SUPPLEMENT

1. Supplementary Methods

1.1. Neuropathological assessment of NFT burden

1.2. MEG data preprocessing

1.3. Source space reconstruction of MEG sensor data and calculation of neuronal synchrony

1.4. Neuropsychological bedside tests

2. Supplementary Figures

2.1. Supplementary Figure 1: Frequency-specific neuronal synchrony within select ROI

2.2. Supplementary Figure 2: Associations of frequency-specific neuronal synchrony abnormalities and clinical deficits

2.3. Supplementary Figure 3: Prediction of NFT density by frequency-specific neuronal synchrony deficits in neocortical ROIs

3. Supplementary Tables

3.1. Supplementary Table 1: Demographic and neuropathological characteristics of patients with AD

3.2. Supplementary Table 2: Biomarkers of patients with AD at the time of MEG evaluation

3.3. Supplementary Table 3: Neuropsychological test performance in patients with AD at the time of MEG evaluation

3.4. Supplementary Table 4: Demographic characteristics of control participants

3.5. Supplementary Table 5: Anatomical regions selected from Brainnetome atlas parcellations to match the histopathologically defined regions

1. Supplementary Methods

1.1. Neuropathological assessment of NFT burden

The neuroanatomical sampling design and procedures for microscopy using thioflavin-S fluorescent dye used in this study were informed by techniques developed originally by Terry and colleagues.[1] Briefly, 8μm-thick paraffin-embedded sections were stained using thioflavin-S, and regions of interest were imaged. Three 0.25 mm^2 areas (500 μm x 500 μm) were sampled at random from each region and quantitative neurofibrillary tangle (NFT) counts were averaged across these three areas to produce a density score. Densities are reported as the number of NFTs per mm^2. Thioflavin-S identifies tau NFT pathology as well as β-amyloid neuritic plaques.[2] NFT pathology was distinguished from β-amyloid pathology based on the distinct morphological differences between the aggregates. NFT pathology was distinguished by flame-shaped or globose morphology of fibrous neuronal aggregates.

1.2. MEG Data preprocessing

Spectral analysis of each recording was visually inspected and those showing known electrophysiological features of sleep were excluded. Artifact detection was confirmed by visual inspection of sensor data, and channels with excessive noise within individual subjects were removed prior to analysis. The sensor time series were segmented into epochs of 12 s duration. An automatic artifact rejection tool implemented in the Fieldtrip toolbox was used to identify and remove muscle artifacts. An Independent Component Analysis (ICA) based criteria were employed to identify and remove the artifacts created by occasional blinks and cardiac pacing. In addition, noisy epochs caused by minor head and body motions were removed after visual inspection. The remaining cleaned epochs were then filtered using a 1-55 Hz band-pass filter and a maximum of 10 epochs of cleaned-sensor-time-series data were chosen for analysis (i.e. a maximum total of 120 s time-series data per subject).

The signal pre-processing and co-registration were performed by utilizing the Fieldtrip toolbox. To provide anatomical head models for MEG analysis, a high-resolution T1-weighted whole-brain MRI scan was acquired for each subject using the 3 Tesla Siemens Magnetic Resonance Imaging (MRI) scanner at the Neuroscience Imaging Center (NIC) at UCSF. For each subject, the outline of the brain on the structural scans was extracted, and the segmented brain was treated as a volume conductor model for

the source reconstruction described below. MEG sensor data was co-registered to each subject's structural MRI using three fiducial coils placed on the nasion and the left and right preauricular points. For source reconstruction, 6 mm regular voxels were generated in the brain region of a template MRI in MNI space and warped into each individual head model. The magnetic lead field vectors as a forward model were calculated using single-shell-model approximation.

1.3. Source space reconstruction of MEG sensor data and calculation of neuronal synchrony

Source space reconstruction was performed on preprocessed data, using custom-built MATLAB software tools. We applied an array-gain scalar beamforming method to the sensor time series to obtain the source localized activity for all brain regions.[3] The beamformer weights were calculated in the time domain. The data covariance matrix was computed by using the time series data and singular value truncation with 220 components when inverting the matrix. This beamforming provided voxel-level source time courses on 6 mm volumetric grid on brain. We generated the source times courses for the 246 anatomic regions as defined in the Brainnetome atlas, by choosing the time courses of voxels with maximum power within each region.[4]

We computed the average imaginary coherence per ROI, for each subject in our patient group and age-matched controls, within the alpha (8-12 Hz) and delta-theta bands (2-8 Hz). Imaginary coherence captures only the coherence that cannot be explained by volume spread,[5] and is a reliable metric for resting state functional connectivity analyses.[6, 7] For computing the imaginary coherence, we first derived the coherence for each band by dividing the cross-spectrum by auto-spectrum, which were obtained by applying short-time FFT (1.7s Hanning window) to the broad-band 1-55 Hz source time series, and then summing up the Fourier components corresponding to alpha and delta-theta bands. We computed the imaginary coherence per ROI, by averaging across the Fisher's z-transformed values of imaginary part of the coherence. Next, for each patient, we computed z-score estimates of regional alpha and delta-theta imaginary coherence, based on the age-matched control group. For each of the six ROIs, we identified the best representative anatomic region from the Brainnetome atlas in both hemispheres (Supplementary Table 5), and computed the average normalized imaginary coherence (z-score) estimate per subject.

1.4. Neuropsychological bedside tests

Executive function: Set shifting or mental flexibility was assessed by modified Trail Making test.[8] The modified Trail Making test requires the patient to draw lines linking items marked on paper and serially alternate between numbers and days of the week for a period of 120 seconds. The number of correct connections and time taken for the task were recorded. To adjust for the fact that some patients do not complete the task within the required time window of 120 seconds, the dependent measure was calculated as the number of correct connections made per second. Cognitive control was assessed by the Stroop tests [9, 10]. Lexical fluency, was assessed with 'D-words', in which patients generate as many words as possible that are not proper nouns within 60 seconds beginning with the letter 'D'[11, 12]. A nonverbal counterpart of fluency comprises design fluency [8], in which patients are required to use 4 lines to connect the dots within boxes each containing five dots, creating a unique pattern each time. We recorded the number of D-words and patterns patients generated, within 60 seconds. Phonological short-term memory was assessed by digit span forward, and verbal working memory was assessed by digit span backward.

Memory: Verbal episodic memory was evaluated with the California Verbal Learning Test–Short Form (CVLT), which includes a list of 9-item words, presented over 4 learning trials [13]. Immediate (30 seconds) and delayed (10 minutes) CVLT were assessed by free recall of the list at 30-seconds and 10-minutes intervals respectively. The correct number of items recalled, out of 9 were recorded. Visual memory was assessed by asking the patients to draw the Benson figure from memory after a 10-minute delay, and scored on a 17-point scale[14].

Language: Confrontation naming was assessed with a 15-item short form of the Boston Naming Test [15, 16]. The number of correctly named items was recorded out of a total score of 15. Repetition was assessed by having participants repeat 5 phonemically complex sentences. Verbal agility was evaluated by having participants rapidly articulate a multi-syllabic word and was measured as the number of repetitions completed correctly within 5 seconds. Category fluency, was assessed with the ability to generate a list of items within a given category, in which patients generated as many as possible names of animals within 60 seconds [11, 12]. Surface dyslexia was tested by having subjects read 6 irregular words and measured as the number correct out of 6. Syntax comprehension was measured using a subset of 5 items from the

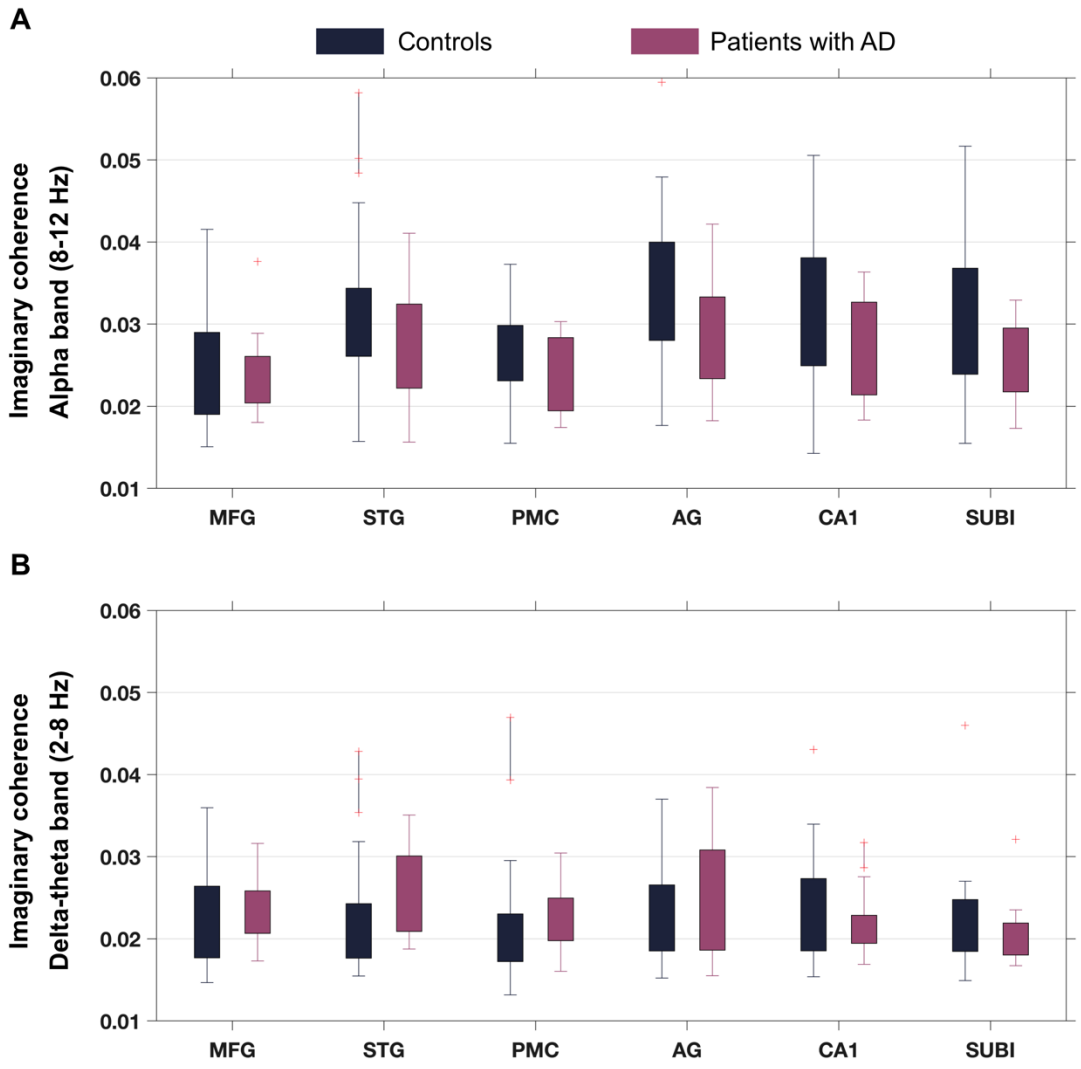
Boston Diagnostic Aphasia Evaluation for which the examiner read a sentence aloud, and the participant had to select from among 4 options the picture that best matched the sentence.

Visuospatial: Subjects were asked to copy a complex figure (Benson figure) as the object of visual construction and the accuracy was scored on a 17-point scale[14]. The Number Location subtest of the Visual Object Space Perception (VOSP)[17] test required the participant to precisely locate a stimulus on a two-dimensional plane, requiring dorsal-stream ("where") visual processing and scored out of 10. The face matching subtest of the Comprehensive Affect Testing System (CATS)[18] is a ventral-stream task involving 12 trials where the participant determined whether two faces are the same or different.

Emotion naming: The affect matching subtest of the CATS[18] contained 16 trials where the participant was shown a photo of an emotional face and required to select the correct label from a list (i.e. 'happy', 'sad', 'angry', 'frightened', 'surprised', 'disgusted' or 'neutral').

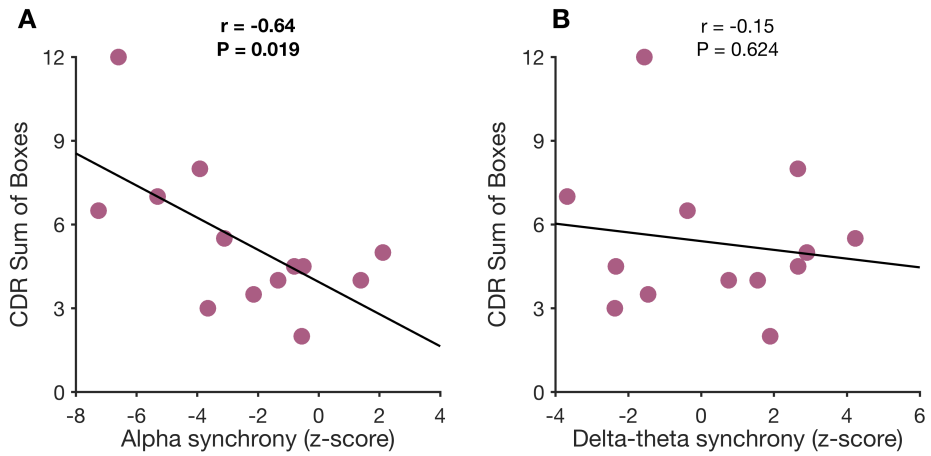
2. Supplementary Figures

Supplementary Figure 1



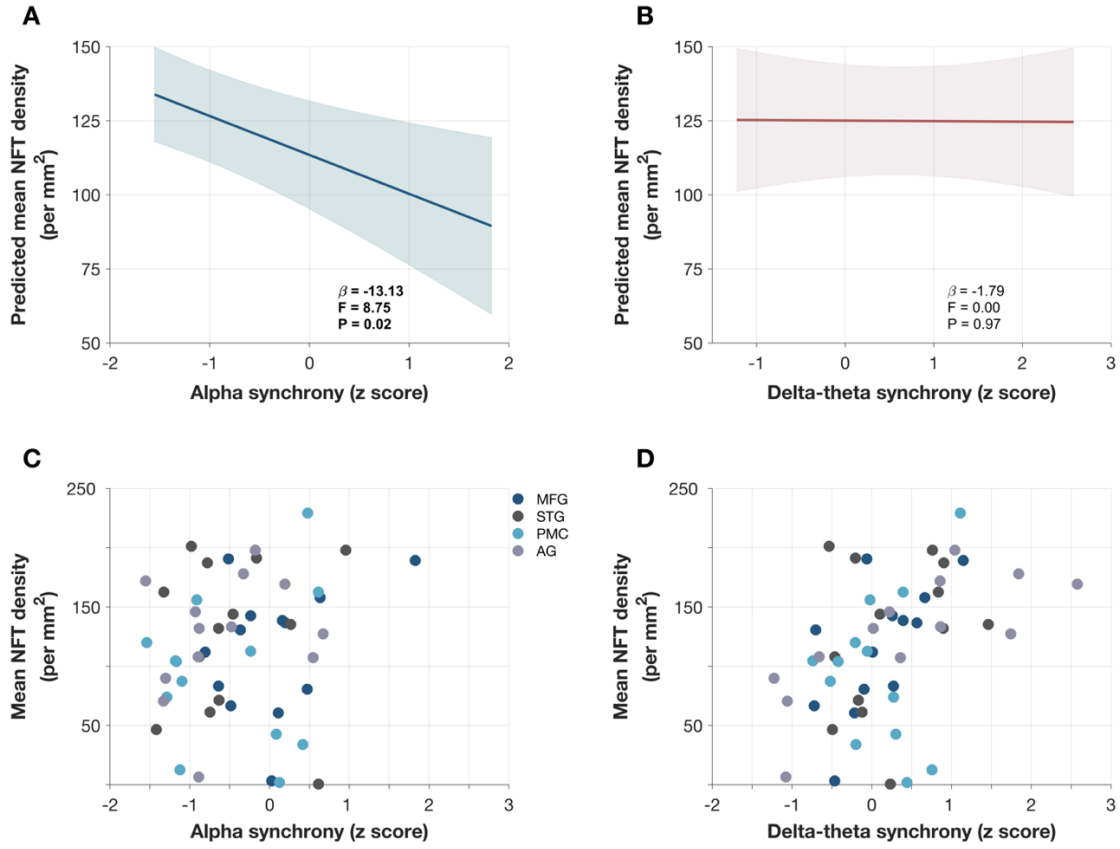
Frequency-specific neuronal synchrony within select ROI: Regional values of imaginary coherence within alpha (A) and delta-theta (B), frequency oscillations in patients with AD and age-matched controls for six regions of interest (ROI) including, angular gyrus (AG), primary motor cortex (PMC), superior temporal gyrus (STG), middle frontal gyrus (MFG), hippocampus-CA1 (CA1), and subiculum (SUBI), in patients with AD. Neuronal synchrony is depicted as the average imaginary coherence estimate per each region (n=13, patients with AD; n=23 age-matched controls). Abbreviations: AD, Alzheimer's disease.

Supplementary Figure 2



Associations of frequency-specific neuronal synchrony abnormalities and clinical deficits: Alpha synchrony deficits showed a significant negative correlation with CDRSOB values (A) while delta-theta synchrony deficits did not show significant correlations with CDRSOB (B) recorded at the time of MEG scan in patients with AD. Each scatter plot depicts the Pearson correlation coefficient and regression lines after correlating the sum of z-scores across the six ROIs within each frequency band and CDRSOB. Abbreviations: CDRSOB, Clinical Dementia Rating Sum-of-Boxes; MEG, magnetoencephalography.

Supplementary Figure 3



Prediction of NFT burden by frequency-specific neuronal synchrony deficits in neocortical ROIs: Estimates from linear mixed-effects models predicting the NFT burden by alpha (8-12) synchrony deficits (A) and delta-theta (2-8 Hz) synchrony deficits (B), based on the four neocortical regions. Each mixed-effects model included a repeated measured design to include four regions per subject and additional variables of CDR at death, CDRSOB difference from MEG to death and time duration from MEG to death. The model fits depicted in A and B were computed at group averages for other additional variables. (2.45, 9.07, and 4.74, for CDR, CDRSOB difference and time difference, respectively). Raw data points depicting the regional (neocortical only) values of mean NFT densities and mean imaginary coherence in alpha (8-12 Hz) band (C), and delta-theta (2-8 Hz) band (D), in patients with AD. Abbreviations: AG, angular gyrus; AD, Alzheimer's disease; CDR, clinical dementia rating; CDRSOB, clinical dementia rating sum-of-boxes; MEG, magnetoencephalography; MFG, middle frontal gyrus; NFT, neurofibrillary tangle; PMC, primary motor cortex; STG, superior temporal gyrus.

3. Supplementary Tables

3.1. Supplementary Table 1: Demographic and neuropathological characteristics of AD patients

Case	Sex	Age at disease onset (years)	Age at death (years)	ApoE allele	Clinical syndrome	Brain weight	Braak stage	Thal stage	CERAD score	ABC score
1	F	54	68	E3/E3	PCA	868	6	5	Freq	A3, B3, C3
2	M	58	72	E3/E4	Amnestic /dysexecutive	1093	6	5	Freq	A3, B3, C3
3	M	58	69	E3/E3	PCA	1101	6	5	Freq	A3, B3, C3
4	M	47	58	E3/E3	lvPPA	1231	6	5	Freq	A3, B3, C3
5	F	59	67	E3/E4	Amnestic /dysexecutive	1000	6	5	Freq	A3, B3, C3
6	M	47	59	E3/E3	Amnestic /dysexecutive	1090	6	5	Freq	A3, B3, C3
7	F	54	64	E3/E4	Amnestic /dysexecutive	870	6	5	Freq	A3, B3, C3
8	F	51	62	E3/E4	PCA	1005	6	5	Freq	A3, B3, C3
9	F	56	67	E4/E4	Amnestic /dysexecutive	1001	6	5	Freq	A3, B3, C3
10	F	56	64	E3/E3	Amnestic /dysexecutive	1061	6	5	Freq	A3, B3, C3
11	M	63	71	E3/E4	Amnestic /dysexecutive	1199	6	5	Freq	A3, B3, C3
12	M	79	85	E3/E3	Amnestic	1032	5	4	Freq	A3, B3, C3
13	F	56	67	E2/E4	lvPPA	970	6	5	Freq	A3, B3, C3

Abbreviations: ABC score, ABC score for Alzheimer's disease neuropathology; Amnestic/dysexecutive, AD patients with predominant amnestic and dysexecutive symptoms; lvPPA, logopenic variant of primary progressive aphasia; PCA, posterior cortical atrophy syndrome.

3.2. Supplementary Table 2: Biomarkers of AD patients at the time of MEG evaluation

Case number	CSF	Amyloid[§]	FDG[¶]	MRI
1	-	Positive	Positive	Bilateral parietal atrophy with posterior predominance
2	-	Positive	Positive	Diffuse cortical atrophy with L > R parietal atrophy
3	Aβ42=143[¥] t-Tau=71[¥] p-Tau=18[¥]	Positive	Positive	Hippocampal atrophy and diffuse cortical atrophy predominantly in the L > R occipital and parietal lobes
4	-	Positive	Positive	L > R parietal atrophy
5	-	Positive	Positive	L > R hippocampal and parietal atrophy, diffuse white matter changes consistent with cerebral amyloid angiopathy
6	-	Positive	Positive	Generalized atrophy, predominantly in L > R hippocampal and parietal regions
7	-	-	-	R > L hippocampal atrophy and diffuse cortical atrophy predominantly in the bilateral dorsal parietal regions
8	-	Positive	Positive	L > R hippocampal, occipital, and parietal atrophy
9	-	Positive	Positive	L > R hippocampal atrophy and diffuse cerebral atrophy with posterior predominance
10	-	Positive	Positive	Bilateral parietal atrophy
11	-	Positive	Positive	Diffuse atrophy predominantly in the hippocampi and posterior cortex
12	-	-	-	Bilateral hippocampal atrophy and diffuse cortical atrophy with posterior predominance
13	-	Positive	Positive	Bilateral parietal atrophy

Abbreviations: Aβ42 = amyloid-β peptide ending in amino acid residue 42; CSF = cerebrospinal fluid; L = left; MRI = magnetic resonance imaging; p-Tau = tau phosphorylated at threonine 181; R = right; t-Tau = total tau.

[§] Positron emission tomography agent was ^{11}C-Pittsburgh compound B.

[¶] Positron emission tomography imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) showing patterns of hypometabolism consistent with Alzheimer's disease.

[¥] Values supporting a diagnosis of Alzheimer's disease are Aβ42 level <192 pg/ml, t-Tau level >93 pg/ml, and p-Tau level >23 pg/ml (Alzheimer's Disease Neuroimaging Initiative Biomarker Core at the University of Pennsylvania).

3.3. Supplementary Table 3: Neuropsychological test performance in patients with AD at the time of MEG evaluation

Variable	Score (Mean ± STD)	z-score (range: min – max)
Episodic memory function		
Visual free recall (Benson 10 minutes)	3.42 ± 3.48	-4.11 – -0.58
Short delay verbal memory (CVLT 30 seconds)	4.31 ± 2.59	-7.76 – 0.99
Verbal free recall (CVLT 10 minutes)	2.77 ± 3.44	-5.51 – 0.78
Executive function & working memory		
Design Fluency	5.08 ± 3.03	-3.85 – 0.15
Cognitive control (Stroop Inhibition/color naming)	0.38 ± 0.25	-4.91 – 1.33
Verbal working memory (Digit span forward)	4.46 ± 1.05	-3.58 – -0.04
Attention (Digit span backward)	3.00 ± 0.58	-2.71 – -1.18
Set shifting (Modified trails – speed)	0.15 ± 0.2	-2.25 – -0.04
Verbal learning (CVLT total score)	16.69 ± 5.84	
Language function		
Reading irregular words	5.25 ± 1.06	-9.8 – 0.2
Syntax comprehension	3.15 ± 1.46	-2.82 – 0.17
Verbal Agility	3.62 ± 1.45	-9.75 – 0.52
Boston Naming Test	11.92 ± 2.53	-9.19 – 0.70
Lexical Fluency (D words/1 minute)	9.00 ± 4.43	-3.96 – -0.10
Category Fluency (Animals/1 minute)	10.38 ± 4.70	-3.28 – -0.80
Repetition	3.00 ± 1.41	-6.57 – 0.57
Visuospatial function		
Face discrimination (CATS – face matching)	10.64 ± 1.29	-5.47 – 0.41
Visuoconstruction (Benson copy)	9.08 ± 5.63	-26.46 – 0.46
Location discrimination (VOSP number location)	6.73 ± 2.53	-5.08 – 0.81
Calculations	2.62 ± 0.87	-6.27 – -1.27
Emotion naming (CATS – affect matching)	11.91 ± 1.45	-2.78 – 0.36

Z-scores were calculated based on age-matched normal control data sets from UCSF-MAC; Abbreviations: CVLT=California Verbal Learning Test; CATS=Comprehensive Affect Testing System; VOSP=Visual Object and Space Perception.

3.4. Supplementary Table 4: Demographic characteristics of controls

Measure	Control Estimate	Statistical comparison with patients with AD
Age at MEG – yr (mean ± SD)	64.88 ± 5.21	t = -0.94, P = 0.351
Sex (Female) – no. (%)	14 (60.87%)	χ^2 = 0.168, P = 0.68
Race (White) – no. (%)	22 (95.65%)	(*Fisher's exact test*), P = 1.000
Handedness (Right) – no.(%)	18 (78.26%)	(*Fisher's exact test*), P = 1.000
Education – yr (mean ± SD)	17.60 ± 1.75	t = -1.98, P = 0.056
CDRSOB at MEG (mean ± SD)	0 ± 0	P < 0.0001
CDR at MEG (mean ± SD)	0 ± 0	P < 0.0001

Abbreviations: AD, Alzheimer's disease; CDR, Clinical Dementia Rating, CDRSOB, CDR Sum-of-Boxes; MEG, Magnetoencephalography

3.5. Supplementary Table 5: Anatomical regions selected from Brainnetome atlas parcellations to match the histopathologically defined regions

Histopathological regional label	Brainnetome atlas region
Middle frontal gyrus (MFG)	A8vl
Superior temporal gyrus (STG)	A22c
Primary motor cortex (PMC)	A4ul
Angular gyrus (AG)	A39rv
Hippocampus: CA1	Caudal hippocampus
Hippocampus: Subiculum	Rostral hippocampus

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