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Medial temporal lobe atrophy relates more strongly to sleep-wake rhythm fragmentation than to age or any other known risk

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ABSTRACT

Atrophy of the medial temporal lobe of the brain is key to memory function and memory complaints in old age. While age and some morbidities are major risk factors for medial temporal lobe atrophy, individual differences remain, and mechanisms are insufficiently known. The largest combined neuroimaging and whole genome study to date indicates that medial temporal lobe volume is most associated with common polymorphisms in the GRIN2B gene that encodes for the 2B subunit (NR2B) of the NMDA receptor. Because sleep disruption induces a selective loss of NR2B from hippocampal synaptic membranes in rodents, and because of several other reports on medial temporal lobe sensitivity to sleep disruption, we hypothesized a contribution of the typical age-related increase in sleep-wake rhythm fragmentation to medial temporal lobe atrophy. Magnetic resonance imaging and actigraphy in 138 aged individuals showed that individual differences in sleep-wake rhythm fragmentation accounted for more (19%) of the variance in medial temporal lobe atrophy than age did (15%), or any of a list of health and brain structural indicators. The findings suggest a role of sleep-wake rhythm fragmentation in age-related medial temporal lobe atrophy, that might in part be prevented or reversible.

1. Introduction

Human aging is associated with volume reduction of the medial temporal lobe (MTL) of the brain. The underlying causes of medial temporal lobe atrophy (MTA) are insufficiently known, yet of major importance given its essential association with the declarative memory problems that confront elderly people, and its predictive value for the development of Alzheimer's disease (De Toledo-Morrell, Goncharova, Dickerson, Wilson, & Bennett, 2000; Golomb et al., 1994; Scheltens et al., 1992). It is thus important to pursue factors involved, because they may give clues on mechanisms and intervention strategies. Marked individual differences in the degree of the characteristic age-related atrophy (Vandenbroucke et al., 2004) suggest involvement of environmental and genetic risk factors. With respect to environmental risk factors, several medical conditions of which the risk increases with age are predictive for MTA (den Heijer et al., 2003, 2005; Hedden and Gabrieli, 2005). With respect to genetic risk factors, the largest combined neuroimaging and whole genome study to date indicates that MTL volume is most associated with common variants in the GRIN2B gene that encodes for the 2B subunit (NR2B) of the NMDA receptor (Stein et al., 2010). Because these environmental and genetic risk factors account for only a part of the variance in MTA, the presence of other, as yet unrecognized, factors is likely, and important to pursue.

Several findings suggest that it could be of value to evaluate a possible contribution to MTA of the 24-hr sleep-wake rhythm fragmentation towards shorter periods of rest and activity, that we showed to be a most characteristic aspect of aging (Hu, Van Someren, Shea, & Scheer, 2009; Huang et al., 2002). An increasing difficulty to stay

Abbreviations: AMP, amplitude; GRIN2B, glutamate (NMDA) receptor subunit epsilon-2; IS, Interdaily Variability; IV, Intradaily Variability; L5, least active 5-hour period; M10, most active 10-hour period; MTA, Medial Temporal Lobe Atrophy; MTL, Medial Temporal Lobe; NMDA, N-methyl-D-aspartate; NR2B, N-methyl D-aspartate receptor subtype 2B; SCN, Suprachiasmatic Nucleus

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asleep at night and awake during the day is not only a significant problem for older people, but has also been demonstrated in aged mice (Wimmer et al., 2013). Chronic experimental sleep fragmentation in mice leads to a loss of select neurons and pro-inflammatory and pro-oxidative mitochondrial stress responses consistent with neurodegeneration (Zhu, Fenik, Zhan, Xin, & Veasey, 2015). In humans, we demonstrated a specific hippocampal sensitivity to experimentally induced fragmentation of slow wave sleep (Van Der Werf et al., 2009), and suggested that fragmentation of periods of sleep and wakefulness, e.g. induced by chronic sleep restriction (Leemburg et al., 2010; Vyazovskiy et al., 2011), may interfere with state-dependent neurobiological processes that require a critical minimum duration (Van Someren, 2010). It has moreover been shown that sleep disruption induces a selective loss of NR2B from hippocampal synaptic membranes (Kim, Grover, Bertolotti, & Green, 2010). This finding is of particular interest given the role of NR2B in MTA (Stein et al., 2010). Whereas the sleep deprivation-induced loss of NR2B from hippocampal synaptic membranes can be rescued by exogenous growth hormone (Kim et al., 2010), fragmented sleep has an adverse effect on endogenous growth hormone secretion in humans as well (van Liempt, Vermetten, Lentjes, Arends, & Westenberg, 2011). Sleep-wake rhythm fragmentation may thus both directly interfere with synaptic membrane maintenance as well as indirectly with rescuing processes. Indeed, several other reports suggest sensitivity of the medial temporal lobe to disrupted sleep.

Firstly, a number of studies in humans reported lower hippocampal volume in association with sleep fragmentation (Noh, Joo, & Bong, 2012; Winkelman et al., 2010), short sleep (Hall, Soreca, Matthews, Kuller, & Gianaros, 2009) and a late bedtime (Kuperczkó et al., 2015). A recent study in rats supports a causal role of chronic sleep restriction in reducing hippocampal volume (Novati, Hulshof, Koolhaas, Lucassen, & Meerlo, 2011). Secondly, we demonstrated that the enforcement of 24-hour rhythms induces a long-term enhancement of cognitive performance in elderly residents of group care facilities (Riemersma-van der Lek et al., 2008). Thirdly, the reverse, an enforcement of *non*-24-hour rhythms disrupts MTL-dependent memory tasks and induces MTA (Cho, 2001; Devan et al., 2001; Tapp and Holloway, 1981). Fourthly, a prospective study in 838 middle aged and older adults showed that sleep complaints at baseline predicted cognitive decline over a period of 3 years (Jelicic et al., 2002). Fifthly, not only our (Van Der Werf et al., 2009) but also other's studies applying functional magnetic resonance imaging and magnetic resonance spectroscopy demonstrated functional deficits in the hippocampus after experimental prolonged total sleep deprivation (Yoo, Hu, Gujar, Jolesz, & Walker, 2007) and in relation to chronic sleep fragmentation due to the obstructive sleep apnea syndrome (Halbower et al., 2006). Finally, support for the sensitivity of the medial temporal lobe is furthermore given by animal studies showing that the experimental prevention of an uninterrupted period of sleep reduced hippocampal cell proliferation (Guzman-Marin et al., 2003) and induced several alterations at the molecular and cellular level that could inhibit hippocampal function (McDermott et al., 2003). Mouse studies have moreover shown that even a brief period of sleep deprivation induces a pronounced loss of dendritic spines in the hippocampus (Havekes et al., 2016), and that a more chronic sleep disruption reduces hippocampal volume (Kreutzmann, Havekes, Abel, & Meerlo, 2015).

A possible association of sleep-wake rhythm fragmentation with medial temporal lobe atrophy, both very characteristic of the aging process, has however not previously been investigated. Given all mentioned findings that directly or indirectly suggest affected MTL functionality in association with disrupted sleep, we here investigated the hypothesis that individual differences in the severity of MTA in elderly people may be predicted by individual differences in the severity of the sleep-wake rhythm fragmentation that is so typical of aging.

Table 1
Sample description. *Verhage education classification system with categories 1 = did not finish primary school, 2 = finished primary school, 3 = did not finish secondary school, 4 = finished secondary school, low level, 5 = finished secondary school, medium level, 6 = finished secondary school, highest level, and/or college degree, 7 = university degree. †Cardiovascular disease: atrial fibrillation, myocardial infarction, coronary artery disease, heart failure and left ventricle hypertrophy.

Demographics	
Age (Years, Mean, St. Dev)	69.1 ± 8.5
Sex (M/F)	85/53
Cognition	
Education* (Median, Q1-Q3)	5 (3–5)
MMSE (Mean, St. Dev)	27.9 ± 1.7
15 Words Test	39.9 ± 10
Health	
Symptoms Checklist Depression (Mean, St. Dev)	24.6 ± 9
Sleep Medication (yes/no)	8/130
Pain Medication (yes/no)	9/129
Type 2 Diabetes (yes/no)	44/94
Hypertension (yes/no)	48/90
Hypercholesterolemia (yes/no)	70/68
Cardiovascular disease† (yes/no)	87/51
Framingham cardiovascular risk profile score (Mean, St. Dev)	9.4 ± 4.6
MRI findings	
MTA score	0.69 ± 0.75
Global cortical atrophyy	0.92 ± 0.74
Lacunar/cortical infarct (yes/no)	30/108
Sleep-wake rhythm	
Interdaily Stability (Mean, St. Dev)	0.73 ± 0.12
Fragmentation (Intradaily Variablity, IV, Mean, St. Dev)	0.57 ± 0.2
Amplitude (Active minutes/hr, Mean, St. Dev)	40 ± 7.7

2. Materials and methods

Data were obtained from 138 participants older than 50 years of age (69.1 ± 8.5 mean ± standard deviation, 85 males and 53 females), selected from medical records of the departments of cardiology and internal medicine of the St. Lucas-Andreas Hospital, Amsterdam, The Netherlands. In order to ensure a large range of variability in MTA scores and promote generalizability to common comorbidity at advanced age (Barnett et al., 2012), we recruited such that 79% of the participants scored positive for at least one risk factor for enhanced MTA (including type 2 diabetes, hypertension, hypercholesterolemia and cardiovascular disease) (den Heijer et al., 2003, 2005). Medical records and interviews indicated that none of the participants had been diagnosed with neurodegenerative disease, stroke, psychiatric illness and abuse of alcohol or other substances. No participant showed cognitive impairment on the Mini Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975). In spite of the lack of a diagnosis of neurodegenerative disease and cognitive impairment, preclinical neurodegenerative processes cannot be excluded. Table 1 shows a description of the population characteristics including age, sex, education (Verhage, 1964), MMSE, the 15 Words Test (Saan and Deelman, 1986), the Symptoms Check List (SCL) – Depression (Derogatis, Lipman, & Covi, 1973), use of sleep medication and pain medication, risk factors for enhanced MTA (type 2 diabetes, hypertension, hypercholesterolemia and cardiovascular disease) and the Framingham cardiovascular risk profile (D'Agostino et al., 2008). Approval for the study was obtained from the medical ethics committee. All subjects signed an informed consent.

The sleep-wake rhythm was assessed for seven days continuously using actigraphy (Actiwatch, Cambridge Neurotechnology, Cambridge, UK). Actigraphy is the ambulatory recording of wrist movements with a small wrist-watch like device, and has been validated as a method for the unobtrusive long-term assessment of sleep, rest-activity rhythms and tremors (Kushida et al., 2001) (Carvalho-Bos, Riemersma-van der

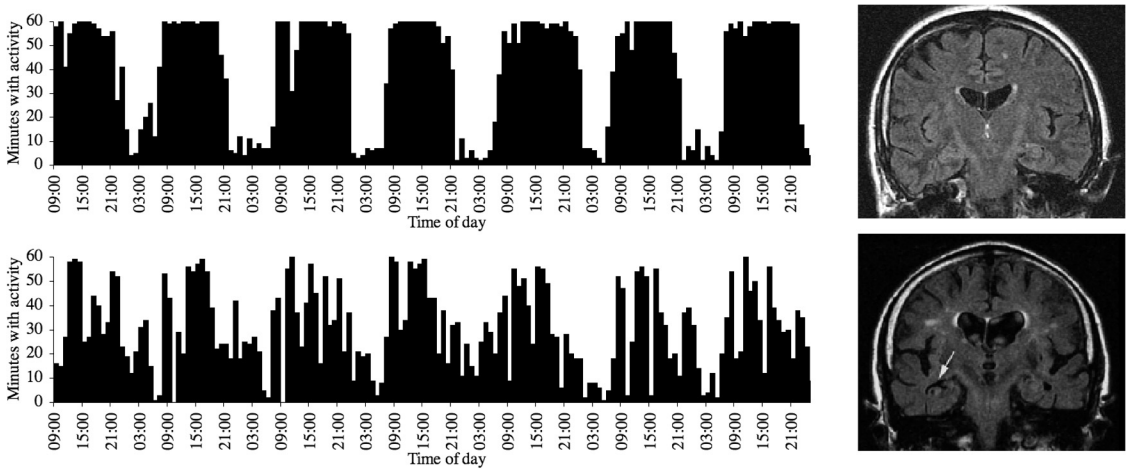

Fig. 1. Examples of activity rhythm and MTA in two participants selected to illustrate the relation found. The upper graphs show a participant that has pronounced 24-hour pattern with the characteristic long periods of rest and of activity in his sleep-wake rhythm (upper left, and relatively little MTA (upper right). The lower graphs show a subject whose sleep-wake rhythm shows pronounced fragmentation, i.e. alternation of periods of rest and of activity (lower left) and more advanced MTA (lower right).

Lek, Waterhouse, Reilly, & Van Someren, 2007; Van Someren et al., 1993, 2006; Van Someren, Vonk, et al., 1998; Van Someren, 2007). The activity profile (see examples in Fig. 1) was quantified with three previously described variables reflecting different aspects of the variability in the hour-by-hour time spent active (Carvalho-Bos et al., 2007). The interdaily stability (IS) quantifies the extent to which all recorded 24-hour activity profiles resemble each other, i.e. the day-by-day regularity of the sleep-wake pattern. The intradaily variability (IV) quantifies the fragmentation of the rhythm, i.e. the frequency and extent of transitions between periods of rest and activity. Finally, a nonparametric measure of the amplitude of the rhythm (AMP) was calculated by subtracting the least active 5-hour period (L5) of the average 24-hour profile from its most active 10-hour period (M10).

Within a month from the actigraphic assessments, participants underwent a brain MRI scan (1.5 Tesla Signa Horizon LX, General Electric, Milwaukee, USA) during which coronal FLAIR images were acquired. The standardized imaging protocol consisting of sagittal T1-weighted (repetition time TR 300 ms, echo time TE 4 ms) and axial T2-weighted (TR 6500 ms, TE 105 ms) and fluid attenuated inversion recovery (FLAIR) weighted (TR 10,000 ms, TE 160 ms) as well as coronal FLAIR images with a slice thickness of 5 mm with a 2 mm gap. MTA was subsequently rated according to validated standard procedures (Scheltens et al., 1992, 1993). Whereas volumetric analysis of brain structures on MRI scans would provide a higher resolution in quantifying individual differences, it is time consuming, not routinely available, and dependent on scan protocol and quality and availability of expertise with specialized software. Scheltens and Barkhof therefore developed a visual rating scale as an easy to learn user friendly alternative (Scheltens et al., 1992, 1993). The score takes into account the height of the hippocampus and the enlargement of the surrounding cerebrospinal fluid space (width of the choroid fissure and temporal horn) as seen on a coronal T1 weighted scan. The severity of medial temporal lobe atrophy (MTA) is scored from 0 (no atrophy) to 4 (most severe atrophy). Several studies compared the rating with quantitative methods and confirmed that it provided a good estimate of medial temporal lobe and hippocampal volumes for cross-sectional studies (see Scheltens and van de Pol, 2012). In our Alzheimer Center, MTA raters are well-trained and supervised to keep to the instructions of the original description of the method (Scheltens et al., 1992). Given the resulting high inter-rater reliabilities (0.87–0.95, e.g. Claus et al., 2017), we relied on a single rater who was blinded to any information about e.g. age and sleep fragmentation. Mean scores of left and right MTA were used for the analyses. We moreover rated global cortical atrophy according to Scheltens, Pasquier, Weerts, Barkhof, and Leys (1997). In brief, the method rates the sulcal width and gyral thinning in the frontal, parieto-occipital, and temporal lobes on a 4-point scale ranging from 0 to 3. Finally, we rated presence or absence of cortical and lacunar 'silent' infarctions, of which the latter were defined by 3–10 mm signal intensities corresponding to cerebrospinal fluid. Experienced raters (AAG, AP, and PS) scored all scans blinded to any information about the participant.

Statistical analyses included Pearson correlation coefficients, *t*-tests, and multiple and stepwise regression analyses with MTA as dependent variable, the sleep-wake rhythm variables as independent variables. A two-sided $p < 0.05$ was considered significant.

3. Results

In 138 participants older than 50 years of age, sleep-wake rhythm fragmentation was quantified using actigraphic recordings (Carvalho-Bos et al., 2007) and MTA using magnetic resonance imaging (Scheltens et al., 1992, 1993). Examples of two cases are given in Fig. 1. Table 1 shows sample means and standard deviations of the sleep-wake rhythm stability (IS), fragmentation (IV) and amplitude (AMP). Simple correlation coefficients (Table 2) revealed strong positive correlations of MTA with age and with the fragmentation of the sleep-wake rhythm, and moderate negative correlations with the interdaily stability and amplitude of the sleep-wake rhythm. Of note, fragmentation accounted for more of the variance in MTA (19%) than age did (15%). Males and females did not differ with respect to MTA (*t*-test, $p = 0.28$). Given the likely partial collinearity between the four MTA predictors, a stepwise regression was performed to exclude redundancy and reveal the most significant MTA predictors. Age (beta = 0.28) and fragmentation of the sleep-wake rhythm (beta = 0.35) turned out to be the most salient

Table 2
Predictive value of age and three parameters describing the sleep-wake rhythm for MTA. The first row shows the individual correlations, the second shows the standardized coefficients that remain in a stepwise regression analysis.

	Age	Interdaily stability	Fragmentation	Amplitude
Individual correlation coefficient	0.38 ****	−0.20 *	0.43 *****	−0.28 **
Stepwise standardized coefficient	0.28 **		0.35 ****	

*p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001; *****p < 0.00001.

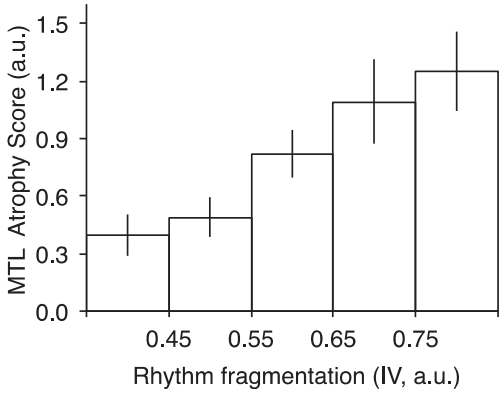

Fig. 2. Increasing average (± s.e.) MTA-score in subjects grouped according to their sleep-wake rhythm fragmentation score (IV, < 0.45, 0.45–0.55, 0.55–0.65, 0.65–0.75, > 0.75). Both MTA and IV are given in arbitrary units.

predictors of MTA, and were not redundant. Together, the two variables accounted for 26% of the variance in MTA, indicating that rhythm fragmentation has an important contribution to MTA on top of the well-described predictive value of age. In fact, if one had to choose between the two single predictors, fragmentation would do slightly better. As visualized in Fig. 2, subjects with a more fragmented activity profile (IV) thus had more MTA than subjects with activity profiles characterized by prolonged periods of activity and of rest.

There was no significant difference ($t(1) = -1.57$, $p = .12$) in age between men (68.3 ± 8.8) and women (70.5 ± 8.1). Simple non-parametric Mann-Whitney U tests revealed that sex was not associated with MTA ($U = 2088.0$, $Z = -0.88$, $p = .38$) or with IV ($U = 2432.0$, $Z = -0.46$, $p = .64$). It is therefore unlikely that sex was somehow involved in the association between MTA and IV.

Finally, multiple regression and stepwise regression including all possibly confounding variables (Table 2) were used to evaluate whether other variables would contribute stronger than, or in addition to, age and fragmentation. In a multiple regression model including, age and IV remained highly significant and only cardiovascular disease additionally contributed to MTA (beta = 0.28, p = 0.012). Also in the stepwise regression model, IV (beta = 0.35, p = 0.000) and age (beta = 0.30, p = 0.000) and remained the first and second most significant predictors, with smaller additional contributions of type 2 diabetes (beta = −0.20, p = 0.011) and silent infarction (beta = 0.16, p = 0.0039). The surprizing negative coefficient for type 2 diabetes suggests a possible overfitting. Indeed, adjusted R-square values suggested only a marginal improvement in explained variance of the four-predictor model ($R^2 = 0.32$) relative to the model including only IV and age ($R^2 = 0.26$). In summary, IV remained the most consistent and strong regressor of MTA across analyses, surpassing the predictive value of age.

4. Discussion

The present study found that age-related MTA is strongly associated with a fragmented sleep-wake rhythm. Our findings are open to multiple interpretations as to the mechanism involved. First, there could be a neuropathological process that not only underlies MTA, but also affects other structures involved in arousal regulation, including the basal forebrain, the locus coeruleus and the hypothalamic suprachiasmatic nucleus (SCN). The SCN accommodates the biological clock of the brain which interacts with information about the environmental light-dark cycle to regulate physiology (e.g. Scheer, van Heijningen, Van Someren, & Buijs, 2005) and shows functional changes with aging (Swaab, Van Someren, Zhou, & Hofman, 1996) that are reflected in the actigraphic readout measures used in the present study (Harper et al., 2008). Second, it may be that MTA induces dysfunction of the SCN and/or its downstream effector systems that mediate the SCN-imposed rhythm in activity. Third, it may be the other way around: that fragmented and irregular activity rhythms aggravate the neuropathological process responsible for MTA.

Although the first two possibilities cannot be discarded, previous work supports the latter. In contrast to the virtual lack of data supporting that manipulation of the MTL system would induce (SCN-mediated) changes in the sleep-wake rhythm, there is considerable support for the reverse, much of which has already been mentioned in the introduction. In mice, an optogenetic hypocretin activation procedure to induce fragmentation of sleep without changing its duration, disrupts novel object recognition learning (Rolls et al., 2011). The experimental enforcement of irregular sleep-wake rhythms to rats and humans induces deficits in MTL-dependent task performance (Cho, 2001; Fekete, van Ree, Niesink, & de Wied, 1985; Tapp and Holloway, 1981). Profession-induced irregularity of the activity rhythm induces MTA (Cho, 2001). Several suggestions regarding the neuropathological mechanisms underlying these findings can be mentioned here. Slice experiments on long term potentiation showed a circadian modulation of synaptic plasticity in the hippocampus (Chaudhury, Wang, & Colwell, 2005). The severe restriction and fragmentation of sleep reduces hippocampal cell proliferation in rats (Guzman-Marin et al., 2003). In mice, sleep deprivation impairs hippocampal cAMP signalling (Vecsey et al., 2009). The lack of a pronounced 24-profile of activity may also induce the loss of a circadian pattern of peripheral clock gene expression (van der Veen et al., 2006), while this pattern is presumed to be essential for the temporal segregation of biochemically incompatible processes of which the simultaneous occurrence within a single cell could harm it (Stratmann and Schibler, 2006). Involvement of glutamatergic transmission derailment is a most interesting possibility to further explore given the role of NR2B in MTA (Stein et al., 2010) and the sensitivity of N2B to sleep disruption (Kim et al., 2010).

It should be noted that different aspects of sleep may be differentially associated with MTL structure and function. A study in community-dwelling middle aged adults found that *sleep quality* was widely correlated with longitudinal measures of cortical atrophy, but *not* hippocampal atrophy (Sexton, Storsve, Walhovd, Johansen-Berg, & Fjell, 2014). The study however assessed only subjective sleep quality using the Pittsburgh Sleep Quality Index, but no objective measure of the quality of the sleep-wake rhythm. Especially in elderly people, subjective sleep quality was found not to be significantly associated with objective accelerometry measures of disturbed sleep-wake rhythms (Anderson et al., 2014; Most, Aboudan, Scheltens, & Van Someren, 2012). Likewise, there is no strong support for hippocampal atrophy in people suffering from insomnia disorder. Although some studies reported reduced hippocampal volume in insomnia (Joo, Kim, Suh, & Hong, 2014; Riemann et al., 2007) or a negative association between hippocampal volume and subjective sleep quality (Koo, Shin, Lim, Seong, & Joo, 2017), other studies including one with the largest sample size to date did not find any volume differences (Leerssen et al., 2018; Noh, Joo, Kim, et al., 2012; Winkelman et al., 2010).

A few possible limitations of the present study should be considered. First, our study was performed on a population of whom 79% were positive for at least one risk factor for MTA. We did so on purpose, because there may have been negligible variance in MTA if we would have recruited among the minority of elderly people without any disorder. It has in fact been argued that generalizability requires the inclusion of cases with morbidity, because over the age of 50 years people without one or more chronic disorders are an exception rather than the rule (Barnett et al., 2012). Another limitation is that – even though we excluded confounding by a several variables (Table 1) – we had no conclusive information on a few variables that may be considered relevant, notably like body mass index (BMI) and sleep disordered breathing. First, overweight should be considered as a possible confounder, because BMI is associated with rhythm fragmentation (Luik, Zuurbier, Hofman, Van Someren, & Tiemeier, 2013) and inversely

associated with hippocampal volume (Cherbuin, Sargent-Cox, Fraser, Sachdev, & Anstey, 2015). However, the strength of the association of rhythm fragmentation with BMI reported by Luik et al. (2013) is small (Beta = 0.09). Because this association is almost a factor five smaller than we here found for the association of rhythm fragmentation with MTA (Beta = 0.43), it is implausible that BMI could have driven the strong association between rhythm fragmentation and MTA we here report. A second relevant variable is sleep disordered breathing (SDB). Medical records mentioned SDB in 6% of our sample, but this number is most likely underestimates the true proportion, since SDB is underdiagnosed. SDB is indeed associated with MTA (Daulatzai, 2015). However, we previously showed in a large epidemiological study (N = 1734) of older people representative of the general population, that possible apnea was neither related to interdaily stability (Beta = 0.02, p = 0.51) nor to intradaily variability (Beta = 0.03, p = 0.21) (Luik et al., 2013). It is therefore implausible that SDB could underlie the strong association between rhythm fragmentation and MTA we here report.

Another potential limitation of the current study is that we did not assess employment status of our participants. As a significant number of the participants was younger than the typical age of retirement (i.e. 65 years of age in the Netherlands at the time the study was conducted), it is possible that working influenced the rest-activity rhythm results in these participants and consequently our study findings. For one, working likely influences the level of physical activity, depending on the precise type of employment (e.g., reduced levels in white-collar workers and increased levels in blue-collar workers, (Fukushima et al., 2018; Wilke, Ashton, Elis, Biallas, & Frobose, 2015). Moreover, previous studies have shown that retirement is associated with altered levels of physical activity (Celidoni and Rebba, 2017; McDonald et al., 2017), increased time spend asleep (Hagen, Barnet, Hale, & Peppard, 2016) and a decrease in sleep difficulties (e.g., waking up too early in the morning (Myllyntausta et al., 2018)). To what extent working status has influenced the association between Intradaily Variability (IV) and medial temporal lobe atrophy (MTA) is unclear, and needs clarification in future studies.

It may be considered a limitation that we did not register menopause status or hormone replacement therapy. It has been documented that post-menopausal hormone therapy is associated with changes in brain morphology, including increased hippocampal volume (Eberling et al., 2003). In the Netherlands, the median age at menopause is 50 years and approximately 78% of all females will have their menopause at the age of 54 (Ossewaarde et al., 2005). Although the menstrual cycle can modulate diurnal rhythms (e.g. Bao et al., 2004; Bao et al., 2003), in our study sample only 8 women were younger than 60 years, the age at which practically all women will have reached menopause. Excluding these women did not change our results: IV was still significantly associated with MTA. It is therefore unlikely that menopause played a significant role in our reported association between IV and MTA.

Actigraphy is a valuable tool in the assessment of sleep-wake rhythm disturbances, as well as their response to a wide range of interventions (e.g. Van Someren, Scherder, & Swaab, 1998). Although sleep-wake rhythm variables can show stronger associations with disease severity than actigraphic estimates of within-sleep variables (Hu et al., 2016; Luik, Zuurbier, Direk, et al., 2015; Luik, Zuurbier, Hofman, et al., 2015; Zuurbier, Ikram, et al., 2015; Zuurbier, Luik, et al., 2015), it would be interesting to use polysomnography to investigate differential contributions of non-REM and REM sleep to MTA (Meerlo, Mistlberger, Jacobs, Craig Heller, & McGinty, 2009).

A final limitation is our use of a cross-sectional design, so it is unknown for how long participants have experienced rhythm fragmentation. From a previous repeated measures follow-up study in demented elderly people (Riemersma-van der Lek et al., 2008), we could derive that IV can be quite consistent within-subject across years, given the intraclass correlation coefficient of 0.64. It would require long-term follow-up studies to better evaluate at what rate a fragmented rhythm accelerates medial temporal lobe atrophy.

Overall, the picture emerging from our findings that the *temporal organization of periods of sleep and wakefulness* across 24 h is more relevant to MTL integrity than the subjectively experienced quality of sleep. Support for this possibility is given by a recent study in which healthy older adults completed the Pittsburgh Sleep Quality Index (PSQI) as well as actigraphic assessment of sleep-wake rhythm before they underwent fMRI while performing an associative memory task (Sherman, Mumford, & Schnyer, 2015). A mediation analysis on the data indicated that – independent of sleep quality measures – a more consistent sleep-wake rhythm facilitated hippocampal activity and thereby successful memory performance. Whereas this study was observational, even stronger support for the importance of sleep continuity could be derived from an fMRI study in middle to old aged volunteers that likewise found attenuated hippocampal activity after experimentally induced sleep fragmentation (Van Der Werf et al., 2009).

Further experimental studies on underlying processes and on their possible reversibility by promoting regular sleep-wake rhythms with prolonged periods of rest and activity (e.g. Gasio et al., 2003; Riemersma-van der Lek et al., 2008) are warranted, especially so because, as compared to age *per se*, sleep-wake rhythm fragmentation appears to have at least as much or even more predictive value for functionally relevant age-related changes in brain structure and Alzheimer pathology (Musiek et al., 2018).

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