Cortico-Cortical Evoked Potentials Reveal Abnormal Effective Connectivity Patterns of Temporal Lobe Structures

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Introduction

Epilepsy is neurological disease characterized by recurring spontaneous seizures caused by hypersynchronous neuronal firing. It was previously shown that the epileptogenic zone exhibits abnormal anatomical and functional brain connectivity of clinical and prognostic value (Kramer and Cash, 2012).

Our aim is to evidence the changes in effective connectivity induced by epilepsy in temporal lobe structures, using cortico-cortical evoked potentials (CCEPs).

Methods

- **45 patients** undergoing SEEG presurgical evaluation with temporal lobe epilepsy (TLE) and non-temporal lobe epilepsy (NTLE).
- **5335 pairs of stimulation-response, sampling 80 brain structures** from both hemispheres (Fig. 1).

Surgical Outcome in 36 out of 45 patients who had surgery	Engel (32±10 months f/u)			
	I	II	III	IV
Percent of patients	61%	11%	14%	14%

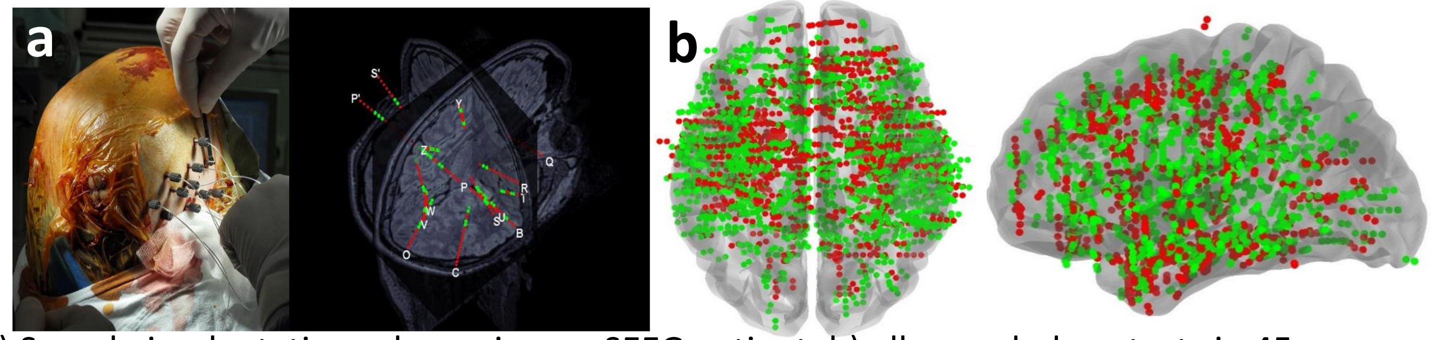


Fig 1. a) Sample implantation scheme in one SEEG patient; b) all recorded contacts in 45 SEEG patients (red contacts are inside EZ, green contacts outside EZ).

- **epileptogenic structures** defined by experienced epileptologists using interictal and ictal SEEG data.
- **single pulse electrical stimulation** (20 biphasic pulses, 0.25-5mA, 3ms pulse width) (Valentin et al. 2002, Donos et al. 2016a, Donos et al. 2016b) (Fig 2)
- **cortico-cortical evoked potentials (CCEPs)** – quantified as RMS over 10-110ms post-stimulation.
- **criteria for contact activation**: (Donos et al. 2016b)
  - a) significant Spearman correlation between the CCEP amplitudes and the stimulation currents
  - b) CCEP amplitudes higher than the 3rd quartile (Q3) of all amplitudes observed within a patient

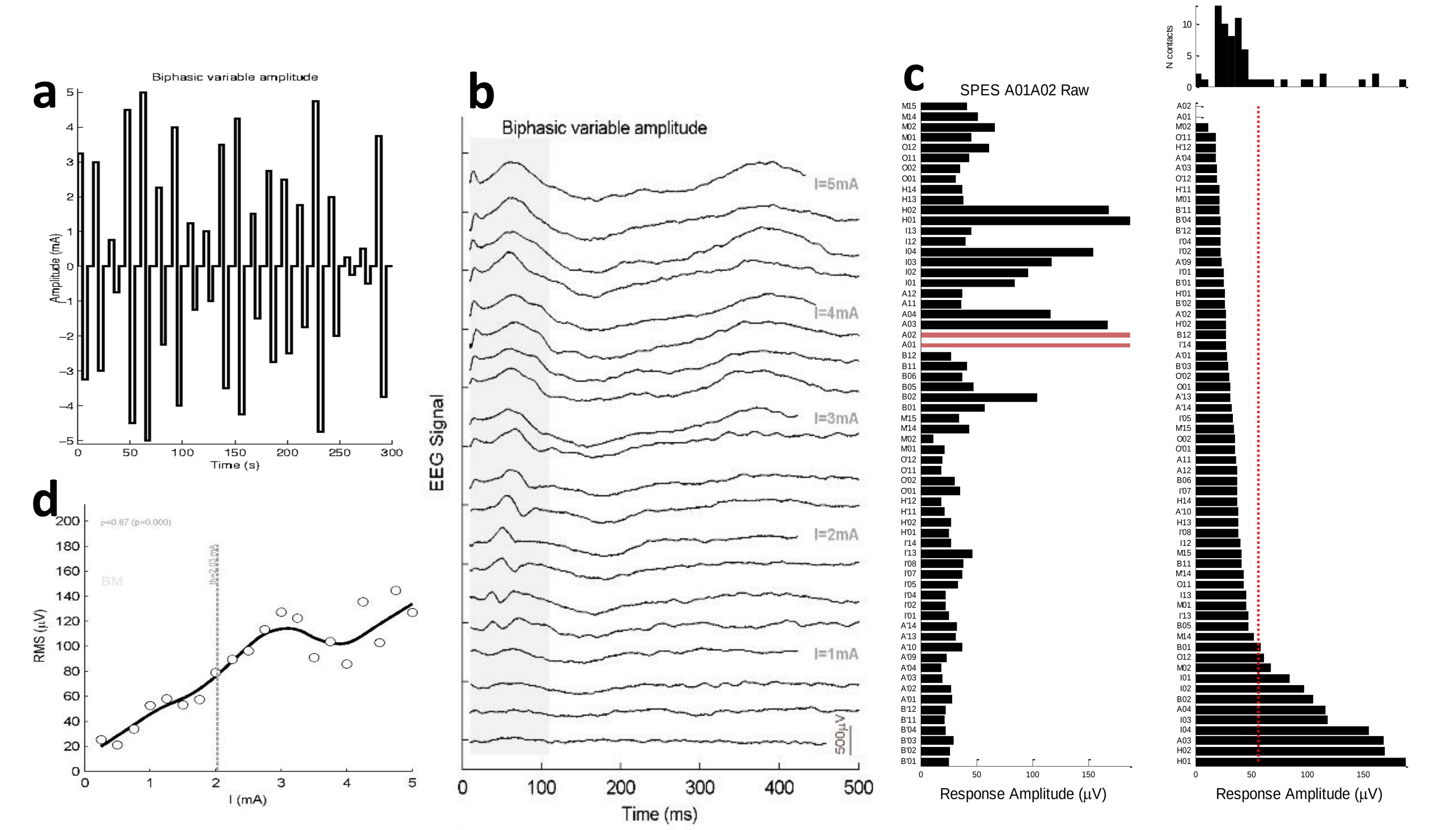


Fig. 2. a) pseudo-random sequence of 20 biphasic stimulation pulses of variable amplitudes; b) sample CCEP recorded on a SEEG contact (sorted by stimulation pulse amplitude); c) distribution of mean CCEP amplitudes obtained while stimulating one contact pair (highlighted in red); d) correlation of CCEP amplitudes with stimulation currents in an individual contact

- **CCEP analysis:** contacts are sorted by epileptogenicity, then grouped at structure level for each patient (Fig 3a). The effective connection strength at the patient level is obtained by averaging CCEPs and normalizing the to the patient's Q3 value (Donos et al. 2016b).
- **the effective connectivity analysis** is performed at the group level, by averaging connections from individual patients.

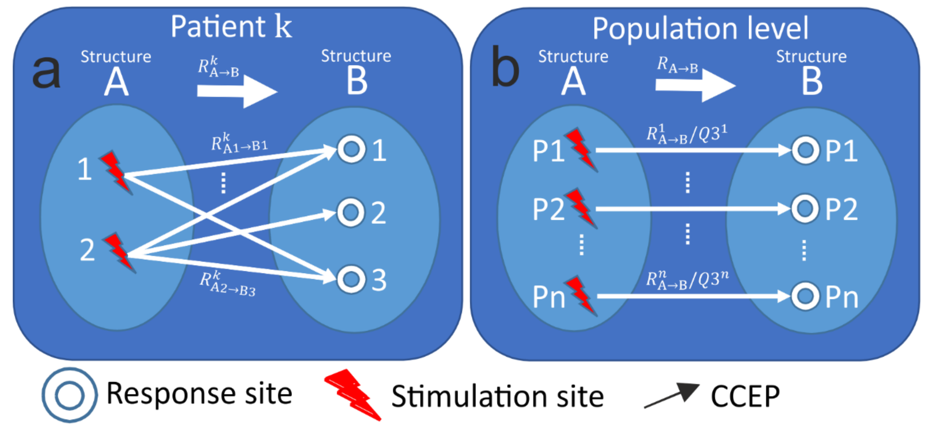


Fig 3. Structure level CCEP analysis in individual patients (a) and at group level (b)

- an Epileptogenicity Modulation Index (EMI) (Donos et al. 2017) quantifies the relationship between the effective connectivity of temporal structures when part of the epileptogenic network (EZ) or not (NEZ).

$$EMI = \frac{R^{EZ}_{A\to B} - R^{NEZ}_{A\to B}}{R^{EZ}_{A\to B} + R^{NEZ}_{A\to B}}$$

where $R^{EZ}_{A\to B}$ is the connectivity between structures A and B, calculated according to the method described in Donos et al. 2016a, in the subset of patients where structure A is part of EZ, and $R^{NEZ}_{A\to B}$ is the connectivity between the same structures when A is part of NEZ.

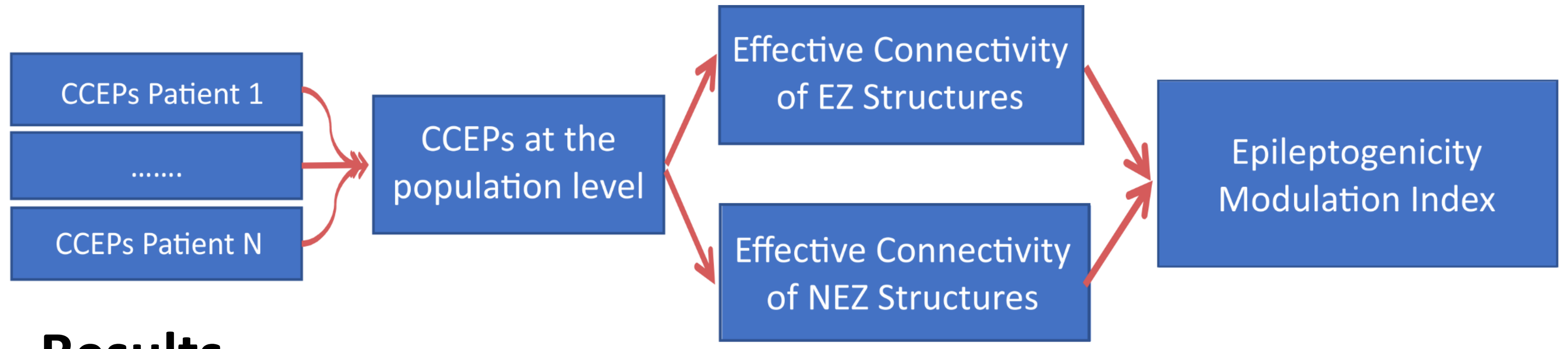
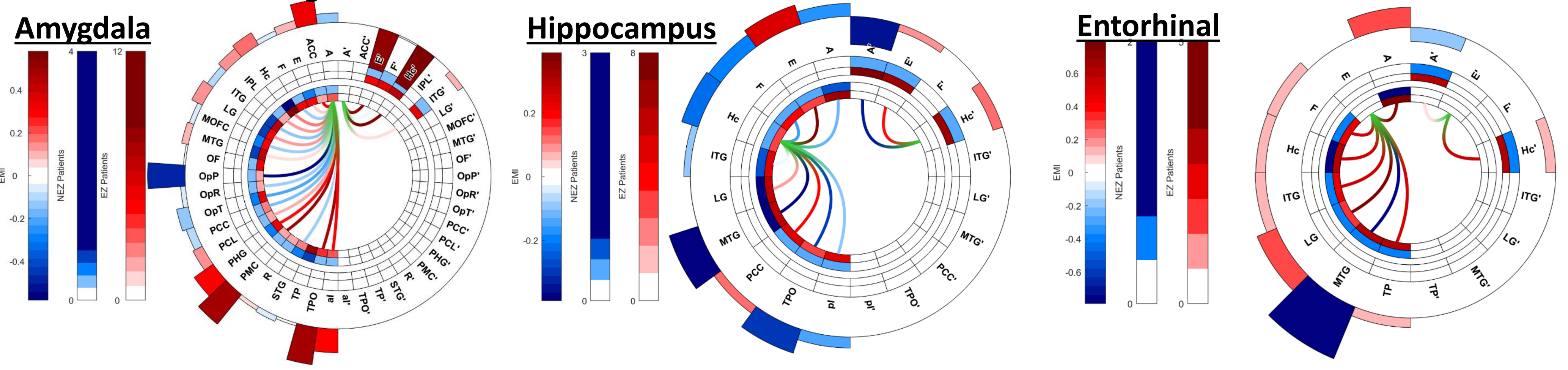


Fig 4. Analysis workflow

Results

Shown below (Fig. 5) are the results of the differential analysis of the effective connectivity of epileptogenic vs non-epileptogenic **temporal lobe structures**, quantified by the EMI values, represented using circular graphs.

The two circles of the circular graphs contain information about the number of patients in which the connection was probed in EZ (red color scale) and NEZ (blue color scale) conditions. The inner circle shows the number of patients for the right hemisphere structures, while the outer circle shows the same for left hemisphere structures. The circle drawn outside the structure labels represents the EMI. To provide a better visualization of the EMI, we color-coded the EMI values in blue-white-red color scale, and its absolute amplitude in the size of the segments. The EMI values on the inside and the outside of the circle are represented for the right and left hemispheres, respectively. The direction of effective connections are shown as arcs having the same colors as the EMI. The direction of the effective connections is from the stimulated structure (green origin of the arcs) to the other structures in which significant CCEP activations were observed.



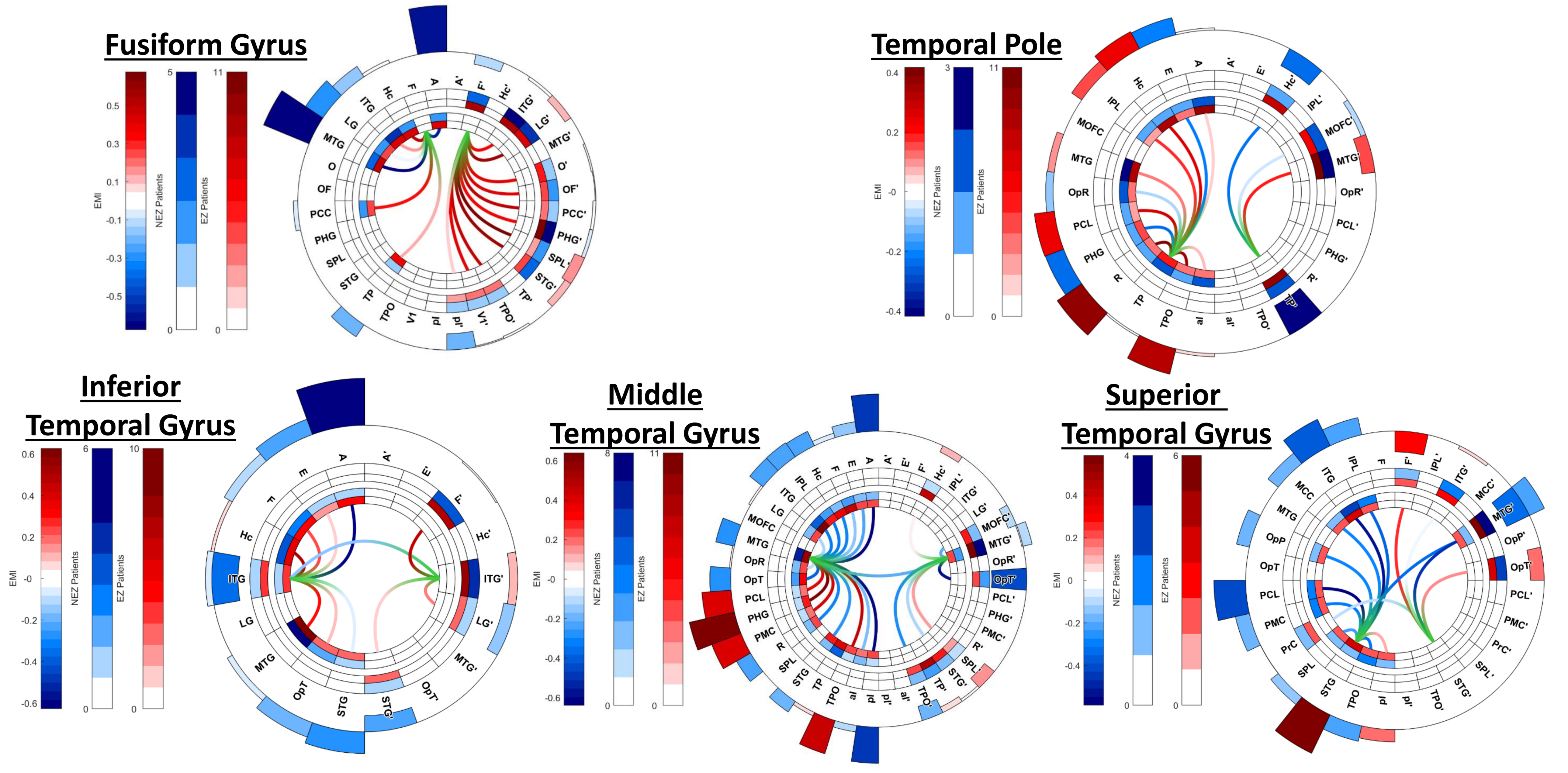


Fig 5. Differential connectivity circular graphs showing EMI values. The labels used in the figures are: MCC - Middle Cingulate Gyrus, MOFC - Mesial Orbito-Frontal Cortex, OF - Orbito-Frontal, PMC - Premotor Cortex, R - Precentral Gyrus, A – Amygdala, E – Entorhinal, F - Fusiform Gyrus, Hc – Hippocampus, ITG - Inferior Temporal Gyrus, MTG - Middle Temporal Gyrus, PHG - Parahippocampal Gyrus, STG - Superior Temporal Gyrus, TP - Temporal Pole, aI - Anterior Insula, OpP - Operculum Parietalis, OpR - Operculum Rolandis, OpT - Operculum Temporalis, pI - Posterior Insula, IPL - Inferior Parietal Lobule, PCC - Posterior Cingulate Cortex, PCL - Paracentral Lobule, PrC – Precuneus, SPL - Superior Parietal Lobule, LG - Lingual Gyrus, O - Lateral Occipital, TPO - Temporo-Parieto-Occipital Junction, V1 - Primary Visual Cortex. Apostrophe (') denotes left hemisphere.

Discussion

Altered connectivity is widespread, affecting connections of pathological structures with other structures outside the EZ. Such changes in connectivity with remote structures that don't need to be included in the resection volume have been observed across multiple modalities (Englot et al. 2016).

Effective connectivity of homologue structures is impacted differently, for example a) pathological left amygdala has stronger connections to ipsilateral hippocampus and entorhinal cortex than pathological right amygdala; b) pathological left hippocampus has weaker connections with ipsilateral amygdala than the pathological right hippocampus. This is in agreement with previous studies showing that left TLE has higher impact on brain connectivity than right TLE, and is correlated with worse cognitive outcomes (Besson et al. 2014).

Conclusions

Our results show that altered effective connectivity patterns can be quantified using CCEPs. This data could be taken into consideration when discussing the tailored resection for surgical treatment, and is of potential prognostic value for surgical outcome.

However, given the inherent problem of sparse brain sampling with intracranial electrodes, such atlas may require a multi-center effort to increase spatial sampling and provide additional statistical power.

Acknowledgments

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