Neuroinflammation and Tau Interact with Amyloid in Predicting Sleep Problems in Aging Independently of Atrophy

Running title: Prediction of sleep

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Abstract (Cerebral cortex max 200 words)

Sleep problems relate to brain changes in aging and disease, but the mechanisms are unknown. Studies suggest a relationship between β-amyloid (Aβ) accumulation and sleep, which is likely augmented by interactions with multiple variables. Here, we tested how different cerebrospinal fluid (CSF) biomarkers for brain pathophysiology, brain atrophy, memory function, and depressive symptoms predicted self-reported sleep patterns in 91 cognitively healthy older adults over a 3-year period. The results showed that CSF levels of total- and phosphorylated (P) tau, and YKL-40-a marker of neuroinflammation/astroglial activation-predicted poor sleep in Aβ positive older adults. Interestingly, although brain atrophy was strongly predictive of poor sleep, the relationships between CSF biomarkers and sleep were completely independent of atrophy. A joint analysis showed that unique variance in sleep was explained by P-tau and the P-tau × Aβ interaction, memory function, depressive symptoms, and brain atrophy. The results demonstrate that sleep relates to a range of different pathophysiological processes, underscoring the importance of understanding its impact on neurocognitive changes in aging and people with increased risk of Alzheimer's disease.

Keywords: amyloid-beta, YKL-40, total-tau, hyperphosphorylated tau, memory, depression

Sleep problems may be both causative and indicative of brain health in normal aging [1] and age-related degenerative conditions [2-4]. Hence, understanding the causes of sleep problems is critical. Especially interesting is the putative relationship between sleep and the Alzheimer's disease (AD) biomarker Aβ. Sleep disturbances may drive pathogenesis early in the course of neurodegeneration [5], but evidence also indicates that Aβ accumulation can cause sleep problems [6], which again may reduce the brains ability to clear Aβ in a positive feedback loop. Several studies have reported that sleep problems are associated with accumulation of Aβ even in healthy older adults [6-12], but the relationships are usually relatively week, with different sleep parameters affected across studies. Combined with the multi-factorial nature of age-related degenerative diseases [13, 14], this implies that it is necessary to explore mechanisms working in synergy with Aβ to cause sleep problems. We approached this challenge by testing whether different CSF biomarkers of relevance for sleep problems interacted with Aβ in predicting sleep quality over a 2 year period in cognitively healthy older adults.

First, tau may be of special relevance to sleep[15] because neurofibrillary tangles originate in the medial temporal lobe (MTL)[16], and hippocampus is critical for non-rapid eye movement (NREM) sleep spindles and slow waves supporting sleep-dependent memory processing [17, 18]. Accordingly, some studies found CSF levels of tau to be associated with sleep problems [19-21]. Thus, understanding possible synergistic relationships between Aβ and tau pathology in accounting for sleep problems is a major task: Is the impact of Aβ and tau on sleep inter-related or independent, and do these interactions forecast the progression of cognitive decline [15]? Second, the inflammation and astroglial activation marker YKL-40 (chitinase-3-like protein-1) has been extensively researched in relation to sleep conditions such as obstructive sleep apnea [22-26], but it has not been tested whether neuroinflammation also impact age-related sleep problems. This is an interesting hypothesis because CSF levels of YKL-40[27] increase with age [28] and AD [27, 29-31] (but see [32]). Inflammation is also related to brain atrophy [33, 34] and is assumed to start early in the cascade of neurodegeneration, as damaged neurons, insoluble Aβ deposits and neurofibrillary tangles provide prime stimuli for inflammation [35, 36]. Thus, it is possible that YKL-40 could interact with Aβ in predicting sleep problems. Third, neurofilament light (NFL),

reflecting axonal degeneration [37, 38], has recently been shown to predict hippocampal atrophy in mild cognitive impairment [39] and normal aging [40]. As argued above, biomarkers related to MTL atrophy are potentially useful tools to help us understand mechanisms for sleep disturbances in aging and neurodegeneration.

In the present study we tested whether CSF levels of tau, YKL-40 and NFL interacted with Aβ in prediction of sleep quality over a 2 year period. Since even normal aging is associated with brain atrophy[41-43] and sleep problems are related to increased atrophy in older adults [44], we further tested whether CSF biomarkers predicted sleep problems independently of brain atrophy, or indirectly by impacting atrophy rates. Finally, as sleep has consistently been related to levels of depression and memory function [15, 45], these variables were also included in the final model.

Materials and Methods

Sample

The study was conducted in accordance with the Declaration of Helsinki and approved by the Regional Committee for Ethics in Medical Research in Norway (REK 2011/2052). All participants provided written informed consent. General recruitment and screening procedures are previously described in Idland et al. [40]. In short, patients were scheduled for elective gynecological (genital prolapse), urological (benign prostate hyperplasia, prostate cancer or bladder tumor/cancer) or orthopedic (knee or hip replacement) surgery in spinal anesthesia turning 65 years or older the year of inclusion. Dementia, previous stroke with sequela, Parkinson's disease and other neurodegenerative diseases likely to affect cognitive function were initial exclusion criteria. From this pool of participants, we further selected only cognitively healthy participants based on clinical examinations at Department of Geriatric Medicine, and participants offered referral to cognitive assessment were excluded. The full sample with available relevant data then consisted of 91 participants. Three participants had MMSE score < 27 at baseline. None of these dropped more than one point during the two year follow up interval, and the one with a score below 25 at baseline (23) improved to 30 at the

follow up. Thus, these three patients were included in the analyses. 4 participants with CSF NFL levels > 4000 pg/mL (i.e. more than ± 3 SD from the mean value) were excluded. After these criteria, the sample with baseline CSF and PSQI data counted 91 (mean age 72 years, range 64-89), while longitudinal MRI data were available for 78 of these. Sample characteristics are described in Table 1.

[*Insert Table 1 about here*]

Participants were assessed with a multi-domain battery of cognitive tests before surgery, comprising the Mini Mental Status Examination (MMSE) [46], Clock Drawing Test [47], Word List Memory Task [48], Trail Making Test A and B [49], Kendrick Object Learning Test [50], and verbal fluency (FAS test and Animal Naming) [51]. Blood and CSF samples were collected by the anesthesiologist in conjunction with spinal anesthesia, and participants underwent magnetic resonance imaging (MRI) after surgery. The mean time between CSF sampling and MRI at baseline was 8 weeks. Participants underwent a second MRI and were tested with the same battery of cognitive tests at two-year follow-up (mean time between MRIs = 2.2 years, SD = 3.3).

Magnetic resonance imaging acquisition and processing

T1-weighted MPRAGE 3D images were acquired with a 1.5 T Siemens Avanto scanner using a 12-channel head coil (TR=2400 ms, TE=3.79ms, Field of View=240mm, slice thickness=1.20mm, pixel size=1.25x1.25mm). Images were processed with the longitudinal stream in FreeSurfer 5.3 (https://surfer.nmr.mgh.harvard.edu). For each MRI, the FreeSurfer pipeline performs a set of automated procedures for the cortical reconstruction and volumetric segmentation, documented elsewhere [46, 47]. The FreeSurfer longitudinal stream includes methods designed to minimize the bias to any time point which lead to increased statistical power, better separation of groups based on atrophy, and higher reproducibility. These include the generation of a subject-specific intermediate template followed by a projection of each time point to this template [48, 49]. For both the individual and longitudinal processing steps, reconstructed surfaces

and volumes were visually inspected and manually corrected when necessary. The output included in the present analyses was symmetrized percent change in volume, thickness and area for each of 33 cortical regions in each hemisphere [50].

APOE genotyping

Blood samples were genotyped for *APOE* (gene map locus 19q13.2) using TaqMan Allelic Discrimination technology (Applied Biosystems, Carlsbad, CA, USA). Genotypes were obtained for the two SNPs that are used to unambiguously define the ε2, ε3, and ε4 alleles (rs7412 and rs429358).

CSF collection and analyses

CSF was collected in polypropylene tubes, centrifuged at room temperature for 10 minutes, the supernatant aliquoted into polypropylene tubes, and frozen at -80 °C pending analyses. Mean time from CSF sampling to freezing was 83 minutes (SD, [range]: 21, [30 to 127]). Samples were sent on dry ice to the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital, Mölndal, Sweden, for analyses. CSF Aβ42, total tau (T-tau) and P-tau concentrations were determined using INNOTEST enzyme-linked immunosorbent assays (Fujirebio, Ghent, Belgium), CSF NFL concentrations using a commercial ELISA (UmanDiagnostics, Umeå, Sweden) and YKL-40 concentrations were measured using a commercially available ELISA (R&D systems, Minneapolis, MN). Analyses were performed by board-certified laboratory technicians masked to clinical data. Intra-assay coefficients of variation were 9-13%. We defined Aβ positive as values below 550 pg/mL, which is within conventionally used cut-off values for CSF Aβ42 described in the literature, ranging from 500 to 650 pg/mL [51-54].

Sleep assessment

Sleep quality was assessed after the second MRI using the Pittsburgh Sleep Quality Inventory (PSQI)[55] in Norwegian. PSQI is a well-validated self-rated questionnaire that assesses seven domains of sleep quality (sleep quality, latency, duration, efficiency, problems, medication and

daytime tiredness) in addition to a global score over a 1-month time interval. The minimum score is 0 and maximum score is 3 for each domain, while the global score ranges from 0 to 21.

Statistics

First, Pearson correlations were run to test the relationship between sleep and a number of confounding variables to decide which should be included as covariates in the following analyses: age, body mass index (BMI), cholesterol, vitamin D and docosahexaenoic acid (DHA: C226n3). To test the relationship between CSF biomarkers and sleep, multiple regressions were run with total sleep score as dependent variable and each of the biomarkers T-tau, P-tau, YKL-40 and NFL in turn as predictors, on the form

Sleep = C + β1×Age + β2×Biomarker + β3×Aβ status + β4×(Aβ status×Biomarker). This way we could test whether each biomarker was differentially related to sleep as a function of Aβ status. As *APOE* has been shown to impact the relationship between sleep and neurofibrillary tangle pathology [56], additional models were run with *APOE* as covariate. Post hoc analyses were run with the different PSQI sub-scores as dependent variables. All variables were z-transformed to avoid problems with multicollinearity.

To test whether effects of biomarkers on sleep could be explained by brain atrophy, we first ran a stepwise multiple regression analysis to identify the optimal linear combination of brain variables to account for the variation in PSQI Global. In the first step, age was forced into the model. In the second step, symmetrized percent change (SPC) in thickness, area and volume in all 33 cortical regions were entered and removed in an iterative stepwise manner. The regions included in the final model were then added as additional covariates in the multiple regression models with the CSF biomarkers, and the β's were inspected. Substantial reduction in the β's for the CSF biomarkers in the prediction of sleep problems would be taken as evidence that brain change could account for the sleep – CSF biomarker associations.

To test the relationship between sleep and clinical and cognitive outcome variables, partial correlations between PSQI Global and the Montgomery and Åsberg Depression Rating Scale

(MADRS)[57] at baseline as well as at follow up, controlling for the effects of age and sex. Further, PSQI Global was correlated with the total score and the number of items recalled from the verbal memory test from the CERAD battery at follow up (The Consortium to Establish a Registry for Alzheimer's Disease)[58], as well as the symmetrized change between baseline and follow up, again controlling for age and sex. Analyses were also run of MADRS and CERAD verbal memory simultaneously to test for the specificity of the relationships.

Finally, path analysis implemented in SPSS AMOS was conducted in an attempt to integrate all tested variables in one comprehensive model. Based on the results from the multiple regression analyses and the partial correlations, we constructed an initial model which included paths between most variables. This model was then recursively improved by removing paths not significant one by one and re-running the model multiple times, until all paths were significant. Akaike Information Criterion (AIC) [59] was used to guide model selection.

Results

Identification of confounding variables

Pearson correlations between PSQI and a number of potential confounding variables are shown in Supplemental Table 1. None of the variables correlated significantly (all p's > .3) with PSQI Global. Higher age was significantly associated with Component 4 - less sleep efficiency ($r = .28$, $p < .01$) and Component 7 – tired ($r = .21$, $p < .05$). Thus, age was included as covariate in all analyses. The other tested variables were not included in further analyses.

Relationship between CSF biomarkers and sleep

<u>Total tau and p-tau</u>

First, the models were run with tau, age, Aβ status and tau × Aβ interaction as covariates. An interaction with Aβ was found for T-tau ($\beta = .63$, $p = .046$) and P-tau ($\beta = .68$, $p = .032$) with PSQI Global. Post hoc analyses revealed a significantly stronger positive correlation between tau and PSQI Global in the Aβ+ group (total-tau: $r = .42$; p-tau $r = .45$) compared to the Aβ- group (total-tau: $r = .00$; p-tau: $r = -.01$). The Aβ interactions survived inclusion of *APOE* status and tau ×

APOE status interactions for P-tau (β = .74, p = .043), while for T-tau, the slight increase in p-value rendered the interaction significant at a trend level only (β = .72, p = .066). No other terms were significant in these models. Post hoc tests were then run to test for relationships with specific PSQI sub components. The tau-Aβ interaction was significant for Component 1 Sleep quality for both P-tau (β = .67, p = .035) and T-tau (β = .64, p = .045), and for Component 6 Medication (P-tau: β = .69, p = .026; T-tau: β = .70, p = .025). For Component 6, there were also main effects of Aβ (model with P-tau: β = .21, p = .043; model with T-tau β = .21, p = .047).

When all covariates except age were removed, significant relationships between tau and Component 2 sleep latency was found (T-tau: β = .23, p = .034; P-tau: β = .22, p = .047), not interacting with age.

YKL-40

YKL-40 interacted with Aβ in prediction of PSQI Global (β = .73, p = .026). This was due to a stronger relationship in Aβ+ (r = .33) than Aβ- participants (r = -.07). Post hoc analyses revealed significant YKL-40 × Aβ interactions for Component 1 Sleep quality (β = .79, p = .016), Component 6 Medication (β = .95, p = .003) and Component 7 Tired (β = .72, p = .025). Adding *APOE* as well as the YKL-40 × *APOE* interaction increased the YKL-40 × Aβ p-value somewhat for PSQI Global, yielding significance at a trend level only (p = .081). YKL-40 was not related to PSQI Global if Aβ status was not taken into account.

NFL

NFL was not significantly related to PSQI Global in the full model including Age and Aβ, and did not interact with Aβ (β = -.13, n.s.). Removing Aβ from the model revealed no significant effects on PSQI Global.

Effects of atrophy

A stepwise multiple regression analysis was first run to identify the optimal linear combination of brain variables to account for PSQI. In the first step, Age was forced into the model. In the

second step, symmetrized percent change in thickness, area and volume in all 33 cortical regions were entered and removed in an iterative stepwise manner. The final model consisted of 7 brain variables (see Table 2), all significantly related to PSQI. Adjusted R^2 was .30 ($p < .00005$) and all variables except age were significant ($p < .05$). Removing age from the model slightly increased adjusted R^2 to .31. A post hoc analysis showed that there was no interaction between atrophy and Aβ-status in prediction of PSQI (β = -.02, n.s.).

[*Insert Table 2 about here*]

After having established the optimal linear combination of brain variables, these were entered into a multiple regression analysis together with age, tau, Aβ-status and the Aβ × tau interaction to test whether the brain variables could account for the relationship between sleep and the CSF biomarkers. The Aβ × tau interaction survived the inclusion of all the brain variables, with an even higher beta (β = .75, $p < .05$). The adjusted R^2 for this model was .37 ($p < .00001$). The results for p-tau were similar, with the interaction with Aβ still significant (β = .83, $p < .01$) and a good overall model fit (adjusted R^2 .39, p < 00001).

The same analyses were then run for YKL-40. As for tau, the interaction with Aβ survived introduction of all the brain change variables (β = .65, $p < .05$), and the total model was significant with an adjusted R of .36 (p < 00005).

Post hoc, these analyses were repeated with sex, BMI and interval between MRIs in turn as additional covariates. Adding sex or interval did not affect any of the reported relationships. Adding BMI, the Aβ × P-tau interaction was still significant, while the p-values for the Aβ × T-tau and Aβ × YKL-40 interactions increased slightly (t-tau: β = .64, p =.061; YKL-40: β = .58, p =.069). The contributions from BMI were not significant in any of the models, the changes in β's for the interaction terms were not significant, and the model fits did not improve (T-tau: adjusted R^2 reduced from .37 to .36, for YKL-40 from .36 to .35). Thus, including BMI in the final models was

not justified, but we still report that BMI may exert a minor influence on the Aβ-interaction terms.

Relationship to clinical and cognitive outcomes

We ran partial correlations between PSQI Global and MADRS at baseline and follow up, controlling for the effects of age and sex. Significant partial correlations were found at both time-points (Baseline: $r = .56$, follow up $r = .46$, $p < .00001$). Further, we correlated PSQI Global with the total score and the number of items recalled from the verbal memory test from CERAD at follow up, again controlling for age and sex, and found significant correlations both for the total score ($r = -.22$, $p < .05$) and for the number of items remembered ($r = -.27$, $p < .05$). No significant correlations between PSQI and change in memory score between baseline and follow up were seen, only a trend for number of items recalled ($r = -.18$, $p = .099$), indicating that worse longitudinal memory outcome tended to be associated with higher PSQI score. The results for the PSQI subcomponents are reported in Table 3.

[Insert Table 3 about here]

We re-ran the memory-PSQI correlations controlling for MADRS scores, and the MADRS-PSQI correlations controlling for memory scores, in both cases also controlling for age and sex. The memory-PSQI correlations were not significant, with a trend only for number of items remembered ($r = -.20$, $p = .07$). The MADRS-PSQI correlations were still significant ($r = .53$ and .47 for baseline and follow-up, respectively, both p's $< .00001$).

Path analysis

Path analysis was conducted to integrate all tested variables in one comprehensive model. PSQI Global score was used as outcome. As a single measure of atrophy, we used the standardized predicted values from the stepwise regression analysis described above (Table 2). P-tau was preferred over t-tau, and the CERAD 10 words number of item recalled was used as the measure of memory. Further we included age, MADRS score at follow up and YKL-40, as well as

the Aβ × P-tau and Aβ × YKL-40 interaction terms. The initial model, with paths between most variables, is shown in Supplemental figure 1. This model was recursively improved by removing not significant paths one by one ($p < .1$ as criterion for removal) and re-running the analysis multiple times. This procedure led to a model with significant paths from age to MADRS, YKL-40 and the Aβ × YKL-40 interaction term, from atrophy to MADRS score and PSQI, from the Aβ × P-tau interaction and P-tau to PSQI, from MADRS to PSQI, from PSQI to CERAD ($p = .055$), and from YKL-40 and the Aβ × YKL-40 interaction term to CERAD. The paths from Aβ status to PSQI and CERAD were not significant, but were initially kept in the model to ease interpretation of the Aβ × P-tau and Aβ × YKL-40 interactions. AIC for this model was 307. Removing Aβ status from the model rendered all paths significant at $p < .05$, except from PSQI to Memory, $p = .066$, and AIC decreased to 291. Swopping the direction of the path from PSQI → Memory to Memory → PSQI, caused this path now to be significant, and resulted in all 11 paths being significant. This further lowered AIC to 290, indicating that this may be the preferred model. The model is shown in Figure 1. Detailed model statistics for these two models are presented in Supplementary Table 2. In this model, 50% of the variance in sleep was explained (adjusted $R^2 = .50$, unadjusted $R^2 = .58$) (see Figure 2).

[Insert Figure 1 and Figure 2 about here]

Discussion

The results showed that CSF levels of tau and YKL-40 interacted with amyloid status in predicting sleep characteristics over two years in cognitively healthy older adults. Further, sleep was predicted from multiple variables, with memory function, depression, brain atrophy, p-tau and Aβ × p-tau interaction all yielding unique contributions. This suggests that sleep is a complex variable affected by a range of different processes in the brain. Thus, age-related changes in sleep patterns can have multiple causes, which will likely be partly independent, partly overlapping and partly synergistically in explaining sleep disturbances.

Aβ interact with tau and YKL-40 in predicting sleep

The relationship between Aβ accumulation and sleep problems has received much attention. Animal studies suggest that Aβ clearance is most efficient during sleep, and that disturbed sleep will lead to increased Aβ accumulation in the brain [60]. Further, several studies have reported that sleep problems are associated with accumulation of Aβ-proteins even in healthy older adults [6, 7]. For instance, at least four recent studies using amyloid Positron Emission Tomography (PET) have found relationships between self-reported sleep parameters and Aβ-accumulation [8-11]. Importantly, however, the relationships reported are usually relatively weak, and the exact sleep parameter showing relationship to Aβ varies. Of the studies cited above, significant relationships with Aβ were found for 1 of 6 sleep variables tested [9], 1 of 4 [8], 3 of 7 [10] and 1-2 (depending on which covariates were used) of 5 [11]. This suggests that the direct association between self-reported sleep problems and Aβ is not strong. This conclusion warrants efforts to look at other pathways to sleep problems, which may work in synergy with Aβ.

There have been few attempts to test how different biomarkers may interact with Aβ in causing sleep disturbances. We found tau to predict poorer sleep better in Aβ positive compared to Aβ negative older adults. This is interesting, as tau accumulation in MTL is one of the first events in AD, likely prior to Aβ accumulation[16], and MTL is critical for many aspects of sleep[15, 17, 18]. In rodents, MTL tau diminishes expression of hippocampal ripples, causing less temporally synchronized ripple events [61] and disrupted network activity during sleep [62]. Human studies have also reported relationships between tau and sleep patterns[19-21]. In one study, better sleep was associated with less neurofibrillary tangle density at autopsy, attenuating the effect of *APOE* ε4 [56]. In this study, no direct effect of sleep was found on plaque load, and sleep modified the *APOE* effect on tangle density in a manner not statistically mediated by Aβ. In the model used in the present study, sleep was predicted from tau, since tau was observed at an earlier point in time. However, in reality, the causality may go both ways. For instance, long-term sleep deprivation has been shown to lead to memory decline and disruptions of tau processing in transgenic mice (3xTg), with some variations across studies[63, 64].

The findings indicate that both Aβ and tau accumulation is related to sleep, in possible vicious causative cycles, leading to the crucial question of if and how they are redundant, independent or work synergistically in explaining sleep. The present results showed that tau is more predictive of sleep patterns over 2 years in Aβ positive than Aβ negative older healthy adults. This can be interpreted within a neural reserve model, where certain levels of Aβ or tau can be coped with without causing sleep problems, but not when faced with high levels of both.

In addition to tau, the neuroinflammation/astroglial activation marker YKL-40 also interacted with Aβ in predicting sleep. YKL-40 in serum has been related to specific sleep conditions and disturbances[22-26]. Aβ accumulation provides prime stimuli for inflammation Aβ[35, 36], which could contribute to explain the interaction between Aβ and YKL-40. CSF levels of YKL-40[27] increase with age [28] and in AD [27, 29-31] (but see [32]), and is related to brain atrophy [33, 34]. Put together, these factors can explain why YKL-40 may play a crucial role in age-related sleep disturbances. It must be noted, however, that when all variables were included in the path model, YKL-40 no longer predicted sleep directly, only indirectly through its relationship with memory function.

We and others have recently shown that NFL is related to hippocampal atrophy[39, 40], but NFL did not interact with Aβ in predicting sleep problems in the current dataset. Further studies are necessary to establish whether NFL is related to sleep characteristics.

Multiple variables predicted sleep

Importantly, the path analysis demonstrated that multiple variables uniquely predicted sleep patterns. In addition to the tau × Aβ interaction, brain atrophy, memory function and depression scores were related to the global sleep variable. This demonstrates the complex nature of sleep, and that variation in sleep patterns index a range of different processes. In the preferred model, sleep was a purely exogenous variable, with a better fit for example when causality was modelled from memory to sleep rather than the other way around. Of course, this should not be taken as evidence that the mechanisms work only one way, as there for instance are obvious effects of sleep on memory function [45, 65, 66] and experimental rodent studies

suggesting possible pathways from sleep deprivation to tau [63, 64] and Aβ accumulation [5]. Still, the results underscores that sleep may be an important variable related to brain health and cognitive function in older adults at increased risk of Alzheimer's disease.

Limitations

There are several limitations to the present study. First, although sleep was measured by a well-validated and much used inventory, it is still a self-report measure. The strength of this approach is that sleep is measured in the participants' natural environment, increasing its ecological validity. Complementary evidence from actigraphy would strengthen the conclusions. Second, participants with cognitive decline were screened out. This may have biased the sample, as for instance older adults with high rates of atrophy, Aβ accumulation and sleep problems also would be more likely to be excluded, thus possibly reducing the observed interrelations between the variables of interest. Still, this approach allowed us to study the relationships among multiple variables in the very important group of cognitively well-functioning older adults with different Alzheimer risk profiles, among other things representing the most promising time window for possible intervention. Finally, although CSF measures yield highly accurate indexes of total biomarker levels, we do not get information about where in the brain accumulation is largest, which is a benefit of e.g. amyloid PET.

Conclusion

The present results demonstrate that Aβ interact with tau and YKL-40 in predicting sleep problems. Further, tau, the tau × Aβ interaction, memory function, depression score and brain atrophy explained unique variance in sleeping patterns, clearly suggesting that sleep is a complex and potentially important measure related to a range of different processes in the brain.

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Disclosure statement

Dr Watne has given a lecture on delirium for Lilly. Dr Bruun Wyller has given lectures on delirium for Pfizer, Roche, AstraZeneca, and Nycomed. Dr Blennow has served on Advisory Boards for IBL International and Roche Diagnostics. Drs Blennow and Zetterberg are co-founders of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg. Dr Zetterberg has served at advisory boards for Roche Diagnostics, Eli Lilly and Pharmasum Therapeutics. Dr Walhovd has given a lecture on lifespan changes in brain and cognition for Shire International Gmbh (2015) and has served in

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Figure legends

Figure 1 Path model

This model was obtained after removing all not significant paths. As can be seen, the global sleep index is uniquely predicted from five variables. Numbers represent partial standardized paths coefficients, and all shown coefficients were significant ($p < .05$).

Figure 2

Scatterplot showing the prediction model (x-axis) and total sleep problems (PSQI total score). The prediction model consisted of age, P-tau, Aβ-status, the Aβ × tau interaction and two year change in seven different cortical regions (see Table 2). In total, this model accounted for 58% of the variance in sleep problems. Similar results were obtained for T-tau and YKL-40.