis of RBD was confirmed on polysomnography. All the participants performed single-photon emission computed tomography imaging 3 h after injection of [¹²³I]FP-CIT. During REM sleep of the RBD patients, each 30-s epoch was rated as 'tonic' when there was at least 50% of tonically maintained chin electromyography (EMG) activity in the epoch. Phasic EMG activities were calculated as the percentage of 3-s mini-epoch containing phasic EMG events (leg and chin, separately).

Results: The RBD patients showed a trend of lower binding in the striatum than the normal controls ($P = 0.07$), and the significance was revealed in the putamen ($P = 0.02$). However, in 11 individual cases of the 14 RBD patients, the dopamine transporter (DAT) densities in the putamen still remained within the normal range. In the RBD patients, there was no correlation between EMG activities and DAT densities.

Conclusions: Nigrostriatal dopaminergic degeneration could be a part of the pathogenesis of RBD, but not essential for the development of RBD. The lack of correlation between RBD severity and DAT densities suggests that another pathogenic process not related to nigrostriatal dopaminergic transmission may be implicated in RBD.

Introduction (1)

- High association between RBD and synucleinopathy neurodegenerative disease
 - 1) Presence of RBD
 - : 33-60% of Parkinson's disease (PD)
 - 50-80% of dementia with Lewy bodies (DLB)
 - 80-95% of multiple system atrophy (MSA)
 - 2) Development of degenerative disorders among RBD patients
 - : Nearly 40% of RBD → PD
 - : 45-50% of RBD → PD and DLB
- The involvement of DA system in the pathogenesis of RBD

Introduction (2)

- Findings **against major role** of DA system in RBD
 - 1) **Clonazepam**
 - : Highly effective in the treatment of RBD
 - : Mechanism of action
 - partly through serotonergic activity with no influence on the dopaminergic system (Mahowald and Schenk, 2005)
 - 2) **Pramipexole**
 - : D2-D3 dopamine receptor agonist
 - : Little effect of RBD-related symptoms in PD (Kumru et al, Sleep, 2008)
- Reevaluation of **DA system** in the pathogenesis of RBD

Objectives

- To find whether the nigrostriatal dopaminergic system is involved in the pathogenesis of RBD by measuring presynaptic DA transporter (DAT) density using FP-CIT SPECT
- To investigate the relationship between the PSG RBD scores and dopaminergic integrity in RBD

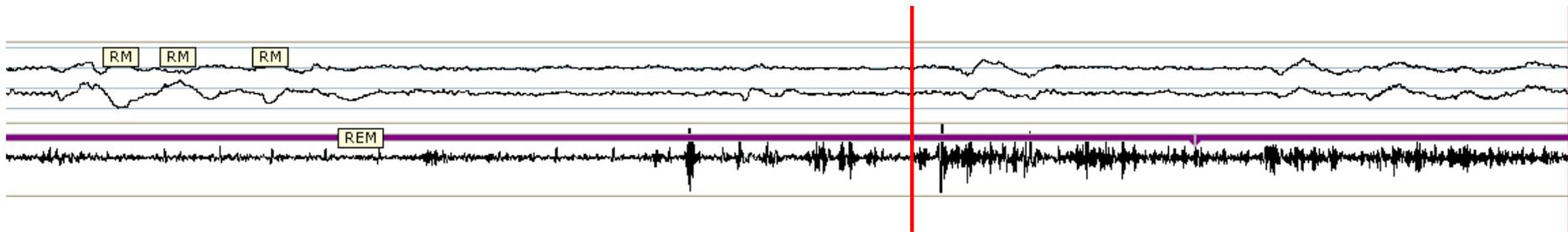
Subjects

- 14 patients with RBD (66.6 ± 4.5 yrs, M:F = 11:3)
14 patients with Parkinson's disease
(67.0 ± 4.1 yrs, M:F = 11:3)
12 healthy elderly control (63.3 ± 5.7 yrs, M:F = 8:4)
- RBD patients – NPSG
All the patients - [^{123}I]-FP-CIT SPECT

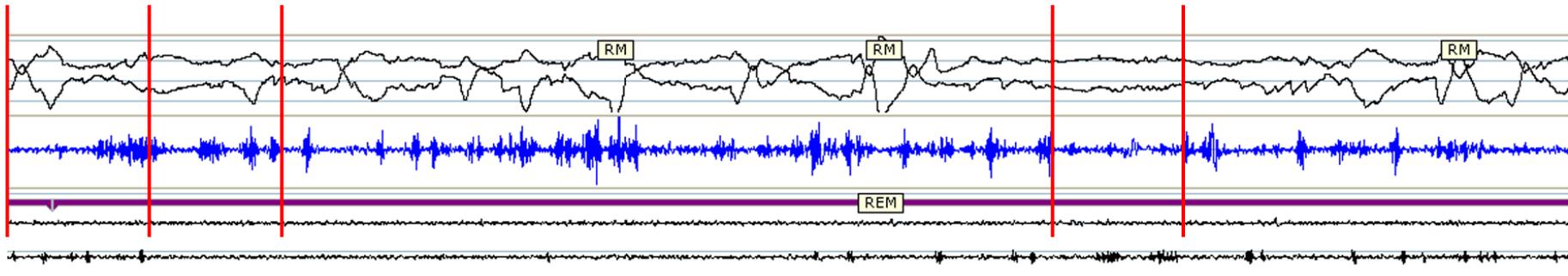
Polysomnography

- Analysis of muscle activity during REM (Lapierre et al., Neurology, 1992)

'Tonic' epoch: at least 50% of tonically maintained chin EMG



Phasic %: % of 3 sec mini-epochs with EMG bursts (chin and leg)



Results (1)

Table 2 [^{123}I]FP-CIT uptake of the patients with rapid eye movement sleep behavior disorder (RBD), Parkinson's disease (PD) and healthy controls

	Controls ($n = 12$)	RBD ($n = 14$)	PD ($n = 14$)	<i>F</i> -value	Significance (<i>P</i> -value) ^a
Caudate	4.38 ± 0.93	3.73 ± 1.16	2.67 ± 0.77	10.49	0.22, 0.016**, 0.001***
Putamen	3.61 ± 0.64	2.82 ± 0.92	1.63 ± 0.51	25.39	0.02*, < 0.001**, < 0.001***
Entire striatum	3.97 ± 0.76	3.24 ± 1.02	2.11 ± 0.61	17.24	0.073, 0.002**, < 0.001***
C/P ratio	1.20 ± 0.09	1.33 ± 0.15	1.65 ± 0.22	27.44	0.153, < 0.001**, < 0.001***

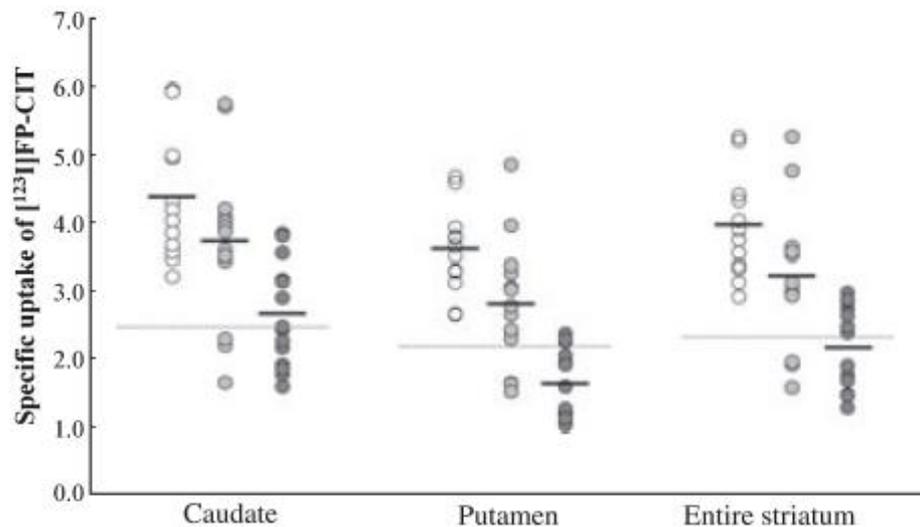
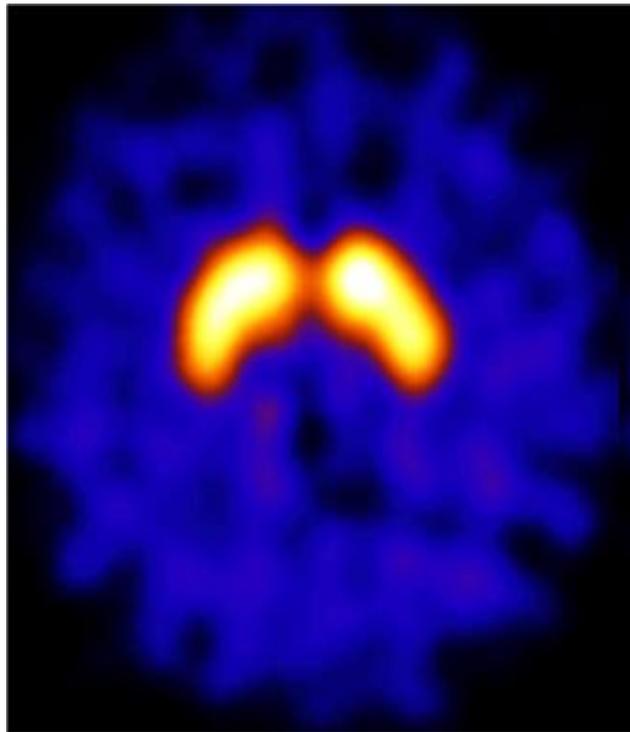
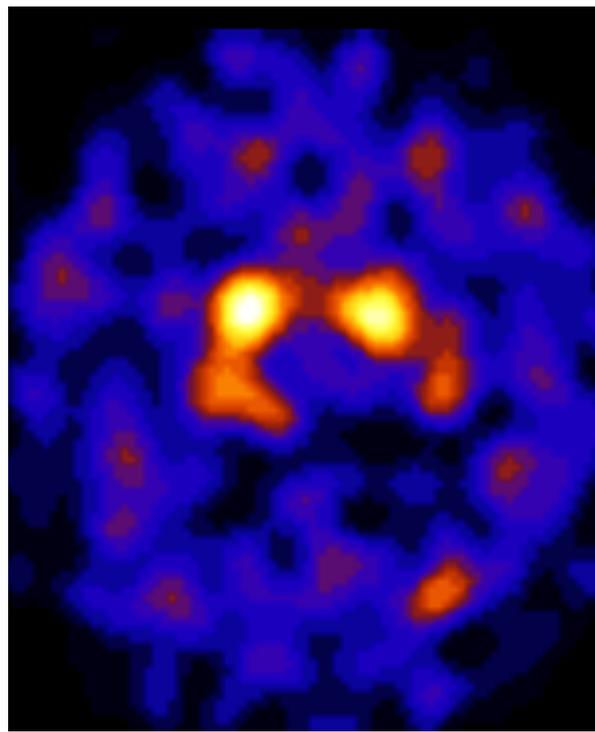


Figure 2 Striatal dopamine transporter density (○ controls, ● RBD, ● PD).

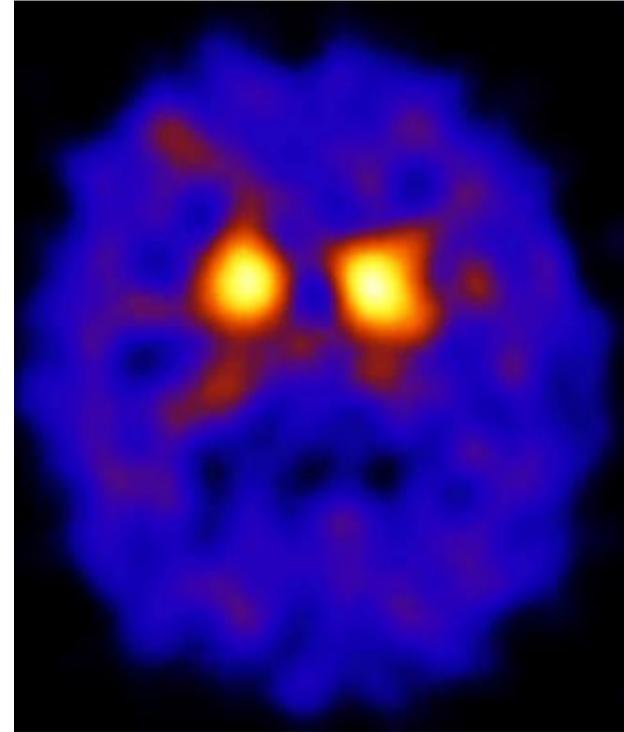
[123I]-FP-CIT SPECT



Healthy Control



RBD



IPD

Results (2)

Table 3 Correlation coefficients between DAT density and polysomnographic EMG activities

	Tonic chin (%)	Phasic chin (%)	Phasic leg (%)
Caudate	0.102	0.167	-0.300
Putamen	-0.030	0.189	-0.112
Striatum	0.039	0.180	-0.212

Tonic chin (%) denotes percent of 30-s epoch of rapid eye movement sleep having at least 50% tonically maintained chin EMG activity in the epoch; phasic chin (%) and leg (%) were calculated as the percentage of 3-s mini-epoch containing phasic EMG events in the leg and chin, respectively; DAT, dopamine transporter; EMG, electromyography; $P < 0.05$.

Conclusion

- DAT ↓ in the putamen of RBD patients, However
 - 1) Most RBD patients; slightly reduced DAT densities, spanning the low normal ranges
 - 2) No rostrocaudal gradient in reduction of DAT density in RBD patients
 - No correlation between DAT density and PSG EMG
 - 1) PSG EMG activities during REM sleep
; representing the severity of RBD
→ No correlation between DAT density in the striatum and clinical severity of RBD
- Questioning the major role of nigrostriatal dopaminergic pathway in RBD

Conclusions

- **High prevalence of insomnia** in the elderly could be closely related with **medical diseases**, which should be thoroughly evaluated in the elderly patients with insomnia.
- **SAS-related complications** such as increased mortality, CV disease, daytime sleepiness and cognitive impairments might be attenuated with aging.
- **DA system** changes in **RLS** might be **functional** unlike structural DA system changes in PD
- **Nigrostriatal dopaminergic degeneration** could be a part of the pathogenesis of **RBD**, but not essential for the development of RBD