

RESEARCH ARTICLE

High-frequency oscillations >250 Hz in people with Down syndrome and associated Alzheimer's disease dementia

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Abstract

INTRODUCTION: Alzheimer's disease (AD) dementia has near full penetrance in adults with Down syndrome (DS) and is strongly linked to late-onset myoclonic epilepsy in Down syndrome (LOMEDS). However, promising biomarkers of epileptogenicity, such as high-frequency oscillations (HFOs >250 Hz), have not been studied. This study is the first to use wideband polysomnography in DS to investigate if HFOs occurred and preceded AD dementia and LOMEDS.**METHODS:** Wideband (0.1 to 500 Hz, 2048 Hz) polysomnography was performed using the international 10-20 system. HFOs were automatically detected during slow-wave sleep, followed by manual review.**RESULTS:** Fourteen individuals with DS and five age-matched euploid controls were studied, with all DS cases showing HFOs. HFOs emerged before AD dementia and LOMEDS and showed hemispheric lateralization in asymptomatic but not symptomatic AD dementia cases. A trend toward increasing HFO rates with age in DS warrants further confirmation.**DISCUSSION:** HFOs are promising biomarkers that may predict symptomatic AD dementia in adults with DS.

KEYWORDS

Alzheimer's disease, amyloid, biomarker, Down syndrome, electroencephalography, interictal, seizures, sleep

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Highlights

- Wideband polysomnography reveals a new electrical abnormality in DS.
- HFOs precede AD dementia in DS.
- The occurrence of HFOs in DS is independent of an epilepsy diagnosis.
- HFOs showed hemispheric lateralization in asymptomatic DS cases.
- A trend of increased HFO rate with advancing age warrants further investigation.

1 | BACKGROUND

Individuals with Down syndrome (DS) face an exceptionally high risk of developing Alzheimer's disease (AD) dementia, with nearly all individuals developing AD neuropathology by age 40 and AD dementia about a decade later.^{1–3} Symptomatic AD dementia in DS negatively impacts outcomes, including accelerated cognitive deterioration, faster disease progression, and significantly elevated mortality.^{4,5} Advances in healthcare have substantially extended the lifespan of individuals with DS,⁶ resulting in not only a higher prevalence of AD dementia but also of other neurological conditions, such as epilepsy.^{7–10} Notably, seizures and epilepsy may be underdiagnosed or diagnosed late during the lifespan of people with DS,¹⁰ which is important to address because early treatment may lead to good seizure control and improved outcomes.^{11,12} This is particularly relevant for late-onset myoclonic epilepsy syndrome in DS (LOMEDS), which is associated with worse cognitive and functional outcomes.^{13,14} Currently, biomarkers of epileptogenicity in DS or AD are unknown. Their identification may aid in stratifying those at risk faster, in turn leading to earlier and more effective interventions with potentially long-term benefits.

High-frequency oscillations (HFOs), brief (~30 ms) electrical events on various types of electrophysiological signals, have garnered significant attention from the epilepsy community due to their potential as an epilepsy biomarker.¹⁵ Specifically, HFOs >250 Hz are particularly notable, as they are typically rare or absent in the normal human brain,^{16,17} unlike lower-frequency oscillations, that is, <250 Hz. Despite their potential significance, such HFOs are understudied using scalp EEG due to their low signal-to-noise ratio and the challenges involved in reliably distinguishing them from artifacts.¹⁸ Nevertheless, scalp HFOs have been identified in children with epileptogenic lesions¹⁹ and in cases of infantile spasms,²⁰ but not in healthy infants.¹⁹ In this context, HFOs have been suggested to hold significant predictive value when resected, particularly in relation to achieving seizure freedom in children.²¹ In adults, HFOs have been observed in patients with focal epilepsy,^{22,23} though it has been emphasized that further studies are warranted. Notably, there is currently no study investigating HFOs in the context of DS or DS-associated AD dementia, representing a significant knowledge gap in our understanding of HFO disturbances beyond neurodevelopmental disorders and the epilepsies.

Given the promising role of EEG biomarkers, particularly those indicating hyperexcitability (e.g., interictal spikes, seizures) in AD-related outcomes²⁴ and treatment stratification,²⁵ we sought to determine whether HFOs occurred in DS and DS-associated AD dementia. Our initial investigation using DS and AD mouse lines was the first to demonstrate that HFOs represent a newly discovered form of abnormal electrical activity in these model systems.²⁶ The hippocampus was identified as a hotspot location, though HFOs were also recorded from the cortical surface, both independently of and concurrently with hippocampal HFOs.²⁶ These preclinical findings were corroborated by a subsequent magnetoencephalography (MEG) study in humans, which reported HFOs in the temporal lobe of already diagnosed AD dementia cases, with comorbid epilepsy cases harboring more HFOs.²⁷ However, our preclinical data²⁶ suggested that HFOs could emerge much earlier in the disease continuum, potentially preceding key disease hallmarks such as the onset of cognitive decline and the appearance of overt neuropathology, including amyloid beta (A β) plaques. Yet there is currently no evidence in humans indicating that HFOs would precede the onset of AD dementia in at-risk individuals, associated cognitive deficits, established AD-related biomarkers, or LOMEDS.

In this study, we investigated whether HFOs occurred in individuals with DS. To this end, we conducted the first wideband polysomnography study in the context of DS and AD and recorded scalp EEG during sleep using the common 10-20 international system. We recruited adults with DS and age-matched euploid controls and asked whether HFOs occurred. Next, we tested whether HFOs differed between asymptomatic and symptomatic AD dementia cases and whether they were associated with LOMEDS. Lastly, we tested whether HFOs showed hemispheric lateralization and how HFOs might change with advancing age. Notably, HFOs were detected in all individuals with DS, including those without cognitive deficits or diagnoses of AD dementia or LOMEDS.

2 | METHODS

2.1 | Study design and participants

The study included adults (≥ 18 years old) with DS from the Down-Alzheimer Barcelona Neuroimaging Initiative (DABNI⁵), a population-based multimodal biomarker cohort to study the AD natural history in

DS. We also included a cohort of euploid cognitively unimpaired control subjects from the Sant Pau Initiative on Neurodegeneration (SPIN) cohort.²⁸ Wideband polysomnography was conducted on all subjects as part of their workup.^{5,28} The study was approved by the Sant Pau Ethics Committee in accordance with standards of medical research involving humans as recommended by the Declaration of Helsinki. All study participants or their legally authorized representatives gave written informed consent before enrolling.

Participants underwent a thorough neurological and neuropsychological evaluation that included the Cambridge Cognitive Examination for Older Adults with Down Syndrome (CAMCOG-DS) Spanish version, which evaluates global cognition.^{29,30} Specifically, the CAMCOG-DS test included a battery of cognitive tests assessing orientation, language, memory, attention, praxis, abstract thinking, and perception. During a consensus meeting composed of neurologists and neuropsychologists, participants were assigned into three categories: asymptomatic (aDS), prodromal (pDS)/mild cognitive impairment (MCI), and AD dementia (dDS). Individuals classified as aDS showed no clinical or neuropsychological suspicion of AD-related cognitive decline, while pDS/MCI had evidence of cognitive decline due to AD, but with no significant impact on daily life activities. Lastly, individuals with dDS presented with cognitive decline that impaired their daily activities. None of the subjects had a history of seizures or epilepsy at the time. Epilepsy diagnosis was based on established definitions by the International League against Epilepsy.³¹

We selected age-matched euploid control subjects for the individuals with DS included in the study. All control subjects scored 0 on the Clinical Dementia Rating scale, had neuropsychological scores within the normal range, and had no neurological/psychiatric disorders interfering with cognition, or a history of seizures and epilepsy.²⁸

2.2 | Wideband polysomnography recording

Wideband polysomnography captures a broader frequency range of brain activity compared to conventional polysomnography, which typically focuses on lower-frequency brain waves, usually in the frequency range of 1 to 70 Hz.³² The wideband approach extends the recording spectrum to higher frequencies, including HFOs such as ripples (80 to 250 Hz) and fast ripples (250 to 500 Hz), which are often missed in standard polysomnography recordings due to limitations in sampling frequency and the use of filters that attenuate frequencies exceeding 70 Hz.³³ Thus, here the EEG was sampled at 2048 Hz using a 0.1-Hz high-pass and a 500-Hz low-pass filter in line with guidelines for recording HFOs.³³ With this higher sampling rate and relatively wide filters, we can better resolve the rapid changes in brain activity, including those operating at frequencies as rapid as HFOs. Overall, wideband polysomnography offers a significant advantage over traditional polysomnography by allowing investigation of a broader frequency range of oscillations that otherwise would have been overlooked using traditional polysomnography recordings. However, despite improved resolution, the reliable detection of HFOs on the scalp EEG remains challenging due to low signal-to-noise

RESEARCH IN CONTEXT

1. **Systematic review:** Individuals with DS are at ultra-high risk for both AD dementia and LOMEDS. Previous studies deemed HFOs (>250 Hz) as one of the most promising epilepsy biomarkers. However, whether HFOs occur in DS or precede the onset of AD dementia and LOMEDS is unknown. Additionally, potential changes in HFOs with age of DS participants are unclear.
2. **Interpretation:** HFOs occurred in DS cases before symptomatic AD and LOMEDS. A trend suggesting increased HFO rates with age warrants further confirmation. HFOs could serve as an early biomarker detectable by scalp EEG and thus amenable to non-invasive detection in individuals at risk of symptomatic AD.
3. **Future directions:** Longitudinal EEG and imaging studies will shed light on how HFOs evolve during the AD continuum, their cortical hotspots, and relation to neuropathology. HFOs may also hold promise in predicting cognitive decline.

ratios and susceptibility to high-frequency electromyographic (EMG) artifacts.

All sleep recordings were conducted in sound-attenuated, temperature-regulated, and individual rooms located in the sleep laboratory of the Sant Pau hospital. Participants were continuously monitored by technical staff, with both video and audio recorded using an infrared camera. Polysomnography tests started at participants' median bedtime as determined by prospective diaries. Each recording lasted about 8 h. The 10-20 international system and 19 channels (namely, Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P5, Pz, P4, T6, O1, O2) were used. Acquisition used the Compumedics E Series System and PSG 3.4 Profusion Sleep Software (Compumedics, Victoria, Australia). Left and right placed electrodes were referenced to the left and right mastoids, respectively. Additional channels included left and right electrooculographic channels (EOG), two EMG channels for limb movements, and three channels to detect chin movements. Three more channels monitored respiration: a chest band, a nasal thermistor, and a finger SaO₂. For analyses using a bipolar montage, signals from electrode pairs were subtracted to minimize EMG activity originating near the mastoid reference electrodes. Unless otherwise specified, electrode pairings typically included electrodes in the temporal (T4, T6), frontal (Fp2, F8), and central (C4, Cz) regions. The exact electrode combinations are detailed in the text.

2.3 | Analyses of sleep

Sleep stages were scored visually using 30-s epochs following the guidelines of the American Academy of Sleep Medicine (AASM).³⁴ We

used Profusion Sleep Software (Compumedics, Victoria, Australia), and scoring was conducted by an experienced sleep technician using video as well as EEG records, which was further reviewed by an accredited sleep somnologist as before.³⁵ More details on the exact sleep stage analyzed for HFOs are provided below in Section 2.4.

Sleep analyses also involved assessing leg movements throughout the entire sleep period using two distinct metrics. The first metric quantified the total number of leg movements by reviewing synchronized video recordings, EEG data, and leg EMG signals. The second metric measured periodic leg movements – repetitive, involuntary leg jerks or twitches typically lasting 20 to 40 s – which were analyzed separately, and, therefore, not included in the first metric. For both metrics, the total number of movements across the entire sleep period is reported.

2.4 | HFO detection and analysis

We define HFOs as oscillations between 250 and 500 Hz, as in our previous studies.^{26,36} We focused on this frequency range because HFOs in this range are typically rare or absent from the normal human brain.^{16,17} Several epilepsy studies showed that HFOs >250 Hz may be more closely linked to epileptogenicity^{37–39} than other oscillations of lower frequency. To detect HFOs, we used sleep records with a predominance of delta (<4 Hz) oscillations and absence of overt EMG activity, consistent with stage 3 of non-rapid eye movement sleep (NREM) sleep.³⁴ We used this sleep stage for several reasons. First, NREM sleep is a sleep stage with relatively low EMG and a state that facilitates the expression of HFOs.⁴⁰ Indeed, HFOs in humans are known to occur more frequently in NREM versus rapid eye movement (REM) sleep or wakefulness.³⁷ Second, our preclinical study showed that HFOs were more frequent during NREM than in REM or wakefulness,²⁶ resembling epilepsy models.^{36,38} Third, people with DS often spend less time in REM sleep compared to euploid individuals, and its duration and quality may be compromised due to factors such as sleep apnea.³⁵ Thus, we reasoned that by analyzing NREM sleep, we would have the best chance to capture any HFOs that might have occurred.

We analyzed continuous periods of NREM sleep lasting at least 2 min (a total of four periods per participant were used, i.e., 8 min in total were analyzed) using an automatic detector⁴¹ and the algorithm developed by Staba.⁴² Putative HFOs were detected if they showed at least four cycles, were >6 ms in duration, and exceeded the filtered (250 to 500 Hz) background by more than five times the standard deviation (SD) of the mean baseline amplitude⁴² calculated in the same recording channel. The same detection criteria were applied across all recording channels, and HFOs were detected separately in each channel. Putative HFOs that did not show at least four peaks in the rectified bandpass-filtered signal that were >3 SDs of the mean of the baseline signal were excluded. Each detected event was then manually reviewed to exclude artifacts related to movement or other sources of noise,^{43,44} as before.^{26,36} Typically, artifacts appeared as candle-shaped events in the time-frequency domain, often occurred almost simultaneously across several channels, and were excluded from analyses. Spectral

analysis was implemented to visualize HFO power in time (Figures 1–4) using RippleLab's⁴⁵ time-frequency function and a 64-point window. All analyses were done with the investigator blinded to the subject group.

2.5 | Assessment of epileptiform activity

To assess the presence of epileptiform activity in our wideband EEG recordings, we reviewed the data for the presence of interictal spikes, as they were previously reported to occur in individuals with MCI and AD dementia.^{24,46} The EEG was reviewed in 10-s epochs using 0.1- to 500-Hz filters in EDFbrowser software. Epileptiform spikes were defined as events lasting 20 to 200 ms that disrupted the ongoing background activity.⁴⁷ Events coinciding with EOG- or EMG-related activity were excluded from analysis. Participants were classified as either epileptiform DS (EDS) if such epileptiform activity was present, or non-epileptiform DS (NEDS) if absent during their entire sleep recording. The same analysis was conducted in all euploid control subjects. The percentage of participants with and without epileptiform activity is reported in the results Section.

2.6 | Laterality and asymmetry analyses

To address whether HFOs exhibited hemispheric lateralization, we quantified the number of HFO-positive (non-zero events/min) and HFO-negative (zero events/min) channels in the left and right hemispheres. Specifically, for the left hemisphere we analyzed channels Fp1, F7, F3, T3, C3, T5, P3, and O1; for the right hemisphere, we included channels Fp2, F8, F4, T4, C4, T6, P4, and O2. Based on these data, we defined three possible outcomes: (1) right preference, which was determined if the number of HFO-positive channels in the right hemisphere exceeded those in the left hemisphere; (2) left preference, if the number of HFO-positive channels in the left hemisphere exceeded those in the right hemisphere; and (3) no preference or equal, when the number of HFO-positive channels was the same between the two hemispheres. For each outcome, we calculated the percentage of subjects in each category, based on the total number of participants in each group (all participants, asymptomatic, prodromal/MCI, and symptomatic AD dementia).

We further investigated regional differences in HFO distribution by comparing the number of HFO-positive channels in the temporal and frontal lobes (bilaterally) among asymptomatic and symptomatic (individuals with prodromal/MCI and AD dementia) cases. Temporal channels included T3, T5, T4, and T6 and frontal channels Fp1, F7, F3, Fp2, F8, and F4. Participants were classified as showing temporal dominance if they had more HFO-positive channels in the temporal lobe than in the frontal lobe, and the opposite was followed for frontal dominance. The results of these analyses are presented as the percentage of subjects within each category (all participants, asymptomatic, prodromal/MCI, and symptomatic AD dementia were pooled together).

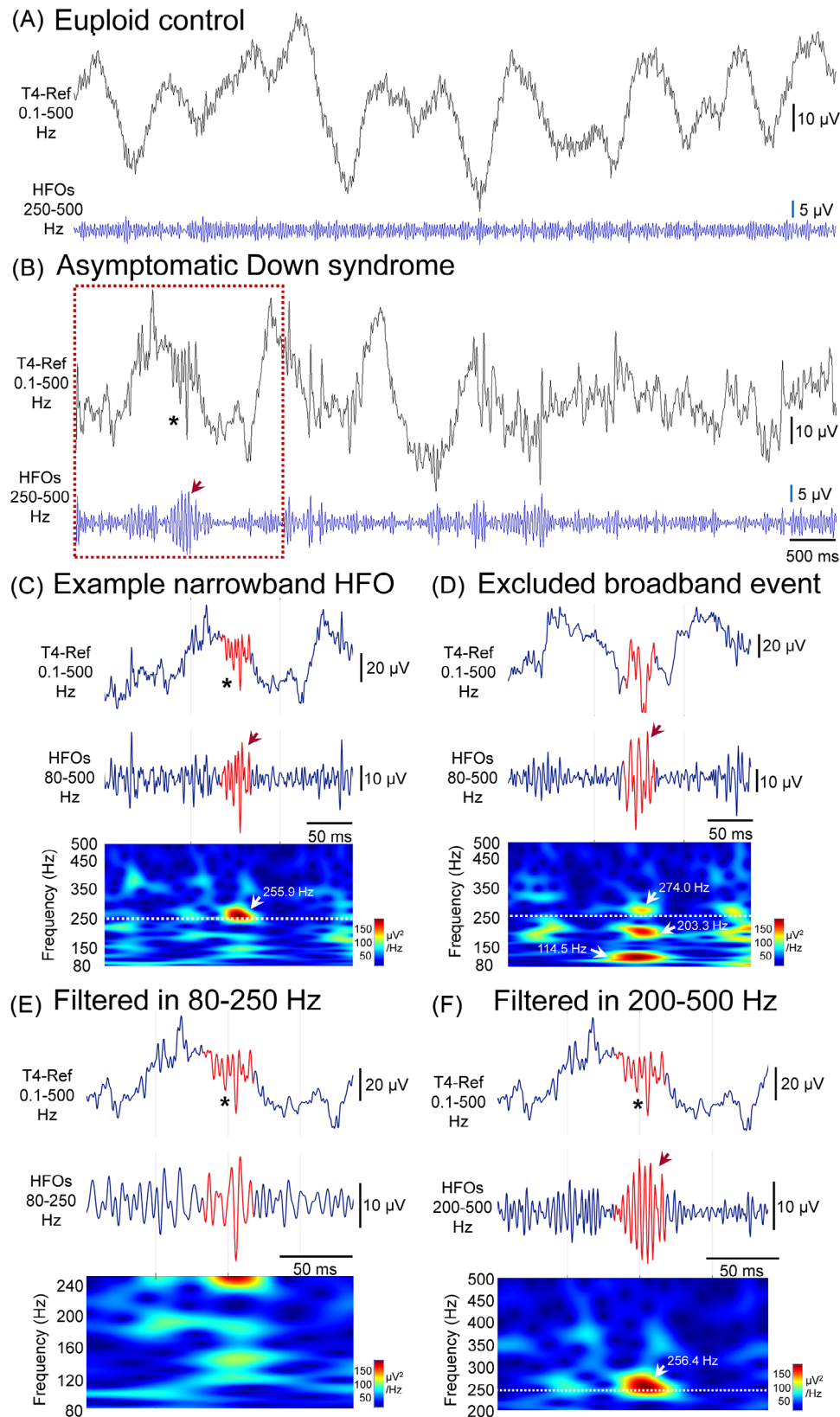


FIGURE 1 High-frequency oscillations (HFOs) recorded from asymptomatic individual with Down syndrome before Alzheimer's disease dementia diagnosis. (A) Example EEG recorded from a female euploid control subject. The upper trace shows raw (unfiltered, 0.1 to 500 Hz) EEG recorded from T4 channel. The lower trace (in blue) shows the same signal filtered in the 250- to 500 Hz frequency range. (B) Example EEG record from a female subject with DS containing HFOs. The red box marks a period when an HFO was detected by the algorithm. The asterisk marks an HFO in the raw signal and the red arrow the corresponding HFO in the filtered signal (C, F). (C) Spectral analysis of EEG period from panel (B) (red

To assess hemispheric asymmetry more quantitatively, we calculated an asymmetry index (AI)^{27,48} based on either HFO rates or the number of HFO-positive channels. The AI was computed using the following formula: $200 \times (\text{Right} - \text{Left}) / (\text{Right} + \text{Left})$. In HFO rates, “right” and “left” refer to the average HFO rates across the channels located in the right (i.e., Fp2, F8, F4, T4, C4, T6, P4, and O2) and left (i.e., Fp1, F7, F3, T3, C3, T5, P3, and O1) hemispheres, respectively. When it came to the number of channels, the number of HFO-positive channels in each hemisphere was used, regardless of HFO rate. A positive AI value indicates greater right-hemisphere predominance, a negative value left-hemisphere predominance; an AI of zero would suggest no lateral preference. We chose to calculate all AIs relative to the right hemisphere, as preliminary observations suggested that HFOs appeared to occur more frequently in the right hemisphere.

2.7 | Statistical analyses

All data are presented as a mean $\pm$ standard error of the mean (SEM), unless otherwise stated. When box plots are used in cases of non-Gaussian data distributions and to better display data distribution using quartiles, the central line of the box plot indicates the median, while the bottom and top edges of the box plot represent the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points. Statistical significance was set at $p < 0.05$. For statistical analyses, we used Prism (Graphpad). To test if the data fit a normal distribution, the Shapiro-Wilk test was used, and Brown-Forsythe was used to test the homogeneity of variance. Welch's correction was implemented when variances between two compared groups were unequal. To compare the means for the parametric data of two groups, we used unpaired two-tailed *t*-tests. To compare data within one group, we used paired two-tailed *t*-tests. When data did not fit a normal distribution, non-parametric statistics were used. The non-parametric test to compare two groups was the Mann-Whitney *U* test or the Wilcoxon signed-rank test. To test for significant deviations from zero (for AI indices), we used one-sample Wilcoxon signed-rank tests because of non-parametric data. For non-parametric data with more than two groups, Kruskal-Wallis was used, followed by Dunn's post hoc tests with corrections for multiple comparisons. For ANOVA with repeated measures, group comparisons were conducted using the Friedman test because of non-parametric data. When a statistically

significant main effect was found, Dunn's post hoc tests were used with corrections for multiple comparisons. We used linear regression for correlation analyses and the Pearson correlation coefficient (*r*) for parametric data and the Spearman *r* for non-parametric data. A Fisher's exact test was used to compare the percentage of participants with HFO-positive channels in the temporal and frontal lobes.

3 | RESULTS

3.1 | Demographics and clinical characteristics

Table 1 shows the clinical and demographic characteristics of the 19 subjects included in the study. We included 14 individuals with DS (78.5% female); five asymptomatic (aDS; 60.0% female), three prodromal/MCI (pDS/MCI; 66.7% female), and six AD dementia (dDS; 100% female). Thus, in total, nine participants were symptomatic (88.9% female). The ages between prodromal/MCI and those with AD dementia were significantly different (unpaired *t*-test, $t_{crit} = 2.83$, $p = 0.02$). Symptomatic cases (pDS/MCI and dDS) were older than asymptomatic individuals, 50.56 ± 1.5 versus 36.8 ± 2.0 , respectively (unpaired *t*-test, $t_{crit} = 5.43$, $p = 0.0002$). Five subjects were euploid controls (80.0% female) and were age-matched to the DS participants (unpaired *t*-test, $t_{crit} = 2.35$, $p = 0.04$), 55.00 ± 2.5 and 45.64 ± 2.1 years, respectively.

3.2 | HFOs in asymptomatic individuals with DS

We found no HFOs in our five euploid control individuals (Figure 1A). In contrast, we found HFOs during sleep in all asymptomatic DS cases (Figure 1B). The spectral analyses (Figure 1C) confirmed these results. Indeed, EEG records showed that during an HFO event, there was a distinct increase in spectral power within the 250- to 500-Hz frequency range (Figure 1C). This relatively narrowband increase in HFO activity contrasted with cases of broadband increase in HFO activity that we excluded from our analyses because they are often associated with artifacts or other sources of noise (e.g., Figure 1D).⁴⁹ The narrowband spectral profile of the HFOs we included in our analyses was further supported by additional bandpass filtering: filtering between 80 and 250 Hz failed to reveal a clear frequency island (Figure 1E), whereas filtering between 250 and 500 Hz highlighted a well-defined frequency

box). The upper trace is the raw signal, the middle trace is the same signal but filtered in the 80- to 500-Hz frequency range, and the bottom panel shows HFO power in the 80- to 500 Hz frequency range. Note the presence of a well-isolated island in the time-frequency domain during the detected HFO event (in red). The asterisk marks the HFO in the raw signal, and the red arrow marks the HFO detected by the algorithm in the filtered signal. The central frequency of this detected event was 255.9 Hz. The spectrogram color calibration is shown in $\mu V^2/\text{Hz}$, and the white horizontal dotted line indicates 250 Hz frequency. (D) Example of event excluded from analysis due to presence of multiple frequency islands in time-frequency domain. Notable peaks are observed at 114.5, 203.3, and 274.0 Hz. This pattern in the time-frequency domain is typically seen during artifactual events, which are often broadband in frequency. (E) The same event shown in panel (C), but bandpass filtered between 80 and 250 Hz to illustrate the absence of a distinct frequency island within this frequency range. Notably, HFO power begins to increase around 250 Hz. (F) The same event as in panel (C), but filtered between 200 and 500 Hz. The event displays a clear time frequency representation with a well-defined frequency island centered around 256.4 Hz. Note the oscillatory/sinusoidal morphology of the HFO in the filtered signal (red arrow). The white horizontal dotted line indicates the 250 Hz frequency.

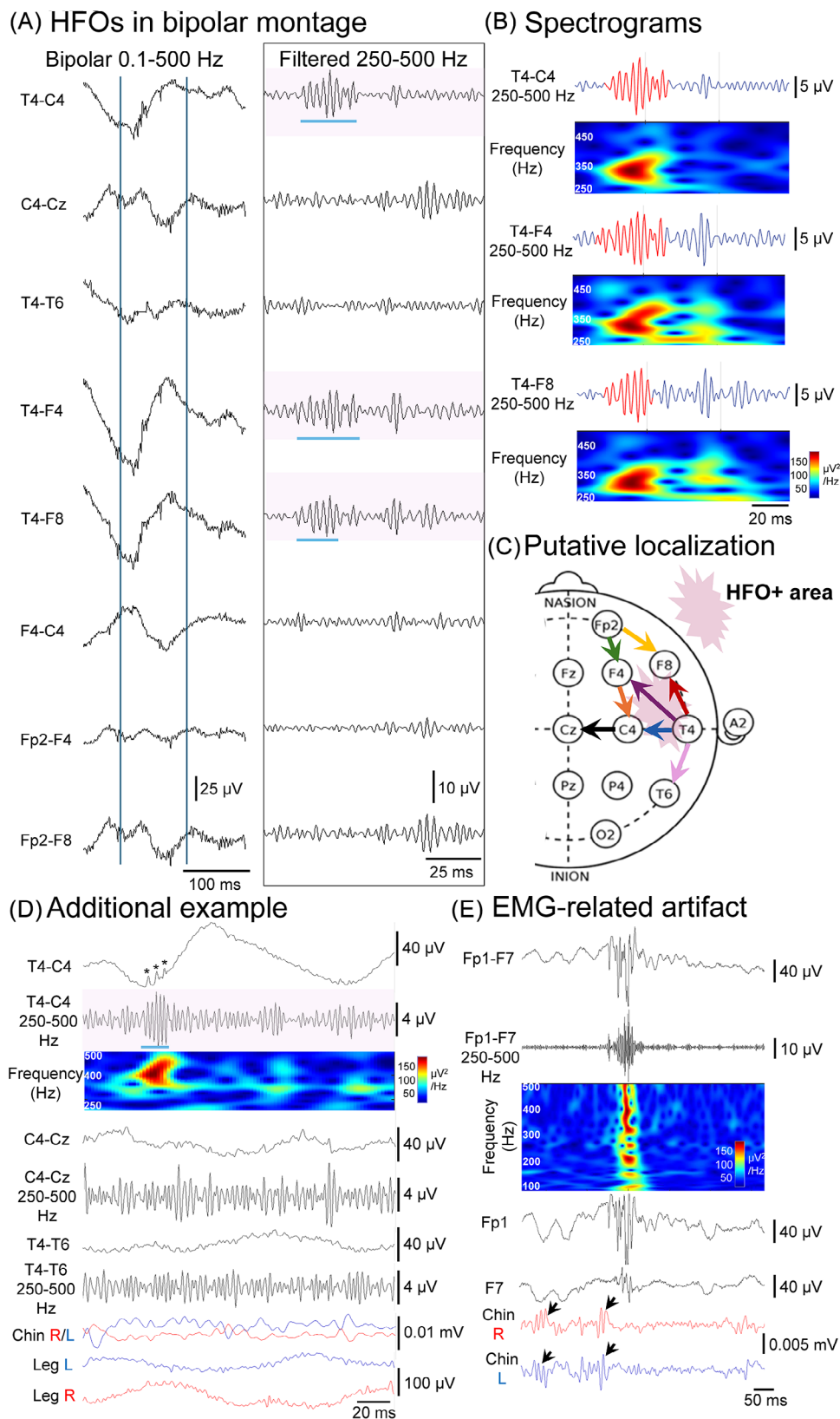


FIGURE 2 High-frequency oscillations (HFOs) in asymptomatic individuals using a bipolar montage. (A) Example bipolar montage used to assess HFOs. Traces on left show unfiltered signals (0.1 to 500 Hz), while traces on right are filtered in 250- to 500-Hz frequency range. The two blue vertical lines on the raw signal mark the period shown on the right, where the signals are filtered. Note the presence of HFOs (underlined events) in bipolar channels involving T4, C4, F4, and F8 channels, as well as their oscillatory morphology. (B) Spectral analyses of channels showing HFO activity from panel (A), using a bipolar montage. HFOs are marked in red, and the spectrogram displays frequencies between 250 and 500 Hz.

island characteristic of putative HFOs of cerebral origin (Figure 1F). However, it is important to acknowledge that definitively ruling out the contribution of artifacts to detected HFO activity remains challenging. To mitigate this, we implemented additional precautions to minimize the inclusion of artifactual events (see below regarding bipolar montage) as well as quantification of two distinct movements during sleep (Supplemental Figure 1A, B).

To further rule out the possibility that brief EMG bursts or artifacts originating from reference electrodes contributed to the observed HFOs, we conducted an additional analysis using a bipolar montage (Figure 2). This approach revealed that the HFO events included in our analyses were spatially restricted, typically seen in a few channels, involving the channel in which we detected the HFO (here channel T4) in the referential montage. The HFO showed oscillatory morphology (Figure 2A, right), and spectral analyses confirmed the presence of well-defined frequency islands across different electrode pairs involving the T4 channel (Figure 2B). Moreover, analyses across multiple bipolar channel combinations (Figure 2A, C, and D) indicated that HFOs were often confined to a rather limited number of channels, primarily in the temporal regions. In contrast, artifactual events were more spatially diffuse, involved multiple channels, were associated with detectable EMG/EOG activity, and displayed a broader frequency distribution across the 80- to 500-Hz frequency range (Figure 2E, see also Supplemental Figure 2A) – features consistent with EMG/EOG-related or other external artifacts. Lastly, we observed that artifacts exhibited markedly higher amplitudes when compared to both HFOs and the surrounding background activity (compare Figure 2A, D, E). They also displayed irregular morphology and pronounced amplitude fluctuations, often throughout the duration of the putative event. These distinguishing characteristics further support the validity of the detected HFOs as putative neural phenomena rather than artifactual events.

3.3 | HFOs in prodromal AD dementia

HFOs were also recorded in individuals with DS and prodromal AD dementia. A representative example from a participant with prodromal AD dementia showed HFOs on the T4 channel (Figure 3A). When analyzed using a bipolar montage (T4-T6), the trace revealed prominent

peaks, possibly reflecting deflections of an HFO occurring in the nearby temporal regions (Figure 3A, inset). Importantly, there was no evidence of EMG-related activity across four EMG channels at the time that the HFO occurred. Spectral analysis confirmed a concurrent increase in HFO power within the 250- to 500-Hz frequency range during this event (Figure 3B).

3.4 | HFOs in AD dementia cases

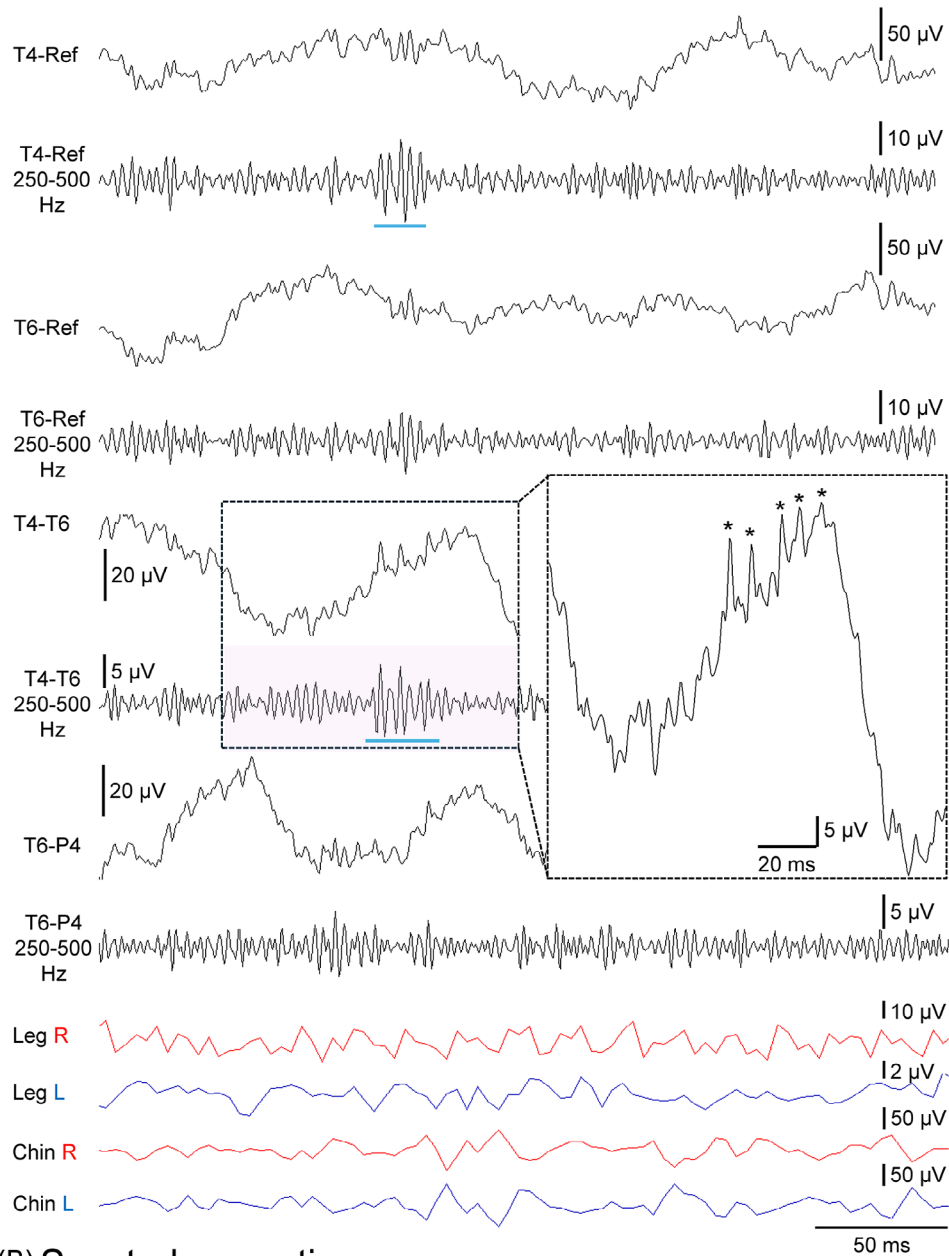
We also analyzed HFOs in individuals with DS who had a clinically confirmed diagnosis of AD dementia. A representative example of HFOs recorded from the F8 channel in a symptomatic participant with DS is shown in Figure 4A. Spectral analyses showed prominent frequency islands at the time that HFOs were detected (Figure 4B), similar to asymptomatic individuals (for comparison, see Figure 1C). However, it should be noted that HFOs in lower frequencies may also be present and may be accompanied by abnormal EEG activity (e.g., interictal spikes). Further analyses using a bipolar montage confirmed that HFOs were prominent in frontal electrodes (see example in Figure 4C, D). Additionally, we identified artifacts attributable to EOG-related activity or the filtering of sharp transients (Supplemental Figure 2A, B). Putative HFO activity associated with these events typically failed to meet our HFO inclusion criteria, also due to an insufficient number of oscillatory cycles (Supplemental Figure 2A, B).

3.5 | Quantification of event rates and the effect of age

We next quantified the total number of HFOs per minute (all channels) in all DS cases (Figure 5A). We found no differences in HFO rates between symptomatic and asymptomatic participants (unpaired t -test, $t_{crit} = 0.68$, $p = 0.50$; Figure 5B). Note that there was no difference in HFO-positive channels between prodromal/MCI and symptomatic AD dementia participants, so we pooled these two categories (Mann-Whitney U test, $U = 4$, $p = 0.26$). Next, we asked whether all recording channels showed HFOs. A significant difference was found between the number of channels with (5.0 ± 1.0 channels) and without (14.0 ± 1.0 channels) HFOs (paired t -test, $t_{crit} = 6.19$,

Note the presence of robust HFO power during the detected HFO event (highlighted in red). (C) Bipolar channel combinations and putative HFO localization. In this subject, T4 was subtracted from T6, C4, F4, and F8. Additional combinations included C4-Cz, F4-C4, Fp2-F4, and Fp2-F8. Not all combinations exhibited HFOs; rather, HFOs were observed in T4-C4, T4-F4, and T4-F8, suggesting that the putative HFO activity may be localized to the region surrounding these electrodes. The putative HFO-positive area is highlighted in red (HFO+). (D) Additional example of an HFO recorded in same participant with Down syndrome. Here, the T4-C4 channel pair showed an HFO. Deflections associated with HFO activity are visible in the bipolar trace (asterisks), along with a prominent frequency island coinciding with the putative HFO event (underlined). Note that there was no EMG-related activity in the chin (left and right) or leg (left and right) channels during the period surrounding the HFO. (E) Representative example of EMG-related artifact in the same participant. This event was excluded from the analyses as it displayed broadband activity across several channels and persisted even after bipolar montage subtractions. This artifact showed the highest amplitude in the frontal channels, particularly Fp1 – this disproportionate amplitude likely contributed to its persistence in the bipolar montage. Compared to the HFOs shown in panels (A), (B), and (D), as well as the ongoing background, this event exhibited greater amplitude and widespread spectral power across the entire 80- to 500-Hz frequency range, consistent with artifact characteristics. Notably, this event was preceded by chin movements (marked by black arrows).

(A) Prodromal AD dementia



(B) Spectral properties

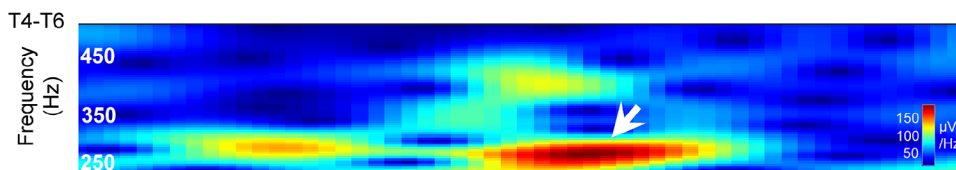
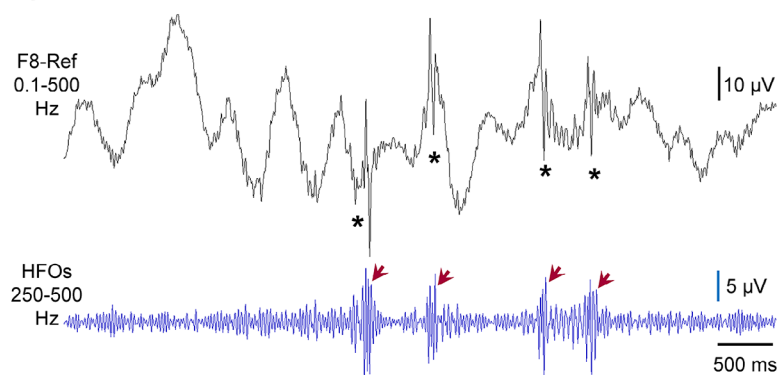
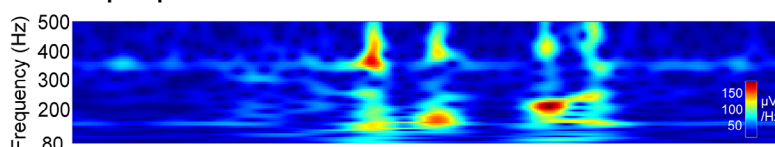


FIGURE 3 High-frequency oscillations (HFOs) in prodromal Alzheimer's disease dementia. (A) Example referential and bipolar montages used to assess HFOs. The top two sets of traces show channels T4 and T6, with HFO activity in T4 (underlined event). When T4 was subtracted from T6, spiky activity appeared in the bipolar trace (T4-T6; asterisks, see inset). An HFO was also visible in T4-T6, but not in T6-P4, suggesting possible localization of the HFO to the right temporal regions. Importantly, no evident EMG-related activity was observed in the chin or leg channels surrounding this event. Referential traces are shown in the 0.1- to 500-Hz frequency range; filtered traces are shown in the 250- to 500-Hz frequency range. (B) Spectral analysis of T4-T6 bipolar channel showing robust HFO activity (white arrow) within the 250- to 500-Hz frequency range corresponding to the event shown in panel (A) (T4-T6, 250 to 500 Hz trace).

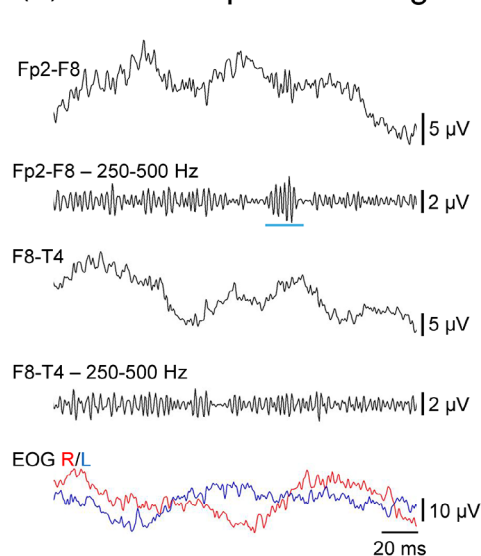
(A) Symptomatic AD dementia



(B) Spectral properties



(C) HFOs in bipolar montage



(D) HFOs during interictal spike

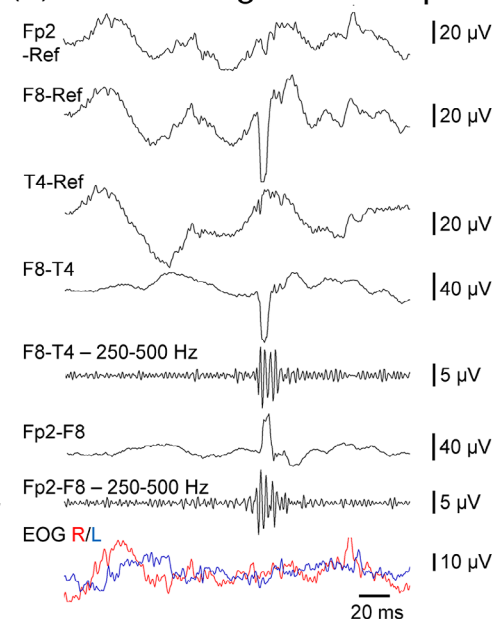


FIGURE 4 High-frequency oscillations (HFOs) recorded from a symptomatic individual with Down syndrome (DS) and Alzheimer's disease (AD) dementia diagnosis. (A) EEG recorded from female subject with DS and AD dementia diagnosis is shown. Upper trace shows raw (unfiltered, 0.1 to 500 Hz) EEG recorded from F8 channel. Lower trace (in blue) shows the same signal filtered in the 250- to 500-Hz frequency range for HFOs. Asterisks mark HFOs in raw signal, and red arrows mark HFOs in filtered signal. (B) Spectral analyses of HFOs showing robust HFO power in 80- to 500-Hz frequency range. Note the presence of isolated islands that correspond to HFOs in the filtered trace, which are marked by red arrows in panel (A). The spectrogram calibration is shown in $\mu\text{V}^2/\text{Hz}$. (C) Example of an HFO from same subject shown in bipolar montage. Channels Fp2-F8 and F8-T4 were subtracted, and both the raw and filtered traces (250 to 500 Hz) are displayed. An HFO is visible in the Fp2-F8 but not in the F8-T4 channel. Note that simultaneous electrooculographic (EOG) signals showed no significant activity during or surrounding the HFO event. (D) HFOs observed during an interictal epileptiform discharge (interictal spike). Three channels are shown in a referential montage (Fp2, F8, T4), with an interictal spike evident in channel F8. Bipolar pairs F8-T4 and Fp2-F8 exhibited inverse polarity during the spike event and concurrent HFOs in both channels. Note that there was no coincident or surrounding EOG activity around this event, suggesting that the event was not related to eye movement artifacts. Other electromyographic channels (chin, leg) were also not active (not shown).

TABLE 1 Demographics and clinical characteristics.

Subject ID	Cohort	Age	Sex	Handedness	History of seizures or LOMEDS?	Medications
Subject 1	Asymptomatic	33	Female	Right	No	
Subject 2	Asymptomatic	37	Female	Right	No	Sertraline, levothyroxine
Subject 3	Symptomatic AD dementia	48	Female	Right	No	
Subject 4	Euploid control	58	Female	Not recorded	No	
Subject 5	Euploid control	52	Female	Right	No	
Subject 6	Symptomatic AD dementia	51	Male	Right	No	Tradozone, rosuvastatin quetiapine, brivaracetam
Subject 7	Symptomatic AD dementia	41	Female	Right	No	Levothyroxine, mirtazapine, sertraline, levonorgestrel + ethinylestradiol
Subject 8	Prodromal (mild cognitive impairment)	54	Male	Right	No	Levothyroxine, omeprazole, hyoscine butylbromide, mesalamine, levetiracetam
Subject 9	Prodromal non-degenerative cognitive disorder (mild cognitive impairment)	56	Female	Right	No	Enalapril, quetiapine
Subject 10	Symptomatic AD dementia	49	Female	Right	No	Donepezil, paracetamol, allopurinol, escitalopram, esomeprazole, levothyroxine, ipratropium, diazepam, salmeterol/fluticasone
Subject 11	Euploid control	47	Female	Right	No	
Subject 12	Symptomatic AD dementia	49	Female	Right	No	Donepezil, escitalopram, trazodone, acetaminophen
Subject 14	Euploid control	56	Female	Not recorded	No	
Subject 16	Euploid control	62	Male	Right	No	
Subject 17	Symptomatic AD dementia	52	Female	Right	No	
Subject 19	Asymptomatic	37	Male	Left	No	Levothyroxine
Subject 23	Prodromal (mild cognitive impairment)	55	Female	Right	No	
Subject 28	Asymptomatic	33	Male	Right	No	Levothyroxine
Subject 29	Asymptomatic	44	Female	Ambidextrous	No	Levothyroxine

Note: Asymptomatic = participants without clinical or neuropsychological suspicion of Alzheimer's disease (AD)-related cognitive decline. Prodromal = participants with evidence of AD-related cognitive decline, but with no significant impact on daily life activities. Symptomatic AD dementia = participants with cognitive decline that impaired their daily activities and a diagnosis of AD dementia.

Abbreviation: LOMEDS, late-onset myoclonic epilepsy in Down syndrome.

$p < 0.0001$; Figure 5C). A Friedman test showed that the HFO rate was dependent on the recording channel (Friedman test $[19] = 66.35$, $p < 0.0001$; Figure 5D). However, by conducting post hoc tests, we failed to show differences in HFO rates between individual channel pairs (all post hoc comparisons $p > 0.05$; Figure 5D). Although in the right hemisphere more channels appear to show increased HFO activity, HFO rates between these channels were not significantly correlated (Supplemental Figure 3A–C).

We also asked whether and how HFOs may change with age. To that end, we correlated the number of HFOs per minute with the age of each participant (Figure 6A). We found a trend suggesting increasing rates of HFOs with age in participants with DS, which warrants further confirmation (Pearson $r = 0.46$, $p = 0.09$; Figure 6A). We also correlated the

number of HFO-positive channels with the age of each participant and found no significant differences (Pearson $r = 0.24$, $p = 0.38$; Figure 6B).

Additionally, we examined whether the timing of the wideband EEG recording relative to diagnosis affected HFO measurements. Most participants underwent wideband EEG in the same year as their diagnosis (Figure 6C). We found no significant differences in HFO rates between participants recorded within the same year versus those recorded ≥ 1 year after diagnosis (unpaired t -test, $t_{crit} = 0.95$, $p = 0.37$; Figure 6D, E). Similarly, no significant difference was observed in the number of HFO-positive channels (unpaired t -test, $t_{crit} = 1.44$, $p = 0.19$; Figure 6F, G). These findings highlight the need for longitudinal recordings to better understand whether and how HFO rates and spatial distribution may evolve.

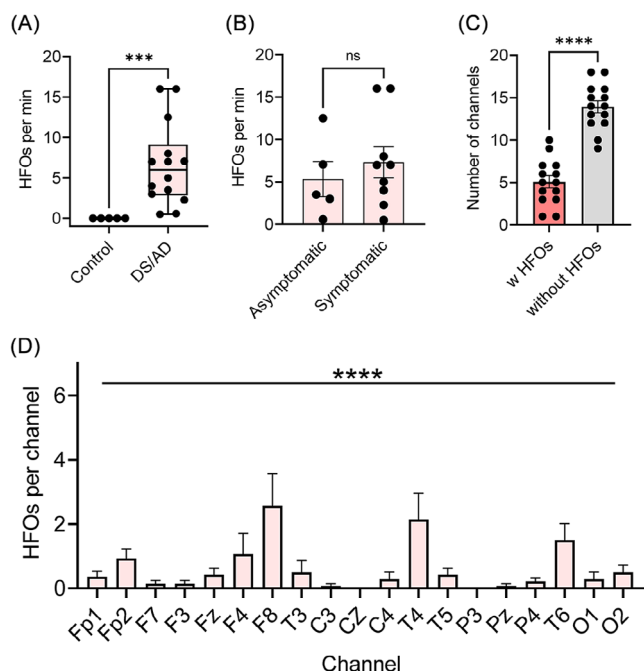


FIGURE 5 High-frequency oscillation (HFO) rates and localization in asymptomatic and symptomatic individuals with Down syndrome (DS). (A) HFOs were more frequent in individuals with DS compared to euploid controls who showed no HFOs (Mann-Whitney U test, $U = 0$, $p = 0.0002$). The central line shows the median, while the bottom and top edges of the box plot indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points. (B) HFO rates were not different between asymptomatic ($n = 5$) and symptomatic (prodromal/mild cognitive impairment and Alzheimer's disease dementia; $n = 9$) participants (unpaired t -test, $t_{crit} = 0.68$, $p = 0.50$). (C) HFOs were detectable in a fraction of recording electrodes. Indeed, the number of electrodes that showed and did not show HFOs was significantly different (paired t -test, $t_{crit} = 6.19$, $p < 0.0001$). (D) The mean number of total HFOs per channel is shown. A Friedman test showed a significant effect between HFO rate per minute and recording channel (Friedman test [19] = 66.35, $p < 0.0001$). However, by conducting post hoc tests, we failed to see significant differences in the mean number of HFOs between the different channels (all $p > 0.05$).

3.6 | Hemispheric asymmetry and regional distribution differences in asymptomatic and symptomatic individuals

Quantification of HFO rates suggested that frontal (Fp1, F8), temporal (T4, T6), and occipital (O2) channels may be among the most frequently capturing HFO channels (Figure 5D). These observations raised the possibility that the right hemisphere may harbor more HFO-generating regions. To test this, we compared the number of HFO-positive channels between the left and right hemispheres in each participant (Figure 7A). The overall HFO rates differed between hemispheres (Wilcoxon signed-rank test, $p = 0.001$), and there were significantly more HFO-positive channels in the right hemisphere (Wilcoxon signed-rank test, $p = 0.002$). Across all participants, 71.5% showed more

HFO-positive channels in the right hemisphere (Figure 7A). Strikingly, all asymptomatic individuals exhibited right-hemisphere dominance in HFO-positive channels, compared to 66.7% of prodromal/MCI and 50% of AD dementia cases (Figure 7A). To further evaluate hemispheric asymmetry more quantitatively, we calculated an AI based on both HFO rates and the number of HFO-positive channels. When all participants were analyzed together, there was no significant deviation from zero (i.e., no overall hemispheric asymmetry; Figure 7B). However, separate analyses of asymptomatic and symptomatic (prodromal/MCI and AD dementia) groups revealed significant differences. A Kruskal-Wallis test identified group differences in AI based on HFO rates (Kruskal-Wallis test, $H[3] = 9.41$, $p = 0.009$; Figure 7C), with Dunn's post hoc tests showing significant asymmetry in asymptomatic individuals ($p = 0.006$; Figure 7C), but not in symptomatic cases ($p = 0.57$; Figure 7C). Similar results were obtained for the number of HFO-positive channels (Kruskal-Wallis test, $H[3] = 10.60$, $p = 0.005$, Dunn's post hoc test, for asymptomatic, $p = 0.003$, symptomatic, $p = 0.72$; Figure 7D). These findings suggest that hemispheric laterality should be considered when evaluating HFO-related biomarkers.

Lastly, we examined whether the regional distribution of HFO-positive channels differed between asymptomatic and symptomatic cases. Specifically, we assessed the percentage of participants with at least one HFO-positive channel in the temporal and frontal lobes. All asymptomatic individuals had at least one HFO-positive channel in the temporal lobe (Figure 7E), compared to only 66.7% of symptomatic cases. In contrast, all symptomatic participants had at least one channel in the frontal lobe, whereas this was true for 80% of asymptomatic individuals (Figure 7F). A Fisher's exact test confirmed that HFO-positive channels were more frequently seen in the temporal lobe in asymptomatic individuals and in the frontal lobe of symptomatic cases (Fisher's exact test, $p = 0.003$; Figure 7G).

3.7 | Influence of epileptiform activity

We found that 57% (8/14) of participants with DS exhibited epileptiform activity (EDS), while the remaining 43% (6/14) did not (NEDS). None of the five euploid controls showed epileptiform activity. Notably, in 62.5% (5/8) of the EDS cases, epileptiform activity was predominantly observed in the left hemisphere (most frequently in channels F3, T3, F7, O1, and T5), while 37.5% (3/8) showed right-hemisphere activity, primarily in channels T4, T6, O2, and F8. Among the EDS cases, 25% (2/8) were asymptomatic, 12.5% (1/8) were prodromal/MCI, and 65.5% (5/8) were symptomatic AD dementia cases. Comparisons between EDS and NEDS groups revealed no significant differences in HFO rates (unpaired t -test, $t_{crit} = 0.77$, $p = 0.45$) or the number of HFO-positive channels (unpaired t -test, $t_{crit} = 0.71$, $p = 0.49$). These findings suggest that the presence of epileptiform activity may not significantly influence HFO rates or their spatial distribution in this DS cohort. Interestingly, unlike HFOs, interictal spikes appear to be more frequently lateralized to the left hemisphere.

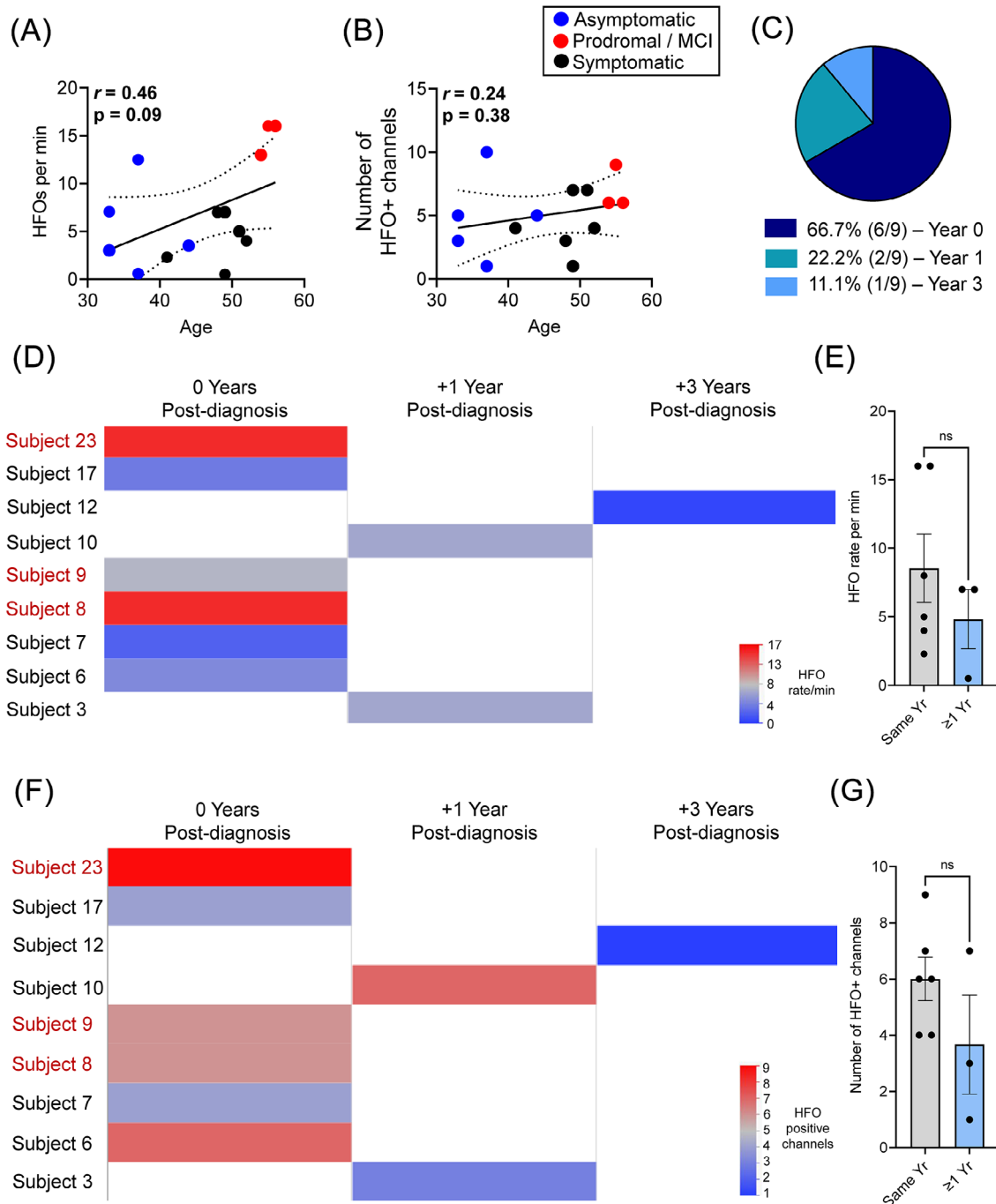
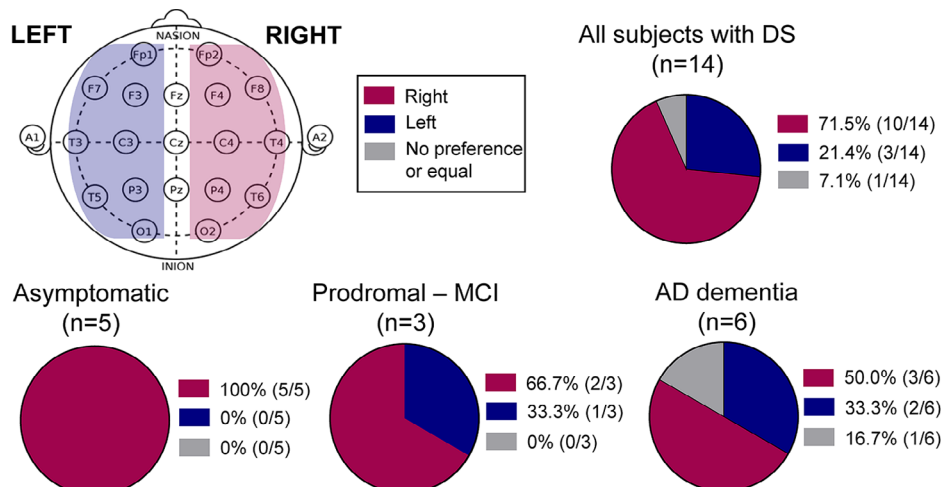
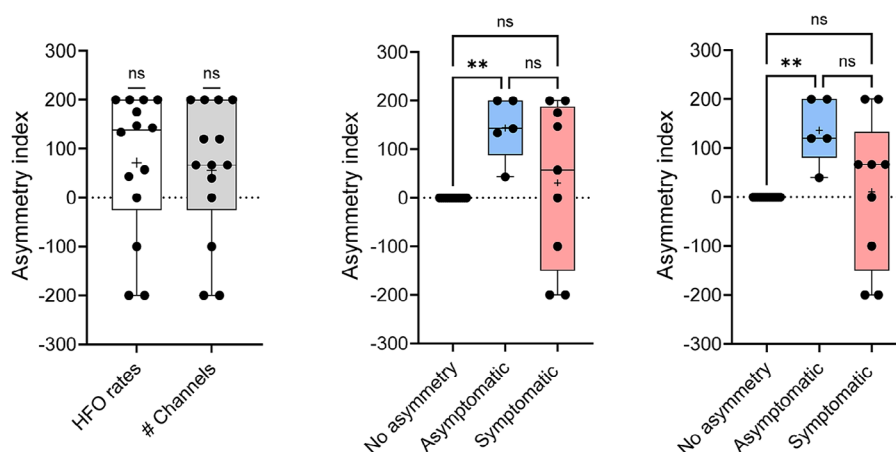


FIGURE 6 Correlation between high-frequency oscillation (HFO) rates and age of participants with Down syndrome (DS). (A) The rate of HFOs per minute showed no statistically significant linear correlation with age of participants with DS (Pearson $r = 0.46$, $p = 0.09$). Asymptomatic cases are shown in blue, prodromal/mild cognitive impairment (MCI) cases in red, symptomatic ones in black. (B) Same as in panel (A), but the number of HFO-positive channels is shown. We found no significant linear correlation between the age of participants with DS and the number of HFO-positive channels (Pearson $r = 0.24$, $p = 0.38$). (C) Percentage of participants that underwent wideband EEG within the same year as their diagnosis, 1 year later, or 3 years later. Note that most participants underwent wideband EEG in the same year as their symptomatic or prodromal/MCI diagnoses. (D) HFO rate per participant and year of Alzheimer's disease (AD) dementia or prodromal/MCI diagnosis. Participants 8, 9, and 23, diagnosed with prodromal/MCI, are highlighted in red; all others were diagnosed with AD dementia. (E) No significant difference in HFO rates was found between symptomatic individuals who underwent wideband EEG in the same year as their diagnosis and those recorded ≥ 1 year following diagnosis (unpaired t -test, $t_{crit} = 0.95$, $p = 0.37$). (F) Same as in (D), but the number of HFO-positive channels is shown. (G) No significant difference in the number of HFO-positive channels was found between symptomatic individuals who underwent wideband EEG in the same year as their diagnosis and those recorded ≥ 1 year after diagnosis (unpaired t -test, $t_{crit} = 1.44$, $p = 0.19$).

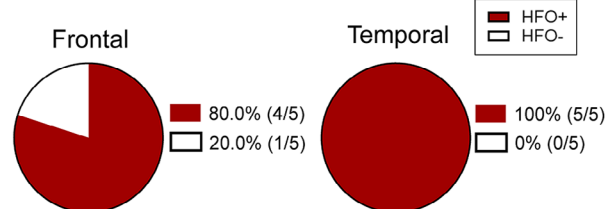
(A) Laterality (number of HFO-positive channels)



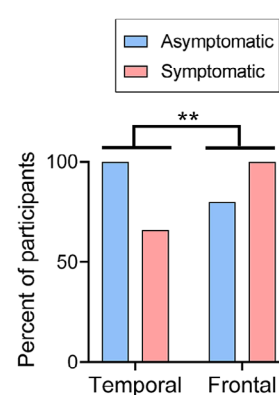
(B) AI – All participants (C) AI – HFO rates (D) AI – # Channels



(E) Asymptomatic cases



(G) Temporal vs Frontal



(F) Symptomatic and Prodromal cases

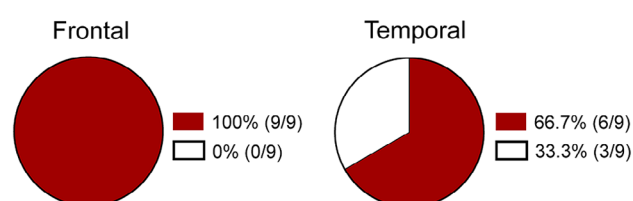


FIGURE 7 Hemispheric asymmetry and regional distribution of high-frequency oscillations (HFOs) in asymptomatic versus symptomatic cases. (A) The majority of participants exhibited a greater number of HFO-positive channels in the right hemisphere. The distribution of participants across categories – right dominant, left dominant, and no hemispheric preference or equal – is presented for each group: all subjects with Down syndrome (DS), as well as asymptomatic, prodromal/mild cognitive impairment (MCI), and Alzheimer's disease (AD) dementia subgroups. (B) Asymmetry indices (AIs) were assessed across all participants (asymptomatic, prodromal/MCI, and AD dementia cases). No statistically significant deviation from zero (i.e., no asymmetry) was found for either HFO rates (one-sample Wilcoxon signed-rank test, $p = 0.13$) or

4 | DISCUSSION

The finding of HFOs in all DS cases but none of the euploid controls is striking and deserves further investigation. The two possible interpretations are that (1) HFOs are related to DS, but not AD dementia in DS, and that (2) HFOs are related to AD dementia in DS, but occur before symptomatic AD. Our data suggesting that HFO rates may change with age would support the latter interpretation, although more studies are needed to confirm this finding.

The use of EEG in neuropsychiatric disease has primarily focused on recording brain activities within the classic Berger frequencies,⁵⁰ which typically include oscillations <70 Hz.³² Historically, the EEG yielded a low EEG abnormality detection rate, which hindered further implementation unless there was a history of seizures or epilepsy.⁵⁰ Indeed, only a fraction of patients with AD show abnormal EEG activity, which ranged between 22% and 53%.^{47,51} Here, we found HFOs in all individuals with DS, suggesting that HFOs are abundant in DS. This finding contrasts with the partial prevalence of epileptiform activity in the same population, which was 57%. One possible explanation would be that HFOs relate to DS *per se*. If so, then HFOs may contribute to intellectual disability by interfering with memory consolidation during sleep.⁵²

If HFOs are related to the AD pathophysiology in DS, they may have predictive value. Our data showing a trend toward increased HFO rates with age are encouraging, although more studies are needed. Our study on mouse models suggested that HFOs occurred before overt AD-related neuropathology (e.g., A β plaques) developed and at an age when memory is not yet impaired.²⁶ We also found that HFOs continued to occur when mice developed A β plaque pathology, supporting longitudinal EEG investigations. Here, we found that HFOs persisted in symptomatic individuals. This finding would allow us to compare and contrast their occurrence before and after AD dementia diagnosis in DS. Although we failed to see differences in HFO rates between asymp-

tomatic and symptomatic cases, this may be related to the relatively small sample size. Nevertheless, we cannot exclude the possibility that HFOs change in other ways besides their rate, which we did not address here.

We determined that asymptomatic cases exhibited hemispheric laterality, a feature not consistently present in all symptomatic individuals. Although longitudinal recordings are needed to conclusively address this finding, it is possible that HFOs initially emerge as a right-predominant phenomenon, presumably confined to one hemisphere, and subsequently expand – in rates, as suggested by our age-correlated measurements, and/or spatially. The potential spatial expansion of HFOs upon AD dementia diagnosis may involve their emergence in regions beyond one hemisphere, as symptomatic cases did not consistently exhibit hemispheric laterality. One contributing mechanism could involve the spread of tau pathology, which is known to be exacerbated by increased neuronal activity.⁵³ Interestingly, a genetic manipulation that reduces endogenous tau in a mouse model was shown to protect against neuronal hyperexcitability and associated memory deficits.⁵⁴ Although it is currently unknown whether and how reducing HFOs might influence disease outcomes, we found that selective disruption of HFOs in epilepsy models could restore memory function.⁵⁵ Considering the promising efficacy of interventions that aim to ameliorate the incidence of HFOs – including pharmacological interventions^{27,56} that may not disrupt normal frequencies⁵⁷ – these interventions are especially warranted and hold therapeutic promise.

A study of subjects with epilepsy suggested that larger lesions were associated with more scalp HFOs.⁵⁸ Thus, in the future, it would be insightful to test whether HFOs were associated with areas of neuropathology. Interestingly, epileptiform activity in patients with AD has been recorded from sites with increased tau pathology using foramen ovale electrodes.⁵⁹ Considering that a wide range of HFOs can be recorded non-invasively from the scalp across different ages,^{18,22,58,60–62} they can potentially be studied using non-invasive

the number of HFO-positive channels (one-sample Wilcoxon signed rank test, $p = 0.17$), indicating no pronounced hemispheric asymmetry. The central line shows the median, while the bottom and top edges of the box plot indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points. (C) AIs were compared between asymptomatic participants, symptomatic participants (including prodromal/MCI and AD dementia cases), and a group with no asymmetry to test deviation from zero and, thus, no asymmetry (matched in number to the asymptomatic and symptomatic groups). A Kruskal-Wallis test showed a significant overall difference between the groups (Kruskal-Wallis test, $H[3] = 9.41$, $p = 0.009$). Dunn's post hoc analyses indicated a significant difference between asymptomatic and no-asymmetry cases ($p = 0.006$), but not between symptomatic and no-asymmetry cases ($p = 0.57$). No significant difference was found between asymptomatic and symptomatic groups ($p = 0.19$). The central line shows the median, while the bottom and top edges of the box plot indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points. (D) Similar to panel (C), but the number of HFO-positive channels is shown. A Kruskal-Wallis test revealed a significant difference between asymptomatic, symptomatic, and no-asymmetry cases (Kruskal-Wallis test, $H[3] = 10.60$, $p = 0.005$). Dunn's post hoc analyses showed a significant difference between asymptomatic and no-asymmetry cases ($p = 0.003$), but not between symptomatic and no-asymmetry cases ($p = 0.72$). No significant difference was observed between asymptomatic and symptomatic groups ($p = 0.10$). The central line shows the median, while the bottom and top edges of the box plot indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points. (E) Percentage of asymptomatic cases with at least one HFO-positive channel in temporal (T3, T5, T4, T6) and frontal (Fp1, F7, F3, Fp2, F8, F4) lobes. All asymptomatic cases exhibited at least one HFO-positive channel in the temporal lobe, whereas 80% showed at least one in the frontal lobe. (F) Percentage of symptomatic (prodromal/MCI and AD dementia) cases with at least one HFO-positive channel in the temporal (T3, T5, T4, T6) and frontal (Fp1, F7, F3, Fp2, F8, F4) lobes. All symptomatic cases showed at least one HFO-positive channel in the frontal lobe, whereas 66.7% showed at least one in the temporal lobe. (G) Distribution of HFO-positive channels across temporal and frontal lobes, along with percentage of asymptomatic and symptomatic participants in each region. Temporal lobe HFO-positive channels were more prevalent in asymptomatic participants, whereas frontal lobe HFO-positive channels in symptomatic individuals (Fisher's exact test, $p = 0.003$).

methods, including MEG.^{63,64} Remarkably, HFOs (80 to 500 Hz) have been identified in individuals with clinically diagnosed AD dementia²⁷; however, the reported rates appeared lower than those observed in the current study. One possible explanation for this is that nocturnal sleep recordings – used in our study – may be more sensitive in capturing HFOs compared to quiet daytime wakefulness,³⁷ though a direct, within-subject comparison is necessary to confirm this hypothesis. Nevertheless, the ability to co-register tau-positron emission tomography (PET) imaging with high-density EEG or MEG offers a compelling opportunity to examine the potential overlap between HFO hotspots and regions of elevated tau-PET signal. This approach may yield valuable insights into the relationship between HFO hotspots and key neuropathological features of AD dementia.

HFOs may also relate to epileptogenicity. Prior epilepsy work showed that scalp HFOs could predict future seizure development in children.⁶⁵ We previously found more HFOs in an AD mouse line exhibiting seizures (versus no seizures) as well as during seizure events.²⁶ Thus, future longitudinal EEG studies will be insightful in determining whether HFOs correlate with the development of epilepsy in DS by enrolling cases with and without LOMEDS.

An interesting observation of this study is that epileptiform activity (interictal spikes) may show an opposing hemispheric dominance compared to HFOs. To our knowledge, this is the first report to document such laterality differences across two distinct EEG abnormalities in individuals with DS. Historically, epileptiform activity in AD dementia has been reported to involve predominantly the left hemisphere,^{47,51} which aligns with our observation in this DS cohort. However, other studies have demonstrated right-hemispheric dominance of epileptiform discharges and seizure onset zones in AD dementia cases with comorbid epilepsy, based on both scalp EEG^{48,51} and MEG²⁷ recordings. This pattern closely resembles the right-hemisphere dominance of HFOs observed in our asymptomatic DS cases, although none of these cases had a LOMEDS diagnosis. Considering that the HFOs analyzed in this study are more closely associated with epileptogenicity,^{37–39} it is plausible that the right hemisphere may play a role in the emergence of seizure-related activity in this population. Alternatively, considering that individuals with DS often exhibit right-hemisphere speech-related dominance, these laterality differences may also reflect underlying speech-related functional processes.⁶⁶

In this study, most of the individuals were females; thus, replication of our findings in males is critical. We were also limited by the number of participants, especially asymptomatic cases, where HFOs could be an early biomarker. Our study may have underestimated the area or number of HFOs that occurred because of the relatively low number of channels. However, we chose to start with the 10-20 system because it is widely available internationally, and future use of high-density EEG/MEG recordings is encouraged. Since epilepsy HFOs are reduced by anti-seizure medications,⁶⁷ including those used in DS (e.g., levetiracetam), it would be important to test if this is the case for HFOs in DS as well. In this regard, it is encouraging that levetiracetam was effective in reducing HFOs in AD dementia cases with comorbid epilepsy,²⁷ supporting the notion that HFOs in these cases possibly reflect underlying hyperexcitability. Because HFOs occur during a sleep stage when

A β clearance is highest,^{68–70} they may interfere with normal A β clearance, thus, future correlations between HFO rates and A β levels are warranted.

A couple of key questions will be important to address in future studies. For instance, do HFOs contribute to memory deficits, and would a reduction in HFOs be associated with better memory performance? Do HFO rates fluctuate over time or show variability in space?⁷¹ Would HFOs contribute to sleep disturbances, including obstructive sleep apnea, which is highly prevalent in the DS population?³⁵ Lastly, how HFOs may be affected by anti-amyloid therapies is another open question.

We propose that wideband EEG should be used in the context of DS and AD, as it may reveal previously unknown EEG disturbances. It only requires relatively simple modifications, such as changes in sampling frequency and acquisition filters, and the use of equipment that is already available in most sleep labs worldwide. Comparisons of HFOs with other AD-related biomarkers are necessary to determine whether they emerge when other biomarkers are relatively low or undetected. Lastly, it is also important to test if tau and amyloid PETs would show increased positivity in brain regions where HFOs are detected. If not, HFOs may predict areas of future neuropathology and assist in determining promising areas that focused ultrasound could be directed when combined with anti-amyloid immunotherapy⁷² to potentially maximize therapeutic benefits.

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CONFLICT OF INTEREST STATEMENT

Christos Panagiotis Lisgaras has no conflicts of interest to report. Sandra Giménez reported receiving personal fees for service on the advisory boards, speaker honoraria, or educational activities from Esteve, Indorsia, and Biogen. María Carmona-Iragui reported receiving personal fees for service on the advisory boards, speaker honoraria, or educational activities from Esteve, Lilly, Neuraxpharm, Adium, and Roche. Juan Fortea reported receiving personal fees for service on the advisory boards and adjudication committees or speaker honoraria from AC Immune, Adamed, Alzheon, Biogen, Eisai, Esteve, Fujirebio, Ionis, Laboratorios Carnot, Life Molecular Imaging, Lilly, Lundbeck, Novo Nordisk, Perha, Roche, Zambón, and outside the submitted work. Juan Fortea reports holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to ADx, EPI8382175.0). Ricardo S. Osorio reports honoraria from Idorsia Pharmaceuticals. Author disclosures are available in the [Supporting Information](#).

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