Corticocortical Evoked Potentials Reveal Projectors and Integrators in Human Brain Networks

Keller et al. (2014) *The Journal of Neuroscience* 34(27):9152-9163

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Introduction

- Resting fMRI and diffusion tensor imaging cannot resolve the direction of corticocortical interactions.
- Granger causality and dynamic causal modelling can demonstrate causal interactions by statistical inference.
- Direct cortical stimulation provides an interventional method to test effective connections.

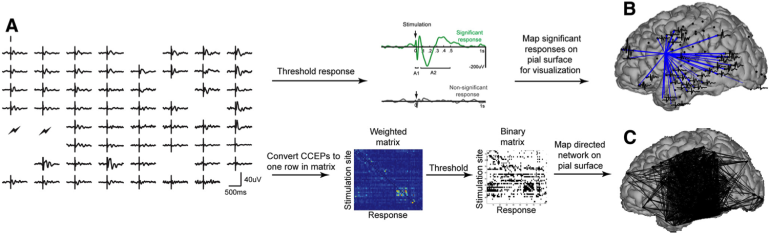
Introduction

- **Corticocortical evoked potentials (CCEPs)**: electrical stimulation can trigger a response at a remote location, proportional to the strength of the effective connection.
- **Advantages**: direction of flow, direct recording of neural activity, high spatiotemporal resolution.
- **Limitations**: cannot provide whole-brain coverage, the neural mechanism underlying CCEPs is not understood.

Methods

- 15 subjects with medically intractable epilepsy.
- Single-pulse stimulation elicited evoked potentials (CCEPs).
- Converted to Z-scores based on the response amplitude of the A1 segment of the CCEP.
- Each row of the matrix corresponds to a stimulation site; each column to the site where the response was measured.

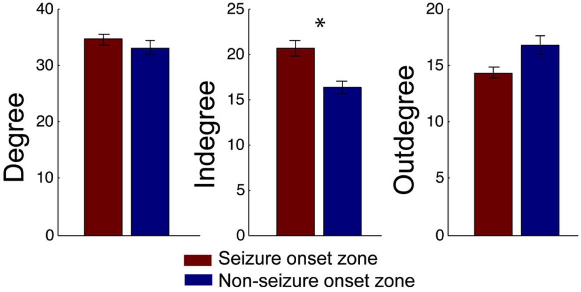
Methods


A
40uV
500ms
Threshold response
Stimulation
Significant response
A1
A2
-200uV
1s
Non-significant response
Map significant responses on pial surface for visualization
B
Convert CCEPs to one row in matrix
Weighted matrix
Stimulation site
Response
Threshold
Binary matrix
Stimulation site
Response
Map directed network on pial surface
C

Graph theory measures

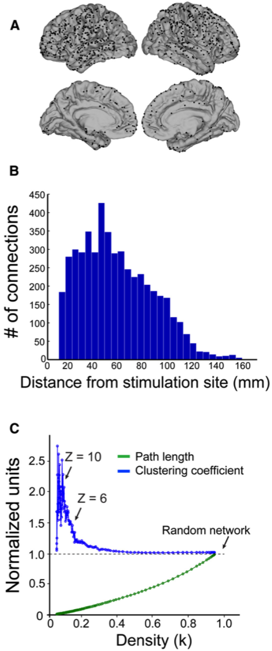
- **Outdegree**: number of significant CCEPs when the ROI is stimulated (outgoing connections)
- **Indegree**: number of times stimulation (of any region) evokes a significant CCEP at the ROI (incoming connections)
- **Degree centrality**: indegree + outdegree
- **Flow**: outdegree − indegree

Relationship of seizure onset zone to CCEP network measures

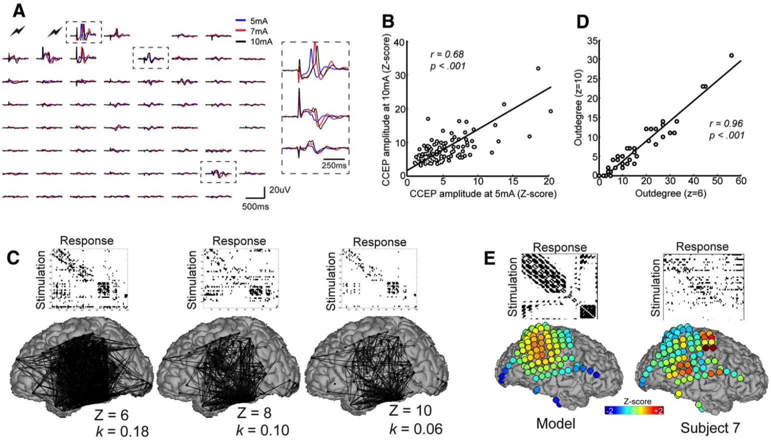


Changes in excitability do not underlie differences in network measures. CCEPs do not reflect intrinsic excitability.

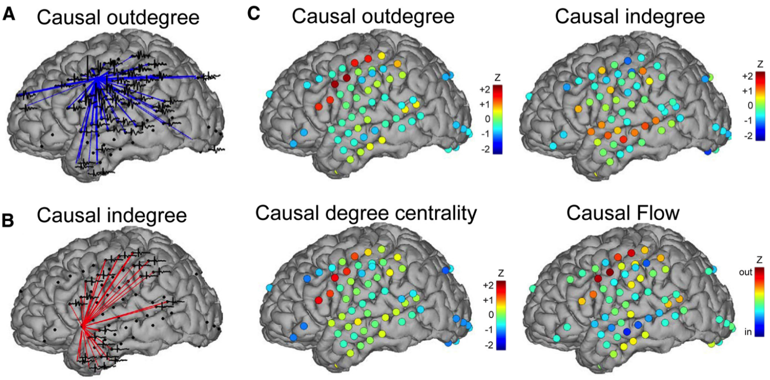
CCEP networks exhibit small-world characteristics



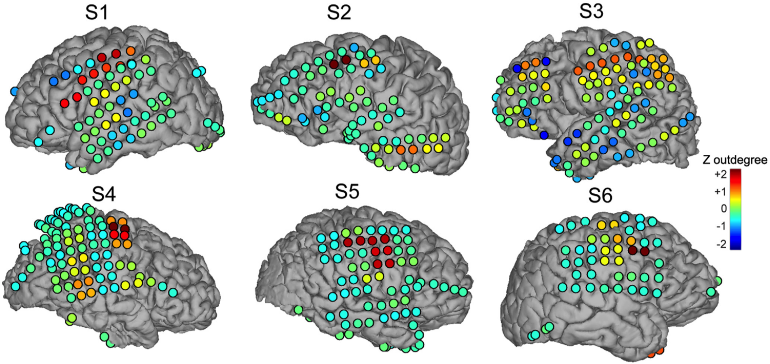
Effect of stimulation intensity and threshold on CCEP networks



Graph theory measures in one subject

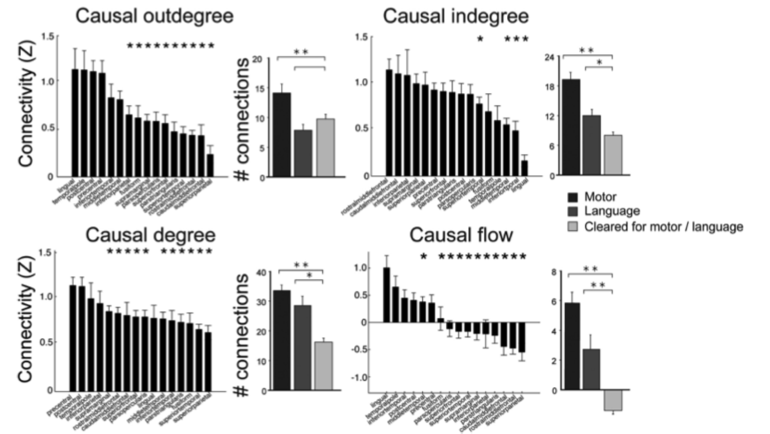


Causal outdegree measures across subjects



Outdegree is strong around the central sulcus.

Functional and anatomical network analysis across subjects

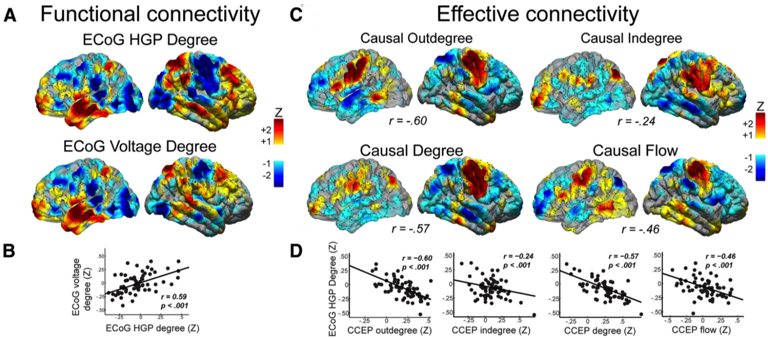


Subject average: the location of each electrode was determined using a cortical parcellation procedure; mean network measures across cortical regions were then calculated.

Electrocorticogram (ECoG)

- High γ power is the best known electrophysiological correlate of the BOLD response (Keller et al., 2013, *The Journal of Neuroscience* 33(15):6333-6342)
- Functional connectivity between electrodes i and j was measured as the correlation coefficient of the ECoG power time courses (at rest).
- The connectivity matrix was binarised to leave only the strongest 5 % of correlations.
- Group-based surface maps.

Distinct global connectivity profiles for effective and functional connections

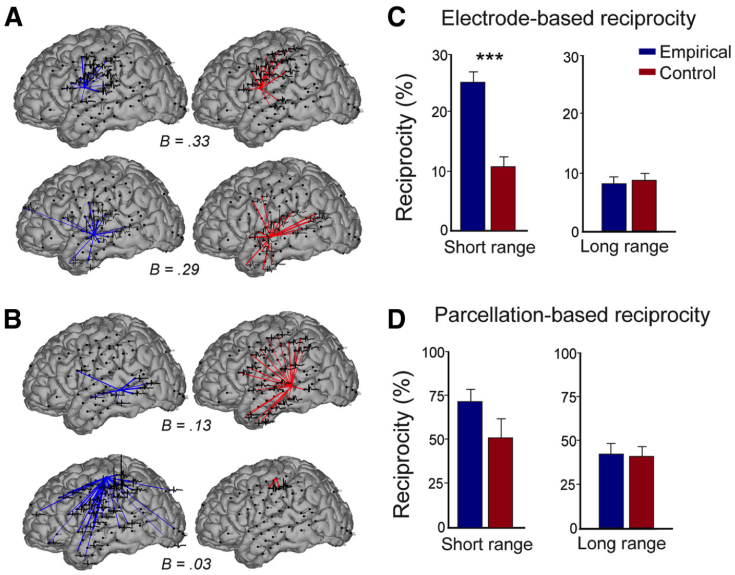


Global connectivity profiles of ECoG and CCEP maps were negatively correlated.

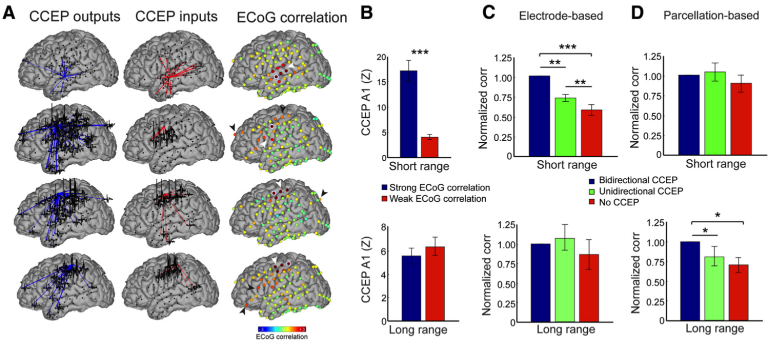
Reciprocity Index

- Categorised stimulation-response electrode pairs according to their Euclidean distance (*short-range* or *long-range*).
- B = reciprocity index $= q/p$, where p = total number of pairs with at least one connection and q = number of pairs consisting of reciprocated connections.
- The number of significant connections for the simulation was made equal to that of the experimental data, and the reciprocity index calculated.

Corticocortical interareal reciprocity is higher than expected



Reciprocal effective connections underlie strong interareal functional connectivity



Resting ECoG correlations are strongest in regions of CCEP bidirectionality.

Discussion

- Sensorimotor regions exhibited abundant connections to other cortical regions.
- The topology of functional connectivity derived from resting ECoG networks supports previous literature.
- Within-subject differences between functional and effective connectivity were unexpected.