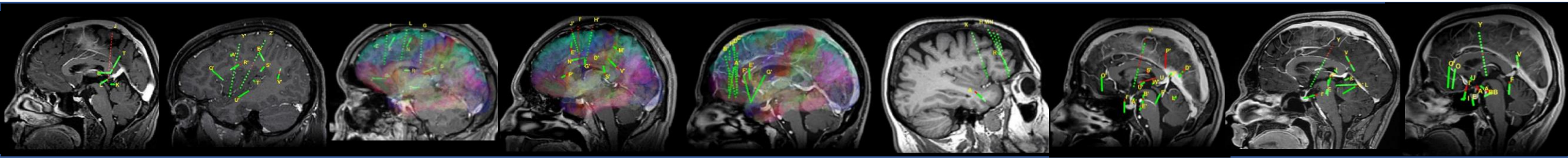
Networks underlying human cortical function revealed by intracranial electrical stimulation

PN-III-P4-ID-PCE-2020-0935

2022 progress report

Activity 2.1 – MRI Processing

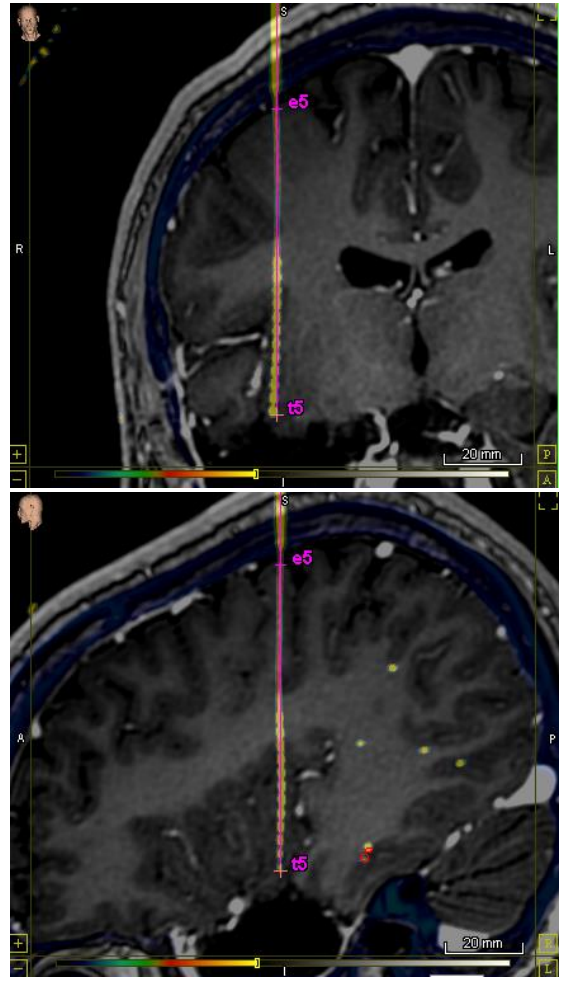
- MRI processed for 9 subjects investigated in 2022.
- For all subjects, invasive exploration using SEEG was considered necessary to delineate the epileptogenic zone (Kahane & Landre, 2008; Munari & Bancaud, 1987), map the functional cortex and to determine the limits of the resection
- All subjects underwent 1.5 or 3T Magnetic Resonance Imaging (MRI) (isotropic 3D T1, axial and coronal FLAIR and T2, T2*or SWI), and functional imaging (inter-ictal FDG-PET-CT scan)



Activity 2.2 – Electrode Localization

- SEEG exploration was performed using depth electrodes (Dixi, Chaudefontaine, France) with 8 to 18 contacts per electrode, 2 mm contact length, 3.5 mm contact spacing, and 0.8 mm diameter.

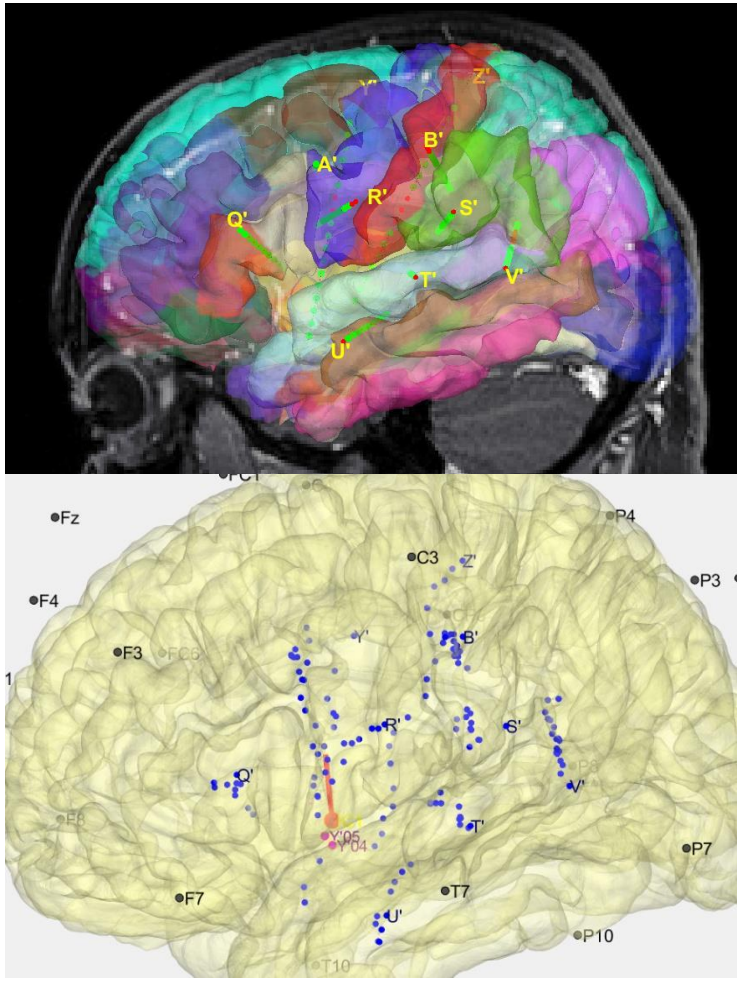
- To determine the exact location of each electrode and contact, the post-implantation CT scan was co-registered with the pre-implantation MRI.



Post-implantation CT, showing the location of electrode Y (#5), merged with the pre-operative MRI in patient SEEG111.

Activity 2.2 – Electrode Localization

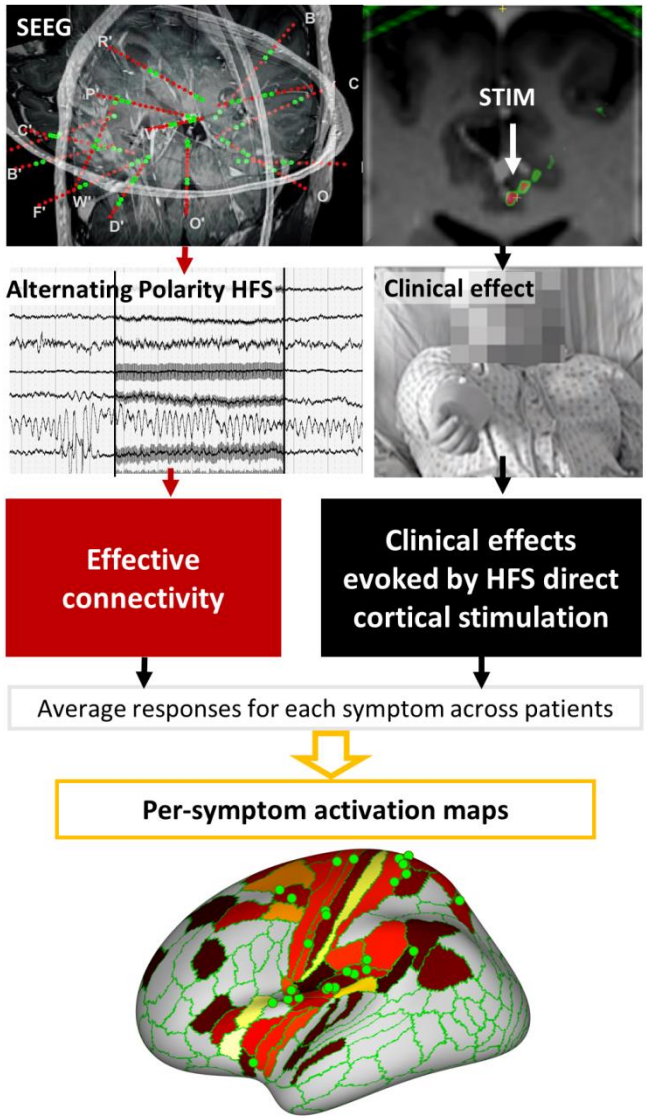
- In view of the group analysis, a non-rigid registration of patients' MRI was performed against MNI152 brain template (FreeSurfer's *mri_cvs_register*).
- The location of SEEG contacts of each patient was therefore mapped to common MNI coordinates.



The location of electrodes in patient SEEG104 in patient space and after non-rigid registration with the MNI brain template.

Activity 2.3 – Electrical stimulation and recording of clinical symptoms.

- Multiple brain direct electrical stimulation protocols were carried out as part of the standard pre-surgical assessment in our center:
  - low-frequency 1 Hz (Munari et al., 1993), high-frequency (HFS) 40-50Hz (Bernier et al., 1990; Trebuchon, Agnès; Chauvel, 2016)
  - single-pulse electrical stimulation (SPES) (Donos, Mălîia, et al., 2016; Donos, Mîndruţă, et al., 2016; Valentín et al., 2002).
- We have analyzed the EEG responses during the application of high-frequency electrical stimulation with a frequency of 43.2 Hz at current levels large enough to evoke a clinical effect (Barborica et al., 2022).



Activity 2.4 – Classification of stimulation evoked clinical symptoms

- Clinical effects were then classified into six large categories according to the common descriptors of ictal behavior presented in the most recent ILAE classification (Fisher et al., 2017) to date, adapted to effects evoked by intracranial stimulation.

- Each large category was then subdivided into multiple levels to better characterize each clinical effect.

Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
Cognitive	Learning	Dyscalculia	Motor	Automatisms	Laughing
	Language	Aphasia			Grimace
		Verbal Fluency			Grasping
	Attention	Working memory			Rubbing
		Forced thinking			Vocalization
		Responsiveness impairment		Elementary	Dysarthria
	Memory	Déjà vu			Dystonia/Tonic
		Jamais vu			Clonia
		Déjà rêvé			Weakness
		Recollection			Versive
		Memory encoding/retrieval	Sensory	Auditory	Hallucination
Autonomic	Cardiac	Bradycardia			Illusion
		Tachycardia		Gustatory	Hallucination
	Respiratory	Hyperventilation			Illusion
		Hypoventilation		Olfactory	Hallucination
	Gastrointestinal	Nausea			Illusion
		Vomiting		Somatosensory	Hallucination
	Vasomotor	Pallor			Illusion
		Flushing		Vestibular	Hallucination
		Piloerection			Illusion
		Hot-cold sensation		Visual	Hallucination
					Illusion
				Pain	Hallucination
					Illusion

Activity 2.4 – Classification of stimulation evoked clinical symptoms

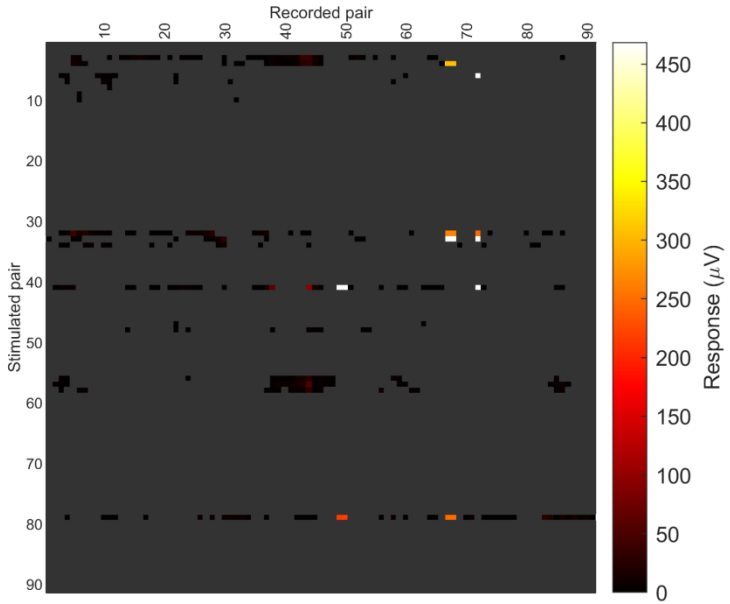
Clinical symptoms obtained in patients investigated in 2022, according to Level 1 ILAE 2017 classification

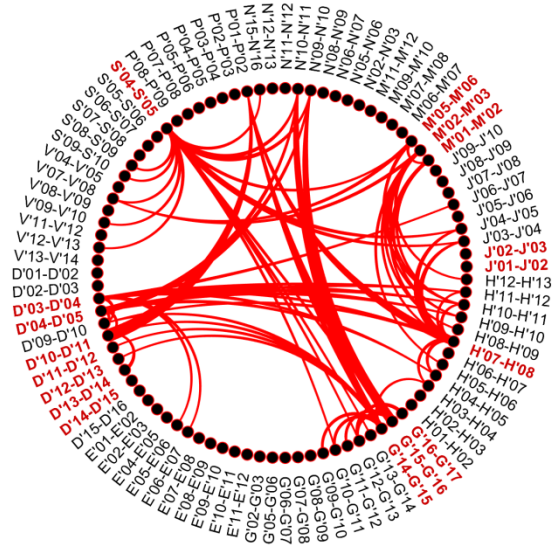
Patient	Cognitiv	Autonomic	Motor	Somatosensory
SEEG 103				
SEEG 104	2	0	21	34
SEEG 105	14	0	3	34
SEEG 106	0	0	0	0
SEEG 107	3	0	3	21
SEEG 108	1	0	0	1
SEEG 109	0	0	0	1
SEEG 110	5	0	0	7
SEEG 111	0	0	0	72
SEEG 112	0	0	0	5

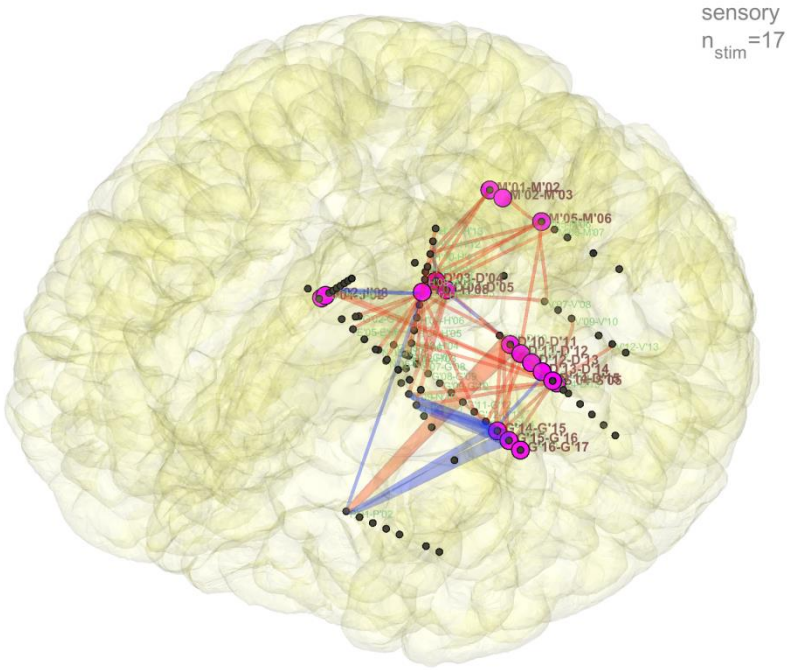
Activity 2.5 – Effective connectivity

- As metric for the effective connectivity we have used the in-band responses (f_0=43.2 Hz and harmonics), time-locked with AP electrical stimulation.
- The responses were analyzed over an interval extending 2 s starting 0.25 s after the stimulation onset and were baseline-subtracted based on a matching 2 s interval ending 0.25 s before stimulation onset.
- At the patient level, connectivity matrices including responses to all stimulations evoking a particular effect were calculated, and based on them, circular diagrams and 3D connectomes of the upper quartile (Q3) of the significant responses were represented.
- The group level connectivity analysis, instead of matrices and circular diagrams, makes use of the more suggestive projections of the average connectivity/responses to inflated brain surfaces, that provides visual cues about spatial locations of the more connected/activated brain areas.

Activity 2.5 – Effective connectivity





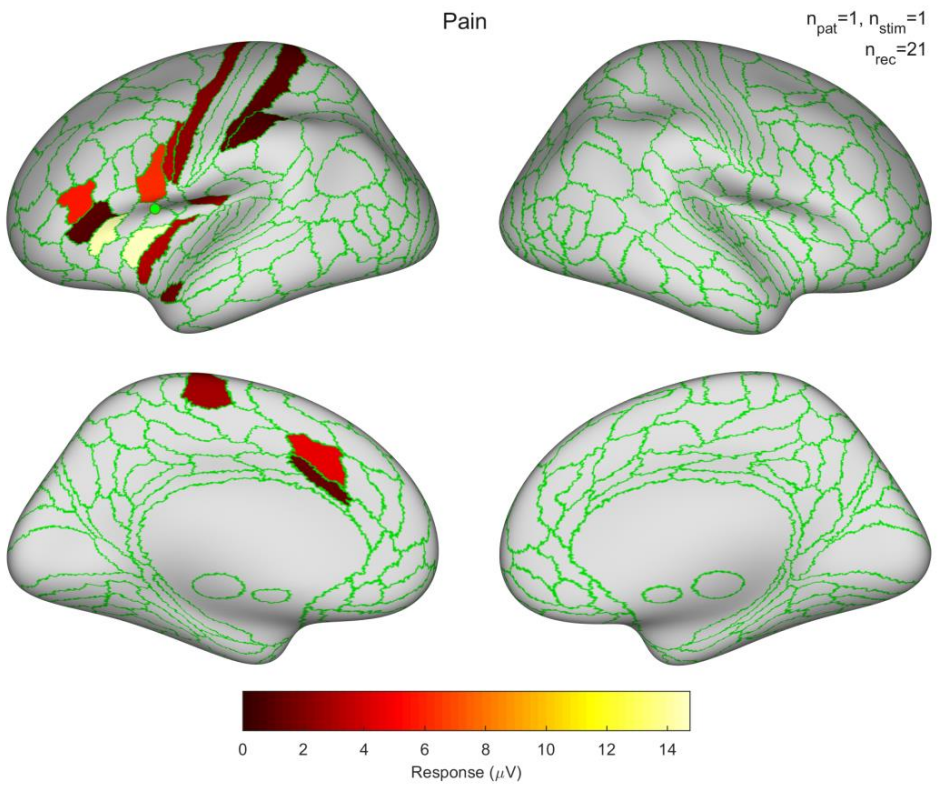


Example of the connectivity analysis for 17 stimulation sites that evoked elementary somatosensory effects in patient SEEG107. A) connectivity matrix. Connections not sampled are shown in dark gray; B) circular diagram of the third quartile of the significant connections (Z-score>3, p<0.05); C) 3D representation of the connections in (B).

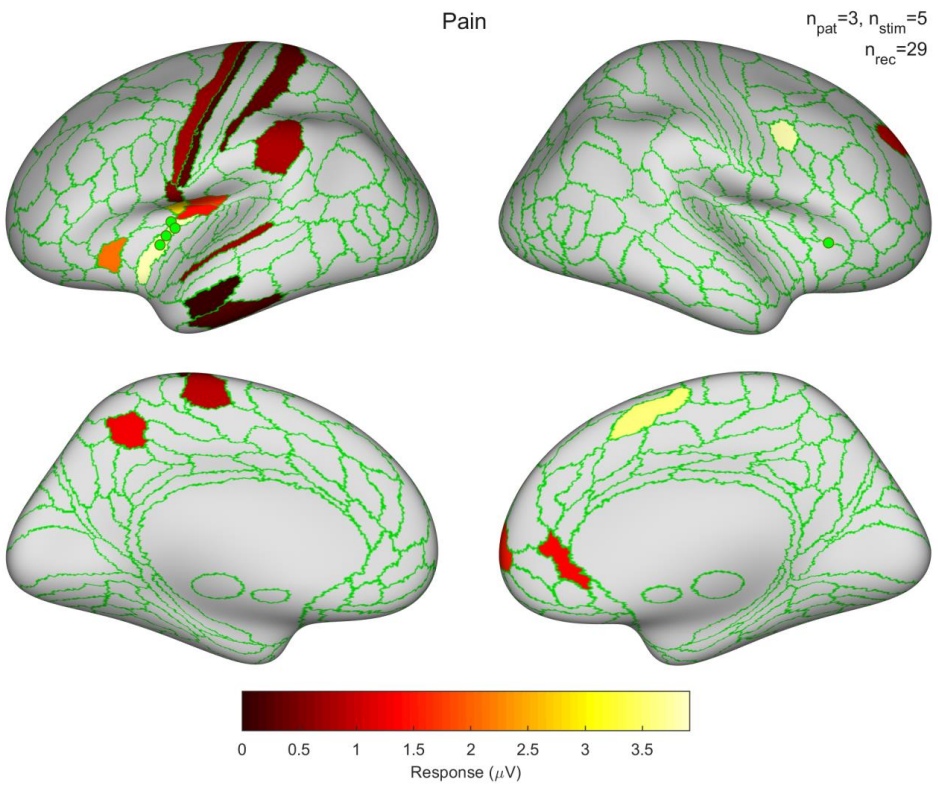
Activity 2.6 – Group level effective connectivity

Comparative analysis of ictal and physiological connectivity for one stimulation evoking ictal pain symptoms and 5 stimulations in 3 patients evoking non-ictal pain symptoms.

Ictal



Physiological



Activity 2.7 – Dissemination of results

- Online on project's website: http://epi.fizica.unibuc.ro/biomol/symnet
- Peer-reviewed scientific papers:
  - Barborica A, Oane I, Donos C, Daneasa A, Mihai F, Pistol C, Dabu A, Roceanu A, Mindruta I. Imaging the effective networks associated with cortical function through intracranial high-frequency stimulation. Hum Brain Mapp. 2022 Apr 1;43(5):1657-1675. https://doi.org/10.1002/hbm.25749. (IF= 5.038)
  - Donos C, Blidarescu B, Pistol C, Oane I, Mindruta I, Barborica A. A comparison of uni- and multi-variate methods for identifying brain networks activated by cognitive tasks using intracranial EEG. Front Neurosci. 2022 Sep 26;16:946240. https://doi.org/10.3389/fnins.2022.946240. (IF=5.152)
  - Lentoiu C, Oane I, Barborica A, Donos C, Pistol C, Daneasa A, Bratu FI, Mindruta I. Motor and emotional facial features in parietal lobe seizures: an ictal functional connectivity study using SEEG. Epileptic Disord. 2022 Oct 1;24(5):838-846. English. https://doi.org/10.1684/epd.2022.1456. (IF= 2.333)
  - Oane I, Barborica A, Mindruta I. Cingulate Cortex: Anatomy, Structural and Functional Connectivity. Accepted for publication in Journal of Clinical Neurophysiology, Aug. 2022. (IF= 2.177)
- Conferences (selected):
  - Andrei Barborica, Ioana Mindruta, Christian G. Benar, Irina Oane, Felicia Mihai, Cristian Donos, Constantin Pistol. Intracranial Stimulations as Ground Truth for Testing Visibility of Deep High-Frequency EEG Sources - A Simultaneous Scalp-SEEG Study, American Epilepsy Society (AES) Anual Meeting 2022, Dec 2-6, Nashville, USA.
  - Irina Oane, Andrei Barborica, Felicia Mihai, Andrei Daneasa, Flavius Bratu, Camelia Lentoiu, Constantin Pistol, Cristian Donos, Ioana Mindruta. Network of Insular Physiologic and Epileptogenic Signs and Symptoms, American Epilepsy Society (AES) Anual Meeting 2022, Dec 2-6, Nashville, USA.
  - Cristian Donos, Bogdan Blidarescu, Irina Oane, Constantin Pistol, Ioana Mindruta, Andrei Barborica. Search light analysis for intracranial EEG recordings, FENS Forum, 9-13 July 2022, Paris, France.
  - Andrei Barborica, Ioana Mindruta, Irina Oane, Felicia Mihai, Cristian Donos, Constantin Pistol. Simultaneous scalp-intracranial EEG recordings in patients with drug-resistant epilepsy as a means to validate source localization algorithms, 13th National Conference of the Romanian Society of Electrodiagnostic Neurophysiology, 21-23 Oct, 2022, Bucharest, Romania.
  - Ionuț-Flavius Bratu, Andrei Barborica, Irina Oane, Camelia Lentoiu, Felicia Mihai, Cristian Donos, Constantin Pistol, Ioana Mindruta. Gray matter heterotopias - is there something more than meets the eye on scalp EEG traces? - a simultaneous scalp EEG-stereo-EEG study, 32nd International Congress of Clinical Neurophysiology, Sep 04-08, 2022, Geneva, Switzerland.
  - Andrei Barborica, Ioana Mindruta, Irina Oane, Cristian Donos, Felicia Mihai, Constantin Pistol. Validation of EEG source localization algorithms through simultaneous scalp-intracranial EEG recordings in patients with drug-resistant epilepsy, SNN, SRF and Brain Day 2022, Sep 29 – Oct 1, 2022, Bucharest, Romania.