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Effects of differences in the availability of light upon the circadian rhythms of institutionalized elderly

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ABSTRACT

The aim of this study was to compare the availability of diurnal and nocturnal light in two residences for aged persons (R1 and R2, Palma de Mallorca, Illes Balears, Spain). We found that the R1 inmates were exposed to lower amounts of light during waking time and higher amounts during sleeping time. The main traits of the circadian rhythms and the quality of sleep in the inmates of the two residences were found to be positively related to the availability of light during waking time and negatively to the increased light exposure during bed time. In addition, the sleep of R1 inmates suffered higher disturbances as a consequence of the different policy for nocturnal diapers check and change. Altogether, these two factors may explain the differences observed in the two residences regarding the circadian rhythms, health status and quality of life. Two conclusions stem from these results: (1) the circadian rhythms of aged people are particularly sensitive to the contrast between diurnal and nocturnal light and (2) the nursing staff of institutions for aged people must receive specific formation on the best practices for maintaining the circadian health of aged people.

ARTICLE HISTORY

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KEYWORDS

Circadian rhythms; aging; light; sleep quality

1. Introduction

The input of the human circadian system depends on specific retinal ganglion cells that send the photic signal, through the retino-hypothalamic tract, to the central pacemaker, the hypothalamic suprachiasmatic nucleus (SCN) (Moore et al., 2002). Then, the output of the SCN drives the secretion of pineal melatonin during the dark period. Melatonin is thus the main effector of the circadian system and the main indicator of the of the whole rhythmic activity organism (Brainard et al., 1983; Honma et al., 1992).

The entrainment of the endogenous clock allows maintaining an appropriate phase between the environmental time and the activity of the suprachiasmatic clock. The capability for entrainment is a fundamental property of circadian systems by which the phase of the internal clock (τ) is synchronized with the phase of the entraining stimuli (T) according to the 24-h light-dark geophysical cycle.

The factors with capacity to entrain the biological clocks are known as Zeitgebers. Daily exposure to environmental light as well as its timing intensity, rate of change, duration and spectrum are the most important traits of the synchronizing properties of light (Binkley, 1981; Czeisler et al., 1989; Duffy, 2005; Pauley, 2004; Wever, 1985). Other periodical cues, such as the environmental temperature, exercise, social contacts, sleep habits and feeding, also contribute to the entrainment of the circadian system (Monk, 2010; Safi and Hodgson, 2014).

The output of the circadian clock also depends on other internal and environmental factors that can cause immediate, short-term effects on the rhythmic physiological functions and are called masking factors. They can be de-masked in constant routine experiments (Minors & Waterhouse, 1984). For instance, in natural environments, the amplitude of the circadian body temperature rhythm may show transitory alterations because of body position, actual light exposure, environmental temperature and sleep (Martinez-Nicolas, 2013).

While a single, short exposure to a Zeitgeber causes effects that persist for many cycles,

reductions in the total amount of light blunt the amplitude of the circadian rhythm (Mishima et al., 2001). This in turn may cause a number of physiological and psychological conditions, standing out among them the metabolic syndrome (Maury et al., 2010) with its associated constellation of physiological disturbances, and the increased frequency of certain types of cancer (Stevens et al., 2007). With respect to the psychological consequences of the disturbances in the circadian rhythms, negative mood (Wirz-Justice et al., 2009a), depressive symptoms (Canellas, 2015) and the seasonal affective disorder (Lam & Levitan, 2000; Magnusson & Boivin, 2003) are perhaps the most significant.

Despite its importance, the availability of environmental light may be, on occasions, less than optimal. This is particularly important during winter at high latitudes, but they can also be of significance in institutionalized elder in temperate regions living in closed spaces, with low light availability, a problem which should be added to the consequences of normal aging (Ancoli-Israel et al., 1989; Campbell et al., 1988). Indeed, an adequate exposure to light is essential for institutionalized elder people to prevent mental degenconditions, and to avoid memory deterioration, impaired cognitive capacity, anxiety and negative mood (Campbell et al., 1988; Hood et al., 2004; Shochat et al., 2000).

Taking into account these facts, the present report aims to obtain evidence of the importance of light on the main indicators of the rhythmic activity in two samples of aged subjects living in different institutions with different availability of natural light.

2. Material and methods

2.1. Institutions

The participants were institutionalized in two different residences located in the island of Mallorca (latitude: ~40°N). The study was performed during two consecutive weeks, between April and May (spring) with a mean of 60% of sunny days, 14°C (night) and 21°C (day) and ~13.2 h of daylight. The institutions were built in 1982 (R1) and 2007 important differences (R2)and show

architectural design. In summary, R2 has wider window openings and a higher open court surface. This resulted in higher sunlight availability, both in common areas and in bedrooms.

The general and sanitary policies of the two residences were similar during waking time, both with well trained and experienced caregivers and under similar medical attendance. R1 is run by a nonprofit and public organization Majorcan Institute of Social Affairs) dependent on the local Government. On the contrary, R2 belongs to a private organization (SARquavitae). Most sleeping rooms in R2 are for single or double occupancy whereas in R1, most subjects share their room with two to three inmates.

Important differences have been found in light exposure during night time. In R1, the rooms were continuously exposed to the light of the nearby aisles that remain on during the entire night. The diapers of most residents are changed at least once every night in both residences. However, this task was regularly performed with full lights on in R1, whereas in R2, the change of diapers was always performed under dim illumination.

2.2. Subjects

A total of 30 institutionalized subjects of both sexes, with a mean age 78.5 ± 5.6 years, were selected for the study. The inclusion criteria were mild cognitive impairment (Minimental test rate ≤26), absence of mobility reductions and absence of pathologies that could modify their circadian rhythms. During the tests, all participants continued taking their usual treatment. Their demographic and sanitary traits are summarized in Table 1.

All participants and caregivers received complete information about the purpose and characteristics of the study and signed an informed consent form before being included. All procedures were performed under permission of the Ethical Committee for Research of the Balearic Islands Government (IB/1409/10 PI).

2.3. Methods

2.3.1. Environmental light-exposure recording

The accumulated amount of light impinging in the diverse rooms of each institution was recorded using

Table 1. Demographic data and sanitary state of the subjects.

R1			R2						
Subjects	Age	Gender	MMSE	Diagnose	Subjects	Age	Gender	MMSE	Diagnose
1	77	F	25	HAP	1	86	F	26	HAP
2	70	F	25	MCD	2	86	F	17	MAD, HAP, DID, DLP, OP, AX
3	79	F	24	MCD	3	82	F	20	ARH
4	80	F	25	HAP, AX	4	80	F	25	CP, OP
5	73	M	25	MAD	5	80	F	24	IX, HTY
6	81	F	23	CP	6	97	F	18	HAP, OA, MAD
7	83	F	24	MCD	7	83	F	20	MAD
8	84	F	23	MCD	8	72	M	22	CCP
9	74	F	25	MCD	9	73	F	25	DID, HAP, CP, DLP, OP
10	72	F	25	MAD	10	84	F	25	HAP, DLP, OP, MCD
11	87	F	25	MAD	11	91	F	21	CCI, DLP, AR
12	82	F	19	MAD	12	81	F	25	MCD
13	76	M	19	MAD	13	81	F	25	MCD
14	81	F	18	MAD	14	79	F	25	MCD
					15	78	F	24	MCD
					16	83	M	24	MCD

MMSE: Minimental rate; HAP: high arterial pressure; MCD: mild cognitive disorder; AX: anxiety; MAD: mild Alzheimer disease; DID: insulin-dependent diabetes; DLP: dislipemia; OP: osteoporosis; CA: cardiac arrhythmia; ICP: ischemic cardiopathy; AR: arthrosis; IC: ictus; HTY: hypothyroidism; ACA: acute cerebrovascular accident cardiovascular; CP: chronic pain; OA: osteoarthrosis.

HOBO pendants, (Light Data Loggers UA-002-64, Onset Computer, Bourne, MA, USA). The sensor was placed hanging in the centre of the sleeping rooms and also in common closed and open spaces at an altitude of ~200 cm from the floor. According to the manufacturer's specifications, the data loggers have a measurement range comprised between 0 and 320,000 lx, (Martinez-Nicolas et al., 2011). For the study, the sensors were programmed to sample the illumination every 10 min during 14 days.

In addition, the amount of light received by each participant was also recorded for the same 14 days with the sensors described for measuring the light in the rooms but placed as neck pendants over the subject's clothes during waking time and on the bedside table during sleep. After ending the experiments, the information stored in the sensors was downloaded to the computer for off-line analysis.

2.3.2. Wrist skin-temperature measurement

The wrist temperature (WT) rhythm was continuously assessed during the same period using temperature sensors (Thermochron iButton DS1921H, Dallas, Maxim) with a sensitivity of 0.1°C and programmed to sample the temperature every 10 min. They were attached to a cotton sport wristband, with the sensor surface placed over the inside of the wrist over the radial artery of the nondominant arm (Sarabia et al., 2008). At the end of the recording period, the information stored in the temperature sensors was downloaded to the computer for off-line analysis. The use of WT as a proxy of the inverse of core temperature constitutes a good, reliable and minimally invasive method for evaluating the circadian rhythm of body temperature (Ortiz-Tudela et al., 2010; Sarabia et al., 2008).

2.3.3. Sleep quality tests

The quality of the sleep of the inmates was assessed by responding to the Oviedo questionnaire (García et al., 2000) that has been validated to quantify sleep satisfaction as well as nocturnal insomnia and diurnal hypersomnia levels. The questionnaire (in Spanish) has been included as supplementary data.

2.3.4. Activity recording

The movement of the subjects was continuously assessed during the experimental period using actimeters (Hobo Pendant G Acceleration Data Logger, MA, USA) placed on the nondominant arm by means of a sports band, with its X-axis parallel to the humeral bone length (Ortiz-Tudela et al., 2010). The actimeter consisted in a three-channel acceleration logger with 8-bit resolution that can record up to 21,800 combined X, Y and Z axis accelerations. The sensor was programmed to record data every 60

s. As in the case of light and temperature, the information stored in the actimeter was downloaded after the end of the experiments for further analysis.

All participants were encouraged to maintain their normal lifestyle. They were allowed to move freely through the different spaces of the institution with the possibility of staying in the open air. The participants and/or caregivers were instructed to complete a sleep agenda with information on sleep onset and offset time as well as the time and duration of eventual naps. However, the reliability of the sleep agenda was rather low and has not been included in the results of the present report.

2.3.5. Data analysis

The information stored in actimeters and light sensors was transferred through an optical USB Base Station system using the software, HOBO-Ware 2.2, provided by the manufacturer. The information stored in the activity sensor was downloaded using the software Viewer 3.22 (Ortiz-Tudela et al., 2010).

In order to eliminate artefacts, for instance, those due to temporary removal for daily hygiene, all data were filtered to remove periods of zero activity counts. Also, the data showing more than 3 standard deviations (±3 SD covers 99.7% of normally distributed data) were deleted (Ortiz-Tudela et al., 2010). As some subjects returned home at weekends, their daily routine was lost. In these cases, their weekend data were also eliminated. The whole procedure for rejecting artefacts was validated in 2008 and again in 2010 (Ortiz-Tudela et al., 2010; Sarabia et al., 2008). To normalize the activity data, the original 60 s data were accumulated every 10 min and the resulting activity was assigned to the time interval of light and temperature data.

Regarding the conversion of the data for later analysis, the light intensities were expressed in Lux (lx). The motor activity was expressed as degrees of position change per minute by dividing original values by 10. The WT was expressed in degrees Celsius.

To facilitate the comparison of the circadian data, two periods were considered according to the wake and sleep routine which was the same in the two residences. The wake time was from 7:00 to 20:50 h and the bedtime from 21:00 to 6:50 h.

WT and motor activity rhythms were analysed, first using the parametric cosinor and

Rayleigh tests. For the graphical representation of the cosinor, we used the program "Ritmes"" (Diaz-Noguera, Universitat de Barcelona, Spain). The test provides an r vector with its origin at the centre of the 24-h circumference. The cosinor adjustment fits the data to the best 24-h sinusoidal regression line and provides the mesor, the acrophase, the amplitude and the significance of the rhythm. The mesor is the average value around which the variable oscillates. The acrophase is the time of day when the highest point of the fitted-cosine curve occurs. The amplitude is the difference between the mesor and the peak of the waveform function fitted to the data (Diez-Noguera, 2006; Haffen, 2009). These parameters were individually calculated for motor activity and WT and for every subject and then were averaged for each group. In addition, we used the Circadianware integrated software package for temporal series analysis (J.A. Madrid, Universidad de Murcia, Spain). The Rayleigh coefficient (r) was calculated after fitting the data to a cosine function with a period of 24 h using least-squares data. The r vector length (between 0 and 1) is proportional to the degree of phase homogeneity during the period analysed and can be considered to be a measure of the rhythm's phase stability during successive days (Baschelet, 1981).

Both Cosinor and Rayleigh tests assume that the rhythm is sinusoidal. However, many circadian rhythms in humans, for instance, WT, are not sinusoidal. In consequence, nonparametric analyses were also performed. This allowed the calculation of three additional variables defined as follows (Carvalho-Bos et al., 2007; Van Someren et al., 1997, 1999):

IS (inter-day stability) which quantifies the regularity or the consistency of the rhythmic pattern and varies between 0 for Gaussian noise and 1 for a perfect stability.

IV (intraday variability) which quantifies the fragmentation of the rhythm and varies between 0 when the wave is sinusoidal and 2 for Gaussian noise.

RA, or relative amplitude, is calculated as the average difference between the M5 (5 consecutive hours of maximum values) and the L10, (10 consecutive hours of minimum values), divided by the sum of M5 and L10 for WT, as well as the difference

between the M10 (10 h of maximum values) and the L5 (5 h of minimum values) divided by the sum of M10 and L5 for motor activity.

CFI, or Circadian Function Index, was calculated from the average of the three variables, IS, IV and RA, and oscillates between 0 (absence of circadian rhythmicity) and 1 (a robust circadian rhythm) (Ortiz-Tudela et al., 2010).

These parameters were individually obtained from each subject and were calculated for motor activity and WT. Then, they were averaged for each residence.

To compare the levels of light, activity and WT between residences and between light and dark time, we used the Student T test after assessing for normality with the Kolmogorov–Smirnov test. We rejected the null hypothesis when p<0.05%.

3. Results

Figure 1 shows the averaged intensity of light exposure in the main common spaces (therapy room, dining room, cafeteria etc.) from 07:00 to 20:50 (marked as wake time in the graph), whereas the light recorded during bed time (from 21:00 to 06:50) corresponds only to the sleeping rooms. The inset table shows the averaged intensity of

light as recorded during total wake and sleep time corresponding to the normal time schedule of the two residences.

The amount of light intensity recorded in R2 during wake time was much higher in the middle of the morning, with light intensities almost reaching the 2500 lx at noon. In contrast, the light in the R1 never exceeded 1400 lx and the difference between both residences was significant (p < 0.02). On the other hand, the light levels showed almost no changes from 18:00 to 00:30 (approx.) in R1 and total darkness was never reached during the whole night, with values oscillating around 200 lx. In contrast, the light levels were constant, with minimal values (\sim 20 lx) in R2 during bed time, a highly significant difference when compared with R1 (p < 0.000).

Figure 2 shows the averaged light intensity recorded by light sensors placed as neck pendants in every subject, during wake time, from 07:00 to 20:50, and from 21:00 to 06:50 (bed time). In correspondence with the amount of light recorded in the common rooms and dormitories, the amount of light perceived during waking time was lower in R1, but the difference was inverted during bedtime, with highly significant differences in both cases.

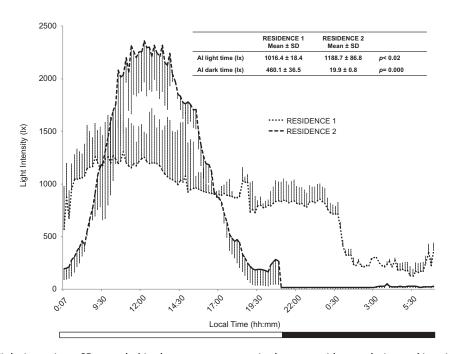


Figure 1. Averaged light intensity \pm SD recorded in the common spaces in the two residences during waking time (white bar) and in sleeping rooms during bed time (black bar). The peak corresponding to R1 is much lower during wake time and, in addition, the lights were put off at 01:00, when the inmates were supposedly sleeping under dark since 21:00. *Al: Average intensity*.

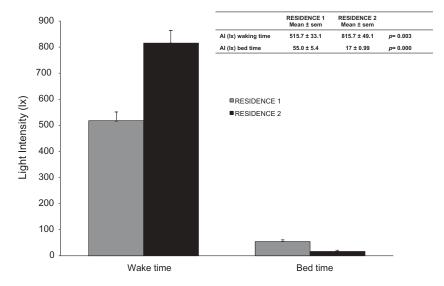


Figure 2. Averaged intensity of light \pm SEM as recorded by light pendants placed in the neck of the subjects. The total light intensity received during waking time was significantly higher (p = 0.003) in R2 subjects during waking time, while the difference was inverted during sleeping time (p = 0.000). Al: Average intensity.

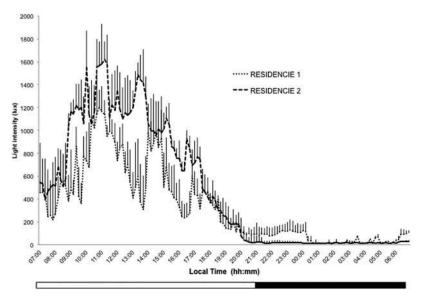


Figure 3. Averaged light intensity ± SD perceived by subjects in the two residences along the 24 h. The dotted segments placed under the graphs show significant differences (p < 0.05). Al: Average intensity.

Figure 3 shows the average \pm SD of light received during the whole/24 h cycle. For the sake of clarity, this figure has been subdivided in Figures 4 and 5 showing the light perceived during morning (Figure 4) and evening (Figure 5).

Figure 4 shows the average \pm SD *amounts of* light intensity received by subjects during morning (from 07:00 to 15:00). The occasional up and down peaks appearing on both groups correspond to room changes for common activities as performed in each residence. The figure shows that the light perceived by subjects from 9:00 to 14:00 h is consistently higher in R2 (p < 0.000). However, the difference vanished between 14:00 and 15:00, the lunchtime, when the subjects of the two residences stayed in dining rooms under similar artificial illumination.

Figure 5 shows the exposure to light during bedtime for the two groups. The R1 inmates received higher amounts of light in the first half of the night. In addition, sudden peaks of light

					RESIDENCE 1 Mean ± DS	RESIDENCE 2 Mean ± SD	
				Al (lx)	578.7 ± 40.8	1070.7 ± 50.1	p=0.000
1800							
	······ RESII	DENCIE 1					
1600	RESII	DENCIE 2					
1400 -			$\Lambda \Pi$		4	M	
1200 -		آ أربر	$\gamma / \gamma / \gamma$	WW	1/1/		
1000		1	1	1		1	
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800 -	1 A	$A \cup A$	M		* W		
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200 -		34 - ES					
		-					
100	150	o 00	10:20	.50	6 6	,s	.30

Figure 4. Averaged light intensity \pm SD perceived by subjects in the two residences during the first half of the wake time, from 07:00 to 15:00. The dotted segments placed under the graphs show significant differences (p < 0.05). Al: Average intensity.

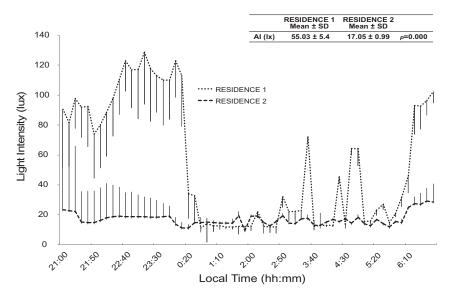


Figure 5. Averaged light intensity ± SD perceived by subjects in the two residences from 21:00 to 06:50. The R1 subjects were exposed to significant amounts of light until 00:30, when the lights were effectively turned off. Nevertheless, the lights were occasionally put on between 03:00 and wake time. On the contrary, the light was permanently off during the entire sleeping time in R2. Al: Average intensity.

intensity were often recorded and the lights-on period always began 1 h earlier (06:00) in R1, when compared with R2 (07:00) in which the light levels during bed time never surpassed 30 lx.

Highly significant differences (p < 0.004 during wake time and p < 0.000 during bed time) in motor activity were found between the two

residences (Figure 6). During the day, R2 subjects were more active than R1. However, the pattern was the opposite during bedtime, with decreased rest in R1 inmates (see inset).

Figure 7 represents the 24-h cosinor diagrams corresponding to the WT of subjects of both residences. The subjects staying in R1

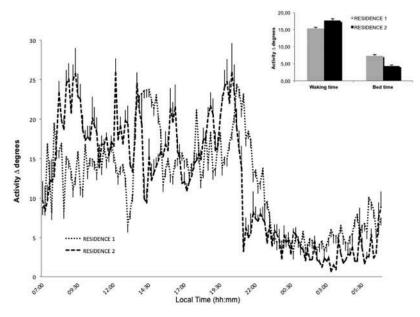


Figure 6. Averaged \pm SD plot of the activity across 24 h cycle as recorded by arm activity-meters placed in every subject in the two residences. Activity showed significant daylight differences with higher the total activity in R2 (p = 0.004) during wake time and lower during bed time (p = 0.000). The inset shows the activity as degrees of movements/min \pm SEM. AA: Average activity

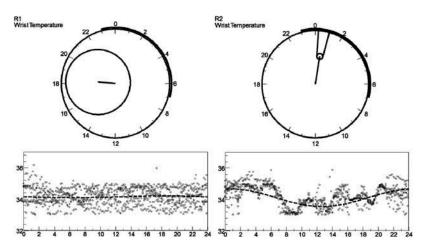


Figure 7. Polar representation of the 24 h oscillations in WT in the two residences. The WT of R1 inmates showed random oscillations with no significant circadian rhythm (p < 0.43). On the contrary, the R2 subjects showed a robust circadian rhythm (p < 0.43). 0.000) that, during light time, was superimposed to a 4–5-h oscillations related to the meals: breakfast (09:00), main meal (14:00) and dinner (20:00).

show no significant circadian pattern (p < 0.43, ns, 0.17% explained variance) with no significant wake-bed time difference (two-tailed T test, p < 0.074, ns; means: wake, 34.29; bed, 34.39). On the other hand, the WT of subjects staying in R2 showed significant 24 h cyclic oscillations (p < 0.000, 32.4% explained variance) with lower WT during wake time (twotailed T test, p < 0.001, means: wake, 33.88; bed 34.71). In addition, R2 subjects showed evident

dips during wake in correspondence with the time of the main meals.

Table 2 shows the results obtained from the Oviedo test, for assessing hypersomnia, insomnia and sleep quality. Taking into account that the questionnaire rates the hypersomnia and the sleep satisfaction between 1 (minimal) and 9 (maximal) and the nocturnal insomnia between 1 and 45, the final figures recorded in both residences were rather discrete, far from optimal levels.

Table 2. Results of the Oviedo sleep questionnaire.

	Diurnal hypersomnia	Sleep satisfaction	Nocturnal insomnia
Residence 1	7.3 ± 0.54	3.9 ± 0.46	28.53 ± 1.46
Residence 2	5.02 ± 0.53	4.4 ± 0.45	23.45 ± 1.94
p Value	<i>p</i> < 0.04	Nonsignificant	<i>p</i> < 0.02
Mean population	Non-available	4.44 ± 1.49	27.74 ± 5.7

All indexes have been expressed as mean \pm SEM.

Table 3. General results of the analysis of circadian rhythms in the two residences.

Temperature	Mesor	Amplitude	Acrophase	Rayleigh	IS	IV	RA	CFI
Residence 1	na	na	na	0.79 ± 0.04	0.51 ± 0.04	0.17 ± 0.04	0.027 ± 0.005	0.52 ± 0.04
Residence2	34.22 ± 1.65	1.77 ± 0.17	$1:22 \pm 0:21$	0.97 ± 0.02	0.56 ± 0.04	0.13 ± 0.01	0.060 ± 0.006	0.52 ± 0.01
<i>p Value R1–R2</i> Activity	ns	ns	na	0.001	0.05	0.001	0.001	ns
Residence 1	14.57 ± 0.76	6.56 ± 0.8	13:45 ± ± 0:24	0.74 ± 0.06	0.32 ± 0.02	0.94 ± 0.05	0.61 ± 0.05	0.48 ± 0.04
Residence2	14.76 ± 1.36	6.79 ± 0.7	$14:38 \pm 0.40$	0.79 ± 0.05	0.46 ± 0.02	0.79 ± 0.09	0.75 ± 0.07	0.54 ± 0.01
p Value	NS	NS	0.012	0.05	0.03	0.000	0.003	0.03

All indexes have been expressed as mean ± SEM. ns: Nonsignificant; na: non-applicable.

Nevertheless, in spite of showing no difference in sleep satisfaction, the subjects of R2 showed lower diurnal hypersomnia (p < 0.04) and nocturnal insomnia (p < 0.02).

Table 3 shows the general results of the analysis of circadian rhythms in the two residences. Considering that no significant circadian cycle was recorded for WT, analyzing the differences in circadian parameters (Mesor, amplitude, acrophase and CFI) between residences has no sense. By contrast, R2 inmates showed higher amplitude and delayed acrophase in activity. Regarding the nonparametric tests, the IS and the RA were always higher in R2 while the IV was lower. Nevertheless, considering the absence of circadian rhythm in R1, their meaning also lacks interest.

4. Discussion

We studied the effects of light availability on the circadian rhythms in old people staying in two institutions, R1 and R2. The morning daylight recorded in the main dependences and in the personal pendants of the R2 residents was higher, with significant differences. The sign of the differences was reversed during night time, with significant light levels (600-800 lx, Figures 1 and 4) from ~17:00 to ~00:30. Oppositely, the light in R2 was reduced from 21.00 onwards (<20 lx), resulting an even higher total difference between wake and resting time. Summarizing, the R1 residents probably suffered light deficits during daytime and excesses during night time, differences which should be causal for the observed impairments in the circadian regulation (Table 3).

The capacity of the SCN clock to maintain the physiological synchrony is extremely sensitive to deficits in morning light (Minors et al., 1991; Rüger et al., 2013). In addition, the circadian system shows age-related impairments (Hofman & Swaab, 2006; Iguchi et al., 1982; Skene & Swaab, 2003). The period (τ) of the circadian rhythms with the geophysical cycles (T) also depend on external masking factors that add or subtract from the light effects, thereby reinforcing or blunting the clock activity (Martinez-Nicolas et al., 2013; Weinert, & Waterhouse, 2007). Consequently, the significant day-night light differences of R2 aided to maintain their rhythms despite their presumably weak circadian system. Oppositely, the blunted day-night differences in illumination must have counteracted the residual activity of the internal clock of R1 inmates and weakened their circadian rhythms. Table 3 shows the differences in the most important parameters of the rhythm, with lower absolute and RA, lower IS and higher IV in R1 residents. However, these changes have low significance taking into account the absence of rhythms in R1. Nevertheless, we found important score reductions in CFI, amplitude and IS, as well as increases in IV in R2 subjects when compared with previous reports (Carvalho-Bos et al., 2009; Luik et al., 2013). According to Oosterman et al. (2009), these impairments could result from the high morbidity of our subjects (see Table 1).

Aiming at minimally invasive procedures, we only recorded general activity, sleep quality and WT which exhibits an inverse phase with core temperature and represents a noninvasive, robust and easy to register index of the circadian rhythms (Martinez-Nicolas, 2013; Ortiz-Tudela et al., 2010). In this regard, the oscillations in WT of R1 inmates were severely blunted (see Figure 7), with no significant rhythm (p < 0.43). Contrasting, the R2 inmates showed a robust rhythm (p < 0.000).

An unexpected result was the meal-related dips in the WT rhythm of R2 subjects (Figure 7). Similar oscillations have been recorded in healthy subjects after food ingestion, accompanied by doubling the splanchnic blood flow, risings in heart activity, together with falls in peripheral blood flow (Mathias & Bannister, 2013). These responses resulted from sympathetic activity which causes postprandial hypermetabolism and peripheral hyperthermia (Blessing et al., 2012; Mathias & Bannister, 2013; Silver & Balsam, 2010; Székely, 2000). Indeed, postprandial hypotension has been observed in institutionalized elder (Lipsitz et al., 1993; Luciano et al., 2010) and is associated to falls, syncope, coronary events and total mortality (Aronow & Ahn, 1994, 1997; Fisher et al., 2005; Puisieux et al., 2000). Thus, the presence of meal-related WT oscillations in R2 inmates suggests a healthy response of their autonomic system, while their absence in R1 should indicate poor autonomic regulation and increased health risks. Indeed, weakening the Zeitgebers reduces the circadian synchronization (Brum et al., 2015; Minors & Waterhouse, 1984; Wever, 1985) which can lead to the metabolic syndrome (Garaulet et al., 2009; Gomez-Abellan et al., 2008; Staels, 2006), with the consequent increase in pathological risk in old people (Karasek, 2004). Thus, R1 inmates showed a probable autonomic dysregulation that, by itself, is a sign of metabolic syndrome (Licht et al., 2013; Vinik et al., 2011).

We observed an extremely long duration of bedtime both residences (600)min). in Contrasting, the total sleep time in healthy, 60-70 years old people is around 360 min (Kurina et al., 2015; Wilckens et al., 2014). Assuming a sleep efficiency of 77.5% (Dijk et al., 1999), the total bed time for healthy aged persons should average less than ~465 min and recent studies show that increasing bed-time in aged people may decrease sleep drive, cause low sleep

continuity and depth and may be detrimental for cognition (Wilckens et al., 2014). Indeed, this may explain the low sleep quality recorded in both residences. The main sleep disturbances recorded in elder are nocturnal insomnia and excessive diurnal sleepiness, in coincidence with the goal of the Oviedo sleep questionnaire (OSQ). However, the OSQ has been used mostly to evaluate sleep complaints in depressive patients and only a single study applied the QSQ to old people (Martinez-Guerrero et al., 2014). Sadly, this study only reported the sleep satisfaction (mean ± SEM: 4.44 \pm 1.49) and insomnia (mean \pm SEM: 27.74 \pm 5.7). So, the subjects of the present study remain within the normality (see Table 2) in spite of keeping significant differences between residences. So, our report is the first one studying the diurnal hypersomnia in institutionalized aged subjects. It is known that the main traits of sleep in healthy old people are not different from those of normal adults; the increased morbidity in aged people is related to other physical and mental disturbances (Bliwise et al., 1992; Charles III et al., 1991; Vitiello et al., 2002). Indeed, the subjects of the present study suffered many comorbidities (see Table 1) which may have increased the sleep complaints. However, it is noteworthy that the differences between R1 and R2 in nocturnal insomnia and in diurnal sleepiness were statistically significant (p <0.02 and p < 0.037, respectively). Most likely, they should be attributed to the differences in light exposure. Remarkably, the excessive daytime sleepiness is a predictor of cognitive impairment (Jaussent et al., 2012; Ohayon & Vecchierini, 2002), which stress the importance of light in institutionalized old people.

Further, the night-time incontinence-related practices cause important sleep disturbances in institutionalized elderly (Vitiello & Borson, 2001) and, surprisingly, the R1 staff seemed to ignore the importance of dark during sleep time. Undoubtedly, both residences were attended by professionals highly concerned with the wellbeing of the residents. This problem has been widely recognized (Bliwise et al., 2009; Ouslander et al., 1998; Schnelle et al., 1998, 1999) and adding the delayed lights-off time, the occasional peaks of light recorded during the second part of the night and the intrusion of the caregivers must have

further contributed to the impairments in circadian rhythms and sleep continuity of R1 residents (Haimov et al., 1994; Huang et al., 2002).

Some effects on nocturnal activity and sleep quality should have been expected given the differences in room sharing. However, after analyzing the difference between rooms with single and multiple occupancy in R1 (data not shown), we found no significant difference neither in general activity nor in sleep quality. Indeed, the procedures for diapers check-change were simultaneously performed by several caregivers in every room and the time and the light exposure seemed to be constant, irrespective of the room occupancy.

Concluding, the different exposure to light most likely was responsible of the differences in circadian rhythms, sleep quality, circadian disruption, probable autonomic dysfunctions and the eventual metabolic syndrome in R1. On the contrary, the high availability of morning light and the low exposure during dark time allowed maintaining good circadian rhythmicity, better sleep quality and improved autonomic function, for R2 residents, altogether indicative of a better health and quality of life. As an additional interesting conclusion, the WT seems to be useful for the diagnosis of autonomic imbalances and a proxy of the health status of aged people.

The problems of R1 arise from the obsolete architectural design of the building (Bullough et al., 1996, Canellas et al., 2015) and stress the importance of high light exposure in public buildings and, in particular, in those dedicated to health care. A solution to this problem could lie in modifying the luminaries. It has been found that the morning exposure to artificial bright light with high contents of blue wavelength causes significant improvements in affective disorders (Tewary et al., 2016; Wirz-Justice et al., 2009a; Wirz-Justice, 2009b; Wirz-Justice et al., 2013), in alertness during wake (Campbell et al., 1995a), in sleep quality (Campbell et al., 1995b) and in age-related disturbances (Campbell et al., 1995c; Fetveit et al., 2003; Gehrman & Ancoli-Israel, 2016; Van Someren, 2000). Another source of problems lies in the poor nursing practices during nighttime (Ancoli-Israel et al., 1989; Ouslander et al., 1988; Schnelle et al., 1999) and shows the need of developing specific training programs both for residents and caregivers (Midorikawa et al., 2013; Tewary et al., 2016).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

Ancoli-Israel S, Parker L, Sinaee R, Fell RL, Kripke DF. (1989). Sleep fragmentation in patients from a nursing home. J Gerontolog. 44:M18–M21.

Aronow WS, Ahn C. (1994). Postprandial hypotension in 499 elderly persons in a long-term health care facility. J Am Geriatr Soc. 42:930–32.

Aronow WS, Ahn C. (1997). Association of postprandial hypotension with incidence of falls, syncope, coronary events, stroke, and total mortality at 29 month follow up in 499 older nursing home residents. J Am Geriatr Soc. 45:1051–53.

Batschelet E. (1981). Circular statistics in biology. London, U. K.: Academic Press.

Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. (2001). Morning sunlight reduces length of hospitalization in bipolar depression. J Affect Disord. 62:221–23.

Binkley S, Muller G, Hernandez T. (1981). Circadian rhythm in pineal N-acetyltransferase activity: Phase shifting by light pulses (I). J Neurochem. 37:798–800.

Blessing W, Mohammed M, Ootsuka Y. (2012). Heating and eating: Brown adipose tissue thermogenesis precedes food ingestion as part of the ultradian basic rest–activity cycle in rats. Physiol Behav. 105:966–74.

Bliwise DL, Foley DJ, Vitiello MV, Ansari FP, Ancoli-Israel S, Walsh JK. (2009). Nocturia and disturbed sleep in the elderly. Sleep Med. 10:540–48.

Brainard GC, Richardson BA, King TS, Matthews SA, Reiter RJ. (1983). The suppression of pineal melatonin content and N-AcetyItransferase activity by different light irradiances in the Syrian hamster: A dose-response relationship. Endocrinology. 113:293–96.

Brum MCB, Dantas Filho FF, Schnorr CC, Bottega GB, Rodrigues TC. (2015). Shift work and its association with metabolic disorders. Diabetol Metab Syndr. 7:45.

Bullough J, Rea MS, Stevens RG. (1996). Light and magnetic fields in a neonatal intensive care unit. Bioelectromagnetics. 17:396–405.

Campbell SS, Kripke DF, Gillin JC, Hrubovcak JC. (1988). Exposure to light in healthy elderly subjects and Alzheimer's patients. Physiol Behav. 42:141–44.

Campbell SS, Dijk DJ, Boulos Z, Eastman CI, Lewy AJ, Terman M. (1995a). Light treatment for sleep disorders: Consensus report III. Alerting and activating effects. J. Biol. Rhythms. 10:129–32.

Campbell SS, Dijk DJ, Boulos Z, Eastman CI, Lewy AJ, Terman M. (1995b). Light treatment for sleep disorders: Consensus report IV sleep phase and duration. J. Biol. Rhythms. 10:135–47.

Campbell SS, Terman M, Lewy AJ, Dijk DJ, Eastman CI, Boulos Z. (1995c). Light treatment for sleep disorders:

- Consensus report V. Age-related disturbances. J. Biol. Rhythms. 10:151–54.
- Canellas F, Mestre L, Belber M, Frontera G, Rey MA, Rial R. (2015). Increased daylight availability reduces length of hospitalisation in depressive patients. Eur Arch Psychiatry Clin Neurosci. 266:277–80.
- Carvalho-Bos SS, Riemersma-van der Lek RF, Waterhouse J, Reilly T, Van Someren EJ. (2007). Strong association of the rest-activity rhythm with well-being in demented elderly women. Am J Geriatr Psychiatry. 15:92–100.
- Charles III, F. R., Jennings, J. R., Hoch, C. C., Monk, T. H., Berman, S. R., Hall, F. T., Kupfer, D. J. (1991). Daytime sleepiness in the healthy "old old": A comparison with young adults. J Am Geriatr Soc. 39, 957–962.
- Czeisler CA, Kronauer RE, Allan JS, Duffy JF, Jeweit ME, Brown EN, Ronda JM. (1989). Bright light induction of strong (Type 0). Science. 244:1328.
- Díez-Noguera A. (2006). Representación gráfica y análisis de datos en Cronobiología. Cronobiología básica y clínica. Madrid: Editec@ red SL.
- Dijk DJ, Duffy JF, Riel E, Shanahan TL, Czeisler CA. (1999). Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. J Physiol. 516:611–27.
- Duffy JF, Wright KP. (2005). Entrainment of the human circadian system by light. J Biol Rhythms. 20:326–38.
- Fetveit A, Skjerve A, Bjorvatn B. (2003). Bright light treatment improves sleep in institutionalised elderly—an open trial. Int J Geriatr Psychiatry. 18:520–26.
- Fisher AA, Davis MW, Srikusalanukul W, Budge MM. (2005). Postprandial hypotension predicts all-cause mortality in older, low-level care residents. J Am Geriatr Soc. 53:1313–20.
- Garaulet M, Lee YC, Shen J, Parnell LD, Arnett DK, Tsai MY, Ordovas JM. (2009). Clock genetic variation and metabolic syndrome risk: Modulation by monounsaturated fatty acids. Am J Clin Nutr. 90:1466–75.
- García JB, G-Portilla MPG, Martínez PAS, Fernández, MTB, Alvarez CI, Domínguez JMF. (2000). Propiedades psicométricas del cuestionario Oviedo de sueño. Psicothema. 12 107–12.
- Gehrman P, Ancoli-Israel S. (2016). Insomnia in the elderly. Diagnosis and treatment. In Sateia MJ, Buysse D, eds. Insomnia: Diagnosis and treatment. London: crc Press, Chapter 20, 224–233 pp.
- Gomez-Abellan P, Hernandez-Morante JJ, Lujan JA, Madrid JA, Garaulet M. (2008). Clock genes are implicated in the human metabolic syndrome. IntJ Obesity. 32:121–28.
- Haimov I, Laudon M, Zisapel N, Souroujon M, Nof D, Shlitner A, Lavie P. (1994). Sleep disorders and melatonin rhythms in elderly people. Bmj. 309:167.
- Haffen E. (2009). Measuring circadian rhythm. L'Encephale. 35:S63-7.
- Hofman MA, Swaab DF. (2006). Living by the clock: The circadian pacemaker in older people. Ageing Res Rev. 5:33–51.

- Honma K, Honma S, Kohsaka M, Fukuda N. O. R. I. K. O. (1992). Seasonal variation in the human circadian rhythm: Dissociation between sleep and temperature rhythm. Am J Physiol-Regul, Integr Comp Physiol. 262:R885–91.
- Hood B, Bruck D, Kennedy G. (2004). Determinants of sleep quality in the healthy aged: The role of physical, psychological, circadian and naturalistic light variables. Age Ageing. 33:159–165.
- Huang YL, Liu RY, Wang QS, Van Someren EJ, Xu H, Zhou JN. (2002). Age-associated difference in circadian sleep-wake and rest-activity rhythms. Physiol Behav. 76:597–603.
- Iguchi H, Kato KI, Ibayashi H. (1982). Age-dependent reduction in serum melatonin concentrations in healthy human subjects. J. Clin. Endocrinol. Metab. 55:27–9.
- Jaussent I, Bouyer J, Ancelin ML, Berr C, Foubert-Samier A., Ritchie K., ... Bliwise DL, King AC, Harris RB, Haskell WL. Prevalence of self-reported poor sleep in a healthy population aged 50–65. Soc Sci Med. 1992;34:49–55.
- Karasek M. (2004). Melatonin, human aging, and age-related diseases. Exp Gerontol. 39:1723–29.
- Kurina LM, Thisted RA, Chen JH, McClintock MK, Waite LJ, Lauderdale DS. (2015). Actigraphic sleep characteristics among older Americans. Sleep Health. 1:285–92.
- Lam RW, Levitan RD. (2000). Pathophysiology of seasonal affective disorder: A review. J Psychiatr Neurosci. 25:469.
- Licht CM, de Geus EJ, Penninx BW. (2013). Dysregulation of the autonomic nervous system predicts the development of the metabolic syndrome. J Clin Endocrinol Metab. 98:2484–93.
- Luik AI., Zuurbier LA., Hofman A, Van Someren EJ, Tiemeier H. (2013). Stability and fragmentation of the activity rhythm across the sleep-wake cycle: The importance of age, lifestyle, and mental health. Chronobiol Int. 30:1223–30.
- Lipsitz LA, Ryan SM, Parker JA, Freeman R, Wei JY, Goldberger AL. (1993). Hemodynamic and autonomic nervous system responses to mixed meal ingestion in healthy young and old subjects and dysautonomic patients with postprandial hypotension. Circulation. 87:391–400.
- Luciano GL, Brennan MJ, Rothberg MB. (2010). Postprandial hypotension. Am J Med. 123:281–e1.
- Magnusson A, Boivin D. (2003). Seasonal affective disorder: An overview: Review. Chronobiol Int. 20:189–207.
- Martinez-Nicolas A, Ortiz-Tudela E, Madrid JA, Rol MA. (2011). Crosstalk between environmental light and internal time in humans. Chronobiol Int. 28:617–29.
- Martinez-Nicolas A, Ortiz-Tudela E, Rol MA, Madrid JA. (2013). Uncovering different masking factors on wrist skin temperature rhythm in free-living subjects. PloS one. 8:e61142
- Martínez, J. M., Correa, M., & Gutiérrez, J. A. (2014). Satisfacción subjetiva del sueño, insomnio y empleo de ayuda para dormir en la población anciana. NURE Inv [Internet], 11, 73.

- Mathias, C. J., & Bannister, R. (2013). Postcibal hypotension in autonomic disorders. Autonomic failure. A textbook of clinical disorders of the autonomic nervous system, 3rd edn. Oxford, United Kingdom: Oxford University Press.
- Maury E, Ramsey KM, Bass J. (2010). Circadian rhythms and metabolic syndrome from experimental genetics to human disease. Circ Res. 106:447–62.
- Midorikawa T, Komatsu T, Mitani T, Togo F. (2013). Effects of bright light exposure on the behavioral and psychological symptoms of dementia and the burden on caregivers in institutionalized elderly with cognitive decline. Nihon Ronen Igakkai zasshi. Jpn J Geriatr. 51:184–90.
- Minors DS, Waterhouse JM. (1984). The use of constant routines in unmasking the endogenous component of human circadian rhythms. Chronobiol Int. 1,:205–16.
- Minors DS, Waterhouse JM, Wirz-Justice A. (1991). A human phase-response curve to light. Neurosci Lett. 133:36–40.
- Mishima K, Okawa M, Shimizu T, Hishikawa Y. (2001). Diminished melatonin secretion in the elderly caused by insufficient environmental illumination 1. J Clin Endocrinol Metab. 86:129–34.
- Monk TH. (2010). Enhancing circadian zeitgebers. Sleep. 33:421.
- Moore RY, Speh JC, Leak RK. (2002). Suprachiasmatic nucleus organization. Cell Tissue Res. 309:89–98.
- Ohayon MM, Vecchierini MF. (2002). Daytime sleepiness and cognitive impairment in the elderly population. Arch Inter Med. 162:201–8.
- Oosterman JM., van Someren EJ, Vogels RL, Van Harten B, Scherder EJ. (2009). Fragmentation of the rest-activity rhythm correlates with age-related cognitive deficits. J Sleep Res. 18, 129–135.
- Ortiz-Tudela E, Martinez-Nicolas A, Campos M, Rol MA, Madrid JA. (2010). A new integrated variable based on thermometry, actimetry and body position (TAP) to evaluate circadian system status in humans. PLoS Comput Biol. 6:e1000996.
- Ouslander JG, Buxton WG, Al-Samarrai NR, Cruise PA, Alessi C, Schnelle JF. (1998). Nighttime urinary incontinence and sleep disruption among nursing home residents. J Am Geriatr Soc. 46:463–66.
- Pauley SM. (2004). Lighting for the human circadian clock: Recent research indicates that lighting has become a public health issue. Med Hypotheses. 63:588–96.
- Puisieux F, Bulckaen H, Fauchais AL, Drumez S, Salomez-Granier F, Dewailly P. (2000). Ambulatory blood pressure monitoring and postprandial hypotension in elderly persons with falls or syncopes. J Gerontol A Biol Sci Med Sci. 55:M535–40.
- Rüger M, St Hilaire MA, Brainard GC, Khalsa SBS, Kronauer RE, Czeisler CA, Lockley SW. (2013). Human phase response curve to a single 6.5 h pulse of short-wavelength light. J Physiol. 591:353–63.

- Safi AJ, Hodgson NA. (2014). Timing of activities and their effects on circadian rhythm in the elderly with Dementia: A literature review. J Sleep Disord Ther. 3:2167–0277.
- Sarabia JA, Rol MA, Mendiola P, Madrid JA. (2008). Circadian rhythm of wrist temperature in normal-living subjects: A candidate of new index of the circadian system. Physiol Behav. 95:570–80.
- Schnelle JF, Cruise PA, Alessi CA, Al-Samarrai N, Ouslander JG. (1998). Individualizing nighttime incontinence care in nursing home residents. Nurs Res. 47:197–204.
- Schnelle JF, Alessi CA, Al-Samarrai NR, Fricker RD, Ouslander JG. (1999). The nursing home at night: Effects of an intervention on noise, light, and sleep. J Am Geriatr Soc. 47, 430–38.
- Shochat T, Martin J, Marler M, Ancoli-Israel S. (2000). Illumination levels in nursing home patients: Effects on sleep and activity rhythms. J Sleep Res. 9:373–79.
- Silver R, Balsam P. (2010). Oscillators entrained by food and the emergence of anticipatory timing behaviors. Sleep Biol Rhythms. 8:120–36.
- Skene DJ, Swaab DF. (2003). Melatonin rhythmicity: Effect of age and Alzheimer's disease. Exp Gerontol. 38:199–206.
- Staels B. (2006). When the clock stops ticking, metabolic syndrome explodes. Nature. 12:53–5.
- Stevens RG, Blask DE, Brainard GC, Hansen J, Lockley, SW, Provencio I, Reinlib L. (2007). Meeting report: The role of environmental lighting and circadian disruption in cancer and other diseases. Environ Health Perspect. 115: 1357– 1362.
- Székely M. (2000). The vagus nerve in thermoregulation and energy metabolism. Auton Neurosci. 1:26–38.
- Tewary S, Cook N, Pandya N, McCurry SM. (2016). Pilot test of a six-week group delivery caregiver training program to reduce sleep disturbances among older adults with dementia-Innovative Practice. Dementia. 1471301216643191.
- Van Someren EJW, Kessler A, Mirmiran M, Swaab DF. (1997). Indirect bright light improves circadian rest-activity rhythm disturbances in demented patients. Biol Psychiatry. 41:955–963
- Van Someren EJ, Swaab DF, Colenda CC, Cohen W, McCall WV, Rosenquist PB. (1999). Bright light therapy: Improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. Chronobiol Int. 16:505–18.
- Van Someren EJW. (2000). Circadian and sleep disturbances in the elderly. Exp Gerontol. 35:1229–37.
- Vinik AI, Maser RE, Ziegler D. (2011). Autonomic imbalance: Prophet of doom or scope for hope? Diabetic Med. 28:643–51.
- Vitiello MV, Borson S. (2001). Sleep disturbances in patients with Alzheimer's disease. CNS Drugs. 15:777–96.
- Vitiello, M. V., Moe, K. E., & Prinz, P. N. (2002). Sleep complaints cosegregate with illness in older adults: Clinical research informed by and informing epidemiological studies of sleep. J Psychosomatic Res. 53:555–559.

- Weinert D, Waterhouse J. (2007). The circadian rhythm of core temperature: Effects of physical activity and aging. Physiol Behav. 90:246–56.
- Wever RA. (1985). Characteristics of circadian rhythms in human functions. J Neural Trans Supplementum. 21:323– 73.
- Wilckens KA, Woo SG, Kirk AR, Erickson KI, Wheeler ME. (2014). Role of sleep continuity and total sleep time in executive function across the adult lifespan. Psychol Aging. 29:658.
- Wirz-Justice A, Bromundt V, Cajochen C. (2009a). Circadian disruption and psychiatric disorders: The importance of entrainment. Sleep Med Clin. 4:273–84.
- Wirz-Justice A. (2009b). From the basic neuroscience of circadian clock function to light therapy for depression: On the emergence of chronotherapeutics. J Affect Disorders. 116:159–60.
- Wirz-Justice A, Benedetti, F, Terman, M. (2013). Chronotherapeutics for Affective Disorders. Basel (CH), Karger Publishers.