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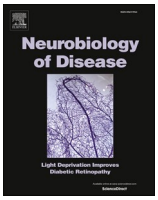

Detection of subclinical epileptiform discharges in Alzheimer's disease using long-term outpatient EEG monitoring

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ABSTRACT

Background: In patients with Alzheimer's disease (AD) without clinical seizures, up to half have epileptiform discharges on long-term in-patient electroencephalography (EEG) recordings. Long-term in-patient monitoring is obtrusive, and expensive as compared to outpatient monitoring. No studies have so far investigated if long-term outpatient EEG monitoring is able to identify epileptiform discharges in AD. Our aim is to investigate if epileptiform discharges as measured with ear-EEG are more common in patients with AD compared to healthy elderly controls (HC).

Methods: In this longitudinal observational study, 24 patients with mild to moderate AD and 15 age-matched HC were included in the analysis. Patients with AD underwent up to three ear-EEG recordings, each lasting up to two days, within 6 months.

Results: The first recording was defined as the baseline recording. At baseline, epileptiform discharges were detected in 75.0% of patients with AD and in 46.7% of HC (p-value = 0.073). The spike frequency (spikes or sharp waves/24 h) was significantly higher in patients with AD as compared to HC with a risk ratio of 2.90 (CI: 1.77–5.01, $p < 0.001$). Most patients with AD (91.7%) showed epileptiform discharges when combining all ear-EEG recordings.

Conclusions: Long-term ear-EEG monitoring detects epileptiform discharges in most patients with AD with a three-fold increased spike frequency compared to HC, which most likely originates from the temporal lobes. Since most patients showed epileptiform discharges with multiple recordings, elevated spike frequency should be considered a marker of hyperexcitability in AD.

1. Introduction

Multiple studies have demonstrated that patients with Alzheimer's disease (AD) are at increased risk of developing epileptic seizures (Scarmeas et al., 2009; Amatniek et al., 2006; Lozsadi and Larner, 2006; Bernardi et al., 2010; Rao et al., 2009; Risse et al., 1990). In addition, the epileptic seizures may mimic symptoms of AD since they often present as focal impaired awareness seizures (Rao et al., 2009; Pandis and Scarmeas, 2012). A common indicator of seizures are epileptiform discharges identified with electroencephalography (EEG). Recently, studies using long-term EEG recordings for 24 h have found that 22%–54% of patients with AD without clinical seizures have epileptiform discharges (Horvath et al., 2021; Lam et al., 2020; Vossel et al., 2016) with a significant increase in epileptiform discharges. However, a single study using over-night polysomnography did not find a significant difference between AD and HC (Brunetti et al., 2020). In some of these studies, a correlation between epileptiform discharges and a more rapid rate of progression has been found (Horvath et al., 2021; Vossel et al.,

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2016). This may suggest that their suppression could have clinical benefits, which has been indicated in randomized clinical trials suggesting both cognitive and neurophysiological beneficial effects of the anti-seizure medication, levetiracetam in patients with AD (Musaeus et al., 2017; Bakker et al., 2012; Vossel et al., 2021).

Although long-term in-patient EEG monitoring can detect epileptiform discharges in patients with AD, it can be difficult for patients with dementia to be hospitalized, moreover, it is expensive and not possible for extended periods. Due to the clinical relevance of detecting epileptiform discharges, there is a need for accessible and dependable continuous EEG monitoring in an outpatient setting. One method is ear-EEG (Kappel et al., 2019), which in a recent study was found to be a feasible approach for long-term EEG monitoring in patients with AD (Musaeus et al., 2022). Ear-EEG is a method where EEG signals are recorded from electrodes placed within a customized earpiece inserted into each ear and is associated with little interference of everyday life (Kappel et al., 2019; Looney et al., 2012; Looney et al., 2011). Previous studies have shown a good correspondence between ear-EEG and scalp EEG (Mikkelsen et al., 2015; Mikkelsen et al., 2019) and ear-EEG has been used for detection of epileptiform discharges in focal temporal lobe seizures (Zibrandtsen et al., 2017), which makes it a prime candidate method.

In the current study, we investigated if epileptiform discharges as measured with ear-EEG occurs with a higher frequency in patients with AD compared to age- and gender-matched healthy controls. To understand the relationship between epileptiform discharges and AD, we examined the variability across time and the relationship with cognitive function.

2. Materials and methods

2.1. Participants

Patients with mild to moderate AD were recruited from the Memory Clinic at Copenhagen University Hospital – Rigshospitalet, Copenhagen and the Memory Clinic at Zealand University Hospital, Roskilde. Ten of the patients have also participated in the feasibility study (Musaeus et al., 2022). All patients met the NIA-AA criteria for probable AD with amnestic presentation (McKhann et al., 2011). The diagnosis was determined based on a consensus conference after clinical evaluation, which included structural imaging and, in most instances, 18F-flourdeoxyglucose positron emission tomography. Some patients underwent lumbar puncture ($n = 18$) with evaluation of amyloid-β42, phosphorylated tau, and total tau while some underwent a (11)C-labelled Pittsburgh Compound-B-PET scan ($n = 2$) or both ($n = 3$). The threshold for phosphorylated tau and total tau were 80 pg/ml and 400 pg/ml respectively. For Amyloid beta 1–42 (Aβ42), an upwards drift in the CSF levels has been observed (Simonsen et al., 2021) and a year-specific threshold was applied. Inclusion criteria were 1) a mini-mental state examination (MMSE) (Folstein et al., 1975) score between 16 and 28, 2) age between 50 and 90 years, 3) native Danish speaker, 4) at least 7 years of education, 5) hearing and vision sufficient for neuropsychological examination, 6) no alcohol or drug abuse within the last two years, 7) no contraindications for MRI, 8) an MRI or CT scan that supported the diagnosis of AD, 9) the general health conditions of the patient allowed participation in the study (as judged by the principal investigator), and 10) living with a caregiver who was able to assist the patient with the home recordings.

The following exclusion criteria were applied: 1) psychiatric (except mild depression) or neurological conditions that affects the brain except AD, 2) epilepsy prior to the diagnosis of AD (no patients were diagnosed with epilepsy before entering the study), 3) focal pathology (except AD related atrophy) in the hippocampus, i.e. hippocampal sclerosis, 4) living with a relative with serious illness or impaired activities of daily living, 5) living in a nursing home, 6) currently treated with anti-epileptic medication, tricyclic antidepressants or antipsychotics, 7) daily or almost daily administration of medication with known anti-cholinergic or adrenergic effect, which may affect cognitive abilities or EEG, 8) large cerebral infarctions or more than four lacunar infarctions on MRI, 9) suffering from facial tics/facial hyperkinetic disorders or 10) daily use of hearing aids.

The healthy controls (HC) had all been participants in other studies and had expressed interest in participating in new studies. The inclusion criteria were 1) normal cognition as judged by the principal investigator. This judgement was based on the totality of the data available to the principal investigator, which included medical history, clinical examination, and cognitive testing, 2) the general health allowed participation in the study, 3) did not suffer from any psychiatric (except mild depressive symptoms or mild depression) or neurological conditions that affect the brain as well as criteria 2–7 as applied in patients with AD. The following exclusion criteria were applied: 1) diagnosed with epilepsy, 2) focal pathology in the brain (except mild hippocampal atrophy as a smaller hippocampal volume is seen with increasing age (Nobis et al., 2019) and was therefore not considered a marker of disease if it was judged to be appropriate for the age of the HC) as well as exclusion criteria 6–10 as applied in patients with AD.

The study was approved by the Capital Region Ethics Committee (H-17035751), by the Danish Medicines Agency (2017112288), and by the Data Protection Agency (P-2021-866). All participants gave their written informed consent before participating in the study. The study is registered at clinicaltrials.gov (NCT04436341).

2.2. Study design

In this longitudinal study, a total of eight visits was planned over a 6-month period for patients with AD and a total of four visits for the HC (Fig. 1).

In patients with AD, the three two-day ear-EEG recordings were planned three months apart, i.e., at the beginning of the study (baseline), at three months and at 6 months follow-up. At visit 1 (baseline), informed consent was obtained followed by assessment of medical history, a physical and neurological examination, the MMSE and an imprint of the ears using Otoform A Soft X (Dreve, Germany), a soft ear impression silicone. Subsequently, the patient underwent the following: visit 2) MRI scan to evaluate exclusion criteria, visit 3) standard EEG recording together with ear-EEG, Functional Assessment Questionnaire IADL (FAQ IADL) (Pfeffer et al., 1982) (to assess everyday function), neuropsychiatric inventory (NPI) (Cummings et al., 1994) (to assess behavioral and psychological symptoms), and the Category Cued Memory Test (CCMT) (Vogel et al., 2018) to assess memory function. Further, the patient and the caregiver were briefly instructed about seizures and introduced to a seizure diary to take home, and information and training on how to use the ear-EEG at home was conducted. This included a log-sheet to take notes on when the patient wore the ear-EEG. After approximately 48 h (visit 4) the patient and/or the caregiver returned with the equipment and the patient filled a questionnaire. The external ear was examined for any minor lesions when the patient was present to return the equipment (visit 4, 6, and 8) and participants were queried regarding any possible adverse events. The visit 5 and 6, and visit 7 and 8 were similar to visit 3 and 4 except that MMSE was performed at visit 5, and 7. Based on the experiences gathered in the feasibility study (Musaeus et al., 2022), breaks were permitted throughout the recording periods where the participants were allowed to take out the ear-EEG. The focus was on the participants performed ear-EEG recordings at night, therefore, the participants were encouraged to wear the ear-EEG device particularly during nighttime. A short questionnaire about the use of the ear-EEG was administered to AD patients at visit 4, 6, and 8. See supplementary material.

2.2.1. Ear-EEG recording

The ear-EEG earpieces were custom-made in silicone and mounted with six dry-electrodes (Kappel et al., 2019) (T&W engineering,

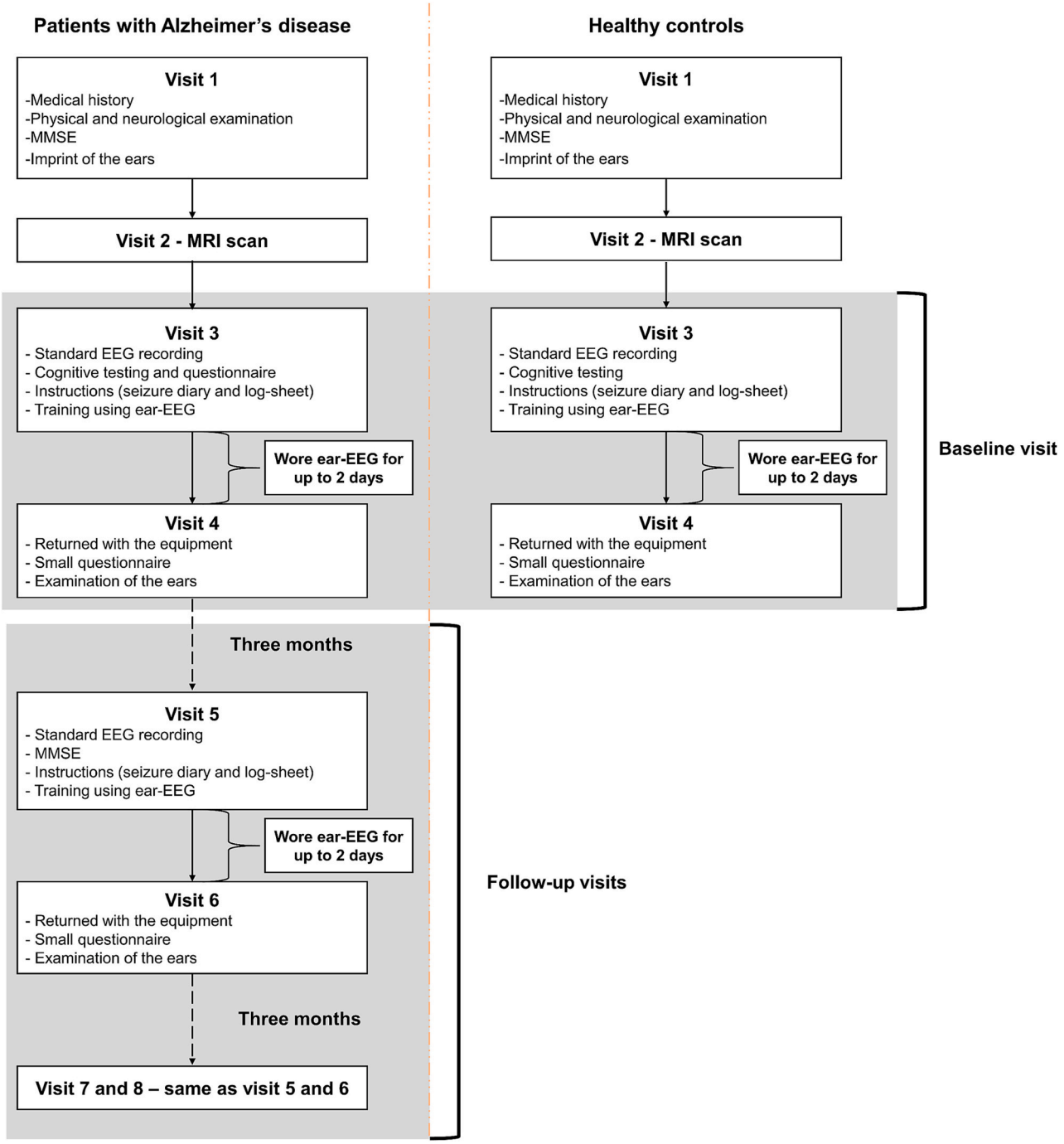

Fig. 1. Study design. Firstly, the patients with AD and healthy controls were included in the study after written informed consent. Both patients with AD and HC underwent the first session of ear-EEG recording (baseline) with the patients with AD also undergoing up to two follow-up visits.

Denmark) and placed inside the ear canal and concha. The ear-piece was placed inside the ear canal and in the concha (Mikkelsen et al., 2015) in both ears with the labeling of the ear-EEG electrodes being previously described (Kidmose et al., 2012). The ground electrode was placed approximately 2 cm under the midline of the clavicle on either one side. The ear-EEG recordings were performed using the TMSi Mobita EEG amplifier (TMSi systems), which was worn in either a small bag around the neck or in a belt bag and connected to the electrodes. Impedance was not checked during the recording. The sampling rate was 1000 Hz.

Before visual inspection, the ear-EEG data was pre-processed. This was performed to ease the visual inspection and to compare the number of artifacts in the recordings conducted in patients with AD as compared to the HC. The EEG data were loaded into MATLAB (v2020b) using a custom script for loading poly5 files. Afterwards, the EEGs were band-pass filtered from 0.5 to 70 Hz and subsequently notch filtered from 49 to 51 Hz and 99–101 Hz using the pop_eegfiltnew function from EEGLAB (Delorme and Makeig, 2004). Next, the following artefact rejection pipeline, which has previously been used in other studies, (Mikkelsen et al., 2019) was used. Firstly, if a channel were outside the dynamical range of the amplifier, which is a typical indication of an electrodes with poor contact to the body, the reading was replaced with a 'NaN'-value, and hence automatically discarded upon loading. The discarded data was considered in the subsequent analysis of data quality. Afterwards, large amplitude samples isolated to a single channel were labelled as

artifacts. Lastly, movement or muscle activation, which may also result in large amplitude deviations across multiple channels were labelled as artifacts.

The amount of time when data from at least one electrode in each ear were present was calculated (afterwards called pre-processed data). The amount of data for each individual electrode and the amount of pre-processed data during the night (10 pm - 8 am) and day (8 am - 10 pm) was examined.

2.2.2. Standard EEG recordings

We performed one 30-min 19-channel EEG recording at visit 4, 6, and 8. This consisted of 10 min of alternating eyes open, and eyes closed (30 s each) followed by 20 min of sleep. If the participants got drowsy, the length of the eyes open/closed segments were adjusted. The EEGs were recorded using Nicolet One EEG (Nervus) recording software 5.82 (Natus) with a standard 44-channel headbox. Each subject was fitted with a cap using silver-silver-chloride-coated electrodes. The EEGs was recorded from 19 electrodes positioned according to the International 10–20 system. For impedance, the aim was to reach below 10 kΩ for all electrodes during the recordings.

The EEGs were assessed by experienced clinical neurophysiologists (TWK and MCH). The results from the EEGs were either classified as 1) Normal EEG, 2) Slowing with subclassification into focal slowing as defined by intermittent or persistent low frequency theta or delta and/or diffuse slowing as defined by a posterior dominant rhythm below 7 Hz and 3) epileptiform discharges.

A comparison of the signal between ear-EEG and scalp-EEG can be found in supplementary material.

2.2.3. Ear-EEG review and annotation

Ear-EEG recordings were visually reviewed and annotated by CSM using the EEGLAB toolbox (v13.6.5b) implemented in MATLAB (MathWorks, 2020b). The average referenced montage was used and 10 s epochs were inspected at a time with ±30 μV amplitude range. In this montage, the first 12 channels were low-pass filtered at 70 Hz, high-pass filtered at 1 Hz, and notch filtered at 50 Hz. The next 12 channels were after pre-processing. The subsequent 36 channels were the comparisons between electrodes with the active electrodes being on the left (e.g., ELA-ERA, ELA-ERB (Kidmose et al., 2012)) and the last 36 channels were created using the opposite laterality. The segments disregarded by the pre-processing pipeline and segments only containing recordings from one ear were not inspected.

A sharp asymmetric negative potential of 20–200 ms duration was considered an epileptiform discharge (spike (20–70 ms)/sharp wave (70–200 ms)) if it met the IFCN criteria (Kural et al., 2020), which compromised of 1) di- or tri-phasic with a pointed peak with 2) a different wave duration than the background activity, 3) asymmetry of the waveform, 4) background activity was disrupted by the presence of the epileptiform discharge and in most cases was 5) followed by a slow after-wave. Due to the nature of ear-EEG, we could not investigate the spatial distribution of the spikes/sharp waves (IFCN criteria 6). Practically, this led to all epileptiform discharges fulfilling at least four out of the six IFCN criteria. Epileptiform discharges were not considered if it was only present in a single electrode. All annotations performed by CSM underwent review by a board-certified clinical neurophysiologist (TWK), who made the final ruling. When we use the term epileptiform discharges it covers both spikes and sharp waves and assumes an underlying irritative process like what is seen in epilepsy, even if this cannot be stated with absolute certainty. Both CSM and TWK were blinded to the diagnosis when reviewing the EEGs.

2.3. Statistics

All statistics were performed in RStudio (v1.2.1335). When comparing age, education, cognitive scores, and the length of ear-EEG recordings between AD (at baseline) and HC, we performed two-sample *t*-tests. The distribution of the data as well as the variance was checked. Chi-squared test or Fisher's exact test (if one input variable being $\leq$5) was performed for comparing sex, co-morbidities, the number of participants in each group with spike/sharp waves at baseline, the number of participants with slowing and the number of spikes/night and spikes/day between AD and HC. A comparison of participant characteristics of the HC with and without epileptiform discharges was performed using two-sample Wilcoxon test for continuous variables and Fisher's exact test for categorical data (see Supplementary material).

When comparing the number of spikes or sharp waves/24 h (spike frequency) between HC, and AD at baseline, we calculated the rate ratio using the function *rateratio* from the *epitools* toolbox.

A delineation plot showing an analysis of the classification accuracy between AD and HC based on the spike frequency using three different thresholds (1.5, 4.5, and 8) was conducted. See supplementary material.

Spearman's correlation between the spike frequency across all recordings and cognitive tests was performed.

Changes in spikes or sharp waves between visits were analyzed using a generalized linear mixed-effect model including visit number (categorical variable) and log-transformed the amount of pre-processed EEG (in minutes) as the offset variable with a person specific random intercept in a Poisson regression model using the *lme4* package. Changes in MMSE over visits were analyzed using a linear mixed model including visit number (categorical) as fixed effect and further assuming an unstructured covariance pattern to account for repeated measurements on the same subjects with the *LMMStar* package.

The R code and output from the subsequent analyses can be found in the supplementary material.

3. Results

3.1. Demographics

A total of 25 patients with AD and 15 HC were eligible for inclusion and gave informed consent. One patient with AD was excluded due to having less than one hour of data after pre-processing. For the follow-up visits, 15 patients with AD participated in two ear-EEG recordings and 11 in all three visits. The patients were followed in the project for an average of 276 days (SD: 118, range: 56–468 days). See Table 1 for demographics, cognitive scores, co-morbidities, and AD markers at time of diagnosis.

3.2. Prevalence of epileptiform discharges with ear-EEG at baseline

See Fig. 2A for examples of epileptiform discharges. Epileptiform discharges were detected in 75.0% (18/24) of patients with AD and in 46.7% (7/15) of HC at baseline (p-value = 0.073) (Fig. 2B). At baseline, the spike frequency was significantly higher in patients with AD and epileptiform discharges (range: 0–13.04 (mean: 3.03 spikes/24 h) as compared to HC (range: 0–6.66 (mean: 1.04 spikes/24 h) with a risk ratio of 2.9 (CI: 1.77–5.01, p-value $\leq$0.001). See Fig. 2C for an overview of the distribution of spikes. A delineation plot of the spike frequency can be found in the supplementary material (Supplementary Fig. 4).

See Fig. 2D for distribution of epileptiform discharges over 24 h. A significant different in epileptiform discharges at night (p-value = 0.014) in AD (64.8%) as compared to HC (31.3%). Two epileptiform discharges that occurred in a patient with AD and a HC were not noted on the log-sheet and therefore not included in this analysis. Furthermore, one patient with AD and one HC did not sleep with the equipment.

3.3. Variability in epileptiform discharges across recordings

No significant difference in spike frequency between the baseline and the follow-up visits (visit 1–2: estimate: 1.34, p-value = 0.239, visit 1–3: estimate: 1.24, p-value = 0.417) were observed. See Table 2 for the patients that completed at least two ear-EEG recordings. A large

Table 1
Baseline demographics, medication, neuropsychological test scores, and questionnaire scores.

	Healthy controls	Alzheimer's diseae	p-value
Number of participants	15	24	
Age, mean (SD)	69.5 (7.93)	70.3 (7.79)	0.8
Males/females	8/7	14/10	0.8
Education, mean (SD)	15.2 (2.04)	14.2 (3.08)	0.3
MMSE, mean (SD)	29.3 (0.88)	23.5 (3.32)	<0.001
CCMT, immediate recall	38.1 (5)	18.4 (5.66)	<0.001
CCMT, delayed recall	37.2 (5.67)	13.2 (5.19)	<0.001
CCMT, recognition	47.5 (0.64)	38.1 (4.66)	<0.001
NPI		4.25 (2.72)	
ADL		14.5 (5.84)	
Hypercholesterolemia, n (%)	3 (20%)	7 (29%)	0.7
Hypertension, n (%)	5 (33%)	12 (50%)	0.3
Arrhythmia, n (%)	3 (20%)	2 (8%)	0.4
Mild depression, n (%)	1 (7%)	4 (17%)	0.6
Cholinesterase inhibitor, n (%)		23 (96%)	
Memantine, n (%)		5 (21%)	
SSRI/SNRI, n (%)	1 (7%)	4 (17%)	
Years from diagnosis, mean (SD)		1.96 (1.74)	
Amyloid positive, n (%)*		18 (90%)	
Phosphorylated tau, mean (SD) #		82.41 (31.19)	
Total tau, mean (SD)#		568.88 (242.34)	

SSRI/SNRI: Selective Serotonin Reuptake Inhibitor/ Serotonin and Noradrenaline Reuptake Inhibitor, MMSE: Mini-Mental State Examination, CCMT: Category Cued Memory Test, ADL: Activities of Daily Living, NPI: Neuropsychiatric Inventory, SD: Standard deviation, * Amyloid positive was defined by either a value below the year-corrected cut-off using CSF amyloid or positive amyloid PIB-PET at the time of diagnosis in patients who had undergone testing in either one of these modalities ($n = 20$), # Both phosphorylated tau (cut-off <60) and total tau (cut-off <400) was measured as part of the initial diagnosis ($n = 18$).

variance between the number of spikes across recordings for each subject was seen (Supplementary Fig. 1). Combining all the recordings, we found that epileptiform discharges were found in 83.3% after the second and in 91.7% after the third recording. The two participants that did not show epileptiform discharges only had a single ear-EEG recording performed. The spike frequency with all recordings combined in patients with AD, we found a spike frequency of 2.94 spikes/24 h. Only two showed epileptiform discharges at all ear-EEG recordings. No significant differences were found for MMSE (Supplementary Fig. 2) across visits (visit1–2: estimate: −0.6, p-value = 0.082, visit1–3: estimate: −1.08, p-value = 0.209).

Table 2
Description of epileptiform discharges in the patients with more than one ear-EEG recording.

	1st ear-EEG recording	2nd ear-EEG recording	p-value (1st vs 2nd)	3nd ear-EEG recording	p-value (1st vs 3rd)
Number of patients, n	15	15		11	
Number with ED, %	73.33%	46.67%		63.64%	
Spikes/24 h	1.96	2.89	0.239	2.78	0.417
Spikes, n	31	36		30	
Clean data, mean hours (SD)	25.4 (6.3)	19.9 (10.6)		23.5 (7.32)	
MMSE, mean (SD)	23.73 (3.37)	23.13 (3.62)	0.082	23.55 (3.72)	0.209
Time since last recording in days, mean (SD)		171 (86.5)		144 (92.2)	

ED: Epileptiform discharges, MMSE: Mini-Mental State Examination.

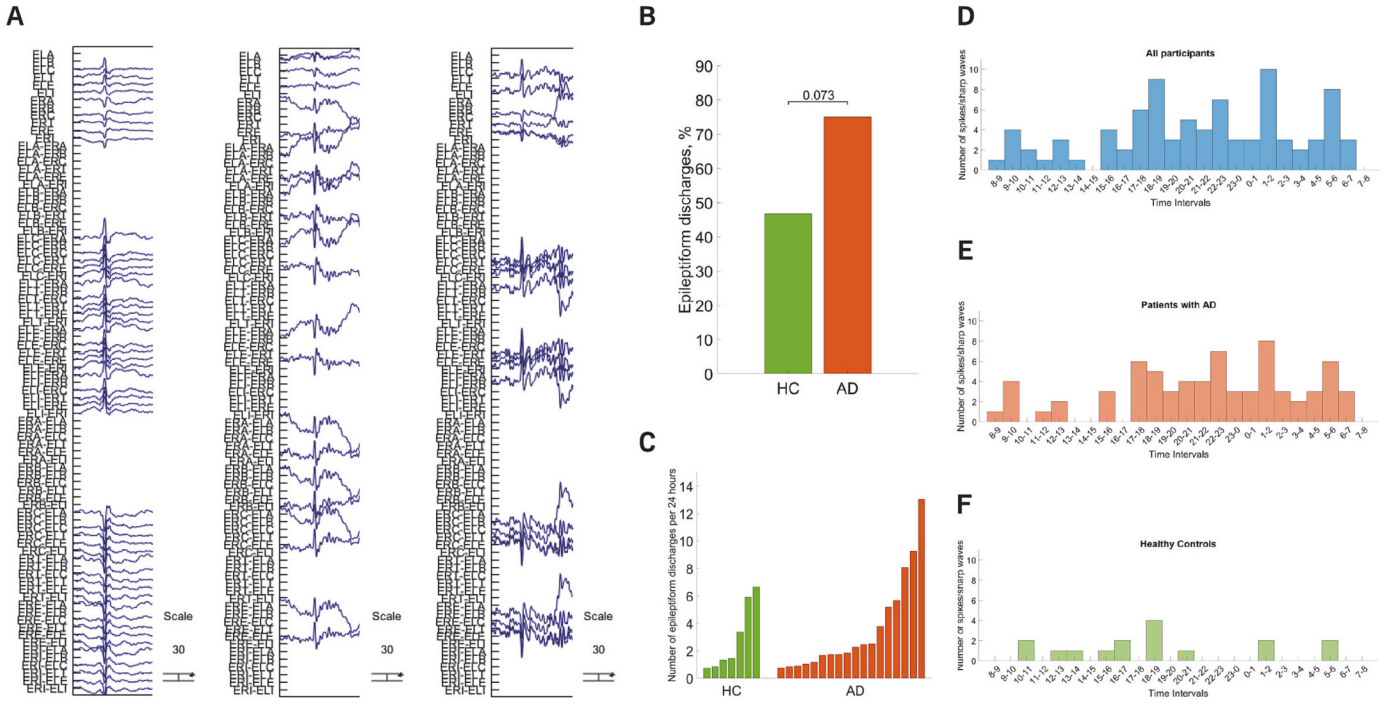

Fig. 2. Characterization of spikes/sharp waves in patients with AD compared to HC at baseline (first ear-EEG recording). (A) Shows examples of epileptiform discharges. (B) The proportion of patients with AD and HC with epileptiform discharges. (C) Spike frequency (spikes/sharp waves per 24 h) in each patient with AD or HC with epileptiform discharges at baseline. (D) Distribution of the total number epileptiform discharges by time intervals for all participants for the baseline recording with (E) for patients with AD and (F) for HC.

3.4. Association between memory function and epileptiform discharges

No significant correlations were found between the spike frequency in patients with AD and the baseline MMSE, immediate recall or delayed recall (Supplementary Fig. 3). See supplementary material for comparison of patients with and without epileptiform discharges.

3.5. Conventional EEG and patient diaries

In AD, 29.2% (7/24) had slowing in the EEG as compared to 6.7% (1/15) of the HC (p-value = 0.121). Location of slowing was mostly temporal. More details can be seen in the supplementary material. No electrographic seizures were found. One patient reported (1/65 recordings) a sense of déjà vu in the patient diaries.

3.6. Data quality

At baseline, the mean number of recorded hours were 34.6 h (SD: 10.1 h) in patients with AD as compared to 40.9 h (SD: 9.5) in HC. The amount of pre-processed data was lower in AD with 23.7 h (SD: 7.6 h, range: 3.1–33.7 h) as compared to HC with 27.7 h (SD: 8.0 h, range: 12.1–37.2 h) but not significant (p-value = 0.1, t-value = −2, df = 37) (Fig. 3C). During the nighttime, 80.1% of the data in patients with AD and 78.7% of data in HC remained after preprocessing as compared to the daytime with 61.1% of data in patients with AD and 63.9% of the data in HC. See Fig. 3 for data quality for each electrode.

3.7. Adverse events at baseline

A larger proportion of patients with AD (79.2%) had adverse events

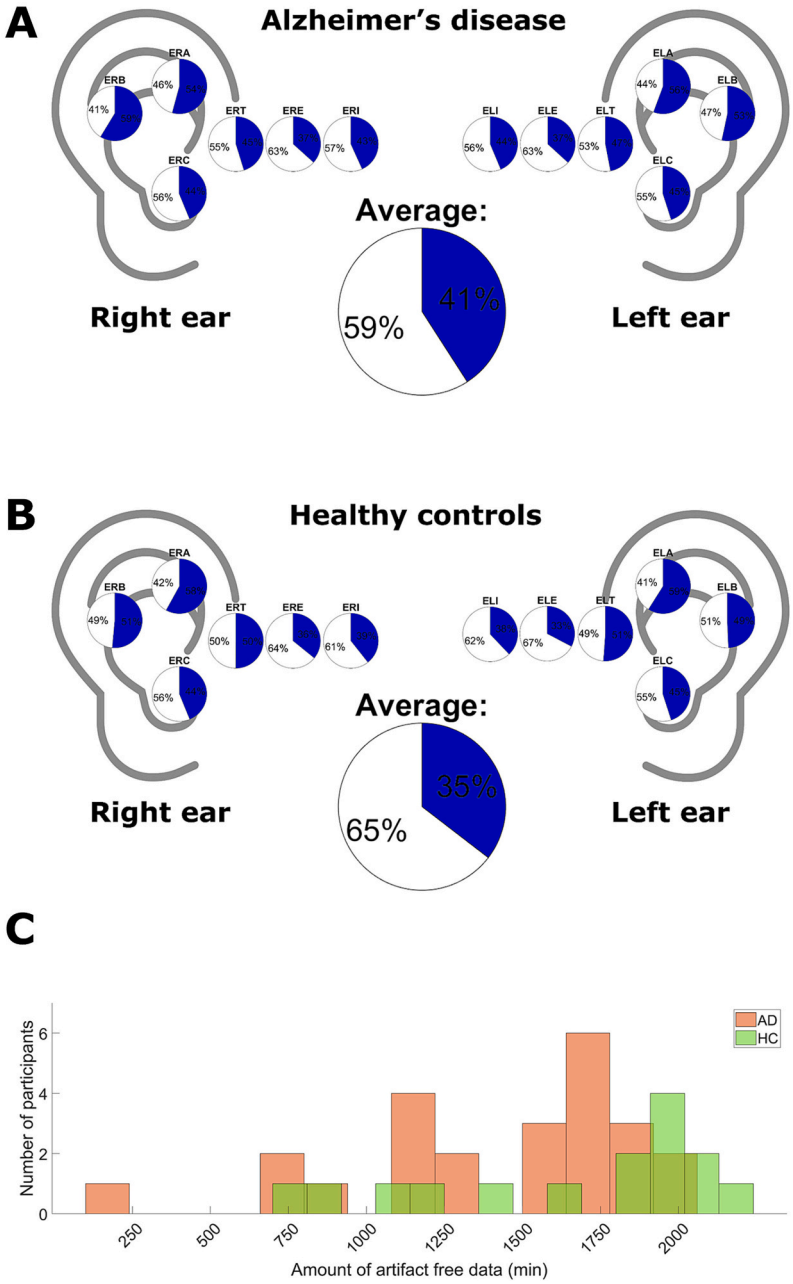

Fig. 3. Data quality for the specific electrodes and length of EEG recordings at baseline. (A) shows the percentage of data kept (white) and removed (blue) for each specific electrode and as an average across electrodes after pre-processing in patients with AD. (B) displays the same for HC. (C) histogram of the distribution of EEG length for AD and HC. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

related to the ear-EEG as compared to HC (60%). In addition, 59.5% of the participants who slept with ear-EEG experienced some difficulty sleeping during the baseline recording. One of the participants with abrasions developed pain and swelling as has previously been reported (Musaeus et al., 2022). None of the AE related to ear-EEG were classified as serious AEs.

The reasons for dropping out of the study were mostly discomfort associated with wearing the ear-EEG ($n = 8$). A full description can be found in the supplementary material.

4. Discussion

This is the first study to provide data on the prevalence of epileptiform discharges using outpatient long-term EEG monitoring in patients with AD. At baseline, 75% of patients with AD had epileptiform discharges with a three-fold higher spike frequency as compared to HC. Most epileptiform discharges occurred at night in AD. The spike frequency showed considerable variability across recordings with a total of 91.7% of patients showing epileptiform discharges when examining all recordings. A negative correlation between cognitive test scores and spike frequency was found but was not significant. The data quality of the ear-EEG was acceptable for application as a method for detection of epileptiform discharges and participants only experienced mild adverse events.

In the current study, there was a trend towards a higher fraction of patients with AD with epileptiform discharges at baseline (75%) compared to HC (46.7%). This is in line with previous studies showing that a larger percentage of patients with AD without epilepsy (22–54%) had epileptiform discharges on 24-h EEG recordings compared to HC (4.7%–25%) (Horvath et al., 2021; Lam et al., 2020; Vossel et al., 2016). The more epileptiform discharges could be explained by longer recordings including up to two nights, which is supported by a study showing a significant correlation between the sensitivity of EEG and the length of recordings (Horváth et al., 2017). No epileptiform discharges were found using conventional EEG recordings, which is in line with a study showing epileptiform discharges being present in only 2% of patients with AD (Liedorp et al., 2010). The length of the recording combined with the majority of epileptiform discharges in AD occurring during sleep (Horvath et al., 2021; Lam et al., 2020; Vossel et al., 2016), likely explain the disparity between ear-EEG and conventional EEG. In addition, we found that more patients showed epileptiform activity if the recording was repeated, which suggests that more recordings are needed to detect epileptiform discharges in AD patients. Taken together, these highlights both the importance and the timing of recordings to capture epileptiform discharges in AD. The fact that almost half the HC had epileptiform discharges using ear-EEG is surprising but may in large part be due to the long recordings and to a lesser extent possible insidious AD pathology without clinical correlate or other comorbidities (e.g., vascular lesions) but this was not investigated. Furthermore, no significant differences were found for the participant characteristics for HC with and without epileptiform discharges, but this may be due to the low sample size. Moreover, the ratio of patients with detected epileptiform discharges varied among the baseline, second, and third recordings (73.33%, 46.67%, and 63.64%, respectively). Therefore, it is possible that the difference in number of epileptiform discharges between the two groups with almost half the HC having epileptiform discharges was affected by this variability. Repeated long-term EEG monitoring in HC is needed to fully understand this aspect. Furthermore, a comparison between ear-EEG and long-term scalp EEG monitoring is needed.

The frequency of epileptiform discharges has previously varied considerably between studies from a median frequency of 3 per 24 h (Lam et al., 2020) to 2.02 spikes/h (Horvath et al., 2021). Although to some degree speculative, the studies showing higher spike frequency included patients with lower MMSE score (mean: 20–22) as compared to the study showing the lowest spike frequency (mean: 26) (Horvath et al., 2021; Lam et al., 2020; Vossel et al., 2016) indicating an association with severity of disease and spike frequency. In support of this, a study showed that seizures became more prevalent as the disease progressed (Amatniek et al., 2006). Since our AD cohort had an average MMSE of 23.5 and due to the low spatial resolution of the ear-EEG and being strongly affected by muscle activity, the lower spike frequency could in part be due to these methodological shortcomings. Conversely, the vast majority of epileptiform discharges appear in the frontotemporal regions in AD (Horvath et al., 2021; Lam et al., 2020; Vossel et al., 2016; Sarkis et al., 2016; Cretin et al., 2016), which is the area best covered by ear-EEG. Combined with studies showing atrophy of the temporal lobes in the early stages of the disease (Ossenkoppele et al., 2015; Harper et al., 2017), this suggest that the epileptiform discharges are associated with neuropathological mechanisms in AD. However, studies are needed to understand if epileptiform discharges appear in other regions as the disease progresses. Another possibility is that hyperexcitability in the temporal lobe is restricted to only a limited number of the patients as suggested by the classification accuracy between AD, and HC based on the spike frequency (Supplementary Fig. 4). Furthermore, it is necessary to investigate if anti-seizure medication should be administered if epileptiform discharges are present as previously suggested (Vossel et al., 2021) or that a specific threshold for the spike frequency warrants treatment with anti-seizure medication.

So far, no studies have investigated changes in the spike frequency across repeated recordings in patients with AD. No significant difference in spike frequency between the baseline and the follow-up visits was found, which may be due to considerable variability between visits. One explanation is that there may be longer periods of time without epileptiform discharges as seen with ultra long-term EEG recordings detecting EEG seizures in patients with epilepsy (Weisdorf et al., 2019). This is supported by epileptiform discharges being present in 91.67% of patients with AD if all recordings were combined. The spike frequency may be a more suitable measure when investigating epileptiform discharges in AD. Although there is no clear consensus on the link between interictal spikes and seizures (Karoly et al., 2016), the spike frequency has been associated with seizure frequency in patients with temporal lobe epilepsy (Janszky et al., 2005), and patient with temporal lobe epilepsy show cognitive impairment (Hermann et al., 1997). In transgenic mice, a study has suggested that the hyperexcitability leads to development of compensatory inhibitory mechanisms that reduce function of specific circuits (Palop et al., 2007). In addition, a clinical trial investigating the effect of levetiracetam in patients with AD only found improvement in patients who had epileptiform discharges (Vossel et al., 2021). This supports the idea that higher spike frequency may warrant treatment with anti-seizure medication. Due to the short intervals between visits, we did not examine the association with cognitive changes, which has previously been shown in both mice models (Kam et al., 2016; Bezzina et al., 2015) and patients with AD (Horvath et al., 2021; Vossel et al., 2016; Høgh et al., 2002).

An interesting finding was that most spikes occurred at night in patients with AD (64.79%) (Fig. 2E). This has previously been reported in long-term EEG studies, (Horvath et al., 2021; Lam et al., 2020; Vossel et al., 2016) but the underlying pathological reason is unknown. However, interictal epileptiform discharges more often occur during sleep in patients with temporal lobe epilepsy (Sammaritano et al., 1991) and hippocampal interictal spikes were negatively correlated with long-term memory consolidation (Lambert et al., 2020). In support of this, a studies in transgenic mice model of beta-amyloid neuropathology found that interictal spikes mostly occurred during REM-sleep (Kam et al., 2016; Szabo et al., 2023) Combined, this indicates that epileptiform discharges during sleep may be associated with memory dysfunction in patients with AD.

Our study has several limitations. First, we did not record simultaneous scalp EEG, which would be preferable when validating the epileptiform discharges. However, ear-EEG has been used for detection of epileptiform discharges in focal temporal lobe seizures (Zibrandtsen et al., 2017). The number of participants was lower than similar studies,

but we were able to conduct longer outpatient EEG recordings using ear-EEG. The HC had more pre-processed data than AD, but this was adjusted for in the analyses. However, we only recorded one session of ear-EEG for the HC and repeated ear-EEG measurement may have provided more information on the variability of epileptiform discharges. The number of patients that dropped-out was similar to the feasibility study, which calls for adjustments to the ear-EEG to increase the comfort. In terms of recording, the TMSi amplifier does not note time-of-day during recordings, which means that the participant/caregiver must do so, but this was rarely a problem (two epileptiform discharges). Another aspect is the lack of characterization of sleep stages, which may have improved the interpretation of the results but so far automatic sleep staging tools for ear-EEG have only been tested in healthy young participants (Mikkelsen et al., 2019). Furthermore, due to the low spatial resolution of the ear-EEG and muscle artifacts, it gives rise to some uncertainty during the annotation of epileptiform discharges, which called for a more restrictive approach. Lastly, we did not perform any measurement of AD biomarkers in the HC, which may have explained the large number of HC with epileptiform discharges.

5. Conclusion

Using long-term outpatient EEG monitoring, most patient with AD showed epileptiform discharges occurring at night, which most likely originated in the temporal lobes. We hypothesize that it is related to disrupted memory consolidation as supported by lower cognitive test performance scores sensitive to temporal lobe function. Larger studies are needed to confirm and further elucidate this possible relationship. Repeated and long-term EEG recordings are necessary to capture all epileptiform activity based on the high degree of variability in spike frequency between recordings. Since most patients showed epileptiform discharges with multiple recordings and almost half the HCs had epileptiform discharges, it is more relevant to consider spike frequency as a marker of hyperexcitability than simply whether spikes are present. Therefore, our findings support using long-term outpatient monitoring of spike frequency when investigating anti-seizure medication in the treatment approach to AD.

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CRediT authorship contribution statement

Christian Sandøe Musaeus: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration, Funding acquisition. **Kristian Steen Frederiksen:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Project administration. **Birgitte Bo Andersen:** Conceptualization, Investigation, Resources, Writing – review & editing. **Peter Høgh:** Conceptualization, Investigation, Resources, Writing – review & editing. **Preben Kidmose:** Conceptualization, Methodology, Software, Writing – review & editing, Visualization. **Martin Fabricius:** Conceptualization, Resources, Writing – review & editing, Formal analysis. **Melita Cacic Hribljan:** Conceptualization, Formal analysis, Resources, Writing – review & editing. **Martin Christian Hemmsen:** Conceptualization, Methodology, Resources, Writing – review & editing. **Mike Lind Rank:** Conceptualization, Methodology, Resources, Writing – review & editing. **Gunhild Waldemar:** Conceptualization, Methodology, Resources, Investigation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Troels Wesenberg Kjær:** Conceptualization, Methodology, Formal analysis, Resources, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

Christian Sandøe Musaeus received an unrestricted grant from T&W engineering. Two authors (Mike Lind Rank, and Martin Christian Hemmsen) who are employees of T&W Engineering contributed to the interpretation and writing of the manuscript. Troels Wesenberg Kjær consults for T&W Engineering.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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