Mapping the human brain with cortical electrical stimulation

PhD thesis

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1 Introduction

Epilepsy surgical candidates with focal epilepsies in selected cases are subject to intracranial electrode placement in order to localize the epileptogenic focus to be resected. The seizure outcome of patients without visible MRI abnormality or with extratemporal seizure focus after resective surgery is still below the results of the patients with temporal epilepsies. To achieve better seizure outcome after a successful surgery we have to increase our knowledge on the different types of epilepsies, the seizure spreading mechanisms and networks involved. And also about the functional areas of the brain which may not be disrupted or removed to guarantee optimal quality of life after surgery.

In order to study both the pathological and physiological functions and networks, invasive and non-invasive methods are in use. To localize the seizure focus with implanted electrodes, electrophysiological data is carefully analyzed parallel with the preoperative functional and structural imaging data. The standard application of high frequency electrical stimulation to the brain is still the gold standard to localize essential functional areas to be kept from surgical resection, but provides also information about epileptic areas.

In the past decade, an interventional approach has been adopted within a few groups which involve single pulse stimulation at one cortical region and recording the response at other regions. SPES typically does not elicit any obvious behavioral effect, but the ability to deliver multiple pulses allows computation of a cortico-cortical evoked potential (CCEP) profile over the array of implanted electrodes. Such mapping has been used to define functional networks related to language and motor function and pathological networks that support ictal onset.

Neuroscientists independently revealed that stimulation of the neocortex can increase slow wave activity during sleep, regardless of the mode of stimulation (transcranial electric or magnetic or intracortical).
The parallel investigations of neuroscientists and clinicians led to the different interpretation of the stimulation evoked responses. While clinicians focused on the diagnostic and therapeutic effects, scientists tried to investigate the electrophysiological changes induced by the stimulation locally and globally both in animals and humans. The first report on SPES in humans in Hungary came from Dr. István Ulbert' laboratory performed by Dr. Loránd Erőss as the operating neurosurgeon at the National Institute of Neuroscience in Budapest, reporting on intraoperative SPES through subdural electrodes over the temporal lobe and the evoked potentials were recorded both from the hippocampal formation with laminar microelectrodes and also from the neocortex with subdural electrodes.

2 Aims

2.1 To evaluate the appropriate settings for single pulse electrical stimulation (SPES).

2.2 To describe the effects of SPES on the neocortex recorded with electrocorticography and with a laminar multielectrode recording system in the deeper layers.

2.3 To compare the spontaneous and cortical stimulation evoked slow oscillation.

2.4 To describe the propagation patterns of human slow wave sleep using non-linear mutual information based correlation technique.

2.5 To standardize electrode reconstruction and visualization for patients with intracranial electrodes.

2.6 To correlate the resting state functional connectivity data acquired with fMRI and the distribution pattern and amplitude of CCEPs.

2.7 Mapping of functional areas using graph theoretical and network based approaches on CCEP data.

3 Methods

3.1 General methodologies and materials

3.1.1 Patient selection

Patients participating in these studies have medically intractable seizures and were referred for epilepsy surgical evaluation. The studies were performed in two different major epilepsy surgical centers either at the Functional Neurosurgical and Epilepsy Departments of the National Institute of Neuroscience (NIN, Budapest, Hungary) or at the Comprehensive Epilepsy Center at North Shore LIJ Health System (NSLIJ, Manhasset, NY USA). All patients had pharmaco-resistant epilepsy and prior to surgical intervention were presented at the local epilepsy surgical conference for multidisciplinary discussion of the planned therapy. Only those patients were included who were offered an invasive presurgical evaluation for better localization of epileptogenic areas solely based on clinical decision. Fully informed consent was obtained from each subject under the

auspices of the Hungarian Medical Scientific Council and local ethical committee; National Institute of Neuroscience, or along institutional review board guidelines (protocol #07-125) of North-Shoe LIJ Health System, according to the World Medical Association Declaration of Helsinki. Patient enrollment started in 2006 and went on till 2012 at NIN and from 2009-2012 at NSLIJ. We analyzed the data of 38 patients coming from both centers (14 patients from NIN and 24 patients from NSLIJ, Male: 20, Female: 18, Average age at surgery: 30,6±11,1 years). 11 patient's preoperative MRI was considered normal, without any known pathology.

3.1.2 Electrode implantation, ECoG recording and imaging

Following non-invasive evaluation patients underwent subdural strip, grid and depth electrode implantation Video-EEG - monitoring was carried out using standard clinical systems at both sites. All signals were recorded to a skull electrode at NSLIJ (Acquisition rate: 2 kHz, no filtering) and to a mastoid reference at NIN (Acquisition rate: 1 kHz, no filtering). ECoG recordings were made over the course of clinical monitoring for spontaneous seizures. The long-term video-EEG monitoring of the patients took place at a highly specialized unit, with 24 hour service of EEG assistants and nursing care.

As a routine most of the patients had extensive functional and structural MRI done as required for localization of eloquent areas including a 5 minute resting state fMRI scan and also diffusion tensor imaging. Every patient received a postimplantation MRI and most of them also a CT, included in the study.

3.1.3 Brain surface reconstruction and electrode localization

In order to map evoked responses to anatomical locations on the cortex, subdural electrodes were identified on the pre-operative MRI by first registering the locations of the electrodes on the post-implantation CT to the equivalent location in the post-implantation structural MRI. Pre- and post-implantation MRIs were both skull-stripped using the BET 2 algorithm from the FSL software library (www.fmrib.ox.ac.uk/fsl/) followed by coregistration to account for possible brain shift caused by electrode implantation and surgery. Electrodes were identified in the postimplantation CT using BioImageSuite and subsequently snapped to the closest point on the reconstructed pial surface of the pre-implantation MRI in MATLAB using custom scripts. The reconstructed pial surface was computed using Freesurfer. Intraoperative photographs were used to corroborate this registration method based on the identification of major anatomical features. See in detail in the results section.

3.1.4 Functional electrical stimulation mapping of the neocortex

For localization of functional cortical areas electrical stimulation mapping (ESM) was carried out according to standard clinical protocol (bipolar stimulation, train lengths: 2-5sec, Amplitude: 3-15mA, Frequency: 20-50Hz, Pulse width: 0,5msec). ESM was always performed in the presence of an epileptologist and neuropsychologist.

3.1.5 Single pulse electrical stimulation of the neocortex

Systematic bipolar stimulation of each pair of adjacent electrodes was administered with single pulses of electrical current (Amplitude: 10mA, Frequency: 0.5Hz, pulse width: 0.2 msec, 20-100 trials per electrode pair) using a Grass S12 cortical

stimulator at NSLIJ (Grass Technologies Inc., West Warwick, RI, USA) and an IRES Surgical 600 cortical stimulator at NIN (Micromed S.p.A. Via Giotto, 2-31021, Mogliano Veneto - Italy). The associated evoked responses (CCEPs) were measured at all other electrode sites. The stimulation was performed extra-operatively on average 5 days after electrode implantation surgery after seizures had been recorded and anti-epileptic medications had been resumed. Stimulation was performed at the bedside while the patient was either in a restfully awake state or in the deep stages of non-REM sleep in the early hours of sleep.

3.1.6 Analysis of CCEP

Electrophysiological data analyses were performed using Neuroscan Edit 4.3 software (Compumedics, El Paso, TX) and custom MATLAB scripts (MathWorks, Natick, MA). Evoked responses to stimulation were divided into 2s epochs (500ms pre-stimulation to 1500ms post-stimulation) time-locked to stimulation pulse delivery. To quantify the magnitude of the CCEPs in the time window of the N2, we measured the peak voltage of the absolute value of the response between 50-500ms and computed z-score. Prior to averaging low pass filtering (30 Hz) and baseline correction (-500 to -50 ms) was performed. CCEPs were considered significant if the N2 peak of the evoked potential exceeded the baseline amplitude by a threshold of ±6SD as determined from the ROC curves. Evoked responses exceeding ± 500μV were excluded as these most likely indicate electrical artifacts.

3.2 Analysis of spontaneous and evoked slow oscillation

3.2.1 Patients and electrodes

Five patients were included in the first part of the study (stage 1) dealing with the analysis of spontaneous slow oscillations of the

brain, which has been published earlier. And four patients were included in the second part of the study (stage 2, Pt. 4 and 5. were included in both stages) describing the effects of SPES evoked potentials with laminar multielectrode.

In addition to the surface electrodes, a 350 μm diameter, 24 contact experimental laminar multichannel microelectrode array (ME) was implanted perpendicular to the cortical surface, underneath the clinical grids. The ME was placed in cortex that was likely to be removed at the definitive surgery.

3.2.2 ME Recordings

ECoG from clinical strip and grid electrodes (32-92 channels, mastoid reference) was recorded concurrently with patient video using the standard hospital system. This reference independent measurement method, using a preamplifier on the head of the patient for the ME was proven to be effective in minimizing the motion related and electro-magnetic artifacts. The LFPg was split to EEG range (0.1-300 Hz) and single (SUA), multiple unit activity (MUA) frequency range (300-5000 Hz) by analogue band-pass filtering at the level of a custom made main amplifier. EEG range signal was sampled at 2 kHz / 16 bit; MUA range was sampled at 20 kHz / 12 bit and stored on a hard drive.

3.2.3 Slow wave activity detection (stage 1.)

We have analyzed the LFPg, MUA, and ECoG data acquired from each patient during one to three nocturnal recording sessions. Partial sleep staging was performed based on readings of the available scalp EEG and ECoG electrodes by expert neurologists. In this study, we have analyzed electrophysiological data obtained only from NREM sleep (N3, or SWS). Behavioral sleep was confirmed by the video recording, while SWS was electrographically identified in accordance with the recent AASM guidelines. Data containing

interictal spikes (within 1 min) and seizures (within 60 min) were excluded from the study to avoid epileptic contamination.

3.2.4 Current source density analysis

CSD analysis identifies synaptic/trans-membrane generators of LFP in laminated neural structures. The negative of the second spatial derivative of the LFP closely approximates the macroscopic current density over unity cell membrane area. Since LFPg is the first spatial derivative of LFP, one additional spatial derivation yielded the CSD for the EEG range (0.1-300 Hz) data.

3.2.5 Multiple unit activity analysis

A continuous estimate of population neuronal firing rate was calculated from the MUA range (300-5000 Hz) data. The signal was further filtered (500-5000 Hz, zero phase shift, 48 dB/octave), rectified and decimated at 2 kHz, applying a 0.5 ms sliding average rectangular window, followed by a final, smoothing low-pass filter (20 Hz, 12 dB/octave).

3.2.6 Evoked slow oscillation analysis (stage 2.)

The same set up and analysis methods were used as described in detail in the spontaneous SO section.

3.3 Methods of non-linear mutual information based correlation technique

Patients (Pts.) participating in this study [n= 6, five men (Pt. 3, 4, 6, 8, 9) and one woman (Pt. 5)] were all referred to NIN for epilepsy surgical evaluation.

Data preprocessing.

Subgrids of 4x4 (Pts. 3, 5, and 8) or 4x5 (Pts. 4, 6, and 9) electrodes were selected for analysis. For each patient, three to five 1-min-long segments (26 segments in total) of normal SWS

were selected. Selected segments were preceded and followed by 30 min of seizure-free activity and were free from interictal spikes. ECoG traces were resampled at 1000 Hz and bandpass filtered (0.1–40 Hz) with a finite impulse response filter using zero phase shift filtering (fir1.m and filtfilt.m built-in Matlab functions) to remove high frequency ECoG components and electrical noise.

Calculation of propagation maps.
We assessed associations between ECoG traces from different channels using mutual information (MI). MI provides the amount of information shared by two variables and is considered a nonlinear measure of covariation.

Linear cross-correlations.
Linear cross-correlation analysis was conducted by replacing time-shifted mutual information values with linear cross-correlations. All data analysis procedures were implemented in Matlab development environment (MathWorks) using custom-built and built-in functions. For further methodologies see reference.

3.4 Resting state connectivity analysis and CCEP

3.4.1 Imaging

Patients were scanned on a General Electric Signa HDx 3T scanner. Resting state fMRI data were acquired using an EPI gradient echo sequence (FOV = 220mm, voxel size 4x3.5x3.5, matrix 64x64, flip angle = 70, TR = 2000ms, TE =30, acquisition plane = axial, 150 contiguous volumes). Participants were instructed to rest with their eyes closed.

3.4.2 Resting State Functional Connectivity

Resting state data preprocessing was performed using AFNI and FSL, and included slice timing correction for interleaved slice acquisition, motion correction, de-spiking, spatial smoothing (6mm full-width at half-maximum Gaussian blur), band-pass filtering (0.009-0.1Hz), and linear and quadratic de-trending. For each patient, and each stimulation site, spherical seed regions of interest (ROI; 6mm radius) were constructed centered at each electrode. The mean time course for the seed was computed by averaging across all voxels within the seed.

3.4.3 Correspondence between CCEPs and RSFC.

To quantify the correspondence between CCEP and RSFC, for each stimulation site, we computed the correlation between CCEP z-scores at each electrode site and Fisher z-transformed correlation (RSFC) values at each corresponding seed. The resultant correlations were transformed to z-values using Fisher's r-to-z transformation, and averaged across all stimulation sites for a given individual.

3.4.4 Mapping of functional areas using CCEP

29 patients (13 Male, 16 Female) were included in the study from both centers.

Co-registering the preoperative MRI to standard MNI space allowed the identification of the nearest BA to each electrode using AFNI. This automated process was corroborated with manual inspection of two independent researchers and set against the results of ESM to avoid any mislabeling. BAs not covered with electrodes: 12, 23, 25, 26, 30, 33, 48, 49, 52.

We computed connectivity among functional regions of the cortex by grouping BAs of similar function. This way we are able to create maps of individual functions rather than strict BAs. The groups created are as follows: BA1-3: somato-sensory

(SS); BA 44,45: Broca's area (BR); BA 11,12,25,47: prefrontal cortex (PFC); BA 23,26,29,30,31: posterior cingular cortex (PCC); BA 24,32,33: Anterior cingular cortex (ACC); BA 13,14,43,52: insula (IN); BA 34,35,36: parahippocampal gyrus (PHG); BA 41,42: auditory cortex (AU).

4 RESULTS

4.1.1 Surface ECoG recordings

We were able to record cortically evoked potentials in every patient in our study. Evokability varied across patients and sites. Typically the evoked potentials consisted of brief biphasic activation between 10-30ms (also called N1-P1 peak) after stimulus, which was followed by a negative trough and peak, lasting from 70-300ms (also called N2-P2). To test the consistency of the latency of the N2 wave, we calculated the delay from the stimulus artifact until the peak of the N2 wave in every patient. We found that the majority of the N2 waves fall between 110 and 250ms on average 199ms±119ms.

To test the effects of the stimulation current on the CCEP, we applied increasing amplitudes of electrical current between the same electrode pairs. The recorded CCEP increased gradually starting with 3ma till 9ma. 3ma was on many electrodes not sufficient to evoke a significant evoked potential, but 6ma was typically enough. By increasing the stimulation amplitude until 9ma-s the evoked potential increased as well. Above 9ma-s we could not register significant increase in the amplitude of the N2 wave, up to 15ma, which is considered the upper limit of safe stimulation. The results are the same also in sleep, meaning that the vigilance state of the patient has no effect on the evoked potential characteristics

4.1.2 Comparison between anesthetized, awake and sleep stages

Cortical stimulation has been performed in different vigilance states (awake, sleep (non-REM, N3) and anesthetized). The cortical evoked potentials in awake and naturally sleeping patients did not show any significant difference. Cortical stimulation under general anesthesia prolonged the evoked potentials, but did not change its shape.

4.1.3 Potential map and time-frequency (TFR) analysis of the CCEPs on the surface recordings

We created surface potential maps of a grid electrode (Pt.5.) to describe the spatial effects of the cortical stimulation. The potential map of the N1 peak show a well circumscribed localized surface negativity in the surrounding electrodes to the stimulation. According to the maximum amplitude of the N2 wave almost the entire grid showed a surface negative potential, even in distant areas from the stimulation site.

We calculated the time frequency spectrum (TFR) on all channels to see the oscillatory power changes in the 0-200Hz range. We found that under the electrical stimulation induced surface negative potentials there is a wide band (0-200Hz) spectral power decrease on the grid electrodes compared to the baseline. This power decrease lasts under the first part of the negative slope of the surface negative potential (N2). During the rebound positivity (P2) we found significant spectral power increase, which was most pronounced during the first part of the positive slope.

4.1.4 Laminar properties of the evoked potential

After histological reconstruction of the penetration tracks we were able to co-localize the 24 electrode contacts of the shaft to the different laminas of the neocortex. According to this the

thumbtack electrode penetrated successfully through all the 6 layers of the cortex, enabling us to record from all of them.
On the local field potential recording (LFP) during the N2 phase we found negative potentials in the upper layers and positive potentials in the deeper layers, during P2 the opposite.
During the descending part of the surface potential N2, wide band (30-200Hz) power decrease was observed mostly in the middle layers, whereas during the ascending phase of N2 (early phase of P2) we found less pronounced but still significant power increase. These spectral changes were consistent across patients and sites.
In parallel with the TFR results during N2 a current source was measured and during P2 a significant current sink on the CSD. These changes spanned between layer II-IV in most of the cases, involving mostly the middle-upper layers.
Multi unit activity (MUA) revealed decreased cellular spiking activity during N2 and increased activity under the P2 phase of the surface CCEP.

4.1.5 Comparison of the evoked SO with the spontaneous SWA

According to our previous findings the cortical generators of the spontaneous SO if time locked to the up-state were localized to the supragranular layers (I-III). Similarly to the spontaneous SO the major changes in the CSD profile was localized also to the middle-upper layers representing the supragranular portion of the cortex after cortical stimulation (SPES) evoked SO. Comparing the changes in the TFR domain did not reveal any difference, both analysis show wide band (0-200) spectral decrease across the whole cortex during don-state and wide band increase during the early up-state phase. We also looked at the local field potential gradient changes where we found negative potentials in the upper layers during the down-state and positive

potentials during the up-state in both situations. The MUA pattern did also prove our hypothesis in trying to corroborate the findings of the evoked SO with the spontaneous ones. The TFR, CSD and MUA changes during the evoked down state fulfill the criteria set for the K-complexes or spontaneous SO, and the rebound surface positivity shares most of the laminar features with the spontaneous SO.

4.2 Non-linear mutual information based correlation show complex SWA propagation patterns

We investigated 1-min-long segments of SWS in six epileptic patients. ECoGs from 16–20 subdural recording sites were analyzed in each patient. We first searched for associations between ECoG waveforms recorded from different brain areas and compared the results of a linear (cross-correlation) and a nonlinear (MI) correlation analysis. Both linear and nonlinear types of dependencies were present in ECoG channels in all analyzed sleep segments. Significant linear correlation and MI values were summed over time for each pair of recording channels for each recording segment, resulting in linear and nonlinear correlation profiles. Although some similarities between the two types of profiles were discoverable significant nonlinear correlations were more abundant [5687 of 7266 channel pairs in all recordings (78.3%) compared with 1292 of 7266 (17.8%)], showing additional associations compared with the linear analysis.

Characteristics of SWA propagation

The significant correlation of time-shifted waveforms recorded from pairs of electrodes was established by the MI technique. The resulting associations at each time point served as unitary events for the subsequent calculations. Significant waveform correlations usually corresponded to the rising phase of cortical

SWA, which further supports the view that waveform correlations detected by the MI method reflect slow-wave propagation between different cortical areas. Next, we calculated general characteristics of SWA propagation. The distribution of propagation distance showed that SWA correlations were most common among neighboring cortical areas, although associations between distant sites were also observed. These unexpected spatial noncontinuities, or jumps, of SWA do not fit the general idea of traveling waves, i.e., propagation of slow waves as single lines over large cortical areas. Fast propagation to short distances was accompanied by higher correlation strength. Expectedly, propagation time was usually positively correlated with propagation distance [positive correlation ($p < 0.01$) in 23 of 26 sleep segments with a mean correlation coefficient of 0.28 ± 0.02; negative correlation in one and no significant correlation in two cases].

4.3 Brain surface reconstruction and co-registration to standard space

In order to avoid the artifacts and distortions caused by the electrode implantation procedure on the postimplantation images with the electrodes, we needed to create a protocol for using preoperative images to display the electrodes and localize them to distinct anatomical regions. As described in the methods section we used a freely available software package (Freesurfer) which allows us to create segmented brain volumes and surfaces, which we can use for any type of imaging as a basis. To be able to create high resolution images we successfully developed a standard imaging protocol at both Centers.

4.3.1 Electrode localization using postimplantation CT

At our co-operational research program between NSLIJ and NIN we developed our own method to visualize the electrodes on the basis of Dykstra et al's publication. After postimplant day 2-3 we perform a spiral CT (1mm) and T1 weighted 3D MR (1mm) without contrast. We first co-register the postimplantation CT to the postimplantation MR. This intermodal linear co-registration is done very precisely due to the same anatomical distortions recorded both after surgery. Having the two skulls stripped MR-s the distortions are less pronounced and the linear transformation can be precisely performed. This protocol has been tested in over 30 patients with regular testing using intraoperative photographs. Once the CT has been transformed to the space where the surface reconstructed preoperative MR is, we can use BIS to localize every electrode.

4.4 Resting state fMRI correlates with CCEP

In 6 patients with intractable epilepsy, we investigated the relationship between RSFC and CCEPs. For each stimulation site, we first computed the correlation between CCEP amplitudes and RSFC values at each electrode without applying any thresholding. The average correlation across all stimulation sites was significant in all subjects, indicating that correlations between RSFC correlation values and CCEP amplitudes are present independent of the stimulated brain area. Next, we computed a binary response matrix for each stimulation site by identifying the electrodes that exhibited a significant CCEP. In all but one patient, electrodes exhibiting a significant CCEP demonstrated higher RSFC relative to those which did not exhibit a significant CCEP ($P < 0.05$). As is to be expected, the

strongest CCEPs and RSFC were observed in electrodes proximal to the stimulation (and 'seed') site.

4.5 Anatomico-functional parcellation using graph theoretical measures

Significant and non-significant evoked potentials, according to the threshold criteria we have set were reliably analyzed and assigned to their respective BA. We calculated the Z-score of the N2 peak to statistically quantify the amplitude of the CCEPs compared to the baseline. The average Z-score was 14,9±66,6 between the stimulation electrode pair and every recording electrode which shows significant CCEP.

Connectivity was calculated between electrodes and averaged according to Brodmann's areas. We found on average 1532 significant connections, with an SD of 1422 per patient. The highest numbers of significant connections are between 2-6cm from the stimulation electrode pair, which describes well the local connections of a brain region. However we found decent amount of significant connection 6, 8cm or even further away from the stimulation electrode pair, which draw our attention to the inter-regional, long distance connections revealed with CCEP mapping.

To identify connectivity, we calculated the percentage of significant connections compared to all possible connections among those electrodes which did not show ictal onset. The results were clustered in respect to their distance (2cm bins) from the stimulation electrode pair. The calculated connectivity show a linear decrease when increasing the distance from the stimulation electrodes, which is also statistically significant (ANOVA: $p= 3 \times 10^{-8}$ (Huynh-Feldt correction for potential violations of sphericity)).

To be able to assess differences in connectivity between patients we standardized the electrode locations using BA as the reference. We calculated the incoming connections and the outgoing connections of every BA of every patient included in the study. To define the degree of connections for every BA as a hub, we calculated the sum of the incoming and outgoing connections.

The average number of outgoing connections exceeds the number of incoming connections which results in a high out/in degree value. According to this the average number of incoming connections is stable even with high number of outgoing connections

To be able to assign a measure between specific brain regions, according to BAs, we created a matrix of the Brodmann's areas and the measure of connection was either the average Z-score between two BAs or the average number of connections (in+out). The Z-score matrix will tell us, if two areas are significantly connected with limited information about the quality and density of the connection. Whereas the other matrix where the number of significant connections represents the measure of connections tells us how densely two BAs are connected to each other.

We created directed graphs of every patient's stimulation map to visualize the networks revealed with CCEP mapping. After creating all of the individual graphs we also calculated the grand mean average of the patients to show how densely every region is connected to another and especially to reveal the major hubs of the neocortical networks. The most consistent connections were seen as outgoing from motor cortex, BA6–BA9, somatosensory (SS) cortex, anterior cingulate cortex, and Broca's area. Network topology revealed motor, SS, and

premotor cortices along with BA9 and BA10 and language areas to serve as hubs for cortical connections.

5 CONCLUSIONS

Single pulse electrical stimulation (SPES) of the human brain is a novel method to map functional and pathological networks. The detailed analysis of the distribution of the evoked potentials on the surface of the brain as well as the laminar properties of the stimulation evoked responses reveal the same cortical generators and intrinsic architecture as it was shown earlier of the spontaneous slow oscillation (SO).

1. We could establish a stimulation protocol, which can be reliably used for evoking cortico-cortical evoked potentials (CCEP) on the cortex.
2. We performed SPES during sleep, awake and anesthetized states and the recorded CCEPs share the same features between the three different vigilance states.
3. We report firstly on the laminar generators of the CCEPs.
4. The formerly known CCEP is the same as an evoked cortical down-state followed by an up-state.
5. The evoked SO is also evocable during awake state and under anesthesia.
6. Detailed mutual information based analysis revealed complex propagation patterns of human SO. Non continuities in the SO propagation to distant areas and also electrodes showing high convergence as well as high divergence may be the cortical hubs involved in SO generation and subject to cortico-thalamical inputs.
7. We correlated the results of spontaneous BOLD fluctuations recorded at rest with an fMRI with the results of CCEP mapping. The two substantially different methodologies

interestingly correlate significantly meaning that if two areas showed a functional connection with CCEP the exact same two anatomical regions were correlated with resting state functional connectivity (RSFC).

8. We developed a method to co register every electrode to its BA and established a standard imaging protocol to visualize electrodes on reconstructed brain surface for precise localization.
9. Using BAs as the reference we created directed graphs of every patient to visualize the interregional connections revealed with CCEP, and also of the group.
10. We have created the first connectivity based matrices which allows to describe the connectivity between any two (except those which were not covered with electrodes) BA. The most consistent connections were seen as outgoing from motor cortex, BA6–BA9, somatosensory (SS) cortex, anterior cingulate cortex, and Broca's area. Network topology revealed motor, SS, and premotor cortices along with BA9 and BA10 and language areas to serve as hubs for cortical connections.

6 List of Author's publications

6.1 Publications related to the present thesis:

1 Entz L; Toth E; Keller CJ; Bickel S; Groppe DM; Fabo D; Kozak LR; Eross L; Ulbert I; Mehta AD. Evoked effective connectivity of the human neocortex. *HUMAN BRAIN MAPPING* 2014 Dec;35(12):5736-53, **IF: 6.878***

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2 Erőss L, Fekete G, Entz L, Fabó D, Borbély C, Kozák LR, Andrejkovics M, Czirják S, Fedorcsák I, Novák L, Bognár L. Az intraoperatív elektromos agyi stimuláció szerepe a nyelvi és beszédfunkciók megőrzése céljából éber betegeken végzett idegsebészeti beavatkozások során. *IDEGGYÓGYÁSZATI SZEMLE* 65:(9-10) pp. 333-341. (2012), **IF: 0.348**

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