Probing cortical excitability under pharmacotherapy

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INTRODUCTION

In focal epilepsy, seizures result from subnetworks of abnormally high cortical excitability (CE) within a relatively normal brain. Practical means of monitoring CE in the human brain, for example to assess the effects of anti-seizure medications are currently lacking. We asked whether directly probing the brain with minute electrical pulses and recording cortico-cortical evoked potentials (CCEPs) may help quantify CE before and after administration of a benzodiazepine (BZD). We used an unsupervised machine-learning method, non-negative matrix factorization (NMF) to delineate subnetwork with similar cortical dynamics.

METHODS

In seven epilepsy patients (Table) undergoing cortical recordings for diagnostic reasons (median number of electrode contacts: 68 [48, 111]), we probed CE with repeated single pulses (median N= 168 [151, 204]) systematically varying in intensity (0.2 – 12mA) at two cortical sites. All brain responses, before and after administration of clonazepam (0.75-1mg) were clustered into subnetworks using NMF (Non-negativity matrix factorization) based on the line-length (LL, only positive values, Fig. 1) of CCEPs. CE in each subnetwork was quantified by the magnitude of the NMF activation coefficients.
Additionally, in 6 patients we probed network connectivity (C) by stimulating all available channels in grey matter using 3 mA single pulses (median N = 336 [216, 414]). All possible connections to a given stimulation site were given a probability value [0,1] defined by the number of trials wirh a significant response among three. Significance was determined by surrogate testing (99th).

ID	Age	Sex	Diagnosis	Etiology	# Electrodes	# Stimulations (BL/BZD)
EL003	33	F	Right temporal	Unknown	8	CE: 93/92
EL004	38	M	Right subcentral gyrus	Unknown	11	CE: 102/102, C: 195/195
EL005	26	F	Left superior temporal gyrus	Post-traumatic lesion	9	CE: 67/84, C: 228/168
EL008	20	F	Right temporal	Encephalitis	4	CE: 84/84, C: 123/123
EL010	45	F	Left mesiotemporal	Lesion	6	CE: 84/84, C: 108 / 108
EL012	56	F	Left temporal	Unknown	3	CE: 84/84, C: 207 /207
EL014	42	M	Temporal	Hippocampal sclerosis	5	CE: 84/84, C: 141/141

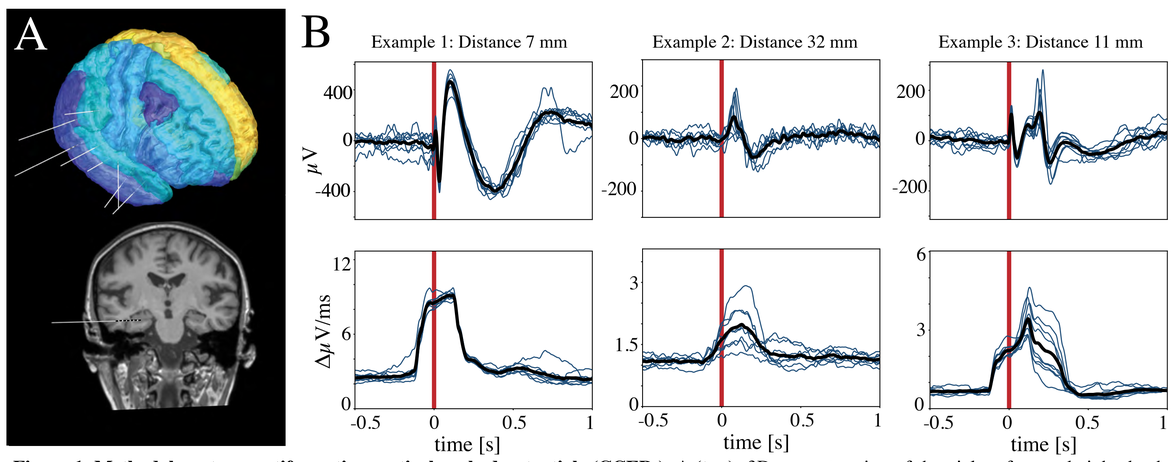


Figure 1. Methodology to quantify cortico-cortical evoked potentials (CCEPs). A (top): 3D-reconstruction of the pial surface and eight depth electrode implanted in the right hemisphere of one patient. **Bottom**: Coronal MRI slice showing the location of the stimulation channels in the right hippocampus. **B:** Examples of three CCEPs in different channels, corresponding to different connection distances (7mm, 32mm, 11mm). Single trials (blue) and the average (black) for the raw EEG traces (top) and the corresponding LL (buttom). Note how LL can measure any waveform with purely positive (non-negative) results.

RESULTS

1. Subnetwork excitablity

Across seven patients, NMF delineated a total of 17 subnetworks that encompassed a collection of brain areas with shorter- and longer-range connections responding conjointly to the administered probing stimulations (Fig 3). Up to a plateau, these subnetworks showed increasing responses with increasing input-stimulation. However, this relation was systemtically attenuated after administratin of a benzodiazepine.

2. Probability Connectivity

After the administration of a benzodiazepine, we observed a reduction of 25% of overlap in the connectivity map with that obtained at baseline. A large majority of connections close to the stimulation site were unaffected, presumably because they are mono-synaptic, via U-fibers. While few new connections were more probable, most connections affected by benzodiazepine showed a decreased probability. This was particularly true for longer-range connections, that are presumably poly-synaptic, of which 41% had decreased probability.

Cortical Excitability (CE)

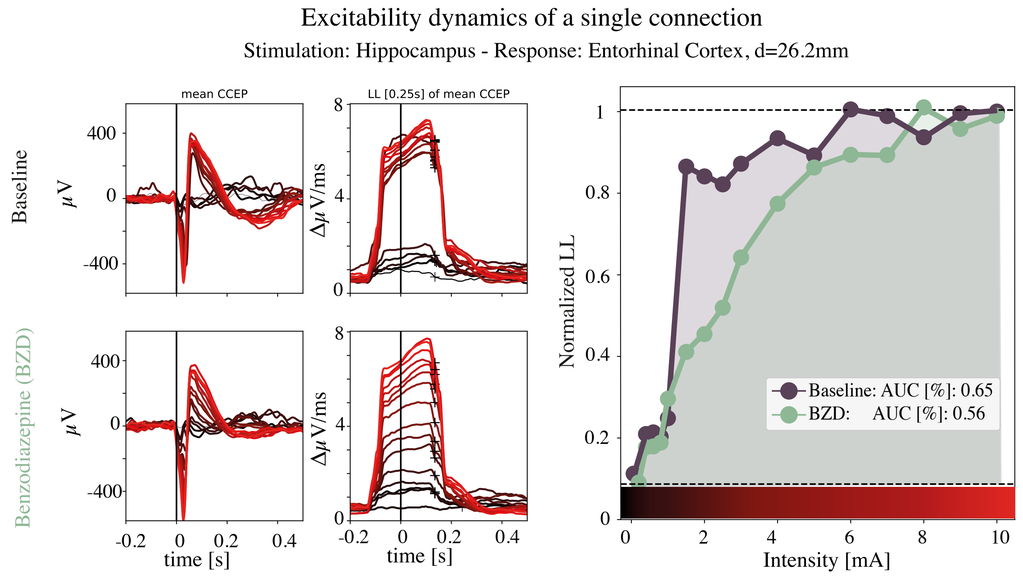
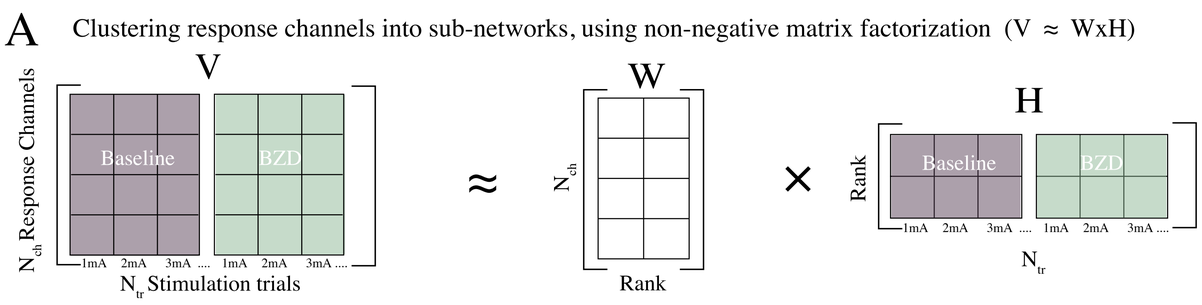


Figure 2. Single connection dynamics. Illustrative example of a single connection showing the mean CCEPs (left column) for each intensity (color-coded) and the corresponding LL (mid column) for both baseline (top) and BZD (bottom) condition. On the right, the LL values, normalized to the maximum LL, are plotted for each condition (color-coded) across intensities. We systematically found non-linear relationships between stimulation current and CCEP amplitude (Fig 2A), typically with a floor effect anda plateau. Note how LL decreases only at certain intensities after the administration of BZD, resulting in decreased AUC.



Input Matrix V: LL of each response channel (N_{ch} rows) for all trials (N_{tr}, columns) including 3 repetitions across pharmacological conditions (2), intensities (16) and stimulation sites (2) n= 192.

Basis Function Matrix W: Weighted association coefficients to the clusters (columns) for each channel (row)

Activation Functions Matrix H: actication coefficient for each cluster (rows) across all trials (columns)

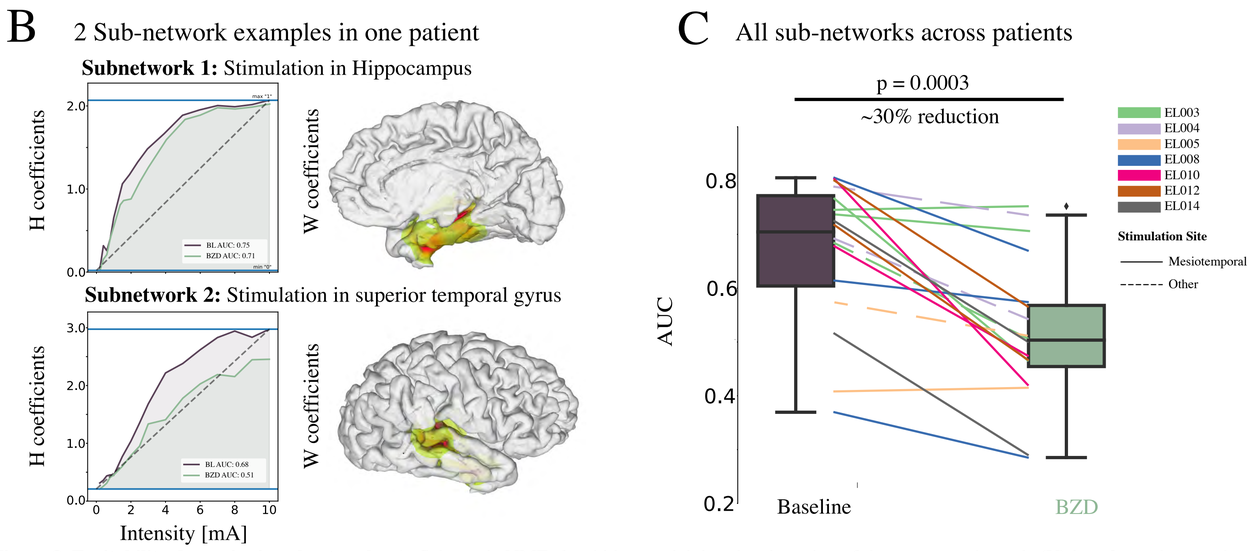


Figure 3. Excitability dynamics in subnetworks. A: Schematic NMF algorhithm explaining the clustering of the response channels (V) into few subnetworks (W). B: Two subnetwork examples where the H coefficients are plotted against stimulation intensities (condition color-coded). Note the similar that unlike in Fig.2, the input-output relation summarizes the excitability in an ensemble of channels shown as a color-scaled projection to the cortical surface (Wi, right).
C: AUC values of 17 subnetworks across seven patients for both conditions (left: baseline, right BZD). Note the decreased AUC in almost all subnetworks (Wilcoxon signed-rank test).

Connectivity (C)

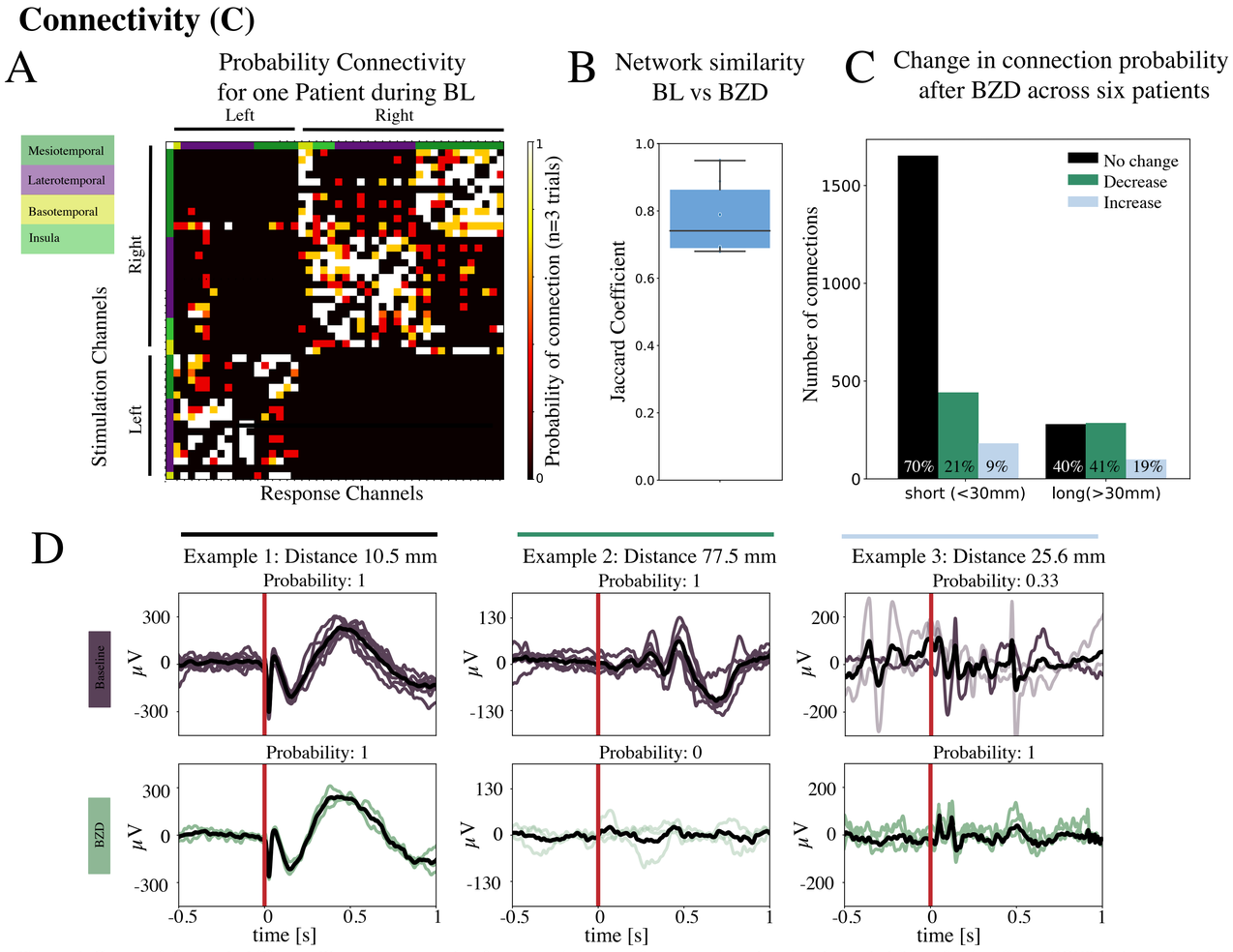


Figure 4. Connectivity probability. A: Illustrative example of a connectivity map for one patient showing the probability of a significant CCEP (color-coded) for all possible connections between response sites (columns) and all stimulation sites (rows). Channels are ordered based on hemisphere and brain area. B: Jaccard index as similarity measure of the connectivity map during BL and BZD condition across patients. C: All connection that have shown at least one significant trial are split into short and long range connections (threshold 30mm) and whether BZD changed the probability value (color-coded). D: Three example connection of 1) no change, 2) decrease and 3) increase of probability after BZD. are shown as single trials (colored) with the Baseline on top and BZD condition on bottom. Black traces indicate the mean across trials for specific condition.

CONCLUSIONS

Combining probing neurostimulations with unsupervised pattern recognition algorithms, we introduce a novel method to quantify CE in the human brain. As a proof-of-principle, we apply this method to uncover the effects of a well-known GABA agonist on cortical dynamics. Applying such methods over longer durations, may help monitor non-linear dynamics in the human cortex, including in epilepsy.