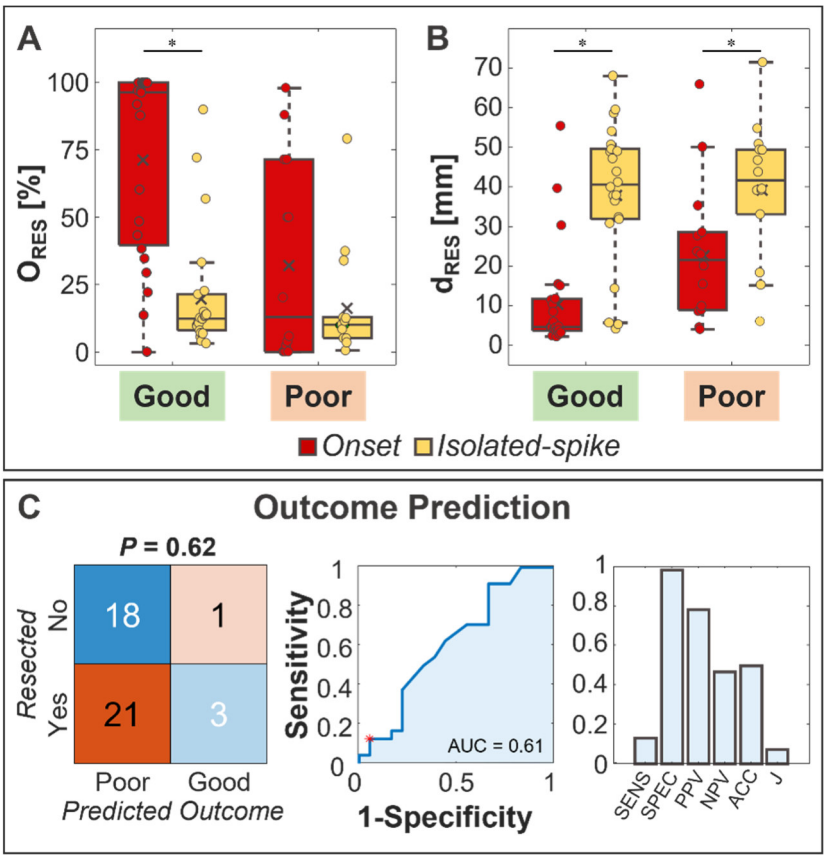
Supplementary Materials

Isolated spikes



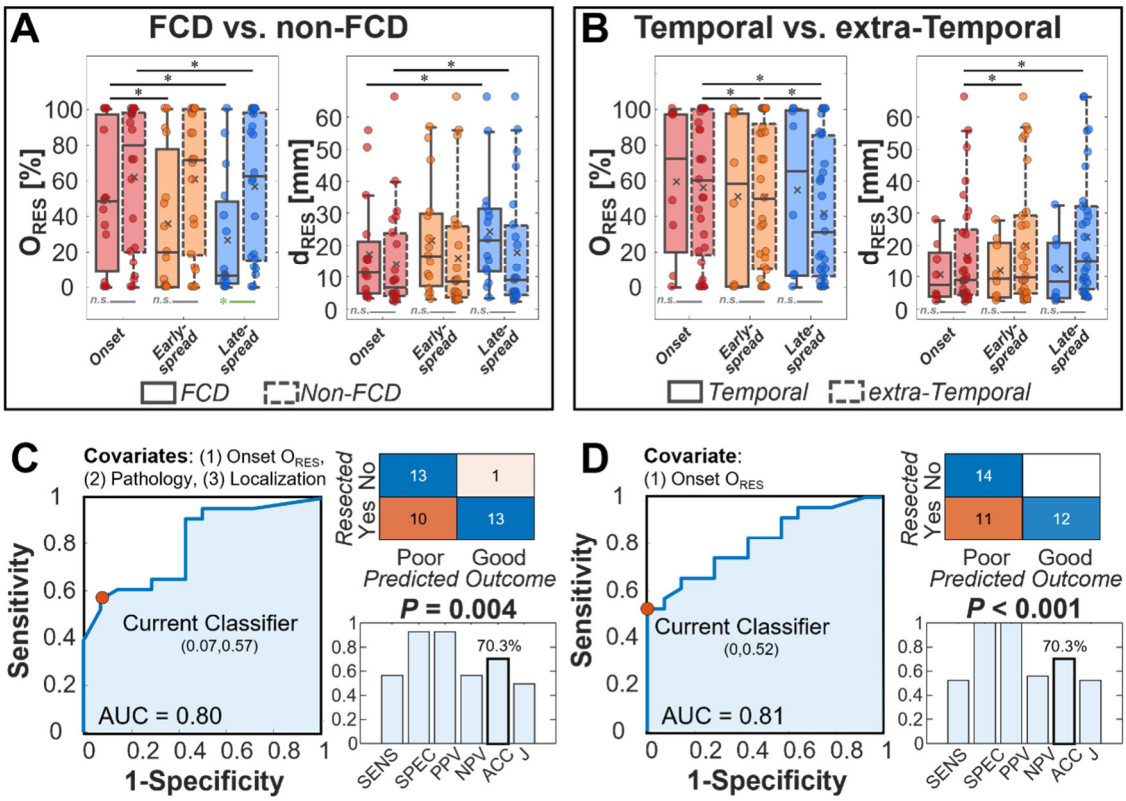
Supplementary Figure 1. Assessment of isolated-spikes to localize the EZ and predict surgical outcome. (A) Overlap with resection in percentage (O_{RES}, left) and **(B)** distance from resection (d_{RES}, right) in mm for the isolated-spikes (yellow) compared with the *onset* zone (red). **(C)** ROC curves for O_{RES} of the *isolated-spike.*

We examined whether the isolated spikes were able to localize the epileptogenic zone (EZ) and tested whether their resection predicted outcome better than the spike onset. We localized with ESI the most frequently occurring isolated spikes in iEEG channels (i.e., isolated spikes only from iEEG channels having a number of events above one standard deviation). For each isolated event, we solved the inverse problem using dSPM obtaining spatiotemporal unconstrained dipole maps of time windows with 500 ms duration (centered at the isolated spike peak). We then computed each source's amplitude along these components and normalized this map with respect to its activation's maximum value following the same approach used for the propagating events. We defined as isolated spike zone for each patient, the union of all sources (above a specific threshold = 70% of the maximum current maps activation) of all the isolated events. To assess the ability of the isolated spike zone to approximate the EZ, we computed the percentage of overlap (O_{RES}) and the mean Euclidean distance from resection (d_{RES}). We then compared O_{RES} and d_{RES} for the isolated spike zone

and the onset zone. Finally, we tested whether the isolated spike zone was able to predict outcome using the receiver operating characteristic (ROC) curves.

We found no difference in the isolated spike zone O_{RES} (good: 12% [8-21%] vs. poor: 10% [5-13%]; P=0.39) and d_{RES} (good: 40 mm [32-50 mm] vs. poor: 42 mm [33-50 mm]; P=0.76) between good vs. poor outcome patients. Comparing the isolated spike with the *onset* zone, we found (i) a lower O_{RES} for isolated spike for good outcome patients (isolated: 12% [8-21%] vs. *onset*: 96% [40-100%]; P<0.001); (ii) no difference of O_{RES} (isolated: 10 [5-13%] vs. *onset*: 13% [0-71%]; P=0.27) for poor outcome patients; and (iii) higher d_{RES} for isolated spike in good (isolated: 40 mm [32-50 mm] vs. *onset*: 5 mm [4-12 mm]; P=0.002) vs. poor outcome patients (isolated: 42 mm [33-50 mm] vs. *onset*: 22 mm [9-29 mm]; P=0.02). From the ROC curve analysis, we observed that the isolated spike was not able to predict outcome (P=0.62), since it had a PPV of 75%, an NPV of 45%, an accuracy of 48% and an AUC of 0.61. In summary, *isolated spikes* are not reliable biomarkers of the EZ and do not predict outcome.

Effect of Pathology and Localizations on Outcome Prediction



Supplementary Figure 2. (A) Overlap with resection in percentage (O_{RES}, left) and distance from resection (d_{RES}, right) in mm for the three spike zones for FCD vs. non-FCD patients; **(B)** Overlap with resection in percentage (O_{RES}, left) and distance from resection (d_{RES}, right) in mm for the three spike zones and for temporal lobe vs. extra-temporal lobe epilepsy patients; **(C)** ROC curve analysis (left) and resulting confusion matrix (right) of the multivariate logistic regression model having as covariates the spike-*onset* O_{RES}, localization (dichotomized into temporal vs. extra-temporal), and pathology (dichotomized into FCD vs. non-FCD), and as output the surgical outcome; **(D)** ROC curve analysis (left) and resulting confusion matrix (right) of the logistic regression model having as covariate the spike-*onset* O_{RES} and as output the surgical outcome.

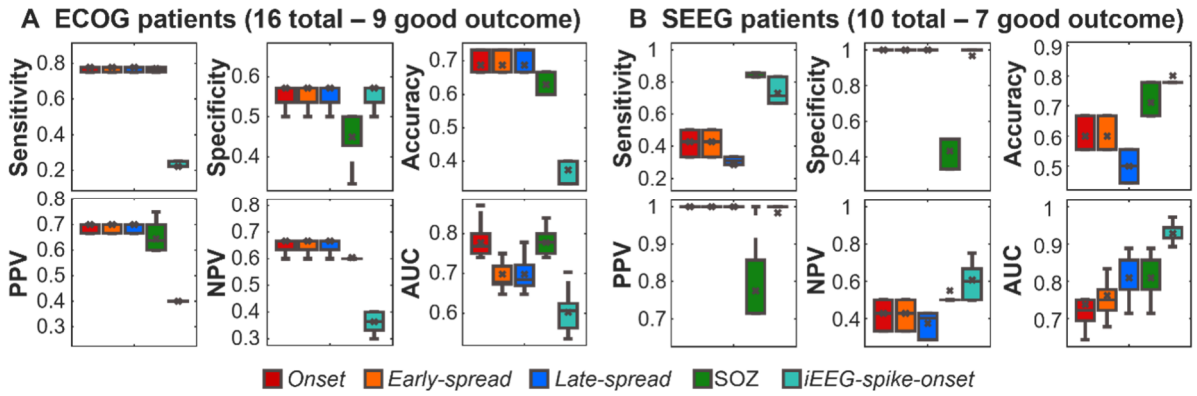
We investigated whether pathology related to cortical malformations or temporal lobe epilepsy introduced a bias in our results by following two different approaches: (i) examine the overlap of ESI zones with resection (O_{RES}) and the distance to resection (d_{RES}) for FCD vs. non-FCD patients, and for temporal lobe vs. extra-temporal lobe epilepsy patients; (ii) perform multivariate logistic regression analysis using two models: one having as covariate the spike onset O_{RES} and as output the surgical outcome, and the other one having as covariates the spike onset O_{RES}, localization (dichotomized in temporal vs. extra-temporal), and pathology (dichotomized in FCD vs. non-FCD), and as output the surgical outcome.

We found that there was no difference in the O_{RES} and d_{RES} between FCD vs. non-FCD patients, and between temporal vs. extra-temporal patients (see Supplementary Fig. 2A-B)

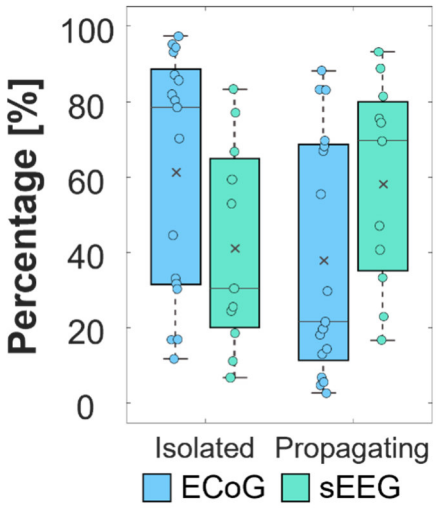
suggesting that this pathology and localization did not introduce any bias. Moreover, both regression models showed an accuracy of 70.3%, indicating that localization and pathology did not affect the prediction of surgical outcome.

We further observed that for patients with FCD the O_{RES} of spike *onset* (48% [9-97%]) was higher compared to both areas of spread (*early-spread*: 20% [0.3-78%], *P*=0.004; *late-spread*: 7% [2-48%], *P*=0.01, Supplementary Fig. 1A). For non-FCD patients, we also found higher spike *onset* O_{RES} compared to *late-spread* (*P*=0.04; *onset*: 80% [20-98%], *late-spread*: 62% [15-98%], Supplementary Fig. 2A). Moreover, we found lower O_{RES} of *late-spread* for patients with FCD vs. non-FCD patients (*P*=0.02). We did not find any differences for the O_{RES} of *onset*, *early-* and *late-spread* zones for patients with temporal lobe epilepsy (*onset*: 72% [20-97%]; *early-spread*: 58% [1-97%]; *late-spread*: 65% [7-99%], *P*>0.05, Supplementary Fig. 2B). However, we observed that for patients with extra-temporal epilepsy: (i) spike *onset* O_{RES} (60% [19-100%]) was higher compared to both areas of spread (*early-spread*: 50% [10-92%], *P*=0.03; *late-spread*: 31% [6-85%], *P*=0.001, Supplementary Fig. 2B) and (ii) early-spread O_{RES} was higher compared to late-spread (*P*=0.02).

We also investigated the ESI zones d_{RES} for FCD vs. non-FCD patients and for temporal lobe vs. extra-temporal lobe epilepsy patients. We observed: (i) lower spike *onset* d_{RES} compared to *late-spread* for both FCD (*onset*: 11 mm [5-21 mm], *late-spread*: 22 mm [12-31 mm], *P*=0.03, Supplementary Fig. 2A) and non-FCD patients (*onset*: 7 mm [4-24 mm], *late-spread*: 9 mm [5-26 mm], *P*=0.04, Supplementary Fig. 2A); (ii) lower spike *onset* d_{RES} (9 mm [4-25mm]) compared to both areas of spread (*early-spread*: 10 mm [5-29 mm], *P*=0.048; late-spread: 15 mm [6-32 mm], *P*=0.004, Supplementary Fig. 2B) for patients with extra-temporal lobe epilepsy.



Supplementary Figure 3. Outcome Prediction performances by Implant Strategy. (A) Sensitivity, Specificity, Accuracy, PPV, NPV and AUC leave-one-out cross validated measures evaluated for each ROIs in patients with ECOG implant. **(B)** Sensitivity, Specificity, Accuracy, PPV, NPV and AUC leave-one-out cross validated measures evaluated for each ROIs in patients with SEEG implant.



Supplementary Figure 4. Percentages of isolated and propagating events in ECoG vs. sEEG implant.