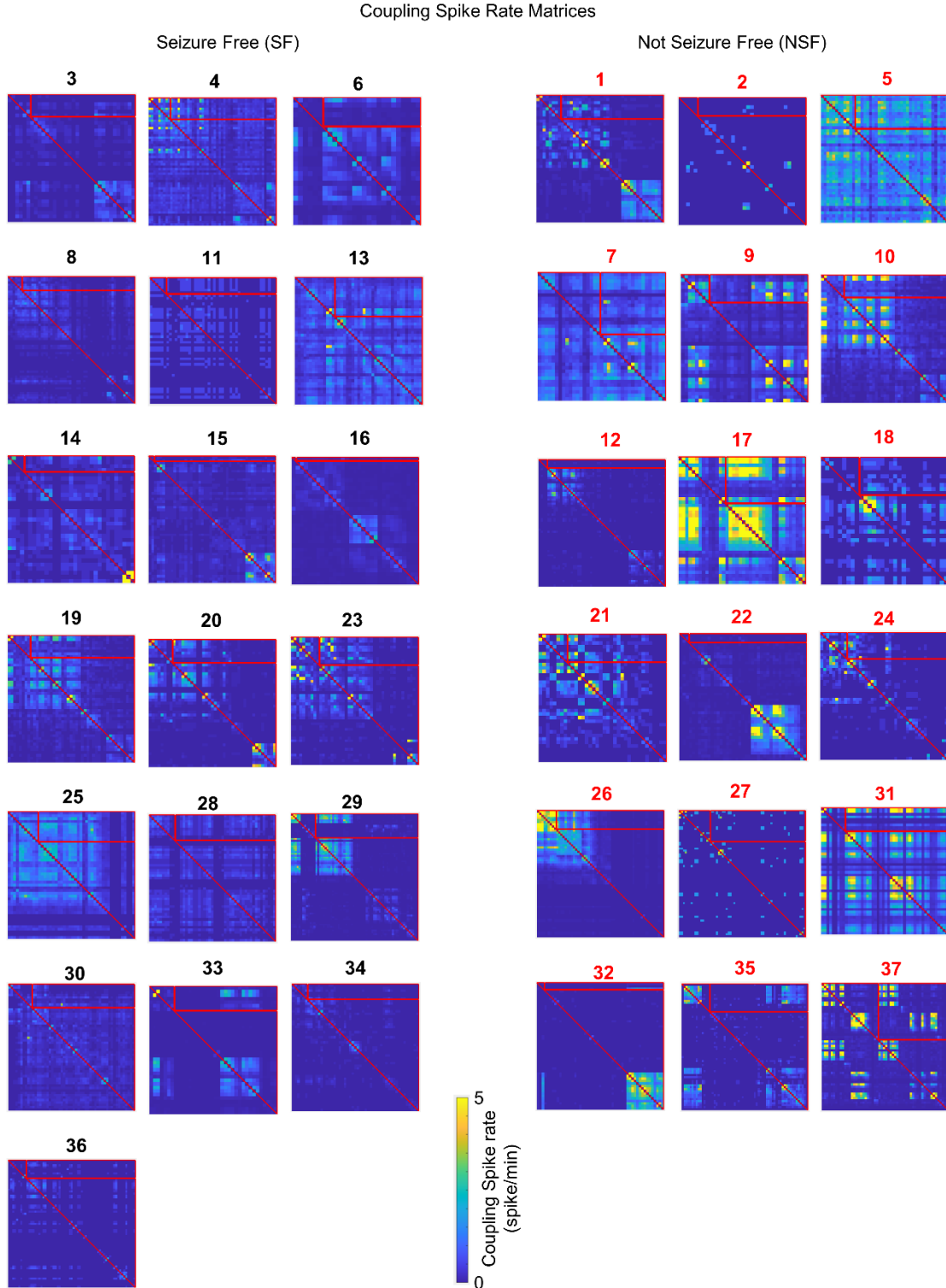
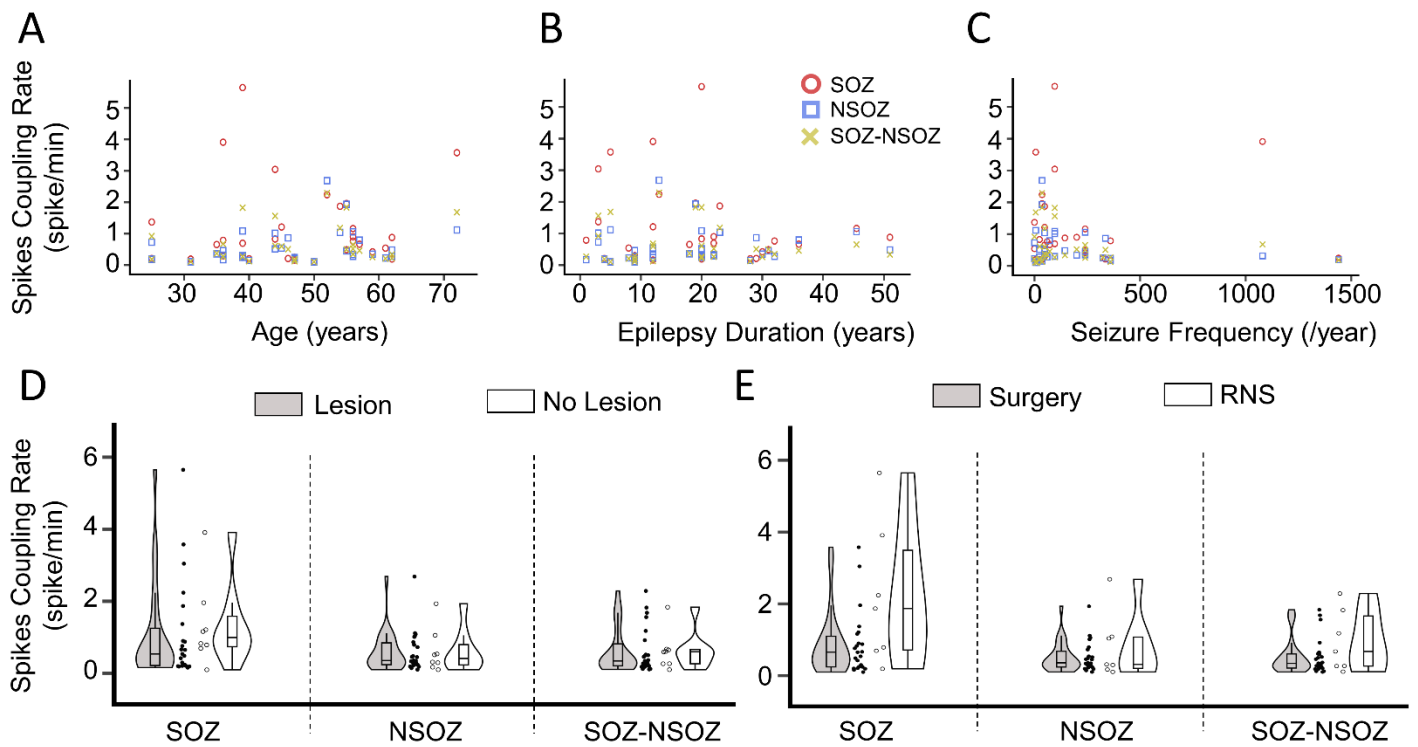


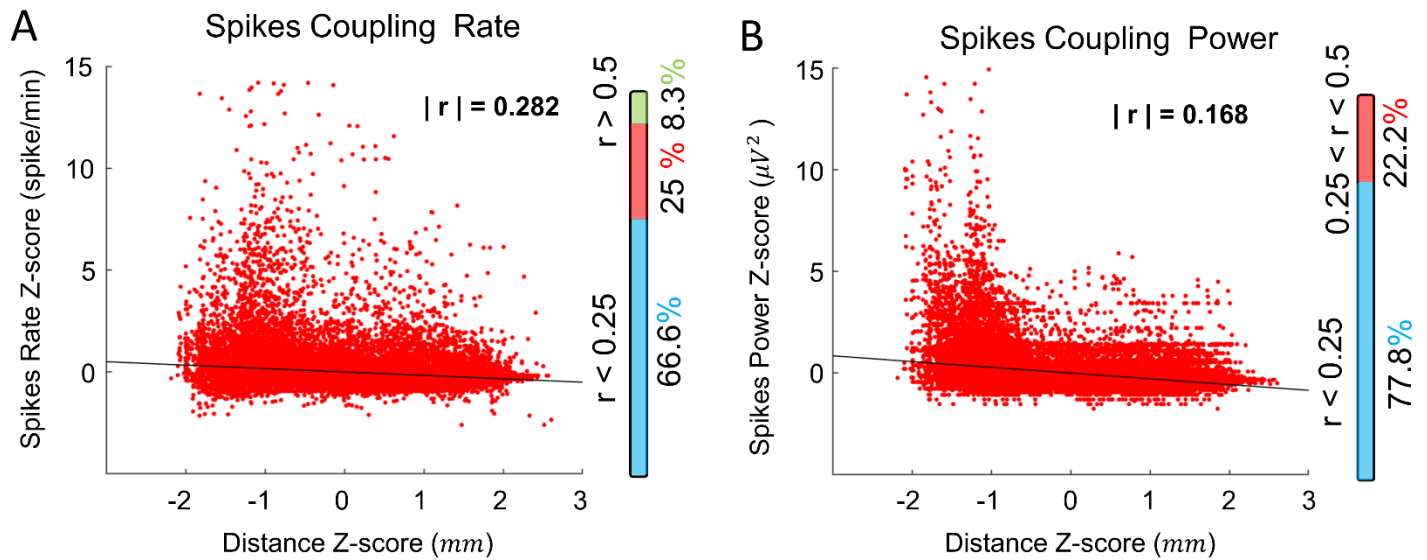
Supplementary Material



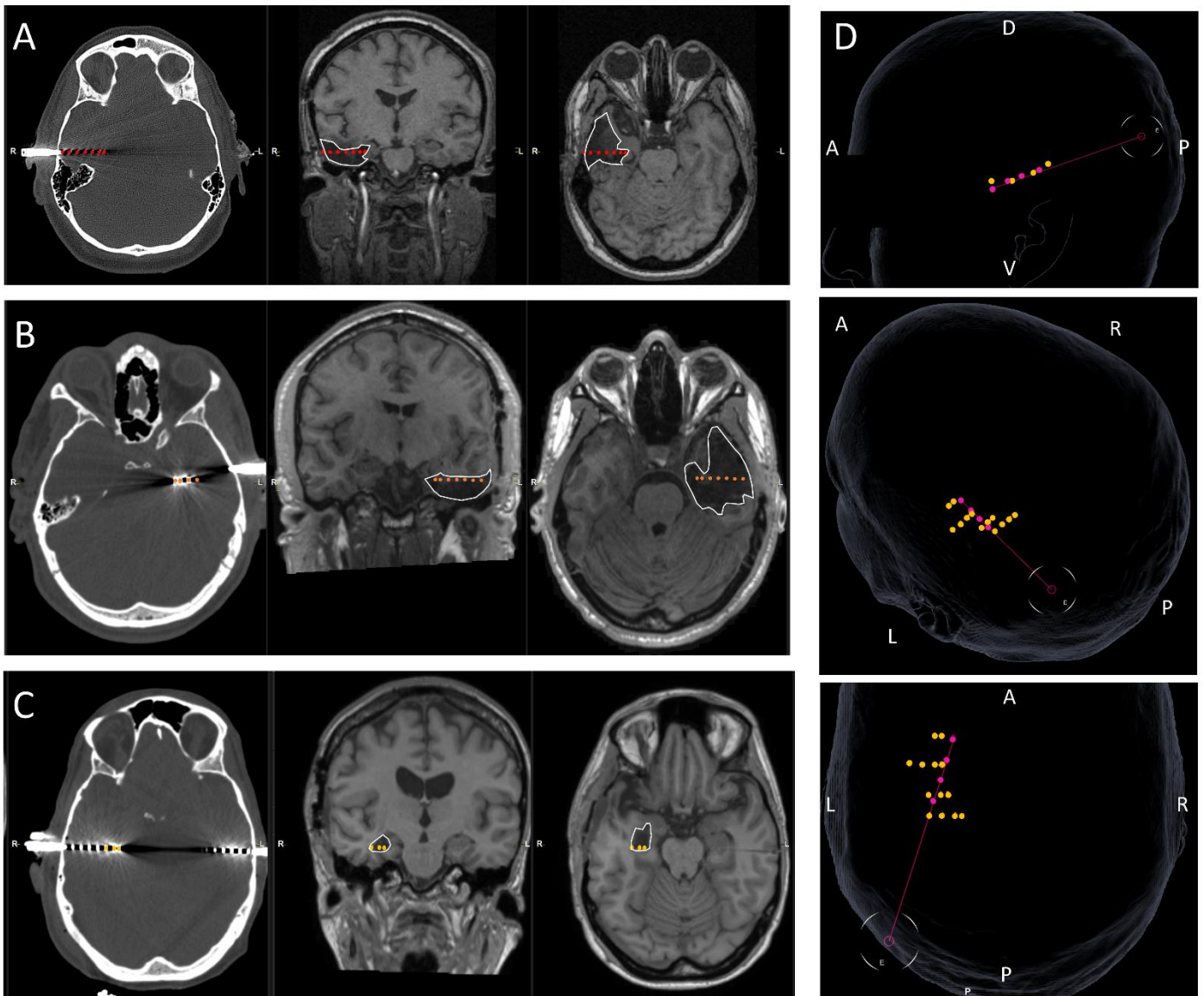
Supplementary Figure 1. Coupled spike rates matrices. Coupled spike rates matrices for all seizure free patients ($n=19$, left) and not-seizure free patients ($n=18$, right). The matrices are divided into 3 networks: in the seizure onset zone (SOZ, upper triangle), in non-SOZ (NSOZ, lower triangle) and between the SOZ and NSOZ (rectangle) networks.



Supplementary Figure 2. Coupled Spikes Rate as a function of clinical features of epilepsy. **(A)** Scatter plot of coupled spike rates as a function of Age. Different colors represent different zone networks, each patient is represented by an average of all pairs in 3 networks: when both contacts are part of the seizure onset zone (SOZ, red, Pearson correlation $r = 0.046$, $p_value = 0.806$), when both contacts are outside of the SOZ (blue, $r = 0.258$, $p_value = 0.162$) and when one is inside and the other outside (yellow, $r = 0.189$, $p_value = 0.309$). **(B)** Same as (A) but as a function of seizure frequency, the correlation coefficients and p-values for all 3 networks are $(-0.142, 0.445)$, $(0.063, 0.737)$ and $(-0.124, 0.508)$. **(C)** Same as (A) but as a function of patients age, the correlation coefficients and p-values for all 3 networks are $(0.051, 0.785)$, $(-0.213, 0.251)$ and $(-0.185, 0.320)$. **(D)** Violin plots comparing the average coupled spikes rates for three different zone networks between patients with MRI lesion (white, $n = 8$) and those without a lesion (grey, $n = 29$). The p_value for Wilcoxon test are 0.232, 0.992 and 0.484 for SOZ, NSOZ and SOZ-NSOZ respectively. **(E)** Violin plots comparing the average coupled spikes rates for three different zone networks between patients who had surgical resection (white, $n = 30$) and those without a lesion (grey, $n = 7$). The p_value for Wilcoxon test are 0.0861, 0.992 and 0.281 for SOZ, NSOZ and SOZ-NSOZ respectively. In all plots, each datapoint corresponds to a measure from a single patient.



Supplementary Figure 3. Correlation between coupled spikes rates, power and electrodes distance. (A) Scatter plots illustrating the z-score of coupled spikes rates for all patients in relation to Euclidean distance between channel pairs. The black line represents the linear least-squares fit. The vertical bar to the right shows the percentage correlation coefficients for individual patients. High $r > 0.5$ (shaded green), medium $0.25 < r < 0.5$ (red), and low correlation $r < 0.25$ (blue). **(B)** same as A but for z-scores of coupled spikes power. Each datapoint corresponds to either spikes coupling rate or coupling power for each single channel pair.



Supplementary Figure 4. Resection or Responsive NeuroStimulation (RNS) therapy in the seizure onset zone (SOZ). (A) Resection of tissue corresponding to SOZ in patient 24. Postimplant CT (left, axial) registered with postsurgical MRI in coronal (middle) and axial planes (right). Red dots denote contacts of depth electrode with distal contacts positioned in right entorhinal cortex. Area outlined in white indicates the margins of resection in the plane of view. (B) Same as panel A, but patient 25 and orange dots denote contacts of depth electrode positioned to sample left entorhinal cortex. (C) Same as panel A, but patient 34 and yellow dots denote contacts of depth electrode positioned to sample right middle hippocampus. (D) RNS therapy of the left mesial temporal lobe SOZ in patient 37. Full-head model illustrates trajectory of RNS probe (magenta line) with entry (E) from occipital cortex with contacts (magenta dots) positioned in left amygdala, hippocampus, and parahippocampal gyrus. Yellow dots denote depth electrode contacts of the left SOZ involving amygdala, entorhinal cortex, middle hippocampus, and parahippocampal gyrus. Sagittal view (top), clockwise-rotated posterolateral view (middle), and axial view (bottom). A=anterior, P=posterior, D=dorsal, V=ventral, L=left, and R=right.

Patient	Electrode	Detected Spikes	True Positives	False Positives	False Negatives	Sensitivity	False Negative Rate
Patient 1	RA1	75	69	6	8	92%	10.39%
	REC2	119	114	5	4	96%	3.39%
	RAH4	19	18	1	3	95%	14.29%
	RPG6	11	10	1	1	91%	9.09%
	LEC1	34	32	2	1	94%	3.03%
Patient 3	RA2	17	14	3	0	82%	0%
	RAC1	10	10	0	0	100%	0%
	LA2	43	36	7	2	84%	5.26%
	LAH6	178	168	10	5	95%	2.51%
	LEC5	57	50	7	1	88%	2%
Patient 6	RA1	68	60	8	2	88%	3.23%
	RAH2	70	70	0	4	100%	5.41%
	LAH3	38	31	7	3	82%	8.82%
	LOF4	1	1	0	0	100%	0%
	LEC2	20	18	2	2	90%	10%
Patient 7	REC3	12	12	0	1	100%	7.69%
	RAH2	426	425	1	0	99.7%	0%
	RPG1	8	8	0	0	100%	0%
	RPG6	28	27	1	2	96%	6.90%
	RPST2	48	47	1	4	98%	7.84%
Patient 10	REC1	224	222	2	15	99%	6.33%
	REC5	90	87	3	6	97%	6.45%
	RMTG3	117	117	0	3	100%	2.5%
	ROF3	2	2	0	0	100%	0%
	LA4	81	78	3	9	96%	10.34%
Patient 12	RA5	20	20	0	2	100%	9.09%
	RMH1	31	31	0	1	100%	3.13%
	RPSMA1	4	4	0	4	100%	0%
	LA3	34	29	5	0	85%	0%
	LAC2	15	13	2	0	87%	0%
Patient 15	RMH2	11	11	0	3	100%	21.43%
	RPHG1	21	20	1	3	95%	13.04%
	LAH5	14	12	2	1	86%	7.69%
	LOF3	7	6	1	1	86%	14.29%
	LOF4	4	3	1	0	75%	0%
Patient 30	LEC2	54	51	3	3	94%	5.56%
	LPHG1	9	7	2	0	78%	0%
	LPHG4	6	5	1	0	83%	0%
	LOF2	5	4	1	0	80%	0%
	LEC1	61	59	2	4	97%	6.35%
Patient 35	LEC1	54	49	5	2	91%	3.92%
	LEC2	55	45	10	2	82%	4.26%
	LAH1	62	54	8	2	87%	3.57%
	LPHG1	17	17	0	1	100%	5.56%
	LSTG4	0	0	0	0	100%	0%
Patient 37	RMH4	153	153	0	14	100%	8.38%
	RPHG1	337	336	1	11	99.7%	3.27%
	LEC2	426	420	6	3	98.5%	0.71%
	LAH5	42	38	4	9	90.48%	19.15%
	RA2	294	281	13	6	95.57%	2.09%
Total		3532	3394	138	148	96%	4.17%

Supplementary Table 1. Quantitative validation of spike detector performance.

patient	Temporal Lobe										Frontal Lobe						Cingulate Cortex			Parietal Lobe				Occipital Lobe	
	A	EC	MH	AH	PH	PHG	STG	TP	PT	FG	OF	SMA	FP	FO	F	SS	AC	MC	PC	IP	AP	PTB	SG	OT	O
1	RL	RL		RL		RL																			
2			RL		R		R				RL						R			R	R				
3	RL	L		L	R	L					L						R								
4	RL	RL		RL		RL					RL														
5	RL	R		RL	RL						RL														
6	RL	RL		RL							RL														
7	RL	R		RL		R	RL								R		R								
8	RL	RL		RL							RL	RL					RL								
9	L	L		RL		L		L			RL						L								
10	RL	R		RL			R				RL						R								
11	RL	RL		RL		RL					RL						RL								
12	RL	RL	RL								RL	RL					RL								
13	RL	RL		RL		RL					RL														
14	R	RL	RL								RL														
15	RL	RL	RL								RL		RL				L								
16	R		RL				RL									R					RL				
17	RL	RL	RL								RL														
18	R		R		R	R	R				RL														
19	RL	RL	RL			RL					RL														
20	RL	RL	RL			RL					RL														
21	R	RL	L			R	R		R							R									
22	L	RL				R				L														RL	
23	RL	RL	R	L		RL					RL														
24	R	RL	RL								RL	RL					R	R							
25	RL	RL	R	L		L					RL	RL												R	
26	R	RL	L	RL	R																			RL	
27	RL	RL	RL			RL													R					R	
28	L	RL	L	R		RL	L				R														
29	RL	RL		RL		RL					RL														
30	L	RL		R	L	L					L		L										L		
31	RL	RL		RL		L					L						L								
32	RL	RL		RL							RL						RL								
33	L	RL	RL			L					L														
34		RL	RL				L		R										L	R					R
35	RL	RL		RL		L	L				RL														
36	RL	R				RL					RL				R							RL			
37	L	RL	R	L		RL					RL														

Supplementary Table 2: Intracerebral electrodes positions in all 37 patients

Abbreviations:

TP: Temporal Pole
A: Amygdala

FP: Frontal Pole
OF: Orbitofrontal

EC: Entorhinal Cortex
AH: Anterior Hippocampus
MH: Middle Hippocampus
PH: Posterior Hippocampus
PHG: Parahippocampal Gyrus
FG: Fusiform Gyrus
PT: Posterior Temporal
STG: Superior Temporal Gyrus
PTB: Parietal-Temporal Border
O: Occipital Lobe
OT: Occipital-Temporal Border

F: Frontal Lobe
FO: Frontal Operculum
AC: Anterior Cingulate
MC: Middle Cingulate
PC: Posterior Cingulate
SMA: Supplementary Motor Area
SS: Supra-Sylvian
AP: Anterior Parietal Lobe
IP: Inferior Parietal Lobe
SG: Supramarginal Gyrus

Patients	Sex/age	Epilepsy duration	Seizure frequency (/month)	Site(s) of SOZ	MRI	Resected area	Surgical outcome/follow-up	Pathology	IIS sites
1	F / 38	36	6	RA, RAH, REC, RPHG	R/L HA	R AMTL	IIIB / 73	HS, gliosis	RAH, RA, REC, RPHG, LA
2	F / 17	8	90	RIP, RAP, RMH	Normal	R parietotemporal neocortex	IIC / 126	Subcortical WM ectopic neurons	NA
3	F / 42	30	20	LA, LEC, LAH	L HA	L AMTL	IB / 51	FCD Ia	NA
4	F / 39	32	5	RAH, RPHG, RA, REC	R/L HA	R AMTL	IA / 43	Gliosis	RA, REC, RAH, RPHG, LA, LEC, LAH, LPHG
5	F / 28	20	2	RA, RAH, REC, RPHG	Normal	R AMTL, temporal neocortical	IVB / 72	Subcortical WM ectopic neurons	RAH, RA, RPH, LAH, REC
6	F / 30	29	28	LA, LAH	L HA	VNS	IA / 12	NA	NA
7	M / 21	9	4	REC, RAH, RPHG	R FCD, PNH	R AMTL, temporooccipital	IIIA / 84	FCD Ic, IIa	RA, REC, RAH, RPHG, RSTP, RMC, LAH
8	F / 25	20	27	RAH, RA, REC	R/L HA	R AMTL	IB / 60	None	LA, LAH, LEC, RA, RAH
9	M / 42	22	16	LEC, LPHG, LA, LAH, RAH	R/L Hippocampal Hyperintensity	L AMTL	II / 36	None	NA
10	F / 48	32	9	RAH, RA	Normal	R AMTL	IIIC / 42	HS	NA
11	M / 40	5	1	LA, LEC, LAH	L Caudate Nucleus Atrophy	L AMTL	IA / 24	None	LAH, LA, LEC, RAH, RA, REC
12	F / 20	9	12	LA, LEC	Normal	L AMTL	IIIB / 51	FCD IIa	NA
13	F / 46	46	6	LA, LEC, LAH	L HA	L AMTL	IB / 9	HS	NA
14	F / 53	51	12	LEC, LMH, LA	L Hippocampal Hyperintensity	L AMTL	IA / 86	None	LEC, LMH
15	M / 45	5	8	LEC, LMH	L HA	L AMTL	IA / 58	None	REC, RMH, LEC, LMH
16	F / 50	24	2	RSTA, RSTP	R Perisylvian polymicrogyria	R temporoparietal neocortex, STG	IB / 2	Gliosis	RSTA, RSTP
17	F / 49	19	3	RA, REC, RMH, LA, LEC, LMH	Normal	R AMTL	IIA / 61	FCD Ic	REC, RMH, LA, LEC, LMH
18	F / 41	12	30	REC, RMH, RPHG, RSTG	Normal	R AMTL, R lateral TL	IIA / 17	HS, gliosis	REC, RMH, RPH, RSTG
19	M / 49	31	20	RA, REC, RMH, RPHG	Normal	R AMTL	IA / 1.5	FCD Ic, gliosis	RA, REC, RMH, RPHG, LA, LEC, LMH, LPHG
20	F / 35	30	110	LEC, LA, RA	L HA	VNS	IA / 10	NA	RA, RMH, LEC, LMH, LA
21	F / 29	18	4	REC, RA, RPHG, RSTP	R TPO polymicrogyria	R AMTL, STP	ID / 53	FCD Ic, IIa, IIb	RSTP, REC, RA, RPHG, LEC, LMH
22	M / 56	20	2	LA, LEC	L Posterior Comm. Artery Infarct	L AMTL	IIIB / 27	Subcortical WM ectopic neurons	LEC, LA
23	F / 40	12	4	RA, REC, RMH, RPHG	R FCD Temporal pole	R AMTL	IB / 45	FCD IIb, gliosis	RA, REC, RMH, LA, LEC, LMH
24	F / 34	22	8	REC, RMH	Normal	R AMTL	IVC / 48	Gliosis	REC, RMH, RA
25	M / 20	3	0	LA, LEC, LAH	L TL Tuber	L tailored resection mesial & lateral TL, inferior TL	IA / 48	TS	LA, LEC, LAH, LPHG, LEC, RA
26	F / 34	20	8	RAH, RA, REC	R/L PNH	RNS RAH and REC	IVB / 45	NA	RAH, RA, REC, RPHG
27	M / 27	9	1	RA, REC, RPHG, LA, LEC, LMH, LPHG	R HA	RNS L/R EC	IIIA / 38	NA	RA, REC, RMH, RPHG, LA, LEC, LMH, LPHG
28	F / 21	4	2	LEC, LA, LMH, LPHG	L Temporal pole encephalocele	L AMTL	IB / 35	HS, gliosis	LEC, LMH, RAH, REC, RPHG
29	M / 51	23	4	LEC, LAH, LPHG, REC, RPHG	R HA, L FCD	RNS L/R medial TL	IB / 24	NA	REC, RAH, RPHG, LAH, LPHG

30	M / 58	8	1	LPH, LEC, LA, RAH, REC	L HA	L AMTL	IB / 34	HS, gliosis	LPH, LEC, LA
31	F / 49	13	3	LA, LAH, LEC, LPHG	L Hippocampal Hyperintensity	RNS L medial TL and L EC	IIB / 28	NA	LAH, LEC, LA, LPHG
32	M / 69	5	0.5	LEC, LAH	L HA	L amygdalo-hippocampectomy w/ Visualase	IIIA / 55	NA	LEC, LAH, REC, RAH
33	M / 41	3	8	LMH, LEC, LPHG	LA hyperintensity	L AMTL	IA / 33	HS, gliosis	LEC, LMH, LA, LPHG
34	F / 44	9	120	REC, RMH	R/L PNH	R AMTL	IB / 31	None	REC, RMH, RMNH, RPNH, RINH, LPC
35	F / 33	1	30	LAH, LEC, LA, LEC	Normal	RNS L posterior and anterior border of the resection cavity, L posterior parietal lobe	IVB / 27	None	LAH, LEC, LA
36	M / 38	28	3	RPHG, REC, ROF, RFA	R Parietal Lobe, Middle Frontal Gyrus Atrophy	R AMTL	IB / 27	HS, gliosis	RPT, RPS, ROF, RPP, RA, RPHG, REC
37	F / 34	12	90	RA, REC, RMH, RPHG, LEC, LAH, LPHG, LA	Normal	RNS L/R longitudinal hippocampal leads, involving RA, RMH, REC and RPHG and LA, LAH, LPHG, LEC	IVB / 9	None	RA, REC, RMH, RPHG, LEC, LAH, LPHG, LA

Supplementary Table 3: Patients Cohort

Table Abbreviations: R=right, L=left, A=amygdala, AH=anterior hippocampus, MH=middle hippocampus, PH=posterior hippocampus, EC=entorhinal cortex, PHG=parahippocampal gyrus, OF=orbitofrontal cortex, FA=anterior frontal, STG/A/P=superior temporal gyrus/anterior/posterior, AMTL=anteromesial temporal lobectomy, RNS=Responsive Neurostimulation, NA=not available, FCD=focal cortical dysplasia, HA=hippocampal atrophy, HS=hippocampal sclerosis, PNH=periventricular nodular heterotopia, TS=tuberous sclerosis

Zone	Outcome	Region	N
SOZ	NSF	M	81
		L	97
		E	36
	SF	M	60
		L	47
		E	33
NSOZ	NSF	M	194
		L	295
		E	167
	SF	M	213
		L	286
		E	179

Supplementary Table 4: This table summarizes the number of data points for each subcategory used in comparison in Figure 2A and 2B. (SOZ = Seizure Onset Zone, NSOZ = Not Seizure Onset Zone, NSF = Not Seizure Free, SF = Seizure Free, M= Mesial, L = Lateral, E= Extra-temporal)

Zone	Outcome	Region	N
SOZ	NSF	M-M	215
		M-L	407
		M-E	85
		L-L	222
		L-E	78
		E-E	20
	SF	M-M	136
		M-L	149
		M-E	48
		L-L	77
		L-E	64
		E-E	36
NSOZ	NSF	M-M	624
		M-L	1616
		M-E	537
		L-L	1228
		L-E	799
		E-E	221
	SF	M-M	874
		M-L	1957
		M-E	755
		L-L	1394
		L-E	1231
		E-E	431
SOZ-NSOZ	NSF	M-M	584
		M-L	1509
		M-E	449
		L-L	746

		L-E	481
		E-E	106
	SF	M-M	499
		M-L	1149
		M-E	443
		L-L	477
		L-E	372
		E-E	89

Supplementary Table 5: This table summarizes the number of data points for each subcategory used in comparison in Figure 2D and 2E. (SOZ = Seizure Onset Zone, NSOZ = Not Seizure Onset Zone, NSF = Not Seizure Free, SF = Seizure Free, M= Mesial, L = Lateral, E= Extra-temporal)

		SOZ	NSOZ
HRL Percentage	Age	0.0171 (0.9310)	- 0.1331 (0.5667)
	Duration of epilepsy	0.0660 (0.7387)	- 0.2711 (0.1630)
	Seizure Frequency	- 0.2874 (0.1380)	- 0.0882 (0.6555)
	Presence of lesion	(0.2806)	(0.9981)
	Surgery type	(0.5506)	(0.6246)
Spikes Rates	Age	0.1454 (0.3976)	0.1867 (0.2755)
	Duration of epilepsy	0.1317 (0.4439)	0.1380 (0.4222)
	Seizure Frequency	0.0130 (0.9398)	- 0.0587 (0.7339)
	Presence of lesion	(0.9998)	(0.6611)
	Surgery type	(0.0967)	(0.7333)

Supplementary Table 6. This table summarizes the correlation between demographic/clinical parameters and HRL percentage as well as spikes rates in both SOZ and outside of it (NSOZ). Correlation coefficient (r) and p-values are given in form of r **(p-value)**.

Abbreviation List:

M-M: Mesial-Mesial Temporal Lobe

M-L: Mesial-Lateral Temporal Lobe

M-E: Mesial-Extra Temporal Lobe

L-L: Lateral-Lateral Temporal Lobe

L-E: Lateral-Extra Temporal Lobe

E-E: Extra-Extra Temporal Lobe