# Seizure onset zone effective connectome as revealed by single pulse electrical stimulation in stereoencephalographic studies Mihai Dragos Maliia<sup>1</sup>, Cristian Donos<sup>2</sup>, Andrei Barborica<sup>2,3</sup>, Irina Popa<sup>1</sup>, Jean Ciurea<sup>4</sup>, Laura Craciun<sup>1</sup>, Ioana Mindruta<sup>1,5</sup>

#### Background

Focal epilepsy is regarded increasingly as a network disease. In this conceptual frame, standardized tools that define the effective connectivity of the seizure onset zone (SOZ) are needed (Yaffe et al 2014). Enatsu et al. demonstrated that low frequency, asymptomatic electric pulses applied to the contacts with ictal debut partially revealed the epileptic propagation requery, asymptotiate textile places applied to the contacts with text beout partially revealed the place propagation areas. This proof of principle stands for the fact that a detailed neurophysiological mapping of the epileptogenic network can be obtained interictally with limited resources. Our objective is to characterize the individual SOZ networks of a heterogeneous group of pharmaco-resistant epilepsies and investigate its properties' in relation with the post-surgical outcome

### Methods

We selected 16 consecutive patients with pharmaco-resistant epilepsy that were explored in the SEEG method during their presurgical evaluation. No constraints were put on their SOZ's location or extent, to best mimic the clinical reality. Single pulse electrical stimulations (SPES) (biphasic, 3ms, 0.25-5mA) were applied to adjacent contacts while recording responses from the rest. (Valentin et al. 2002) We calculated the early responses in the 10-110ms interval and considered only connections between contacts having a RMS value within the 3 rd quartile (Q3) of all the responses in an individual patient, correlated with the stimulation current (Spearman's rho> 0.5, p < 0.05). (Donos et al, 2015)

Sublobar anatomical structures projecting to SOZ (inbound connections), as well as SOZ's projections to other structures (outbound connections) were systematically assessed. These were classified as either pathologic (containing at least one contact with epileptic interictal activity) or physiologic. (Kahane P et al 2006) We thus defined SOZ's connectome in each patient , naming it generically "epileptome", and listed it's nodes before and after tailored resections. Postsurgical outcome was evaluated after >6 months interval (mean 9) firstly in respect to seizure freedom (10 yes vs. 6 no) and then as Engel class. Nonparametric statistical tests (Mann-Whitney U and Spearmann) were employed to asses the correlation and monotony between different characteristics of these identified networks and clinical evolution.











## Results

A large range of structures 8-100% (mean 55%, SD=25%), sampled for the SEEG exploration, were part of each patient's epileptome. SOZ's outbound projections were on average more numerous than the inbound ones (10.7 +/- 5.4 vs. 8.2 +/- 4.9, average ratio 0.76). Figures 2-7 demonstrate that the number of inbound or outbound connections per seare not of prognostic value (for example both Pat 3 with a small epileptome and Pat 5 with a large one experienced a relapse post-operatively).

However, postsurgical outcome was highly correlated with the proportion of pathologic structures in the inbound connections, both pre and post-surgery (62% in seizure free lot vs. 88% in not seizure free lot, MannWhitney-Up=0.02, Spearmann for Engel score rho=0.654, p=0.006), on the same order of magnitude as it was to the ratio of unresected to total SOZ contacts (p=0.03). The initial extent of the SOZ, or its outbound connections were not associated with seizure relapse, neither were the implantation's extent, the total number or the ratio of pathological structures from those sampled, (please see Tabel 3.)

		Surgical Outcome	Nr. of SQ2 structures	Percentage of 102 contacts from 1054	Percentage of unreacted \$22 contacts from all \$22 contacts.	Nr. of pathological Oraclaritis	Nr. of univected pathological counteries		Pecentage of pathological indocend connections	Pacentage of pathological unreacted inboard connections.	No. of outbound citractures	Precise tage of pathological outbound connections.	Pecerage at pathological uninvected outboard connections.	Inbound/ Ourbound
1	Y	Engd I	4	26%	29%	10	1	2	70%	70%	1	100%	100%	20
2	Υ	Engd I	1	115	14%	4	2	5	69%	70%	2	100%	100%	25
2	Υ	Engd I	3	15%	0%	7	2	6	35%	33%	13	54%	54%	05
4	Y	Engel I	7	31%	10%	10	5	11	50%	50%	14	64%	64%	0.8
5	Υ	Engel I	2	16%	20%	17	5	12	56%	56%	14	36%	36%	0.9
6	Υ	Engd I	1	6%	0%	10	7	17	41%	34%	20	50%	47%	0.9
7	Υ	Engel I	9	34%	36%	10	6	11	74%	70%	11	64%	62%	1.0
5	Υ	Engel I	4	23%	27%	14	4	5	52%	52%	17	71%	71%	0.5
9	Y	Engd I	3	16%	20%	14	13	15	20%	87%	15	87%	87%	1.0
10	Y	Engel I	4	13%	23%	÷	0	0			6	83%	67%	0.0
11	N	Engel II	2	25%	44%	8	1	1	100%	100%	7	71%	71%	0.1
12	N	Engel II	3	28%	79%	0	4	7	85%	88%	5	100%	100%	1.4
13	N	Engel III	1	6%	50%	15	2	7	68%	49%	12	67%	56%	0.0
14	N	Engel III	3	255	50%	13	9	12	87%	36%	15	87%	85%	0.0
15	N	Engel III	3	33%	44%		3	4	91%	100%	11	73%	67%	0.4
16	N	Engel III	3	13%	25%	11	7	12	84%	82%	9	89%	89%	1.3
MANN-WHITNEYU- 2TAL			19.5	30	8	29.5	29.5	26	7	٥	23	30	30	24.5
7-SCORE			1.08	0.05	-2.18	0.00	0.00	0.38	-2.30	-2.42	0.80	0.05	0.05	0.54
P-significance			0.28	0.96	0.03	1.00	1.00	0.70	0.02	0.02	0.48	0.96	0.96	0.59
SIGNFICANT			NO	NO	165	NO	NO	NO	105	105	NO	NO	NO	ND
abel 3. The 5 iours free cu	OZ dimension baroup and pr	s, number of	pathological subotrum	structures imp	a bna betnak	plleptomes' c	haracteristics	in our 16 pat	ients, ordere	d by surgery o	outcome. Stat	istical analysis	performed b	etween the

Grouping the subjects based on their SOZ anatomical location, significant differences appear between the 3 types of lobar epilepsies. The frontal group had received inbound connections from the most of coimplanted lobes while the temporal one from the least (95% vs 60%). The posterior epilepsies had the highest ratio of pathological structures in the outbound connections. No significant associations were demonstrated between the duration of the disease and the properties of the epileptomes.

Epilopsy type	No. of patients	No. of S implant.	\$02/T	PAI/I	ND/T (3)	patiNB (3)	885/T (1)	0UT/T (R)	patOUT (2)	0UT/T (1)	OUT /NS
FRONTAL	5	16	225	695	70%	62%	95% ·	675	82%	ans.	0.9
TEMPORAL	8	17	21%	71%	41%	262	60%*	68%	69%	89%	0.63
POSTERIOR	1	17	22%	855	45%	22%	71%	585	865.1	75%	1.4
ALL LOT	16	17	22%	745	47%	72%	62%	67%	78%	MX	1.04

fabel 4. Implantation chalacteristics and epile respective subgroup and the rest of the pop

### Conclusions

The balance between pathologic and physiologic structures projecting to SOZ is associated with postsurgery outcome in our lot and can be assessed preoperatively. An ictal generator receiving mainly projections from cortex displaying epileptiform activity appears to be a risk factor for a negative result, supplementary to its incomplete resection. As these networks are multi-lobary extended, they can rarely be interfered via lesional surgery, but might be addressed with post-surgical neuro-modulatory chronic protocols in relapsed patients. Acknowledgements

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