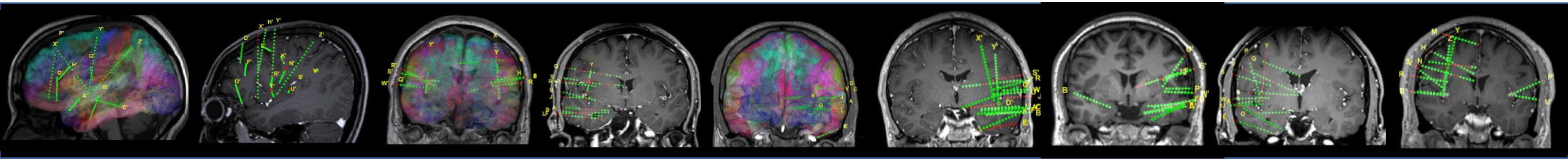
Networks underlying human cortical function revealed by intracranial electrical stimulation

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

2023 progress report

Activity 3.1 – MRI Processing

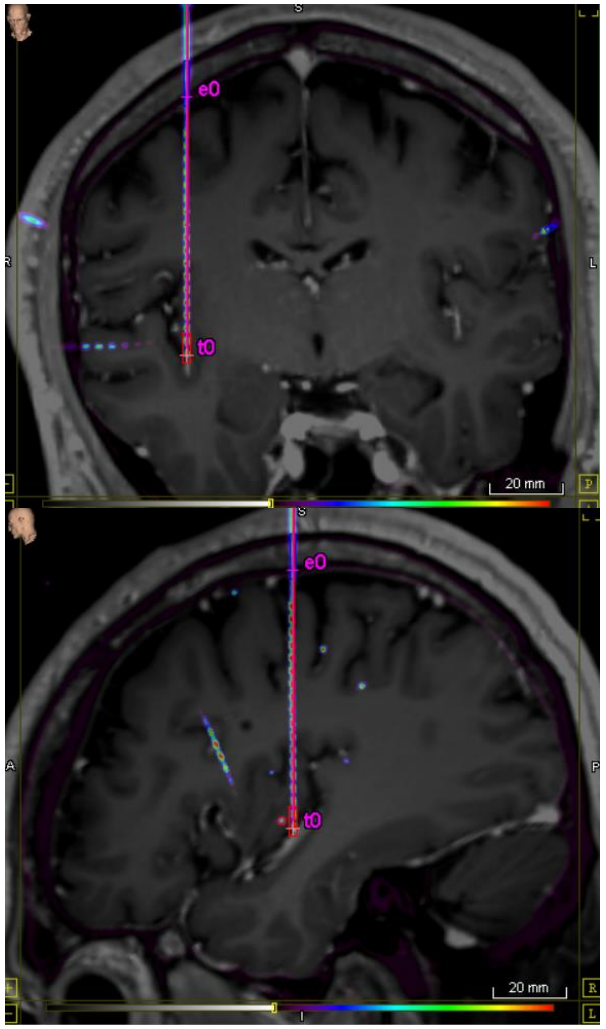
- MRI processed for 15 subjects investigated in 2023, of which 10 met the inclusion criteria for the group analysis
- For all subjects, invasive exploration using SEEG was considered necessary to delineate the epileptogenic zone (Kahane & Landre, 2008; Munari & Bancaud, 1987), map the functional cortex 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 3.2 – 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.

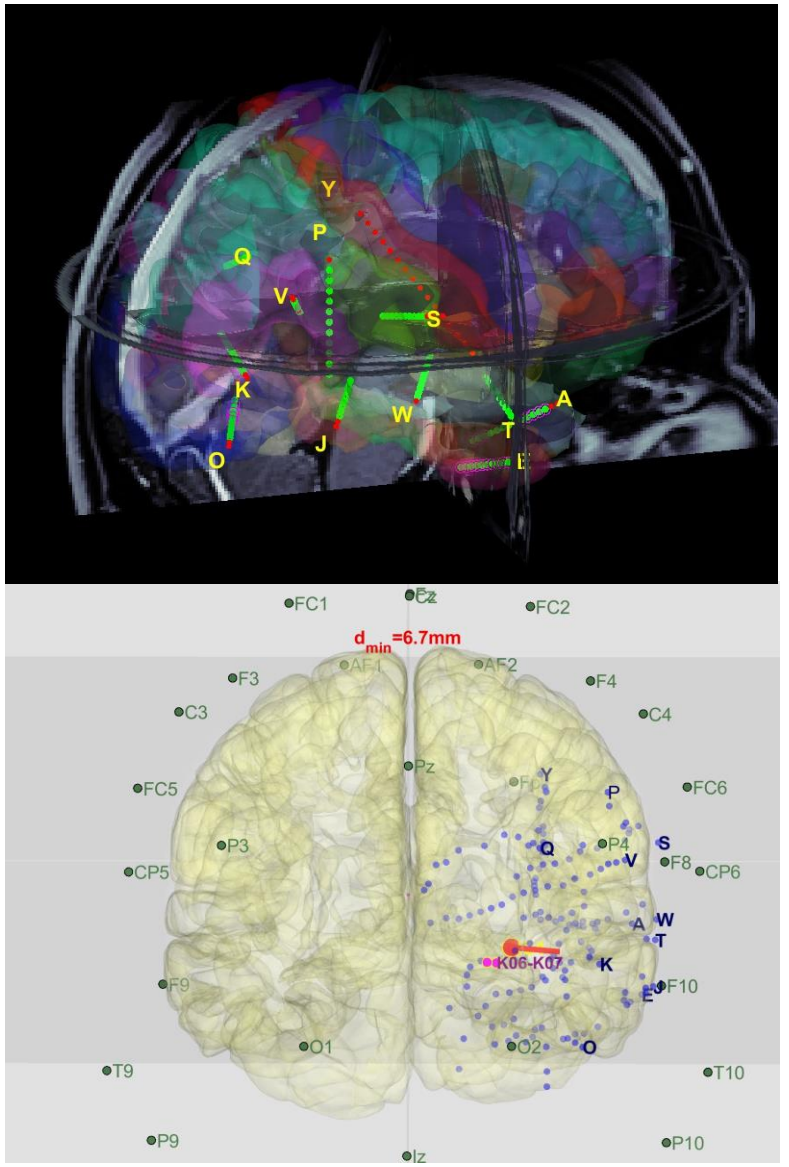
- To determine the exact location of each electrode and contact, the post-implantation CT scan was co-registered with the pre-implantation MRI.



Post-implantation CT, showing the location of electrode Z (#0), merged with the pre-operative MRI in patient SEEG127.

Activity 3.2 – Electrode Localization

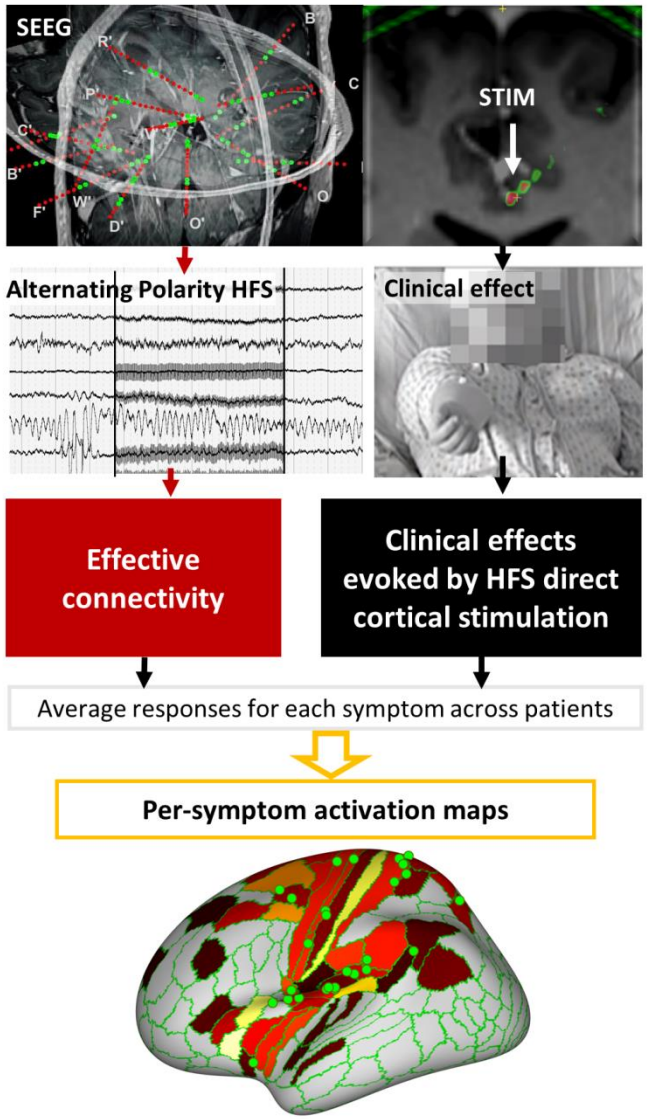
- In view of the group analysis, a non-rigid registration of patients' MRI was performed against MNI152 brain template (FreeSurfer's *mri_cvs_register*).
- The location of SEEG contacts of each patient was therefore mapped to common MNI coordinates.



The location of electrodes in patient SEEG124 in patient space (top) and after non-rigid registration with the MNI brain template (bottom).

Activity 3.3 – 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 3.4 – 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 3.4 – Classification of stimulation evoked clinical symptoms

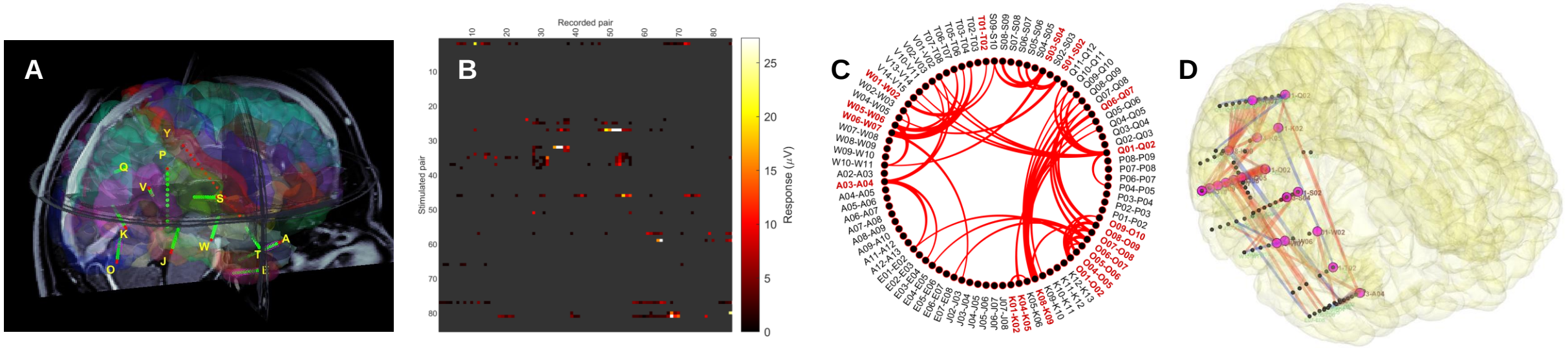
Clinical symptoms , according to Level 1 ILAE 2017 classification. obtained in 10 patients investigated in 2023 that passed the inclusion criteria for group analysis

Patient	Cognitiv	Autonomic	Motor	Somatosensory
SEEG 113	1	4	3	5
SEEG 116	1	7	2	13
SEEG 118	5	1	3	18
SEEG 119	2	4	1	12
SEEG 121	0	2	0	40
SEEG 122	0	0	0	63
SEEG 123	1	1	1	7
SEEG 124	0	4	3	42
SEEG 125	0	2	0	25
SEEG127	2	0	3	29

Activity 3.5 – Patient-level 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 3.5 – Patient-level effective connectivity

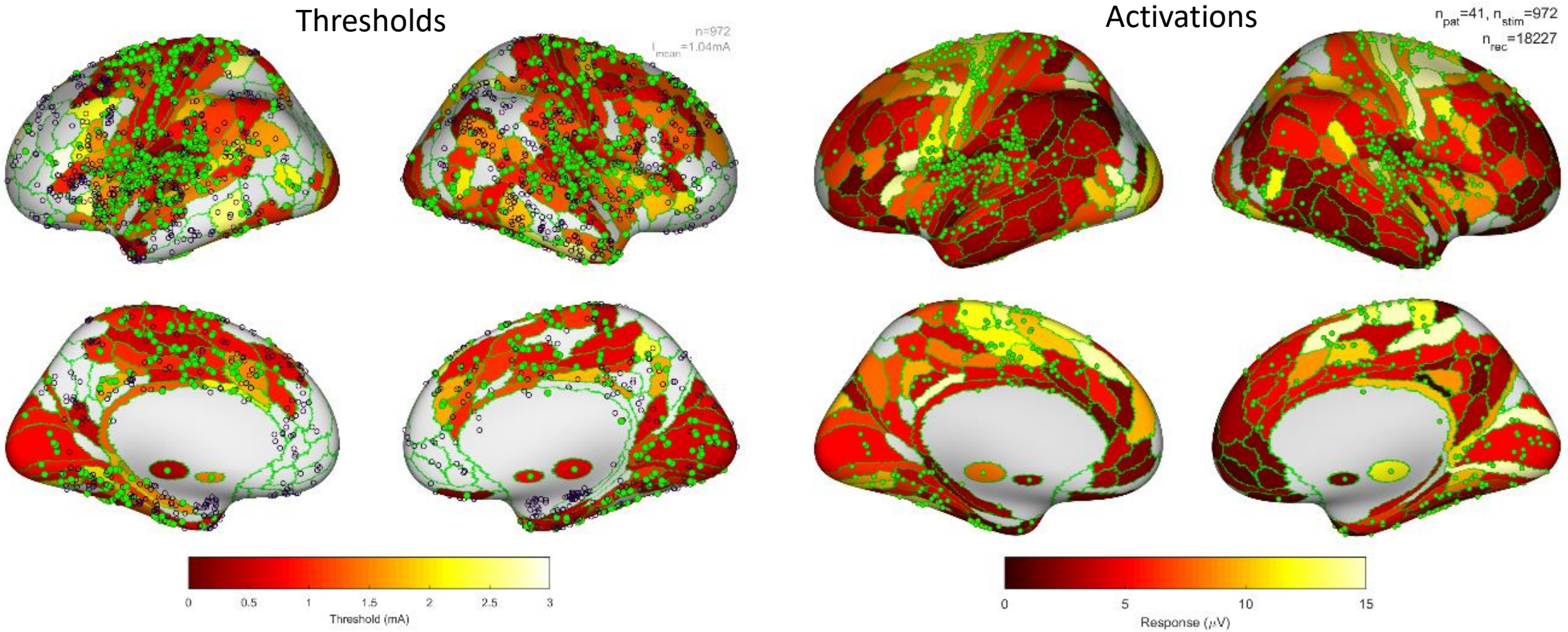


Example of the connectivity analysis for 19 stimulation sites that evoked elementary somatosensory effects in patient SEEG125. A) electrode location; B) connectivity matrix. Connections not sampled are shown in dark gray; C) circular diagram of the third quartile of the significant connections (Z-score>3, p<0.05); D) 3D representation of the connections in (C).

Activity 3.6 – Group-level analysis

Per-effect maps

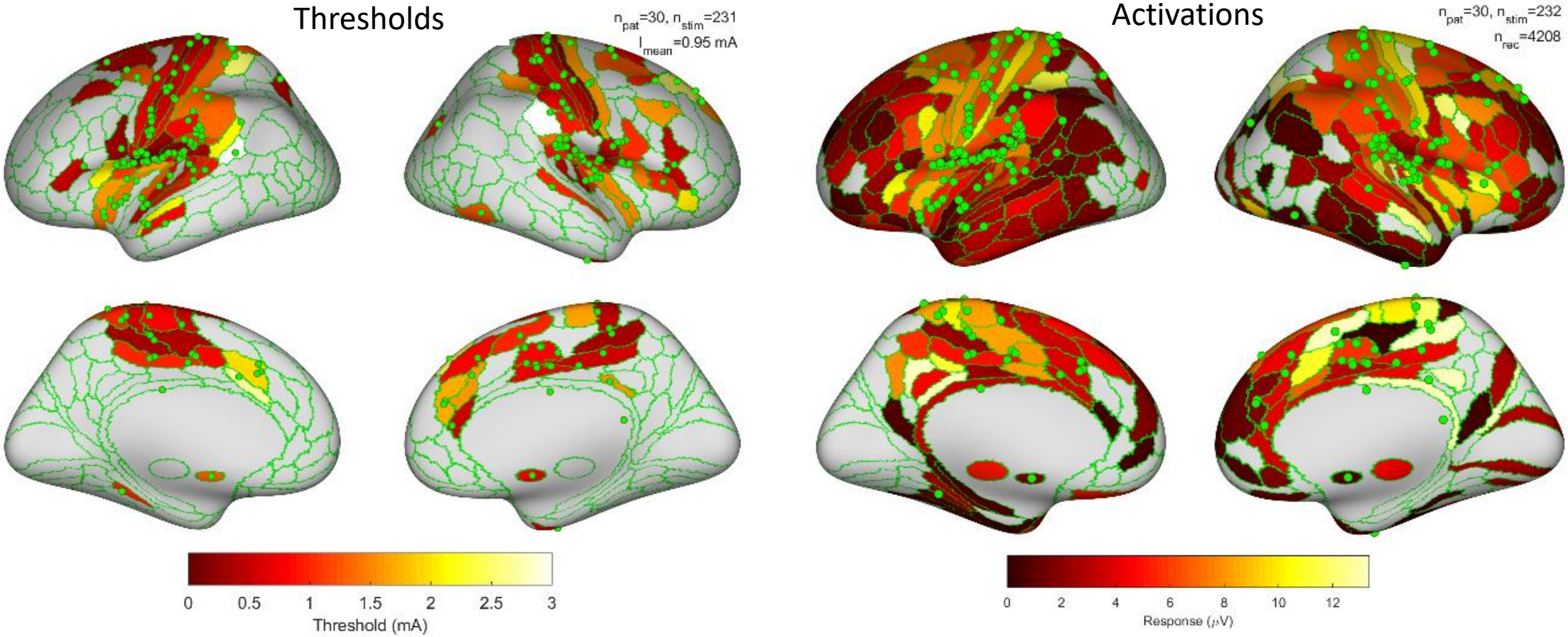
- Current thresholds for evoking clinical effects and activated regions for 972 stimulations in 41 patients are shown below.



Activity 3.6 – Group-level analysis

Per-effect maps

- Current thresholds for evoking somatosensory hallucinations and activated regions for 231 stimulations in 30 patients are shown below.



Activity 3.7 – Dissemination of results

- Online SYMNET atlas: http://epi.fizica.unibuc.ro/symnet
- Online project's website: http://epi.fizica.unibuc.ro/biomol/symnet
- Peer-reviewed scientific papers:
  - Barborica A, Mindruta I, López-Madrona VJ, Alario FX, Trébuchon A, Donos C, Oane I, Pistol C, Mihai F, Bénar CG. Studying memory processes at different levels with simultaneous depth and surface EEG recordings. Front Hum Neurosci. 2023 Apr 4;17:1154038. doi: 10.3389/fnhum.2023.1154038. (IF= 2.9)
  - Bratu IF, Nica AE, Oane I, Daneasa A, Stoica S, Barborica A, Mindruta I. Musicogenic seizures in temporal lobe epilepsy: Case reports based on ictal source localization analysis. Front Neurol. 2023 Feb 20;14:1072075. doi: 10.3389/fneur.2023.1072075. (IF=3.4)
  - Oane I, Barborica A, Mindruta I. Cingulate Cortex: Anatomy, Structural and Functional Connectivity. J Clin Neurophysiol. 2023 Mar 16. doi: 10.1097/WNP.0000000000000970 (IF= 2.4)
  - Oane I, Barborica A, Daneasa A, Maliia MD, Ciurea J, Stoica S, Dabu A, Bratu F, Lentoiu C, Mindruta I. Organization of the epileptogenic zone and signal analysis at seizure onset in patients with drug-resistant epilepsy due to focal cortical dysplasia with mTOR pathway gene mutations-An SEEG study. Epilepsia Open. 2023 Aug 13. doi: 10.1002/epi4.12810. (IF=4.0)
- Conferences (selected):
  - Andrei Barborica, Ioana Mindruta, Christian G. Benar Simultaneous EEG-SEEG during electrical cortical stimulation, 18th European Congress of Clinical Neurophysiology, May 9-12, Marseille, France.
  - Cristina Ghita, Irina Oane, Camelia Lentoiu, Ionut-Flavius Bratu, Ioana Mindruta. Cum interpretăm clinic informația examenului EEG? Al XXI-lea Congres al Societății de Neurologie din România, 7-9 Iunie 2023, Sinaia, România.
  - Irina Oane, Camelia Lentoiu, Flavius Bratu, Cristina Ghita, Constantin Pistol, Felicia Mihai, Laurentiu Tofan, Andrei Barborica, Ioana Mindruta. Multiscale EEG and ictal semiology correlates. A 14-a Școală de Vară ASNER, 7-9 Iulie 2023, Eforie Nord, România.
  - Irina Oane, Ioana Mindruta. Midline and parasagittal EEG epileptiform abnormalities and seizure semiology correlates. A 14-a Școală de Vară ASNER, 7-9 Iulie 2023, Eforie Nord, România.
  - Laurentiu Tofan, Felicia Mihai, Irina Oane, Ana-Maria Zagrean, Andrei Barborica, Ioana Mindruta - Exploration of the brain connectivity in patients with pharmacoresistant epilepsy and visual hallucinations. 3rd International Conference on Neuroscience, Neuroinformatics, Neurotechnology and Neuro-Psycho-Pharmacology ICON4N, 26-28 Octombrie 2023, București, România.