APOEε4 and slow wave sleep in older adults

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Abstract

Slow wave (or stage N3) sleep has been linked to a variety of cognitive processes. However, the role of stage N3 in the elderly is debated. The link between stage N3 and episodic memory may be weakened or changed in the older adult population, possibly due to several altered mechanisms impacting the cellular structure of the brain. The bases for the age-related dissociation between stage N3 and cognition are not understood. Since *APOE*ε4 status is the strongest genetic risk factor for cognitive decline, we assessed whether the ε4 allele is associated with stage N3 sleep. Participants were from the population-based Osteoporotic Fractures in Men (MrOS) cohort with polysomnography and *APOE*ε4 genotype data (n = 2,302, 100% male, mean age 76.6 years). Sleep stages were objectively measured using overnight in-home polysomnography and central electroencephalogram data were used to score stage N3 sleep. Cognitive function was assessed using the Modified Mini Mental State Exam (3MS). The *APOE* rs429358 single nucleotide polymorphism, which defines the *APOE*ε4 allele, was genotyped using a custom genotyping array. Total time in stage N3 sleep was significantly higher (p<0.0001) among the 40 MrOS participants carrying two copies of the ε4 allele (62±5.2 minutes) compared with 43±1.5 minutes for carriers of one ε4 allele (n = 515) and 40±0.8 minutes for ε4 non-carriers (n = 1747). All results were independent of sleep efficiency, number of sleep cycles, and apnea hypopnea index. These findings support an association between *APOE*ε4 genotype and sleep stage N3 in the elderly. Increased total stage N3 duration among ε4/ε4 carriers does not appear to reflect compensation for prior cognitive decline and may reflect overactive downscaling of

synapses during sleep. If confirmed, these results might in part explain the high risk of age-related cognitive decline and AD among APOE ε4/ε4 carriers.

Introduction

Sleep disturbances and specific sleep disorders increase with advancing age [1–6] and elevate the risk for a variety of diseases and conditions [7–22] including cognitive impairment [23–33]. Recent research indicates that sleep may specifically impact the cellular structure of the brain, including the ability of the brain to clear toxic metabolites that accumulate with normal neuronal function [34]. This includes beta-amyloid [34], which accumulates in apolipoprotein E (*APOE*) ε4 genotype carriers [35] and contributes to synaptic degeneration and cognitive decline. While the *APOEε4* allele is a well-established risk factor for Alzheimer's disease (AD) and age-related cognitive decline [36–42] as well as a risk factor for sleep apnea [43–51], *APOEε4* has not been assessed in relation to sleep stage distributions. To explore the hypothesis that *APOEε4* influences sleep architecture, we examined the effect of the *APOEε4* allele on sleep stage distribution measured in a large, population-based cohort of elderly participants with a focus on stage N3, which represents the synchronization of cortical EEG activity and has been implicated in memory formation in young populations [52–57]. Given the high risk of cognitive decline and AD among *APOEε4* carriers, identifying a genetic link with stage N3 sleep could advance the development of new approaches for interventions to slow the decline in cognitive function among ε4 allele carriers and that may also benefit the health and well-being of the elderly.

Materials and methods

Participants

Data were collected from participants of the Osteoporotic Fractures in Men (MrOS) Study which included participants who were at least 65 years old and excluded participants who required assistance with ambulation or had undergone bilateral hip replacement. In the MrOS study, 5994 older men were recruited from six geographical areas (Birmingham, AL; the Monongahela Valley near Pittsburgh, PA; Minnaepolis, MN; Palo Alto, CA; San Diego, CA; and Portland, OR) between 2000 and 2002. The MrOS Sleep Study, an ancillary study of the parent MrOS cohort, was conducted between December 2003 and March 2005 and recruited 3135 MrOS participants (68%) for a comprehensive sleep assessment and assessment of circadian gene polymorphisms. Of the 2,859 men who did not participate in this ancillary study, 344 died before the sleep visit, 36 had already stopped participating in the study, 332 were not invited because recruitment goals had already been met, 150 were not eligible and 1,997 refused. Among the participants of the MrOS Sleep Study, 2480 self-identified white men who had DNA extracted for genetic studies. Details regarding the studies have been published previously [58,59]. All data were collected with written informed consent as approved by the institutional review boards of the clinical sites (University of Alabama at Birmingham; University of Minnesota; University of Pittsburgh; Stanford University; Oregon Health & Science University; and University of California, San Diego) and the coordinating center (University of California, San Francisco). The Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep Study) [60], an ancillary study of the parent MrOS Study, enrolled 3,135 participants from 2003–2005. Of the 3135 enrolled participants, 2911 had usable PSG data and, of these, 2745 (94%) with evaluable sleep staging data. The Modified Mini Mental State Exam [61,62] (3MS),

an expanded 100 point version of the original MMSE, was administered in MrOS at the baseline and sleep exams (~3 years) [63]. The Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) questionnaires were administered at the sleep exam.

Polysomnography

In-home, single night sleep studies using unattended polysomnography (PSG, Safiro, Compumedics, Inc., Melbourne, Australia) were performed as previously described [64,65]. The recording montage consisted of C_3/A2 and C_4/A_1 electroencephalograms, bilateral electroculograms, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, airflow (using nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry, electrocardiogram, body position (mercury switch sensor), and bilateral leg movements (piezoelectric sensors). Trained certified staff members performed home visits for setup of the sleep study units. After sensors were placed and calibrated, signal quality and impedance were checked, and sensors were repositioned as needed to improve signal quality, replacing electrodes if impedances were elevated, using approaches similar to those in the Sleep Health Heart Study [66]. After studies were downloaded, they were transferred to the Case Western Reserve University Reading Center (Cleveland, OH) for centralized scoring of sleep stages and sleep disorders by a trained technician using standard criteria [67,68]. Sleep was staged in 30-sec scoring epochs and electroencephalogram data were used to score stage N3 using the criteria of Rechtschaffen and Kales [67]. Total time (minutes) and percent time [100*(Number of minutes scored as stage 3–4)/(total sleep time)] in stage N3 were calculated for these analyses. The apnea hypopnea index (AHI) was calculated as the total number of apneas and hypopneas per hour of sleep (4% desaturation) [69]. Sleep cycles were defined using a modified version of the rules detailed by Feinberg and Floyd [70]. A cycle was defined as a period of at least 15 minutes of NREM sleep starting with stage N2 or N3 and terminated by the end of a period of REM sleep lasting at least 5 minutes for all cycles except cycle 1, or a period of wake or stage N1 lasting 15 minutes or longer. Two epochs of REM sleep separated by no more than 15 minutes of NREM sleep or wake were merged into a single REM period. Average absolute spectral power density in $\log_{10}$(uV^2/Hz) was calculated for each sleep cycle for the following bands: Slow oscillation: 0.25–1 Hz, Delta: 1.25–4 Hz, Theta: 4.25–8 Hz, Alpha: 8.25–12 Hz, Sigma: 12.25–15 Hz, and Beta: 15.25–20 Hz. There was excellent interscorer reliability for the key sleep parameters, including stage N3 (ICCs >0.92). Several additional sleep parameters were scored, including: wake after sleep onset time and sleep efficiency.

APOE genotyping

The *APOE* rs429358 SNP, which defines the *APOEε4* allele, was genotyped using a custom Illumina Golden Gate assay (Illumina, San Diego, CA, USA) that included 529 SNPs as previously described [71]. All individuals in this study are of European ancestry and are unrelated. Of 2,745 MrOS participants with PSG, 2,302 were genotyped for the rs429358 C/T alleles, which define *APOEε4* status by the presence of the C allele. All participants in this analysis are of European ancestry.

Statistical analyses

Associations between *APOEε4* status and sleep staging were based on 2,302 MrOS participants with both PSG and rs429358 genotype data. All PSG and cognition measures were treated as continuous variables in analyses examining both additive and dominant genetic models to examine *APOEε4* associations for total time and percent time spent in stage N3. All regression

models were adjusted for age and clinic site with additional models including measures of sleep duration (TST), quality (WASO time and sleep efficiency) and AHI. Cognitive function change (~3 years) from the visit prior to sleep assessment was calculated and used to stratify stage N3-cognition analyses into high and low decline groups. All analyses were analyzed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Differences in age, cognition, sleep performance and stage N3 across three *APOEε4* categories are shown in Table 1. Total stage N3 time was significantly higher among 40 MrOS participants carrying two copies of the ε4 allele (62±5.2 minutes) compared with 43±1.5 minutes for carriers of one ε4 allele (n = 515) and 40±0.8 minutes for ε4 non-carriers (n = 1747). The *APOEε4* association with stage N3 time (p = 0.0002) was not altered by adjustment for 3MS (p = 0.0001). We examined the *APOEε4*-stage N3 association among MrOS participants who had experienced either ≥2 point decline or <2 point decline (based on median change) from the previous 3MS assessment to the 3MS measured at the sleep visit. Total stage N3 time was significantly higher among participants carrying two copies of the ε4 allele when compared to the other genotype categories in both the group with ≥2 point 3MS decline (p<0.0001) and the group with <2 point decline (p = 0.0002) and the test for interaction between *APOE* allele and 3MS decline was not significant (p = 0.21). In addition, the APOEε4 association with 3MS

Table 1. Characteristics of MrOS participants with PSG sleep staging and *APOE* genotyping.

		APOEε4 alleles		p-value[a]	p-value[b]
	0	**1**	**2**		
n (%)	1747 (75.8)	515 (22.5)	40 (1.7)		
	mean (SE)	mean (SE)	mean (SE)		
Age, y	76.6 (0.1)	76.5 (0.2)	75.6 (0.9)	0.48	0.13
3MS (0 to 100)*	93.4 (0.1)	92.4 (0.2)	90.2 (0.8)	< .0001	0.003
Change 3MS*[c]	-1.01 (0.1)	-1.47 (0.2)	-3.34 (0.7)	0.0025	0.0026
Time in stage N3 (min)*	40 (0.8)	43 (1.5)	62 (5.2)	< .0001	< .0001
Change 3MS ≥ -2	41 (1.0)	42 (1.8)	61 (7.4)	0.03	0.008
Change 3MS < -2	38 (1.4)	45 (2.5)	64 (7.5)	0.0005	0.002
Time in REM (min)*	70 (0.7)	68 (1.2)	65 (4.5)	0.21	0.13
Time in stage N1 (min)*	24 (0.3)	24 (0.6)	22 (2.1)	0.68	0.48
Sleep efficiency (%)*	76 (0.3)	76 (0.5)	81 (1.9)	0.05	0.01
Wake after sleep onset (min)	115 (1.6)	116 (2.8)	86 (10)	0.02	0.005
Apnea hypopnea index (4% desat)*	13 (0.3)	12 (0.6)	14 (2.1)	0.57	0.56
Number of sleep cycles*	4.7 (0.03)	4.6 (0.1)	4.6 (0.2)	0.50	0.97
Spectral power density- SOsc ($\log_{10}$(uV^2/Hz))*[d]	1.9 (0.01)	1.9 (0.02)	2.0 (0.6)	0.15	0.06
Arousal index	24 (0.3)	23 (0.5)	24 (1.9)	0.10	0.93
PSQI*	5.6 (0.1)	5.5 (0.1)	5.3 (0.5)	0.69	0.55
ESS*	6.1 (0.1)	6.1 (0.2)	5.7 (0.6)	0.76	0.47
Hypnotics, n	38	10	0		

* Adjusted for age

[a] Linear p-value across three genotypes

[b] P-value comparing carriers of two ε4 alleles to all others

[c] Baseline to sleep visit ~ 3 years.

[d] Spectral power density of the C3-A2 EEG in the slow oscillation (0.25–1 Hz) band for the final sleep cycle.

PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale

(p<0.0001) was not altered by adjustment for stage N3 time (p<0.0001) and the test for inter-action between APOEε4 and stage N3 time in the association with 3MS was statistically significant (p = 0.006). The APOE ε4/ε4 genotype was associated with higher sleep efficiency and lower WASO but not the PSQI or ESS assessments. Spectral power density of the C3-A2 EEG in the slow oscillation (0.25–1 Hz) band was calculated for the final sleep cycle and did not differ among *APOE* alleles (Table 1). The total number of sleep cycles did not differ among *APOE* alleles (Table 1). The *APOE* associations with total stage N3 time did not change after additional adjustment for sleep efficiency (ε4/ε4 = 59±5.2 minutes, p = 0.0003), wake after sleep onset (ε4/ε4 = 60±5.2 minutes, p = 0.0002), number of sleep cycles (ε4/ε4 = 64±5.6 minutes, p = 0.0001), or AHI (ε4/ε4 = 62±5.1 minutes, p<0.0001).

Discussion

In the present study of >2,300 older men, we confirmed a significant association between *APOEε4* status and lower cognitive function scores and unexpectedly found that *APOEε4* was associated with increased stage N3 duration. Average total stage N3 time was >50% longer among elderly *APOE* ε4/ε4 carriers (those who at the highest risk of developing AD and age-related cognitive decline [36–42]) when compared to those with one or no copies of the ε4 allele. While those with the *APOE* ε4/ε4 genotype had more stage N3 time, stage N3 was not associated with cognitive decline in MrOS [72], even after adjustment for APOEε4 statusConsistent with increased stage N3 time among ε4/ε4 genotype carriers, the *APOE* ε4/ε4 genotype was also associated with higher sleep efficiency and decreased WASO, indicating overall less arousability. This finding was unexpected but could reflect a compensatory mechanism wherein the consolidation process is upregulated in reaction to declining cognition. In order to test this possibility we examined the *APOEε4*-stage N3 association among *APOE* ε4/ε4 participants who had experienced either high or low ~3-year decline from the previous 3MS assessment. Total stage N3 time did not differ between participants who had experienced either high or low declines suggesting that the longer stage N3 time among ε4/ε4 carriers is not compensating for prior cognitive decline. It has been suggested that the negative correlations previously observed between stage N3 and subsequent learning in older adults is unlikely due to memory consolidation [73], and might be explained by another function of stage N3 such as synaptic downscaling or pruning [74]. During waking hours, encoding leads to increased synaptic weights which eventually results in the saturation of synaptic networks. The downscaling of certain synapses which takes place during stage N3 likely serves to ensure the maintenance of balanced synaptic input. The negative correlations observed between stage N3 and memory in older adults, however, may reflect an altered balance between daytime encoding and nighttime downscaling wherein older adults engage in less daytime encoding than younger adults [75] but over-downscale if they are still gaining relatively high amounts of stage N3. Thus, an age-related proportional increase in downscaling would presumably become detrimental to memory functioning if synapses that could otherwise help encode new memories are pruned. Such sleep-dependent synaptic downscaling has been observed in Drosophila [76,77].

Synaptic plasticity and scaling are crucial mechanisms in memory flexibility and AD onset [73,78,79] with experimental downscaling of AMPA receptors contributing directly to AD pathology [78]. In light of the genetic association data presented herein, it is possible that *APOE* ε4/ε4 carriers are experiencing "overactive downscaling" [73]. APOE is produced by the glia in the central nervous system [80], while APOE receptors are expressed on the neuronal cell surface where they mediate lipoprotein uptake and signal transduction [81,82]. It has been proposed that APOE isoforms may differentially accelerate synapse dysfunction and AD

dementia by interfering with APOE receptor-dependent neuromodulation [81]. Of the three *APOE* isoforms (ε2, ε3, and ε4), *APOEε4* selectively impairs synaptic plasticity and NMDA receptor phosphorylation by Reelin, a modulator of synaptic strength [79]. This selective impairment of APOE receptor signaling by the APOEε4 isoform leads to a decrease in synaptic responsiveness [79]. The APOEε4 isoform also reduces glutamate receptor function and synaptic plasticity by selectively impairing APOE receptor recycling in primary neurons [79].

Sleep also impacts the cellular structure of the brain, including the ability of the brain to clear beta-amyloid, contributing to synaptic degeneration and cognitive decline [34]. For example, chronic sleep restriction increases amyloid-B plaque formation in the amyloid precursor protein transgenic mic [34]. Sleep also impacts the ability of the brain to remove potentially toxic biomolecules that accumulate with normal neuronal function, including beta-amyloid [34], which accumulates in *APOEε4* genotype carriers [35]. This "glymphatic system" is strongly stimulated by sleep and is associated with an increase in interstitial volume, possibly by shrinkage of astroglial cells, leading to clearance activity. Clearance during sleep is as much as two-fold faster than during waking hours [34]. Thus, glymphatic dysfunction may play a role in the pathogenesis of neurodegeneration as well as maintenance of cognition. However, it is also possible that accumulation of beta-amyloid and other toxic metabolites may influence synaptic connectivity, and thus influence neurophysiological mechanisms of sleep, altering sleep state distributions [83].

Few studies have examined the role of *APOE* genotype in both sleep and cognitive performance [84,85]. In a study of 126 cognitively normal adults (30–70 years), chronic daytime somnolence was associated with a distinctive decline in verbal memory among *APOE* ε4/ε4 carriers as compared to *APOEε4* heterozygotes and noncarriers [84]. A second study examined how sleep parameters in AD patients change over time as a function of *APOEε4* status [85]. Among forty-four community-dwelling adults with a diagnosis of probable AD there was greater deterioration on sleep parameters (increased WASO time and decreased TST and sleep efficiency) in non-*APOEε4* carriers when compared with positive *APOEε4* carriers [85]. Associations between sleep performance and cognition also differed between *APOEε4* carriers and non-carriers [85]. The *APOEε4* allele has also been identified in studies as a risk factor for sleep apnea, although the associations have not been consistent [43–51]. Despite these previous *APOEε4* -sleep associations, the *APOEε4*-stage N3 results reported herein were independent of objective measures of sleep continuity as well as apnea hypopnea index.

In conclusion, these findings support a role for *APOEε4* genotype in the regulation of stage N3 in the elderly. Despite the established role of stage N3 in executive function [52,53] and memory consolidation [54–57] in younger and middle-aged adults, the link between stage N3 and cognitive function may be weakened or changed in older adult population [73,86–89] (including the MrOS study [72]). The negative correlations between stage N3 and subsequent learning in older adults could involve several altered mechanisms [74,90] (including memory consolidation, synaptic downscaling, or other macromolecular changes during stage N3 [83]). As demonstrated in previous studies, increased stage N3 might predicts worse episodic memory consolidation in the elderly [88] and may be detrimental to morning recall [73,91–94]. Similar changes to the sleep–memory link have also been reported for old rodents [95,96] showing that normal hippocampal reactivation is not preserved in older rats and that deep sleep was associated with worse memory performance as measured by performance on the Morris Water Maze task. Further research is needed to confirm the *APOEε4*- stage N3 associations and to identify the mechanism(s) by which *APOEε4* alterations impact sleep architecture. Quantitative EEG analysis will be useful also to elucidate whether *APOE* influences homeostatic drive and sleep dynamics, and whether such changes associate with cognition. The important strengths of this study are the large number of participants with overnight PSG,

longitudinal cognitive function measures, and *APOEε4* genotyping. An additional study strength is the use of a large cohort of older adults who were not selected on the basis of sleep or cognition characteristics. This study, however, was limited to white men and may not be generalizable to other populations or women. If it is confirmed that increased total stage N3 time among *APOE* ε4/ε4 carriers reflects an overactive downscaling of synapses during sleep, these results might in part explain the high risk of AD and age-related cognitive decline among *APOE* ε4/ε4 carriers.

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References

1. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, et al. (1995) Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep 18: 425–432. PMID: 7481413

2. Ancoli-Israel S, Klauber MR, Stepnowsky C, Estline E, Chinn A, et al. (1995) Sleep-disordered breathing in African-American elderly. Am J Respir Crit Care Med 152: 1946–1949. https://doi.org/10.1164/ajrccm.152.6.8520760 PMID: 8520760

3. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, et al. (1991) Sleep-disordered breathing in community-dwelling elderly. Sleep 14: 486–495. PMID: 1798880

4. Ancoli-Israel S, Kripke DF, Klauber MR, Parker L, Stepnowsky C, et al. (1993) Natural history of sleep disordered breathing in community dwelling elderly. Sleep 16: S25–29. PMID: 8178017

5. Ancoli-Israel S, Alessi C (2005) Sleep and aging. Am J Geriatr Psychiatry 13: 341–343. https://doi.org/10.1176/appi.ajgp.13.5.341 PMID: 15879581

6. Ancoli-Israel S, Kripke DF (1991) Prevalent sleep problems in the aged. Biofeedback Self Regul 16: 349–359. PMID: 1760457

7. Al-Delaimy WK, Manson JE, Willett WC, Stampfer MJ, Hu FB (2002) Snoring as a risk factor for type II diabetes mellitus: a prospective study. Am J Epidemiol 155: 387–393. PMID: 11867347

8. Ayas NT, White DP, Al-Delaimy WK, Manson JE, Stampfer MJ, et al. (2003) A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care 26: 380–384. PMID: 12547866

9. Elmasry A, Janson C, Lindberg E, Gislason T, Tageldin MA, et al. (2000) The role of habitual snoring and obesity in the development of diabetes: a 10-year follow-up study in a male population. J Intern Med 248: 13–20. PMID: 10947876

10. Ficker JH, Dertinger SH, Siegfried W, Konig HJ, Pentz M, et al. (1998) Obstructive sleep apnoea and diabetes mellitus: the role of cardiovascular autonomic neuropathy. Eur Respir J 11: 14–19. PMID: 9543264

11. Grunstein RR, Stenlof K, Hedner J, Sjostrom L (1995) Impact of obstructive sleep apnea and sleepiness on metabolic and cardiovascular risk factors in the Swedish Obese Subjects (SOS) Study. Int J Obes Relat Metab Disord 19: 410–418. PMID: 7550526

12. Jennum P, Sjol A (1993) Snoring, sleep apnoea and cardiovascular risk factors: the MONICA II Study. Int J Epidemiol 22: 439–444. PMID: 8359959

13. Newman AB, Enright PL, Manolio TA, Haponik EF, Wahl PW (1997) Sleep disturbance, psychosocial correlates, and cardiovascular disease in 5201 older adults: the Cardiovascular Health Study. J Am Geriatr Soc 45: 1–7. PMID: 8994480

14. Newman AB, Nieto FJ, Guidry U, Lind BK, Redline S, et al. (2001) Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. Am J Epidemiol 154: 50–59. PMID: 11434366

15. Newman AB, Spiekerman CF, Enright P, Lefkowitz D, Manolio T, et al. (2000) Daytime sleepiness predicts mortality and cardiovascular disease in older adults. The Cardiovascular Health Study Research Group. J Am Geriatr Soc 48: 115–123. PMID: 10682939

16. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, et al. (2001) Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 163: 19–25. https://doi.org/10.1164/ajrccm.163.1.2001008 PMID: 11208620

17. Ancoli-Israel S, Kripke DF, Klauber MR, Fell R, Stepnowsky C, et al. (1996) Morbidity, mortality and sleep-disordered breathing in community dwelling elderly. Sleep 19: 277–282. PMID: 8776783

18. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR (2002) Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 59: 131–136. PMID: 11825133

19. Manabe K, Matsui T, Yamaya M, Sato-Nakagawa T, Okamura N, et al. (2000) Sleep patterns and mortality among elderly patients in a geriatric hospital. Gerontology 46: 318–322. https://doi.org/10.1159/000022184 PMID: 11044786

20. Mant A, King M, Saunders NA, Pond CD, Goode E, et al. (1995) Four-year follow-up of mortality and sleep-related respiratory disturbance in non-demented seniors. Sleep 18: 433–438. PMID: 7481414

21. Rockwood K, Davis HS, Merry HR, MacKnight C, McDowell I (2001) Sleep disturbances and mortality: results from the Canadian Study of Health and Aging. J Am Geriatr Soc 49: 639–641. PMID: 11380758

22. Stone KL, Ewing SK, Ancoli-Israel S, Ensrud KE, Redline S, et al. (2009) Self-reported sleep and nap habits and risk of mortality in a large cohort of older women. J Am Geriatr Soc 57: 604–611. https://doi.org/10.1111/j.1532-5415.2008.02171.x PMID: 19220560

23. Blackwell T, Yaffe K, Ancoli-Israel S, Schneider JL, Cauley JA, et al. (2006) Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 61: 405–410. PMID: 16611709

24. Cricco M, Simonsick EM, Foley DJ (2001) The impact of insomnia on cognitive functioning in older adults. J Am Geriatr Soc 49: 1185–1189. PMID: 11559377

25. Meguro K, Ueda M, Kobayashi I, Yamaguchi S, Yamazaki H, et al. (1995) Sleep disturbance in elderly patients with cognitive impairment, decreased daily activity and periventricular white matter lesions. Sleep 18: 109–114. PMID: 7792490

26. Ohayon MM, Vecchierini MF (2002) Daytime sleepiness and cognitive impairment in the elderly population. Arch Intern Med 162: 201–208. PMID: 11802754

27. Bonnet MH (1993) Cognitive effects of sleep and sleep fragmentation. Sleep 16: S65–67. PMID: 8178030

28. Crenshaw MC, Edinger JD (1999) Slow-wave sleep and waking cognitive performance among older adults with and without insomnia complaints. Physiol Behav 66: 485–492. PMID: 10357438

29. Dealberto MJ, Pajot N, Courbon D, Alperovitch A (1996) Breathing disorders during sleep and cognitive performance in an older community sample: the EVA Study. J Am Geriatr Soc 44: 1287–1294. PMID: 8909342

30. Edinger JD, Glenn DM, Bastian LA, Marsh GR (2000) Slow-wave sleep and waking cognitive performance II: Findings among middle-aged adults with and without insomnia complaints. Physiol Behav 70: 127–134. PMID: 10978487

31. Engleman HM, Kingshott RN, Martin SE, Douglas NJ (2000) Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). Sleep 23 Suppl 4: S102–108.

32. Granat P (1990) Sleep loss and cognitive performance. J Fam Pract 30: 632.

33. McCann UD, Penetar DM, Shaham Y, Thorne DR, Gillin JC, et al. (1992) Sleep deprivation and impaired cognition. Possible role of brain catecholamines. Biol Psychiatry 31: 1082–1097. PMID: 1356024

34. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, et al. (2013) Sleep drives metabolite clearance from the adult brain. Science 342: 373–377. https://doi.org/10.1126/science.1241224 PMID: 24136970

35. Lim YY, Mormino EC, Alzheimer's Disease Neuroimaging I (2017) APOE genotype and early beta-amyloid accumulation in older adults without dementia. Neurology.

36. Berlau DJ, Corrada MM, Head E, Kawas CH (2009) APOE epsilon2 is associated with intact cognition but increased Alzheimer pathology in the oldest old. Neurology 72: 829–834. https://doi.org/10.1212/01.wnl.0000343853.00346.a4 PMID: 19255410

37. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, et al. (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261: 921–923. PMID: 8346443

38. Burt TD, Agan BK, Marconi VC, He W, Kulkarni H, et al. (2008) Apolipoprotein (apo) E4 enhances HIV-1 cell entry in vitro, and the APOE epsilon4/epsilon4 genotype accelerates HIV disease progression. Proc Natl Acad Sci U S A 105: 8718–8723. https://doi.org/10.1073/pnas.0803526105 PMID: 18562290

39. Mahley RW, Rall SC Jr. (2000) Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet 1: 507–537. https://doi.org/10.1146/annurev.genom.1.1.507 PMID: 11701639

40. Weisgraber KH, Innerarity TL, Newhouse YM, Young SG, Arnold KS, et al. (1988) Familial defective apolipoprotein B-100: enhanced binding of monoclonal antibody MB47 to abnormal low density lipoproteins. Proc Natl Acad Sci U S A 85: 9758–9762. PMID: 3200853

41. Cosentino S, Scarmeas N, Helzner E, Glymour MM, Brandt J, et al. (2008) APOE epsilon 4 allele predicts faster cognitive decline in mild Alzheimer disease. Neurology 70: 1842–1849. https://doi.org/10.1212/01.wnl.0000304038.37421.cc PMID: 18401023

42. Mahley RW, Huang Y (2006) Apolipoprotein (apo) E4 and Alzheimer's disease: unique conformational and biophysical properties of apoE4 can modulate neuropathology. Acta Neurol Scand Suppl 185: 8–14. https://doi.org/10.1111/j.1600-0404.2006.00679.x PMID: 16866905

43. Cosentino FI, Bosco P, Drago V, Prestianni G, Lanuzza B, et al. (2008) The APOE epsilon4 allele increases the risk of impaired spatial working memory in obstructive sleep apnea. Sleep Med 9: 831–839. https://doi.org/10.1016/j.sleep.2007.10.015 PMID: 18083630

44. Craig D, Hart DJ, Passmore AP (2006) Genetically increased risk of sleep disruption in Alzheimer's disease. Sleep 29: 1003–1007. PMID: 16944667

45. Foley DJ, Masaki K, White L, Redline S (2001) Relationship between apolipoprotein E epsilon4 and sleep-disordered breathing at different ages. Jama 286: 1447–1448. PMID: 11572727

46. Gozal D, Capdevila OS, Kheirandish-Gozal L, Crabtree VM (2007) APOE epsilon 4 allele, cognitive dysfunction, and obstructive sleep apnea in children. Neurology 69: 243–249. https://doi.org/10.1212/01.wnl.0000265818.88703.83 PMID: 17636061

47. Kadotani H, Kadotani T, Young T, Peppard PE, Finn L, et al. (2001) Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. Jama 285: 2888–2890. PMID: 11401610

48. Larkin EK, Patel SR, Redline S, Mignot E, Elston RC, et al. (2006) Apolipoprotein E and obstructive sleep apnea: evaluating whether a candidate gene explains a linkage peak. Genet Epidemiol 30: 101–110. https://doi.org/10.1002/gepi.20127 PMID: 16374834

49. Saarelainen S, Lehtimaki T, Kallonen E, Laasonen K, Poussa T, et al. (1998) No relation between apolipoprotein E alleles and obstructive sleep apnea. Clin Genet 53: 147–148. PMID: 9611077

50. Gottlieb DJ, DeStefano AL, Foley DJ, Mignot E, Redline S, et al. (2004) APOE epsilon4 is associated with obstructive sleep apnea/hypopnea: the Sleep Heart Health Study. Neurology 63: 664–668. PMID: 15326239

51. Kalra M, Pal P, Kaushal R, Amin RS, Dolan LM, et al. (2008) Association of ApoE genetic variants with obstructive sleep apnea in children. Sleep Med 9: 260–265. https://doi.org/10.1016/j.sleep.2007.05.001 PMID: 17658295

52. Aeschbach D, Cutler AJ, Ronda JM (2008) A role for non-rapid-eye-movement sleep homeostasis in perceptual learning. J Neurosci 28: 2766–2772. https://doi.org/10.1523/JNEUROSCI.5548-07.2008 PMID: 18337406

53. Landsness EC, Crupi D, Hulse BK, Peterson MJ, Huber R, et al. (2009) Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. Sleep 32: 1273–1284. PMID: 19848357

54. Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265: 676–679. PMID: 8036517

55. Yaroush R, Sullivan MJ, Ekstrand BR (1971) Effect of sleep on memory. II. Differential effect of the first and second half of the night. J Exp Psychol 88: 361–366. PMID: 4326302

56. Diekelmann S, Wilhelm I, Born J (2009) The whats and whens of sleep-dependent memory consolidation. Sleep Med Rev 13: 309–321. https://doi.org/10.1016/j.smrv.2008.08.002 PMID: 19251443

57. Walker MP (2009) The role of sleep in cognition and emotion. Ann N Y Acad Sci 1156: 168–197. https://doi.org/10.1111/j.1749-6632.2009.04416.x PMID: 19338508

58. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, et al. (1993) Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet 341: 72–75. PMID: 8093403

59. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189–198. PMID: 1202204

60. Rao MN, Blackwell T, Redline S, Stefanick ML, Ancoli-Israel S, et al. (2009) Association between sleep architecture and measures of body composition. Sleep 32: 483–490. PMID: 19413142

61. Teng EL, Chui HC, Schneider LS, Metzger LE (1987) Alzheimer's dementia: performance on the Mini-Mental State Examination. J Consult Clin Psychol 55: 96–100. PMID: 3571664

62. Teng EL, Chui HC (1987) The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 48: 314–318. PMID: 3611032

63. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12: 189–198. PMID: 1202204

64. Blackwell T, Redline S, Ancoli-Israel S, Schneider JL, Surovec S, et al. (2008) Comparison of sleep parameters from actigraphy and polysomnography in older women: the SOF study. Sleep 31: 283–291. PMID: 18274276

65. Mehra R, Stone KL, Blackwell T, Ancoli Israel S, Dam TT, et al. (2007) Prevalence and correlates of sleep-disordered breathing in older men: osteoporotic fractures in men sleep study. J Am Geriatr Soc 55: 1356–1364. https://doi.org/10.1111/j.1532-5415.2007.01290.x PMID: 17767677

66. Redline S, Sanders MH, Lind BK, Quan SF, Iber C, et al. (1998) Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. Sleep 21: 759–767. PMID: 11300121

67. Hori T, Sugita Y, Koga E, Shirakawa S, Inoue K, et al. (2001) Proposed supplements and amendments to 'A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects', the Rechtschaffen & Kales (1968) standard. Psychiatry Clin Neurosci 55: 305–310. https://doi.org/10.1046/j.1440-1819.2001.00810.x PMID: 11422885

68. (1992) EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 15: 173–184. PMID: 11032543

69. Khan A, Harrison SL, Kezirian EJ, Ancoli-Israel S, O'Hearn D, et al. (2013) Obstructive sleep apnea during rapid eye movement sleep, daytime sleepiness, and quality of life in older men in Osteoporotic Fractures in Men (MrOS) Sleep Study. J Clin Sleep Med 9: 191–198. https://doi.org/10.5664/jcsm.2474 PMID: 23493839

70. Feinberg I, Floyd TC (1979) Systematic trends across the night in human sleep cycles. Psychophysiology 16: 283–291. PMID: 220659

71. Evans DS, Parimi N, Nievergelt CM, Blackwell T, Redline S, et al. (2013) Common Genetic Variants in ARNTL and NPAS2 and at Chromosome 12p13 are Associated with Objectively Measured Sleep Traits in the Elderly. Sleep 36: 431–446. https://doi.org/10.5665/sleep.2466 PMID: 23449886

72. Blackwell T, Yaffe K, Ancoli-Israel S, Redline S, Ensrud KE, et al. (2011) Associations between sleep architecture and sleep-disordered breathing and cognition in older community-dwelling men: the Osteoporotic Fractures in Men Sleep Study. J Am Geriatr Soc 59: 2217–2225. https://doi.org/10.1111/j.1532-5415.2011.03731.x PMID: 22188071

73. Scullin MK (2013) Sleep, memory, and aging: the link between slow-wave sleep and episodic memory changes from younger to older adults. Psychol Aging 28: 105–114. https://doi.org/10.1037/a0028830 PMID: 22708533

74. Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 62: 143–150. PMID: 14638388

75. Cirelli C (2012) Brain plasticity, sleep and aging. Gerontology 58: 441–445. https://doi.org/10.1159/000336149 PMID: 22398514

76. Donlea JM, Ramanan N, Shaw PJ (2009) Use-dependent plasticity in clock neurons regulates sleep need in Drosophila. Science 324: 105–108. https://doi.org/10.1126/science.1166657 PMID: 19342592

77. Gilestro GF, Tononi G, Cirelli C (2009) Widespread changes in synaptic markers as a function of sleep and wakefulness in Drosophila. Science 324: 109–112. https://doi.org/10.1126/science.1166673 PMID: 19342593

78. Chang EH, Savage MJ, Flood DG, Thomas JM, Levy RB, et al. (2006) AMPA receptor downscaling at the onset of Alzheimer's disease pathology in double knockin mice. Proc Natl Acad Sci U S A 103: 3410–3415. https://doi.org/10.1073/pnas.0507313103 PMID: 16492745

79. Chen Y, Durakoglugil MS, Xian X, Herz J (2010) ApoE4 reduces glutamate receptor function and synaptic plasticity by selectively impairing ApoE receptor recycling. Proc Natl Acad Sci U S A 107: 12011–12016. https://doi.org/10.1073/pnas.0914984107 PMID: 20547867

80. Mahley RW, Weisgraber KH, Huang Y (2006) Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc Natl Acad Sci U S A 103: 5644–5651. https://doi.org/10.1073/pnas.0600549103 PMID: 16567625

81. Herz J, Chen Y (2006) Reelin, lipoprotein receptors and synaptic plasticity. Nat Rev Neurosci 7: 850–859. https://doi.org/10.1038/nrn2009 PMID: 17053810

82. Chen Y, Beffert U, Ertunc M, Tang TS, Kavalali ET, et al. (2005) Reelin modulates NMDA receptor activity in cortical neurons. J Neurosci 25: 8209–8216. https://doi.org/10.1523/JNEUROSCI.1951-05.2005 PMID: 16148228

83. Mackiewicz M, Shockley KR, Romer MA, Galante RJ, Zimmerman JE, et al. (2007) Macromolecule biosynthesis: a key function of sleep. Physiol Genomics 31: 441–457. https://doi.org/10.1152/physiolgenomics.00275.2006 PMID: 17698924

84. Caselli RJ, Reiman EM, Hentz JG, Osborne D, Alexander GE, et al. (2002) A distinctive interaction between memory and chronic daytime somnolence in asymptomatic APOE e4 homozygotes. Sleep 25: 447–453. PMID: 12071547

85. Yesavage JA, Friedman L, Kraemer H, Tinklenberg JR, Salehi A, et al. (2004) Sleep/wake disruption in Alzheimer's disease: APOE status and longitudinal course. J Geriatr Psychiatry Neurol 17: 20–24. https://doi.org/10.1177/0891988703261994 PMID: 15018693

86. Pace-Schott EF, Spencer RM (2011) Age-related changes in the cognitive function of sleep. Prog Brain Res 191: 75–89. https://doi.org/10.1016/B978-0-444-53752-2.00012-6 PMID: 21741545

87. Spiegel R, Koberle S, Allen SR (1986) Significance of slow wave sleep: considerations from a clinical viewpoint. Sleep 9: 66–79. PMID: 3961369

88. Rauchs G, Schabus M, Parapatics S, Bertran F, Clochon P, et al. (2008) Is there a link between sleep changes and memory in Alzheimer's disease? Neuroreport 19: 1159–1162. https://doi.org/10.1097/WNR.0b013e32830867c4 PMID: 18596620

89. Peters KR, Ray L, Smith V, Smith C (2008) Changes in the density of stage 2 sleep spindles following motor learning in young and older adults. J Sleep Res 17: 23–33. https://doi.org/10.1111/j.1365-2869.2008.00634.x PMID: 18275552

90. Soudmand R, Ward LC, Swift TR (1982) Effect of height on nerve conduction velocity. Neurology 32: 407–410. PMID: 7199664

91. Cai ZJ (1995) An integrative analysis to sleep functions. Behav Brain Res 69: 187–194. PMID: 7546310

92. Mazzoni G, Gori S, Formicola G, Gneri C, Massetani R, et al. (1999) Word recall correlates with sleep cycles in elderly subjects. J Sleep Res 8: 185–188. PMID: 10476004

93. Feinberg I (1974) Changes in sleep cycle patterns with age. J Psychiatr Res 10: 283–306. PMID: 4376564

94. Foulkes D (1993) Symposium: Normal and abnormal REM sleep regulation: Dreaming and REM sleep. J Sleep Res 2: 199–202. PMID: 10607095

95. Gerrard JL, Burke SN, McNaughton BL, Barnes CA (2008) Sequence reactivation in the hippocampus is impaired in aged rats. J Neurosci 28: 7883–7890. https://doi.org/10.1523/JNEUROSCI.1265-08.2008 PMID: 18667620

96. Buechel HM, Popovic J, Searcy JL, Porter NM, Thibault O, et al. (2011) Deep sleep and parietal cortex gene expression changes are related to cognitive deficits with age. PLoS One 6: e18387. https://doi.org/10.1371/journal.pone.0018387 PMID: 21483696