

## Distortions in rest–activity rhythm in aging relate to white matter hyperintensities

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Received 3 October 2006; received in revised form 7 February 2007; accepted 7 February 2007

Available online 21 March 2007

### Abstract

Distortions in the rest–activity rhythm in aging are commonly observed. Neurodegenerative changes of the suprachiasmatic nucleus have been proposed to underlie this disrupted rhythm. However, based on previous studies, it can be proposed that white matter hyperintensities (WMH) may also play a role in the altered rest–activity rhythm in aging. The present study focused on the rest–activity rhythm, as assessed with actigraphy, and WMH in nondemented aging. With regard to the rest–activity rhythm, the interdaily stability (IS), intradaily variability (IV) and the amplitude (AMP) of the rhythm were of interest. The white matter hyperintensities were examined separately for the periventricular (PVH) and deep white matter (DWMH) regions, while distinguishing between the various locations within these regions (e.g. occipital PVH). The results indicated that frontal DWMH related to both IS and AMP. A reduction in the most active 10-h period mediated the relationship between frontal DWMH and AMP. Possible underlying mechanisms of these associations are discussed.

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**Keywords:** Aging; Rest–activity rhythm; White matter; Actigraphy

### 1. Introduction

Changes in the circadian rhythm are a common observation in the aged population and include distortions in the rest–activity rhythm. Changes are expressed as nocturnal activity, increased sleep fragmentation and daytime naps, and a reduction of circadian amplitude (Bliwise et al., 2005; Haimov and Lavie, 1997; Huang et al., 2002). Age-related degenerative changes of the suprachiasmatic nucleus (SCN), a structure commonly acknowledged as the biological clock of the mammalian brain (Pace-Schott and Hobson, 2002), partially account for the altered rest–activity rhythm. The rest–activity rhythm can be considered as an indirect

measure of the sleep–wake pattern (De Souza et al., 2003; Tobler and Borbely, 1993). Evidence suggests that sleep distortions may be related to reductions in the white matter integrity, denoted as white matter hyperintensities (WMH) (Kanda et al., 2003; Meguro et al., 1995). As the white matter forms the cortico-cortical and cortico-subcortical connections, it has been argued that the cortical disconnection caused by WMH mediates this relationship (Kanda et al., 2003; Meguro et al., 1995). Considering the high agreement between sleep and rest–activity rhythm measurements (De Souza et al., 2003; Tobler and Borbely, 1993) it can be suggested that WMH may be involved in the rest–activity rhythm as well.

The importance of WMH in age-related rest–activity rhythm distortions should be acknowledged considering the high prevalence of WMH in normal aging. More specifically, aging poses the major risk factor for WMH (Ylikoski et al., 1995), followed by cardiovascular risk factors such

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as hypertension and diabetes (Lazarus et al., 2005; Liao et al., 1997; Ylikoski et al., 1995). Since the prevalence of these risk factors increases with age as well (Jo et al., 2001; Stolk et al., 1997), aging with cardiovascular risk factors may have devastating effects on white matter integrity. This stresses the importance of assessing possible associations between WMH and the circadian rest–activity rhythm in aging. Despite that previous studies suggest an association between sleep and WMH, a specific differentiation within white matter regions (e.g. frontal periventricular hyperintensities) is lacking. This is important to determine possible processes underlying alterations in the rest–activity rhythm. The focus of the present study is therefore to examine a possible relationship between WMH and the rest–activity rhythm by means of an objective registration method, namely actigraphy. Furthermore, detailed WMH subscores are incorporated in examining a relationship between the rest–activity rhythm and WMH.

## 2. Methods

### 2.1. Study population

Participants were recruited in cooperation with the Sint Lucas Andreas Hospital in Amsterdam, The Netherlands. Medical records from subjects visiting the outpatient clinic (e.g. of cardiology or internal medicine) were screened. Because of the age relation of WMH, the lower limit of inclusion was set at 50 years (Walhovd et al., 2005). The vast majority of the participants (82.7%) scored positive for at least one cardiovascular risk factor, such as hypertension, diabetes mellitus, hypercholesterolemia, smoking, and cardiac disease. A prerequisite for subjects to participate was to be free of neurodegenerative disease (e.g. dementia), stroke, pacemaker implant, psychiatric illness, and alcohol or other substance abuse. The mini mental state examination (MMSE) (Folstein et al., 1975) was used as a screening instrument to exclude possible dementia: a score of 24 and higher was required for participation (Grut et al., 1993). Most common reasons for exclusion included no informed consent, a history of stroke, and pacemaker implant. Use of hypnotic medication (e.g. benzodiazepine) was deduced from both a patient interview and medical records. One hundred and sixty-two subjects participated. Ninety-one participants were under treatment at the department of cardiology, 34 subjects were under treatment at the department of internal medicine, and 26 subjects, with no symptoms suggestive of neurological disorders based on medical history and physical examination, were recruited from the department of neurology. A small number of participants ( $n = 11$ ) were either volunteers or spouses or friends from participants under treatment. Subject characteristics are presented in Table 1. Depressive symptoms were rated with the Symptom Checklist (SCL-90), on which scores can range between 16 (no depressive symptoms) and 80

Table 1  
Subject characteristics ( $N = 162$ )

Variable	Value
Age (mean $\pm$ S.D.)	69.1 (8.6)
Sex (% male)	61.7
MMSE (mean $\pm$ S.D.)	27.9 (1.6)
Depressive symptoms (mean $\pm$ S.D.)	24.6 (9.3)
Use of hypnotic medication ( $n$ )	9
Cardiac disease (%)	65.4
Diabetes mellitus (%)	32.1
Hypercholesterolemia (%)	50.0
Hypertension (%)	38.3
Smoking (%)	18.5

Depressive symptoms were rated with the SCL-90, on which score can range between 16 (no depressive symptoms) and 80 (most severe depressive symptoms). MMSE: mini mental state examination.

(most severe depressive symptoms) (Arrindell and Ettema, 1986).

Approval for this study was obtained from the medical ethics committee. All subjects signed an informed consent.

### 2.2. Rest–activity rhythm

The rest–activity rhythm was assessed using actigraphy (Actiwatch, Cambridge Neurotechnology, Cambridge, UK). Three variables were calculated (Van Someren et al., 1997a). The first variable was interdaily stability (IS), which quantifies the strength of coupling of the rest–activity rhythm with *zeitgebers* (e.g., light). In an intact rest–activity rhythm, there is high resemblance of the daily rhythm between different days, that is high stability of the rhythm over days. Secondly, intradaily variability (IV) was considered, which indicates the fragmentation of the rhythm, i.e. the frequency and extent of transitions between rest and activity within a 24-h period. Low IV is characterized by relative few transitions between activity and rest during day, where much activity can be expected, and night, where inactivity is expected. Finally, the amplitude of the rhythm (AMP) was calculated by subtracting the least active 5-h period (L5) from the most active 10-h period (M10). A rhythm with high amplitude suggests an intact rest–activity rhythm. Such a rhythm is characterized by high levels of activity during daytime and low levels of activity during night-time. A minimum of 5 days of actigraphy recording was required for these variables to be reliably calculated.

### 2.3. Magnetic resonance imaging

A 1.5 T scan was used to obtain brain MRIs (General Electric, Milwaukee, USA). Whole brain axial and coronal fluid attenuated inversion recovery (FLAIR) (repetition time [TR] = 10000 ms, echo-time [TE] = 150 ms, inversion time [TI] = 2200 ms, slice thickness 5 mm, interslice gap 0 mm, 24 slices) and axial T2-weighted images (TR = 6500 ms, TE = 102 ms, echo train 24, slice thickness 5 mm, interslice gap 1 mm, 22 slices) were acquired to allow detailed

visualization of WMH. The white matter hyperintensities were rated according to the Scheltens scale (Scheltens et al., 1993). Two independent raters (PS and AG) scored the MRI scans. The interrater weighted Cohen's kappa's of both raters were >0.85 (against an internally established gold-standard). Periventricular hyperintensities (PVH) were examined in three regions, frontal and occipital caps and periventricular bands, and rated on a three-point scale: none (score 0); 5 mm or less (score 1); 6 mm or greater (score 2). The deep white matter hyperintensities (DWMH) were examined in four regions of the brain, the frontal, parietal, temporal, and occipital lobes, and were rated as follows: none (score 0); less than 4 mm and five or less lesions (score 1); less than 4 mm and six or more lesions (score 2); 4–10 mm and five or less lesions (score 3); 4–10 mm and six or more lesions (score 4); 10 mm or greater and one or more lesions (score 5); and large confluent lesions (score 6).

#### 2.4. Statistical analysis

Serious violations of normality were subjected to either natural logarithmic or square root transformations, or cases were ranked with normal distribution if appropriate. Due to the low prevalence of both temporal and occipital DWMH (26.7% and 7.4%, respectively), implicating severe violations of normality, both variables were dichotomized into absence (score 0) or presence (score 1) of WMH.

Pearson correlations were calculated between the rest-activity rhythm variables (IS, IV, AMP) and the white matter subscores. Next, hierarchical multiple regression analyses were performed to determine which WMH subscore strongest predicted the rest-activity rhythm. The rest-activity rhythm variables were entered as the dependent variable. In the first step, confounding effects of age, gender, use of hypnotic medication, and depressive symptoms were examined by means of stepwise selection. In the next model, the white matter subscores were examined, again by means of stepwise selection. Significance for entry was set at  $p < .05$ .

### 3. Results

Of the 162 subjects initially enrolled into the study, 10 subjects were not included in the analysis due to technical error (e.g. malfunctional actigraphic registration). Furthermore, five subjects were excluded due to insufficient actigraphy registration. Despite explicit instructions, both insufficient wearing (e.g. 3 days only) and severe fractionated actigraphy registration (due to frequent periods of not wearing the actigraph) were present. MRI scans were furthermore not obtained for eight subjects (e.g. due to claustrophobia). An additional four subjects did not complete the SCL-90. As such, data collection was complete for 135 subjects. WMH were present in 94.8% of these participants (median = 5.0, range = 0–27).

Table 2

Correlations between white matter and the rest-activity rhythm ( $N = 135$ )

	IS	IV	AMP
Frontal PVH	0.011	0.123	−0.036
Lateral PVH	−0.085	0.108	−0.061
Occipital PVH	−0.171*	0.139	−0.180*
Frontal DWMH	−0.173*	0.108	−0.237**
Parietal DWMH	−0.145	0.111	−0.160
Temporal DWMH	−0.027	0.140	−0.044
Occipital DWMH	0.016	0.121	−0.159

AMP: amplitude; DWMH: deep white matter hyperintensities; IS: interdaily stability; IV: intradaily variability; PVH: periventricular hyperintensities.

\*  $p < .05$ .

\*\*  $p < .01$ .

Correlations between the WMH subscores and the rest-activity rhythm variables are presented in Table 2. IS significantly correlated with frontal DWMH and occipital PVH and, marginally, with parietal DWMH. IV did not significantly correlate with any of the white matter subscores. Finally, AMP correlated with frontal DWMH and occipital PVH and, marginally, with parietal, and occipital DWMH.

The hierarchical multiple regression analysis revealed that frontal DWMH was the sole predictor of IS ( $\beta = -0.173$ ,  $p < .05$ ); no further significant associations between IS and other white matter subscores or confounders (age, depressive symptoms, hypnotics, gender) were present. Age entered as a significant predictor of IV ( $\beta = 0.197$ ,  $p < .05$ ), after which no other confounder or white matter subscore could significantly contribute. Finally, frontal DWMH was the only significant predictor of AMP variance ( $\beta = -0.237$ ,  $p < .01$ ). No effects of any of the confounders or other white matter subscores were noted. Since AMP reflects the difference between L5 and M10, the analysis was repeated for these variables in order to examine whether either an increase in nighttime activity, a decrease in daytime activity, or possibly changes in both variables mediates the AMP-frontal DWMH association. This revealed that frontal DWMH predicted M10 ( $\beta = -0.223$ ,  $p < .01$ ), but not L5. Examples of a normal and disrupted rest-activity rhythm are presented in Fig. 1.

It can be argued that, as the majority of the participants suffered from at least one cardiovascular risk factor, controlling for these risk factors might attenuate the association between WMH and the rest-activity rhythm. To examine this possibility, the cardiovascular risk factors were allowed to enter the analysis using stepwise selection, after which the effects of WMH subscores were examined. Results were fully comparable to previous observations: frontal DWMH, but no other WMH subscores, predicted IS, AMP, and M10.

### 4. Discussion

The present study suggests that WMH disrupt the rest-activity rhythm in aging. Several white matter subscores correlated significantly with IS and AMP, but not IV. Frontal DWMH turned out to be the most important predictor of both

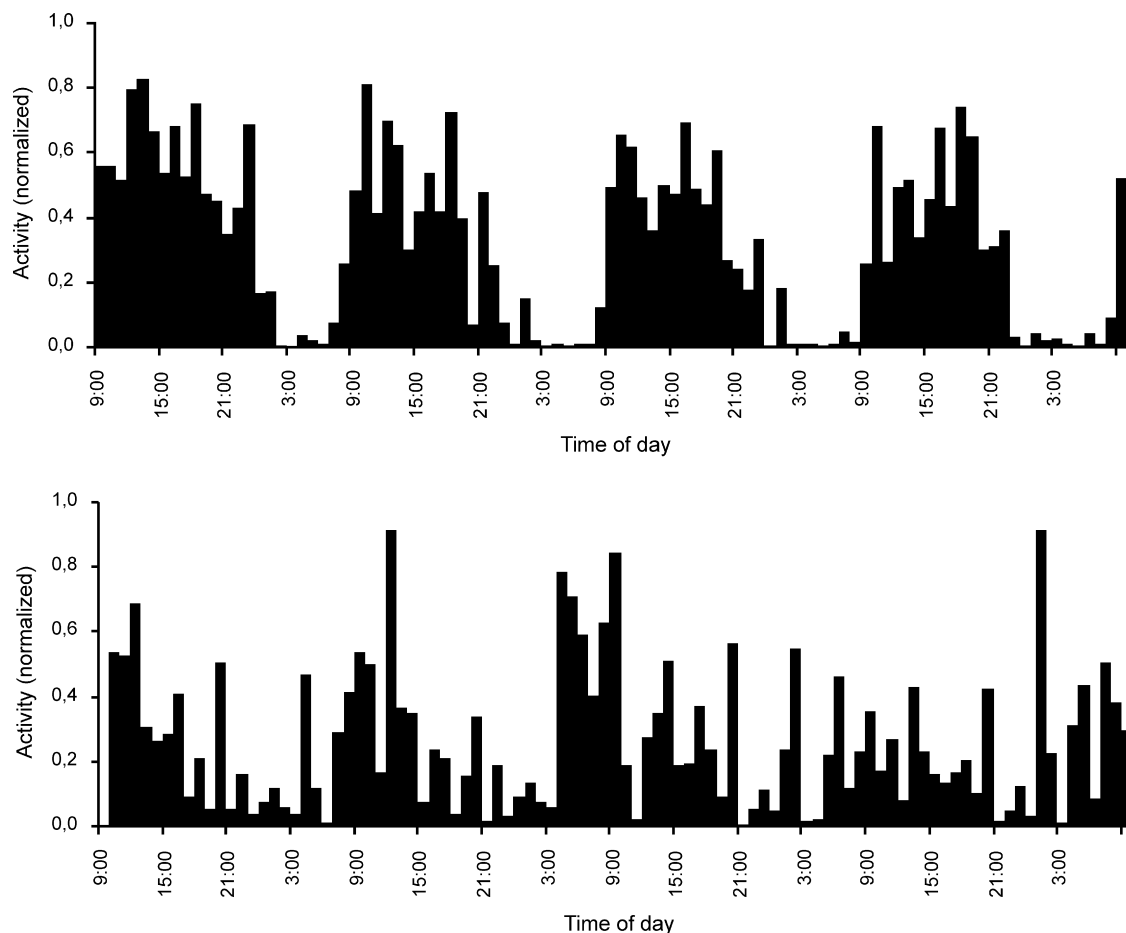


Fig. 1. Circadian rest–activity rhythm in two participants. Upper panel represents a female diabetic participant, age 72, without WMH and high IS, low IV, and high AMP. Lower panel displays the rest–activity rhythm of a male cardiac patient, age 82, with severe WMH (Scheltens et al., 1993) (score of 25 out of 30), including frontal DWMH (6/6) and low IS, high IV, and low AMP. AMP: amplitude; DWMH: deep white matter hyperintensities; IV: intradaily variability; IS: interdaily stability; WMH: white matter hyperintensities.

IS and AMP. It was further examined whether the association between frontal DWMH and AMP could be attributed to an increase in L5 or a decrease in M10, revealing that the association between AMP and white matter was mainly attributed to a decrease in M10 due to frontal DWMH.

Previous studies do suggest altered circadian rhythms both in aging (Huang et al., 2002; Yoon et al., 2003) and dementia (Harper et al., 2001; Scherder et al., 1999; Van Someren et al., 1996, 1997a). Although disruption of the rest–activity rhythm in the nondemented aged population has been suggested to result from SCN degeneration, the present results implicate that a WMH-related effect might be present in this population as well. More specifically, the high prevalence of WMH in both normal aging (De Leeuw et al., 2001) and dementia (Varma et al., 2002) highlights the possible widespread influence of WMH on the rest–activity rhythm in these populations.

How do WMH disrupt the rest–activity rhythm? Deafferentation has been optioned as an explanation (Kanda et al., 2003; Meguro et al., 1995). The SCN, being the central regulatory mechanism of the rest–activity rhythm, receives

input from cortical and subcortical areas (Moore et al., 2002; Pace-Schott and Hobson, 2002). As such, a disruption in one of the various connecting pathways might lead to a disturbed rest–activity rhythm. As the white matter forms an essential part of cortico-cortical and cortico-subcortical connections, next through factors in aging such as a decrement in light sensitivity (Duffy et al., 2007) and physical activity (Elia et al., 2000), it can be argued that WMH may reduce SCN input. A lack of input to the SCN may furthermore decrease neuronal activation necessary for generation or output of the circadian rhythm (Van Someren, 2000). Also, the SCN contains several (indirect) efferent connections with various brain structures, such as the brain stem (Pace-Schott and Hobson, 2002), which may be disrupted as a consequence of WMH. Further support for the notion of disconnection of cortical and subcortical structures underlying disturbed circadian rhythms comes from studies of vascular dementia patients. These patients display severely disturbed circadian rhythms, with deafferentation suggested as the main cause of these alterations (Aharon-Peretz et al., 1991; Mishima et al., 1997).

Since distinct subregions of both PVH and DWMH correlated with the rest–activity rhythm variables in the present study, it could be argued that the present results do imply a more general involvement of white matter in maintaining a stable rhythm. However, these results may alternatively be interpreted as implicating a specific role of WMH subregions in the rest–activity rhythm, with frontal DWMH as the strongest predictor of both IS and AMP. The association of frontal DWMH with AMP was mainly reflected in a reduction in M10, the average activity in the most active 10-h period, as a result of hyperintensities in this white matter region. It is likely that self-initiated movements contribute to this activity. Both imaging and lesion studies suggest specific involvement of the dorsolateral prefrontal cortex (DLPFC) in self-initiated movement (Jahanshahi et al., 1995; Jenkins et al., 2000; Wiese et al., 2004, 2006). It has been suggested that specifically the dorsal PFC white matter is strongly related to both functioning of the PFC itself as well as brain areas functionally and anatomically related to the PFC (Nordahl et al., 2006). As such, the present observation of frontal DWMH relating to M10 fits in the idea of frontal white matter being most important for PFC functioning, which includes self-initiated activity. Equally, as physical fitness and exercise have been shown to have beneficial effects for the rest–activity rhythm in aging (Van Someren et al., 1997b), it could be argued that a reduction in activity mediates the association between frontal DWMH and IS as well.

Alternatively, a reduction in visual input might mediate the association of WMH with an altered rest–activity rhythm. In the processing of light, retinofugal pathways include projections to the lateral geniculate nucleus (LGN), the midbrain (superior-colliculus (SC) and pretectum (PT)), and the SCN. The geniculo-hypothalamic tract originates from a portion of the LGN, the intergeniculate leaflet, and conveys photic and non-photoc information to the SCN (Harrington, 1997). The SC and PT are associated with the mediation of light on sleep and wake in rats (Miller et al., 1998). Finally, the retinohypothalamic tract projects directly to the SCN (Moore et al., 1995). It could be argued that frontal DWMH, by affecting the retinofugal tracts, reduces visual input to the SCN. As photic input is related to amplitude (Satlin et al., 1992) and IS (Van Someren et al., 1997a), the observation of frontal DWMH to induce a reduction in IS and AMP in the present study seems a logical consequence. However, these postulations are speculative and require further research.

Despite that subjects with a history of depression were excluded, depressive symptoms were taken into account when performing the multiple linear regression analyses. Considering the strong relationship of depression with both WMH (Firbank et al., 2005) and the rest–activity rhythm (Haynes et al., 2006), it could be argued that these symptoms may still relate to both variables. However, the regression analyses revealed that the degree of depressive symptoms did not significantly contribute to any of the rest–activity

variables. Therefore, it can be concluded that these symptoms did not mediate (part of) the observed relationship of WMH with both IS and AMP.

The present study contains several potential limitations. One of them concerns the fact that no objective screening was performed to examine the possible presence of sleep apnea. The prevalence of sleep apnea might have been substantial in our study population, considering the existing overlap between cardiovascular risk factors and sleep apnea (Olson and Somers, 2006). The high prevalence of these risk factors in the present study might actually indicate an increased prevalence of sleep apnea. As WMH severity correlates with the severity of sleep-disordered breathing (Harbison et al., 2003), it can be argued that the presence of sleep apnea accounts for part of the observed association between WMH and the rest–activity rhythm variables examined in the present study. However, based on both patient interview and the careful screening of patients' medical records it is justified to conclude that a history of sleep apnea is unlikely to have mediated the observed effects.

Furthermore, several correlations between the WMH sub-scores and the rest–activity variables were calculated, which induces the risk of type 1 error. The results of these correlations should therefore be interpreted with caution. However, multiple linear regression analyses revealed a remaining effect of frontal DWMH for both IS and AMP, which is likely to reflect genuine effects.

The high prevalence of cardiovascular risk factors limits generalizability of the present results to the aged population, as the prevalence of these factors is likely to be lower in this population. However, cardiovascular risk factors were allowed to enter the multiple linear regression analyses and this did not alter the previous observed effects of frontal DWMH. This finding supports an independent association between the rest–activity rhythm and WMH in the present study, regardless of some subject characteristics.

A possible limitation is the use of a visual rating scale instead of volumetric ratings to assess the degree of WMH. It could be argued that volumetric ratings are more accurate than Scheltens' semiquantitative rating scale that was used in the present study (Van Straaten et al., 2006). However, strong correlations between the Scheltens scale and volumetric measurements have been reported (Kapeller et al., 2003; Van Straaten et al., 2006). As white matter ratings in the present study might deviate from volumetric ratings, the observed associations between WMH and both IS and AMP may underestimate the true relationship. These associations might only prove stronger when volumetric rating methods are applied.

The present study confirms involvement of the white matter in the rest–activity rhythm. As both the normal aged and the demented population may present with moderate to severe WMH, alterations in the rest–activity rhythm in these populations as a result of WMH can be anticipated. Future research should focus on underlying mechanisms of the relationship between WMH and the rest–activity rhythm.

## Conflict of interest

There are no actual or potential conflicts of interest.

## Acknowledgements

We would like to thank Eric van Rossum for technical support. Part of this research was supported by grants from the “Roomsche Catholiek Oude-Armenkantoer” of Amsterdam and the “Stichting Alzheimer & Neuropsychiatrie Foundation Amsterdam” to Barbera van Harten.

## References

- Aharon-Peretz, J., Masiah, A., Pillar, T., Epstein, R., Tzischinsky, O., Lavie, P., 1991. Sleep–wake cycles in multi-infarct dementia and dementia of the Alzheimer type. *Neurology* 41, 1616–1619.
- Arrindell, W.A., Ettema, J.H.M., 1986. SCL-90: Handleiding bij een multidimensionele psychopathologie-indicator [SCL-90: Manual for a Multidimensional Indicator of Psychopathology]. Swets & Zeitlinger, Lisse.
- Bliwise, D.L., Ansari, F.P., Straight, L.B., Parker, K.P., 2005. Age changes in timing and 24-hour distribution of self-reported sleep. *Am. J. Geriatr. Psychiatry* 13, 1077–1082.
- De Leeuw, F.-E., De Groot, J.C., Achten, E., Oudkerk, M., Ramos, L.M., Heijboer, R., Hofman, A., Jolles, J., van Gijn, J., Breteler, M.M., 2001. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam scan study. *J. Neurol. Neurosurg. Psychiatry* 70, 9–14.
- De Souza, L., Benedito-Silva, A.A., Pires, M.L., Poyares, D., Tufik, S., Calil, H.M., 2003. Further validation of actigraphy for sleep studies. *Sleep* 26, 81–85.
- Duffy, J.F., Zeitzer, J.M., Czeisler, C.A., 2007. Decreased sensitivity to phase-delaying effects of moderate intensity light in older subjects. *Neurobiol. Aging* 28, 799–807.
- Elia, M., Ritz, P., Stubbs, R.J., 2000. Total energy expenditure in the elderly. *Eur. J. Clin. Nutr.* 54 (Suppl. 3), 92–103.
- Firbank, M.J., O'Brien, J.T., Pakrasi, S., Pantoni, L., Simoni, M., Erkinjuntti, T., Wallin, A., Wahlund, L.O., van Straaten, I., Inzitari, D., 2005. White matter hyperintensities and depression—preliminary results from the LADIS study. *Int. J. Geriatr. Psychiatry* 20, 674–679.
- Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198.
- Grut, M., Fratiglioni, L., Viitanen, M., Winblad, B., 1993. Accuracy of the mini-mental status examination as a screening test for dementia in a Swedish elderly population. *Acta Neurol. Scand.* 87, 312–317.
- Haimov, I., Lavie, P., 1997. Circadian characteristics of sleep propensity function in healthy elderly: a comparison with young adults. *Sleep* 20, 294–300.
- Harbison, J., Gibson, G.J., Birchall, D., Zammit-Maempel, I., Ford, G.A., 2003. White matter disease and sleep disordered breathing after acute stroke. *Neurology* 61, 959–963.
- Harper, D.G., Stopa, E.G., McKee, A.C., Satlin, A., Harlan, P.C., Goldstein, R., Volicer, L., 2001. Differential circadian rhythm disturbances in men with Alzheimer disease and frontotemporal degeneration. *Arch. Gen. Psychiatry* 58, 353–360.
- Harrington, M.E., 1997. The ventral lateral geniculate nucleus and the intergeniculate leaflet: interrelated structures in the visual and circadian systems. *Neurosci. Biobehav. Rev.* 21, 705–727.
- Haynes, P.L., McQuaid, J.R., Ancoli-Israel, S., Martin, J.L., 2006. Disrupting life events and the sleep–wake cycle in depression. *Psychol. Med.* 36, 1363–1373.
- Huang, Y.L., Liu, R.Y., Wang, Q.S., Van Someren, E.J., Xu, H., Zhou, J.N., 2002. Age-associated difference in circadian sleep–wake and rest–activity rhythms. *Physiol. Behav.* 76, 597–603.
- Jahanshahi, M., Jenkins, I.H., Brown, R.G., Marsden, C.D., Passingham, R.E., Brooks, D.J., 1995. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. *Brain* 118, 913–933.
- Jenkins, I.H., Jahanshahi, M., Jueptner, M., Passingham, R.E., Brooks, D.J., 2000. Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow. *Brain* 123, 1216–1228.
- Jo, I., Ahn, Y., Lee, J., Shin, K.R., Lee, H.K., Shin, C., 2001. Prevalence, awareness, treatment, control and risk factors of hypertension in Korea: the Ansan study. *J. Hypertens.* 19, 1523–1532.
- Kanda, A., Matsui, T., Ebihara, S., Arai, H., Sasaki, H., 2003. Periventricular white matter lesions and sleep alteration in older people. *J. Am. Geriatr. Soc.* 51, 432–433.
- Kapeller, P., Barber, R., Vermeulen, R.J., Ader, H., Scheltens, P., Freidl, W., Almkvist, O., Moretti, M., del Ser, T., Vaghfeldt, P., Enzinger, C., Barkhof, F., Inzitari, D., Erkinjuntti, T., Schmidt, R., Fazekas, F., 2003. Visual rating of age-related white matter changes on magnetic resonance imaging: scale comparison, interrater agreement, and correlations with quantitative measurements. *Stroke* 34, 441–445.
- Lazarus, R., Prettyman, R., Cherryman, G., 2005. White matter lesions on magnetic resonance imaging and their relationship with vascular risk factors in memory clinic attenders. *Int. J. Geriatr. Psychiatry* 20, 274–279.
- Liao, D., Cooper, L., Cai, J., Toole, J., Bryan, N., Burke, G., Shahar, E., Nieto, J., Mosley, T., Heiss, G., 1997. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC study. *Neuroepidemiology* 16, 149–162.
- Meguro, K., Ueda, M., Kobayashi, I., Yamaguchi, S., Yamazaki, H., Oikawa, Y., Kikuchi, Y., Sasaki, H., 1995. Sleep disturbance in elderly patients with cognitive impairment, decreased daily activity and periventricular white matter lesions. *Sleep* 18, 109–114.
- Miller, A.M., Obermeyer, W.H., Behan, M., Benca, R.M., 1998. The superior colliculus-prepectum mediates the direct effects of light on sleep. *Proc. Natl. Acad. Sci. U.S.A.* 95, 8957–8962.
- Mishima, K., Okawa, M., Satoh, K., Shimizu, T., Hozumi, S., Hishikawa, Y., 1997. Different manifestations of circadian rhythms in senile dementia of Alzheimer's type and multi-infarct dementia. *Neurobiol. Aging* 18, 105–109.
- Moore, R.Y., Speh, J.C., Card, J.P., 1995. The retinohypothalamic tract originates from a distinct subset of retinal ganglion cells. *J. Comp. Neurol.* 352, 351–366.
- Moore, R.Y., Speh, J.C., Leak, R.K., 2002. Suprachiasmatic nucleus organization. *Cell Tissue Res.* 309, 89–98.
- Nordahl, C.W., Ranganath, C., Yonelinas, A.P., Decarli, C., Fletcher, E., Jagust, W.J., 2006. White matter changes compromise prefrontal cortex function in healthy elderly individuals. *J. Cogn. Neurosci.* 18, 418–429.
- Olson, L.J., Somers, V.K., 2006. Modulation of cardiovascular risk factors by obstructive sleep apnea. *Chest* 129, 218–220.
- Pace-Schott, E.F., Hobson, J.A., 2002. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. *Nat. Rev. Neurosci.* 3, 591–605.
- Satlin, A., Volicer, L., Ross, V., Herz, L., Campbell, S., 1992. Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. *Am. J. Psychiatry* 149, 1028–1032.
- Scheltens, P.F., Barkhof, D., Leys, D., Pruvo, J.P., Nauta, J.J., Vermersch, P., Steinling, M., Valk, J., 1993. A semiquantitative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J. Neurol. Sci.* 114, 7–12.
- Scherder, E.J., Van Someren, E.J., Swaab, D.F., 1999. Transcutaneous electrical nerve stimulation (TENS) improves the rest–activity rhythm in midstage Alzheimer's disease. *Behav. Brain Res.* 101, 105–107.

- Stolk, R.P., Pols, H.A., Lamberts, S.W., de Jong, P.T., Hofman, A., Grobbee, D.E., 1997. Diabetes mellitus, impaired glucose tolerance, and hyperinsulinemia in an elderly population. The Rotterdam Study. *Am. J. Epidemiol.* 145, 24–32.
- Tobler, I., Borbely, A.A., 1993. European isolation and confinement study. Twenty-four hour rhythm of rest/activity and sleep/wakefulness: comparison of subjective and objective measures. *Adv. Space Biol. Med.* 3, 163–183.
- Van Someren, E.J., 2000. Circadian and sleep disturbances in the elderly. *Exp. Gerontol.* 35, 1229–1237.
- Van Someren, E.J., Hagebeuk, E.E., Lijzenga, C., Scheltens, P., de Rooij, S.E., Jonker, C., Pot, A.M., Mirmiran, M., Swaab, D.F., 1996. Circadian rest–activity rhythm disturbances in Alzheimer’s disease. *Biol. Psychiatry* 40, 259–270.
- Van Someren, E.J., Kessler, A., Mirmiran, M., Swaab, D.F., 1997a. Indirect bright light improves circadian rest–activity rhythm disturbances in demented patients. *Biol. Psychiatry* 41, 955–963.
- Van Someren, E.J., Lijzenga, C., Mirmiran, M., Swaab, D.F., 1997b. Long-term fitness training improves the circadian rest–activity rhythm in healthy elderly males. *J. Biol. Rhythms* 12, 146–156.
- Van Straaten, E.C., Fazekas, F., Rostrup, E., Scheltens, P., Schmidt, R., Pantoni, L., Inzitari, D., Waldemar, G., Erkinjuntti, T., Mantyla, R., Wahlund, L.O., Barkhof, F., 2006. Impact of white matter hyperintensities scoring method on correlations with clinical data: the LADIS study. *Stroke* 37, 836–840.
- Varma, A.R., Laitt, R., Lloyd, J.J., Carson, K.J., Snowden, J.S., Neary, D., Jackson, A., 2002. Diagnostic value of high signal abnormalities on T2 weighted MRI in the differentiation of Alzheimer’s, frontotemporal and vascular dementias. *Acta Neurol. Scand.* 105, 355–364.
- Walhovd, K.B., Fjell, A.M., Reinvang, I., Lundervold, A., Dale, A.M., Eilertsen, D.E., Quinn, B.T., Salat, D., Makris, N., Fischl, B., 2005. Effects of age on volumes of cortex, white matter and subcortical structures. *Neurobiol. Aging* 26, 1261–1270.
- Wiese, H., Stude, P., Nebel, K., Osenberg, D., Ischebeck, W., Stolke, D., Diener, H.C., Keidel, M., 2004. Recovery of movement-related potentials in the temporal course after prefrontal traumatic brain injury: a follow-up study. *Clin. Neurophysiol.* 115, 2677–2692.
- Wiese, H., Tonnes, C., de Greiff, A., Nebel, K., Diener, H.C., Stude, P., 2006. Self-initiated movements in chronic prefrontal traumatic brain injury: an event-related functional MRI study. *Neuroimage* 30, 1292–1301.
- Ylikoski, A., Erkinjuntti, T., Raininko, R., Sarna, S., Sulkava, R., Tilvis, R., 1995. White matter hyperintensities on MRI in the neurologically nondiseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. *Stroke* 26, 1171–1177.
- Yoon, I.Y., Kripke, D.F., Youngstedt, S.D., Elliott, J.A., 2003. Actigraphy suggests age-related differences in napping and nocturnal sleep. *J. Sleep Res.* 12, 87–93.