HHS Public Access

Author manuscript

Sleep Med. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Sleep Med. 2017 April ; 32: 236–243. doi:10.1016/j.sleep.2016.08.023.

Excessive daytime sleepiness and fatigue may indicate accelerated brain aging in cognitively normal late middle-aged and older adults

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Abstract

Excessive daytime sleepiness (EDS) and fatigue increases with age. The aim of this study was to investigate the association between EDS and fatigue with cortical thickness and hippocampal volume in cognitively normal, late middle-aged and older adults. We performed a cross-sectional observational study of 1374 cognitively-normal subjects aged 50 years and older who had a structural MRI. Regional cortical thickness and hippocampal volume were measured. Multiple linear regression models were fit to explore associations between EDS and fatigue and structural MRI measures in different brain regions, adjusting for multiple covariates. EDS was defined as Epworth Sleepiness Scale ≥10. Fatigue severity was assessed with the Beck Depression Inventory-2. 208 participants had EDS, 27 had significant fatigue, and 11 had both. Participants with EDS or fatigue had significantly lower cognitive scores, more disturbed sleep, and medical comorbidities. The presence of EDS was associated with both global and regional atrophy, whereas fatigue was more associated with frontal and temporal changes. Cortical thinning predicted by EDS and fatigue was maximal in the temporal region with average reduction of 34.2 μm (95% CI, −54.1, −14.3; P=.001) and 90.2 μm (95% CI, −142.1, −38.2; P=.001), respectively. Fatigue was also associated with hippocampal volume reduction of −374.2 mm^3 (95%CI, −670.8, −77.7; P=.013). Temporal cortical thinning predicted by presence of EDS and fatigue was

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equivalent to more than 3.5 and nine additional years of aging, respectively. EDS and fatigue were associated with cortical thickness reduction primarily in regions with increased age-susceptibility, which may indicate accelerated brain aging.

Keywords

sleepiness; fatigue; structural MRI; cortical thickness; hippocampal volume; aging

1. Introduction

Sleep disturbances increase with aging (Coleman, et al., 1981,Foley, et al., 1995,Phillips and Ancoli-Israel, 2001) and are often associated with excessive daytime sleepiness (EDS) and fatigue (Endeshaw, 2015,Hossain, et al., 2005,Young, 2004), which significantly impact patient's daily functioning (Gooneratne, et al., 2003). EDS is defined as difficulty in maintaining desired wakefulness, or a complaint of an excessive amount of sleep (American Academy of Sleep Medicine, 2005). Large longitudinal studies suggest that EDS has become more prevalent (Ford, et al., 2015). It is estimated to affect up to 20% of adults overall and increases with age, especially when the propensity of falling asleep in the daytime is considered (Hara, et al., 2004,Hayley, et al., 2014,Young, 2004). Elderly subjects with EDS are at higher risk of developing cognitive decline and dementia (Elwood, et al., 2011,Foley, et al., 2001,Jaussent, et al., 2012,Keage, et al., 2012,Merlino, et al., 2010,Tsapanou, et al., 2015).

EDS and fatigue often overlap, but are also separate entities (Shen, et al., 2006). Fatigue has been defined as an overwhelming sense of tiredness, lack of energy, and a feeling of exhaustion, associated with impaired physical and/or cognitive functioning (Shen, et al., 2006). The estimated prevalence of fatigue in the general US population is approximately 14.3% in men and 20.4% in women (Chen, 1986). Fatigue-related symptoms in the general German population were shown to increase with advancing age (Schwarz, et al., 2003). Fatigue is independent and complementary to EDS in the assessment of sleep disorders. In insomnia, fatigue is especially prominent while EDS is less common (Hossain, et al., 2005,Pigeon, et al., 2003,Shen, et al., 2006). Unfortunately, most studies have overlooked fatigue symptoms or failed to evaluate both EDS and fatigue within the same study. Although much less explored than EDS, fatigue has also been associated with more rapid cognitive decline and with dementia in the elderly (Lin, et al., 2013,Sterniczuk, et al., 2013).

If EDS and fatigue are associated with cognitive decline, then one would also expect these symptoms to be associated with structural brain abnormalities, akin to the specific cortical thinning signature related to brain pathology in preclinical Alzheimer's disease (AD) (Dickerson, et al., 2009,Vemuri, et al., 2008). In light of recent findings suggesting that normal sleep physiology serves a vital role in the clearance of neurotoxic metabolic byproducts, (ie, beta-amyloid (Xie, et al., 2013)), disturbed sleep manifested by EDS and fatigue may also be a harbinger of an ongoing neurodegenerative process. It remains unknown whether EDS or fatigue are associated with global or regional cortical abnormalities in individuals who are clinically determined to be cognitively normal.

Understanding how novel (and especially prevalent and modifiable) risk factors for cognitive impairment affect the brain is fundamental to allowing appropriate interventions. The aim of this study was to quantify the independent association between EDS and fatigue, with cortical thickness and hippocampal volume in cognitively-normal late middle-aged and older adults.

2. Methods

2.1. Participant Selection

Study participants were a population-based sample of Olmsted County (Minnesota) residents aged 50 years and older enrolled in the Mayo Clinic Study of Aging (MCSA) from November 2004 through November 2014. This study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards and informed consent was obtained from all participants or their surrogates. Details of the MCSA design have been published elsewhere (Roberts, et al., 2008). For the present study, we included all 1374 cognitively normal participants who completed all core questions of the sleep and fatigue assessment and also had a usable 3T structural MRI scan available. There were no subsequent exclusion criteria.

2.2. Cognitive Assessments

Participants underwent a neuropsychological battery as previously described (Roberts, et al., 2008). Four cognitive domains (executive, language, memory, and visual spatial) were assessed. Individual test scores were converted to z-scores using the mean and standard deviation of this sample.

2.3 Sleep and Fatigue Assessments

Participants responded to core questions of the Mayo Sleep Questionnaire (Boeve, et al., 2013), assessing for general sleep disorder symptoms. When individuals had a bed partner, collateral information was obtained. The questionnaire assessed whether subjects had been experiencing 1) changes in their sleep duration,2) dream enactment behavior (acting out of dreams), 3) snoring or choking during sleep, 4) stopping breathing during sleep (witnessed apneas), 5) bedtime restlessness, 6) bedtime leg cramps, and 7) sleepwalking. Subjective daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS) (Johns, 1991). Subjects with ESS score ≥ 10 were considered to have excessive daytime sleepiness (EDS). The ESS has been found to be a valid and reliable tool to separate normal adult subjects from patients with sleep disorders (Johns, 1991,Pallesen, et al., 2007). Studies have shown that ESS scores correlate at least moderately with objective measures of sleepiness (Cai, et al., 2013,Johns, 1991,Leng, et al., 2003). Scores range from 0–24. Although there are no universally adapted cut-off scores for EDS, studies with similar population have utilized ESS score ≥ 10 (Hayley, et al., 2014). Fatigue was assessed using question #20 of the Beck Depression Inventory-II (BDI-II) (Beck, et al., 1996). Subjects that endorsed being too tired or fatigued “to do a lot” (Score=2) or “most of things they used to do” (Score=3) were considered to have clinically significant fatigue. This method of assessing fatigue is exploratory and has not been previously validated. We chose a cut-off score (≥ 2) as a proxy f or clinically significant fatigue given that scores of 2 or more are higher than the average

scores seen in chronic fatigue syndrome (mean 1.48 ± 1.06) (Brown, et al., 2012) and in primary care settings (mean 0.65 ± 0.72) (Arnau, et al., 2001). For individuals with reported and witnessed apneas, CPAP use was inquired. However, due to the epidemiological nature of the present study, polysomnographic confirmation of obstructive sleep apnea (OSA) diagnosis or compliance data were not obtained.

2.4. Medical and Psychiatric Comorbidities Assessment

History of medical conditions (diabetes, hypertension, atrial fibrillation, dyslipidemia) was abstracted by trained nurses using the Rochester Epidemiology Project (REP) medical records-linkage system. Information about obesity (body mass index [BMI]>30), history of tobacco use, and depression (defined by BDI-II score ≥13) (Beck, et al., 1996) were acquired from the structured interview conducted and direct measurement of height and weight by the nurses.

2.5. Structural MRI assessment

Cortical thickness from 3-Tesla magnetization-prepared rapid acquisition gradient echo (MP RAGE) image sequences were estimated using FreeSurfer version 5.3 (Fischl, et al., 2002). Thicknesses were computed from a total of 34 regions of interest (ROIs) with automated cortical parcellation using the Desikan-Killiany Atlas (Desikan, et al., 2006). They were further averaged over left and right hemispheres and grouped into thickness in four lobes: frontal, parietal, temporal, and occipital. The average thickness for each lobe and the global thickness (overall average of all lobes) were used as the primary outcome measures. Additionally, we also used hippocampal volume estimation using FreeSurfer as an outcome measure and computed total intracranial volume using SPM12 software.

2.6. Statistical Analysis

Participants were categorized into 4 groups: 1) without EDS or fatigue (No EDS/fatigue), 2) with EDS only (EDS), 3) with fatigue only (fatigue) and 4) with both EDS and fatigue (EDS and fatigue). Due to the low number of individuals in the EDS and fatigue group (n=11), they were described separately in the results section only. Parametric numerical variables were compared by means of ANOVA followed by Tukey's HSD or Games-Howell post-hoc tests, as appropriate. Non-parametric data were compared by means of the Kruskal-Wallis test followed by Dunn’s post-hoc test. Chi-Square test or Fisher’s exact test followed by post-hoc pairwise comparisons with Bonferroni correction were applied to compare categorical variables, as applicable.

In order to test the association between EDS and fatigue with structural MRI measures, multiple linear regression models were generated using averaged cortical thickness and hippocampal volume as the dependent variable. Multiple linear regression models were created for regional and global cortical thickness. Using the simultaneous entry method, whereby all variables are included at the same time (as opposed to stepwise) (Mundry and Nunn, 2009), EDS and fatigue were included as independent factors. Age, gender, years of education, respiratory symptoms (snore, choke or witnessed apneas), dream enactment, hypertension, diabetes, obesity, depression, and total intracranial volume were also analyzed as independent variables for appropriate control of potential confounders. A secondary

analysis checked for a possible interaction between EDS and Fatigue. P-value was set at 0.05 for two-tailed significance levels. Statistical Analyses were performed with IBM SPSS Statistics for Windows Version 20 (Armonk, NY: IBM Corp).

3. Results

3.1. Demographic characteristics

Of the 1374 cognitively normal participants included in this study, 208 (15%) subjects had EDS only, 27 (2%) had fatigue only, and 11 (0.8%) had both EDS and fatigue symptoms. 1128 participants (82%) had neither EDS nor Fatigue. As shown in Table 1, EDS and fatigue individuals were older than those with No EDS/fatigue. There were no age differences between subjects with EDS and fatigue. There were more men in the EDS group, when compared to the No EDS/fatigue and fatigue groups. No EDS/fatigue subjects had significantly more years of education when compared to fatigue individuals. Subjects with both EDS and fatigue were similarly aged to individuals with either alone and level of education was comparable to the individuals with fatigue only.

3.2. Cognitive assessment

EDS and fatigue subjects had significantly lower scores in all cognitive domains tested, when compared to No EDS/fatigue individuals. Average z-scores demonstrated lower performance in the fatigue group when compared with EDS for all cognitive domains, but this was only significant for the executive domain. Individuals with both EDS and fatigue had even lower scores than fatigue subjects in most domains (global zscore 0.06 ± 0.82).

3.3. Sleep disturbance

The EDS subjects had significantly higher frequency of sleep disturbances compared with the No EDS/fatigue group, including symptoms of snoring or choking, witnessed apneas, dream enactment, bedtime restlessness, and leg cramps. Fatigue subjects reported more frequent reduced sleep and less frequent snore or choke symptoms than all groups. Individuals with both EDS and fatigue had the highest symptom frequency of snoring or choking (54.5%), witnessed apnea (54.5%), and leg cramps (54.5%). Approximately 20% of all subjects were reported to have witnessed apneas by their bed partners. The use of CPAP on this subsample was similar between all groups: 45.5% (No EDS/fatigue), 42.3% (EDS), 33.3% (fatigue) and 33.3% (EDS and fatigue).

3.4. Medical Comorbidities

EDS and fatigue groups had more frequent comorbidities of diabetes, atrial fibrillation, and depression compared to No EDS/fatigue individuals. Hypertension was also more frequent in the EDS and fatigue groups, but only reached statistical significance in the comparison between EDS and No EDS/Fatigue groups. EDS and fatigue groups were similar in their comorbidity profile, except for depression, which was significantly more frequent in the fatigue group. Subjects with both EDS and fatigue had the highest frequency of hypertension (90.9%), obesity (45.5%), dyslipidemia (100%) and depression (63.6%).

3.5. Cortical Thickness and Hippocampal Volume

Cortical thickness was reduced in both the EDS and fatigue groups, when compared to No EDS/fatigue subjects in all regions. The same effect was also seen for hippocampal volume (Figure 1). EDS and fatigue were independently associated with cortical thickness after controlling for multiple confounders (Table 2).

EDS was significantly associated with reduction of cortical thickness in all studied regions, which was maximal in the temporal region. The estimated change was equivalent to more than 3.5 years of aging (95% CI, 1.4–6.2) when compared to the average cortical thinning of 9.6 μm reduction/year predicted by our model. Although fatigue was also associated with overall averaged cortical thickness reduction, this was likely attributed to associations in the frontal and temporal regions. Fatigue- associated cortical thickness reduction was also maximal in the temporal region, and was equivalent to approximately nine additional years (95% CI, 3.6–16) of aging. As opposed to EDS, presence of fatigue also predicted hippocampal volume reduction, which was equivalent to 5.7 years of aging (95% CI, 1–11.1), estimated in 65.7 mm^3 reduction/year by our model. In the hippocampus, only age and fatigue were significantly associated with volume reduction. Cortical thickness was significantly associated with age, gender, years of education, diabetes and obesity, in addition to EDS and fatigue. However, presence of EDS and fatigue were associated with the most prominent reductions in cortical thickness. A secondary analysis failed to reveal a significant interaction between EDS and fatigue, or the association between cortical thicknesses and reduced sleep. Figure 2 illustrates the reduction in temporal cortical thickness predicted by EDS and fatigue over time in comparison to diabetes or obesity.

A sensitivity analysis excluding subjects with witnessed apneas on CPAP from the regression analysis had less power to identify associations between fatigue and cortical thickness other than in the temporal region. The overall results were very similar to the ones herein described (Table A.1 - Appendix).

4. Discussion

To our knowledge, this study is the first to assess the association between EDS and fatigue with regional brain structure in cognitively normal late middle-aged and older adults. EDS was associated with global cortical thinning, whereas fatigue was more associated with regional changes in the frontal and temporal region, including the hippocampus. Cortical thickness reduction predicted by presence of EDS or fatigue was larger than the reduction predicted by presence of obesity and diabetes. Subjects with EDS or fatigue had more frequent medical comorbidities, sleep symptoms, and depression.

4.1. Complex Interplay with Comorbid Disorders

Our results corroborate previous findings indicating the presence of multiple comorbidities in patients with EDS or fatigue (Chen, 1986, Lin, et al., 2015, Ohayon, 2012), and suggest a multifactorial cause for these symptoms. EDS and fatigue symptoms may signal a more profound level of sleep disturbance, which has been associated with increased dementia risk (Benedict, et al., 2015,Sterniczuk, et al., 2013,Yaffe, et al., 2015). Snoring or choking,

reduced sleep duration, and depression were the most important discriminating factors between subjects with EDS or fatigue. More frequent symptoms of snoring, choking, and witnessed apneas in EDS subjects are likely associated with underlying obstructive sleep apnea (OSA). OSA patients appear to be at higher risk of developing mild cognitive impairment (MCI) and AD-dementia (Chang, et al., 2013,Osorio, et al., 2015,Yaffe, et al., 2011). They were found to have similar brain structural abnormalities as the ones attributed to EDS and fatigue in our study, with reduced grey matter volume (GMV) or cortical thickness in frontal, parietal and temporal regions (Joo, et al., 2013,Macey, et al., 2002,Torelli, et al., 2011), including the hippocampus (Dusak, et al., 2013,Macey, et al., 2002,Morrell, et al., 2003,Torelli, et al., 2011). In one study, hippocampal volume reduction was associated with ESS scores (Dusak, et al., 2013). Interestingly, in our regression analysis, symptoms of snoring, choking, or witnessed apneas did not predict cortical thinning, possibly because EDS is a more sensitive marker of severe OSA (Seneviratne and Puvanendran, 2004). However, EDS is not simply a surrogate of severe OSA (Ohayon, 2012,Whitney, et al., 1998) and may be influenced by other factors such as sleep duration, depression, sedating medications and obesity (Sforza, et al., 2015). EDS may also represent a higher degree of sleep fragmentation, which is associated with a reduction in the total cortical GMV (Lim, et al., 2015).

On the other hand, reduced sleep duration was more frequent in the fatigue group, suggesting inadequate sleep duration or more frequent insomnia. Our results may corroborate previous findings of bilateral hippocampal atrophy and frontal cortical thinning in insomniacs (Joo, et al., 2014,Suh, et al., 2016) as well as greater age-related brain atrophy with reduced sleep in healthy older adults (Lo, et al., 2014). However, there is likely a complicated relationship between reduced sleep, fatigue, and depression, which often coexist. Reduced sleep duration increases dementia risk, but the association disappeared after controlling for depression (Hahn, et al., 2014). Moreover, there is a significant body of evidence suggesting that depression increases the risk for AD-dementia (Ownby, et al., 2006). Similar to our findings in subjects with fatigue, depression is associated with reduced hippocampal and frontal GMV, especially in more severe disease (Lorenzetti, et al., 2009). However, fatigue cannot be considered a surrogate of depression alone, as subjects in this group also had high frequencies of medical comorbidities.

Our study focused primarily on cardiovascular and psychiatric comorbidities, but sleepiness and fatigue in the elderly have also been associated with other important comorbid disorders, especially chronic pain and chronic pulmonary diseases (Chen, 1986). Pain and sleep appear to have an important reciprocal relationship. Poor sleep seems to reduce pain threshold and predispose to chronic pain, which may worsen sleep quality (Finan, et al., 2013). Akin to our findings in fatigue patients, hippocampal volume reduction has been reported in healthy elderly adults with increased pain duration and intensity (Zimmerman, et al., 2009). Primarily frontal cortical thickness (Chen, et al., 2016) and fronto-temporal GMV (Zhang, et al., 2013) reduction has also been described in chronic obstructive pulmonary disease.

4.2. EDS and Fatigue may Indicate Brain Atrophy

Very little is known about EDS-related brain structural abnormalities in the elderly. One historical community-based study failed to find an association between daytime sleepiness and brain atrophy in an elderly population using less sensitive imaging measures of global atrophy (ventricle size, central sulcus, and bifrontal distance) (Whitney, et al., 1998). The only study that specifically evaluated the relationship between daytime sleepiness and GMV in healthy individuals was a small sample of nonelderly adults, where left frontal GMV reduction (ventromedial pre-frontal cortex) was associated with higher ESS scores (Killgore, et al., 2012). Nothing is known about fatigue-related brain structural abnormalities in the normal elderly population, only in neurological diseases, which are likely different than normal aging and beyond the scope of the present work.

It is possible that EDS and fatigue may indicate accelerated brain aging. Normal aging is associated with global cortical thinning in longitudinal studies, but the identification of the most susceptible areas remains controversial (Shaw, et al., 2016,Storsve, et al., 2014,Thambisetty, et al., 2010). The cortical thickness reduction predicted by age, EDS and fatigue was maximal in the temporal region, which is consistent with studies showing more age-related susceptibility in this region (Shaw, et al., 2016,Storsve, et al., 2014,Yang, et al., 2016).

However, changes in the temporal lobe, particularly in the hippocampus, are involved with pre-clinical Alzheimer's disease (Andrews, et al., 2016,Dickerson, et al., 2009,Vemuri, et al., 2008) as well as time to progression from MCI to dementia (Jack, et al., 2010), suggesting that EDS and fatigue could be associated with underlying neurodegeneration. This association may occur through the interaction between sleep disorders, cardiovascular risk factors, and depression. Although not fully elucidated, there is a growing body of evidence suggesting that sleep is crucial for the removal of neurotoxic byproducts (Berezuk, et al., 2015,Lucey and Bateman, 2014,Sanchez-Espinosa, et al., 2014,Spira, et al., 2013,Sprecher, et al., 2015,Xie, et al., 2013). However, poor sleep (reduced, fragmented, with apneas) leads to metabolic and cardiovascular dysfunction (Mesas, et al., 2014,Mullington, et al., 2009,Roux, et al., 2000,Strand, et al., 2015), which are also associated with imaging (Goldstein, et al., 2002,Kharabian Masouleh, et al., 2016,Kumar, et al., 2015,Langbaum, et al., 2012,Moran, et al., 2015,Peng, et al., 2015,Soininen, et al., 1992,Villeneuve, et al., 2014) and neuropathological (Gelber, et al., 2015) findings of neurodegeneration, to which depression may also contribute (Elcombe, et al., 2015). Therefore, EDS and fatigue can possibly be an epiphenomenon of impaired clearance/accumulation of metabolic neurotoxic byproducts during sleep or neurodegeneration of areas related to maintenance of wakefulness.

4.3. Limitations

The cross-sectional design did not allow determination of the temporal relationship between EDS and fatigue with changes in cortical thickness. Due to the epidemiological nature of this study, EDS and fatigue were based solely on self-reported subjective variables. Although the Epworth Sleepiness Scale has been extensively used in the literature, it has not been validated in the elderly. A sleep quality assessment such as the Pittsburgh Sleep Quality

Index might have been more sensitive to detect self-reported sleep disturbance (Niu, et al., 2016,Waller, et al., 2016). Lack of a detailed assessment of sleep duration might have limited its potential association with cortical thickness (Spira, et al., 2016). Although fatigue assessment was not optimal, through more comprehensive scales (Shen, et al., 2006), our methods were similar to previously reported methodology in epidemiological studies (Chen, 1986,Sterniczuk, et al., 2013). The low sample size in the fatigue group may have obscured potential group differences and the interaction with EDS. Subjects with both EDS and fatigue were also rare in this sample, not allowing for appropriate comparison. We accounted for only the most common medical comorbidities associated with cognitive decline.

5. Conclusion

EDS and fatigue may indicate accelerated brain aging in cognitively normal late middle-aged and older adults. Our work corroborates the literature suggesting that EDS and fatigue symptoms may also be risk factors for cognitive decline or dementia, especially given their association with significantly altered brain structure primarily in the temporal region, and potential relationship with comorbid sleep disorders, cardiovascular disease and depression. Future large scale longitudinal prospective studies are necessary to clarify the association between incident EDS and fatigue, comorbid disorders, and neurodegeneration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIH grants R00 AG37573, P50 AG16574/P1, R01 AG11378, R01-AG041851, R01AG034676, U01 AG06786; and Opus building NIH grant C06 RR018898. The funding institutions did not participate in study design, data collection, data analysis, manuscript writing, or submission process. Carvalho and Vemuri contributed to study concept and design. All authors participated in data collection. Carvalho contributed to the statistical analysis and drafting of the first manuscript. All co-authors participated in the critical revision of the manuscript.

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Highlights

- Sleepiness and fatigue are associated with significantly altered brain structure
- Sleepiness is associated with global cortical thinning in cognitively-normal elderly
- Fatigue is associated with fronto-temporal cortical thinning in normal elderly
- Fatigue is associated with hippocampal volume reduction in normal elderly
- Sleepiness and fatigue may suggest accelerated brain aging

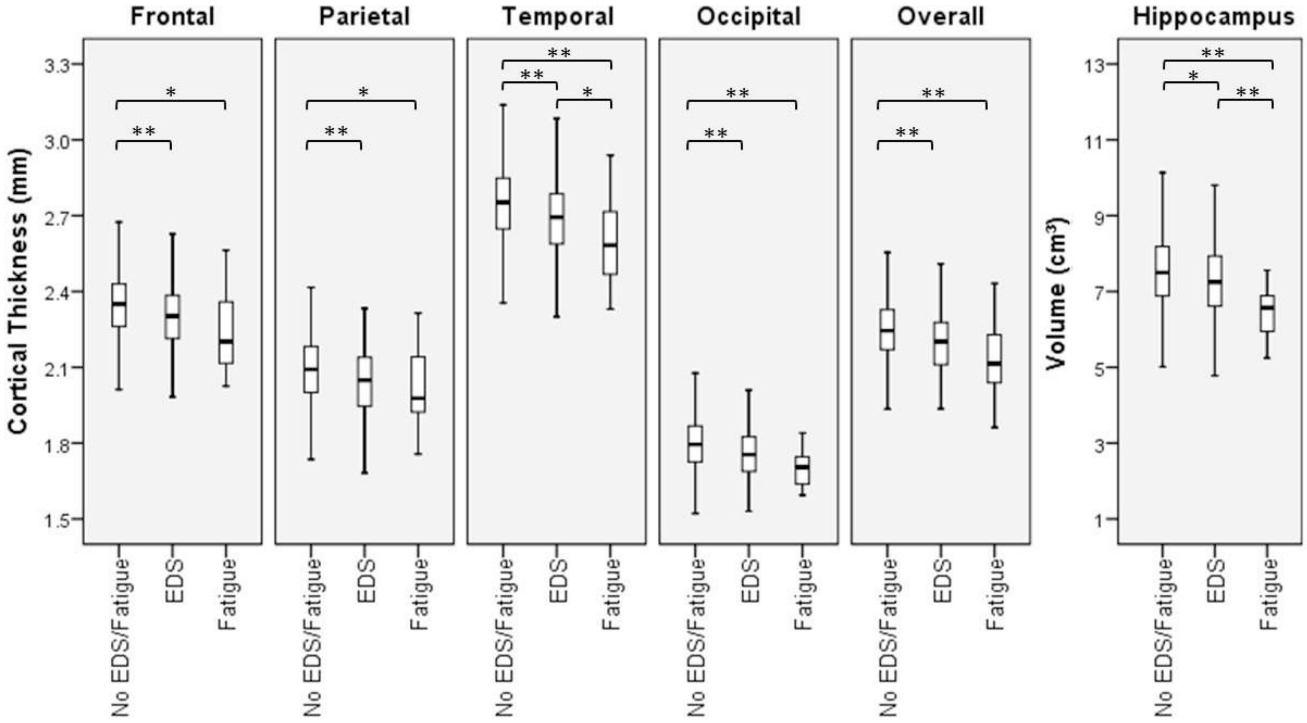

Figure 1.

Boxplot representation shows decrease in cortical thickness in different brain regions and reduced hippocampal size in subjects with EDS and fatigue when compared to individuals without these symptoms. EDS: excessive daytime sleepiness; *: $p<0.05$; **:$p<0.01$.

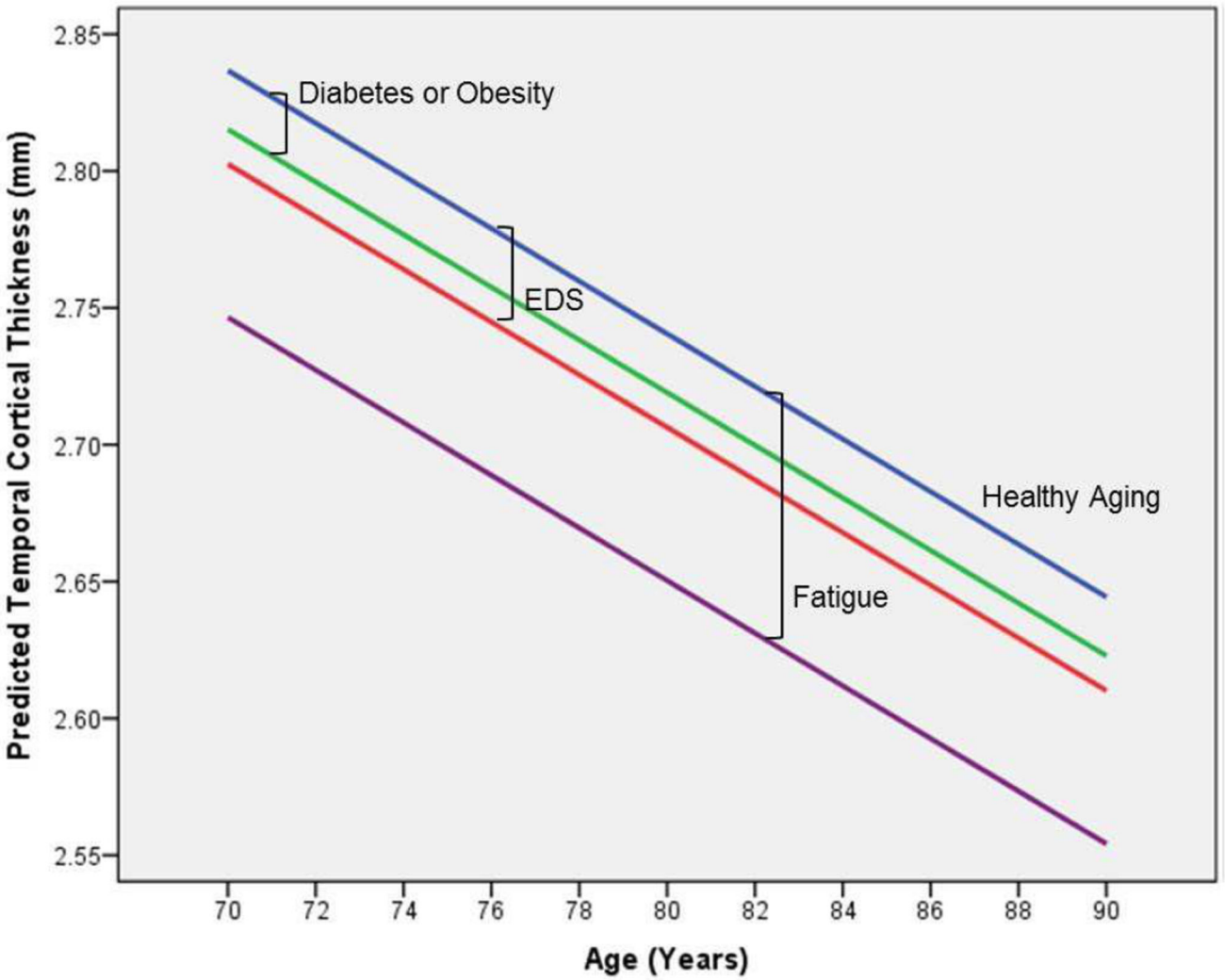

Figure 2.

Illustration reveals the predicted temporal cortical thickness by age according to presence of EDS, fatigue or either diabetes or obesity (similar predicted reduction). EDS: excessive daytime sleepiness. Healthy Aging: individuals without the predictors associated with temporal cortical thickness by our model.

Table 1

Subject demographic and clinical characteristics

Variables	No EDS/Fatigue (N=1128)	EDS (N=208)	Fatigue (N=27)	P-values		
				No EDS/Fatigue vs. EDS	No EDS/Fatigue vs. Fatigue	EDS vs. Fatigue
Age (Years)	71.6 ± 8.7	74.5 ± 8.6	77.2 ± 7.8	<.001	.002	.266
Gender (Male) (%)	699 (62)	167 (80.3)	15 (55.6)	<.001	1	.011
Education (Years) *	15 (12 – 16)	14 (12 – 16)	12 (12 – 15)	.079	.007	.116
Cognitive Evaluation						
Executive (z-score)	0.78 ± 0.87	0.44 ± 0.86	−0.05 ± 0.99	<.001	<.001	.018
Memory (z-score)	0.82 ± 0.96	0.47 ± 0.94	0.33 ± 1.05	<.001	.023	.753
Language (z-score)	0.63 ± 0.85	0.41 ± 0.88	0.18 ± 1.16	.003	.021	.398
Visual spatial (z-score)	0.71 ± 0.94	0.51 ± 0.95	0.12 ± 1.12	.013	.005	.121
Global (z-score)	0.91 ± 0.89	0.55 ± 0.91	0.19 ± 1.08	<.001	<.001	.124
Sleep Screening						
ESS Score *	4 (3 – 6)	11 (10 – 13)	4 (2 –7)	<.001	1	<.001
Bedpartner (yes)	988 (87.6)	175 (84.1)	20 (74.1)	.518	.210	.553
Reduced sleep (yes)	240 (21.3)	32 (15.8)	11 (47.8)	.157	.046	.009
Snore or choke (yes)	266 (23.6)	87 (41.8)	4 (14.8)	<.001	.862	.020
Witnessed apneas (yes)	180 (16)	71 (34.1)	6 (22.2)	<.001	1	.644
Dream enactment (yes)	78 (6.9)	35 (16.8)	3 (11.1)	<.001	1	1
Bedtime restlessness (yes)	81 (7.2)	34 (16.3)	5 (18.5)	<.001	.134	1
Leg cramps (yes)	332 (29.4)	82 (39.4)	9 (33.3)	.013	1	1
Sleepwalking (yes)	7 (0.6)	3 (1.4)	0 (0)	.619	1	1
Comorbidities						
Hypertension (yes)	704 (62.4)	148 (71.2)	21 (77.8)	.048	.308	1
Diabetes (yes)	161 (14.3)	45 (21.6)	11 (40.7)	.021	.003	.085
Obesity (yes)	319 (28.3)	63 (30.3)	11 (40.7)	1	.470	.814
Dyslipidemia (yes)	898 (79.6)	174 (83.7)	23 (85.2)	.535	1	1
Atrial Fibrillation (yes)	96 (8.5)	37 (17.8)	7 (25.9)	<.001	.022	.924
Smoking history (yes)	518 (45.9)	104 (50)	18 (66.7)	.836	.098	.309

Variables	No EDS/Fatigue (N=1128)	EDS (N=208)	Fatigue (N=27)	P-values		
				No EDS/Fatigue vs. EDS	No EDS/Fatigue vs. Fatigue	EDS vs. Fatigue
Depression (yes)	37 (3.3)	16 (7.7)	12 (44.4)	.008	<.001	<.001

*Data are shown as median (25 – 75% percentiles). ESS: Epworth Sleepiness Scale. P-values for all post-hoc pairwise comparisons (Chi-square or Fisher's exact test) between categorical variables underwent Bonferroni Correction. Numerical variables were compared with ANOVA followed by Tukey's HSD post-hoc tests (age, cognitive evaluation) or Kruskal-Wallis followed by Dunn's post-hoc test (education and ESS).

Table 2

Multiple linear regression models estimates for predicted cortical thickness and hippocampal volume.

	Frontal Thickness (μm)		Parietal Thickness (μm)		Temporal Thickness (μm)		Occipital Thickness (μm)		Overall Thickness (μm)		Hippocampal Volume (mm^3)	
Predictors	**B (95% CI)**	**p**	**B (95% CI)**	**p**	**B (95% CI)**	**p**	**B (95% CI)**	**p**	**B (95% CI)**	**p**	**B (95% CI)**	**p**
Age (years)	−6.3(−7;−5.5)	<.001	−7.1(−7.9; −6.4)	<.001	−9.6(−10.5; −8.7)	<.001	−5.5(−6.1; −4.9)	<.001	−7.1(−7.8; −6.5)	<.001	−65.7(−70.7; −60.7)	<.001
Gender (male)	−5.9(−22.9;11.1)	.494	−31.7(−48.4; −14.9)	<.001	−12.1(−31.3;7.1)	.216	−24.7(−38.2;−11.1)	<.001	−18.6(−33; −4.2)	.011	−52(−161.5;57.5)	.352
Education (years)	2.6(0.3;4.9)	.030	2.1(−0.2;4.4)	.078	2(−0.6;4.6)	.132	1.8(0;3.7)	.053	2.1(0.2;4.1)	.035	−9.1(−24.1;5.9)	.235
EDS	**−26.5(−44.1; −8.9)**	**.003**	**−23.1(−40.4; −5.7)**	**.009**	**−34.2(−54.1; −14.3)**	**.001**	**−20.9(−34.9; −6.8)**	**.004**	**−26.1(−41.1; −11.2)**	**.001**	−52.1(−165.7;61.4)	.368
Fatigue	**−48.7(−94.7; −2.7)**	**.038**	−14.2(−59.6;31.1)	.539	**−90.2(−142.1; −38.2)**	**.001**	−27.4(−64.1;9.2)	.142	**−45.1(−84.1; −6.2)**	**.023**	**−374.2(−670.8; −77.7)**	**.013**
Dream Enactment	−1.5(−23.7;20.6)	.892	2.4(−19.4;24.2)	.830	−1.2(−26.2;23.8)	.925	4.2(−13.5;21.8)	.643	1(−17.8;19.7)	.920	26.3(−116.5;169.1)	.718
Respiratory Symp.	−6.8(−20.4;6.7)	.323	−1(−14.3;12.4)	.889	−1.5(−16.9;13.8)	.846	−1.2(−12;9.7)	.835	−2.6(−14.1;8.9)	.655	17.8(−69.7;105.3)	.690
Hypertension	−4.2(−18.1;9.7)	.553	−0.6(−14.3;13.1)	.930	−11.6(−27.3;4.2)	.150	−5.2(−16.3;5.9)	.359	−5.4(−17.2;6.4)	.369	−63.2(−152.9;26.5)	.167
Diabetes	**−27.2(−44.7; −9.6)**	**.002**	**−21.9(−39.2; −4.6)**	**.013**	**−21.5(−41.3; −1.7)**	**.034**	**−14.4(−28.4; −0.4)**	**.044**	**−21.2(−36.1; −6.4)**	**.005**	−83.1(−196.1;30)	.150
Obesity	−13.9(−28.1;0.3)	.055	−5.7(−19.7;8.3)	.424	**−20.7(−36.7; −4.6)**	**.012**	−0.3(−11.6;11)	.960	−10.1(−22.1;1.9)	.098	−20.7(−112.2;70.7)	.656
Depression	−18(−47.8;11.9)	.237	−13.1(−42.5;16.3)	.383	−21.2(−54.9;12.6)	.219	−14.6(−38.4;9.2)	.228	−16.7(−42;8.6)	.195	−177.8(−370.2;14.6)	.070
Model performance	R	0.49	R	0.53	R	0.59	R	0.52	R	0.59	R	0.69
models p< 0.001	Adj. R^2	0.24	Adj. R^2	0.28	Adj. R^2	0.35	Adj. R^2	0.27	Adj. R^2	0.35	Adj. R^2	0.47

EDS: excessive daytime sleepiness; Respiratory symp. (snore, choke or witnessed apneas).