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ALICE: A tool for Automatic Localization of Intra-Cranial Electrodes for clinical and high-density grids

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Abstract

Background—Electrocorticographic (ECoG) measurements require the accurate localization of implanted electrodes with respect to the subject's neuroanatomy. Electrode localization is particularly relevant to associate structure with function. Several procedures have attempted to solve this problem, namely by co-registering a post-operative computed tomography (CT) scan, with a pre-operative magnetic resonance imaging (MRI) anatomy scan. However, this type of procedure requires a manual and time-consuming detection and transcription of the electrode coordinates from the CT volume scan and restricts the extraction of smaller high-resolution ECoG grid electrodes due to the downsampling of the CT.

New Method—ALICE automatically detects electrodes on the post-operative high-resolution CT scan, visualizes them in a combined 2D and 3D volume space using AFNI and SUMA software and then projects the electrodes on the individual's cortical surface rendering. The pipeline integrates the multiple-step method into a user-friendly GUI in Matlab®, thus providing an easy, automated and standard tool for ECoG electrode localization.

Results—ALICE was validated in 13 subjects implanted with clinical ECoG grids by comparing the calculated electrode center-of-mass coordinates with those computed using a commonly used method.

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Comparison with Existing Methods—A novel aspect of ALICE is the combined 2D-3D visualization of the electrodes on the CT scan and the option to also detect high-density ECoG grids. Feasibility was shown in 5 subjects and validated for 2 subjects.

Conclusions—The ALICE pipeline provides a fast and accurate detection, discrimination and localization of ECoG electrodes spaced down to 4 mm apart.

Keywords

ECoG; Electrode localization; ALICE; clinical grid; high-density grid; integrated pipeline

1. Introduction

Intracranial electrocorticography (ECoG) in humans has recently received an increased interest in the clinical and scientific community, since it provides a direct measure of neuronal activity in the human brain with high spatial and temporal resolution (Crone et al., 1998; Freeman et al., 2000; Jacobs and Kahana, 2010; Miller et al., 2009). In particular, ECoG has been increasingly used as a diagnostic tool for patients with intractable epilepsy, providing not only additional seizure localization information (Salles et al., 1994; Diehl and Lüders, 2000; Lesser et al., 2010), but also allowing for the functional mapping of eloquent cortical areas, such as motor, language and visual areas. Besides the characterization of epileptic tissue, ECoG recordings provide measurements from regions of the cortex that are considered normal in terms of expected location and functional response to tasks (Jacobs and Kahana, 2010). Therefore, ECoG has also been used as a tool to investigate normal human brain function, such as the characterization of spontaneous neuronal activity (Foster et al., 2016; Liu et al., 2015), the study of the coupling between blood-oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI) responses and features of the ECoG signals (Gaglianese et al., 2017; Hermes et al., 2012; Jacques et al., 2016; Ojemann et al., 2013; Siero et al., 2013), and for the design of advanced neuro-implants such as Brain-Computer Interfaces (BCIs) (Yanagisawa et al., 2012; Hotson et al., 2016; Vansteensel et al., 2016).

For all the above cited purposes, the accurate localization of ECoG electrodes on the individual subjects' cortex is crucial to determine the area from which the specific neuronal responses profiles are being recorded, and for the optimal co-localization with, for instance, fMRI activations. To date, electrode localization can be assisted by a combination of computational algorithms and advanced medical imaging techniques. Ideally, post-implantation MRI scans would be a promising solution to extract electrode coordinates (Schulze-Bonhage et al., 2002; Studholme et al., 2001). However, many medical institutions have prohibited this procedure due to the risk of electrode induction heating (Bhavaraju et al., 2002). Another attempt to reconstruct the electrode positions is through cranial X-rays (Dalal et al., 2008; Miller et al., 2007). Although medically safe, these methods lack either information about the individual subjects' anatomy (i.e., they project directly on a standardized brain) or require information from intraoperative photos, which may not be available for electrodes placed away from the trepanation site.

More recently, some alternative methods have been proposed, which use a post-operative computed tomography (CT) scan to localize the electrodes on the individual's anatomical space (Brang et al., 2016; Dykstra et al., 2012; Groppe et al., 2017; Hermes et al., 2010; Qin et al., 2017; Blenkmann et al., 2017). One of these methods has been previously presented by Hermes et al. (2010) and has become a commonly accepted method (cited over 100 times) to localize the electrodes using postoperative CT. This method detects and projects the electrodes by automatically correcting for possible brain shifts caused by the surgical intervention (Hill et al., 1998). However, this and other available procedures present a few limitations. In previous methods such as (Dykstra et al., 2012; Hermes et al., 2010) the detection and transcription of the electrode coordinates is done manually in 2D space, making the entire process user-dependent and time consuming. The 2D space visualization makes it rather hard to separate overlapping electrodes, especially in the cases where the overlapping occurs in the frontal-opercular, inferior temporal and inferior visual cortices. For that, recent open-source pipelines have presented a method based on a 3D space (Qin et al., 2017; Groppe et al., 2017; Blenkmann et al., 2017), as a solution for this problem. However, to our knowledge, these pipelines do not present a solution to visualize and manually intervene in case of complex grid implantations where multiple grids and strips overlap. Additionally, none of the published pipelines localized and validated the localization of electrodes from high-density ECoG arrays. Indeed, for these increasingly used grids (Bouchard et al., 2013; Siero et al., 2013; Kellis et al., 2016; Wang et al., 2016), with inter-electrode space of 3–5 mm, a solution has yet to be presented. In this case, electrode detection may be difficult since these tend to merge with one another due to the small electrode size and spacing. Co-registering and re-slicing of the CT scan to the space of the T1, as available pipelines appear to do (Dykstra et al., 2012; Qin et al., 2017; Groppe et al., 2017; Blenkmann et al., 2017), limit the accuracy of detection of such small electrodes.

To overcome these issues, we present an improved and fast pipeline that automatically detects electrodes on the original high-resolution post-operative CT scan and visualizes them in a synchronized 2-dimensional (2D) and 3-dimensional (3D) spaces using AFNI (<http://afni.nimh.nih.gov/afni>) (Cox, 1996) and SUMA (<https://afni.nimh.nih.gov/afni/suma>) (Saad and Reynolds, 2012), respectively. This procedure, named ALICE, allows users to detect and visualize ECoG electrodes of both clinical and high-density grids, to manually separate overlapping electrodes, and to easily sort and label them according to a given layout. Electrodes are then projected using the brain shift correction method previously published by Hermes et al. (2010), and are visualized on the individual's cortical surface rendering obtained using FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>). This pipeline is integrated and controlled through a graphical user interface designed in Matlab 9.0®.

2. Materials and Methods

2.1 Subjects

Seventeen patients (median age 22, range 11–49; see Table 1) with intractable epilepsy were intracranially implanted with subdural standard clinical (13 subjects) or high-density (5 subjects) ECoG grids in order to localize seizure focus. One patient (S13) had both. The standard clinical ECoG grids (subjects S1–13) had an inter-electrode distance center-to-

center of 1 cm and 2.3 mm exposed surface diameter (AdTech, Racine, USA). The high-density grids had either 32 electrodes (S13 and S17) with 1.3 mm exposed surface diameter and inter-electrode distance of 3 mm center-to-center (AdTech, Racine, USA), or 64 (S14 and S16) with 1 mm exposed surface diameter and 4 mm center-to-center distance (PMT Corporation, Chanhassen, USA), or 128 electrodes (S15) with 1.17 mm exposed surface and 4 mm inter-electrode distance (AdTech, Racine, USA). The ethical committee of the University Medical Centre Utrecht approved this study in accordance with the Declaration of Helsinki 2013, and all patients gave written informed consent.

2.2 Pre- and post-operative imaging scans

For each patient included in the study a T1-weighted structural pre-operative MRI scan was acquired on a 3T scanner (Philips Achieva, Best, the Netherlands), with an isotropic voxel size of 1 mm. Cortical surface segmentation of each subject's anatomy was performed using FreeSurfer (<https://surfer.nmr.mgh.harvard.edu/>). Additionally, a post-operative high-resolution 3D-CT scan was acquired to locate the electrodes (Philips Tomoscan SR7000), with voxel sizes of 0.49 mm × 0.49 mm × 1 mm for subjects S3–6, S10, S14 and S15; 0.49 mm × 0.49 mm × 0.7 mm for subjects S1–2, S7, S13, S16 and S17; 0.49 mm × 0.49 mm × 0.45 mm for subjects S8–9 and S11; and, lastly, 0.43 mm × 0.43 mm × 0.5 mm for subject S12. Resolutions differed due to availability of one of multiple CT scanners at the time of the clinical CT scan.

2.3 ALICE procedure

The ALICE procedure consists of 5 steps (Figure 1) that use the pre- and post-operative imaging scans (see **section 2.2**) as input and display the ECoG electrodes on the individual subject's brain surface in Matlab®. The following sections explain in detail the procedure implemented in each step.

Step 1: Pre-operative MRI and Post-operative CT co-registration—Alignment (co-registration) of the high-resolution post-operative CT to the pre-operative MRI scan was implemented by resampling the CT to a 1×1×1 mm grid (anatomical MRI scan resolution), shifting the center of the CT scan to the center of the anatomical MRI scan, and aligning the scans using the local Pearson correlation cost function (`align_epi_anat.py` in AFNI) with a rigid-body constraint (Saad et al., 2009). Additionally, the MRI contrast was inverted to emphasize the skull, normally seen as a thin, dark layer in T1-weighted images.

The output aligned CT was only used to confirm the alignment was successful, since the electrode selection steps (**Steps 2 and 3**) are performed on the native, high-resolution CT. The resulting affine transformation matrix (T_{affine}) is saved for later translation of the electrodes' center-of-mass coordinates to the MRI in **Step 4**.

Step 2: Electrode identification—Electrodes were detected by identifying electrode-containing voxels (in the CT) and clustering such voxels for each electrode separately. Electrode voxels were automatically defined and clustered on the native CT using a 3D clustering function implemented in AFNI (`3dclust.py`). This function allows for intensity-based cluster detection in 3D datasets defined by a connectivity radius parameter: only the

voxels closer than the given radius are included in the cluster. The function requires three parameters. First, a threshold based on the electrode voxel intensity values, which isolates the electrode voxels from other features on the CT, such as the skull and artifacts. Second, a minimum cluster volume, which is a measure of electrode size (in micro-liters). And lastly, the connectivity radius (in millimeters), used to separate electrode clusters, which depends on the inter-electrode space distance of the ECoG grid. For example, given a grid with 4 mm electrode diameter and 1 cm inter-electrode space, the minimum cluster volume could range from 3 uL to 10 uL, and the connectivity radius could be 1 mm size.

The obtained clusters are further refined by a series of morphological operations of erosion by one voxel (to remove very narrow clusters), followed by dilation of two voxels. The clustering algorithm is then re-applied to the output dataset. Finally, each electrode cluster is indexed, color-coded and transformed into individual surfaces using the IsoSurface function in AFNI. The method works reliably because the electrodes have a density determined by CT that is different than tissue. With standardization by Hounsfield units, these will be the same even across CT scanners. The centers-of-mass of each color-coded electrode-cluster, calculated as the mean voxel coordinates, are used in **Step 3**.

Step 3: Electrode selection and sorting in 3D space—Once the electrode-clusters are detected, these need to be sorted and labeled according to the layout of the electrode leads. We were able to considerably simplify and accelerate this process by creating an interface that displays the electrode-clusters (see **Step 2**) simultaneously in both slice and surface views using AFNI (Figure 2B) and SUMA (Figure 2A), respectively. These two programs are linked and synchronized, such that a point selected in the 3D space immediately updates the position in the 2D space. With the surface view in 3D space, the electrode-clusters can be easily identified and selected in the appropriate order (i.e., according to the layout of the electrode leads) using a semi-automatic procedure. Electrode sorting is done manually by clicking on electrodes in the correct order using the 2D-3D interface, while numbering is automatically assigned to each electrode, in the same step. Labeling (attributing a grid label to each electrode) is done semi-automatically in the last step of the pipeline (see Video 1), where the grid label, electrode numbers and grid size are specified in the interface. To overcome the issue of overlapping or missing electrode clusters, the interface allows the manual selection of the voxel of the correct electrode's center-of-mass in the 2D slice view of the volumes, and the automatic creation of a cluster centered on the selected voxel respectively (using a sphere with a radius equal to the electrode size). During this step, for each selected cluster (electrode) the number and center-of-mass coordinates are automatically saved in a text file.

Step 4: Electrode co-registration—This coordinate text file is loaded in Matlab 9.0® and the coordinates are converted to MRI space using the affine transformation matrix (T_{affine}), produced in **Step 1**. For this CT space, $\vec{X}$, is projected to the MRI space, $\vec{X}_{aligned}$ as follows:

$$\vec{X}_{aligned} = T_{affine}^{-1} \cdot \vec{X}_{\Leftrightarrow} \quad (1)$$

$$\Leftrightarrow \begin{bmatrix} x_a \\ y_a \\ z_a \\ 1 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & a_{13} & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ a_{31} & a_{32} & a_{33} & a_{34} \\ 0 & 0 & 0 & 1 \end{bmatrix}^{-1} \cdot \begin{bmatrix} x \\ y \\ z \\ 1 \end{bmatrix}, \quad (2)$$

where a_{ij} are the elements of the matrix that represent rotation, translation, scaling, aspect ratio and shearing transformations.

Step 5: Electrode projection and visualization—The projection of the electrodes is a crucial step for precise localization, especially due to the inevitable leakage of cerebrospinal fluid (CSF) that causes the brain to sag away from the skull due to the opening of the skull during surgery (Hill et al., 1998). This mismatch between the MRI and the CT is often visible on the post-operative scan where the electrodes may seem to fall inside the cortex on the MRI image. The mismatch is corrected by projecting each electrode orthogonally to the surface defined by the electrode and its neighbors, onto a smoothed convex hull of the cortex extracted from the pre-operative MRI scan (Hermes et al., 2010). This method, validated for clinical grids using operative photos, was implemented in the current pipeline by projecting the electrodes to a convex hull computed from the FreeSurfer ribbon mask of the implanted hemisphere. Finally, the electrodes are visualized on the FreeSurfer brain surface rendering.

For high-density ECoG grids, we use and validate the method described in Kubanek and Schalk (2015), which projects the high-density electrodes by finding the intersection of the mean normal vector of the surface triangles of a smoothed hull of the cortex with vertices within a radius of the electrode position.

2.4 Method validation

To evaluate the accuracy of the current pipeline in the detection of clinical grids, we compared the projected electrodes coordinates obtained in **Step 5** for subjects S1–S13, with the projected electrodes coordinates computed by the currently validated method of Hermes et al. (2010). In both cases, electrodes were projected onto the same 3D FreeSurfer brain surface rendering. Mean Euclidean distances between electrode coordinates obtained with both pipelines were computed. To validate the detection of high-density grids, the projected electrode center-of-mass coordinates of two subjects (S14 and S17) were compared with surgical pre-operative photographs, a method previously used by Hermes et al. (2010).

3. Results

3.1. ALICE implementation

The ALICE pipeline was integrated and controlled through a graphical user interface designed in Matlab 9.0® and tested for Linux and Mac OS platforms. The program uses AFNI and SUMA open-source software in order to visualize and localize the electrode-clusters. The implementation is designed such that the user follows three consecutive steps, from co-registering the CT and MRI scans to projecting the electrodes on a cortical surface.

An example of using the program to localize electrodes for subject S12 can be seen in the Video 1.

3.2 Clinical grids validation

Electrode coordinates obtained with both the ALICE pipeline and the validated procedure (Hermes et al., 2010) were mapped onto the rendering of the cortical surface of each subject's brain (Figure 3, white dots and blue cross, respectively). The mean Euclidean distance ($\pm$ standard deviation) across electrode coordinates computed by the two procedures was calculated per subject (Figure 3) and across subjects (Figure 4). Results showed a mean distance between methods of 1.66 ± 1.06 mm (mean $\pm$ standard deviation), ranging from a minimum average across electrodes per subject of 0.82 mm and a maximum of 3.02 mm (Figure 4). The mean distance value is well within the projection error of 2.6 mm found in (Hermes et al., 2010) and within the average of 3 mm as reported by (Dykstra et al., 2012).

3.3 Overlapping electrodes

Sometimes grids overlap, making it difficult to disentangle overlapping electrodes belonging to different grids. Here, we illustrate the advantage of presenting the detected electrode clusters simultaneously on a 3D surface space. Indeed, using a 3D visualization of the ECoG grids with overlapping electrodes (Figure 5), even in strongly curved cortical areas, are easier to identify. After manually selecting one electrode's center-of-mass voxel, a spherical cluster is automatically created, thereby enabling disentanglement of overlapping electrodes (Figure 5).

3.4 High-Density grids

The current pipeline allowed the detection of electrodes in high-density ECoG grids with inter-electrode distance as small as 3 mm (Figure 6A). Here we show the results (Figure 6) for five patients implanted with high-density grids (3 mm and 4 mm inter-electrode distance, respectively), where the electrodes were displayed on the rendering of the cortical (FreeSurfer) surface of each patient. Since the electrode-clustering algorithm may fail to separate nearby electrodes with inter-electrode distance smaller than 4 mm (Figure 6B), the pipeline also allows the manual identification of the center-of-mass of each electrode in a 3D volume space and create electrode-clusters by using a sphere of a given radius centered on a specific voxel (see **section: 2.3 - Step 3**).

3.4.1 Validation—To estimate the accuracy of the high-density grid projection, the location of the projected electrodes was compared to photos taken during implantation (pre-operative photo). Due to poor visibility of the high-density grid of S13, S15 and S16 on the operative photo (mostly located underneath the skull), we show results for only S14 and S17 (Figure 7 and Supplementary Figure 1). For that, the distance between the electrodes on the rendered brain (Figure 7C, H and I) and the operative photo (Figures 7A, B, F and G) was computed. This procedure, previously used in (Hermes et al., 2010), uses anatomical features, such as sulci (Figure 7E) and blood vessels (Figure 7D) to match the brain rendering to the pre-operative photo. Results (Figure 8) show a mean distance between electrodes on the CT and electrodes visible on the operative photo of 1.01 ± 0.41 mm for S14 and 1.94 ± 0.50 mm for S17.

4. Discussion

Accurate localization of the electrodes on the brain surface is crucial for the interpretation of the electrocorticography, both in a clinical context and in research. Here we present an integrated pipeline that provides a fast and automatic extraction, discrimination and localization of electrodes' center-of-mass from ECoG grids with inter-electrode distance down to 3 mm, and allows visualizing them in a combined 2D and 3D space using open-source software (AFNI and SUMA).

The pipeline was validated for the clinical grids by comparing the electrode position obtained with ALICE with the previously validated procedure by Hermes et al. (2010). The error was comparably smaller than the error expected from the projection alone (1.66 mm against 2.6 mm; (Hermes et al., 2010)), and within the 3 mm average error found by (Dykstra et al., 2012), showing that this pipeline yields electrode positions consistent with the already validated methods.

A unique feature of ALICE is the detection of the electrodes' center-of-mass from the original high-resolution CT scan, before any resampling is performed. A transformation matrix is then directly applied to the electrode coordinates, in order to co-register the electrode positions to the MRI scan. This feature is essential to accurately localize electrodes in high-density ECoG grids and was validated in two subjects, yielding electrode positions highly similar (less than 2 mm distance) to those obtained from intraoperative photographs. This feature has not been shown by other pipelines (e.g., Blenkmann et al., 2017; Dykstra et al., 2012; Groppe et al., 2017).

ALICE also introduces a combined and synchronized 2D-3D grid visualization of the high-resolution CT scan that allows an efficient identification of electrodes according to the electrode grid placement. This feature allows for easy detection of overlapping electrodes even in the presence of multiple grids and strips. The pipeline automatically detects electrode-clusters from the CT scan, allowing for high reproducibility of the results. Moreover, it enables accurate manual identification of overlapping electrodes, and electrodes less than 3 mm apart, in an easy and time-efficient manner. Of note, with ALICE the complete procedure takes only 0.5–1 hour per patient, depending on the number of implanted and overlapping electrode grids. Similar features and performance have been recently shown in alternative toolboxes (Blenkmann et al., 2017; Groppe et al., 2017), though neither of them show or validate accurate electrodes localization for high density ECoG grids with inter-electrode distance down to 3 mm; nor they provide a simultaneous 2D and 3D display of both the electrode-clusters and the CT scan.

The pipeline does have limitations. First, ALICE does not allow for a fully automatic sorting and labeling of the electrodes according to the given layout (as shown in Blenkmann et al., 2017), a procedure that can be inevitable tiresome. However, manual labeling may be important to avoid errors when selecting a group of electrodes belonging to different grids, or in the case of multiple overlapping grids and strips. Second, ALICE does not yet allow for the projection of electrodes over previously resected cortical areas. Indeed, these resected cortical areas present neither gray nor white matter, but are typically filled with a gelatinous

substance, supporting the grids. Hence, any brain rendering based on white and gray matter segmentations fails to display the correct electrode position. Additionally, the current program has implemented only one projection and one visualization method (Hermes et al., 2010; Kubanek and Schalk, 2015). Any solution to these problems or improvements upon current components can be readily incorporated in the freely available current package.

5. Conclusion

We tested a new method for localizing ECoG electrodes and presented the features of the software pipeline. The key features of ALICE include automatic (hence reproducible) localization requiring minimal, user-friendly, interaction, short duration of the complete analysis (one hour or less) and good performance with high-density grids. The ALICE scripts are freely available upon request to the correspondent author, and will be available on GitHub (<https://github.com/UMCU-RIBS/ALICE.git>) upon publication of the manuscript.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Open-source MATLAB interface to localize intracranial electrodes.
- Combined 2D-3D visualization and detection of the electrodes.
- Automatic detection and discrimination of electrodes spaced down to 4 mm apart.
- Detection of both clinical and high-density intracranial grids.

Figure 1. ALICE pipeline back-end procedure

The back-end of the pipeline consists of 5 steps. The first step co-registers the high-resolution post-operative CT scan (post-CT) with the pre-operative anatomical MRI scan (pre-MRI). The second step extracts the center-of-mass for every electrode using a new automated voxel clustering function in AFNI. Then in step 3 one can sort and label each electrode's center-of-mass according to a pre-defined layout. Step 4 co-registers the center-of-mass of each electrode extracted from the CT space to the MRI anatomy space, using the affine transformation matrix resulting from step 1. Finally, in step 5 the electrodes are projected and visualized on the surface rendering of each individual's brain by means of the standard orthogonal projection method presented in Hermes et al. (2010).

Figure 2. AFNI-SUMA interface for electrode selection

A) SUMA displays the information in a 3D surface space. B) AFNI displays the CT and the electrode-clusters in the volume space. These two programs are linked and synchronized, such that an electrode selected in (A) (black arrow) immediately updates the position in the volumetric view in (B) (green vertical and horizontal crosshair lines).

Figure 3. Validation

For each subject, the electrode coordinates calculated using the method implemented in Hermes et al. (2010) (white circles) and ALICE (blue crosses) were displayed (in Matlab 9.0®) on each individuals' FreeSurfer cortical surface rendering of the implanted hemisphere. The mean and standard deviation distance (in mm) across the electrode coordinates, d , obtained by the two methods is displayed beneath each subject's brain surface. N represents the number of projected electrodes for each subject. The black shaded region in S13 indicates previously resected cortex. Whether the blue cross or the white circle is displayed on top depends on the 3D coordinates of the electrode.

Figure 4. Validation results for clinical grids

Box-plots of the Euclidean distance between projected electrodes obtained using ALICE and Hermes et al. (2010) methods for all subjects (i.e., median distance from all subjects) and per individual subject. In total 744 electrodes. White circles with gray dot in the middle indicate the median distance value; the thick gray bars indicate the 50% of the distribution; the thin black lines indicate the maximum and minimum distance; and the outliers are indicated by empty white circles (i.e., points that are larger than $Q3 + 1.5 \times (Q3 - Q1)$ or smaller than $Q1 - 1.5 \times (Q3 - Q1)$, with $Q1$ and $Q3$ the 25th and 75th percentile, respectively). A uniform random displacement jitter is used in order to make duplicate outlier-points visible.

Figure 5. Detection of overlapped electrodes

Example of 6 overlapping electrodes in subject S12. The 3D visualization of the grids allows the user to identify to which grid the electrode belongs to and by knowing in advance the clinical grid layout. Even though these were not separated in the clustering process, these could be manually detected and added as an extra cluster by placing a sphere with center coincident with the center of the electrode as detected in the volume space (see Figure 2). The small (yellow) electrode indicated with * is the standard platinum marker of the grid.

Figure 6. High-density grid electrode detection

Electrode clustering in SUMA (insets) of high-density ECoG grids. Visualization of the electrodes was achieved using the method described in Kubanek and Schalk (2015) and displayed on the FreeSurfer cortex rendering. A) For a grid with 4mm inter-electrode spacing the high-resolution CT has enough resolution to separate all electrodes automatically. 3D SUMA surface visualization (inset) shows independent clusters for all electrodes. B) Grids with 3 mm electrode distance require some manual interaction (white-circled electrodes). The black shaded region in S13 indicates previously resected cortex.

Figure 7. Validation of high-density grid projection

An intraoperative photo (B) is used to mark the blood vessels (blue, D) and sulci (green, E) for subject S14. The sulci in the brain rendering (C) were also identified (red, H). Linear and non-linear transformation (to account for cortical curvature lost in the photo) were used to map the sulci between (H) and (E), resulting in a match (I) between the sulci in the reference photo (B) and the sulci in (H) using Photoshop®. A similar procedure was used to match the blood vessels (D) to the intraoperative photo with the high-density grid. The electrodes mapped to the reference photo (yellow circles) could be then compared with ones from the CT (blue circles) (J). The gray circles in (J) had no match with intraoperative photo due to lack of visibility.

Figure 8. Validation results for high-density grids

Box-plots of the Euclidean distance between projected electrodes obtained using ALICE and the electrodes mapped to an intraoperative photo. White circles with gray dot in the middle indicate the median distance value; the thick gray bars indicate the 50% of the distribution; the thin black lines indicate the maximum and minimum distance; and the outliers are indicated by empty white circles (i.e., points that are larger than $Q3 + 1.5 \times (Q3 - Q1)$ or smaller than $Q1 - 1.5 \times (Q3 - Q1)$, with $Q1$ and $Q3$ the 25th and 75th percentile, respectively).

Table 1

Patient characteristics and ECoG grid information.

Patient No.	Age	Gender	Implanted hemisphere	Grid type	Grid location
S1	14	F	Right	Clinical	Frontal-parietal
S2	14	F	Right	Clinical	Superior frontal-parietal
S3	16	M	Right	Clinical	Inferior frontal-parietal and posterior temporal
S4	11	M	Left	Clinical	Frontal, anterior parietal
S5	15	F	Left	Clinical	Frontal, anterior parietal
S6	41	F	Left	Clinical	Inferior frontal parietal and temporal
S7	22	F	Right	Clinical	Temporal, inferior frontal-parietal
S8	21	M	Left	Clinical	Inferior frontal-parietal
S9	25	M	Left	Clinical	Frontal-parietal
S10	49	M	Left	Clinical	Temporal, inferior parietal
S11	45	M	Left	Clinical	Temporal, inferior parietal
S12	26	M	Left	Clinical	Posterior frontal, anterior parietal and superior temporal
S13	29	M	Left	Clinical and high-density	Parietal (previous superior parietal resection)
S14	19	M	Left	High-density	Inferior parietal
S15	36	F	Left	High-density	Inferior and superior parietal
S16	22	M	Left	High-density	Superior parietal
S17	19	M	Left	High-density	Superior parietal