Refining Detection of Subclinical Epileptiform Activity in Alzheimer's Disease: A Case–Control Study and Call for a Consensus

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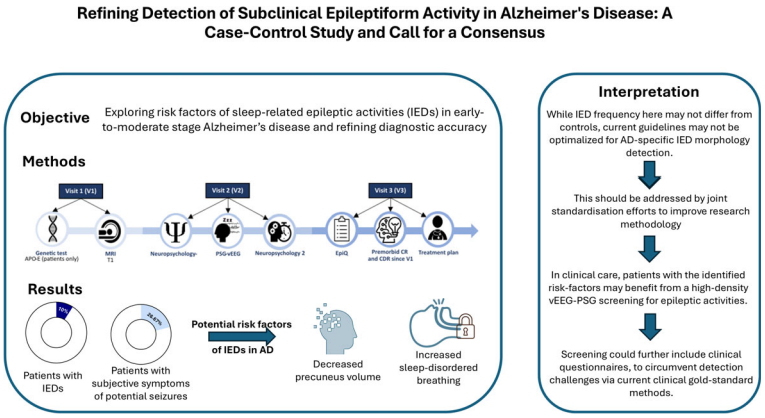

Objective: Sleep-predominant network hyperexcitability is increasingly recognized as a potential disease-accelerating comorbidity in Alzheimer's disease (AD). However, its prevalence and risk-factors remain debated, largely due to cohort-specific and methodological differences across studies. In this prospective case-control study, we investigated

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potential ways of improving detection, from translational approaches focusing on rapid eye movement (REM)-sleep to refined electroencephalogram (EEG) setups and added clinical questionnaires.

Methods: We recruited 30 patients with early-stage AD without a history of epilepsy and 30 age-matched controls. Participants underwent overnight polysomnography with video-EEG. Interictal epileptic discharges (IEDs) were identified through a structured 3-step review by multiple independent experts using recommended criteria. Neuroanatomic patterns and sleep-related abnormalities were investigated as potential risk factors. Clinical symptoms in favor of epileptic seizures were evaluated through a tailored questionnaire at follow-up.

Results: IEDs were detected in 3 patients (10%) and 1 control (3.33%), a difference not reaching statistical significance ($p = 0.612$). Most events occurred during non-REM (NREM) sleep. Eight patients (26.67%) reported symptoms compatible with epileptic seizures—one of whom also presented with IEDs. Patients with IEDs or reported symptoms suggestive of potential seizures exhibited more severe sleep-disordered breathing and reduced precuneus volume compared with those without.

Interpretation: Despite efforts to optimize detection accuracy, our findings reveal a lower-than-expected percentage of patients with AD with IEDs, yet support previous findings suggesting that sleep-disordered breathing and specific atrophy patterns could flag at-risk patients, guiding screening in clinical settings. Our findings also favor validation efforts of questionnaires to support the diagnostic process. Finally, we highlight methodological issues in IED detection and call for the re-evaluation and standardization of diagnostic methods and criteria in this population to improve patient care.

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An association between Alzheimer's disease (AD) and network hyperexcitability, manifesting as interictal epileptic discharges (IEDs) and seizures, particularly during sleep,[1–3] has been well-documented in both AD mouse models[4] and patients.[5] Importantly, these aberrant network activities have been linked to accelerated cognitive decline across several clinical cohorts.[1,6–9] Although their prevalence increases with disease severity,[6] IEDs have consistently been observed even in patients with mild cognitive impairment (MCI) and mild-to-moderate stage AD.[1,10,11]

Targeting network hyperexcitability using antiseizure medications, particularly levetiracetam, has shown promise. Studies report significant improvements in multiple cognitive domains among patients with MCI and AD experiencing IEDs,[12,13] indicating a potential disease-modifying strategy in the face of the growing burden of AD-type dementia.

However, whereas IEDs are consistently detected early in nearly all AD rodent models,[14] human studies report highly variable percentages of patients with IEDs across clinical cohorts—from as low as 6%[15] to as high as 75%[10]—likely due to cohort-specific and methodological discrepancies.[16]

One potential avenue for better understanding this comorbidity and its discrepancies involves translational approaches that apply findings from preclinical models to human diagnostics. For example, in AD mouse models, IEDs predominantly occur during sleep and are 3 times more frequent during rapid eye movement (REM) sleep compared to slow-wave sleep (SWS).[17,18] This is surprising, as REM sleep is generally considered to have an IED-suppressive effect.[19,20] One hypothesis is that this suppressive mechanism is less effective in the mesial temporal lobe (MTL),[21] where network hyperexcitability is thought to originate in AD.[2,22] Nonetheless, most clinical studies do not differentiate between REM and non-REM (NREM) sleep, and the characteristic electroencephalogram (EEG) slowing[23,24] or brief, unstable REM phases in patients with AD may contribute to underestimating REM sleep or misclassifying IEDs as benign variants. Moreover, widespread use of antidepressants in AD[25] may further reduce the ability to detect REM-related IEDs as these medications are known to suppress REM sleep.[26,27]

A second promising strategy involves optimizing electrode coverage and analytic methods. Enhancing coverage of the MTL could improve IED detection.[11] Complementary qualitative tools, such as symptom-based questionnaires developed from clinical observations,[16] may also aid in identifying patients with potential underlying epileptic abnormalities,[11] helping to guide screening.

This guidance is an important point as a lack of access to examinations investigating epileptic activities is a major issue, making standard screening for all patients with AD for IEDs unlikely, in spite of advocacy for this to change.[28] Therefore, a third approach to improve diagnostic accuracy of IEDs in AD could focus on identifying high-risk subgroups among patients with early-stage AD. This could be supported by tools, from the above-mentioned clinical questionnaires to flagging patients with comorbidities or distinct neuroanatomic patterns that might be linked to hyperexcitability. Although data are limited, risk factors, such as more severe sleep-disordered breathing[11] or precuneus-dominant atrophy,[29] have been proposed. However, all options mentioned above—translational approaches, electrode coverage, qualitative tools, and risk-factor identification—are under-investigated and require further evaluation before clinical translation is possible.

Hence, in this paper, we present findings from a prospective observational cohort study investigating the

occurrence of epileptic activity during sleep in 30 patients with AD without a history of epilepsy, compared with cognitively healthy, age- and sex-matched older adults. Quantitative data on IED frequency were obtained using overnight polysomnography with concurrent video EEG (PSG-vEEG), using extended temporal electrode coverage (25 scalp electrodes, including P9, P10, F9, F10, T9, and T10) and a rigorous 3-step IED detection protocol. Qualitative data were collected through a questionnaire designed to identify symptoms suggestive of epileptic seizures.[16]

Initially, the study was designed to focus on REM-related IEDs in patients with AD, building on preclinical findings that suggest a disproportionately high frequency of such discharges during REM sleep in AD models.[17,18] In parallel, and informed by prior clinical reports, we also aimed to investigate potential risk factors associated with network hyperexcitability, including sleep-disordered breathing (eg, apneas) and structural magnetic resonance imaging (MRI) features, such as precuneus-dominant atrophy. However, given the considerable variability in IED prevalence reported across studies published during the inclusion period, as well as the practical challenges encountered in accurately detecting IEDs using noninvasive methods in the present study, we also address key methodological limitations in the current diagnostic approaches and propose strategies to improve the reliability and clinical utility of IED detection in AD.

Methodology

Participants

The EREMAD study (NCT03923569) was a prospective, observational, single-center case-control study conducted between April 2019 and October 2022 at the University Hospital of Toulouse and the Brain and Cognition Research Centre (France). Participants provided written informed consent. The study was approved by the regional ethics committee (CPP Ile de France VIII) and adhered to the Declaration of Helsinki.

The AD group comprised 31 patients with mild-to-moderate sporadic AD (Mini-Mental State Examination [MMSE] ≥18)[30] between 50 and 90 years of age, diagnosed according to International Working Group (IWG)-2 criteria, with lumbar puncture, neuropsychological assessment, and, in most cases, supplementary MRIs supporting diagnosis. Note that for one patient, the diagnosis was solely based on neuropsychological assessment, overall clinical presentation, a strong family history, and APOE4 homozygosity. Exclusion criteria included untreated sleep apnea, major psychiatric/neurological illness, history of epilepsy, current use of anti-seizure medication, MRI contraindications, and drugs significantly affecting sleep architecture, such as antidepressant medications or dopaminergic agonists. Neuroleptics and benzodiazepines were allowed at a maximum of 1 and 2 daily doses, respectively. None of the patients had isolated aphasia, apraxia or agnosia, sudden-onset cognitive deficits, nor non-degenerative lesions or substantial lesions in white matter with flair hyperintensities on previous MRIs. The control group included 30 cognitively healthy, age- and sex-matched adults (MMSE >25, ≥9/10 on the 5-word test of Dubois).[31]

Study Design

The protocol included 2 initial visits separated by no more than 60 days (V1: MRI and APOE genotyping; and V2: neuropsychological assessment, overnight video-polysomnography); and one follow-up visit (V3). At V3, clinical feedback was provided, and the Epilepsy Questionnaire (EpiQ)[16] and additional questionnaires were administered (Supplementary Fig S1 and Supplementary Table S1). The mean interval between V1 and V3 was 336 ± 206 days for controls and 295 ± 184 days for patients ($p = 0.42$). All procedures are detailed below.

Video-EEG and IED Analysis

Overnight EEG (sampling rate = 1024 hertz [Hz]) was recorded with a 27-electrode setup according to the standard 10 to 20 setup, with extended lower temporal coverage (F9/P9/T9, and F10/P10/T10). Electrodes were attached to the scalp with conductive adhesive gel (Natus), and a medical-grade tubular elastic net hood held the setup in place. A caregiver was allowed to be present throughout the recording for both groups. Recordings were manually reviewed using the DeltaMed/Natus system in 3 steps (see Supplementary Fig S2 for details) by 3 experts blinded to group allocation. These steps included:

Step 1: During this initial analysis carried out by 2 independent evaluators, the EEG recordings were scrutinized in order to detect and annotate graphoelements suggestive of IEDs, and to conclude whether or not the recording contained potential IEDs, and, if so, how many. In cases of disagreement, the graphoelements labeled as potential IEDs were reviewed and relabeled by a third expert.

Step 2: Artifact rejection and classification of all graphoelements that were labeled at the end of step 2 by a single rater using a 5-level confidence scale: Non-IED (artifacts or non-pathological variants such as Wickets spikes or Benign Sporadic Sleep Spikes [BSSS]), doubtful events, possible IEDs, probable IEDs and typical IEDs. The latter 3 groups were analogous to the grouping applied by Lam et al.[2] Only possible, probable, and typical IEDs were considered for the final step (see below).

Step 3: The final evaluation was based on qualitative features and quantitative criteria defined by the

International Federation of Clinical Neurophysiology (IFCN).[32] Note that the software used for the current analyses has limited ability to evaluate the sixth IFCN criterion, so decisions were based on the first 5 criteria and thresholds were adjusted (see Supplementary Fig S2 for details).

Polysomnography and Sleep Scoring

The PSG-vEEG (sampled at 1024 Hz) was obtained and analyzed using custom-made equipment and sensors from Natus, following American Academy of Sleep Medicine (AASM) version 2.4 guidelines.[33] The setup included 2 disposable adhesive electrooculography (EOG) electrodes, 2 chin electromyography (EMG) electrodes, 4 Grass cup leg EMG electrodes, 2 electrocardiogram (ECG) electrodes; thoracic and abdominal Piezo respiratory effort belts, pulse oximetry (Nonin xPod and Nonin PureLight disposable adhesive sensor), a nasal airflow sensor connected via an Ultima Dual Pressure Flow/Snore Sensor box, a thermistor, a microphone (Ultima), and synchronized infrared video. Sleep stages and respiratory events were scored by sleep specialists blinded to the diagnostic group.

MRI Examination

The MRI took place at the Toulouse Neuroimaging Center on the site of the University Hospital in a 3T Philips ACHIEVA dStream machine (Intera Achieva, Philips, Best, The Netherlands). The current article reports T1-related data acquired with the following parameters: 180 sagittal slices in 3D scan mode, multishot, voxel resolution of $1 \times 1 \times 1$ mm^3, T1-related data analysis was performed using FreeSurfer version 7,[34–36] via a previously outlined pipeline.[37] For further sequences used, see Supplementary Figure S1.

APOE Genotyping

APOE genotyping was performed exclusively for patients. The following kits were used, according to the manufacturer's instructions: MagNA Pure 24 Total Nucleic Acid Kit (Roche) for nucleic acid extraction and the Fast Start DNA Master HybProbe Kit (Roche) together with the LIGHTMIX APOE C/112R R158C (TIB MOLBIOL GmbH) for the identification of APOE haplotypes.

Neuropsychological Assessment

As the initial study objectives also extended to investigating the impact of epileptic activities on memory consolidation, neuropsychological assessments targeting memory consolidation and general cognition were conducted before and after sleep (see Supplementary Fig S1). Note that given the unexpectedly uneven group distributions, and the low number of IEDs detected (see the Results section), this planned analysis had to be omitted, although descriptive results are reported in Supplementary Table S1.

Follow-Up Visit (V3)–The EpiQ Questionnaire

At follow-up, several questionnaires were completed, including the EpiQ (see Supplementary Fig S1 and Supplementary Data S1), by participants, with observation-based input from caregivers whenever possible. To assess the responses, follow-up questions were asked for positive responses to each item to elucidate the frequency, severity, and specificity of the symptoms. A decision based on these factors was made by clinical experts and participants were classified as having "potential symptoms in favor of epileptic seizures" or not.

Main Outcome Variables and Statistics

Sample size was determined using a power analysis based on mean IED rates from previous studies.[1–3,15] This indicated that with estimated effect of 5% versus 40%, and a criterion of $\alpha = 0.05$, a power of 0.85 could be achieved with 29 participants per group.

The primary outcome variables included the percentage of participants with IED on their EEG in both groups and the distribution of these IED over the sleep–wake cycle. In addition, the percentage of patients with symptoms in favor of epileptic seizure at V3 based on the EpiQ[16] was evaluated. We also evaluated whether key structural variables from the MRI, particularly those related to temporal-lobe[38] and the precuneus,[29] or sleep-disordered breathing-related variables differed between patients with and without IED.

Data were analyzed using JASP.[39] Group comparisons were made using t tests, chi-square tests, Fisher's exact test, or nonparametric equivalents as appropriate. Descriptive statistics are presented as mean (M) ± standard deviation (SD) unless otherwise noted. Due to unequal group sizes, patient group-related analyses along the IED absence/presence axis are considered exploratory and reported p values are uncorrected. All values are rounded to 2 decimal places unless otherwise noted. All comparisons were 2-tailed, and p values < 0.05 were considered significant.

Results

Cohort Characteristics

A total of 31 patients with AD and 31 matched controls were enrolled (Fig 1). After exclusion of one participant per group (due to technical failure and incidental findings), the final sample comprised 30 participants in each group. All completed the initial 2 visits, and all but one control attended the follow-up.

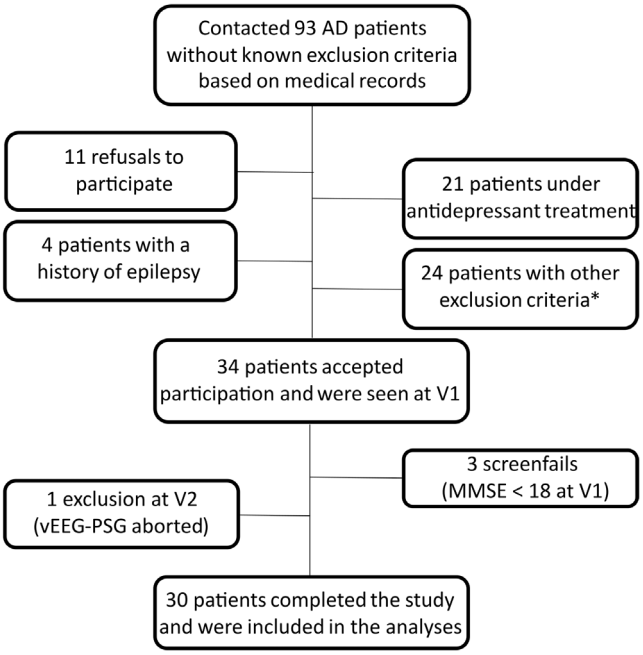

FIGURE 1: Flow chart of patient inclusions. *: Including contraindication to MRI examination, regular alcohol use, impossibility to attend the visits, neurological antecedents other than AD, participation in other clinical trials incompatible with the EREMAD study, chronic systemic pathologies, diagnosed but untreated sleep apnea syndrome, important loss of autonomy or patient already under legal guardianship/institutionalized. AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; vEEG-PSG = video-electroencephalogram with polysomnography.

Groups were comparable in age, sex, and key clinical variables, except for the expected MMSE difference ($p < 0.001$; Table 1). APOE $\varepsilon 4$ carriers made up 80% of the AD group. Four patients with AD (13.3%) presented with atypical variants (2 logopenic and 2 occipital). Use of medications affecting sleep was within protocol thresholds.

Prevalence, Morphology, and Topography of Epileptic Activities

An example of the obtained signal is shown in Figure 2A. No seizures were recorded during PSG-vEEG. In the initial visual screening (step 1), 5 patients with AD (17%) and 2 controls (7%) showed graphoelements suspicious for IEDs. All annotated events from these 7 recordings (totaling 582, with 455 from patients with AD, and 127 from controls) were analyzed in step 2. The majority of which were ultimately discarded as non-epileptic due to low voltage or morphology consistent with benign variants (eg, BSSS; Fig 2B or wicket spikes, Fig 2C).

In step 3, there were 24 events from 4 patients with AD (13%) and 21 from one control (3%) were reviewed against IFCN criteria. Events meeting at least 2 criteria were classified as confirmed IEDs. Ultimately, IEDs were confirmed in 3 patients with AD (10%) and one control (3.3%), with 9 IEDs retained per group. Most events were temporal in location, mostly unilateral in AD and bilateral in the control with IED and consisted primarily of simple spikes (see Fig 2D).

The difference in IED prevalence between groups was not statistically significant (odds ratio [OR] = 3.22, 95% confidence interval [CI] = 0.32–32.89; $\chi^2 = 1.071$; $p = 0.30$).

The observed comparability of REM sleep percentages between patients and controls (Fig 3A) suggests that removing antidepressants from the study indeed increased REM percentages and allowed for sufficient REM to detect eventual IEDs in this stage. Furthermore, no differences in REM sleep percentages were observed when comparing IED+ and IED− patients (Fig 3B), suggesting that the lack of REM sleep would not be a reason for missing out on REM-related IEDs. Yet, the majority of detected IEDs occurred during NREM2 or other NREM stages and never during REM (Fig 3C), suggesting that the observed IED pattern in AD models does not translate to clinical populations.

Questionnaire-Reported Seizure Symptoms (EpiQ)

No patient nor control has been hospitalized with or treated for epileptic seizures, during the follow-up period. According to the EpiQ, 8 of 30 patients with AD (27%) but no controls reported symptoms indicative of possible epileptic seizures, and these symptoms led to initiate anti-seizure medication (ASM), at the follow-up visit, in 2 of

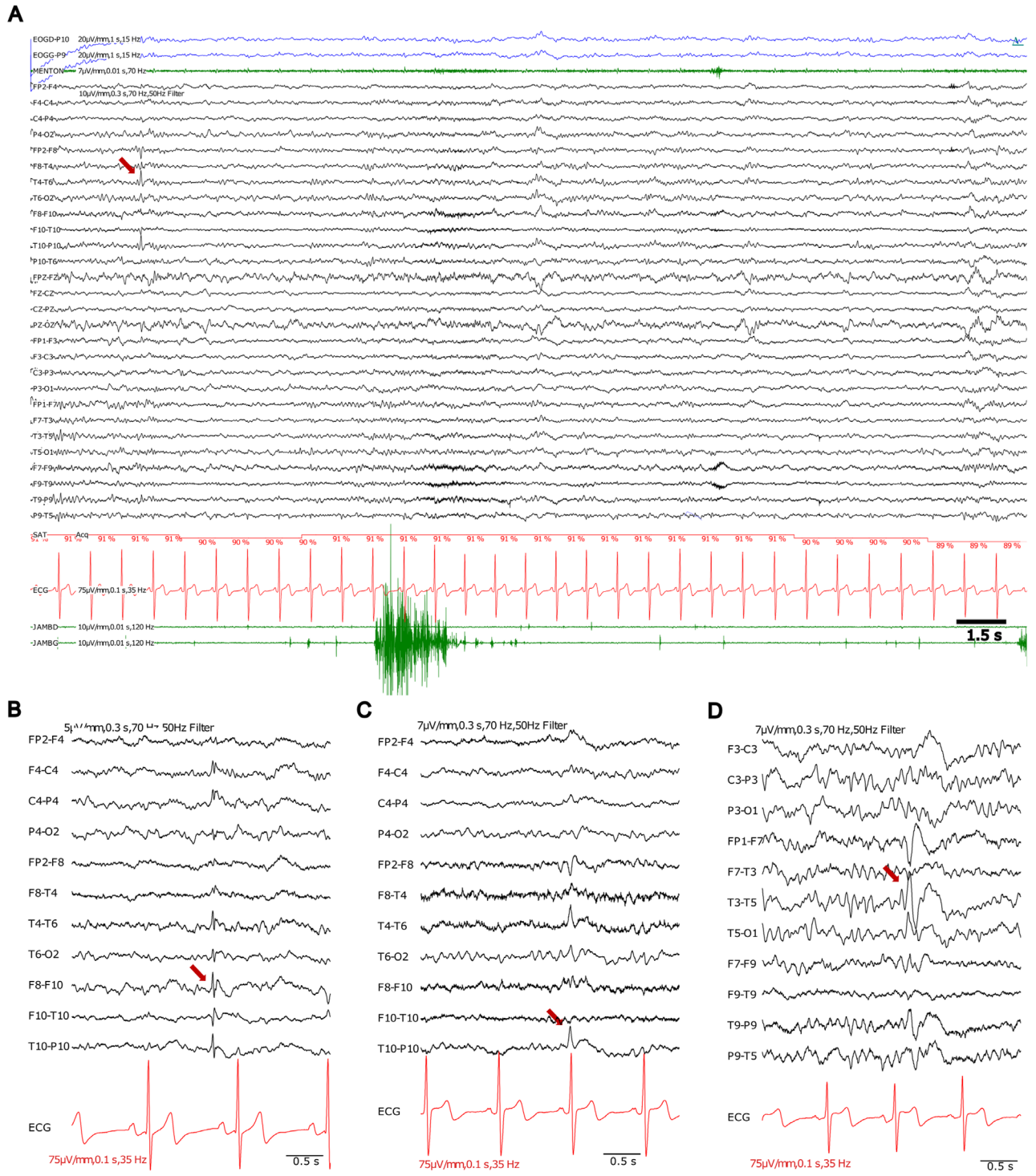

FIGURE 2: Details of the IED detection process and examples of retained IEDs and discarded graphoelements. (A) Thirty-second-long section of the PSG-vEEG signal with spiky graphoelements detected at step 1 (*arrow*). Both sleep and epilepsy experts were free to modify the view (gain, channels shown, etc.). For clarity, breathing-related channels were removed from the illustration. (B) Graphoelements discarded as a benign variant, (BSSS). (C) IED-like graphoelements with a temporal synchrony with ECG activity. This sharp wave was initially qualified as a possible IED (step 1), and was requalified during step 2, as a nonpathological variants (probable wicket spike) and excluded. (D) Retained IED. For (B–D), the segments are approximately 3.5 seconds long, with scales shown in the bottom right for time and on the top (EEG) or bottom (ECG) left for gain. BSSS = Benign Sporadic Sleep Spikes; ECG = electrocardiogram; EEG = electroencephalogram; IED = interictal epileptic discharge; PSG-vEEG = polysomnography with concurrent video electroencephalogram.

TABLE 1. Demographics and clinical characteristics of participants

	Controls (n = 30)	AD Pts (n = 30)	*p*	IED− AD (n = 27)	IED+ AD (n = 3)	*p*	IED/EpiQ− AD (n = 20)	IED/EpiQ+ AD (n = 10)	*p*
Age	68.2 ± 5.35	69.67 ± 6.79	0.357		74.67 ± 7.64	0.283	69.2 ± 6.65	70.6 ± 7.35	0.603
Age at onset	NA	68.23 ± 6.91	NA	67.78 ± 6.79	72.33 ± 8.02	0.387	68.7 ± 6.23	67.3 ± 8.38	0.609
AD duration, mo	NA	18.16 ± 27.81	NA	17.04 ± 28.32	28.47 ± 24.74	0.489	10.35 ± 20.23	33.86 ± 34.91	**0.026**
MMSE V1	28.83 ± 1.05	24.2 ± 2.87	**< 0.001**	23.93 ± 2.56	26.67 ± 4.9	0.265	24.05 ± 2.48	24.5 ± 3.66	0.693
MMSE V3[a]	28.45 ± 1.45	22.93 ± 4.7	**< 0.001**	22.56 ± 4.63	26.33 ± 4.73	0.165	23.6 ± 4.1	21.6 ± 5.72	0.279
CRIq Education scale[a]	112.83 ± 10.92	115.93 ± 8.53	0.228	116.7 ± 8.66	109 ± 1	0.062	117.45 ± 9.13	112.9 ± 6.54	0.173
Women, % (n)	50 (15)	50 (15)	1	48.14 (13)	66.66 (2)	0.543	45 (9)	60 (6)	0.439
CPAP (n)	1	1	NA	1	0	NA	1	0	NA
Atypical AD, % (n)	NA	13.33 (4)	NA	14.8 (4)	0% (0)	NA	5 (1)	30 (3)	*0.058*
APO-E4 carriers, % (n)	NA	80 (24)	NA	81.48 (22)	66.66 (2)	0.543	85 (17)	70 (7)	0.333
APO-E4 homozygote, % (n)[b]	NA	23.33 (7)	NA	30.43 (7)	0	0.343	25 (5)	20 (2)	0.568
Statins and AHT medications	33.33% (10)	40% (12)	0.592	37% (10)	66.66% (2)	0.32	35% (7)	50% (5)	0.429
Cholinesterase inhibitor	NA	40% (12)	NA	40.74% (11)	33.33% (1)	0.804	40% (8)	40% (4)	1
Benzodiazepines/ nonbenzodiazepine sleep medication, % (n)	3.33 (1)	6.67 (2)	0.554	7.41 (2)	0% (0)	0.626	5 (1)	10 (1)	0.605

Note: Table of demographic variables in the final cohort of the study for the entire patient and control groups, as well as for patients with (IED+ AD) or without IED on their EEG (IED− AD) and for patients with either IED on the EEG or an epilepsy suspicion based on EpiQ (IED+/EpiQ+ AD) and patients without IED or EpiQ-based epilepsy suspicion (IED− and EpiQ− AD). Values indicate mean (M) ± standard deviation (SD) unless stated otherwise. Reported *p* values results from *t* tests for the control-patient comparisons and for the IED− and EpiQ− AD versus IED+/EpiQ+ AD groups and from Mann–Whitney *U* tests for the IED− versus IED+ patient comparison. Values in bold indicate statistically significant differences.

AD = Alzheimer's disease; AHT = anti-hypertension; CPAP = Continuous Positive Airway Pressure machine; CRIq = Cognitive Reserve Index Questionnaire; EEG = electroencephalogram; EpiQ = Epilepsy Questionnaire; IED– = interictal epileptic discharge negative; IED+ = interictal epileptic discharge positive; MMSE = Mini Mental State Examination (Folstein version); NA = not applicable; V1 = visit 1; V3 = visit 3 (follow-up).

[a]The n = 29 for controls.

[b]Comparison of APOE4 heterozygotes and homozygotes.

these 8 patients. Only 1 of these 8 patients had confirmed IEDs; the remaining showed either unconfirmed graphoelements or none.

Of note, EpiQ+ symptoms were more common in patients with any suspicious EEG features in step 1 (4/7, 57%) than in those without (4/23, 17%; $p = 0.037$), suggesting that current morphological criteria may exclude true epileptiform activity in this patient population.

Risk Factors Associated with IED in AD

Based on the results of the questionnaire, and to better capture the risk factors of subclinical epileptic activity, we analyzed 2 sets of contrasts: (1) confirmed IEDs (IED+, n = 3) versus no IEDs (IED−, n = 27), and (2) patients with either IEDs or EpiQ+ symptoms (IED/EpiQ+, n = 10) versus neither (IED/EpiQ−, n = 20). Note that both of these analyses are considered exploratory due to the unequal sample sizes.

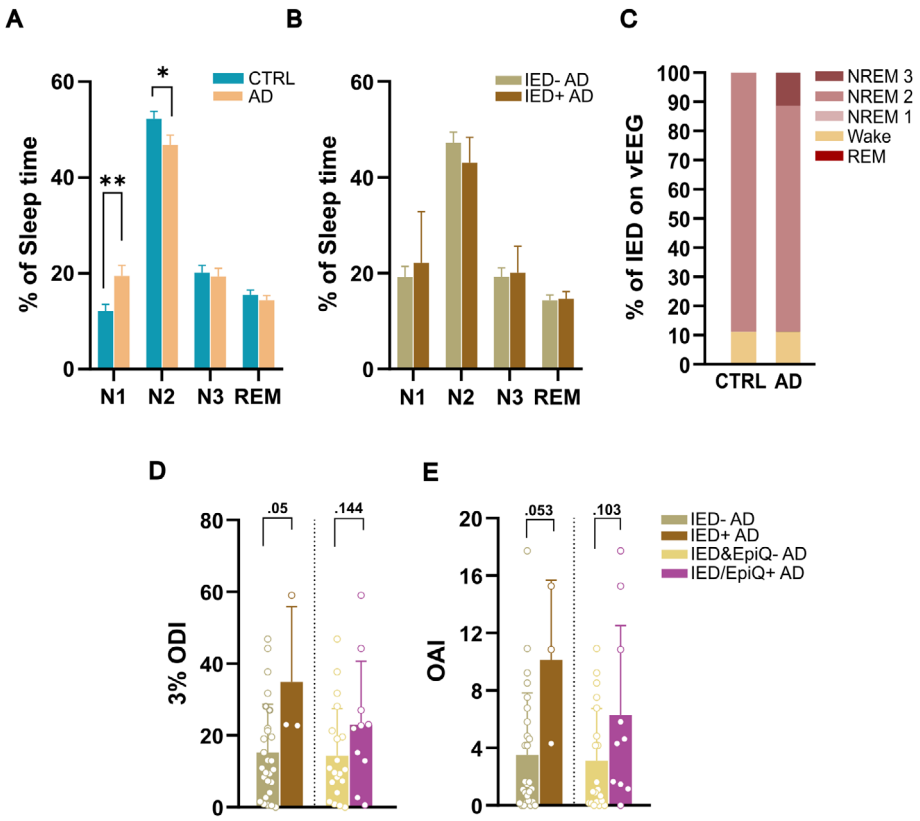

FIGURE 3: Comparison of percentage spent in different sleep stages between (A) all controls and patients and (B) between patients with or without IEDs on their EEGs, showing no significant difference between REM percentages, indicating that any observed differences for IEDs in this stage could not be attributed to REM differences. (C) The distribution of IED over the sleep–wake cycle across patients and controls, showing no REM-related IEDs. (D) 3% ODI and (E) OAI, indicating a slight increase of sleep-disordered breathing in patients with IED compared with those without. Color codes for panels D and E are identical. Bars and error bars on each panel represent mean + SEM. Statistics result from *t* tests. EEGs = electroencephalograms; IEDs = interictal epileptic discharges; OAI = Obstructive Apnea Index; ODI = Oxygen Desaturation Index; REM = rapid eye movement.

No significant differences in age, MMSE, or disease duration were found between IED+ and IED− patients. However, IED/EpiQ+ patients had longer disease duration (M = 33.9 vs. 10.4 months, $p = 0.026$) and a trend toward more atypical AD variants (30% vs. 5%, $p = 0.058$) than IED/EpiQ− patients, although the low proportion of atypical patients in the cohort (n = 4) warrants caution with interpretation.

However, in line with a previous report suggesting higher IED prevalence in patients with AD with sleep-disordered breathing, we observed an increased 3% oxygen desaturation index (3% ODI) in the IED+ group compared to the IED− group (23 ± 18 vs. 11 ± 16, $p = 0.05$; Fig 3D). This is likely due to the tendency of IED+ patients to have more obstructive apneas (Obstructive Apnea Index = 11 ± 5 vs. 1 ± 5, $p = 0.053$; Table 2 and Fig 3E). Furthermore, all patients in the IED+ group received a diagnosis of moderate (n = 2) or severe (n = 1) sleep apnea syndrome. Although the same comparisons were not significant between IED/EpiQ+ versus IED/EpiQ− patients (see Fig 3E), moderate-to-severe obstructive sleep apnea (OSA) was diagnosed in almost all IED/EpiQ+ patients (90%) and only about half of the IED/EpiQ− patients (55%, $p = 0.055$), which may point toward more severe sleep-disordered breathing in this group.

On the MRI, IED/EpiQ+ patients had significantly lower total and left precuneus volume and thickness ($p = 0.019$–0.026), with a similar trend on the right ($p = 0.06$). Whole left-hemisphere cortical volume was also reduced ($p = 0.033$; Table 3). Hippocampus-related metrics were not significantly different across groups.

Discussion

In this prospective case-control study, we deployed a full-night vEEG-PSG with an electrode setup extended with lower temporal electrodes to maximize our chances to detect IEDs during sleep in AD. Using a rigorous method for IED identification, only 10% of the patients and 3% of the

TABLE 2. Polysomnography parameters of controls and AD patients

	Controls (n = 30)	AD PTs (n = 30)	*p*	IED− AD (n = 27)	IED+ AD (n = 3)	*p*	IED/ EpiQ− AD (n = 20)	IED/EpiQ+ AD (n = 10)	*p*
NREM 1%	12.09 ± 7.85[a]	19.46 ± 11.98	*0.017*	19.17 ± 11.51	22.14 ± 18.56	0.845	18.64 ± 12.2	21.11 ± 11.99	0.559
NREM 2%	52.21 ± 8.85	46.8 ± 11.26	*0.043*	47.22 ± 11.53	43.04 ± 9.16	0.509	47.59 ± 12.11	45.22 ± 9.71	0.619
NREM 3%	20.16 ± 8.22	19.35 ± 9.36	0.725	19.26 ± 9.53	20.12 ± 9.5	0.948	18.83 ± 8.56	20.4 ± 11.23	0.650
REM %	15.53 ± 5.51	14.36 ± 5.37	0.412	14.33 ± 5.62	14.68 ± 2.59	0.897	14.92 ± 5.64	13.25 ± 4.87	0.350
OAI	2.8 ± 4.26	4.17 ± 4.8	0.245	3.51 ± 4.33	10.15 ± 5.53	*0.053*	3.12 ± 3.63	6.29 ± 6.24	0.103
AHI	13.36 ± 14.57	16.58 ± 13.46	0.378	15.42 ± 12.52	27 ± 20.04	0.3	20.08 ± 15.25	28.58 ± 15.04	0.118
3% ODI	13.34 ± 12.91	17.24 ± 15.07	0.287	15.27 ± 13.4	34.93 ± 20.89	**0.050**	14.37 ± 13.08	22.96 ± 17.77	0.143
Moderate-to-severe SAS diag.[b]	46.67% (14)	66.67% (20)	0.12	62.96% (17)	100% (3)	N/A	55% (11)	90% (9)	0.056

Note: Table of sleep-related variables between different groups. Values indicate mean ± standard deviation unless stated otherwise. Reported *p* values results from *t* tests for control-AD comparisons (unless otherwise indicated) and from Mann–Whitney *U* tests for the IED−/IED+ AD comparison, and, given a high number of compared variable with failed assumption checks, for the IED− and EpiQ− versus IED+/EpiQ+ AD comparisons as well. Values in bold and italic indicate statistically significant differences and tendencies towards statistical significance, respectively.

AD = Alzheimer's disease; AHI = Apnea-Hypopnea Index; EpiQ = Epilepsy Questionnaire; IED– = interictal epileptic discharge negative; IED+ = interictal epileptic discharge positive; NREM = non-rapid eye movement sleep; OAI = obstructive apnea index; ODI = oxygen desaturation index; SAS = sleep apnea syndrome.

[a]Mann–Whitney *U* test due to violated assumptions of the Student's *t* test.

[b]χ^2 test.

controls exhibited IEDs. In patients, IEDs were mainly detected on temporal electrodes during NREM2 sleep but, contrary to our hypothesis, never during REM sleep. The EpiQ questionnaire allowed identifying 8 patients with AD who presented symptoms in favor of epileptic seizure, one of whom had confirmed IEDs. Although further validation is needed, our findings align with prior reports suggesting an association between epileptic activity and both sleep-disordered breathing and reduced precuneus volume.[11,29]

IED Frequency and Distribution Over Sleep Stages

Our findings fall at the lower end of the wide range of IED prevalence reported in AD (6–75%).[1–3,6,11,15] Furthermore, in contrast to AD mouse models overexpressing mutated APP—where REM sleep is associated with increased IEDs—we detected no IED during REM, despite efforts to preserve REM architecture by excluding REM-suppressing medications. Instead, similar to patterns seen in non-AD-related MTL epilepsy, IEDs occurred predominantly during NREM2 sleep, when hippocampal synchrony is elevated.[40]

Because we used an optimized methodology for IED detection during a night-long video-EEG session, we expected to detect a prevalence of epilepsy in AD at least as high as previously reported in the literature[1] (see the "Main outcome variables and Statistics" section in the Methods above). Our data clearly do not corroborate this hypothesis. Instead, we observed a smaller effect size that did not reach statistical significance, likely due to insufficient statistical power ($p = 10\%$; an estimated sample size of >200 participants per group would be required to achieve adequate power). This low prevalence of IED in patients with AD may stem from specific characteristics of our cohort or from methodological factors, as discussed below.

Cohort-Specific Factors Behind Discrepant Results

Variability across studies likely reflects cohort and protocol differences. Our AD group had a relatively high average MMSE (24), possibly contributing to the low IED prevalence, as epileptic activity increases with disease severity.[5,41] The exclusion of patients on antidepressants may also have played a role. Although these drugs reduce REM

TABLE 3. MRI parameters of AD patients with and without IEDs, as well as patients with or without subjective and/or objective symptoms of subclinical epileptic activities

Variables	IED− AD (n = 27)	IED+ AD (n = 3)	*p*	IED/EpiQ− AD (n = 20)	IED/EpiQ+ AD (n = 10)	*p*
V total hippocampus	5,290 ± 943	5,504 ± 978	0.795	5,242 ± 942	5,451 ± 943	0.571
V right hippocampus	2,700 ± 569	2,827 ± 527	0.744	2,651 ± 575	2,836 ± 527	0.401
V left hippocampus	2,590 ± 432	2,678 ± 451	0.897	2,591 ± 416	2,615 ± 471	0.886
V total precuneus	15,308 ± 1825	13,335 ± 828	*0.072*	15,631 ± 1800	14,070 ± 1,513	**0.026**
V right precuneus	7,826 ± 984	6,748 ± 558	*0.061*	7,959 ± 920	7,235 ± 1,023	*0.060*
V left precuneus	7,482 ± 950	6,588 ± 272	*0.072*	7,672 ± 961	6,835 ± 627	**0.019**
T right precuneus	2.13 ± 0.12	2.06 ± 0.02	0.189	2.16 ± 0.16	2.07 ± 0.1	0.120
T left precuneus	2.14 ± 0.15	2.04 ± 0.08	0.253	2.16 ± 0.1	2.05 ± 13	**0.022**
V total cortex	384,629 ± 34,816	361,632 ± 13,691	0.176	390,797 ± 34,794	365,394 ± 25,851	*0.051*
V right cortex	192,879 ± 18,303	1,800,861 ± 7,530	0.226	195,304 ± 17,589	184,191 ± 16,894	0.110
V left cortex	191,750 ± 18,179	181,546 ± 6,247	0.226	195,494 ± 18,294	181,203 ± 11,695	**0.033**

Note: Table of morphometric variables for patients with (IED+ AD) or without IED on their EEG (IED− AD) and for patients with either IED on the EEG or an epilepsy suspicion based on EpiQ (IED/EpiQ+ AD) and patients without IED or EpiQ-based epilepsy suspicion (IED and EpiQ− AD). Reported *p* values results from *t* tests for the IED− and EpiQ− AD versus IED+/EpiQ+ AD groups and from Mann–Whitney *U* tests for the IED− versus IED+ patient comparison. Values indicate mean ± SD rounded to 2 decimals for thickness and to integers for volume values, unless stated otherwise. Volumes are calculated in mm^3, thickness in mm. Values in bold and italic indicate statistical significance and a tendency towards statistical significance, respectively.

AD = Alzheimer's disease; EEG = electroencephalogram; EpiQ = Epilepsy Questionnaire; IED– = interictal epileptic discharge negative; IED+ = interictal epileptic discharge positive; T = thickness; V = volume.

sleep, they may also increase seizure susceptibility in temporal lobe epilepsy,[42,43] whereas depression may increase the risk of epilepsy in itself.[44] One report also suggests that fluoxetine triggers seizures in an AD mouse model.[45] Interestingly, Brunetti et al,[15] who excluded patients on psychoactive medications including antidepressants, reported similarly low IED prevalence (6.38% in patients with AD and 11.63% in patients with MCI). However, 2 other studies that included antidepressant users and reported on related group differences did not observe a significant effect.[1,6] Given the growing use of antidepressants in AD,[46] further investigation is warranted regarding this point.

Methodology Related Factors Behind Discrepant Results

The method used to detect IED on the EEG is of central interest when examining discrepant results. In particular, standard clinical tools, such as scalp EEG using the 10 to 20 setup and single-night recordings, have limited sensitivity. For instance, single-night EEG captured IEDs in only approximately 50% of patients with AD with known epilepsy.[2] Similarly, combined intracranial and scalp EEG data from 2 patients with AD showed that merely 5% of events recorded intracranially were visible on scalp EEG.[47] This would imply that (1) the 3 patients with 2 to 4 IEDs detected in our study could have, in reality, 100 throughout the night, and that (2) we may not have been able to detect any IEDs in some patients.

However, whereas stereoEEG (sEEG) or other alternatives, for example magnetoencephalography (MEG), may offer higher sensitivity,[1,6,48] their use is restricted by ethical, logistical, or financial limitations. While emerging technologies, such as optically pumped magnetometer-based MEG and advanced computational analysis tools,[49–51] may offer more viable diagnostic solutions in the future, the current clinical reality calls for improved noninvasive strategies to enhance the detection of epileptic activity in AD and MCI. This could facilitate earlier intervention and clinically meaningful cognitive improvements.

Within the current clinical context and array of diagnostic options, we used lower temporal electrodes to improve detection accuracy—now supported by another study[11]—and concomitant PSG recording to eliminate

artifacts. Whereas the reported IED-occurrence is not in favor of improved detection, the added lower temporal electrodes proved to be a valuable addition to the setup, based on the subjective evaluation of the experts. Nevertheless, our use of IFCN criteria to minimize false positive results may have excluded genuine IEDs due to their atypical morphology in AD, which remains to be clarified. For example, based on the morphology of the examples presented in Lam et al, using our methodology would likely have led us to retain only what they called "definite" IED and to discard IED classified as "probable," or "equivocal," which accounted for 59% of the IEDs in that study.

The EpiQ questionnaire added a subjective clinical dimension. Although only one EpiQ+ patient had confirmed IEDs, many patients with suspicious but unconfirmed graphoelements also reported relevant symptoms, echoing findings via a similar clinical tool.[11] This may suggest that AD-related IEDs may differ morphologically from typical MTL epilepsy and may not always align with existing criteria. Some rejected elements (eg, >400 BSSS in one patient) might in fact reflect pathological activity. In light of potential morphological differences and differences in IED definitions across studies, consensus on IED morphology and detection methods specific to AD—based on expert review and machine learning approaches—is urgently needed if we are to better understand this comorbidity. Until then, questionnaires like EpiQ may complement an EEG in identifying network hyperexcitability and merit further validation in larger cohorts.

Potential Risk Factors of IEDs in AD Warranting Screening

EpiQ could, therefore, be a useful questionnaire to identify patients with AD who might require EEG screening for IEDs—although, once again, this would require better screening tools. Consensus based on accumulated data from studies published so far could help identify other useful biomarkers and standardize their use in this patient group.

Nonetheless, the fact that 2 out of 3 patients with confirmed IEDs reported no symptoms in favor of possible epileptic seizures may call for the identification of further risk factors that might guide screening. According to our results and in light with previous reports,[11,29] this could include precuneus-dominant atrophy patterns and more severe forms of obstructive sleep apneas. Although results are still based on few patients and require further studies, especially for understanding the direction of the links, such relationships are mechanistically plausible. Indeed, OSA is linked to increased amyloid burden in older adults in the hippocampus and the precuneus,[52,53] and these areas have been identified as the primary loci of network hyperexcitability in AD models or patients.[54,55] Interestingly, a recent hypothesis suggest an initial role of Aβ accumulation in the posteromedial cortex (PMC; including the precuneus) to the dysconnectivity between the MTL and the PMC, that would drive hyperexcitability in the MTL in AD.[56] In this context, it is possible that, over time, undetected OSA accelerates hippocampal and precuneal Aβ generation, increasing the risk of AD and exacerbating Aβ-induced neuronal hyperexcitability. Whereas OSA may be a notable contributor, its treatment, even in mild-to-moderate AD, may face challenges related to continuous positive airway pressure (CPAP) machine tolerance. This pledges toward better screening for OSA in middle-aged and older adults to initiate treatment before cognitive difficulties impede treatment tolerance and to explore alternative treatment options, such as mandibular advancement devices, or, when appropriate, positional therapy or other treatment options.

Conclusions

In summary, we aimed at optimizing IED detection in AD through enhanced EEG electrode coverage, rigorous diagnostic criteria, and the addition of a questionnaire intended to capture symptoms suggestive of underlying epileptic seizures. We also tested, in a translational approach, whether REM sleep could be a target for improved IED detection. Still, only 10% of patients with AD exhibited IED, and these occurred preferentially during NREM2. In spite of the low IED rate, our study brings important methodological insights, and suggests, in accordance with previous studies, potential for improving screening through clinical questionnaires or through flagging patients at risk for IEDs based on comorbidities such as moderate-to-severe OSA or a precuneus-dominant atrophy pattern.

Detection of subclinical epileptic activities in AD remains a significant challenge. Future advances in the field will depend on developing more sensitive automated IED detection tools[49,50] and validating tailored clinical screening instruments. Although our study had several limitations—many brought up previously, such as the use of scalp EEG, or the limited statistical power in subgroup comparisons, and the necessity to validate the EpiQ questionnaire—it adds valuable insights to the field regarding potential underlying factors of discrepancies between clinical studies, and calls for the re-evaluation and standardization of IED detection methods for patients with MCI and AD. Given that treatment of subclinical epileptic events may improve cognition in both AD and MCI,[1,13] optimizing detection remains a clinical priority.

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AUTHOR CONTRIBUTIONS

Anna B. Szabo: Conceptualization; investigation; writing – original draft; funding acquisition; methodology; validation; visualization; formal analysis; data curation. **Jonathan Curot:** Investigation; writing – original draft; methodology; formal analysis; writing – review and editing. **Fleur Gérard:** Investigation; formal analysis; writing – review and editing. **Florence Rulquin:** Investigation; writing – review and editing. **Rachel Debs:** Investigation; formal analysis; writing – review and editing; conceptualization. **Claire Georges:** Formal analysis; investigation; writing – review and editing. **Marie Denuelle:** Investigation; formal analysis; writing – review and editing. **Amel Bouloufa:** Investigation; formal analysis; writing – review and editing. **Beatrice Lemesle:** Investigation; formal analysis; conceptualization; writing – review and editing. **Patrice Péran:** Conceptualization; formal analysis; writing – review and editing. **Claire Thalamas:** Conceptualization; investigation; funding acquisition; writing – review and editing; methodology; project administration; resources. **Emmanuel J. Barbeau:** Conceptualization; funding acquisition; writing – original draft; validation; methodology; resources. **Jérémie Pariente:** Conceptualization; investigation; funding acquisition; methodology; writing – review and editing. **Lionel Dahan:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; supervision; resources. **Luc Valton:** Conceptualization; investigation; funding acquisition; writing – original draft; validation; methodology; formal analysis; supervision; resources.

Potential Conflicts of Interest

Nothing to declare.

Data Availability

Data are available in the supplementary tables. All PSG raw data are available upon request by email to lionel.dahan@univ-tlse3.fr, except for video data, which have been deleted to conform to the ethics committee's recommendations.

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