Reduced overnight memory consolidation and associated alterations in sleep spindles and slow oscillations in early Alzheimer's disease

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ABSTRACT

Spatial navigation critically underlies hippocampal-entorhinal circuit function that is early affected in Alzheimer's disease (AD). There is growing evidence that AD pathophysiology dynamically interacts with the sleep/wake cycle impairing hippocampal memory. To elucidate sleep-dependent consolidation in a cohort of symptomatic AD patients ($n = 12$, 71.25 ± 2.16 years), we tested hippocampal place learning by means of a virtual reality task and verbal memory by a word-pair association task before and after a night of sleep. Our results show an impaired overnight memory retention in AD compared with controls in the verbal task, together with a significant reduction of sleep spindle activity (i.e., lower amplitude of fast sleep spindles, $p = 0.016$) and increased duration of the slow oscillation (SO; $p = 0.019$). Higher spindle density, faster down-to-upstate transitions within SOs, and the time delay between SOs and nested spindles predicted better memory performance in healthy controls but not in AD patients. Our results show that mnemonic processing and memory consolidation in AD is slightly impaired as reflected by dysfunctional oscillatory dynamics and spindle-SO coupling during NonREM sleep. In this translational study based on experimental paradigms in animals and extending previous work in healthy aging and preclinical disease stages, our results in symptomatic AD further deepen the understanding of the memory decline within a bidirectional relationship of sleep and AD pathology.

1. Introduction

Impairments in spatial learning, navigation and orientation are hallmarks of Alzheimer's disease (AD) (Coughlan et al., 2018; Henderson et al., 1989). Difficulties in orienting and navigating in familiar environments is a component in approximately one third of AD patients and can already manifest at preclinical stages of the disease (MCI) (Henderson et al., 1989; Schöberl et al., 2020). Spatial navigation deficits in AD are clinically relevant as patients have a tendency to become lost, especially in new environments. Depending on the disease stage, this condition leads to further spatial withdrawal and, in turn, can facilitate further impairments of cognitive and motor skills.

The neural substrate of spatial navigation has been found to include a large scale network of neocortical regions (Ekstrom et al., 2003; Maguire et al., 1998), but critically depends upon entorhinal-hippocampal circuits (O'Keefe and Dostrovsky, 1971). Decades of work in rodents have demonstrated the existence of a multitude of functionally-specialized neurons, including place cells (O'Keefe and Dostrovsky, 1971) and grid cells (Hafting et al., 2005), which are thought to contribute to an internal representation of external space and self-location (Moser et al.,

2008). More recently, such specialized neurons have also been identified in humans (Ekstrom et al., 2003; Nadasdy et al., 2017) and their dysfunction (in particular of grid-like representations) have been observed in adults at genetic risk of AD (Kunz et al., 2015). The pathophysiological process involving both Amyloid-beta (Aβ) peptide deposition as well as neurofibrillary tangles of the microtubule binding tau protein (Busche et al., 2019) leads to neurodegeneration including atrophy, neuron loss, and gliosis with subsequent changes in synaptic connectivity and neuronal excitability ultimately leading to a decline of cognitive functions (Jack et al., 2010; Weintraub et al., 2012).

Histopathological studies provide evidence that the medial temporal lobe is initially affected by pathological changes, where neurofibrillary tangles are observed in the entorhinal cortex and hippocampus (Braak and Braak, 1991).

The consolidation of hippocampus-dependent memories is assumed to be particularly mediated by sleep (Diekelmann and Born, 2010; Klinzing et al., 2019). Hippocampal neural firing sequences are reactivated during subsequent periods of slow wave sleep (SWS) which is thought to support the transmission of information from hippocampal short-term to neocortical long-term stores (O'Neill et al., 2010; Wilson and McNaughton, 1994). In this process, reactivation in the hippocampus is accompanied by slow oscillatory activity in neocortical areas that synchronizes further EEG rhythms of other brain regions, specifically thalamic spindles and hippocampal sharp-wave ripples (Clemens et al., 2007; Staresina et al., 2015).

Sleep disturbances are thought to play a critical role in AD pathophysiology (Mander et al., 2016). Previous studies have emphasized a reduction of SWS and sleep spindles in AD which is assumed to contribute to a disruption of hippocampus-dependent memory consolidation (Rauchs et al., 2008; Varga et al., 2016). Furthermore, sleep deprivation was accompanied by an increase of Aβ levels in both rats (Chen et al., 2017) and humans (Shokri-Kojori et al., 2018). These results suggest a highly entangled connection between Aβ burden, sleep, and hippocampal dysfunction.

The novelty of our study is underscored by its multifaceted investigation of sleep-dependent memory consolidation, with a particular focus on spatial memory, in the context of AD. In particular, our study introduces an allocentric spatial memory task, a highly sensitive metric that is closely linked to hippocampal function, providing a novel perspective for the early detection of cognitive impairments associated with AD.

Spatial memory and navigation have a high clinical relevance given its specificity in distinguishing AD from other dementias (Coughlan et al., 2018), and its sensitivity in detecting preclinical stages (Levine et al., 2020). Thus, in addition to verbal declarative memory, here we particularly focused on spatial memory as a readout of hippocampal function. Furthermore, the inclusion of the allocentric spatial memory task, which has a high degree of comparability with analogous assessments in animal studies, enhances the uniqueness and translational relevance of our investigation within the scientific landscape. (Bartsch et al., 2010; Ekstrom et al., 2003; Schoenfeld et al., 2017). The aim of the study was to test the hypothesis that there would be reduced consolidation of both verbal and spatial memory, depending on changes in sleep-dependent markers of hippocampus-dependent memory consolidation, specifically SO, spindles and their interactions.

2. Methods

2.1. Participants

Twelve AD patients (71.25 ± 2.16 years, range 53–85 years, 6 male) were recruited from the Memory and Dementia Clinics of the Departments of Neurology and Psychiatry of the University of Kiel. Patients were diagnosed according to the criteria of 'probable AD dementia with increased level of certainty' as defined in the latest version of diagnostic guidelines (McKhann et al., 2011). Twelve healthy control participants

(72.67 ± 1.58 years, range 65–84, 5 male) recruited via open platforms in the University Hospital Schleswig-Holstein, Campus Kiel as well as from our healthy control database were tested. Exclusion criteria included any significant neurological disease other than AD in the patient cohort or any psychiatric disease (including substance dependence, major depression other neurodegenerative disease) or any medication that could affect cognition or sleep. All participants gave written informed consent prior to the experiments. The study was approved by the ethical committee of the University of Kiel. All procedures were in accordance with the Declaration of Helsinki.

2.2. Neuropsychological and neurocognitive assessment

Normal cognitive functioning of the control group was assessed via a neuropsychological test battery including Mini-Mental State Examination (MMSE) and Trail-Making-Test (TMT) A and B. Emotional state and functioning of daily living were assessed by the Geriatric Depression Scale (GDS) and the Bayer Activities of Daily Living scale (B-ADL), respectively, in the patient and control group. Premorbid intelligence was measured by the German version of the National Adult Reading Test (NART), Mehrfachwahl-Wortschatz-Intelligenztest-B (MWT-B). To support AD diagnosis, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was used.

2.3. Clinical MRI acquisition and rating

T1-weigthed images of AD patients were recorded on a 1.5 Tesla MRI Scanner (Philips Achieva, Philips, Best, The Netherlands) using a three-dimensional magnetization prepared rapid gradient-echo sequence (3D MPRAGE, matrix size = 240 × 240, 176 slices, voxel size = 1x1x1 mm^3). Analysis was performed by visual inspection of the MR images by two raters experienced in the detection of hippocampal volume changes. For the precise quantification of hippocampal atrophy, a medial temporal lobe atrophy (MTA) score (range 1–4, no atrophy – severe loss of hippocampal tissue) was specified (Scheltens et al., 1992).

2.4. CSF biomarkers

An analysis of Aβ$_{42}$, total tau and tau protein levels in cerebrospinal fluid (CSF) was performed within the clinical diagnostic work-up. To counter different reference frames of immunoassays in CSF analysis, the ratio of t-tau and Aβ$_{42}$ was used for correlational analysis regarding behavioral and sleep data. Moreover, t-tau/Aβ$_{42}$ has been found to strongly reflect positron emission tomography images in the diagnosis of AD (Hansson et al., 2018).

2.5. Procedure

All participants spent one adaptation night in the laboratory prior to the experimental day to habituate to sleeping under laboratory conditions and to screen for sleep apnea syndrome. The recordings of both adaptation and test night were conducted in the University Sleep Laboratory (accredited by the German Sleep Society). Encoding and immediate recall of both a spatial and verbal memory task were performed in the evening of the test night from 7 to 9 pm. After setting up the polysomnographic recordings, lights were turned off at 11 pm. Participants were allowed to sleep until 7 am. The delayed recall took place at 8 am, approximately 12 h after encoding trials of the tasks. During the experimental days, all participants were not allowed to take a nap or drink alcohol or caffeine.

2.6. Spatial memory and navigation task

To test spatial memory and navigation, the Virtual Water Maze task (VWM) was applied. The VWM is based on the hidden platform paradigm in the Morris water maze, a standard test of learning and memory

in rodents (Morris, 1984). The VWM has already been used to test spatial memory (Bartsch et al., 2010; Schoenfeld et al., 2017) and has been used for cross-species comparisons (Schoenfeld et al., 2017). The aim of the VWM is to learn and retrieve the location of a hidden treasure box by navigating on a circular island via joystick. The island is sectioned into four quadrants that are marked by different distal cues (i.e., bridge, wind turbine, sailing boat, and water tower, Fig. 1a). In this study, the target was located in the area of the bridge. From the first-person view during the task, the location of the target is not visible until getting very close to the target position (Fig. 1b).

The experiment comprised 12 learning trials with different starting position, and one delayed recall trial taking place after a night of sleep. For the analysis of the 12 learning trials, performance was averaged across 3 succeeding trials, resulting in four trial blocks (Fig. 1c and d). As a reference for the delayed recall and to measure overnight retention, the best learning trial was used. Memory for the target position was quantified by the relative dwell time in the target quadrant: the longer participants remained near the target, the better the memory performance. For the analysis of the VWM two of the AD patients and one control participant dropped out because of not reaching the criterion of 25% relative dwell time in the target quadrant during learning.

2.7. Verbal declarative memory

To assess verbal declarative memory, a word pair association task was used. Participants were required to learn a list of 10 semantically related word pairs and name the second word of each pair when presented with the corresponding first word during a recall test. The list of word pairs was orally presented. Cued recall was tested in random order. The procedure was repeated five times. The recall performance of the run with the highest number of remembered pairs was used as a reference for the delayed recall.

2.8. Polysomnographic recording and EEG analysis

Polysomnography included the electroencephalogram (EEG) from F3, F4, C3, C4, O1, and O2 (International 10–20 system, referenced to mastoids), electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG). EEG signals were filtered between 0.2 and 35.0 Hz and EOG between 0.2 and 10.0 Hz. The EMG was recorded with a high-pass filter of 10.0 Hz and a 50.0 Hz band-pass filter. ECG underwent a 50.0 Hz low-pass filter. All signals were recorded using the SOMNOscreen™ plus (Somnomedics, Randersacker, Germany) and AU cup electrodes of a diameter of 10 mm (Natus Medical Inc.®, Middleton, USA). Sampling rate was 128 or 256 Hz. Prior to the analysis, signals were down-sampled to a common rate of 128 Hz. The offline scoring of sleep stages was based on central channels, followed the standard criteria of the American Academy of Sleep Medicine, and was carried out by a trained rater.

Post-processing and analysis were performed by means of the SleepTrip toolbox (http://www.sleeptrip.org; RRID: SCR_017318) based on MATLAB 2015a (Mathworks, Natick, USA) and FieldTrip (Oostenveld et al., 2011; RRID: SCR_004849). Power spectral density estimates were calculated for the following frequency bands: SO (0.5–1 Hz), delta (1–4 Hz), slow wave activity (SWA; 0.5–4 Hz), theta (4–8 Hz), slow spindles (9–12 Hz), and fast spindles (12–15 Hz). For the detection of SOs and fast spindle events, epochs of NonREM sleep (N2 and SWS) free of visually identified artifacts were used. Individual variations in frequency peaks were visually identified from NonREM power spectra according to their expected power maximum (i.e. 12–15 Hz) for every participant (peaks AD: 13.56 ± 0.11 Hz, peaks controls: 13.43 ± 0.21 Hz). Moreover, we identified SO-spindle events, i.e. slow waves that nested at least one detected spindle (i.e. within the duration of a SO). Spindles were counted once for the first slow wave in which they occurred. Then all detected SOs, spindles, and SO-spindle events were characterized by count, density, amplitude, duration, down-to-up slope and up-to-down-slope. As to SOs synchronizing with spindles the mean delay of the spindle to the SO down state was calculated. The algorithms for power
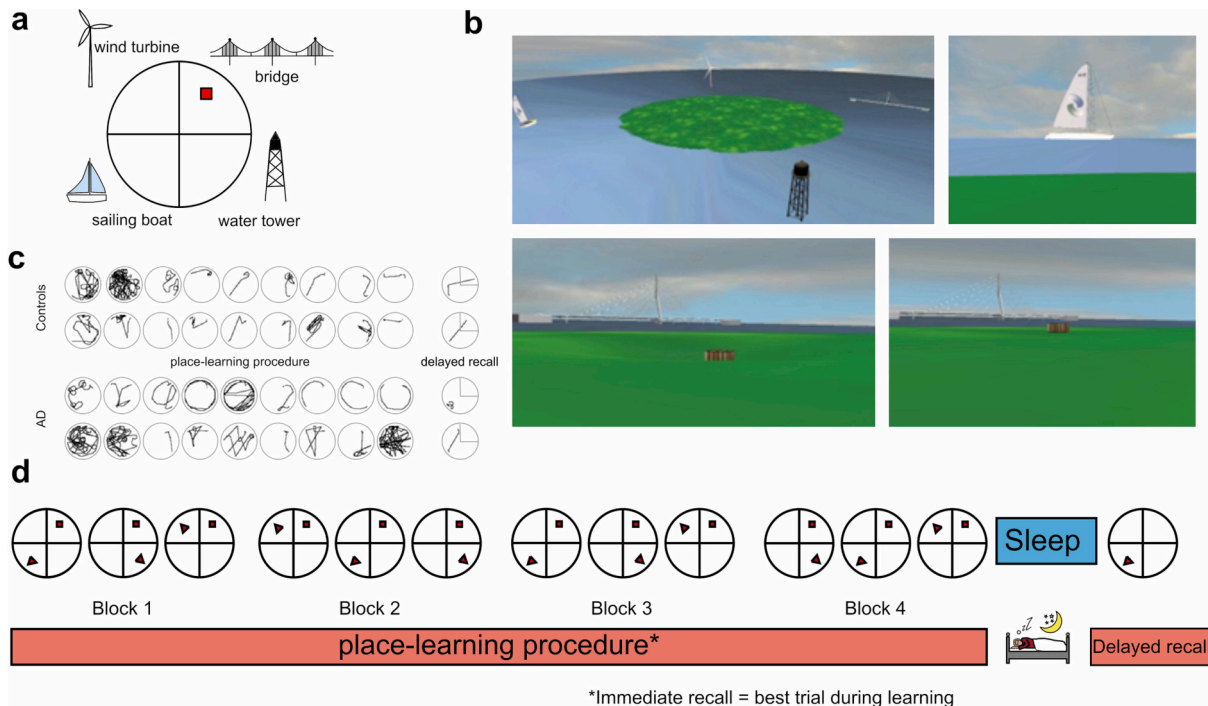

Fig. 1. Virtual Water Maze Task. a) & b) Map and bird's eye view on the locations of target (red square) and landmarks. Perspective view (upper row, left side) and participant's perspective (upper row, right side and lower row). c) Examples of covered paths by AD patients and controls in the first 3 learning blocks and delayed recall trial. d) Study protocol: starting positions (red triangle changing counterclockwise). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

spectral analysis, SO, and spindle detection as well as time-frequency analysis to evaluate coupling of SOs and fast spindles are described in detail elsewhere (Hanert et al., 2017; Wang et al., 2018). Regarding the detection of SOs and spindles one patient was excluded from the analyses showing an extreme outlier (>3 times Inter-Quartile-Range). Analyses are reported for representative C4 channels referenced to A2.

2.9. Statistical analyses

Pretesting of normal distribution and homogeneity of variances was performed by the Shapiro-Wilk test and Levene's test, respectively. Box's M test of the equality of covariance was used to identify homogeneity of the variance-covariance matrix. Multivariate and univariate analyses of variance models for repeated measures with group as between-subjects factor and trial as within-subjects factor were calculated. For multivariate statistics, Wilks' lambda was computed. Learning curves were evaluated by means of polynomial contrasts. To show significant group differences in memory decay and sleep parameters, independent samples *t*-tests or Mann-Whitney-*U* tests were used. A calculation of the effect sizes was performed and reported as eta squared for t-tests and one-way ANOVA and partial eta squared for repeated measures ANOVA and MANOVA, respectively. For non-parametric test, R squared was reported. Pearson correlation coefficients were calculated to examine relationships between sleep and memory performance. Overnight memory decay as reference for correlational analyses was computed as the difference between delayed and immediate recall. For significant correlations, simple linear regression models were established. Between group comparisons of regression coefficients were done by multiple regression. In this context, independence of observations was examined by the Durbin-Watson statistic. Homoscedasticity was evaluated by means of the Breusch-Pagan-Test. Alpha error inflation was not mathematically corrected but considered for interpreting results. The significance level was set to $p < 0.05$, two-tailed for all tests. Data were specified as mean ± SEM if not otherwise stated.

3. Results

3.1. Clinical characteristics and neurocognitive assessment

Table 1 shows the clinical characteristics of the AD group. With regard to cognitive functions assessed by the CERAD, patients performed at least one standard deviation below the mean except in naming of objects. In the context of diagnostic criteria for AD, at least one typical AD biomarker (Aβ, total tau, and tau protein) was abnormal in all AD patients whose CSF was assessed (11 of 12 patients). As to MRI evaluation assessing the imaging biomarker of regional atrophy (Fig. 2), the MTA score was 2.67 ± 0.24 (range: 1–4) thus showing typical medial-temporal atrophy. In seven patients at least one white matter hyperintensity was found.

Processing speed of AD patients was normal and there was no difference in premorbid intelligence between the groups. However, as expected, patients showed impaired memory, executive function as well as deficits in activities of daily living. Also, the evaluation of the GDS implies a tendency towards depressive symptoms in the patient group (Table 2). In summary, our AD group displayed clinical characteristics of early symptomatic AD.

B-ADL, Bayer Activities of Daily Living; GDS, Geriatric Depression Scale; MMSE., Mini Mental State Exam; MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest-B; TMT, trail making test.

3.2. Impaired overnight consolidation of spatial navigation and verbal declarative memory in AD patients

Next, we investigated whether memory consolidation was affected in our AD cohort. To this end, we compared both groups' memory performance before and after sleep. Learning for patients and controls from

Table 1
Clinical characteristics of AD patients.

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Sex, female (No. (%))	6/12 (50%)
Age	71.25 ± 2.16
Clinical imaging	Mean ± SEM
MTA score (left)	2.75 ± 0.25
MTA score (right)	2.58 ± 0.23
MTA score	2.67 ± 0.24
T2/FLAIR hyperintensities (No. (%))	7 (84.00)
Lacunes (No. (%))	4 (33.33)
CSF biomarkers (ng/L)*	Mean ± SEM
Aβ	546.27 ± 104.24
t-tau	423.09 ± 45.38
p-tau	68.18 ± 8.50
CERAD subtests (*n* = 8)	Mean ± SEM (z)
Verbal fluency	16.00 ± 1.70 (−1.30)
Boston Naming Test	13.75 ± 0.25 (−0.58)
MMSE	26.5 ± 0.82 (−1.89)
Word list learning total	15.60 ± 1.36 (−1.66)
Word list learning trial 1	4.13 ± 0.52 (−0.92)
Word list learning trial 2	5.38 ± 0.50 (−1.35)
Word list learning trial 3	6.00 ± 0.46 (−1.75)
Word list recall	4.25 ± 0.70 (−1.54)
Word list savings	69.62 ± 9.94 (−0.63)
Discriminability	91.25 ± 2.27 (−1.18)
Figure drawing	9.63 ± 0.42 (−0.97)
Figure recall	5.25 ± 0.73 (−2.08)
Phonematic fluency	13.00 ± 1.75 (−1.04)

Note. Values are given as mean ± SEM or frequency. For the CERAD subtests z-scores are given in parentheses. Aβ, amyloid beta; CERAD, Consortium to Establish a Registry for Alzheimer's Disease, CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; MMSE, Mini Mental State Exam; MTA, medial temporal lobe atrophy; p-tau, phosphorylated tau; t-tau, total tau. * Analysis of CSF concentration was based on different assays (*n* = 11).

the first to the last learning block in the spatial navigation task was comparable (ANOVA for repeated measures shows significant linear effect in polynomial contrasts: AD: F(1, 6) = 71.04, $p < 0.001$, $\eta_p^2 = 0.92$; controls: F(1, 8) = 29.87, $p = 0.001$, $\eta_p^2 = 0.79$). There was no significant difference between any of the learning blocks between patients and controls (all p's > 0.093) (Fig. 3a). Regarding verbal memory, patients performed worse than the healthy control group during the learning trials (all *p*'s < 0.017). However, the ANOVA for repeated measures showed a significant learning curve for both the patient (F(1,11) = 17.06, $p = 0.002$, $\eta_p^2 = 0.61$) and control group (F(1, 11) = 23.43, $p < 0.001$, $\eta_p^2 = 0.68$) indicating that learning dynamics were comparable between groups (Fig. 3b).

A repeated-measures MANOVA with the verbal and spatial memory tasks as dependent variables confirmed that there were significant multivariate effects for group (Λ = 0.57, F(2, 14) = 5.22, $p = 0.020$, $\eta_p^2 = 0.43$), time (Λ = 0.16, F(2, 14) = 35.98, $p < 0.001$, $\eta_p^2 = 0.84$) and the interaction between group and time (Λ = 0.64, F(2, 14) = 4.02, $p = 0.042$, $\eta_p^2 = 0.37$). Univariate analyses showed that the interaction was significant for the verbal memory task indicating a better consolidation effect for the control group (F(1, 15) = 5.91, $p = 0.028$, $\eta_p^2 = 0.28$) (Fig. 3d), with the similar difference between groups not reaching statistical significance for the spatial memory task (F(1, 15) = 2.27, $p = 0.153$, $\eta_p^2 = 0.13$) (Fig. 3c). The addition of the third factor (verbal vs. spatial memory task) revealed a significant interaction (Λ = 0.76, F(1,15) = 4.79, $p = 0.045$, $\eta_p^2 = 0.24$).

3.3. AD patients showed reduced amplitude of spindles during SOs

The above data point to a dysfunctional overnight consolidation especially of verbal memory. To investigate the underlying mechanisms, we monitored NonREM sleep macro- and microarchitecture. We found the sleep macroarchitecture of AD patients mainly differed from controls in higher wake after sleep onset while the other sleep parameters were unchanged (Table 3). As to the NonREM sleep microarchitecture, AD patients showed a trend towards reduced fast spindle power density
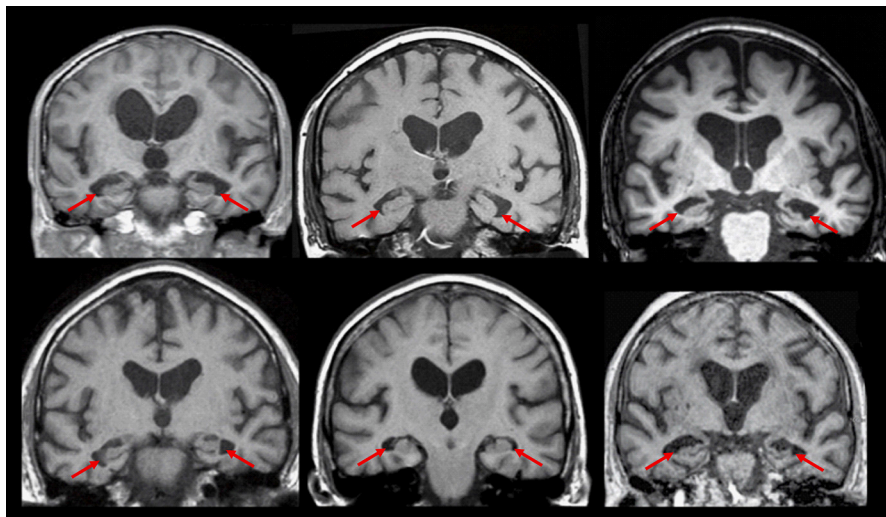
Fig. 2. Coronal T1-weighted MR scans of representative AD patients. Note the detectable hippocampal volume changes (red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Mean and SEM of AD patients and controls in neuropsychological, emotional state, and daily functioning tests.

Test	n	AD patients	n	Controls	p	η^2
MMSE	12	25.67 ± 0.71	10	28.00 ± 0.73	0.034	0.21
TMT A	11	60.45 ± 4.30	12	51.58 ± 6.32	0.267	0.06
TMT B	11	164.64 ± 15.32	12	107.75 ± 12.77	0.009	0.28
GDS	12	3.17 ± 0.67	10	1.60 ± 0.86	0.161	0.10
B-ADL	12	3.26 ± 0.46	10	1.54 ± 0.17	0.004	0.34
MWT-B	12	30.08 ± 1.28	12	31.5 ± 1.36	0.455	0.03

Note. Values are given as mean ± SEM. *P*-values are derived from *t*-tests.

(Table 3). Moreover, spindle detection revealed that patients expressed markedly lower amplitudes of fast spindles (t(22) = −2.64, p = 0.015, η^2 = 0.24). As to SOs, the duration of the detected SOs during NonREM sleep was significantly longer in AD patients than controls (t(22) = −2.53, p = 0.019, η^2 = 0.23).

Concerning SOs synchronizing with spindles we identified SO-spindle events representing SOs that co-occurred with a spindle (typically after the negative SO peak, see Table 3). In comparison with the healthy controls, AD patients showed significantly fewer SO-spindle events (t(21) = −2.38, p = 0.027, η^2 = 0.21, Table 3), although the interaction in an ANOVA with nested vs. non-nested spindles as within subjects factor remained non-significant (F(1,22) = 2.26, p = 0.147, η^2_p = 0.09). A comparison between SOs co-occurring with a fast spindle and isolated SOs (without nested spindle) confirmed the lower spindle amplitude (Z = 2.60, p = 0.008, R^2 = 0.28) and the longer SO duration in AD patients (t(22) = 2.31, p = 0.031, η^2 = 0.20) to be also present in the subset of SOs nesting a spindle (Table 3), with the size of these group differences being comparable for SOs nesting a spindle and isolated SOs (p > 0.612, for the respective isolated vs. nested x AD vs. controls interaction effect). In summary, these data indicate an alteration of AD patients' sleep architecture, which likewise may be causally related to the disruption of memory consolidation mechanisms.

3.4. Slopes of SOs, density of spindles, and SO-spindle synchronization predicted memory performance in the control group

Previous studies have shown that the density of spindle oscillations was a reliable marker of memory consolidation and memory performance (Gais et al., 2002; Hanert et al., 2017; Schabus et al., 2007). Indeed, confirming previous work, we found that in the control group, linear regression models demonstrated that more effective overnight

retention of the target location in the virtual reality task was predicted by a higher density of detected fast spindles (R^2 = 0.42, β = 0.65, p = 0.042; Fig. 4d) and by faster down-to-upstate transitory slopes of the SOs (R^2 = 0.52, β = 0.72, p = 0.019; Fig. 4e). Retention of verbal memory was predicted by a greater delay between spindles and associated SOs (R^2 = 0.39, β = 0.62, p = 0.03, Fig. 4f). The corresponding regression coefficients of the patient group were not significant (spatial memory consolidation*spindle density: R^2 = 0.08, β = 0.29, p = 0.42, spatial memory consolidation*down to up slope: R^2 = 0.14, β = −0.37, p = 0.287, verbal memory consolidation*SO-spindle delay: R^2 = 0.03, β = 0.17, p = 0.609). In summary, the significant relation between memory and sleep, including fine-tuned coupling of spindles and SOs, only in the control group indicate a link of early AD-related processes in sleep-dependent memory consolidation.

3.5. T-tau and β-amyloid burden are associated with SO microarchitecture in AD

Since previous work suggests a relation of AD-specific biomarkers tau/Aβ-burden (Shokri-Kojori et al., 2018; Winer et al., 2019) we investigated whether there was a correlation with parameters of sleep architecture. Indeed, there was an unexpected significant correlation between the ratio of t-tau and $A\beta_{42}$ and the up-to-down slope of the SO that did not nest a spindle (r_s = −0.718, p = 0.013; Fig. 5) and all spindles (r_s = −0.718, p = 0.013), with this correlation approaching significance for the up-to-down slope of SOs that nested a spindle (r_s = −0.536, p = 0.089). Relationships between biomarkers and other sleep parameters as well as behavioral data were all not significant (p's > 0.05). These data indicate that clinically-relevant biomarkers of AD are related to alterations of sleep microarchitecture essential for hippocampus-dependent memory consolidation.

4. Discussion

In accordance with previous studies in the aging brain, our results demonstrate a distinctly diminished spindle activity as reflected by lower spindle amplitude in AD patients. Also, AD patients showed fewer spindles nesting in a SO upstate suggesting a disease related weakening of the temporal synchronization of SOs and spindles. With regard to SOs, there was a prolonged duration in AD regardless of SOs nesting a spindle or occurring separately. As expected, consolidation of memories across sleep was impaired in the patient group with this effect being significant for the verbal but not the spatial task. Importantly, a higher spindle
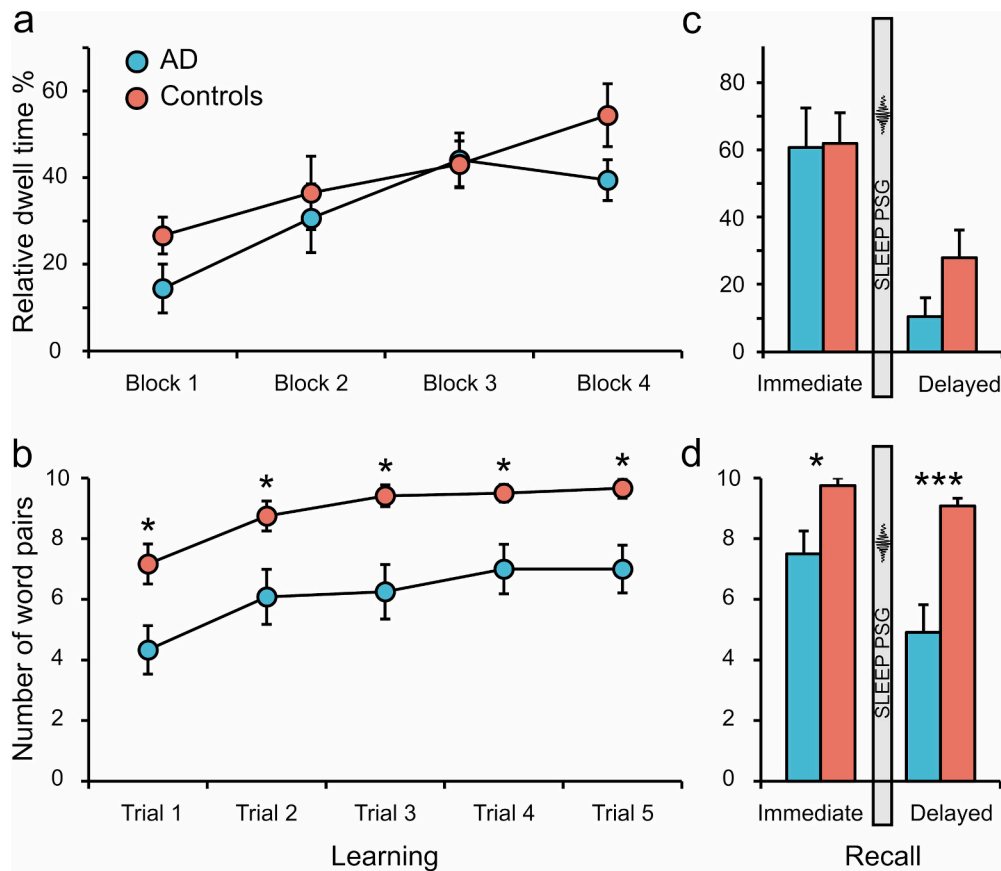
Fig. 3. Spatial and verbal learning and recall in Alzheimer's disease and a control group. a) Patients' vs. controls' learning curves regarding relative dwell time in the target quadrant. b) AD patients were impaired in all learning trials in the word pair learning task compared to the healthy controls, still there was a significant learning curve from the first to the last trial. c) Controls spent (non significantly) longer periods of time in the target quadrant in delayed recall compared with AD. d) Patients remembered significantly less word pairs in both immediate and delayed recall. A significant interaction indicates impaired consolidation in the patient group. * $p < 0.05$, ** $p < 0.01$, *** $p > 0.001$.

density and a steeper (down-to-up transitory) slope of SOs during consolidation sleep predicted high spatial memory performance in the controls. Complementing the assumption that uncoupled SO-spindle events have a detrimental effect on memory consolidation in AD, the delay in seconds between SOs and the nested spindle was correlated with verbal memory consolidation in the control group, whereas in the AD patients these relationships were entirely lost. These findings highlight the AD pathology-dependent dysfunction in hippocampus-associated memory consolidation and provide insights into how sleep-related alterations may contribute to the disease progression.

Deficits in spatial navigation are a hallmark of AD and have been examined in a variety of functional aspects including spatial orientation and path integration (Henderson et al., 1989; Mokrisova et al., 2016). Neuronal spatial firing patterns, like entorhinal grid cells and hippocampal place cells, are thought to represent the neural correlates of a cognitive map (Ekstrom et al., 2003; Nadasdy et al., 2017), and hence to support allocentric navigation strategies and spatial memory (Maguire et al., 1998). Indeed, those regions are the first to be affected by pathophysiological hallmarks of AD: the deposition of senile plaques, neurofibrillary tangles and consequent neuronal cell loss (Braak and Braak, 1991). By comparing the results from the verbal and spatial memory tasks, we see a more pronounced effect of AD pathology on verbal than spatial memory consolidation. The effect of poorer overnight consolidation on spatial memory in AD did not reach statistical significance. Several key arguments contribute to this unexpected finding. First, neuropathological changes in our study cohort, may not have reached a threshold in our early-stage AD patients. It is possible that spatial memory, being an area relatively less affected by normal

aging and other types of dementia (Cerman et al., 2018; Coughlan et al., 2018; Tu et al., 2017) may take longer to manifest clear deficits, especially in individuals in the prodromal or preclinical stages of the disease. Therefore, our study may have captured the cohort at an early stage when spatial memory deficits were not yet pronounced, consistent with the concept that spatial memory may be a more sensitive marker of AD pathophysiology at a later stage (see Coughlan et al., 2018). Second, it is worth considering that the verbal memory task may be inherently more difficult than the spatial memory task. This is supported by the fact that our patients showed verbal memory deficits in immediate recall, whereas their immediate recall performance in the VWM was comparable to that of the healthy control group. The higher cognitive demands of the verbal memory task may explain the observed differences in consolidation between verbal and spatial memory. Finally, another factor to consider is the possibility of hemispheric differences in our patient cohort, particularly in the left medial temporal lobe, which is more involved in verbal memory tasks (Ezzati et al., 2016; de Toledo-Morrell et al., 2000). In particular, our cohort tended to have higher scores for medial temporal atrophy in the left hemisphere (see Table 1). This asymmetry may have contributed to the observed differences in memory consolidation. These findings challenge our initial assumptions and highlight the importance of exploring the potential value of spatial memory as a diagnostic marker at different stages of the disease.

The formation of long-term hippocampus-dependent memory during sleep is thought to be mediated by an active system consolidation process which is reliant on the reactivation of memory information in the hippocampus and its transmission to extrahippocampal areas during SWS (Diekelmann and Born, 2010). Within this process, neocortical SOs

Table 3

Between group comparisons of sleep stages, power density, SOs, spindles and temporal coupling.

	AD	Controls	t/Z	p	η^2/R^2
Total sleep time (min)	387.92 ± 15.47	410.54 ± 15.41	−1.04	0.311	0.05
Sleep onset (min)	48.33 ± 11.22	49.88 ± 11.05	−0.10	0.923	<0.001
N1 (%)	19.02 ± 2.96	20.77 ± 2.36	−0.46	0.648	0.01
N2 (%)	35.09 ± 3.78	42.21 ± 1.90	−1.68	0.107	0.11
SWS (%)	9.70 ± 3.59	6.60 ± 1.46	0.29[a]	0.799	0.004
REM (%)	12.09 ± 1.52	14.56 ± 1.26	−1.25	0.223	0.07
Wake after sleep onset (%)	23.16 ± 4.44	11.99 ± 6.92	2.29	0.036	0.19
N2/SWS	0.28 ± 0.33	0.16 ± 0.11	0.12[a]	0.932	<0.001
NonREM/REM	8.20 ± 9.46	5.21 ± 1.80	0.06[a]	0.977	<0.001
Power density (μV^2/Hz)					
SO (0.5–1 Hz)	208.70 ± 60.47	131.39 ± 14.22	1.25	0.237	0.07
SWA (0.5–4 Hz)	61.75 ± 13.93	54.08 ± 3.91	0.53	0.605	0.01
Delta (1–4 Hz)	35.57 ± 6.20	40.98 ± 3.09	−0.78	0.446	0.03
Theta (4–8 Hz)	6.19 ± 1.05	8.71 ± 1.85	−1.18	0.250	0.06
Slow spindles (9–12 Hz)	2.26 ± 0.41	3.06 ± 0.45	−1.32	0.202	0.07
Fast spindles (12–15 Hz)	1.02 ± 0.11	1.76 ± 0.38	−1.88	0.074	0.14
Fast spindles					
Count	561.00 ± 77.26	698.42 ± 47.87	−1.51	0.145	0.09
Density (per 30 s)	1.76 ± 0.141	1.81 ± 0.10	−0.32	0.749	0.01
Length (s)	0.73 ± 0.013	0.73 ± 0.01	−0.21	0.839	<0.01
Amplitude (μV)	14.71 ± 0.96	19.86 ± 1.70	−2.64	0.015	0.24
SO					
Count	647.75 ± 136.34	672.08 ± 67.90	−0.16	0.875	<0.01
Density (per 30 s)	1.86 ± 0.25	1.73 ± 0.15	0.46	0.653	<0.01
Duration (s)	1.25 ± 0.021	1.18 ± 0.02	−2.53	0.019	0.23
Down-to-up slope (μV/s)	−188.74 ± 15.61	−211.86 ± 11.38	1.20	0.245	0.06
Up-to-down slope (μV/s)	151.12 ± 13.68	177.84 ± 8.66	−1.85[a]	0.068	0.14
Amplitude (μV)	73.48 ± 6.31	78.79 ± 3.36	−1.33[a]	0.198	0.07
SO-spindle events					
Count	38.36 ± 07.09	59.92 ± 5.76	−2.38	0.027	0.21
Density (per 30 s)	0.14 ± 0.03	0.16 ± 0.02	−0.40	0.691	<0.01
Fast spindle duration (s)	0.66 ± 0.01	0.68 ± 0.01	−1.27	0.217	0.07
Fast spindle amplitude (μV)	14.33 ± 1.01	19.72 ± 1.46	2.60	0.008	0.28
SO duration (s)	1.24 ± 0.02	1.17 ± 0.02	2.31	0.031	0.20
SO amplitude (μV)	73.28 ± 6.43	80.23 ± 3.62	−0.94	0.359	0.04
SO up-to-down slope	−185.97 ± 23.41	−235.66 ± 15.70	1.76	0.092	0.12
SO down-to-up slope	157.65 ± 17.63	188.45 ± 9.86	−1.52	0.142	0.10
Delay (s)[b]	0.46 ± 0.03	0.43 ± 0.03	0.69[a]	0.514	0.02
Delay dispersion (s)[c]	0.30 ± 0.015	0.27 ± 0.02	0.84	0.409	0.03

Table 3 (*continued*)

	AD	Controls	t/Z	p	η^2/R^2
Isolated spindles and SOs[d]					
Spindle count	510.25 ± 68.81	638.50 ± 48.07	−1.53	0.141	0.10
Spindle density (per 30 s)	1.61 ± 0.13	1.65 ± 0.10	−0.24	0.810	<0.01
Spindle duration (s)	0.73 ± 0.01	0.73 ± 0.01	−0.23	0.818	<0.01
Spindle amplitude (μV)	14.71 ± 0.96	19.86 ± 1.72	2.08[a]	0.039	0.18
SO count	597.17 ± 125.42	612.83 ± 64.80	−0.11	0.913	<0.01
SO duration (s)	1.26 ± 0.02	1.18 ± 0.02	2.51	0.020	0.22
SO amplitude (μV)	73.47 ± 6.30	78.63 ± 3.34	1.33[a]	0.198	0.07
SO up-to-down slope	−187.97 ± 15.40	−209.13 ± 11.26	1.11[a]	0.279	0.05
SO down-to-up slope	150.19 ± 13.42	176.72 ± 8.68	−1.79	0.078	0.133

Note. Values are given as mean ± SEM.

N1, sleep stage 1; N2, sleep stage 2; REM, rapid-eye movement; SO, slow oscillations; SWA, slow wave activity; SWS, slow wave sleep.

[a] The non-parametric test was used.

[b] Delay between detected spindles and negative SO-down-state peak in seconds.

[c] Standard deviation of the delay between coupled spindles and SO.

[d] Spindles and SO occurring in isolation.

synchronize with hippocampal ripples and thalamic spindles (Clemens et al., 2007; Staresina et al., 2015). There is growing evidence that SWA is reduced in both normal aging and AD, and that this reduction is dependent on the underlying neuropathology, specifically Aβ (see Mander et al. (2016) for a review). While significant progress is being made regarding the intriguing relationship between SWA, Aβ burden and memory performance (Mander et al., 2022; Varga et al., 2016), the most obvious shortcoming of our work is that we do not show a significant reduction in SWA in our patient cohort. In fact, studies in older individuals have observed a significantly reduced SWA during NREM sleep, with this reduction also being associated with the degree of memory impairment observed (Carrier et al., 2011; Dijk et al., 1989). This age-related disruption becomes more pronounced in amnestic MCI and, further along the continuum, in symptomatic AD (Hita-Yañez et al., 2013; Prinz et al., 1982; Westerberg et al., 2012). Notably, these NREM sleep disturbances predict the severity of observed memory impairment (Liguori et al., 2014). Recent studies also show an association between Aβ burden and reduced SWA (Mander et al., 2015). This activity appears to act as a moderating factor for the effects of Aβ on memory consolidation (Zavecz et al., 2023). Specifically, the study found that NREM SWA selectively supports superior memory function in individuals with high Aβ load.

The absence of a reduction in SWA in our study cohort, particularly in comparison with the healthy control group, may be due to a number of factors. One key factor may be the characteristics of our study population, as mentioned above, where individuals in our cohort may be in earlier stages of AD. Another influencing factor could be the already below average time spent in SWS of our control group. Compared to other healthy populations (e.g. Luca et al., 2015; Mander et al., 2015; or see in this review Ohayon et al., 2004), the retention time in deep sleep was only 6.60 ± 1.46%. These findings can also be applied to the power density of the SWA frequency band in our control group, which shows a strongly reduced activity compared with other studies (Landolt et al., 1996; Luca et al., 2015). Beside the individual characteristics of our study cohort, recent evidence shows that different segments of the SWA spectrum show different changes and responses to AD pathology. In particular, a reduction in K-complex density within the low-frequency SWA range has been observed alongside a lack of SWA reduction
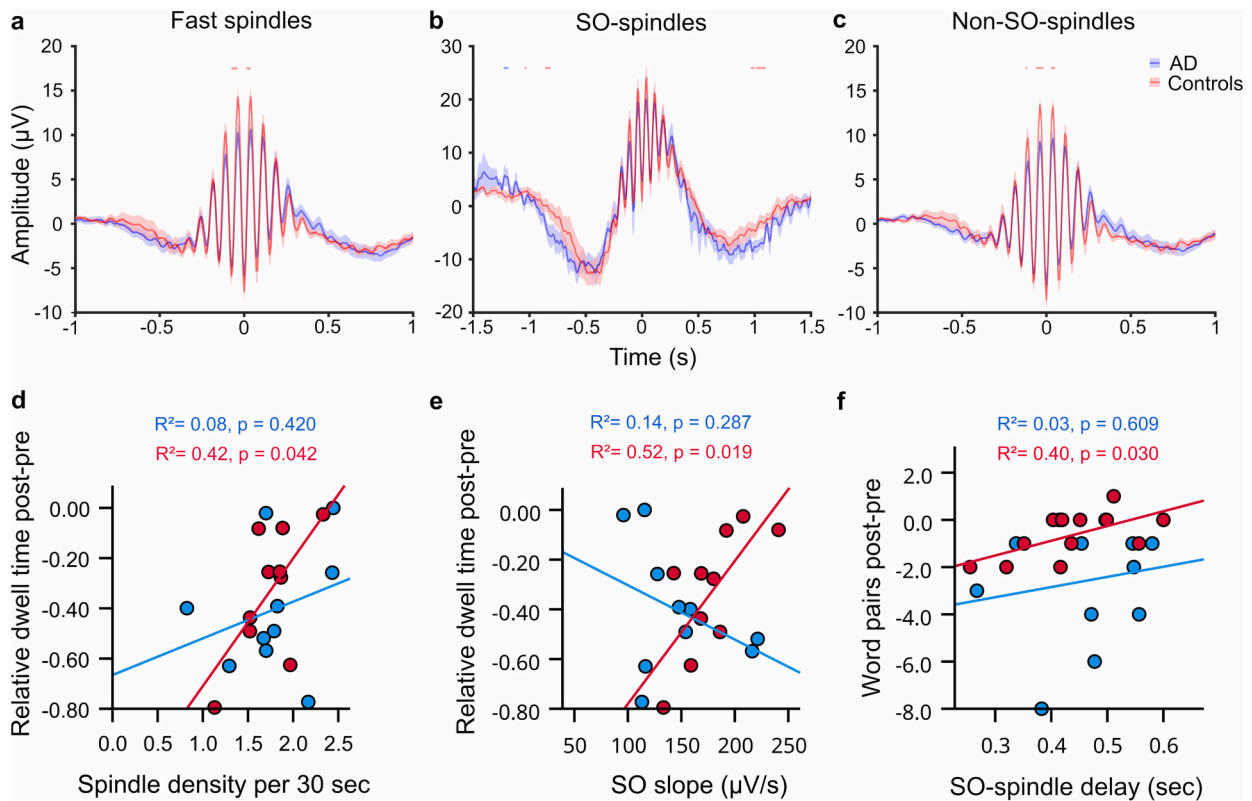
Fig. 4. a) Amplitude (μV) of fast spindles in AD (blue) and controls (red). Note the higher mean amplitude in the control group. b) Amplitude (μV) of fast spindles during SOs in both groups. c) Amplitude (μV) of fast spindles not occurring during SOs which is also higher in the control group. d) Simple linear regression shows that spindle density in the control group predicted overnight retention in the VWM. e) The prediction of consolidation of the target position in the VWM by the slope of the SO was only significant in the control group. f) Consolidation of associated word pairs was predicted based on the variation of the delay between spindles and SOs during NonREM sleep only in AD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
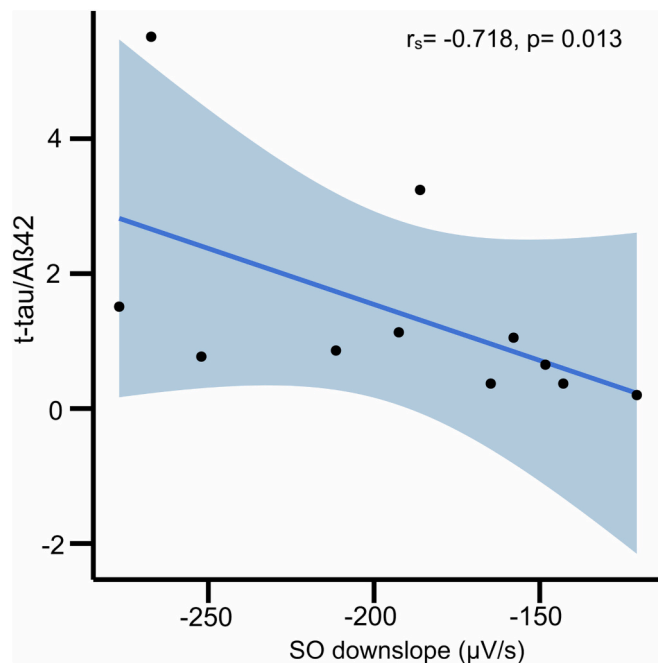
Fig. 5. Regression line depicts relationship between t-tau/Aβ$_{42}$ and the downslope of the SO that was not synchronized to spindles during NonREM sleep in AD patients. A higher tau and Aβ burden in AD go along with flatter slopes of SOs. Light blue area covers the confidence interval of the coefficient. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

across the entire frequency range in AD (De Gennaro et al., 2017; Gorgoni et al., 2023). This leads to the hypothesis that the pronounced reduction in K-complex density masks specific changes in the entire SWA range, potentially contributing to the observed variability between studies (D'Atri et al., 2021). While SWA itself was not changed in our AD patients, our finding of longer SO durations is in line with previous findings, showing an impairment of hippocampus-dependent memory consolidation during sleep in AD pathology.

Sleep disruptions together with alterations of SWS and sleep spindles are common observations in healthy aging as well as preclinical and clinical AD (Liguori et al., 2014; Mander et al., 2022; Mander et al., 2013; Rauchs et al., 2008). These findings are directly in line with the most robust finding of our study indicating overall reduced spindle power in AD patients. Two reasons for the decline of spindle activity in AD patients are to be discussed: First, it has been found that spindle density was sensitive to prior learning experience (Gais et al., 2002). Accordingly, in our study, less spindle activity may result from reduced encoding which we see most pronounced in the verbal memory task. Second, on the cellular level, electrophysiological abnormalities in AD may affect the generation of sleep spindles because of its high dependence on synaptic and dendritic integrity: Cognitive changes and memory decline in the course of AD pathology are thought to be causally related to neuronal hyperexcitability as well as hypersynchronous network activity due to synaptic dysfunction that has been examined in vivo and in vitro (Busche et al., 2019; Caccavano et al., 2020; Palop and Mucke, 2016). Sleep spindles are highly connected to neurophysiological processes that foster plasticity (Peyrache and Seibt, 2020; Schabus et al., 2007). Synaptic plasticity appears to be optimized when spindles are nested in SO upstates (Niethard et al., 2018). From this perspective, a decrease of spindle power during SO upstates that we show in AD

patients can be considered the most likely reason for less efficient consolidation of mnemonic information.

A substantial body of research has been devoted to investigating alterations in sleep spindles in the context of normal aging and AD (for a detailed review, see Mander, 2020). In cognitively unimpaired older adults, disruptions in sleep spindles of the fast frequency range have been shown to be associated with reduced grey matter volume (Fogel et al., 2017), impaired white matter integrity (Mander et al., 2017), and increased tau protein levels (Kam et al., 2019). Notably, the presence of tau in the medial temporal lobe is associated with reduced expression of hippocampal ripples, resulting in reduced occurrence of temporally synchronized spindle-ripple events (Jack et al., 2010; Staresina et al., 2015). This disruption subsequently impairs the reactivation of memory content during sleep and the transfer from hippocampal short-term to neocortical long-term memory stores. Furthermore, a more pronounced reduction in sleep spindles is observed as pathology progresses in MCI and AD (Gorgoni et al., 2016; Rauchs et al., 2008). There is substantial evidence that supports the idea that a reduction in fast spindles in both aging and AD is strongly associated with cognitive decline, particularly affecting hippocampal memory function (Ladenbauer et al., 2017; Mander et al., 2013). Importantly, the results of our study are consistent with these previous findings, showing significantly reduced amplitudes and power density of fast frequency spindles (Liu et al., 2020; Taillard et al., 2019). Furthermore, the potential of spindle amplitude as an early biomarker for predicting cognitive decline in older adults, particularly in the early stages of dementia, has been suggested (Taillard et al., 2019). However, it is important to recognize that spindle density and duration may provide more reliable biomarkers for AD, as they have shown correlations with CSF tau levels (Kam et al., 2019; Liu et al., 2020). In our study, a significant reduction in spindle amplitude was observed, but not in spindle density. This discrepancy may be due to methodological considerations, as fast spindle density reductions are particularly localized in the parietal areas (Gorgoni et al., 2016), which was not captured in our study because of low topographical resolution. Another explanation, consistent with the suggestion of reduced spindle amplitude as an early biomarker, could be the early stage of disease in our study cohort.

It has been suggested that low-frequency oscillations regulate large-scale networks and spatial-temporal coupling of multiple brain areas (Canolty et al., 2010). Time-locked coupling of neural oscillations affects action potentials and coordinates dynamic interactions of functionally coactive cell ensembles (Bergmann and Born, 2018; Canolty et al., 2010). During NonREM sleep, the faster oscillations of spindles occur during the up-state of the lower frequency of SOs (Oyanedel et al., 2020; Staresina et al., 2015; Steriade, 2006). Thus, coupling of SOs and spindles are assumed to coactivate hippocampus, thalamus, and neocortex thereby facilitating the gradual hippocampal-neocortical transfer of memories towards neocortical long-term stores (Clemens et al., 2007; Diekelmann and Born, 2010). Indeed, in rodents, powerful coupling of SOs, spindles, and ripple oscillations consolidated memory and promoted plastic changes (Latchoumane et al., 2017; Niethard et al., 2018). Enhanced spatiotemporal coupling of SOs and spindles predicted better overnight memory consolidation of word pairs in humans (Helfrich et al., 2018). Remarkably, atrophy in medial frontal regions in older adults was associated with disruptions of the precise coupling of both events that in turn predicted deficits in memory consolidation during sleep, i.e., evidence for an age-related memory decline possibly caused by sleep alterations (Chylinski et al., 2022; Helfrich et al., 2018). Even more notable, in a recent study disruptions in SO-spindle phase-amplitude coupling predicted tau accumulation in the MTL (Winer et al., 2019). As to spatial memory, mutant mice expressing pathological Aβ and tau levels showed a less close temporal association of sharp-wave ripples (SWRs) and spindles to SO, in comparison with control mice (Benthem et al., 2020). Moreover, memory performance on a virtual spatial re-orientation task was correlated with SO-coupled SWR in healthy mice, whereas behaviour of mutant mice was uncorrelated

(Benthem et al., 2020). These findings are in line with our observations, where the strong associations in healthy controls of memory performance with higher spindle density, steeper SO slopes, and time delay between events in SO-spindle coupling were entirely abolished in AD patients. In combination our findings support the view that impairments in SOs and spindles and their synchronized occurrence substantially contribute to the memory impairment of AD patients.

Although our study provides valuable insights into the relationship between sleep-dependent memory consolidation and memory performance in AD, it is not without limitations that need to be considered. A major limitation is our relatively small sample size, consisting of 12 AD patients and 12 healthy controls. To address this issue, we have reported effect sizes; however, the statistical significance of some of our findings should be interpreted with care. In this regard, it should be noted that our study includes a large number of variables, which increases the susceptibility to type I errors. Furthermore, our results are also limited by the spatial resolution of our sleep data acquisition and analysis, as sleep spindles and SOs are locally expressed (i.e. spindles in parietal regions and SOs in frontal regions) (Nir et al., 2011). However, we focused on a single central electrode, which may not fully capture the nuances of spatially distributed changes in sleep patterns. This limitation affects the precision of our findings, as we cannot account for the spatial dynamics of sleep oscillations, which are known to change with disease progression (Mander, 2020). As a result, we may not fully capture region-specific changes in sleep patterns, potentially masking important localized abnormalities that could contribute to our understanding of AD. There is a large body of evidence suggesting a bidirectional interaction of AD pathophysiology and sleep that is assumed to dynamically mediate memory deficits (Holth et al., 2019; Mander et al., 2016). In our study, surprisingly, CSF biomarkers of AD were robustly associated with diminished up-to-down SO slopes, with this finding underlying the significance of sleep-related mechanisms for AD pathophysiology. Pathways possibly mediating an augmenting effect of sleep disturbances on AD pathology involve the glymphatic system (Xie et al., 2013) and orexinergic dysregulation of the sleep/wake cycle (Kang et al., 2009; Liguori et al., 2014). CSF levels of the wake-promoting neuropeptide orexin have been found to be increased in AD at least in moderately to severely affected patients (Liguori et al., 2014). Direct orexin infusion increases Aβ, whereas blockage of orexin has the opposite effect (Kang et al., 2009). NonREM sleep promotes the clearance of metabolic waste and regulates oxidative stress by means of glymphatic activation (Xie et al., 2013). Conversely, the waking brain promotes the aggregation of neurotoxins and elevates oxidative stress (Everson et al., 2014) that have both been found to increase Aβ synthesis (Misonou et al., 2000). Thus, a disruption of NonREM sleep increases Aβ levels, whereas Aβ burden conversely impairs NonREM sleep resulting in self-maintaining dynamics of Aβ accumulation and disruption of sleep (Mander et al., 2016).

Besides Aβ, there is growing evidence that tau within the MTL disrupts mechanisms of healthy sleep rhythms: In transgenic mice showing an overexpression of tau proteins, hippocampal ripples were diminished (Witton et al., 2016). In humans, CSF tau was associated with increased orexin levels and reduced sleep spindles (Kam et al., 2019). At this stage of understanding, it appears that damage to hippocampal structures (Braak and Braak, 1991) decreases the generation of hippocampal sharp-wave ripples and their synchronization to spindles and SOs during NonREM sleep (Mander et al., 2016). In fact, increased tau burden in the medial temporal lobe are associated with a diminished coupling of SO and spindles (Winer et al., 2019), a mechanism that could well accelerate forgetting in healthy aging (Helfrich et al., 2018). Against this backdrop, we assume that the reduced spindle activity and signs of weakened SO-spindle coupling associated with reduced memory performance in our cohort reflects a disturbance in forming enduring hippocampal memory representations during sleep as a core symptom of AD pathology. In this way, our findings corroborate the increasing evidence that sleep contributes to and possibly even augments AD pathology, in

general, and specifically the memory impairment in this disease.

5. Conclusions

Our study provides evidence for a dysfunctional sleep-dependent memory consolidation in Alzheimer's disease. We found a significant reduction in spindle activity in AD patients, consistent with previous studies on age-related brain changes. In addition, AD patients had fewer spindles nested within SO upstates, suggesting a disease-specific weakening of the temporal synchronization of these oscillatory dynamics during sleep. In particular, hippocampus-associated verbal memory consolidation was significantly impaired in AD patients, highlighting the specific vulnerability of this memory domain. In contrast, healthy controls showed associations between spindle density, SO down-to-upstate transitions, and the timing of SOs and nested spindles with better memory performance, which were notably absent in AD patients. On a mechanistic level, our findings suggest that AD pathology interferes with temporal synchronization of oscillatory EEG dynamics during sleep leading to impaired systems consolidation of hippocampus-associated mnemonic information and thus impacts on the cognitive sequelae in Alzheimer's disease.

Author contributions

T.B., R.S., P.H. and R.G. were responsible for the design; A.H. and T. B. were responsible for the analyses, interpretation of results, and drafting of the manuscript; J.D. and A.N. collected the data; R.S., F.D.W. and J.B. contributed to the analyses, interpretation of results and writing the manuscript. S.P., O.G., A.B. and D.B. contributed to writing the manuscript.

CRediT authorship contribution statement

Annika Hanert: Formal analysis, Visualization, Writing – original draft, Methodology. **Robby Schönfeld:** Conceptualization, Formal analysis, Methodology, Software, Supervision, Visualization, Writing – review & editing. **Frederik D. Weber:** Formal analysis, Methodology, Software, Visualization, Writing – review & editing. **Alexander Nowak:** Methodology. **Juliane Döhring:** Methodology. **Sarah Philippen:** Writing – review & editing. **Oliver Granert:** Writing – review & editing. **Andrea Burgalossi:** Writing – review & editing. **Jan Born:** Funding acquisition, Writing – review & editing. **Daniela Berg:** Writing – review & editing. **Robert Göder:** Conceptualization, Writing – review & editing. **Peter Häussermann:** Conceptualization, Writing – review & editing. **Thorsten Bartsch:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Resources, Software, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare no competing interests.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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