Cerebrospinal Fluid Hypocretin and Nightmares in Dementia Syndromes

Lynn Marie Trotti\textsuperscript{a, b}, Donald L. Bliwise\textsuperscript{a, b}, Glenda L. Keating\textsuperscript{a}, David B. Rye\textsuperscript{a, b}, William T. Hu\textsuperscript{a}

\textsuperscript{a}Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA; \textsuperscript{b}Emory Sleep Center, Emory University School of Medicine, Atlanta, GA, USA

Keywords
Hypocretin · Alzheimer disease · Dementia · Nightmares · Dreams

Abstract

Background/Aims: Hypocretin promotes wakefulness and modulates REM sleep. Alterations in the hypocretin system are increasingly implicated in dementia. We evaluated relationships among hypocretin, dementia biomarkers, and sleep symptoms in elderly participants, most of whom had dementia. Methods: One-hundred twenty-six adults (mean age 66.2 ± 8.4 years) were recruited from the Emory Cognitive Clinic. Diagnoses were Alzheimer disease (AD; \( n = 60 \)), frontotemporal dementia (FTD; \( n = 21 \)), and dementia with Lewy bodies (DLB; \( n = 20 \)). We also included cognitively normal controls (\( n = 25 \)). Participants and/or caregivers completed sleep questionnaires and lumbar puncture was performed for cerebrospinal fluid (CSF) assessments. Results: Except for sleepiness (worst in DLB) and nocturia (worst in DLB and FTD) sleep symptoms did not differ by diagnosis. CSF hypocretin concentrations were available for 87 participants and normal in 70, intermediate in 16, and low in 1. Hypocretin levels did not differ by diagnosis. Hypocretin levels correlated with CSF total \( \tau \) levels only in men (\( r = 0.34 \); \( p = 0.02 \)). Lower hypocretin levels were related to frequency of nightmares (203.9 ± 29.8 pg/mL in those with frequent nightmares vs. 240.4 ± 46.1 pg/mL in those without; \( p = 0.05 \)) and vivid dreams (209.1 ± 28.3 vs. 239.5 ± 47.8 pg/mL; \( p = 0.014 \)). Cholinesterase inhibitor use was not associated with nightmares or vivid dreaming. Conclusion: Hypocretin levels did not distinguish between dementia syndromes. Disturbing dreams in dementia patients may be related to lower hypocretin concentrations in CSF.

Introduction

Disturbed sleep in dementia may result from cell loss in neuronal populations affecting circadian rhythms, homeostatic sleep regulation, and autonomic and respiratory functions [1]. The neurobiological substrates for these dysfunctions remain incompletely understood, with recent attention focusing on hypocretin-1 (orexin A). Hypocretin is a hypothalamic peptide that promotes wakefulness and regulates REM sleep, and hypocretin de-
iciency is the biomarker for sleepiness and REM-related phenomena, including vivid dreaming and hallucinations, in narcolepsy type 1 (NT1). Animal models indicate that hypocretin may impact β-amyloid 1–42 (Aβ42). In particular, higher hypocretin may prevent phagocytosis of Aβ42 by microglia, exogenous administration of hypocretin increases Aβ42 in brain interstitial fluid, and reductions in hypocretin signaling via hypocretin receptor antagonists or in receptor knockout animals reduce Aβ42 [2–4].

Consistent with this animal literature, human studies have generally, although not universally [5], concluded that patients with Alzheimer disease (AD) or mild cognitive impairment (MCI) with subsequent conversion to AD have higher hypocretin levels than controls [6, 7], than patients with non-AD dementia syndromes [8], or than people with other non-dementing neurologic diseases [9]. However, studies examining associations between hypocretin and cerebrospinal fluid (CSF) AD biomarkers, such as Aβ42, have shown mixed results [6, 8–12] to date. CSF τ is more consistently associated with higher hypocretin [5, 6, 10], with evidence of effect modification by gender [11].

We examined CSF hypocretin across 3 dementia types (AD, dementia with Lewy bodies [DLB], and frontotemporal dementia [FTD]) and controls to examine associations between CSF-derived hypocretin and AD biomarkers. Because hypocretin deficiency is so strongly associated with excessive daytime sleepiness and abnormal dreaming experiences in NT1, we also examined relationships between hypocretin and patient/caregiver-reported sleepiness, sleep quality, and dream experiences.

**Materials and Methods**

Participants were recruited from our tertiary referral, university-based medical center [13–16]. Age-matched normal-cognition (NC) subjects were prospectively recruited for a biomarker study, which included detailed neuropsychological, imaging, and CSF biomarker analyses [13].

Diagnoses of NC and AD were made according to consensus criteria for AD [11]. We examined the consensus criteria for MCI whose CSF biomarkers were consistent with pathologic AD were included in the AD group. Diagnoses of FTD (behavioral or language variant) [17] and DLB [18] were made by a board-certified cognitive neurologist (W.T.H.) with international consensus criteria.

CSF Biomarkers

CSF was collected using a 24-gauge atraumatic needle into polypropylene tubes using a modified ADNI protocol without overnight fasting [19] and immediately aliquoted, labeled, and frozen at −80°C. CSF AD biomarkers, including Aβ42, total τ (t-Tau), and τ phosphorylated at threonine 181 (p-Tau_{181}), were measured using Alzbio3 kits (Fujirebio, Malvern, PA, USA) in the Luminex 200 platform [19]. Ratio values of t-Tau/Aβ42 > 0.39 or p-Tau_{181}/Aβ42 > 0.15 were used as AD cutoffs. When ratios were discordant, p-Tau_{181}/Aβ42 was used.

Hypocretin-1 (orexin-A) levels were measured in unextracted CSF using a highlysensitive, commercially available, 125-I radioimmunoassay kit (Phoenix Pharmaceuticals, Burlingame, CA, USA) on all participants with sufficient CSF volume available. Each run included a positive control from the kit and known low and normal reference samples from our biobank. Samples were blindly measured in 100-μL duplicates and values were averaged. The standard curve range was 10–1,280 pg/mL. We have demonstrated an excellent interassay correlation (r = 0.79) between samples measured at our lab and the Stanford University reference lab [20]. Hypocretin values were defined as: low (<110 pg/mL), intermediate (110–200 pg/mL), or normal (>200 pg/mL).

**Sleep Symptom Questionnaires**

The Neurodegenerative Disease Sleep Questionnaire (NDSQ) [21] was completed by the participant or by the participant and caregiver and was it available on a subset of participants. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) [22].

**Statistical Analyses**

CSF biomarkers, ESS scores, and sleep durations on the NDSQ were analyzed as continuous variables. For questions assessing frequency of symptoms, responses were dichotomized, with symptoms considered present if endorsed at least “sometimes” for 5-point scales and at least “often” for 4-point scales. “Don’t know” responses were considered missing for question-specific analyses. For sensitivity analysis, we limited analyses for items responded to by the patient alone or by both the patient and the caregiver. Cholinesterase inhibitor exposure was determined by medical record review and based on taking a cholinesterase inhibitor at the time of lumbar puncture, questionnaire completion, or both. Sleep symptoms were compared across diagnoses by a χ² or Fisher exact test for categorical variables and by a one-way, mixed-model ANOVA (to control for unequal sample sizes and variabilities) for continuous variables. For significant ANOVA results, pairwise multiple comparisons were performed via a Tukey test. For biomarker interrelationships Pearson correlations were used. Sleep symptoms and biomarker associations were examined via a t test (correcting for unequal variance). p < 0.05 were considered statistically significant.

**Results**

Participants were 126 adults (58 women) with a mean (±SD) age of 66.2 (±8.4) years. Participants’ diagnoses were AD (n = 60), FTD (n = 21), DLB (n = 20), or NC (n = 25). There were significantly fewer women with DLB and FTD (Table 1). Except for reported sleepiness (ESS), worse in DLB than in controls, and nocturia, worse in DLB and FTD, sleep symptoms did not differentiate di-
agnostic groups (Table 1). These differences were not modified meaningfully by whether the patient had completed the questionnaire alone or with caregiver assistance (data not shown).

AD participants had significantly lower Aβ42 and significantly higher t-Tau and p-Tau181 values than NC and the other 2 patient groups (Table 1). Participants with FTD had higher t-Tau values than those with DLB or NC. Hypocretin (n = 87) was normal in 70, intermediate (range 143.8–198.0 pg/mL) in 16 (all 4 diagnoses), and low (106.8 pg/mL) in 1 patient (AD). Hypocretin did not differ by diagnosis. Across all of the participants, Aβ42 was negatively correlated with p-Tau181 (r = –0.39; p < 0.0001) but not with t-Tau (r = –0.16; p = 0.08). The 2 τ biomarkers were strongly correlated (r = 0.53; p < 0.0001). Hypocretin levels were uncorrelated with Aβ42, t-Tau, or p-Tau181 across all groups or in AD only. Among men, hypocretin and t-Tau were moderately correlated (r = 0.34; p = 0.02), particularly for AD (r = 0.68; p = 0.001), but hypocretin was unrelated to p-Tau181 or Aβ42. Among women, no such associations were noted.

AD biomarkers were unrelated to sleep symptoms (all p values ns), except leg restlessness, which was associated with lower t-Tau values (39.2 ± 14.7 vs. 75.8 ± 54.6). ESS and hypocretin were unrelated (r = –0.06; p = 0.66); however, REM-sleep dyscontrol symptoms correlated with hypocretin. Participants with frequent nightmares had significantly lower hypocretin levels than those without (203.9 ± 29.8 vs. 240.4 ± 46.1 pg/mL, t = 2.01; p = 0.05), and participants having frequent vivid dreams showed lower hypocretin levels than those without (209.1 ± 28.3 vs. 239.5 ± 47.8 pg/mL, t = 2.62; p = 0.014). The directionality of these differences was not impacted by whether the caregiver had assisted with questionnaire completion, although p values in those subanalyses became nonsignificant, likely reflecting smaller samples. No other questionnaire items were related to hypocretin.

Associations between hypocretin and reported dreaming were not mediated by cholinesterase inhibitors. Reported nightmares occurred in 10.0% of those receiving cholinesterase inhibitors and in 9.4% of those not receiving them (p = 1.00; Fisher exact test), whereas the corresponding proportions reporting vivid dreaming were 16.7 and 22.6%, respectively (p = 0.52; χ² test).

Trotti et al.: Hypocretin and Dreams

### Table 1. Demographic characteristics, sleep symptoms, and biomarker levels

| Characteristic | AD (n = 60) | FTD (n = 21) | DLB (n = 20) | CTL (n = 25) | p value | Significant pairwise differences |
|---------------|------------|-------------|-------------|-------------|---------|---------------------------------|
| Female gender | 29 (48.3)  | 7 (33.3)    | 5 (25.0)    | 17 (68.0)   | 0.02    | CTL > FTD                      |
| Age, years    | 65.5 (7.7) | 66.3 (9.2)  | 64.9 (9.8)  | 69.6 (9.2)  | 0.52    | –                               |
| ESS score     | 6.0 (4.7)  | 6.9 (6.3)   | 9.8 (3.7)   | 4.8 (3.1)   | 0.04    | DLB > CTL                      |
| Nightly sleep duration, h | 7.7 (1.3)  | 7.6 (1.1)   | 8.8 (1.9)   | 7.6 (0.9)   | 0.45    | –                               |
| Vivid dreams   | 7 (15.9)   | 4 (22.2)    | 3 (37.5)    | 3 (23.1)    | 0.51    | –                               |
| Nightmares     | 3 (6.7)    | 1 (5.9)     | 2 (25)      | 2 (15.4)    | 0.22    | –                               |
| Nocturia       | 10 (20.8)  | 8 (42.1)    | 5 (62.5)    | 1 (7.7)     | 0.01    | CTL < FTD = DLB; AD < DLB      |
| Snoring        | 24 (53.3)  | 12 (70.6)   | 7 (100)     | 6 (60.0)    | 0.09    | –                               |
| Sleep onset insomnia | 10 (20.4) | 2 (11.1)    | 2 (25.0)    | 6 (46.2)    | 0.13    | –                               |
| Sleep maintenance insomnia | 20 (40.8) | 10 (52.6)   | 6 (75.0)    | 4 (30.8)    | 0.20    | –                               |
| Early morning awakenings | 14 (28.6) | 4 (21.1)    | 5 (62.5)    | 5 (38.5)    | 0.19    | –                               |
| Leg restlessness at bedtime | 2 (4.4)   | 0 (0)       | 1 (12.5)    | 1 (7.7)     | 0.36    | –                               |
| Leg restlessness during nocturnal awakenings | 2 (4.3)   | 1 (5.3)     | 2 (25)      | 1 (7.7)     | 0.16    | –                               |
| CSF Aβ42       | 118.8 (63.1) | 271.2 (148.4) | 255.5 (90.4) | 301.0 (137.5) | 0.44*    | –                               |
| CSF t-Tau      | 93.8 (71.8) | 61.0 (36.8) | 33.1 (16.6) | 37.9 (20.7) | 0.01*   | FTD > DLB = CTL                |
| CSF p-Tau181   | 50.2 (26.0) | 21.8 (13.6) | 18.5 (8.0)  | 24.8 (19.6) | 0.31*   | –                               |
| CSF hypocretin | 256.8 (59.0) | 245.0 (50.5) | 240.3 (60.2) | 248.1 (53.3) | 0.79    | –                               |

Values are reported as means (SD) or numbers (%). CTL, control. * Aβ42, t-Tau, and p-Tau181 were used to assign an AD diagnosis and therefore differ between AD and other groups by definition; this p value is for the 3-group comparison of FTD, DLB, and CTL. Bold text indicates statistical significance with p < 0.05.
Discussion/Conclusions

Although biomarkers differentiated AD patients from controls [19], the absence of associations with hypocretin was unexpected. Among moderate-to-severe AD patients, Ligori et al. [6] reported moderate effects ($r^2$ values of 0.31–0.40) relating CSF hypocretin and p-Tau$_{181}$ and t-Tau (but not Aβ42). In a community-based, non-dementia cohort, Osorio et al. [23] reported more modest positive relationships ($r^2$ values of 0.18–0.25) between hypocretin, t-Tau, and p-Tau$_{181}$, with a still weaker relationship with Aβ42. In lateral hypothalamic postmortem analyses, hypocretin immunoreactivity was reduced in AD relative to NC, while neuronal counts were robustly related to neurofibrillary stage ($r^2 = 0.45$) [24]. From these findings, one might expect AD to be associated with a greater neurofibrillary tangle count, elevated CSF t-Tau and p-Tau$_{181}$ levels, and decreased CSF hypocretin. Our and others’ observation of a positive correlation between τ and hypocretin in AD thus suggests a functional up-regulation independent of neuronal loss. Because CSF t-Tau levels in AD also mirror biology beyond tangle deposition [25], increased CSF hypocretin may reflect bystander effects with clinical consequences. Even stronger neuropathologic relationships were noted with hypocretin immunoreactivity in DLB [24], but we detected no relationship between τ and hypocretin in DLB. This could reflect a small sample, a floor effect associated with low CSF t-Tau and p-Tau$_{181}$ levels in DLB, different biological pathways activated in AD vs. DLB, or a stronger gender influence because of the DLB male predominance. Women have been shown to have higher postmortem ventricular CSF hypocretin levels than men [26]; this occurs in both AD and NC and could reflect estradiol’s effects on hypocretin receptor expression [27]. Higher hypocretin in relation to higher τ was reported in a small-sample study comprised mainly of women [10].

We noted relatively few associations between sleep symptoms and AD biomarkers and, except for dreaming experiences, hypocretin. AD biomarkers show a complex relationship to sleep in human studies. For example, 1 night of experimentally induced slow-wave sleep fragmentation in controls elevated CSF Aβ40 [28] and decreased Aβ42 [29], suggesting that sleep disruption dys-regulates the Aβ isoform. Paralleling these results are cross-sectional, observational studies demonstrating that a poorer self-reported sleep quality [30], a lower actigraphically defined sleep efficiency [31], and lower levels of slow wave sleep [32] were all associated with altered CSF Aβ42. Using neuroimaging, similar associations occurred between subjectively assessed poor sleep and a greater PET-based amyloid burden [33], and impaired overnight memory consolidation was related to both decreased slow-wave activity and prefrontal amyloid burden in a causally dependent manner [34].

In contrast to much of this research, however, Olsson et al. [35] reported that a 5-night restriction of 4 h in bed had no effect on Aβ isoforms in middle-aged adults, and a community-based study showed that Aβ42 levels were unrelated to incident AD in 2 cohorts totaling about 1,000 participants [36]. Among AD patients and patients with MCI with likely incipient AD, lower Aβ42 levels were associated with a longer, not a shorter, sleep duration [9]. A complex interaction between actigraphically assessed disturbed sleep measured antemortem and greater postmortem Aβ neuropathology has also been suggested, in which sleep per se may not directly mediate associations but may operate only within the context of apolipoproteinE4 [37] risk alleles.

Findings are also inconclusive regarding CSF τ and sleep, with some experimental studies in normals showing no effects of sleep deprivation/fragmentation [28, 29, 35] and several descriptive studies reporting associations between poor sleep and higher τ values [6, 30]. An observational study in a population with no or only very mild cognitive impairment demonstrated that a lower spectral power in slow-wave (1–4.5 Hz) activity was related to a widespread higher τ activity on PET across the amygdala and various cortical regions, as well as higher t-Tau and p-Tau$_{181}$ values in CSF (though not Aβ42) [38]. Additionally, mouse models have recently implicated τ deposition as a consequence of sleep loss [39].

Although it has been investigated in fewer studies, a similar lack of consensus occurs for hypocretin, where some reports have suggested higher CSF levels associated with poor nocturnal sleep in AD measured both subjectively [7] and polysomnographically [6], findings not reported by others [9, 23, 40]. One study reported that lower, rather than higher, hypocretin related to increased daytime napping, as assessed actigraphically [40], and total sleep deprivation had no effect on hypocretin in normal subjects [29]. Taken together, this literature shows a lack of uniformity between various measures of sleep disturbances and AD biomarkers or hypocretin, findings that likely vary depending on the biomarker under evaluation, the population studied, and how sleep was measured.

We found few differences in sleep-related symptoms across diagnoses, and perhaps most surprising was their lack of differentiation of AD and DLB. An analysis of
nearly 4,600 patients on the single NPI sleep item showed that DBL patients were reported by caregivers to experience disturbed sleep more often, and earlier in the disease course, compared to AD patients [41]. In the current much smaller sample, we found that the DBL patients reported more severe daytime sleepiness than all of the other groups, compatible with the sleepiness ascribed to the condition via diagnostic criteria [42]. Additionally, nocturia, both a cause and an effect of poor sleep [43], was more common in DBL and is compatible with both worse nighttime sleep and daytime sleepiness.

Disturbing dreams accompany many forms of dementia, particularly in cases with prior war exposures leading to PTSD [44]. Perhaps paradoxically, early studies (e.g., [45]) suggested that the lack of dream recall was an early predictor of incipient cognitive decline, and polysomnographic studies indicate that dream recall is less likely among more demented patients when awakened from REM [46]. Seminal polysomnographic studies of unmedicated AD patients have shown graded associations between a greater severity of cognitive impairment and lower amounts of REM (e.g., [47]), findings that may reflect disruption of REM cholinergic systems. These findings have a new impetus in a 12-year follow-up of elderly participants from the Framingham Heart Study, which showed that a 1% decrease in the REM percentage increased the incident dementia risk by 9% [48]. We did not document altered REM sleep here, but we noted associations between a biochemical marker related to REM sleep regulation and the frequency of adverse dream experiences. This could not be accounted for by cholinesterase inhibitors despite the fact that this medication class is often associated with increased REM [49] and despite reports of increased and distressing dream experiences in both case reports [50] and randomized clinical trials [51]. Insofar as we know, our data are the first to suggest that relatively low hypocretin levels might represent a trans-diagnostic marker of dreaming across different types of dementia. Several small-scale studies (i.e., 15 or fewer patients) have reported reduced CSF hypocretin in relation to poor-quality sleep or increased daytime sleepiness in AD [40] or FTD [52], and one reported that increased hypocretin corresponded with REM without atonia [53] but none reported on abnormal dream experiences among those patients. In 26 MCI patients, Liguori et al. [7] reported higher, rather than lower, CSF hypocretin levels in relation to REM.

Despite novel findings, our study has clear limitations, including reliance on patient and/or caregiver reports about sleep rather than more objective measures. Also, our analyses did not adjust for multiple testing. We did not control for time of day of CSF collection, though the circadian amplitude of CSF hypocretin is small (11.5 pg/mL) and not different between those with and those without AD [12]. Dementia severity, dementia duration, and presence of an REM sleep behavior disorder might impact these findings and should be evaluated in future studies. We acknowledge that our reported associations between hypocretin and abnormal dreaming constituted relatively small effects, though they are compatible with the magnitude of effects seen in other studies involving subjective sleep measures in relation to AD biomarkers (e.g., [30]). Furthermore, our sample size did not allow a detailed assessment of these effects within each diagnosis. Within these interpretative constraints, however, these data imply that vivid and troubling dreams experienced by at least some dementia patients may have their origin not in pharmacology but rather in dysregulation of a neuropeptide controlling REM sleep.

Acknowledgement

We are grateful to Christina Howell and Alexander Kollhoff for their assistance with sample and data management.

Statement of Ethics

This work was approved by the Emory University Institutional Review Board and all of the participants (and legal representatives, when appropriate) provided written informed consent.

Disclosure Statement

Dr. Lynn Marie Trotti reports grants from NINDS/NIH during the conduction of this study and personal fees from Medscape and Oakstone for providing CME lectures. Dr. Donald L. Bliwise reports grants from the Alzheimer’s Association during the conduction of this study and personal fees from Merck, Ferring, Eisai, and Jazz outside of the submitted work. Dr. Glenda L. Keating has no conflict of interests to declare. Dr. David B. Rye reports grants from NIH/NINDS during the conduction of this study and personal fees from Jazz, Harmony, and Eisai outside of the submitted work. In addition, Dr. David B. Rye has a patent (US9616070B2) issued and licensed to Balance Therapeutics and a patent (US10029-053W01)pending and licensed to Balance Therapeutics and Expansion Therapeutics. Dr. William T. Hu reports grant funding from NINDS/NIH during the conduction of this study and grants from Fujirebio US, personal fees from ViveBio LLC, Roche Diagnostics, and AARP, and nonfinancial support from Advanced Brain Monitoring outside of the submitted work. In addition, Dr. William T. Hu has a patent (US9618522B2) issued.
Funding Sources

This work was supported by the National Institutes of Health under award No. K23 NS083748 (L.M.T.), R01 NS111280 (L.M.T.), R01 NS089719 (D.B.R.), K23 AG042856 (W.T.H.), and R21 AG043885 (W.T.H.) and by the Alzheimer’s Association (D.L.B.). The funders were not involved in the preparation of data or this paper. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Author Contributions

L.M.T., D.L.B., and W.T.H.: conception/design of this work. L.M.T. and D.L.B. drafting of this work. All authors: acquisition/analysis/interpretation of data, critical revision of this work for important intellectual content, final approval of the version to be published, and accountability for this work.

References

1. Naismith SL, Lewis SJ, Rogers NL. Sleep–wake changes and cognition in neurodegenerative disease. Prog Brain Res. 2011;190:21–52.
2. An H, Cho MH, Kim DH, Chung S, Yoon SY. Orexin Impairs the Phagocytosis and Degradation of Amyloid-β Fibrils by Microglial Cells. J Alzheimers Dis. 2017;58(1):253–61.
3. Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science. 2009 Nov;326(5955):1005–7.
4. Roh JH, Jiang H, Finn MB, Stewart FR, Mahan TE, Cirrito JR, et al. Potential role of orexin and sleep modulation in the pathogenesis of Alzheimer’s disease. J Exp Med. 2014 Dec; 211(13):2487–96.
5. Johansson P, Almqvist EG, Wallin A, Johansson JO, Andreason US, Blennow K, et al. Cerebrospinal fluid substance P concentrations are elevated in patients with Alzheimer’s disease. Neurosci Lett. 2015 Nov;609:58–62.
6. Liguori C, Romigi A, Nuccetelli M, Zannino S, Sancesario G, Martorana A, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. JAMA Neurol. 2014 Dec;71(12):1498–505.
7. Liguori C, Nuccetelli M, Izzo F, Sancesario, G, Romigi A, Martorana A, et al. Rapid eye movement sleep disruption and sleep fragmentation are associated with increased orexin-A cerebrospinal-fluid levels in mild cognitive impairment due to Alzheimer’s disease. Neurobiol Aging. 2016 Apr;40:120–6.
8. Daunvilliers YA, Lehmann S, Jaussent I, Gabelle A. Hypocretin and brain β-amyloid peptide interactions in cognitive disorders and narcolepsy. Front Aging Neurosci. 2014 Jun;6:119.
9. Gabelle A, Jaussent I, Hirtz C, Vialaret J, Navuet S, Grasselli C, et al. Cerebrospinal fluid levels of orexin-A and histamine, and sleep profile within the Alzheimer process. Neurobiol Aging. 2017 May;59:39–46.
10. Deuschle M, Schilling C, Leweke FM, Enning F, Pollmücher T, Esselmann H, et al. Hypocretin in cerebrospinal fluid is positively correlated with Tau and pTau. Neurosci Lett. 2014 Feb;561:41–5.
11. Wennström C, London E, Minthon L, Nielsen HM. Altered CSF orexin and α-synuclein levels in dementia patients. J Alzheimers Dis. 2012;29(1):125–32.
12. Slats D, Claassen JA, Lammers GJ, Melis RJ, Verbeek MM, Oudshoorn V, et al. Association between hypocretin-1 and amyloid-β42 cerebrospinal fluid levels in Alzheimer’s disease and healthy controls. Curr Alzheimer Res. 2014 Feb;11(1):2487–96.
13. Howell JC, Watts KD, Parker MW, Wu J, Kollhoff A, Wingo TS, et al. Race modifies the relationship between cognition and Alzheimer’s disease cerebrospinal fluid biomarkers. Alzheimers Res Ther. 2017 Nov;9(1):88.
14. Hu WT, Howell JC, Ozturk T, Gangishetti U, Kollhoff AL, Hatcher-Martin JM, et al. CSF Cytokines in Aging. Multiple Sclerosis, and Dementia. Front Immunol. 2019 Mar;10:480.
15. Hu WT, Watts K, Grossman M, Glass J, Lah JJ, Hales C, et al. Reduced CSF p-Tau181 to Tau ratio is a biomarker for FTLD-TDP. Neurology. 2013 Nov;81(22):1945–52.
16. Hu WT, Watts KD, Tailor P, Nguyen TP, Howell JC, Lee RC, et al.; Alzheimer’s Disease Neuro-Imaging Initiative. CSF complement 3 factor H are staging biomarkers in Alzheimer’s disease. Acta Neuropathol Commun. 2016 Feb;4(1):14.
17. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011 Sep;134(Pt 9):2456–77.
18. McKeith IG, Dickson DW, Lowe J, Emre M, O’Brien JT, Feldman H, et al.; Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005 Dec;65(12):1863–72.
19. Hu WT, Watts KD, Shaw LM, Howell JC, Trojanowski JQ, Basra S, et al. CSF beta-amyloid-1–42 – what are we measuring in Alzheimer’s disease? Ann Clin Transl Neurol. 2012 Feb;3(2):131–9.
20. Keating G, Bliwise DL, Saini P, Rye DB, Trotti LM. Hypocretin measurement: shelf age of radioimmunoassay kit, but not freezer time, influences assay variability. Scand J Clin Lab Invest. 2017 Sep;77(5):390–3.
21. Scullin MK, Harrison TL, Factor SA, Bliwise DL. A Neurodegenerative Disease Sleep Questionnaire: principal component analysis in Parkinson’s disease. J Neurol Sci. 2014 Jan;336(1-2):243–6.
22. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540–5.
23. Osorio RS, Ducca EL, Wohlbéher ME, Tanzi EB, Gumb T, Twumasi A, et al. Orexin-A is associated with slow wave sleep and cerebrospinal fluid Phosphorylated-Tau in Cognitively Normal Elderly Subjects. Sleep (Baltimore). 2016 Jun;39(6):1253–60.
24. Kasanuki K, Isei K, Kondo D, Fujishiro H, Minegishi M, Sato K, et al. Neuropathological investigation of hypocretin expression in brains of dementia with Lewy bodies. Neurosci Lett. 2014 May;569:68–72.
25. Wharton W, Kollhoff AL, Gangishetti U, Verble DD, Upadhya S, Zetterberg H, et al. Interleukin 9 alterations linked to alzheimer disease in african americans. Ann Neurol. 2019 Sep;86(3):407–18.
26. Fronczenk R, van Geest S, Frölich M, Overeem S, Roelandse FW, Lammers GJ, et al. Hypocretin (orexin) loss in Alzheimer’s disease. Neurobiol Aging. 2012 Aug;33(8):1642–50.
27. Silveyra P, Cataldi NI, Lux-Lantos YA, Liber- tun C. Role of orexins in the hypothalamic-pituitary-ovarian relationships. Acta Physiol (Oxf). 2010 Mar;198(3):355–60.
28. Ooms S, Verbeek S, Beske K, Rikkerk MO, Verbeek M, Claassen JA. Effect of 1 night of total sleep deprivation on cerebrospinal fluid β-amyloid 42 in healthy middle-aged men: a randomized clinical trial. JAMA Neurol. 2014 Aug;71(8):971–7.
29. Ju YS, Ooms SJ, Sutphen C, Macauley SL, Zan- grilli MA, Jerome G, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. Brain. 2017 Aug;140(8):2104–11.
30. Sprecher KE, Koscik RL, Carlsson CM, Zetterberg H, Blennow K, Okonkwo OC, et al. Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults. Neurology. 2017 Aug;89(4):445–53.
31. Ju YE, McLeod JS, Toedebusch CD, Xiong C, Fagan AM, Duntley SP, et al. Sleep quality and preclinical Alzheimer disease. JAMA Neurol. 2013 May;70(5):587–93.
32. Varga AW, Wohlbéher ME, Gìmenez S, Romero S, Alonso JF, Ducca EL, et al. Reduced Slow-Wave Sleep Is Associated with High Cerebrospinal Fluid Aβ42 Levels in Cognitively Normal Elderly. Sleep (Basil). 2016 Nov;39(11):2041–8.
Sprecher KE, Bendlin BB, Racine AM, Ökonkwo OC, Christian BT, Kosck RL, et al. Amyloid burden is associated with self-reported sleep in nondemented late middle-aged adults. Neurobiol Aging. 2015 Sep;36(9): 2568–76.

Olsson M, Arlig J, Hedner J, Blennow K, Zetterberg H. Sleep deprivation and cerebrospinal fluid biomarkers for Alzheimer’s disease. Sleep (Basel). 2018 May;41(5).

Benedict C, Byberg L, Cedernaes J, Hogenkamp PS, Giedraitis V, Kilander L, et al. Self-reported sleep disturbance is associated with Alzheimer’s disease risk in men. Alzheimers Dement. 2015 Sep;11(9):1090–7.

Lucey BP, McCullough A, Landsness EC, Toderedusich CD, McLeland JS, Zaza AM, et al. Reduced non-rapid eye movement sleep is associated with tau pathology in early Alzheimer’s disease. Sci Transl Med. 2019 Jan;11(47):1544–51.

Holth JK, Fritschy SK, Wang C, Pedersen NP, Cirrito JR, Mahan TE, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. Science. 2019 Feb;363(6429):880–4.

Friedman LF, Zeitzer JM, Lin L, Hoff D, Mignot E, Peskind ER, et al. In Alzheimer disease, increased wake fragmentation found in those with lower hypocretin-1. Neurology. 2007 Mar;68(10):793–4.

Bliwise DL, Merscaldo ND, Avidan JY, Boeve BF, Greer SA, Kukull WA. Sleep disturbance in dementia with Lewy bodies and Alzheimer’s disease: a multicenter analysis. Dement Geriatr Cogn Disord. 2011;31(3):239–46.

McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology. 2017 Jul;89(1):88–100.

Araujo AB, Yaggi HK, Yang M, McCVary KT, Fang SC, Bliwise DL. Sleep related problems and urological symptoms: testing the hypothesis of bidirectional in a longitudinal, population based study. J Urol. 2014 Jan;191(1):100–6.

Yaffe K, Vittinghoff E, Lindquist K, Barnes D, Covinsky KE, Neylan T, et al. Posttraumatic stress disorder and risk of dementia among US veterans. Arch Gen Psychiatry. 2010 Jun;67(6):608–13.

Persson G, Skoog I. Subclinical dementia: relevance of cognitive symptoms and signs. J Geriatr Psychiatry Neurol. 1992 Jul-Sep;5(3):172–8.

Kramer M, Roth T, Trinder J. Dreams and dementia: a laboratory exploration of dream recall and dream content in chronic brain syndrome patients. Int J Aging Hum Dev. 1975;6(2):179–82.

Prinz PN, Vitaliano PP, Vitiello MV, Bokan J, Raskind M, Peskind E, et al. Sleep, EEG and mental function changes in senile dementia of the Alzheimer’s type. Neurobiol Aging. 1982;3(4):361–70.

Pase MP, Himji JG, Grima NA, Beiser AS, Satizabal CL, Aparicio HJ, et al. Sleep architecture and the risk of incident dementia in the community. Neurology. 2017 Sep;89(12):1244–50.

Schredl M, Weber B, Leins ML, Heuser I. Donepezil-induced REM sleep augmentation enhances memory performance in elderly, healthy persons. Exp Gerontol. 2001 Feb;36(2):353–61.

Ross JS, Shua-Haim JR. Aricept-induced nightmares in Alzheimer’s disease: 2 case reports. J Am Geriatr Soc. 1998 Jan;46(1):119–20.

Ridha BH, Crutch S, Cutler D, Frost C, Knight W, Barker S, et al. A double-blind placebo-controlled cross-over clinical trial of DONEpezil In Posterior cortical atrophy due to underlying Alzheimer’s Disease: DONIPAD study. Alzheimers Res Ther. 2018 May;10(1):44.

Liguori C, Romigi A, Mercuri NB, Nuccetelli M, Izzì F, Albanese M, et al. Cerebrospinal-fluid orexin levels and daytime somnolence in frontotemporal dementia. J Neurol. 2014 Sep;261(9):1832–6.

Bridoux A, Moutereau S, Covali-Notarc A, Migator L, Palfi S, Nguyen JP, et al. Ventricular orexin-A (hypocretin-1) levels correlate with rapid-eye-movement sleep without atonia in Parkinson’s disease. Nat Sci Sleep. 2013 Jun;5:87–91.