Neurophysiological trajectories in Alzheimer's disease progression

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Abstract Alzheimer's disease (AD) is characterized by accumulation of amyloid-β and misfolded tau proteins causing synaptic dysfunction and progressive neurodegeneration and cognitive decline. Altered neural oscillations have been consistently demonstrated in AD. However, the trajectories of abnormal neural oscillations in AD progression and their relationship to neurodegeneration and cognitive decline are unknown. Here, we deployed robust event-based sequencing models (EBMs) to investigate the trajectories of long-range and local neural synchrony across AD stages, estimated from resting-state magnetoencephalography. Increases in neural synchrony in the delta-theta band and decreases in the alpha and beta bands showed progressive changes along the EBM stages. Decreases in alpha and beta-band synchrony preceded both neurodegeneration and cognitive decline, indicating that frequency-specific neuronal synchrony abnormalities are early manifestations of AD pathophysiology. The long-range synchrony effects were greater than the local synchrony, indicating a greater sensitivity of connectivity metrics involving multiple regions of the brain. These results demonstrate the evolution of functional neuronal deficits along the sequence of AD progression.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by amyloid-β (Aβ) and neurofibrillary tangles of abnormally phosphorylated tau (***DeTure and Dickson*** (***2019***)). Clinical and epidemiological studies have suggested that Aβ accumulation occurs early in the timeline of neuropathological changes in AD, likely preceding the accumulation of tau, and subsequent neurodegeneration and cognitive decline (***Jack Jr et al., 2010***; ***Sperling et al., 2011***). The neuropathological changes of AD are therefore described as a continuum, starting from the presymptomatic stage of proteinopathy and continuing to progress during the symptomatic stage with increasing stages of disease severity (***Sperling et al., 2011***; ***Jack Jr et al., 2018***). Transgenic mouse models of AD have shown that AD proteinopathy of Aβ and tau is associated with synaptic and circuit dysfunctions in neural networks (***Busche et al., 2008***; ***Ahnaou et al., 2017***; ***Busche et al., 2019***). However, the

temporal change in synaptic and circuit dysfunction along disease progression in patients with AD remains largely unknown.

Functional deficits in neural networks, especially in the presymptomatic stage, have attracted attention in recent years with the rapidly evolving landscape of plasma-biomarkers of early detection and the novel therapeutics showing the benefits of early intervention (***Dubois et al., 2016***). In fact, abnormal synchrony of neural oscillations has been reported not only in patients along the clinical spectrum of AD, including mild cognitive impairment (MCI) due to AD and AD-dementia (***Jeong, 2004***; ***Fernández et al., 2006***; ***Stam et al., 2006***; ***Koelewijn et al., 2017***; ***Nakamura et al., 2018***; ***Hughes et al., 2019***; ***Ranasinghe et al., 2020***; ***Meghdadi et al., 2021***; ***Schoonhoven et al., 2022***) but also during the preclinical stages of AD (***Nakamura et al., 2018***; ***Ranasinghe et al., 2022a***). Neuronal oscillations observed by noninvasive electrophysiological measures, such as electroencephalography (EEG) and magnetoencephalography (MEG), represent the synchronized activity of excitatory and inhibitory neurons and thus provide sensitive indices of altered neuronal and circuit functions in AD. As synaptic dysfunction is strongly associated with AD proteinopathy, altered synchrony of neural oscillations may capture the early functional deficits of neural networks even before clinical symptoms appear. However, it remains unknown which neurophysiological signature changes capture such deficits and the temporal evolution of these changes along the timeline of preclinical to MCI to AD dementia stages in clinical populations.

In this study, we investigated the trajectories of neurophysiological changes along the course of clinical AD progression, by examining long-range and local neural synchrony patterns in the resting brain. We hypothesized that frequency-specific long-range and local synchrony abnormalities in neuronal oscillations may precede both neurodegeneration and cognitive deficits. To examine the temporal relationship amongst altered neural synchrony, neurodegeneration, and cognitive deficits, we used data-driven disease progression models–event-based sequencing models (EBMs), which have been successfully used to predict AD progression from cross-sectional biomarker data (***Fonteijn et al., 2012***; ***Young et al., 2014***, ***2018***). In an EBM, disease progression is described as a series of discrete events, defined as the occurrence of a particular biomarker reaching a threshold abnormal value, and the estimated likelihood of temporal sequence of events defines the disease trajectory. Modifying the conventional EBMs, to find the neurophysiological trajectories, we developed a robust EBM framework that is less sensitive to abnormal threshold determinants and hence with unbiased subject assignments to disease stages.

We considered two representative neuronal oscillatory synchrony metrics: amplitude-envelope correlation (AEC) and regional spectral power. The AEC and spectral power quantify long-range and local neural synchrony, respectively. Recent test-retest studies of MEG resting-state metrics have revealed that both metrics are highly reliable (***Colclough et al., 2016***; ***Wiesman et al., 2021a***). To evaluate the frequency specificity of neurophysiological trajectories, three canonical frequency bands, delta-theta, alpha, and beta bands, were considered. For a metric of global cognitive ability, we used the mini-mental state examination (MMSE) score. Neurodegeneration, which is related to neuronal loss as well as synaptic loss and synapse dysfunction (***Selkoe, 2002***; ***Spires-Jones and Hyman, 2014***), is detectable as brain atrophy on structural MRI, and therefore we evaluated neurodegeneration as loss of gray matter (GM) volume, specifically volume loss of the parahippocampal gyrus (PHG), extracted from individual T1 MRIs. We first deployed an Atrophy-Cognition EBM (AC-EBM) with only the neurodegeneration and cognitive decline measures, and then quantitatively examined metrics of long-range and local synchrony of neuronal oscillations corresponding to each estimated disease stage. Next, we deployed two separate Synchrony-Atrophy-Cognition EBMs (SAC-EBMs) which respectively included long-range or local neural synchrony measures along with PHG volume and global cognition, and investigated how the synchrony metrics stratify AD progression. Consistent with our hypothesis, we found that long-range and local neural synchrony in the alpha and beta bands, but not in the delta-theta band, becomes abnormal at the earliest preclinical stages of AD, preceding both neurodegeneration and cognitive deficits.

Materials and methods

Participants

The present study included 78 patients who met National Institute of Aging–Alzheimer's Association (NIA-AA) criteria for probable Alzheimer's disease or MCI due to AD (***McKhann et al., 2011***; ***Albert et al., 2011***; ***Jack Jr et al., 2018***), and 70 cognitively-unimpaired older adults. All participants were recruited from research cohorts at the UCSF Alzheimer's Disease Research Center (UCSF-ADRC). The clinical diagnosis of AD patients was established by consensus in a multidisciplinary team; 67 of the 78 patients were confirmed with positive AD biomarkers. The eligibility criteria for the cognitively normal controls included normal cognitive performance, normal MRI, and absence of neurological, psychiatric, or other major medical diseases. The neuropsychological evaluation for each participant was performed by MMSE within an average of 0.48 years (range: −2.83–1.50) and 0.22 years (range: −1.52–1.01) of the MEG evaluation for controls and patients, respectively. A structured caregiver interview was used to assess the clinical dementia rating scale (CDR) in each participant. Informed consent was obtained from all participants or their assigned surrogate decision makers. The study was approved by the Institutional Review Board of the UCSF.

MRI acquisition and analyses

Structural brain images were acquired using a unified MRI protocol on 3T Siemens MRI scanners (MAGNETOM Prisma or 3T TIM Trio) at the Neuroscience Imaging Center (NIC) at UCSF, within an average of 1.05 years (range: −6.91–0.78) and 0.29 years (range: −2.13–1.29) of the MEG evaluation for controls and patients, respectively. The acquired MRI was used to generate the head model for source reconstructions of MEG sensor data and to evaluate GM volumes. The region-based GM volumes corresponding to the 94 anatomical regions included in the automated anatomical labelling 3 (AAL3) atlas (***Rolls et al., 2020***) (Appendix 1—table 1) were computed using the Computational Anatomy Toolbox [CAT12 version 12.8.1 (1987)] (***Gaser et al., 2022***), which is an extension of SPM12 (***Penny et al., 2011***). The regional GM volumes were evaluated by the morphometry pipeline implemented in CAT12 with default parameters. The total intracranial volume (TIV), the sum of all segments classified as gray and white matter, and cerebrospinal fluid, was also calculated for each subject.

Resting-state MEG

Data acquisition

Each participant underwent 10–60-minutes resting-state MEG at the UCSF Biomagnetic Imaging Laboratory. MEG was recorded with a 275 channel full head CTF Omega 2000 system (CTF MEG International Services LP, Coquitlam, British Columbia, Canada). Three fiducial coils including nasion and left and right pre-auricular points were placed to localize the position of head relative to sensor array and later coregistered to individual MRI to generate an individualized head shape. Data collection was optimized to minimize head movements within the session and to keep it below 0.5 cm. For analysis, a 10 min continuous recording was selected from each subject lying supine and awake with the eyes closed (sampling rate $f_s = 600$ Hz). From the continuous recordings, we further selected a 1-min continuous segment with minimal artifacts (i.e. minimal excessive scatter at signal amplitude) for each subject.

Pre-processing

Each 1-min sensor signal was digitally filtered using a bandpass filter of 0.5–55 Hz. The power spectral density (PSD) of each sensor signal was computed, and artifacts were confirmed by visual inspection. Channels with excessive noise within individual subjects were removed prior to the next process. When environmental noises larger than a few pT/$\sqrt{\text{Hz}}$ were observed around 1–5-Hz range in a PSD, the dual signal subspace projection (DSSP) (***Sekihara et al., 2016***) with the lead-field vectors computed for each individual subject's head model was applied to the filtered sensor signal

for the removal of the environmental noises. As a parameter, we chose the dimension of pseudo-signal subspace μ as 50. DSSPs were needed to be applied to thirteen of the total 148 subject's signals. For the thirteen data, the resulting dimension of the spatio-temporal intersection, i.e., the degree of freedom to be removed, was 3 or 4. We also applied a preconditioned independent component analysis (ICA) (***Ablin et al., 2018***) to the signal to identify cardiac components and remove them. In each data set, one or two clear cardiac ICA-component waveforms with approximately 1 Hz rhythms were observed, which were easily identified by visual inspections.

Atlas-based source reconstruction

Isotropic voxels (5 mm) were generated in a brain region of a template MRI, resulting in $15,448$ voxels within the brain region. The generated voxels were spatially normalized into individual MRI space, and subject-specific magnetic lead field vectors were computed for each voxel with a single-shell model approximation (***Nolte, 2003***). The voxels for each subject were indexed to 94 cortical/sub-cortical regions included in the AAL3 atlas.

Array-gain scalar beamformer (***Sekihara et al., 2004***) was applied to the 60-sec cleaned sensor time series to obtain source-localized brain activity at the voxel level, i.e., voxel-level time courses. Lead field vectors were normalized to avoid the center-of-the-head artifact, and a generalized eigenvalue problem was solved to determine the optimal source orientation (***Sekihara and Nagarajan, 2008***). The beamformer weights were calculated in the time domain; a data covariance matrix was calculated using a whole 60-sec time series, and a singular value truncation (threshold of $10^{-6} \times$ maximum singular value) was performed when inverting the covariance matrix. Ninety-four regional time courses were extracted with alignment with the AAL3 atlas by performing principal component analysis (PCA) across voxel-level time courses within each of the regions and taking a time course of the first principal component. These pre-processing and source reconstructions were performed using in-house Matlab scripts utilizing Fieldtrip toolbox functions (***Oostenveld et al., 2011***). We also used BrainNet Viewer toolbox (***Xia et al., 2013***) to obtain brain rendering images of regional MEG metrics and GM atrophy.

MEG resting-state metrics

Based on the regional time courses derived from MEG, we evaluated two measures of neural synchrony: the amplitude-envelope correlation (AEC) and the spectral power, which describe long-range and local neural synchrony, respectively. Three canonical frequency bands were considered: 2–7 Hz (delta-theta), 8–12 Hz (alpha), and 15–29 Hz (beta) bands (see also Appendix 1—figure 1).

Amplitude-envelope correlation

The AECs is defined as Pearson's correlations between any two amplitude envelopes of regional time courses (total $94 \times 93/2 = 4,371$ pairs). Regional time courses were first processed by a band-pass filtering and then their envelopes were extracted by Hilbert transform. To discount spurious correlations caused by source leakages, we orthogonalized any two band-limited time courses before computing their envelopes by employing a pairwise orthogonalization (***Hipp et al., 2012***; ***Sekihara and Nagarajan, 2015***). The AEC with leakage correction is often expressed as AEC-c and is known as a robust measure (***Briels et al., 2020b***). The pairwise orthogonalization provides asymmetric values between two time courses; the value depends on which time course is taken as a seed. Therefore, Pearson's correlations between orthogonalized envelopes for both directions were averaged, resulting in a symmetric AEC matrix. Regional AECs, which represent the node degrees, were computed by averaging over row/column components of the symmetric AEC matrix.

Spectral power

The spectral power of a given band, which has often been used as a metric to discriminate patients with AD from controls (***Jeong, 2004***; ***Engels et al., 2016***; ***Wiesman et al., 2021b***), is defined by the ratio of a band power to total power and was calculated from regional PSDs. Regional PSDs were

calculated from the 94 regional time courses using Welch's method (50% overlap) with 0.293-Hz ($= f_s/2048$) steps.

Scalar neural synchrony metrics

To identify general trends in changes in the long-range and local synchrony with the severity of AD, we performed group comparisons of the regional synchrony metrics between AD patients and controls. Based on the group contrasts of regional metrics observed, we introduced scalar synchrony metrics by calculating the averages within several regions where large region-level group contrasts were identified. The scalar MEG metrics were used in the SAC-EBMs.

Metric trajectory analyses

Event-based sequencing modeling

Imaging and neuropsychological biomarkers for AD are continuous quantities taking values from normal to severe, while the stages of the disease are discrete and are identified by estimating the values of the biomarkers (***Sperling et al., 2011***). As a data-driven disease progression model, an event-based sequencing model (EBM) has been proposed that allows us to make inferences about disease progression from cross-sectional data (***Fonteijn et al., 2012***; ***Young et al., 2014***, ***2018***). In an EBM, disease progression is described as a series of metric events, where events are defined as the occurrences of abnormal values of metrics, and the values of events act as thresholds to determine discrete stages of disease (***Fonteijn et al., 2012***). The model infers temporal sequences of the events from cross-sectional data.

It is also possible to set multiple events per metric by defining them as occurrences of taking certain z-scores within the range from initial to final z-scores ($[z_{\text{initial}}\ z_{\text{final}}]$), in which z-scores for each metric linearly increase between all consecutive events and stages are located at temporal midpoints between the two consecutive event occurrence times (***Young et al., 2018***). In this linear z-score event model, a metric trajectory is described as a series of metric values evaluated at estimated stages.

We developed a robust EBM framework to quantify metric trajectories on the basis of the linear z-score model, employing a multivariate-Gaussian-form data likelihood:

$$P(Z|S) = \prod_{j=1}^{J} \sum_{k=1}^{N+1} p(\text{stage}(j) = k|S) p(Z_j|S, \text{stage}(j) = k), \tag{1}$$

where a conditional probability, $p(Z_j|S, \text{stage}(j) = k)$, describes the probability that a subject j takes biomarker values of Z_j given a sequence of events S and that $\text{stage}(j) = k$ (i.e. the subject j has been in a stage k). The probability is proportional to a Gaussian distribution:

$$p(Z_j|S, \text{stage}(j) = k) \propto \exp\left(-\sum_{i=1}^{I} \frac{(z_{ij} - \mu_i(k))^2}{2}\right). \tag{2}$$

In ***Equation 1***, N denotes a total number of events, and i, j, and k are the indices of metric, subject, and stage, respectively. J is the number of subjects ($J = 148$). I is the number of metrics: $I = 2$ for an AC-EBM and $I = 3$ for an SAC-EBM, respectively. The symbol $Z_j = [z_{1j}, z_{2j}, \ldots, z_{Ij}]^{\mathrm{T}}$, where z_{ij} denotes the z-score of a metric i for the subject j, and the symbol $Z = [Z_1, Z_2, \ldots, Z_J]$ describing the data matrix with $I \times J$-dimension. The symbol $\mu_i(k)$ denotes a value of the k-th stage of a metric i and is given by a linearly interpolated midpoint z-score between two z-scores evaluated at consecutive event occurrence times. Since there are $N + 2$ event occurrence times including initial and final times, $N + 1$ stages are provided. When employing ***Equation 1***, we assumed that the prior distribution is uniform: $p(\text{stage}(j) = k|S) = (N + 1)^{-1}$. A linear z-score model and the relationship between a set of events and the estimated stages are illustrated in Appendix 1—figure 2.

The most likely order of events is given by the sequence of events, S, which maximizes the posterior distribution $P(S|Z) = P(S)P(Z|S)/P(Z)$. On the assumption that the prior $P(S)$ is uniformly distributed (***Fonteijn et al., 2012***), the most likely sequence is obtained by solving the maximum

likelihood problem of maximizing ***Equation 1***. To solve the problem, for a given set of events, we performed Markov chain Monte Carlo (MCMC) sampling on sequences (***Young et al., 2018***) and chose the maximum likelihood sequence from $50,000$ MCMC samples.

z-scoring of metrics

We computed z-scores of the PHG volume, MMSE score, and scalar neural synchrony metrics to utilize them in the EBM frameworks. Since a linear z-score model assumes a monotonous increase in z-scored metrics along disease progression (i.e., higher stage denotes more severity), "sign-inverted" z-scores were introduced to the metrics with decreasing trends along disease progression. Specifically, for GM volumes, MMSE score, and neural synchrony metrics in the alpha and beta bands, the z score of a metric i for a subject j was defined by $z_{ij} = (\bar{x}_i^{\mathrm{C}} - x_{ij})/\sigma_i^{\mathrm{C}}$, where x_{ij} denotes a value of a metric i for a subject j, and $\bar{x}_i^{\mathrm{C}}$ and σ_i^{C} denote the mean and standard deviation (SD) of the metric values of the controls, respectively. For the delta-theta-band neural synchrony metrics, z-scores were defined in a standard way as $z_{ij} = (x_{ij} - \bar{x}_i^{\mathrm{C}})/\sigma_i^{\mathrm{C}}$. Using these z-scored metrics, the initial and final events, z_{initial} and z_{final}, for each metric were set as the bottom and top 10% average z-scores, respectively.

Events-setting optimization

In addition to the initial and final events of the z-score, we set three events for each metric because various possible curves of the metric trajectories were supposed to be well expressed by three variable points with two fixed points. For example, in an AC-EBM analysis, that is, a two-metric trajectory analysis for PHG volume loss and MMSE decline, a total of six events were considered $(N = 6)$. The metric trajectory as a series of stage values $\mu_i(k)$ is sensitive to event settings because predefined events do not necessarily capture appropriate boundaries between disease stages. To determine disease stages less sensitive to specifications of the z-score events, we tried several sets of events and selected the set of events with the largest data likelihood amongst the trials. Specifically, we searched for the set of events that better fit the data Z by trying all combinations of three z-scores from $\{0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8\}$-quantiles for each metric. The number of combinations of events for each metric was accordingly $({}_7C_3 =)35$. Therefore, MCMC samplings ($50,000$ samples for each set of events) were performed $1,225$ times for an AC-EBM and $42,875$ times for an SAC-EBM, respectively, to find the set of events and their sequence $\bar{S}$ with the highest data likelihood. This exhaustive search of optimal event settings, which was not implemented in a conventional linear z-score EBM (***Young et al., 2018***), is diagrammatically shown in Appendix 1—figure 2.

Trajectory computations

Given the most likely sequence $\bar{S}$ as a result of the exhaustive search, the probabilities that a subject j falls into stage k are evaluated by the posterior distribution

$$p(\mathrm{stage}(j) = k | Z_j, \bar{S}) = \frac{p(Z_j | \bar{S}, \mathrm{stage}(j) = k)}{\sum_{k'} p(Z_j | \bar{S}, \mathrm{stage}(j) = k')}. \tag{3}$$

The probabilities, $p_j(k) \equiv p(\mathrm{stage}(j) = k | Z_j, \bar{S})$, describe the contribution of a subject j to stage k, which allows us to evaluate a stage value of a metric i at stage k as a weighted mean:

$$\bar{x}_i(k) = \frac{p_1(k) \cdot x_{i1} + p_2(k) \cdot x_{i2} + \cdots + p_J(k) \cdot x_{iJ}}{p_1(k) + p_2(k) + \cdots + p_J(k)}. \tag{4}$$

Then, we represented the trajectory of the metric i by a series of the stage values, $\bar{x}_i(k)$. The standard error (SE) of the weighted mean at stage k was evaluated by

$$\mathrm{SE}(k) = \sigma_i \cdot \left[\frac{p_1(k)^2 + p_2(k)^2 + \cdots + p_J(k)^2}{(p_1(k) + p_2(k) + \cdots + p_J(k))^2} \right]^{1/2}, \tag{5}$$

where σ_i is a standard deviation of a metric i. This definition of SE provides an usual expression of the standard error of the mean, $\sigma_i/\sqrt{J}$, if all subjects contributed equally to stage k.

These formulations of trajectories were applied to several metrics. In the AC-EBM, the metrics i denote the PHG volume loss z-score and the MMSE scores. In the SAC-EBM, they denote each scalar neural synchrony metric in addition to the PHG volume loss z-score and the MMSE score. We also used ***Equation 4*** to evaluate the progressions of the regional neural synchrony z-scored metrics and the GM volume loss z-scores along the estimated EBM stages. When evaluating the ratio of subjects categorized to each stage, we treated $(x_{i1}, x_{i2}, \dots, x_{iJ})$ as an one-hot vector, where a metric i represents a subjects' category provided by CDR scale. For example, when evaluating the ratio of subject with CDR 0.5, $x_{ij} = 1$ only when a subject j has CDR scale of 0.5, otherwise $x_{ij} = 0$.

Statistical analyses

To test demographic differences between AD patients and controls, unpaired t-test was used for age, and chi-square test was used for sex. Age was defined at the time of the MEG scan date. In the statistical analyses, p-values below 0.05 were considered statistically significant. For group comparisons of GM volumes, MMSE scores, and neural synchrony metrics, two-sided significance tests (against a null value of zero) were performed using the general linear model (GLM). For statistical tests on GM volumes, TIV, age, and the difference between MRI and MEG dates were included as covariates. For statistical tests on MMSE scores, age and the difference between the MMSE and MEG dates were included as covariates. For statistical tests on neural synchrony metrics, age was included as a covariate. The problem of multiple comparisons between 94 regions was solved by controlling the Benjamini-Hochberg false discovery rate (FDR) (***Benjamini and Hochberg, 1995***). The FDR adjusted p-value (i.e. q-value) below 0.05 or 0.01 was considered statistically significant.

A nonparametric test was performed to statistically compare metrics between stages, i.e., to test statistical significance of the difference between stage values represented by weighted means [e.g., stage k vs. k': $\delta x = \bar{x}_i(k) - \bar{x}_i(k')$]. For a metric i, we used bootstrap resampling ($50,000$ samples) of an original data set, $\boldsymbol{x}_i = (x_{i1}, x_{i2}, \dots, x_{iJ})$, to generate new data sets, $(x^\star_{i1}, x^\star_{i2}, \dots, x^\star_{iJ})$, using a random number generator, where each $x^\star_{ij}$ is one of the components in the original data set $\boldsymbol{x}_i$. We then calculated the weighted means $\bar{x}^\star_i(k)$ (***Equation 4***) for each sample. The same procedures were performed for stage k', obtaining weighted means $\bar{x}^\star_i(k')$ for each sample. We then tested the null hypothesis that a weighted mean in stage k, $\bar{x}_i(k)$, is equal to a weighted mean in stage k', $\bar{x}_i(k')$, evaluating the null distribution of differences in weighted mean values, $\delta x^\star = \bar{x}^\star_i(k) - \bar{x}^\star_i(k')$. The problem of multiple comparisons across stages was solved by controlling the FDR. The q-value below 0.05 was considered statistically significant.

Results

Participant demographics

This study included a cohort of 78 patients with AD (50 female; 28 male) including 35 patients with AD dementia and 43 patients with MCI due to AD. and also included 70 cognitively-unimpaired older adults as controls (41 female; 29 male). The CDR scales were 0 for cognitively-unimpaired controls, 0.5 for patients with MCI, and 1 ($n = 27$) or 2 ($n = 8$) for patients with AD dementia. There was no difference in sex distribution between the AD and control groups [$\chi^2(1) = 0.477$; $p = 0.49$]. Average age at the time of the MEG was slightly higher in the control group than patients with AD (controls, mean±SE: 70.5 ± 0.99, range: 49.5–87.7; AD, mean±SE: 63.9 ± 1.01, range: 49.0–84.4) [unpaired t-test: $t(146) = -4.708$; $p < 0.001$]. Average MMSE in patients with AD was 22.7 ± 0.43 (mean±SE) while the average MMSE in the controls 29.2 ± 0.48 (***Figure 1***C, D).

Group comparisons of GM volumes for each of the anatomical regions included in the AAL3 atlas showed that GM volumes in the temporal regions are significantly smaller in AD patients than in controls (Appendix 1—figure 3, Appendix 1—table 2). Amongst the temporal GM volumes, we focused on a volume of PHG as a key indicator of neurodegeneration in AD progression. The PHG includes perirhinal and entorhinal cortices of the medial temporal lobe (MTL), and MRI-based studies have reported that the volume of MTL reduces, especially in the perirhinal and entorhinal

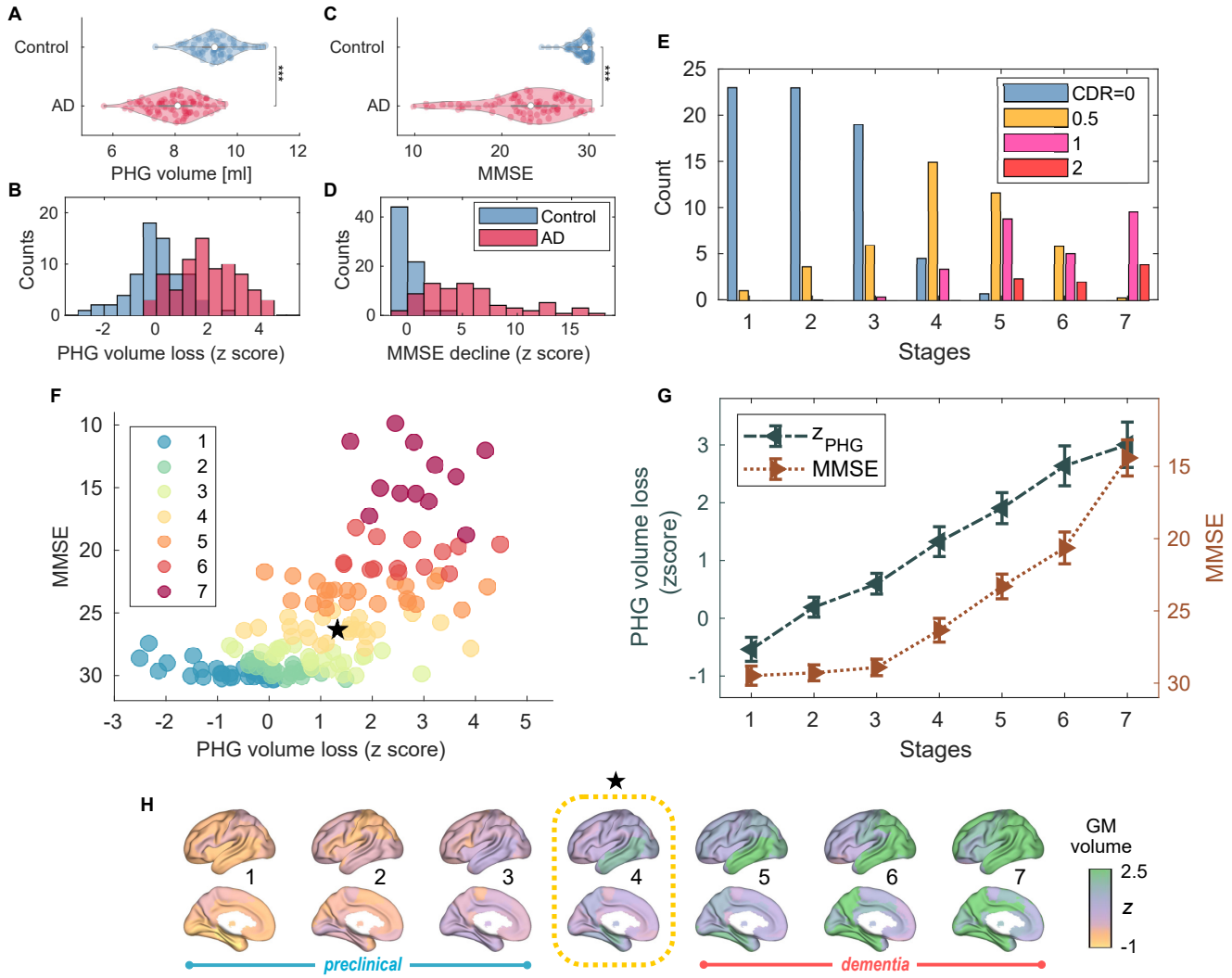

Figure 1. Atrophy-cognition EBM staging of AD progression. (A) Group comparison of PHG volume [unpaired t-test: $t(143) = -9.508$; $^{***}p < 0.001$]. The average PHG volume in patients with AD was $7.99\ \mathrm{ml} \pm 0.09$, and the average PHG in controls was $9.28\ \mathrm{ml} \pm 0.11$. (B) Histogram of PHG volume loss z-scores, z_{PHG}. (C) Group comparison of MMSE scores [unpaired t-test: $t(144) = -10.171$; $^{***}p < 0.001$]. (D) Histogram of MMSE-decline z-scores, z_{MMSE}. (E) The ratio of subjects classified to each stage; blue: Control (CDR 0), orange: MCI due to AD (CDR 0.5), pink: mild AD dementia (CDR 1), and red: moderate AD dementia (CDR 2). (F) Distribution of the stages in the space spanned by PHG volume loss and MMSE score, which was obtained by distinctly assigning each subject to one of the stages with the highest probability. The colors of the dots denote the seven stages. A star symbol denotes weighted means of z_{PHG} and MMSE scores at stage 4: $z_{\mathrm{PHG}} = 1.33(\pm 0.258)$ and MMSE= $26.3(\pm 0.82)$. The values in parentheses denote the standard error (SE; ***Equation 5***) of the probability-based weighted means. (G) Trajectories of PHG volume loss and MMSE score as a function of the seven stages. Probability-based weighted means ($\pm$ SE) are shown. The initial and final z-scores used in this AC-EBM were: $(z_{\mathrm{initial}}, z_{\mathrm{final}}) = (-1.372, 3.804)$ for PHG volume loss and $(-0.902, 12.712)$ for MMSE decline, respectively. (H) Progression of GM volume loss (z-scores) from stage 1 to 7. Regional GM atrophy in the MCI stage (stage 4) was circled with dotted lines.

cortices, in early stages of typical AD (***Teipel et al., 2006***; ***Echávarri et al., 2011***; ***Matsuda, 2016***). The average PHG volume in patients with AD was siginificantly smaller than in the controls (***Figure 1***A, B).

Abnormal frequency specific long-range and local neural synchrony in AD

For regional long-range synchrony (AEC), increases in delta-theta-band synchrony in patients with AD were identified in frontal regions, and reductions in alpha- and beta-band synchrony were identified in the whole brain (Appendix 1—figure 4C, E; Appendix 1—table 3). These regional contrasts were similar to those observed between AD dementia and subjective cognitive decline (SCD) in MEG/EEG studies (***Schoonhoven et al., 2022***; ***Briels et al., 2020a***). For regional local synchrony (spectral power), increases in delta-theta-band power in patients with AD were identified in the whole brain, and reductions in alpha- and beta-band power were identified in temporal regions and the whole brain, respectively (Appendix 1—figure 4D, F; Appendix 1—table 4). These regional contrasts were similar to those observed between MCI and controls in an MEG multicenter study (***Hughes et al., 2019***).

Based on the group contrasts of regional metrics observed, we introduced six scalar metrics to quantify long-range and local synchrony: [i] frontal delta-theta-band AEC, [ii] whole-brain alpha-band AEC, [iii] whole-brain beta-band AEC, [iv] whole-brain delta-theta-band spectral power, [v] temporal alpha-band spectral power, and [vi] whole-brain beta-band spectral power. We computed the average within several regions where large region-level group contrasts were identified (the temporal and frontal regions of interest are illustrated in Appendix 1—figure 5). Consistent with the regional-level group comparisons, the long-range and local synchrony scalar metrics in the delta theta band were increased in AD patients compared to controls, and the long-range and local synchrony scalar metrics in the alpha and beta bands were reduced in AD patients compared to controls (Appendix 1—figure 4A, B). We also calculated the z scores, z_{MEG}, of each scalar metric that were used in the SAC-EBMs.

PHG volume loss precedes the MMSE decline in AD progression

An AC-EBM analysis with the two metrics, PHG volume loss, z_{PHG}, and MMSE decline, z_{MMSE}, was performed for six events ($N = 6$; three events for each metric). Robust event thresholds were determined by the exhaustive search of multiple event thresholds (z-score thresholds) and choosing the set of event thresholds that maximize the data likelihood (***Equation 1***). The AC-EBM provided seven stages, each located between consecutive event occurrence times. Based on the probabilities that each subject is assigned to each of the seven stages, the ratio of subjects classified to each stage was calculated (***Figure 1***E). The ratio of subjects with CDR 0.5 was highest at stage 4, and the ratio of controls with CDR 0 at stage 4 was small compared to those in less severe stages of 1–3, indicating that stage 4 corresponds best to clinical MCI due to AD.

The trajectory of PHG volume loss preceded that of MMSE decline (***Figure 1***G), consistent with the relationship between brain atrophy and cognitive decline described in a hypothetical model of biomarker trajectories (***Jack Jr et al., 2010***; ***Sperling et al., 2011***). ***Figure 1***F visualizes the distribution of the seven stages in the PHG volume loss versus MMSE score. At stage 4, the value of z_{PHG} of 1.33 ± 0.258 was in the range of 1–2. This z-score range of PHG volume loss corresponds to a mild-atrophy range representing approximately MCI stage, e.g., in the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) software (***Hirata et al., 2005***; ***Matsuda et al., 2012***). Furthermore, the MMSE score of 26.3 ± 0.82 at stage 4 was in the range of 23–27. This range of MMSE scores is considered to be typical for MCI due to AD (***Tsoi et al., 2015***). Stage 4 therefore corresponds to MCI stage, whereas stages 3 and 5 correspond to preclinical-AD and mild AD-dementia stages, respectively.

The GM volume z-scores as a function of the seven stages showed that prominent atrophy with $z > 1$ is observed in the temporal regions starting at stage 4 (***Figure 1***H). This trajectory of GM volume approximated the evolution of brain atrophy in the typical progression of AD reported in

MRI-based studies; GM volume loss in AD starts in the MTL in the MCI stage, spreads to the lateral temporal and parietal lobes in the mild AD-dementia stage, and spreads further to the frontal lobe in moderate AD-dementia (***Scahill et al., 2002***; ***Tondelli et al., 2012***; ***Jack Jr et al., 2013***).

These results of the AC-EBM indicate that the PHG volume loss precedes the MMSE decline, and their metric changes track the stages of AD from preclinical AD to moderate AD-dementia. The order of events for GM volume loss and cognitive decline was consistent with the observation that cognitive decline in the early stage of AD progression reflects neuronal loss in the medial temporal regions (***Jack Jr et al., 2018***; ***DeTure and Dickson, 2019***).

Neural synchrony progressively changes throughout AD stages estimated by AC-EBM

For the seven stages determined by the AC-EBM (***Figure 1***E–H), profiles of long-range and local neural synchrony were estimated (***Figure 2***). Along the EBM stages, the delta-theta-band synchrony was consistently increased and the alpha and beta-band synchrony was consistently decreased. Neural synchrony showed prominent changes around stage 4 (clinical stage of MCI due to AD). Alpha- and beta-band long-range synchrony decreased steadily across stages 1–3 and then decreased further in stage 4 (***Figure 2***A). Beta-band local synchrony also decreased by half from 1 to 4 (***Figure 2***B). In contrast, there were little changes in delta-theta-band long-range synchrony and delta-theta and alpha-band local synchrony from stage 1 to 3 but these changes became prominent after stage 3.

Regional patterns of long-range and local synchrony as a function of the seven stages indicated that prominent changes manifeste at stage 4 (***Figure 2***E, F; Appendix 1—table 5 and Appendix 1—table 6). The regions with prominent deviations overlapped with the regions where significant increase and decrease in the neural synchrony were observed in the group comparisons (Appendix 1—figure 4E, F).

The changing patterns of neural synchrony metrics with AD progression indicate that neural synchrony are sensitive indicators of functional change along the AD progression. To further investigate the temporal association of functional deficits with neurodegeneration and cognitive decline, we included neural synchrony in addition to the PHG volume loss and MMSE decline into the EBM frameworks, performing SAC-EBMs.

Long-range synchrony changes in the alpha and beta bands precede PHG volume loss and MMSE decline

SAC-EBMs that include PHG volume loss, z_{PHG}, MMSE decline, z_{MMSE}, and long-range synchrony metric z-scores, z_{MEG}, were performed setting a total of nine events ($N = 9$). SAC-EBMs separately included long-range neural synchrony metrics in the delta-theta, alpha, and beta bands. Each EBM determined the order of nine events, thus defining ten stages (Appendix 1—figure 6).

For all frequency bands, around stages 5 and 6, the weighted means of PHG volume loss z-scores were in the range of 1–2 and the MMSE scores were in the range of 23–27 (***Figure 3***B, F, J). Furthermore, the ratio of subjects with CDR 0.5 was large around stage 5 (***Figure 3***A, E, I). These indicated that stage 5 best represents the onset of clinical MCI stage, and stages 1-4, where MMSE scores remain almost constant at or near 30, correspond to the preclinical stages of AD. The changes in long-range synchrony during the preclinical stages are shown as statistical bars, and the region-level changes are shown in ***Figure 3***C–D, G–H, and K–L.

Long-range synchrony in the alpha and beta bands decreased markedly during the preclinical stages of AD, preceding both PHG volume loss and MMSE decline. Specifically, between stages 1 and 4, the alpha- and beta-band long-range synchrony decreased by more than $80\ \%$ of the total drop seen from stage 1 to 10. The whole brain regions, but especially the temporal regions, were involved in these prominent preclinical changes (***Figure 3***H, L). In contrast, the trajectory of delta-theta-band long-range synchrony (***Figure 3***B, C) was almost identical to the evolution of PHG volume loss throughout the stages, but a large variation occurred around the MCI stages (stages

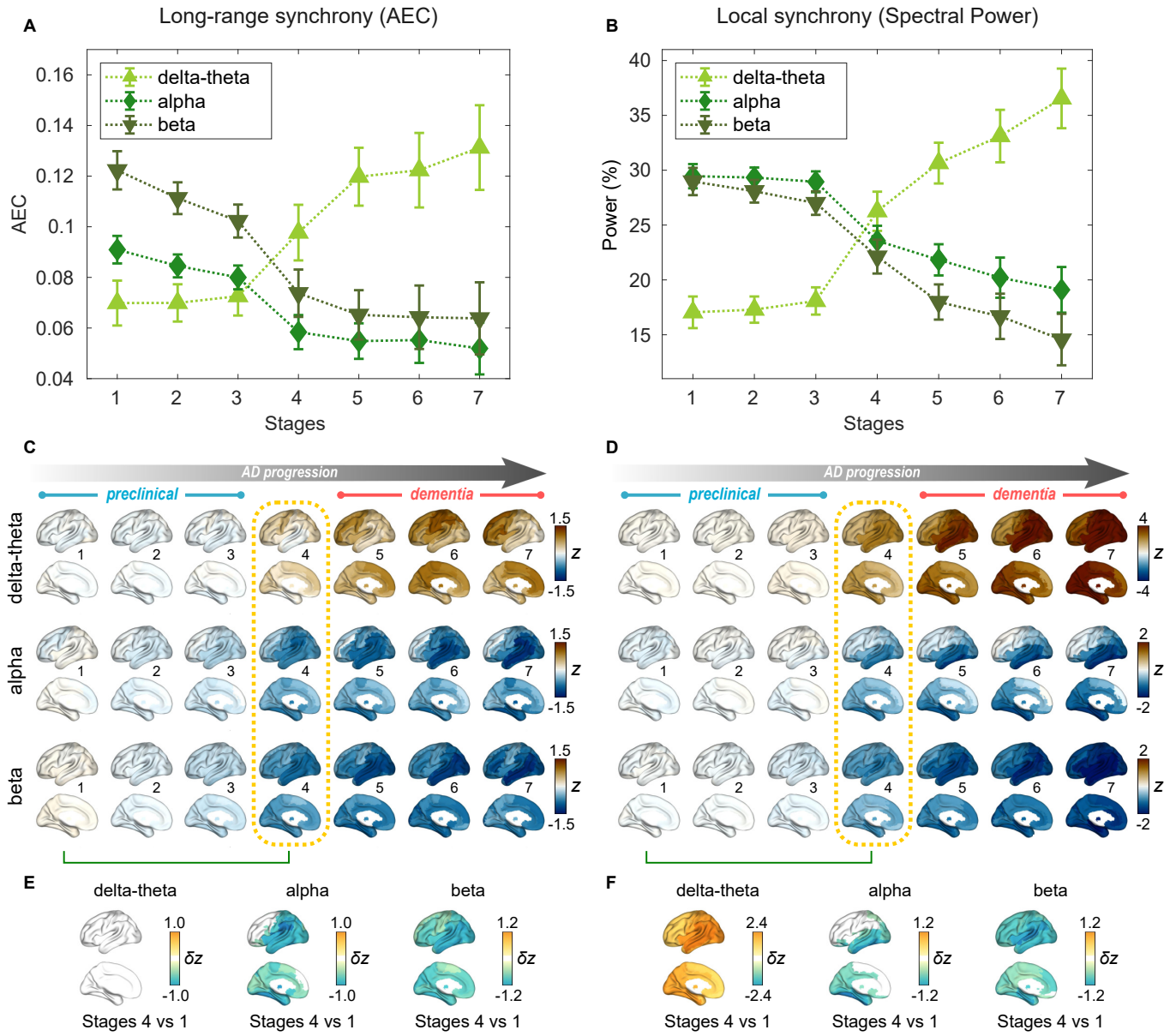

Figure 2. Profiles of neural synchrony as a function of the AD stages estimated by AC-EBM. (A,B) Profiles of AEC (A) and spectral power (B) as a function of the seven stages, showing probability-based weighted means (± SE). Neural synchrony increased monotonously with AD progression in the delta-theta band and decreased monotonously in the alpha and beta bands. (C,D) Regional AEC (C) and spectral power (D) as a function of the seven stages. Deviations from the neural synchrony spatial patterns averaged over the controls are displayed. The deviations were calculated by using probability-based weighted means of the z-scores standardized by the controls. Spatial patterns in the MCI stage (stage 4) were circled with dotted lines. (E,F) Changes in neural synchrony during the preclinical stages. Regional comparisons between two stages (stages 4 vs. 1) are shown based on non-parametric tests of the weighted mean differences δz. Differences that exceed the threshold ($q < 0.05$) are displayed. There were no significant differences in long-range synchrony in the delta-theta band.

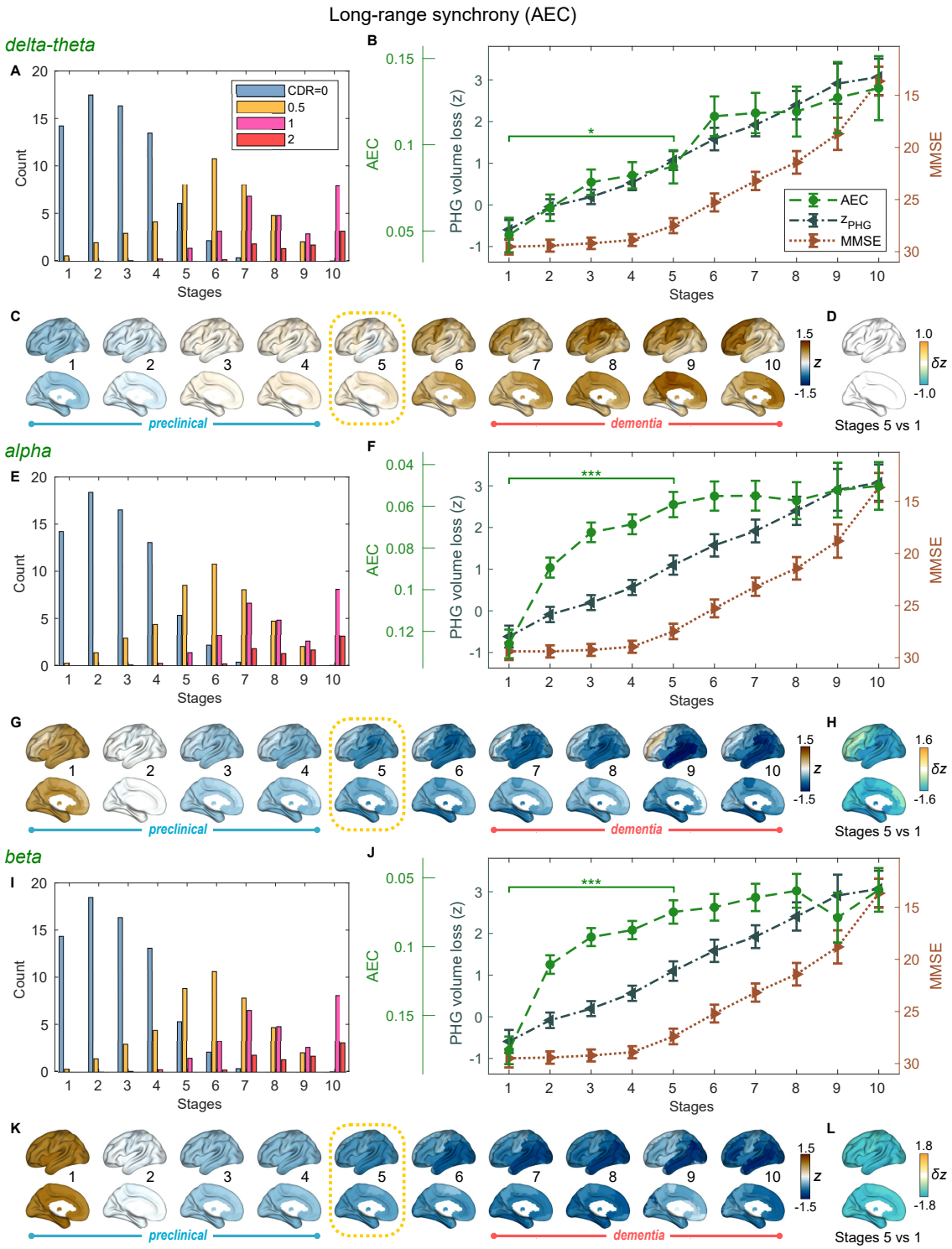

Figure 3. Trajectories of long-range neural synchrony in delta-theta, alpha, and beta-bands from SAC-EBMs. (A,E,I) The ratio of subjects classified to each stage. The ratio was evaluated on the basis of the probabilities that each subject is assigned to each of the ten stages. (B,F,J) Trajectories of long-range synchrony, PHG volume loss, and MMSE score as a function of the ten stages, showing probability-based weighted means (± SE). The asterisks ($^{*}q < 0.05$ and $^{***}q < 0.001$, FDR corrected) denote statistical significance in comparisons between stages 5 vs. 1. All pairs of stages with significant weighted-mean differences are listed in Appendix 1—table 7. Initial and final z-scores of long-range synchrony used in the SAC-EBMs were: $(z_{\text{initial}}, z_{\text{final}}) = (-1.083, 2.811)$, $(-1.542, 1.605)$, and $(-1.624, 1.641)$ in the delta-theta, alpha, and beta bands, respectively. (C,G,K) Regional AEC along the stages. The deviations from the regional patterns of the control group are displayed. The regional patterns at the onset of the MCI stage were circled with dotted lines. (D,H,L) Changes in regional patterns during the preclinical stages. Regional comparisons between two stages based on nonparametric tests of weighted mean differences δz are shown. Differences exceeding threshold ($q < 0.05$, FDR corrected) are displayed. The top 10 regions with significant differences are listed in Appendix 1—table 8.

5 and 6) as was found in the AC-EBM (***Figure 2***A). There were no significant synchrony region-level increases in delta-theta band during preclinical stages (***Figure 3***D), consistent with an observation seen in the AC-EBM (***Figure 2***F).

The trajectory shapes of the PHG volume loss (almost linear) and MMSE scores (half parabola) were similar to those obtained in the AC-EBM (***Figure 1***G). This indicates that prominent changes in alpha- and beta-band long-range synchrony during preclinical stages can be utilized to stratify the preclinical stages determined only by neurodegeneration and cognitive deficits.

Local synchrony changes in the alpha and beta bands precede PHG volume loss and MMSE decline

SAC-EBMs including PHG volume loss, MMSE decline, and local synchrony metric z-scores were performed, separately considering delta-theta-, alpha-, and beta-band local synchrony metrics. When considering delta-theta and alpha bands, around stages 6 and 7, the PHG volume loss z-scores were in the range of 1–2 and the MMSE scores were in the range of 23–27 (***Figure 4***B, F), indicating that stage 6 best represents the onset of the MCI stage. Furthermore, the ratios of the subjects with CDR 0.5 were high in stages 6 and 7 (***Figure 4***A, E). For the beta band, based on similar observations, stage 6 best represented the MCI stage (***Figure 4***I, J). For all frequency bands, stages 1-5, where MMSE scores remain almost constant at or near 30, corresponded to the preclinical stages of AD. The changes in local synchrony during the preclinical stages are shown as statistical bars, and the corresponding region-level changes are shown in ***Figure 4***C–D, G–H, and K–L.

Local synchrony in the alpha and beta bands decreased during the preclinical stages of AD, preceding both PHG volume loss and MMSE decline (***Figure 4***F, G and ***Figure 4***J, K). On the contrary, local synchrony in the delta-theta band increased, lagging the evolution of PHG volume loss (***Figure 4***B, C). Specifically, the alpha-band local synchrony decreased considerably by the onset of the MCI stage, showing significant reductions in the temporal regions (***Figure 4***H) during the preclinical stages (stages 6 vs 1). It is noted that these trends were inconsistent with those found in the AC-EBM (***Figure 2***B), especially within the preclinical stages, where there was little change found in the alpha-band local synchrony. This can be interpreted as evidence that early stages in AD progression may be better characterized by including neurophysiological markers as AD indicators. Beta-band local synchrony also decreased during preclinical stages, preceding PHG volume loss and MMSE decline; by stage 5, the beta-band power decreased by approximately 55 % of the total drop seen throughout the stages, and the reductions were observed in the whole brain (***Figure 4***L). In contrast to the local synchrony trajectories in the alpha and beta bands, the local synchrony in the delta-theta band increased and the *hyper*-synchrony lagged the evolution of the loss of PHG volume in the preclinical stages and made a large jump around the stages 6 and 7 (***Figure 4***D).

As shown in the previous section, large alpha- and beta-band *hypo*-synchrony during the preclinical stages was also observed in long-range synchrony (***Figure 3***F, J). Notably, the decreases in the long-range metrics were much greater than those in the local metrics, especially in the early stages during the phase of the preclinical AD (stages 1–3).

Discussion

We demonstrated that functional deficits of frequency-specific neural synchrony show progressive changes across AD stages. Both long-range and local neural synchrony in the alpha and beta bands, but not in the delta-theta band, was found to decrease in preclinical stages of AD, preceding neurodegeneration and cognitive decline, with more robust findings for long-range neural synchrony. These findings highlight the frequency-specific manifestations of neural synchrony in AD and that synchrony reductions in the alpha and beta bands are sensitive indices reflecting functional deficits in the earliest stages of disease progression.

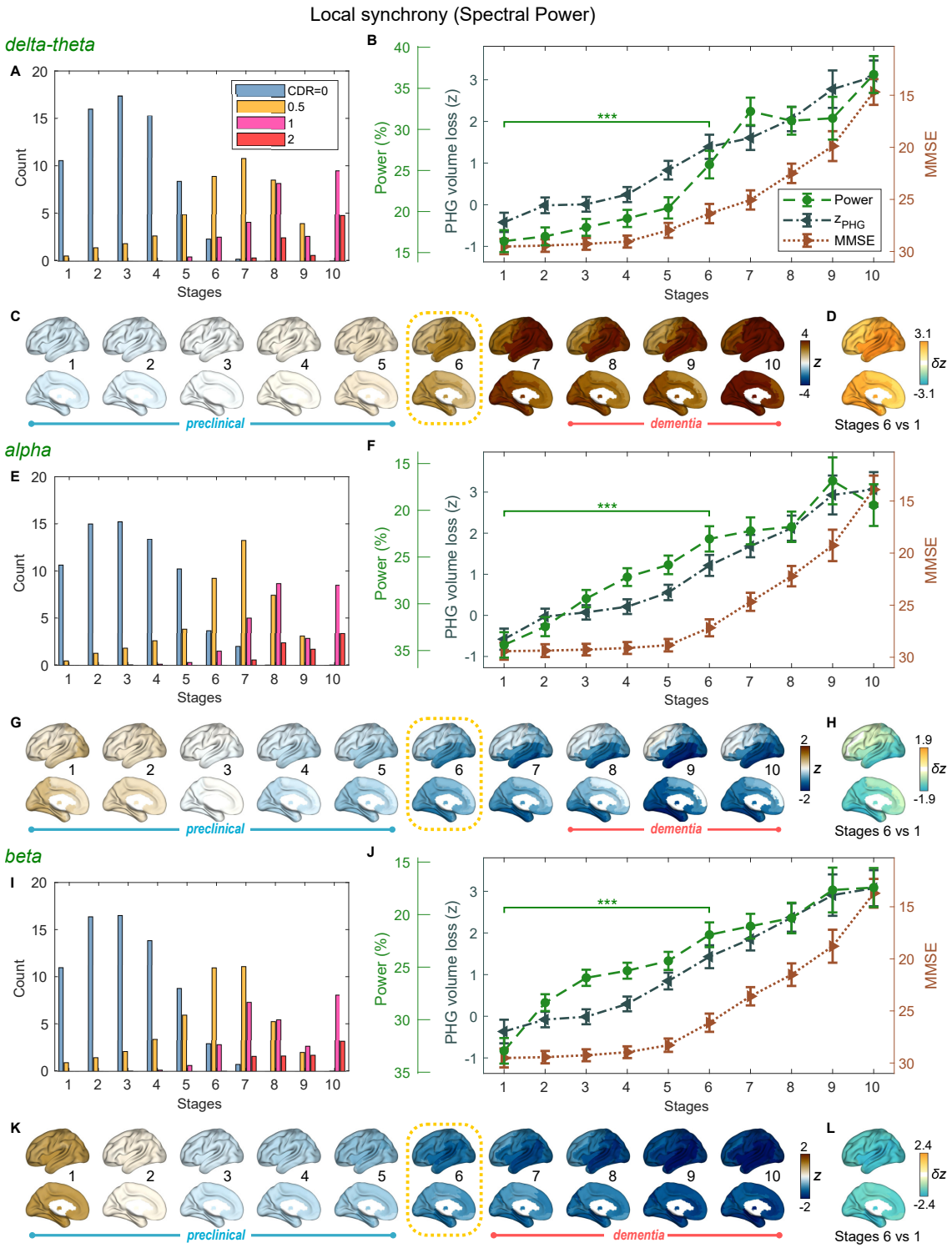

Figure 4. Trajectories of local neural synchrony in delta-theta, alpha and beta bands from SAC-EBMs. (A,E,I) The ratio of subjects classified to each stage. (B,F,J) Trajectories of local synchrony, PHG volume loss, and MMSE score as a function of the 10 stages, showing the weighted mean ($\pm$ SE). Asterisks ($^{***}q < 0.001$, FDR corrected) denote statistical significance in comparisons between stages 6 vs. 1. All pairs of stages with significant weighted-mean differences are listed in Appendix 1—table 9. Initial and final z-scores of local synchrony used in the SAC-EBMs were: $(z_{\text{initial}}, z_{\text{final}}) = (-1.329, 6.097)$, $(-1.461, 2.866)$, and $(-1.810, 2.784)$ in the delta-theta, alpha, and beta bands, respectively. (C,G,K) Regional spectral power along the stages. Departures from the regional patterns of the control group are shown. The regional patterns at the onset of the MCI stages were circled with dotted lines. (D,H,L) Changes in regional patterns during the preclinical stages. Regional comparisons between two stages are shown based on nonparametric tests of weighted mean differences δz. Differences exceeding threshold ($q < 0.05$, FDR corrected) are displayed. The top 10 regions with significant differences are shown in Appendix 1—table 10.

Electrophysiological metrics of neural synchrony precede volume loss and cognitive decline

A key finding from the current study is that functional deficits as depicted by reduced neural synchrony precede structural volume loss and cognitive deficits. The EBMs on cross-sectional data clearly demonstrated that alpha- and beta-band synchrony within the inferior temporal and posterior parieto-occipital regions show significant deficits in the early disease stages–stages where volumetric and clinical deficits are still not significantly deviated from their baseline trajectory. This is consistent with the finding that functional changes occur earlier in the time course than structural changes in AD (***Jack Jr et al., 2010***; ***Sperling et al., 2011***).

Previous functional MRI studies have demonstrated disrupted connectivity especially between the hippocampus and several cortical default mode network (DMN) areas in subjects with amyloid deposition but without cognitive impairment (***Sperling et al., 2014***). Such a disruption in the DMN has also been observed in clinically normal older individuals without prominent brain atrophy in MTL preserving hippocampal activity (***Miller et al., 2008***; ***Hedden et al., 2009***), indicating altered functional connectivity during the period of preclinical AD. In contrast to fMRI data reflecting the cascade of neural, metabolic, hemodynamic events in AD, our findings from MEG, which captures the synaptic physiology as the collective oscillatory spectra, demonstrate direct observations of AD-related altered neuronal activity.

Frequency-specific manifestations of neural synchrony deficits along the progression of the disease

We demonstrated that the oscillatory deficits and their temporal association to neurodegeneration and cognitive decline are frequency specific. In particular, it is alpha and beta hyposynchrony that precedes PHG atrophy and MMSE decline, whereas delta-theta hypersynchrony does not seem to show such precedence. This is consistent with previous findings that alpha and beta hyposynchrony is more tightly associated with tau accumulation which is closely allied to neurodegeneration and cognitive decline (***Pusil et al., 2019***; ***Ranasinghe et al., 2020***, ***2021***). Neural hyposynchrony in the alpha and beta bands may represent harbingers of altered synaptic physiology associated with tau accumulation. In fact, in human postmortem studies, the strongest correlate of cognitive deficits in AD patients is loss of synapse (***DeKosky and Scheff, 1990***; ***Terry et al., 1991***). A study using transgenic AD mice has also shown that synaptotoxicity is an early phenomenon in AD pathophysiology (***Zhou et al., 2017***). In the context of fluid biomarkers to detect plasma amyloid, alpha and beta hyposynchrony may detect and quantify tau-associated neurodegenerative mechanisms and hence may provide crucial information for early therapeutic interventions.

Previous studies have also shown that delta-theta oscillatory activity is increased in AD and is strongly associated with amyloid accumulation (***Ranasinghe et al., 2020***, ***2022b***). In particular, increased delta-theta activity is a robust signal in individuals who are amyloid positive and cognitively unimpaired as well as those who harbor APOE-$\epsilon 4$ allele and an increased risk of AD (***Cuesta et al., 2015***; ***Nakamura et al., 2018***). These previous findings indicate that delta-theta hypersynchrony is an early change in AD spectrum and may even precede the neurodegeneration and cognitive deficits. However, in the current results, the trajectory of the delta-theta hypersynchrony was identical to or lagged that of the PHG volume loss. This apparent controversy may be due to the possibility that oscillatory changes in the delta-theta band are more closely related to amyloid accumulations in AD, which become saturated early in the disease course and have a poor association with neurodegeneration and cognitive trajectories. It would be worth exploring how the trajectory of early saturated variables may be captured by EBM approaches.

Distinction between long-range and local synchrony deficits in disease progression

The decrease in alpha and beta-band long-range metrics in the preclinical stages was much greater than that in the local metrics. This is consistent with the fact that AD-related abnormal brain activities are observed as disruptions of functional networks. Long-range cross-regional metrics, such as

AECs, directly capture network disruptions involving all brain regions, while local metrics capture features of individual regions. From the definition, local synchrony describes collective neuronal oscillations in each local region, and thus the change along AD progression may depend mainly on long-term, slowly changing regional neuronal loss. On the other hand, long-range synchrony describes temporal coherence amongst regional collective neuronal oscillations and is vulnerable to altered neuronal oscillations. Therefore, long-range metrics are more sensitive to abnormal rhythms, gathering local abnormalities.

Preclinical neurophysiological markers that indicate the pathophysiology of AD are clinically important but have not been established. Aβ accumulation in preclinical stages is just a necessary condition for AD, and additional preclinical markers are required to fully predict the progression of AD. From this point of view, the present study indicates that alpha and beta-band MEG metrics, especially long-range-synchrony metrics (AEC), which were found to be sensitive to preclinical stages, might be promising candidates as such additional markers.

Limitations

A limitation of the current study is that there were differences in age between controls and AD patients. Although we adjusted the age of each metric employing GLMs, age trajectories in neurophysiological measures have been reported to be nonlinear even in healthy aging (***Sahoo et al., 2020***). Age-related changes in brain atrophy have also been reported to follow a nonlinear time course depending on the brain areas (***Coupé et al., 2019***). These studies indicate that it may be better to employ a non-linear method beyond GLM to perfectly correct aging effects.

Another limitation is that we have not examined the heterogeneity in AD progression although we clarified for the first time the time courses of MEG neurophysiological metrics in AD progression. In fact, AD is a heterogeneous multifactorial disorder with various pathobiological subtypes (***Jellinger, 2022***). In this context, an EBM called *Subtype and Stage Inference* (SuStaIn) capable of capturing spatio-temporal heterogeneity of diseases (***Young et al., 2018***) has been proposed for subtyping of neurodegenerative diseases including typical AD and has been applied to find different spatio-temporal trajectories of longitudinal tau-PET data in AD (***Vogel et al., 2021***). Since oscillatory rhythms are thought to depend on AD subtypes (***Ranasinghe et al., 2017***, ***2022a***), an extended trajectory analysis considering both spatial and temporal variations of MEG/EEG metrics is warranted in the future and such analyses would provide distinct neurophysiological trajectories depending on AD subtypes.

Data availability

The informed consent did not include a declaration regarding the public availability of the data, and the data for this study will not be made publicly available. Anonymized data may be shared on request from qualified investigators for the purposes of replicating procedures and results within the limits of participants' consent. Matlab scripts used in this study are available from the corresponding author upon reasonable requests.

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Competing interests

K.K. and H.M. are employees of Ricoh Company, Ltd. The authors declare that no other competing interests exist. The other authors declare no competing financial conflicts of interest to disclose.

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