Networks underlying human cortical function revealed by intracranial electrical stimulation

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

2021 scientific report

Activity 1.1 – Ethical approvals for human data collection

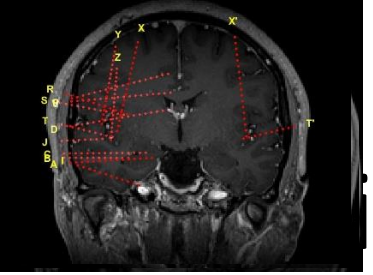
- The ethical committee approval was obtained from the University of Bucharest (UNIBUC), based on the collaboration protocol signed with the University Hospital of Bucharest (SUUB).

- The ethical approval has the registration id: 393/09.06.2021

- The ethical approval allows UNIBUC to access and process data recorded from epileptic patients at SUUB.

Activity 1.2 – MRI Processing

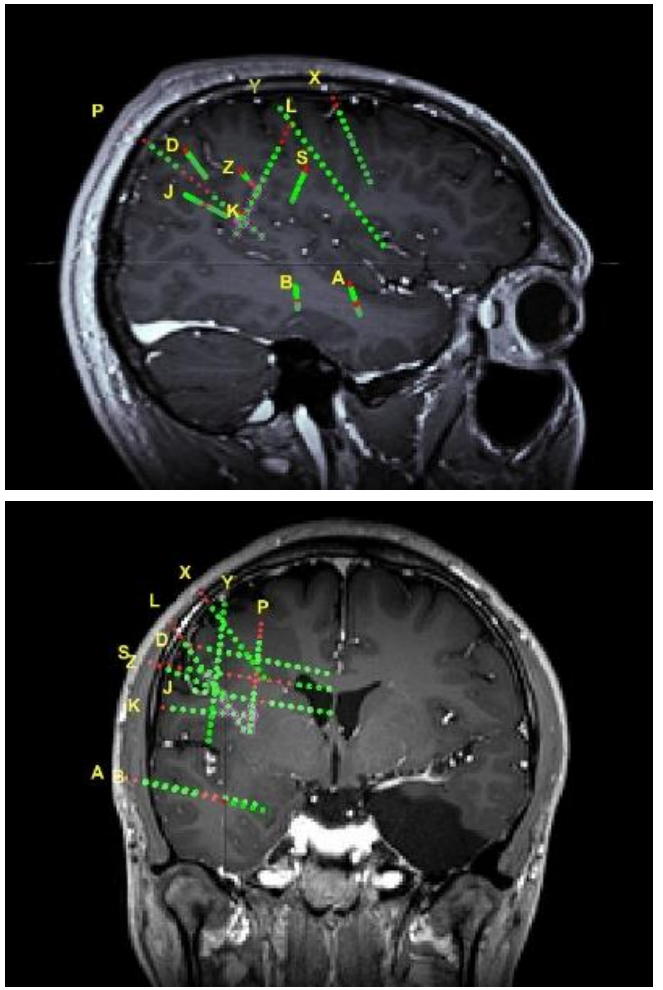
- MRI processed for 20 retrospective subjects and 7 prospective subjects, implanted in 2020.
- For all subjects, invasive exploration using SEEG was considered necessary to delineate the epileptogenic zone (Kahane & Landre, 2008; Munari & Bancaud, 1987), map the functional cortex and to determine the 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)



ivity 1.3 – Electrode Localization

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

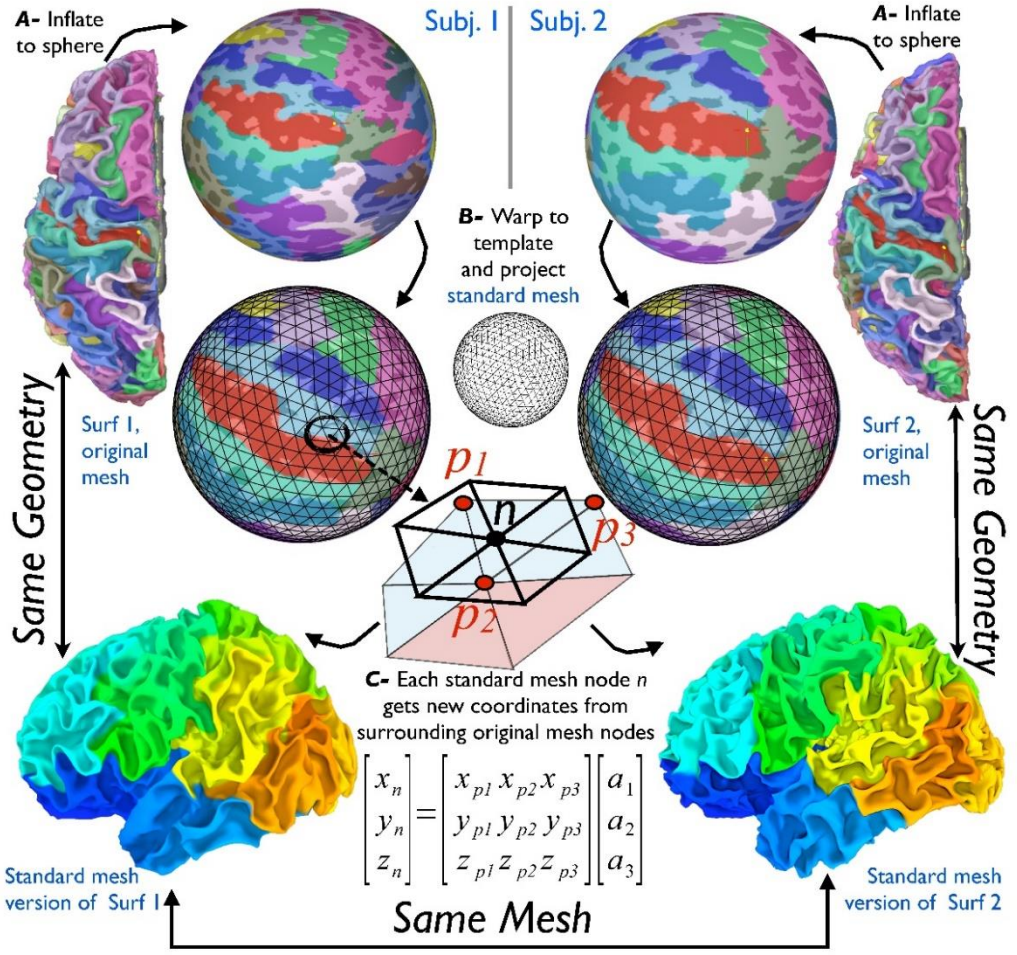
- To determine the exact location of each electrode and contact, the post-implantation CT scan was co-registered with the pre-implantation MRI.



Sample implantation scheme from one of our subjects.

Activity 1.3 – Electrode Localization

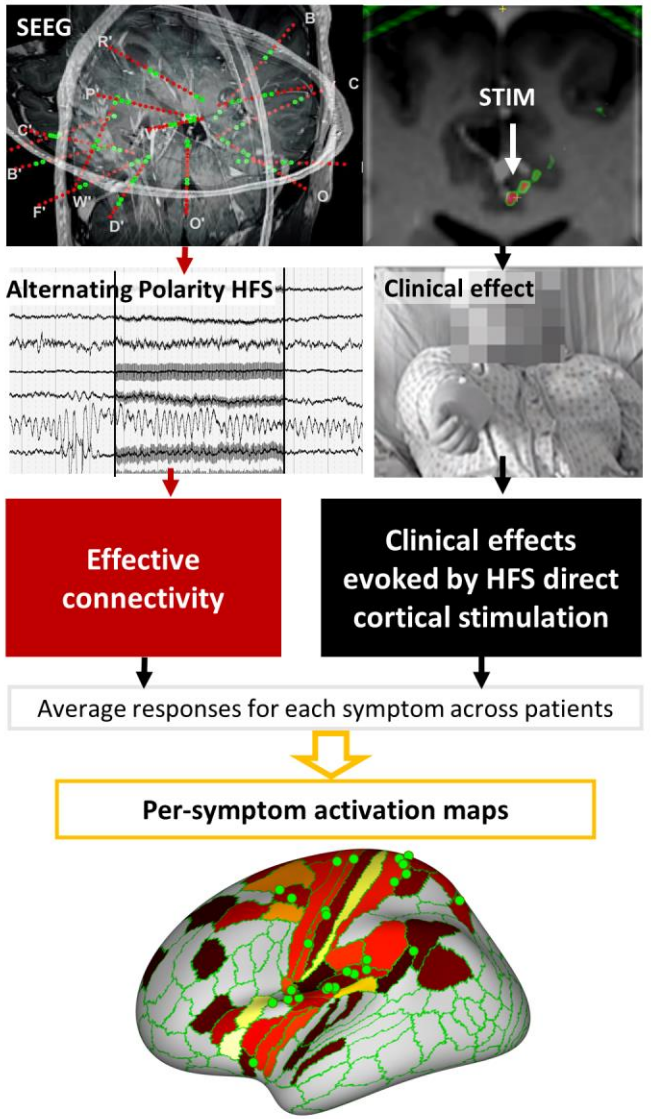
- The location of SEEG contacts was normalized to a brain atlas.
- Electrodes of individual subjects were represented on a standard surface using standard intersubject registration (Fischl et al., 1999) and assigned a label based on the HCP-MMP parcellation (Glasser et al., 2016).



Group level normalization of spatial coordinates (after Saad and Reynolds, Neuroimage 2012)

Activity 1.4 – 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 50 Hz (patients 1–12) or 43.2 Hz (patients 13–26) at current levels large enough to evoke a clinical effect. Stimulation frequency was decreased to 43.2 Hz starting patient 13 to reduce the confounding effect of the response at 50 Hz and the interference from 50 Hz power lines in Europe.



Activity 1.5 – 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.

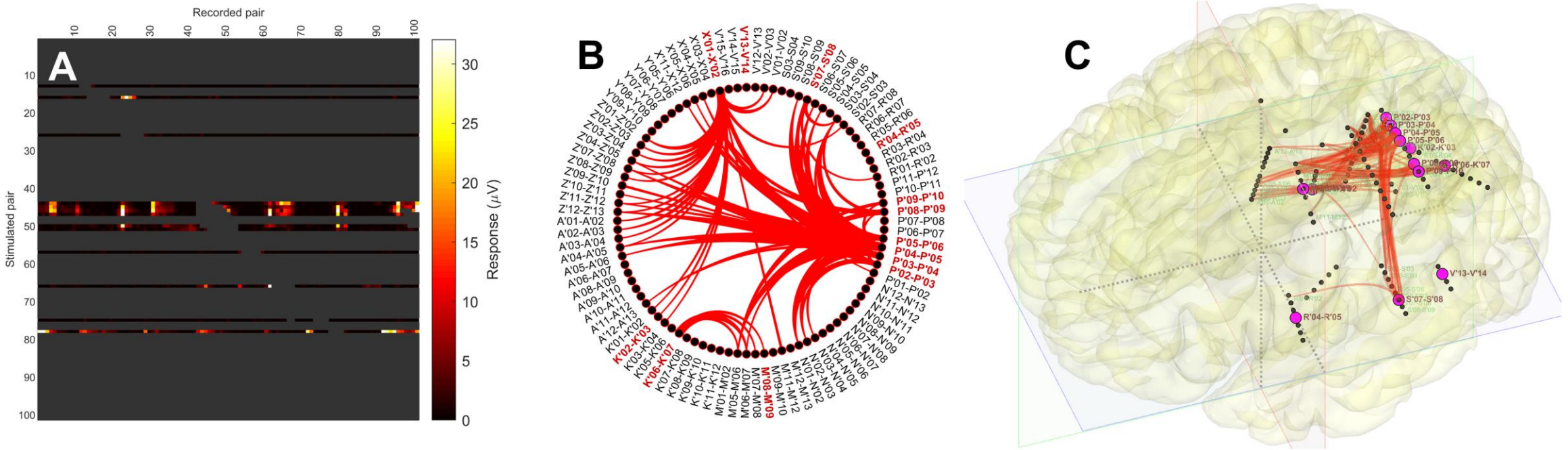
- Each large category was then subdivided into multiple levels to better characterize each clinical effect.

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 1.6 – 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 1.6 – Effective connectivity

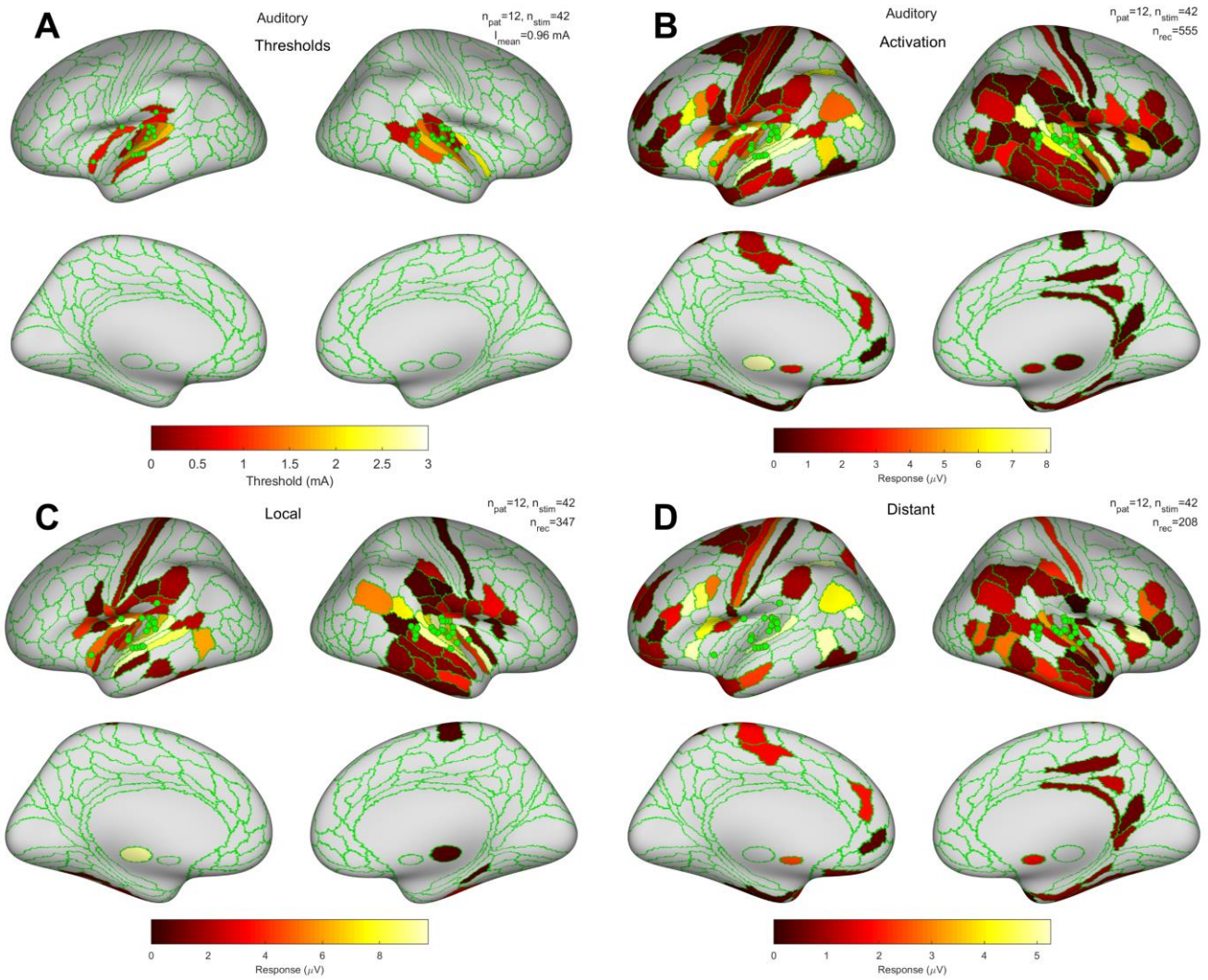


Example of the connectivity analysis for 13 stimulation sites that evoked elementary somatosensory effects in patient 12. A) connectivity matrix. Connections not sampled are shown in dark gray; B) circular diagram of the third quartile of the significant connections (Z-score>3, p<0.05); C) 3D representation of the connections in (B).

Activity 1.6 – Group level effective connectivity

The thresholds for the 42 stimulated sites evoking auditory effects (A);

All evoked activations are shown in B, whereas local (Euclidean distance from stimulated site d<30mm) and distant (d<30mm) ones are shown in C and D, respectively.



Activity 1.7 – Dissemination of results

- Online on project's website: http://epi.fizica.unibuc.ro/biomol/symnet
- Peer-reviewed scientific papers:
  - Bratu, F.-I., Oane, I., Barborica, A., Donos, C., Pistol, C., Daneasa, A., Lentoiu, C., & Mindruta, I. (2021). Network of autoscopic hallucinations elicited by intracerebral stimulations of periventricular nodular heterotopia: An SEEG study. Cortex, 145, 285–294. https://doi.org/10.1016/J.CORTEX.2021.08.018. (IF=4.314)
  - Andrei Barborica, Irina Oane, Cristian Donos, Andrei Daneasa, Felicia Mihai, Constantin Pistol, Aurelia Dabu, Adina Roceanu, Ioana Mindruta. (2021) Imaging the effective networks associated with cortical function through intracranial high-frequency stimulation. In evaluare la Human Brain Mapping, Oct. 2021. (IF= 5.038)
- Conferences:
  - Andrei Barborica, Ioana Mindruta, Christian G. Benar, Serge Vulliemoz, Irina Oane, Felicia Mihai, Cristian Donos, Constantin Pistol. What Scalp Recordings Tell Us About Intracranial Stimulations? A Simultaneous Scalp-SEEG Study, American Epilepsy Society (AES) Anual Meeting 2021, Dec 3-7, Chicago, USA.
  - Ioana Mindruta, Irina Oane, Flavius Bratu, Camelia Lentoiu, Felicia Mihai, Cristian Donos, Andrei Barborica. Insular-Cingulate Resting State and Symptom Related Connectivity Interplay in Patients with Drug-Resistant Epilepsy, American Epilepsy Society (AES) Anual Meeting 2021, Dec 3-7, Chicago, USA.
  - Irina Oane, Andrei Barborica, Cristian Donos, Constantin Pistol, Andrei Daneasa, Camelia Lentoiu, Flavius Bratu, Ioana Mindruta. Reflex seizures and the brain networks involved. 12th Summer School of the Romanian Society of Electrodiagnostic Neurophysiology (ASNER), 9-10 July 2021, Eforie, Romania.
  - Irina Oane, Andrei Barborica, Cristian Donos, Andrei Daneasa, Flavius Bratu, Camelia Lentoiu, Constantin Pistol, Bogdan Blidarescu, Aurelia Dabu, Cornel Tudor, Ioana Mindruta. Rolul stimularii cerebrale directe cu electrozi intacraniani in explorarea epilepsiei farmacorezistente. Al XIX-lea Congres National al Societatii de Neurologie din Romania. 16-19 Noiembrie 2021, Congres Virtual