

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (<i>n</i>) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☒	☐ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection	No novel code or software was used for data collection. Behavioral data for the Gradual Onset Performance Task were collected using Psychophysics Toolbox extension in MATLAB (MathWorks). iEEG data were collected using Tucker Davis Technologies (TDT) system.
Data analysis	No novel code or software was developed for data analysis. CCEP preprocessing followed our previously established and published pipeline (Lyu et al., 2025, *Mapping human thalamocortical connectivity with electrical stimulation and recording*, *Nature Neuroscience*). All code is available at the public repository https://zenodo.org/records/15330862 . Unless otherwise specified in the respective Methods sections, data processing, statistical analyses, and figure generation were performed in Python (v3.13.14) using NumPy (v2.5.1), pandas (v2.3.3), SciPy (v1.18.0), scikit-learn (v1.8.0), statsmodels (v0.15.0), Matplotlib (v3.11.0), seaborn (v0.13.2), Plotly (v7.0.0), Nilearn (v0.14.1), NiBabel (v5.4.2), openpyxl (v3.1.5), and Selenium (v4.48.0). Electrode localization was performed using Biolume Suite, FSL, FreeSurfer, iELVis Toolbox, and ANTs (v2.6.0). ANTs (v2.6.0), NiBabel (v5.4.2), and Nilearn (v0.14.1) were additionally used for atlas transformation into native space, electrode labeling, and surface visualization.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The fsaverage7 template for visualization can be obtained using the `nilearn.datasets.fetch_surf_fsaverage` function in Python. The Brainnetome Atlas and Jubrain Atlas used for labeling and parcellation in this study are publicly available at <https://atlas.brainnetome.org/download.html> and <https://search.kg.ebrains.eu/instances/f1fe19e8-99bd-44bc-9616-a52850680777>. We have mapped the four insular regions in MNI152 ICBM 2009c Nonlinear Asymmetric space and have made them available for download on this platform:

<https://github.com/lbcn-stanford/Nature2026>. Electrophysiological connectivity data from our study, along with the exact coordinates of the stimulated and recorded sites in MNI space are also shared on the same GitHub platform. Due to patient confidentiality issues and HIPAA regulations, we cannot share any data with patient identifiers. However, the anonymized raw iEEG data can be obtained from the corresponding author after completing a data sharing agreement.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	In this study, 87 participants (53 male, 34 female; age range: 19-67 years) were recruited.
Reporting on race, ethnicity, or other socially relevant groupings	The ethnicity composition of the participants in the study are self-identified Asian (8.24%), Black (4.71%), Hispanic (31.76 %), Mixed (3.54%) and White (50.59%).
Population characteristics	87 patients with focal epilepsy (53 male, 34 female; age range: 19-67 years) participated in our study. They underwent implantation with stereotactic electroencephalography (sEEG) electrodes to pinpoint the location of their seizure onset zone based solely on clinical considerations. All patients in this cohort had implanted electrodes in the insular cortex. Before participating in the experiment, participants gave informed consent and volunteered to participate in research.
Recruitment	All participants undergoing invasive electrophysiological monitoring as part of their treatment for refractory epilepsy at Stanford Health Care are offered to participate voluntarily in research activities. Prior to their recruitment, all participants are informed about the purpose of the research studies and once they provide written informed consent, they are recruited to take part in experimental studies. The study protocol is approved by the Institutional Review Board for human experimentation and reviewed annually. In our study, we analyzed data from patients who had insular electrodes. Of note, the placement of electrodes was determined exclusively based on clinical requirements and not for research purposes.
Ethics oversight	The SEP data included in our manuscript were collected entirely by our collaborators at Ospedale Niguarda, Milan, Italy, under a separate institutional ethics approval (ID 939-2.12.2013). Some of these data have been previously published (Avanzini et al., NeuroImage, 2018) and were made available to our team in de-identified form for secondary analysis. As these data were already published and fully de-identified, no additional ethics approval was required for their use in the present study. Institutional Review Board #11357 covered the following procedures: - Intracranial EEG recordings at rest and during cognitive experiments (including GradCPT task) - Retrospective review of clinical data acquired during high-frequency functional mapping stimulations (50 Hz) - Stanford Cohort. During this clinical procedure, stimulation with 50Hz signals is applied as a routine clinical standard of care for all patients undergoing presurgical intracranial monitoring - entirely independent of the patients' research participation. High-frequency stimulation is ordered and performed by the clinical epilepsy team for two purposes: (a) functional cortical mapping to identify eloquent cortex prior to potential resection or ablation, and (b) elicitation of the patient's habitual auras to help localize the epileptic network. Every patient with implanted electrodes undergoes this procedure as part of their clinical evaluation. The research described in this manuscript consisted of systematically (and retrospectively) analyzing the subjective reports generated by these clinical stimulations, within the framework of our IRB-approved research protocol. - Single-pulse CCEP stimulation, Stanford Cohort - Research Procedure: The cerebrocerebral evoked potential (CCEP) stimulations with repetitive 0.5Hz signals used for connectivity mapping were performed as a dedicated research procedure, conducted under our IRB-approved protocol (IRB #11354) with specific informed research consent obtained from each participant prior to the procedure. These stimulations do not cause any side effects (e.g., nausea) Peripheral nerve stimulation for somatosensory evoked potentials (SEPs), Italian Cohort - Research Procedure (Separately Approved): The SEP data included in our manuscript were collected entirely by our collaborators at Ospedale Niguarda, Milan, Italy, under a separate institutional ethics approval (ID 939-2.12.2013). Some of these data have been previously published (Avanzini et al., NeuroImage, 2018) and were made available to our team in de-identified form for secondary analysis. As these data were already published and fully de-identified, no additional ethics approval was required for their use in the present study.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Similar to the majority of iEEG studies, we did not conduct a priori sample size estimation. Sample size was determined by the availability of patients with drug-resistant focal epilepsy who underwent intracranial monitoring and had electrodes implanted in the insula during the study period (2012–2025). A total of 87 participants were recruited over this 14-year timespan. Different subsets of participants contributed data to specific analyses. For functional mapping, 50 participants were included (478 insular electrodes). For the Gradual Onset Continuous Performance Task (Grad-CPT), 35 participants contributed data (455 insular electrodes). Insular CCEP connectivity analyses included 47 participants (413 stimulated electrode pairs, 751 recording pairs within the insula). The full cortical-insular connectivity dataset comprised 56 participants with 460 insular stimulation pairs, 930 insular recording sites, 2,643 cortical stimulation pairs, and 5,112 cortical recording sites.
Data exclusions	For functional mapping, responses were excluded if they failed to meet the following criteria: (1) reproducibility during real but not sham stimulation, (2) reproducibility across multiple stimulations of the same site, or (3) clear dose–response relationship with increasing stimulation intensity. For Grad-CPT behavioral analyses, channels were excluded if they (a) showed variance exceeding 5× or falling below 0.2× the cross-channel median variance, (b) contained spikes exceeding 1 spike/second (defined as inter-sample voltage changes ≥ 80 μV), (c) exhibited pathological high-frequency oscillations, or (d) displayed abnormal power spectral characteristics upon visual inspection. For CCEP analyses, data underwent notch filtering (60, 120, 180 Hz) followed by exclusion of noisy channels and trials. Channels were excluded based on extreme raw amplitude (>5 SD), frequent spikes ($>3\times$ median spike rate), high mean absolute voltage (>4 SD), or elevated trial variance (>3.5 SD); trials with mean amplitudes exceeding 4 SD were also discarded. For statistical analyses, we applied conservative dual-criterion outlier detection combining IQR and z-score methods. Data points were excluded only if flagged by both the IQR method (values $< Q1 - 1.5\times IQR$ or $> Q3 + 1.5\times IQR$) and z-score method ($z > 3$), preserving biological variability while eliminating technical artifacts.
Replication	To ensure reproducibility, CCEP connectivity data, stimulation data, and electrode coordinates in MNI space will be made publicly available upon publication. Detailed descriptions of all methods are provided in the manuscript. To ensure generalizability, all statistical analyses were performed at two levels: (1) electrode-pair level, analyzing individual connections, and (2) subject level, aggregating data within participants. This hierarchical approach accounts for within-subject correlation while enabling population-level inference.
Randomization	Randomization was not performed. Electrode implantation locations and stimulation sites were determined entirely by clinical needs for presurgical epilepsy evaluation. We analyzed data from all available electrodes meeting inclusion criteria.
Blinding	Blinding was not applicable to this study. Electrode placement and stimulation sites were determined entirely by clinical needs rather than experimental design. For functional mapping, patients reported subjective experiences during stimulation; however, responses were only included if they met strict reproducibility criteria: (1) occurrence during real but not sham stimulation, (2) reproducibility across multiple trials, and (3) dose-response relationship with stimulation intensity. These criteria minimized expectation bias. All other outcome measures were objective electrophysiological recordings (iEEG signals, CCEP responses) analyzed using automated algorithms that do not depend on researcher or participant expectations.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Plants

Seed stocks	Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.
Novel plant genotypes	Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.
Authentication	Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.

Magnetic resonance imaging

Experimental design

Design type	Electrode localization without experiment design
Design specifications	A thin cut head-CT, obtained after electrode implantation, was co-registered to pre-operative 3Tesla MRI data for verification of the trajectory. Precise electrode positioning in the FreeSurfer surface space, voxel space and MNI space were automatically extracted by the iELVis toolbox. The T1-weighted MRI scan was used to generate 3D cortical volume and subcortical segmentation using recon-all command of Freesurfer v7.3.2. The post-implant CT scan were co-registered to the pre-implant MRI using the flirt from the Oxford Centre for Functional MRI of the Brain Software Library or using bbrregister from Freesurfer to get the best results. We manually labelled each electrode on the T1-registered CT image using BiImageSuite . The anatomical localization of electrodes was determined using a two-step approach. First, a trained anatomist (J.P.) identified the location of each electrodes based on macroscopic anatomical landmarks in the native anatomical space, and labeled those within the insular boundaries, as "insula". Second, the microstructural subdivision of the human insula from the Julich Brain Atlas was co-registered from MNI-152 space to each participant's T1-weighted native space using ANTs . The coordinates of each Insula electrode contact were then used to automatically extract the corresponding atlas label. For insula contacts, microanatomical labeling was additionally reviewed and verified by another anatomist and specialist in the cytoarchitectonic map of the insula (J.Q.)
Behavioral performance measures	Not applicable

Acquisition

Imaging type(s)	structural T1-weighted
Field strength	3T
Sequence & imaging parameters	TR = 3000 ms, TE = 1.6 ms, TI = 1100 ms, flip angle = 8°, 0.9 × 0.9 × 1.0 mm voxels, and matrix = 256 × 256 × 156.
Area of acquisition	whole brain scan
Diffusion MRI	☐ Used ☒ Not used

Preprocessing

Preprocessing software	Freesurfer, FSL
Normalization	Freesurfer. Normalization was used only for visualizing electrode coverage at the group level. All analyses including region identification of the contacts were conducted in the individual's native brain space.
Normalization template	FS_LR surface template for insular electrodes visualization (e.g. Figure 1a); MNI305 volume template for electrode localization within the hippocampus in the Figure 1b and insula in the Supplementary Figure S3
Noise and artifact removal	Not applicable
Volume censoring	Not applicable

Statistical modeling & inference

Model type and settings	Not applicable
Effect(s) tested	Not applicable

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

(See [Eklund et al. 2016](#))

Correction

Models & analysis

n/a		Involved in the study
☒	☐	Functional and/or effective connectivity
☒	☐	Graph analysis
☒	☐	Multivariate modeling or predictive analysis