Cingulate cortex function and multi-modal connectivity mapped using intracranial stimulation

Irina Oane a,b,1, Andrei Barborica c,*,1, Filip Chetan a, Cristian Donos c, Mihai Dragoş Maliia b,c, Anca Adriana Arbune a,b, Adrian Daneasa a, Constantin Pistol c, Adriana Elena Nica c, Ovidiu Alexandru Bajenaru a,b,e, Ioana Mindruta a,b,e

a Epilepsy Monitoring Unit, Neurology Department, Emergency University Hospital Bucharest, 169 Splaiul Independentei Street, Bucharest, Romania
b Neurology Department, Medical Faculty, Carol Davila University of Medicine and Pharmacy Bucharest, 8 Eroi Sanitari Boulevard B, Bucharest, Romania
c Physics Department, University of Bucharest, 405 Atomistilor Street, Bucharest, Romania
d Intensive Care Unit Department, Emergency University Hospital Bucharest, 169 Splaiul Independentei Street, Bucharest, Romania
e Brain Research Group, Romanian Academy, 125 Calea Victoriei Street, Bucharest, Romania

ARTICLE INFO

Keywords:
Cingulate cortex
Stereo-electroencephalography
Direct electrical stimulation
Functional connectivity
Effective connectivity
Multimodal connectivity

ABSTRACT

The cingulate cortex is part of the limbic system. Its function and connectivity are organized in a rostro-caudal and ventral-dorsal manner which was addressed by various other studies using rather coarse cortical parcellations. In this study, we aim at describing its function and connectivity using invasive recordings from patients explored for focal drug-resistant epilepsy.

We included patients that underwent stereo-electroencephalographic recordings using intracranial electrodes in the University Emergency Hospital Bucharest between 2012 and 2019. We reviewed all high frequency stimulations (50 Hz) performed for functional mapping of the cingulate cortex. We used two methods to characterize brain connectivity. Effective connectivity was inferred based on the analysis of cortico-cortical potentials (CCEPs) evoked by single pulse electrical stimulation (SPES) (15 s inter-pulse interval). Functional connectivity was estimated using the non-linear regression method applied to 60 s spontaneous electrical brain signal intervals. The effective (stimulation-evoked) and functional (non-evoked) connectivity analyses highlight brain networks in a different way. While non-evoked connectivity evidences areas having related activity, often in close proximity to each other, evoked connectivity highlights spatially extended networks. To highlight in a comprehensive way the cingulate cortex’s network, we have performed a bi-modal connectivity analysis that combines the resting-state broadband \( h^2 \) non-linear correlation with cortico-cortical evoked potentials. We co-registered the patient’s anatomy with the FreeSurge template to perform the automatic labeling based on HCP-MMP parcellation. At a group level, connectivity was estimated by averaging responses over stimulated/recorded or recorded sites in each pair of parcels. Finally, for multiple regions that evoked a clinical response during high frequency stimulation, we combined the connectivity of individual pairs using maximum intensity projection.

Connectivity was assessed by applying SPES on 2094 contact pairs and recording CCEPs on 3580 contacts out of 8582 contacts of 660 electrodes implanted in 47 patients. Clinical responses elicited by high frequency stimulations in 107 sites (pairs of contacts) located in the cingulate cortex were divided in 10 groups: affective, motor behavior, motor elementary, versive, speech, vestibular, autonomic, somatosensory, visual and changes in body perception. Anterior cingulate cortex was shown to be connected to the mesial temporal, orbitofrontal and prefrontal cortex. In the middle cingulate cortex, we located affective, motor behavior in the anterior region, and elementary motor and somatosensory in the posterior part. This region is connected to the prefrontal, premotor

Abbreviations: ACC, anterior cingulate cortex; CCEP, cortico-cortical evoked potentials; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; (a/ p)MCC, (anterior/posterior) middle cingulate cortex; PCC, posterior cingulate cortex; PVNH, periventricular nodular heterotopia; RFTC, radiofrequency thermo-coagulation; RMS, root mean square; RSC, retrosplenial cortex; SEEG, stereo-electroencephalography; SPES, single-pulse electrical stimulation.

* Corresponding author. Physics Department, University of Bucharest, P.O. Box MG-11, Bucharest, Magurele, RO 077125, Romania.

E-mail addresses: dr.popairina@gmail.com (I. Oane), andreii.barborica@fizica.unibuc.ro (A. Barborica), filip.chetan@gmail.com (F. Chetan), cristian.donos@g.unibuc.ro (C. Donos), mihaidragos@yahoo.com (M.D. Maliia), anca.arbune@gmail.com (A.A. Arbune), daneasa.andrei@gmail.com (A. Daneasa), costi.pistol@gmail.com (C. Pistol), adriana.nica@asub.ro (A.E. Nica), alstov9157@gmail.com (O.A. Bajenaru), ioanamindruta@me.com (I. Mindruta).

1 the two authors have contributed the same.
1. Introduction

The cingulate cortex is a complex, heterogeneous region in terms of anatomical and neurobiological segmentation and its organization has been recently revisited in order to match in detail its functional correlates. The cytoarchitectonic model of cingulate has been first described by Brodmann (Brodmann and Garey, 2006) who divided it in an anterior, agranular part and a posterior, granular part. However, subsequent studies have introduced a four-region model according to the topology of cytoarchitectonic areas, major afferent connections, regional composition, and functional properties: anterior cingulate cortex (ACC), middle cingulate cortex (MCC), posterior cingulate cortex (PCC) and retrosplenial cortex (RSC) (Palomero-Gallagher et al., 2009).

Previous studies have explored the function of the cingulate cortex using direct electrical stimulation (Caruana et al., 2018; Chassagnon et al., 2008; Parviz et al., 2013; Talairach et al., 1973), but did not report any results related to physiological connectivity of the studied region in human subjects. Anatomical and functional connectivity of the cingulate regions was, however, described by various other studies using lower specificity imaging methods like resting-state fMRI (Beckmann et al., 2009; Jin et al., 2018). Several methods can be used for inferring brain functional connectivity based on EEG signal analysis, that resort to calculating various types of linear or non-linear interdependencies between signals recorded at different locations, like linear cross-correlation (Kramer et al., 2009), non-linear correlation (Wendling et al., 2001), directed or non-directed coherence (Baccala and Sameshima, 2001; French and Beaumont, 1984), Granger causality (Bressler and Seth, 2011), mutual information (Pluim et al., 2003), among others. Another approach refers to highlighting the influence that one region exerts over another (Friston, 2011), by actively perturbing one region and recording the responses at other locations. This can be achieved by means of low-frequency or single-pulse intracranial electrical stimulation (SPES) (David et al., 2013; Valentin et al., 2002) and recording the cortico-cortical evoked potentials (CCEP) at other locations (Donos et al., 2016b; Entz et al., 2014; Matsumoto et al., 2004). The effective (stimulation-evoked) and functional (non-evoked) connectivity analyses highlight brain networks in a different way. While non-evoked connectivity evidences areas having related activity, and it is highly state-dependent (task-related or resting-state), CCEP-based connectivity is highly robust across successive sessions and highlights spatially extended networks (Hebbrink et al., 2019). Also, analysis in the higher frequency range (particularly gamma) tends to capture local connectivity, while lower frequencies evidence broader cortical networks (Baria et al., 2011; He and Raichle, 2009; Kopell et al., 2000; Miller et al., 2007; Singer, 1999; Tallon-Baudry, 2009).

In this study, we focus on addressing three topics: 1) to highlight in a comprehensive way the cingulate cortex’s network by performing a bi-modal, functional and effective, connectivity analysis for each subdivision using the resting-state broadband $H^2$ non-linear correlation (Wendling et al., 2001) and CCEPs evoked by intracranial single-pulse electrical stimulation (Donos et al., 2016a); 2) evidence connectivity patterns of areas exhibiting a specific group of clinical effects (Fig. 1) elicited by high-frequency stimulation; 3) use a fine-grained multi-modal parcellation of the cingulate cortex (Glasser et al., 2016) for labeling recording and stimulation sites and ROI-based analysis.

2. Materials and methods

2.1. Patients

We selected 47 patients explored by stereo-electroencephalography (SEEG) in the Emergency University Hospital Bucharest between 2012 and 2019 (Table 1). All patients were diagnosed with focal drug-resistant epilepsy of structural etiology and were admitted as possible surgical candidates. They initially underwent phase one non-invasive pre-surgical evaluation that included patient and family history followed by video-electroencephalography and neurocognitive evaluation. Consequently, each patient underwent 1.5 or 3 T Magnetic Resonance Imaging (MRI) and functional imaging (inter-ictal FDG-PET scan). In all patients, invasive exploration using SEEG was considered necessary to delineate the epileptogenic zone (Kahane and Landre, 2008; Munari and Bancada, 1987), map the functional cortex and to determine the limits of the resection (Cardinale et al., 2013; Isnard et al., 2018; Jayakar et al., 2016; Kahane et al., 2003b; Munari et al., 1994).

We included all patients that had at least one electrode sampling any part of the cingulate cortex. We further used the following patient exclusion criteria: a) patients with cognitive and psychiatric co-morbidities whose condition would interfere with a proper interaction and would therefore question the reliability of the clinical responses and b) patients that did not undergo low frequency brain direct electrical stimulation protocol. In addition, we used the following contact-exclusion criteria: a) contacts located in the cingulate cortex that were also part of the epileptogenic zone b) contacts on which high frequency brain direct electrical stimulation elicited ictal symptoms, c) contacts that displayed continuous interictal epileptiform discharges which might subsequently interfere with connectivity analysis.

All patients signed a written informed consent in accordance with the Declaration of Helsinki for all the procedures.

2.2. Invasive exploration using SEEG and data acquisition

SEEG exploration was performed using depth electrodes (Dixi Medical, Chaudefontaine, France) with 8–18 contacts per electrode, 2 mm contact length, 3.5 mm contact spacing and 0.8 mm diameter. Multiple electrodes were placed following an individual hypothesis allowing for up to 258 contacts to be recorded in each patient. Structures sampled during SEEG were selected entirely for clinical purpose with no relation to this study or other research intentions. Electrodes were placed intracranially using the Leksell stereotactic frame (Elekta AB, Stockholm, Sweden) or the microTargeting™ Multi-Oblique Epilepsy StarFix Platform (FHC, Bowdoin, ME USA) (Balanescu et al., 2014; Dewan et al., 2018; Yu et al., 2018). To determine the exact location of each electrode and contact, the post-implantation CT scan was co-registered with the pre-implantation MRI. Video-SEEG recordings were performed in clinical conditions for 7–14 days at the University Emergency Hospital Bucharest using a 64-channel Nicolet Wireless Amplifier or a 128-channel Amplifier (Natus Neuro, Middleton, WI). 64 to 128 contacts located in the cortical gray matter were continuously recorded (depending on the equipment that has been used over the course of time) at a sampling rate of 4096 Hz.

Multiple brain direct electrical stimulation protocols were carried out routinely as part of the standard pre-surgical assessment (Trebuchon and Chauvel, 2016); stimulations were performed in bipolar manner through pairs of adjacent contacts using a programmable clinical stimulator (Guideline4000LP+, FHC, Bowdoin, ME) with a square, biphasic, 1 ms pulse-width.

We used low frequency stimulation 1 Hz (Munari et al., 1993) and single-pulse electrical stimulation (Donos et al., 2016b; Matsumoto et al., 2017) to determine effective connectivity and high frequency 50 Hz (Bernier et al., 1990) stimulation to map the functional cortex.

High-frequency stimulations were performed by gradually increasing the current intensity from 0.1 mA to 3 mA, usually in 0.1 or 0.25 mA steps until a clinical or electrographic response (after-discharges) were
Fig. 1. Workflow of the data collection and analysis. Signals recorded through intracranial electrodes are used to calculate functional connectivity ($h^2$), while CCEP evoked by SPES are used as an estimate of effective connectivity. Group-level analysis is performed by co-registering patient’s anatomy with FreeSurfer template and averaging on regions of the HCP-MMP atlas. Sites evoking symptoms as a result of high-frequency stimulation are distributed across several parcels, whose combined connectivity is represented using a red-green colormap. The color representation is obtained by summing RGB values of a red hue colormap encoding effective connectivity values and a green hue colormap encoding functional connectivity values.
Table 1
List of patients investigated. Stereo-EEG implantation hypothesis, number of electrodes and of contacts used for each patient, epilepsy etiology, surgical outcome and clinical follow-up. In a minority of situations where the epileptogenic zone encompassed part of the cingulate cortex, the analysis has been performed on the remaining cingulate subdivisions that were non-epileptogenic.

| Patient | Sex | Age | Pathology | Side | SEEG implantation | Regions Resected | Number of Electrodes | Number of Contacts | Surgical Outcome | Follow up (months) |
|---------|-----|-----|-----------|------|-------------------|------------------|---------------------|--------------------|------------------|------------------|
| 1       | F   | 40  | Type II B cortical dysplasia | L    | Prefrontal        | Inferior Frontal Gyrus cortectomy | 11               | 141               | Engel IA         | 65               |
| 2       | F   | 35  | Type III cortical dysplasia  | R    | Mesial-temporal   | Temporal lobectomy             | 12               | 160               | Engel IA         | 54               |
| 3       | F   | 24  | Type II A cortical dysplasia | R    | Frontal-central   | Premotor cortectomy             | 15               | 138               | Engel IIIA       | 63               |
| 4       | F   | 25  | Type I cortical dysplasia    | R    | Temporal          | Temporal lobectomy             | 10               | 111               | Engel ID         | 67               |
| 5       | M   | 33  | Type II A cortical dysplasia | L    | Frontal           | Mesial prefrontal cortectomy    | 17               | 174               | Engel IA         | 57               |
| 6       | F   | 11  | Type II A cortical dysplasia | R    | Frontal           | Premotor-prefrontal cortectomy  | 16               | 205               | Engel IA         | 63               |
| 7       | F   | 35  | Not available               | R    | Insular-Opercular | Not operated                    | 14               | 169               | Not operated Engel IA | 62               |
| 8       | M   | 28  | Type I cortical dysplasia    | R    | Temporal          | Temporal lobectomy             | 17               | 188               | Engel IB         | 59               |
| 9       | M   | 25  | Type I cortical dysplasia    | B    | Bitemporal        | Anterior Temporal lobectomy     | 17               | 219               | Engel IVA        | 48               |
| 10      | F   | 36  | Type II B cortical dysplasia | R    | Opercular         | Parietal operculum cortectomy   | 15               | 205               | Engel IA         | 57               |
| 11      | F   | 42  | Type I cortical dysplasia    | R    | Temporal plus     | Temporal lobectomy             | 14               | 205               | Engel IA         | 57               |
| 12      | F   | 36  | Not available               | L    | Frontal           | RFTC (SMA, MCC)                | 9                | 135               | Engel IA         | 55               |
| 13      | M   | 39  | Not available               | B    | Bitemporal        | Not operated                    | 11               | 167               | Not operated Engel IB | 44               |
| 14      | M   | 29  | Type II B cortical dysplasia | R    | Frontal           | Mesial premotor cortectomy      | 9                | 112               | Engel IA         | 52               |
| 15      | M   | 42  | Type II cortical dysplasia   | L    | Frontal           | Mesial prefrontal cortectomy    | 13               | 155               | Engel IA         | 49               |
| 16      | M   | 30  | Not available               | R    | Frontal           | Frontal pole and orbitofrontal cortectomy | 15 | 199 | Engel IA | 48 |
| 17      | F   | 18  | Type II A cortical dysplasia | L    | Frontal           | Inferior Frontal Gyrus cortectomy | 14 | 180 | Engel IIIA | 20 |
| 18      | M   | 28  | Type IIA cortical dysplasia  | L    | Frontal           | pre-supplementary motor area cortectomy | 13 | 173 | Engel IIIB | 44 |
| 19      | F   | 34  | Type I A cortical dysplasia  | R    | Temporal          | Temporal lobectomy             | 13               | 157               | Engel IVC        | 47               |
| 20      | F   | 22  | Not available               | L    | Temporal          | Not operated                    | 13               | 161               | Not operated Engel IA | 32 |
| 21      | F   | 24  | Type II A cortical dysplasia | R    | Temporal-occipital| Temporal basal cortectomy       | 16               | 214               | Engel IA         | 49               |
| 22      | M   | 26  | Not available               | L    | Frontal           | Not operated                    | 15               | 204               | Not operated Engel IA | 38 |
| 23      | M   | 38  | Type II cortical dysplasia   | L    | Frontal           | Frontal pole and orbitofrontal cortectomy | 18 | 254 | Engel IA | 37 |
| 24      | F   | 48  | Hippocampal sclerosis       | L    | Frontal           | Temporal lobectomy             | 15               | 195               | Engel IA         | 20               |
| 25      | F   | 34  | Not available               | L    | Temporal          | Temporal lobectomy             | 18               | 212               | Engel IA         | 36               |
| 26      | M   | 7  | Type IIA cortical dysplasia  | L    | Frontal           | Mesial prefrontal cortectomy    | 17               | 248               | Engel IA         | 20               |
| 27      | M   | 18  | Type III cortical dysplasia  | R    | Frontal           | Mesial premotor cortectomy      | 17               | 249               | Engel IA         | 35               |
| 28      | F   | 11  | Not available               | B    | Temporal          | Not operated                    | 16               | 214               | Not operated Engel IA | 30 |
| 29      | F   | 17  | Not available               | B    | Frontal           | Not operated                    | 14               | 188               | Not operated Engel IB | 31 |
| 30      | F   | 34  | Type IIA cortical dysplasia  | R    | Temporal          | Temporal lobectomy and anterior insular cortectomy | 14 | 197 | Engel IA | 30 |
| 31      | F   | 3  | Type IA cortical dysplasia   | R    | Temporal          | Anterior temporal lobectomy, posterior insula and inferior parietal lobule | 15 | 211 | Engel IA | 19 |
| 32      | M   | 21  | Type IIA cortical dysplasia  | R    | Opercular         | Rolandic operculum cortectomy   | 15               | 212               | Engel IA         | 19               |
| 33      | M   | 20  | Type IIA cortical dysplasia  | L    | Frontal           | Mesial prefrontal cortectomy    | 16               | 208               | Engel IA         | 23               |
| 34      | M   | 38  | Hippocampal sclerosis       | L    | Temporal          | Temporal lobectomy             | 14               | 189               | Engel IA         | 22               |
| 35      | M   | 39  | Cortical dysplasia          | L    | Frontal           | Frontal pole and orbitofrontal cortectomy | 16 | 209 | Engel IA | 19 |
| 36      | M   | 39  | Type IIA cortical dysplasia  | R    | Parietal          | Mesial parietal cortectomy      | 11               | 171               | Engel III        | 18               |

(continued on next page)
To determine the outbound effective connectivity of the cingulate cortex we used cortico-cortical evoked potentials elicited by SPES. The detailed methodology for calculating and visualizing the connectivity is described in Donos et al. (2016a). In summary, in our center, SPES stimulations consist in applying variable pulse amplitudes (20 pulses per trial, 15 s inter-pulse interval, 3 ms pulse duration, 0.25-5 mA stimulation current, varied in 0.25 mA steps) on two adjacent contacts. CCEPs elicited by SPES performed on an adjacent pair of contacts located in the cingulate cortex were recorded on 62 or 254 other contacts. While HFS was performed for 1–3 s after the clinical testing started. A new stimulation trial was initiated only after the returning to the baseline pattern of the SEEG trace or after the clinical signs and symptoms had ceased.

2.3. Effective connectivity based on single pulse electrical stimulation

To determine the outbound effective connectivity of the cingulate cortex we used cortico-cortical evoked potentials elicited by SPES. The detailed methodology for calculating and visualizing the connectivity is described in Donos et al. (2016a). In summary, in our center, SPES stimulations consist in applying variable pulse amplitudes (20 pulses per trial, 15 s inter-pulse interval, 3 ms pulse duration, 0.25–5 mA stimulation current, varied in 0.25 mA steps) on two adjacent contacts. CCEPs elicited by SPES performed on an adjacent pair of contacts located in the cingulate cortex were recorded on 62 or 254 other contacts. While HFS was performed for 1–3 s after the clinical testing started. A new stimulation trial was initiated only after the returning to the baseline pattern of the SEEG trace or after the clinical signs and symptoms had ceased.

2.4. Functional connectivity estimation using non-linear regression method

Spontaneous, functional connectivity of the cingulate cortex was estimated using non-linear non-parametric regression between pairs of signals and was characterized by the $h^2$ correlation coefficient. This computational approach has been shown to be suitable for the analysis of intracranial EEG signals in the context of epilepsy (review in Bartolomei et al., 2017b) (Bartolomei et al., 2017a, 2012; Koubeissi et al., 2014).

The $h^2$ coefficient aims at quantifying the dependency between two neural signals $X$ and $Y$, independently of the type of relation between them by considering the amplitude of signal $Y$ as a function of the amplitude of signal $X$ and estimate the variance of this relation (Wendling et al., 2001). The $h^2$ is bounded between 0 (no correlation) and 1 (maximal correlation) and captures the directionality of the coupling due to the asymmetry of the values $h_{X-Y}^2 \neq h_{Y-X}^2$. Furthermore, using the asymmetry we can also define the time lag ($\tau$) between $X$ and $Y$. Consequently, by using time delay and asymmetry information for each pair of structures we calculated a directionality factor: $DF_{XY} = \frac{1}{2} [\text{sgn}(\Delta h2) + \text{sgn}(\Delta t)]$ (Wendling et al., 2001) for each interval, averaged over all analysis intervals.

In the present study, $h^2$ values were computed on broadband EEG 0.5Hz-100Hz (Bettus et al., 2011), to equally capture local and long-range connectivity (Baria et al., 2011; He and Raichle, 2009; Kopell et al., 2000; Miller et al., 2007; Singer, 1999; Tallon-Baudry, 2009). We calculated multiple correlation coefficients for each possible combination of pairs of recording contacts for 1 s intervals having a 50% overlap, during an interval of 60 s before SPES. We then calculated the median $h^2$ value over the 1 s sub-intervals and assessed its significance by performing a Wilcoxon sign-rank test ($p < 0.05$) on the directionality factor of the correlation between pairs of contacts (Lagarde et al., 2018) to determine functional resting state connectivity of the cingulate cortex.

The non-linear correlation coefficient ($r^2$) and time lag ($\tau$) was computed using AnyWave open-source software (Colombet et al., 2015) (available at http://meg.univ-amu.fr/wiki/AnyWave). Further analysis of the set of $h^2$ values, connectivity analysis and graphical representation was performed using Matlab (Natick, MA).

2.5. Cingulate cortex parcellation, contact position identification and data representation

Cortical surface reconstructions were performed using FreeSurfer
software package (Fischl, 2012) (available at http://surfer.nmr.mgh.harvard.edu). Using the method of Dale et al. (1999) and Fischl et al. (1999), reviewed in Winkler et al. (2012), population-level analysis of the contacts’ topography was performed by mapping the individual contacts to the cortical surface reconstruction of each patient, then projecting them on a spherical surface model, followed by pooling across patients and projection back to the FreeSurfer fsaverage template. The location of each pair of contacts was automatically labelled based on parcellation of the cortex performed by FreeSurfer package using Glasser et al. (2016) anatomical nomenclature (using annotation files available at https://dx.doi.org/10.6084/m9.figshare.3498446.v2). Two additional parcels corresponding to the sub-cortical structures, amygdala and hippocampus, of particular importance for epileptic networks, have been added as generic elliptical patches located on the FreeSurfer medial wall. In all figures, the displayed number of stimulated sites always refer to the number of pairs of contacts, while the graphical markers always display the individual contacts in the stimulated pairs. Contacts labelled as part of the cingulate cortex were further grouped in the following specific subdivisions: anterior cingulate cortex - ACC (s32, p32, a24, p24, d32), anterior part of the middle cingulate cortex - aMCC (a32pr, p32pr, a24pr, 33pr), posterior part of the middle cingulate cortex – pMCC (p24pr, 24dv and 24dd), posterior cingulate cortex – PCC (RSC, 23d, 23c, d23ab, v23ab, 31a, 31pd, 31pv). While there is variability in defining the subdivisions of the cingulate cortex, we have decided to follow a hybrid model derived from Palomero-Gallagher et al. (2009) and Vogt et al. (2003): ACC, aMCC, pMCC, PCC which also includes RSC. Connectivity between different cingulate cortex areas and other brain regions were represented using a color map that uses red hue for effective connectivity based on CCEP and green hue for functional connectivity using the non-linear correlation (Fig. 1). The scaling of the color representations was chosen to be roughly twice the mean of the responses or $h^2$ values (as shown in Supplementary Fig. 2), that is 2 for the patient-normalized responses and 0.5 for $h^2$. In addition, we represented connectivity patterns of multiple areas associated with each clinical effect (Figs. 4–6 and Supplementary material). Connectivity maps for ROIs encompassing multiple parcels were obtained by taking the maximum intensity projection of individual pairwise connectivity values. In these figures, contacts that were stimulated using SPES protocol that also elicited a response during HFS protocol are represented using yellow and red markers.

2.6. Data availability

The effective and functional connectivity data (patient-normalized responses and $h^2$ coefficient values) between HCP-MMP parcels can be found online at the address http://epi.fizica.unibuc.ro/atlas/. The additional source code and data can be provided by the authors upon reasonable request.

3. Results

We included 47 patients (23 male and 24 female) aged 3 - 48 years (mean 27.7 ± 9.89 SD). These were explored using a frontal lobe epilepsy hypothesis (19 patients), temporal (18), insular-opercular (6) or posterior cortex (4). Electrodes were placed exclusively on the left hemisphere in 20 patients, in the right hemisphere in 23 and in 4 patients were placed bilaterally. We used a total of 660 electrodes (mean 14 ± 2.5 SD) having 8582 contacts (mean 182.6 ± 37.7 SD). A subset of 2904 contact pairs was stimulated using SPES and the CCEPs have been recorded on 3580 contacts, after excluding white matter, artefacted or epileptogenic contacts. Three quarters of the 36 operated patients were Engel I with a mean follow-up of 40.48 ± 17.96 SD months. Eleven patients were not operated because of multifocal epileptogenic zone (example: temporal bilateral) or because they refused surgery after invasive recordings (Table 1).

We stimulated using SPES protocol 290 sites (pairs of contacts) at the level of the cingulate cortex (Fig. 2). In 107 sites stimulated using HFS we were able to elicit a clinical response (Table 2). We were able to analyze 53022 significant SPES responses out of 107644; 71926 $h^2$ coefficients were significant out of 125160 analyzed (Supplementary Material Fig. 2a and b). The functional and effective connectivity matrices are represented in supplementary Fig. S3.

3.1. Sub-regional connectivity of the cingulate cortex

Anterior cingulate cortex (s32, p32, a24, p24, d32) was sampled bilaterally using 67 pairs of contacts (28 right, 39 left, Fig. 3a and b) probing up to 70 stimulated-recorded pairs of contacts between the ACC and other brain regions (Supplementary Material). In general, we probed around 100 of stimulated-recorded pairs of contacts that served to analyze connectivity between the cingulate cortex and other regions, because contacts that were tested had to fulfill very strict inclusion and
Table 2
List of clinical responses elicited during high frequency brain stimulation, grouped in ten categories.

|                  | ACC Left | ACC Right | ACC Total | aMCC Left | aMCC Right | aMCC Total | pMCC Left | pMCC Right | pMCC Total | PCC Left | PCC Right | PCC Total | Cingulate cortex Total |
|------------------|----------|-----------|-----------|-----------|------------|------------|-----------|------------|------------|-----------|-------------|-----------|------------------------|
| affective        | 1        | 1         | 2         | 4         | 4          | 8          | 0         | 0          | 0          | 3         | 3           | 6         | 13                     |
| autonomic        | 4        | 1         | 5         | 1         | 4          | 5          | 0         | 0          | 0          | 4         | 2           | 6         | 16                     |
| body perception  | 0        | 0         | 0         | 2         | 4          | 6          | 1         | 0          | 1          | 0         | 1           | 1         | 8                      |
| motor            | 0        | 0         | 0         | 4         | 2          | 6          | 5         | 3          | 8          | 3         | 0           | 3         | 17                     |
| motor behavior   | 0        | 0         | 0         | 0         | 4          | 4          | 0         | 0          | 0          | 0         | 0           | 0         | 4                      |
| somatosensory    | 0        | 0         | 0         | 4         | 5          | 9          | 0         | 2          | 2          | 4         | 9           | 13        | 24                     |
| speech           | 1        | 1         | 2         | 1         | 3          | 4          | 2         | 0          | 2          | 1         | 0           | 1         | 9                      |
| versive          | 0        | 0         | 0         | 1         | 0          | 1          | 1         | 1          | 2          | 0         | 0           | 0         | 3                      |
| vestibular       | 5        | 0         | 5         | 0         | 0          | 0          | 0         | 0          | 0          | 3         | 0           | 3         | 8                      |
| visual           | 0        | 0         | 0         | 0         | 0          | 0          | 0         | 0          | 0          | 5         | 0           | 5         | 5                      |
| Total            | 11       | 3         | 14        | 17        | 26         | 43         | 9         | 6          | 15         | 20        | 15          | 35        | 107                    |

Fig. 3. Combined connectivity of cingulate cortex subregions. Right (a) and left (b) anterior cingulate ACC (area s32, p32, a24, p24, d32), right (c) and (d) left anterior part of the middle cingulate aMCC (a32pr, p32pr, a24pr, 33pr), right (e) and left (f) posterior part of the cingulate pMCC (p24pr, 24DV and 24dd), right (g) and left (h) PCC (RSC, 23d, 23c, d23ab, v23ab, 31a, 31pd, 31pv). Figure displays only regions exhibiting both functional and effective connectivity with the ROIs; strength of connectivity is showed using different color shades and intensities.
exclusion criteria. The ACC shows increased combined connectivity with ipsilateral mesial prefrontal cortex (area 9m, 8BM, 25), frontal pole cortex (a10p) orbitofrontal cortex, anterior insular regions, amygdala, entorhinal cortex and contralateral ACC (a32, a24, p24 - Fig. 3a,b).

Anterior division of the middle cingulate cortex – aMCC (a32pr, p32pr, a24pr, 33pr) was sampled by 79 electrode contact pairs (42 right-side and 37 left-side, Fig. 3c and d). Connectivity analysis evidences strong connections with prefrontal-regions (9m, d32, 8BM), premotor and supplementary motor areas (SCEF, 5m, 5mv) and mesial parietal regions – PCC (RSC, area 23d, v23ab) on the right side. On the left side strongest connections are with left RSC (area 23d and v23ab) and pMCC (area p24pr) (Fig. 3c and d).

Posterior division of the middle cingulate cortex (p24pr, 24dd and 24dv) represents the motor part of the cingulate cortex. These areas were sampled bilaterally with 56 pairs of contacts (35 right-side, 21 left-side, Fig. 3e and f). The pMCC is connected with primary motor cortex (area 4), premotor cortex (area 6a), supplementary motor area (area SCEF, 6mp), somatosensory regions (areas 3a, OP4), mesial parietal regions (5m, 5l, 5mv, 21pd, 21pv, 23c) and dorsal prefrontal cortex (8c, 8Av, i6-8) (Fig. 3e,f).

Finally, the posterior cingulate cortex divided in 8 areas (RSC, 23d, 23c, d23ab, v23ab, 31a, 31pd, 31pv) was sampled by 117 pairs of contacts (70 right-side and 47 left-side, Fig. 3g,h) that had more than 200 pairs of significant CCEPs between the PCC and visual areas (Supplementary Material). The PCC shows increased connectivity with the primary and early visual areas (V1, V2, V3, V4), mesial and lateral temporal (H, A, EC, PeEC), temporal and suprasylvian operculum (mainly frontal – area 44) and parietal operculum, lateral parietal (areas PFM, PGs, IPS1, AIP) and prefrontal cortex (area 9m) (Fig. 3g,h).

3.2. Functional responses and their associated connectivity patterns

In 27 patients (107 stimulation sites) we recorded positive and/or negative clinical responses during high-frequency stimulation of the cingulate cortex. We identified 10 categories of clinical responses as follows: affective, speech, motor, motor behavior, versive, somatosensory, autonomic, vestibular, body perception, visual (Table 2).

Affective responses were defined as subjective or objective behavioral changes related to emotional processing. Patients reported fear, anxiety, panic, unpleasant agitation or sensation of happiness accompanied by the need to smile. These effects were elicited in 13 sites and were clustered in areas p24, a24pr and 33pr, 8 stimulation-sites (61.5%) related to these responses were located in the aMCC (Table 2). Joint multimodal connectivity maps of these regions show increased connectivity with mesial prefrontal cortex, temporal mesial regions, retrosplenial cortex (Fig. 4a,b,c).

Complex motor behavior effects were elicited in 4 stimulation sites all located in the ventral part of the right aMCC, area 33pr (Table 2). During

![Fig. 4](image-url)

Fig. 4. Regions eliciting affective and motor behavior, and their connectivity. Stimulating contacts that elicited affective (a,b,c) and motor behavior (d,e,f) responses that were also included in SPES protocol are indicated with yellow or red markers. The small light blue markers indicate location of other recording or stimulating contacts. Figures in the first column (a,d) display patterns of effective connectivity (CCEP); second column (b,e) presents patterns of functional connectivity (h2) and last column (c,f) displays combined, multi-modal, connectivity for each clinical response; g) and h) display examples of motor behavior in patient 23 that puts his hand on his face or wipes his nose with the left hand; i) patient 18 feels the urge to move his right hand and he rubs his nose.
these stimulation trials, patients present complex, integrated gestural automatism directed towards their own body or peripersonal space for example they rub their nose or eyes (Fig. 4g and h,i). This behavior might be accompanied by urgency of action when patients report that they also feel an imminent need to move their hands. Combined multi-modal connectivity of area 33pr highlights connections with mesial prefrontal cortex (area 9m), supplementary motor area – SCEF and RSC (Fig. 4d and e,f).

**Motor responses** were elicited in 17 stimulation sites clustered in the caudal region of the cingulate cortex at the level of the MCC and PCC bilaterally - Table 2, caudal part of area33pr, area p24pr, area 23d and in the rostral part of RSC (Fig. 5a; these sites were located inferior to the supplementary motor area and the paramedian lobule). Clinically, patients presented simple elementary motor responses mostly tonic and clonic contractions (Fig. 5d) that involved the contralateral upper limbs (9 sites) or lower limbs (8 sites). Network analysis shows increased multi-modal connectivity with the premotor cortex, supplementary motor area and primary motor cortex, primary (area 3) and secondary (parietal operculum) somatosensory regions and prefrontal cortex (Fig. 5b).

**Versive responses** were elicited in 3 sites in the MCC (1 site in the caudal area 33pr and 2 sites in pMCC, area p24pr) Table 2, Fig. 5 b. In this category, we included tonic versive movements of the head (Fig. 5 e) and eyes (Fig. 5 f). Both SPES and $h^2$ analyses shows increased connectivity with the primary motor cortex, pMCC and PCC, SCEF, FEF, 6mp, 6d, 5mv (Fig. 5b). A particular oculomotor effect was recorded in patient P43; while stimulating the left aMCC patient presented tonic internal deviation of the right eye (right eye convergent strabismus) (Fig. 5f).

**Speech related clinical responses** were elicited in 9 sites located in all cingulate cortex subdivisions (ACC, aMCC, pMCC and PCC), bilaterally (Table 2, Fig. 5c). Semiology of speech responses may vary from dysarthria when patients present a slurred speech to anarthria when we elicited speech arrest (patients explaining that they cannot say the words out loud although they know what they are supposed to answer). In addition, in two patients (P13 and P16) we observed an inhibition in word generation while stimulating ACC. Connectivity maps of the areas eliciting these responses show highest connectivity, in both modalities, with mesial prefrontal cortex, supplementary motor regions and mesial parietal cortex (area 9m, SCEF, 24dv, p24pr and 23c) (Fig. 5c).

**Somatosensory** responses were elicited in 24 sites: aMCC (33pr, a24pr), pMCC (p24pr, 24dv) and PCC (23d, 23c, RSC, d23ab, v23b, 24dv) bilaterally (Table 2). During these clinical responses, patients report electric-like sensation, numbness or pins-and-needles sensation involving the contralateral limbs (18 stimulations), bilateral upper limbs or eyes (4 stimulations) and ipsilateral limbs (1 stimulation). Areas where somatosensory responses were elicited show increased connectivity with mesial parietal regions, supplementary motor regions, inferior parietal cortex and temporal-occipital cortex (Supplementary Material).

**Autonomic** responses were elicited in 16 stimulation sites clustered in the ventral part of ACC, aMCC and PCC (Table 2), circulate areas a24, p24, 33pr, RSC (Fig. 6a and b,c). Patients report heat sensation (at the level of one or several limbs usually laterized ipsilateral or contralateral to the stimulated hemisphere or axial, in the thorax), shiver, tachycardia, pressure in the thorax or sensation to sneeze. Combined connectivity maps show high intensity of the mesial prefrontal and parietal regions, dorsal inferior parietal, temporal mesial and lateral structures as well as insular cortex, to a lower degree (Fig. 6c).

**Vestibular** responses were defined as vertigo and dizziness and were elicited in 8 sites in the ACC, aMCC and PCC (Table 2) areas a24, p24, RSC, 31a, 23d. Connectivity analysis of these areas highlights important connections with lateral and mesial parietal regions (areas 23c, 7pm, PGs), parietal operculum (OP1, PFop) and prefrontal cortex (Fig. 6d and e,f).

**Body perception** responses were defined as altered perception related to location, gravity or displacement of whole-body or body-parts. These were elicited by stimulating 8 sites in MCC and PCC (Table 2) specifically areas 33pr, a24pr, p24pr, a32pr, p32pr, 24dv and RSC (Supplementary Material). These areas show increased multimodal connectivity with the mesial parietal and prefrontal cortex and temporo-occipital junction.

![Fig. 5. Regions eliciting motor, versive and speech responses, and their connectivity. Stimulating contacts that evoked clinical effects on HFS and were also included in SPES protocol are indicated using red markers, whereas other recording or stimulating contacts are displayed in light blue. Stimulation sites and combined connectivity of areas that elicited: a) motor effects; b) versive movements of the eyes or head; c) speech related responses (speech arrest or dysarthria) d) example of tonic contraction of the distal part of right upper limb while the contralateral pMCC is stimulated e) tonic version of the head during stimulation of the right, contralateral, pMCC (area p24pr) f) saccadic convergent strabismus with adduction of the contralateral eye while stimulation the left pMCC (area p24pr).](image-url)
Visual responses were elicited in 5 sites located in the PCC (RSC, v23ab, 23d, p24pr) and connectivity analysis reveals increased responses in temporal-occipital and frontal-parietal regions following the distribution of both ventral and dorsal streams (Supplementary Material). During these stimulations, patients reported blurred vision, visual hallucination or difficulty of visual focusing.

4. Discussion

In this study we focused on highlighting multi-modal connectivity (functional, effective) and clinical responses elicited by direct electrical stimulation of the cingulate cortex (Fig. 1).

4.1. Cingulate cortex connectivity

What distinguishes our study is that it provides a detailed mapping of the cingulate cortex based on a fine-granularity multi-modal atlas (Glasser et al., 2016). We analyzed SPES responses to determine effective connectivity between the cingulate cortex and other brain regions sampled by intracerebral electrodes. Functional connectivity was estimated using an observational, non-interventional method based on a non-linear regression that analyses the interdependencies between the electrical activities of different neural populations. In this study, we combined these two methods to increase the specificity and highlight those robust connections in both modalities.

We found that the ACC displays both effective and functional connections with the ipsilateral amygdala, OFC, mesial prefrontal cortex and contralateral ACC. This pattern of connectivity is also pointed out by previous tractography studies where two clusters at the level of the ACC show connections with the amygdala, hippocampus, ventral striatum, hypothalamus, medial and lateral OFC (Beckmann et al., 2009). Diffusion-weighted imaging and resting-state functional imaging studies have also highlighted primary connections of the ACC with the insula and the temporal pole (Jin et al., 2018) but our combined electrophysiological methods fail to confirm a strong connection (Fig. 3a and b). Our results are also in line with previous studies that find no resting-state and no task-dependent fMRI correlation between the ACC and temporal pole in patients with autistic spectrum disorders (Balsters et al., 2016). However, when using cingulate cortex area involved in reward-guided learning and decision making (e.g. value of abstract goods, tracking values) as seeds, a functional connection could be identified between the ACC and temporal pole (Neubert et al., 2015).

The MCC is anatomically connected with the prefrontal, premotor, precentral, parietal cortex and dorsal striatum (Beckmann et al., 2009). Our findings are similar and in addition we pointed out that the anterior MCC subdivision is also connected with the anterior insula and suprasylvian operculum. This pattern is reported by Jin et al. (2018) that further highlights connections with the dorsolateral prefrontal cortex as well. In Fig. 3, combined connectivity maps display this latter relation between the aMCC and DLPFC but not a strong one which could be due to the resting state condition, these two structures show an intense coupling during cognitive tasks (Bush et al., 2000).

The posterior part of the cingulate cortex (including RSC) is connected with the mesial occipital and parietal cortex, lateral inferior and superior parietal, hippocampus and temporal neocortex, mesial prefrontal cortex and premotor regions. Anatomical DTI connectivity between the PCC and the hippocampus and parietal cortex is also highlighted by Beckmann et al. (2009) and resting state fMRI has provided evidence of functional connections between the PCC and frontal lobe (Jin et al., 2018).

4.2. Functional mapping

Functional mapping performed using high frequency electrical stimulation elicited clinical effects, in line with previous studies. As in Caruana et al. (2018), we found motor simple responses or motor behavior located mainly in the MCC, somatosensory responses clustered in the aMCC and PCC, autonomic responses in the ACC and MCC and visual responses elicited by PCC stimulation. However, affective, vestibular and
speech related clinical responses differ in terms of locations of sites. The majority of affective responses were negatively valenced and considered discomfort (fear, anxiety, panic) and were elicited during stimulation of sites clustered in the aMCC (33pr, a24pr) Fig. 5 a,b,c. In the prefrontal anterior cingulate we elicited happiness associated with desire of smiling, as reported by Caruana et al. (2015), too. Previous studies have reported affective responses in the prefrontal ACC (Caruana et al., 2018) but the clinical effects selected in this category differ from ours since they included laughter (mirthful or not), interoceptive sensations (like feeling of emptiness) and autonomic responses (e.g. hot flushes, tachycardia with a clear emotional aspect). We have included the autonomic responses in a single category together with interoceptive sensations which are elicited by ACC, MCC and PCC stimulation (ventral part of p24, 33pr, a24 and RSC Fig. 6). Patients report localized heat sensation, thorax pressure, tachycardia or epigastric sensations. Previous stimulation-based studies of the ACC elicited visceromotor responses like fluctuations in heart and respiratory rate, myridaxis and rubefaction of the face (Talairach et al., 1973). On the other hand, heart rate variability during cognitive or motor tasks was related to activation of the aMCC and prefrontal ACC, bilateral insula, orbitofrontal cortex, retrosplenial cortex, and medial parietal (Amiez and Procyk, 2019; Critchley et al., 2000). In our study, combined connectivity analysis of these multiple regions that elicited autonomic responses highlights a wide distributed network involving a strong activation of the limbic system, mesial frontal-parietal structures as well as lateral temporal and parietal regions (Fig. 6c). An autonomic activation is an accompanying symptom in a large range of other clinical responses (motor, cognitive, emotion). Our subjects report intense fear associated with epigastric sensation or generalized anxiety like a panic attack; patient 32 reports that the sounds in the room irritate him and he exhibits intense agitation and distress. Previous stimulation studies have elicited positive emotions like mirth and anxiolysis in the anterior region of the cingulum (Bijanik et al., 2019) that could be modulated by the magnitude of stimulation (Yih et al., 2019). These findings are in line with new studies that emphasize the role of the aMCC in integration of negative affect, pain and cognitive control (Rizolli et al., 2016). Our connectivity analysis shows that regions associated with fear, anxiety and panic in the aMCC are strongly connected with the mesial prefrontal cortex and supplementary motor area (Fig. 4 c).

Furthermore, we were able to elicit complex integrated motor behavior exclusively during stimulation of the aMCC, area 33pr (Fig. 4 b,c) similar with Amiez and Petrides (2014). As shown in Fig. 4, emotional and complex motor behavior share the aMCC as area of stimulation and the prefrontal-premotor regions as a network of activation. It is hypothesized that the aMCC represents a hub where emotional information is linked to motor networks responsible for goal-directed behavior (Shackman et al., 2011). Our study is in line with previous ones that point out the dual role of the aMCC as an integrator of emotion and behavior. Carrillo et al. (2019) show the neurons in the rat’s ACC respond to pain experience and observation but most of these neurons do not respond to fear. Previous electrophysiologic studies highlight the existence of neurons responsible for voluntary movements most of the in relation to reward (Quilodran et al., 2008; Shima and Tanji, 1998; Williams et al., 2004).

Speech-related clinical responses comprised anarthria and dysarthria because of difficulties in tongue or perioral muscles coordination were elicited during MCC stimulation similar with (Caruana et al., 2018). These stimulations were performed anterior to the areas that elicited simple motor movements of the hand, leg or mouth (Fig. 5). Speech organization of motor responses in the cingulate motor areas was identified by (Amiez and Petrides, 2014; Lab et al., 2018) and also display a somatotopic configuration for each motor cluster. We highlight here that, in the cingulate cortex, motor responses related to hands, legs and face are clustered in aMCC/pMCC, sites that are characterized by bi-modal connections with primary motor, premotor, supplementary motor and prefrontal cortex. In addition, we observed a second cluster of speech related clinical responses manifested as decrease in verbal fluency during stimulations in the ACC (P29 and P37).

Vestibular responses were elicited in the ACC and PCC which is different from (Caruana et al., 2018) that report a significant cluster of vestibular responses in the pMCC. In primates, vestibular cortex has been shown to be located in the intraparietal sulcus, temporal neocortex, visual posterior sylvian area and parietal insular cortex (Guldin and Grüsser, 1998). In addition, in humans, previous stimulation studies have mapped vestibular responses in the frontal lobe - anterior cingulate gyrus (BA 32 and 24) and parietal lobe – cingulate sulcus (BA 7) (Kahane et al., 2003a) and PCC (Kremmyda et al., 2019) sites that are similar with our findings. One explanation for this different topography for vestibular responses could be the fact that this type of clinical effects is strongly influenced by other activities and patients might not disentangle dizziness from other motor or cognitive effects and in consequence they do not report it.

Vestibular responses are also related to one’s own body perception and play an important role in self-identification. This is a function that we have previously shown to involve the cingulate cortex (Popa et al., 2019). This role of the cingulate cortex in self-oriented processes is further emphasized by the somatosensory, and body perception changes that were elicited while stimulating the PCC. These self-related findings are integrated in a larger network dedicated to multisensory processing together with insular cortex, inferior parietal, temporal and frontal (Supplementary Material). Finally, one important sensory modality that is represented in the cingulate cortex is the visual perception. We have found visual responses in the PCC when patients report elementary hallucinations or difficulties in eye movement coordination (Vogt et al., 2006).

There are several limitations of this study. One limitation of the study is that the process of performing cortical surface reconstructions, mapping the contacts to the nearest vertice. coregistration with the template and automatic labeling of the contacts is inherently approximate (McCarthy et al., 2015). Therefore, the results of the positioning of the contacts on the template and labeling must be treated with certain level of caution. Moreover, the cingulate cortex parcellation is performed following HCP-MMP atlas based on multimodal domains (myelin, cortical thickness, functional connectivity and task activation) which provides a combination of architectural and functional organization. Since this is a comprehensive atlas, we decided to follow the segmentation proposed by HCP-MMP despite the anatomical differences among subjects (e.g. the presence or absence of the paracingulate sulcus, Amiez et al., 2013; Vogt et al., 1995).

5. Conclusion

This study provides detailed information related to functional organization and bi-modal connectivity of the cingulate cortex in patients explored using intracranial electrodes for drug-resistant epilepsy. We highlight connectivity clusters characterized by a rostro-caudal configuration, for each of the four regions of the cingulate cortex. The most responsive subdivision of the cingulate cortex is the aMCC which is involved in emotional processing of negative stimuli (fear, anger, panic) and is able to elicit integrated motor behavior suggesting a final path ready to act on emotions. Further, motor responses (upper/lower limb, mouth-tongue and eyes) are clustered in the MCC area, displaying strong connections with motor-premotor regions. Finally, we mapped self-related effects (changes in body perception, somatosensory responses) and visual responses in the PCC, and highlighted its increased connectivity with visual areas and prefrontal regions.

Funding

This work was supported by Romanian UEFISCDI research grants PN-III-P4-ID-PCE-2016-0588, PN-III-P1-1.1-TE-2016-0706, EU COFUND-FLAGERA II-SCALES and COFUND-FLAGERA II-CAUSALTOMICS.
Declaration of competing interest

Andrei Barborica PhD is also Vice-President and Chief Technological Officer of FHC Inc, the manufacturer of the electrical stimulator and stereotactic fixture used in Bucharest. The other authors have nothing to disclose in relation to this work.

CRediT authorship contribution statement

Irina Oane: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Writing - review & editing. Andrei Barborica: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Funding acquisition. Filip Chetan: Data curation. Cristian Donos: Methodology, Software. Mihai Dragoș Malia: Investigation. Anca Adriana Arbune: Project administration. Ovidiu Alexandru Bajenaru: Supervision. Ioana Mindruta: Conceptualization, Investigation, Writing - original draft, Writing - review & editing, Supervision.

Acknowledgements

We would like to thank Ciurea Jean MD, PhD, Alin Rasina MD part of the functional Neurosurgical Team for helping with intracerebral electrode placement and Felicia Mihai for helping us with SEEG signal analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.117059.

References

Amiez, C., Neveu, R., Warrot, D., Petrides, M., Knoblauch, K., Procyk, E., 2013. The organization of the human cingulate motor areas. Cerebr. Cortex 24, 563–576. https://doi.org/10.1093/cercor/bhs329.
Bartolomei, F., Lagarde, S., Wendling, F., Chauvel, P., Cozzone, P.J., Lemieux, L., Bartolomei, F., Chauvel, P., Cozzone, P.J., Lemieux, L., Bartolomei, F., Chauvel, P., Cozzone, P.J., Lemieux, L., 2011. Intracortical functional connectivity of human epileptic networks assessed by intracerebral EEG and BOLD signal fluctuations. PloS One 6, e20701. https://doi.org/10.1371/journal.pone.0020701.
Jirsa, V., Boudot, S., Guye, M., 2017. Cortico-cortical effective connectivity in the human anterior cingulate cortex: A functional connectivity study. Neuroimage 157, 68–78. https://doi.org/10.1016/j.neuroimage.2017.03.019.
Kahane, P., 2011. Transcranial magnetic stimulation of the human anterior cingulate cortex. Trends Cognit. Sci. 15, 122–128. https://doi.org/10.1016/j.tics.2011.03.001.
Kahn, L.R., Erhardt, E.B., Fabo, D., Litt, B., 2010. Cortical stimulation-evoked evoked responses in patients with mesial temporal lobe epilepsy. Clin. Neurophysiol. 121, 173–181. https://doi.org/10.1016/j.clinph.2009.10.013.
Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influence on anterior cingulate cortex. Trends Cognit. Sci. 4, 215–222. https://doi.org/10.1016/S1364-6613(00)01483-2.
Buzsaki, G., 2002. Rhythms of the Brain. Oxford University Press, New York.
Donos, C., Malia, M.D., Mindruta, I., Popa, I., Ene, M., Balanescu, B., Ciurea, A., Barborica, A., 2016a. A connectomics approach combining structural and effective connectivity assessed by intracranial electrical stimulation. Neuroimage 132, 323–331. https://doi.org/10.1016/j.neuroimage.2015.07.024.
Fischl, B., 2012.自由空間の利用による脳の3D立体構造の三次元的測定：神経科学応用における可能性。日本精神神経学会誌 67, 1286–1294. https://doi.org/10.1016/j.clinph.2015.02.013.
Irimia, I., Oane et al. NeuroImage 220 (2020) 117059

Irene Oane et al. NeuroImage 220 (2020) 117059
