SUPPORTING INFORMATION
for
Structural and functional asymmetry of medial temporal subregions in unilateral temporal lobe epilepsy: a 7T MRI study

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1. Mathematical definitions and intuitive descriptions of network metrics

As described in the main text, we characterized the MTL networks as graphs, comprised of nodes and edges. Such graphs can display heterogeneous structure that is important for the system's function (Bassett, Zurn, & Gold, 2018). While a number of graph statistics have been defined to understand this heterogeneous structure, many of them are correlated with one another, especially in brain networks (Li, Wang, De Haan, Stam, & Mieghem, 2011; Lynall et al., 2010). It is useful to choose a set of graph statistics that describe important dimensions of variation in brain networks but that are not necessarily redundant. Historically, measures that have proven particularly useful in characterizing brain graphs include the connectivity strength, clustering coefficient, and network efficiency (Bullmore & Sporns, 2009), largely due to their sensitivity to the markers of small-world architecture (Bassett & Bullmore, 2016). We therefore computed local connectivity strength, clustering coefficient, and network efficiency for the functional networks. Because the most widely-applied definitions for these metrics require non-negative edge weights (Rubinov & Sporns, 2010), and because the meaning of negative correlations is not well understood (Chai, Castañón, Öngür, & Whitfield-Gabrieli, 2012; Fox, Zhang, Snyder, & Raichle, 2009; Murphy & Fox, 2016), we set negative edge weights to zero. We define the network metrics used in this study below.

1) Connectivity Strength: The local connectivity strength *k(i)* at node *i* for a weighted network with a set of nodes, *N*, is the sum of the weights of all connections to node *i* as follows:

$$k_i = \frac{1}{N}\sum_{j \in N} w_{ij} \, , \qquad \text{(Eq. S1)}$$

where w_{ij} is the edge weight between node *i* and node *j*.

2) Clustering Coefficient: The local clustering coefficient *c(i)* at node *i* can be conceptualized as the likelihood that the neighbors of *i* are interconnected. One way in which to quantify this concept for weighted networks is:

$$c_i = \frac{2}{k_i(k-1)}\sum_{j,h \in N}\left(\widetilde{w}_{ij}\widetilde{w}_{ih}\widetilde{w}_{jh}\right)^{1/3}, \qquad \text{(Eq. S2)}$$

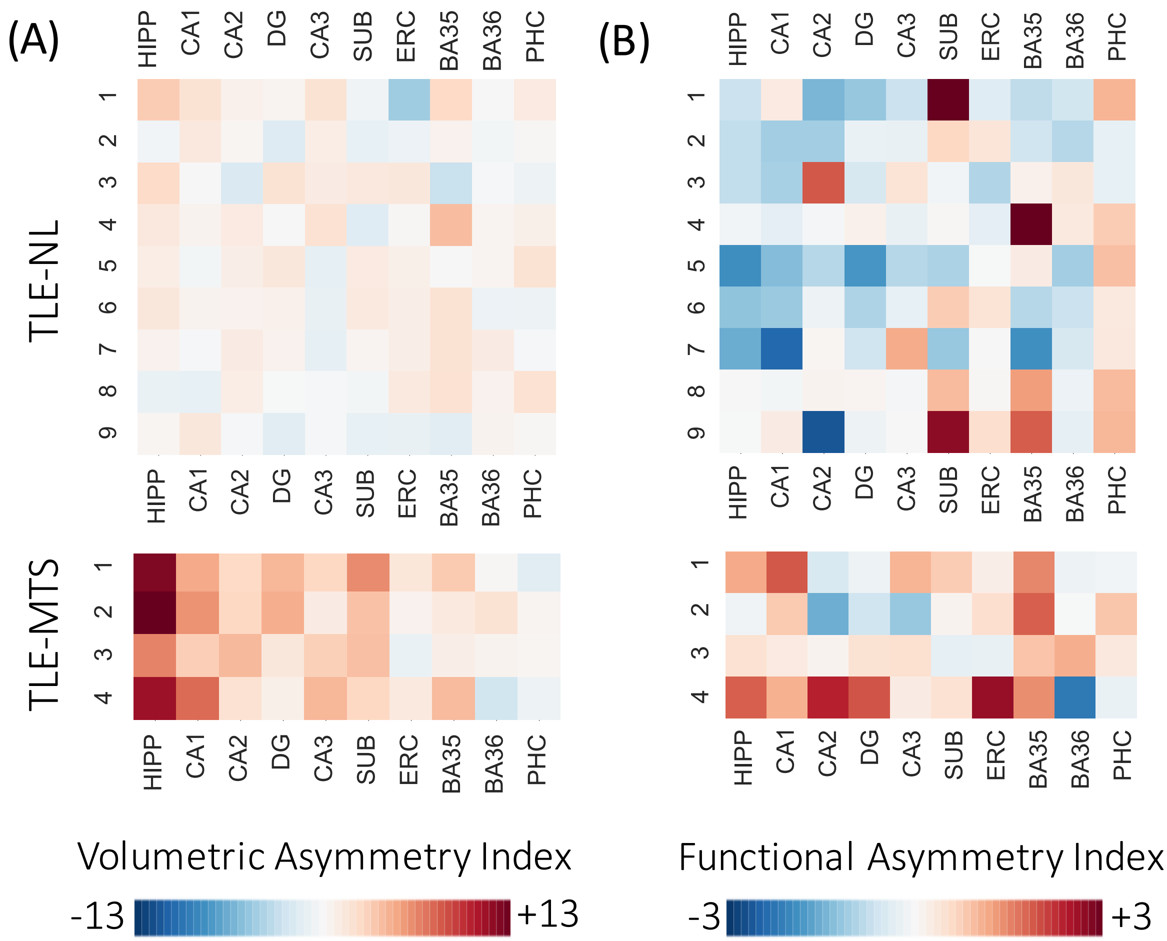
where the weights are scaled by the largest weight in the network, i.e. $\widetilde{w}_{ij} = w_{ij}/max(w_{ij})$ (Onnela, Saramäki, Kertész, & Kaski, 2005).

3) Network Efficiency: The local network efficiency *e(i)* is often thought of as a measure of the capacity of node *i* to transfer information throughout the network (V Latora & Marchiori, 2003; Vito Latora & Marchiori, 2001), although for caveats in this interpretation, see also Rubinov and Bassett, 2011. It can be defined as follows (Achard & Bullmore, 2007):

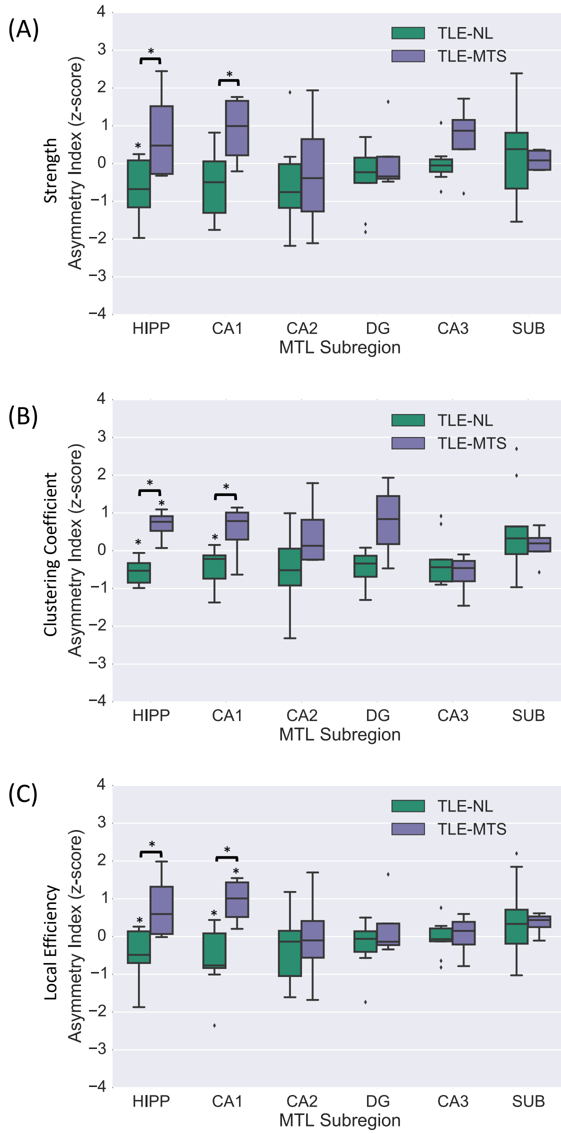
$$e_i = \frac{1}{N-1}\sum_{i \neq j \in N}\frac{1}{L_{ij}}, \qquad \text{(Eq. S3)}$$

where L_{ij} is the shortest weighted path length between node *i* and node *j*, where the length of each edge is given by the reciprocal of the edge weight, $1/w_{ij}$.

2. Supplementary Figures



Supplementary Figure 1: Individual subject level heat maps of (A) volumetric and (B) functional network asymmetries for the whole-hippocampus and for individual MTL subregions in TLE-NL patients and TLE-MTS patients.



Supplementary Figure 2: Normalized MTL functional subregional asymmetries in TLE-NL and TLE-MTS patients, using (A) strength asymmetry (B) clustering coefficient asymmetry, and (C) local efficiency asymmetry (*p < 0.05).

	Z-SCORED VOLUMETRIC ASYMMETRY			Z-SCORED FUNCTIONAL NETWORK ASYMMETRY		
SUBREGION	**TLE-MTS (mean +/- SD)**	**TLE-NL (mean +/- SD)**	***P***	**TLE-MTS (mean +/- SD)**	**TLE-NL (mean +/- SD)**	***p***
HIPP	10 +/- 2.7	0.98 +/- 1.2	*	0.8 +/- 0.71	-0.66 +/- 0.58	*
CA1	5.3 +/- 1.5	0.45 +/- 0.89	*	0.9 +/- 0.53	-0.62 +/- 0.70	*
CA2	2.9 +/- 0.8	0.36 +/- 0.89	*	0.02 +/- 1.27	-0.54 +/- 0.98	n.s
DG	2.8 +/- 1.7	0.18 +/- 1.12	*	0.42 +/- 0.84	-0.4 +/- 0.52	n.s

CA3	2.8 +/- 1.2	0.28 +/- 1.19	*	0.11 +/- 0.72	-0.11 +/- 0.48	n.s
SUB	4.1 +/- 1.2	-0.06 +/- 1.06	*	0.19 +/- 0.29	-0.53 +/- 1.2	n.s
ERC	0.6 +/- 0.93	-0.10 +/- 1.78	n.s	0.78 +/- 1.13	-0.09 +/- 0.48	n.s
BA35	2.4 +/- 1.36	0.94 +/- 2.01	n.s	0.99 +/- 0.30	0.34 +/- 1.15	n.s
BA36	-0.01 +/- 1.6	0.18 +/- 0.51	n.s	-0.29 +/- 1.0	-0.38 +/- 0.38	n.s
PHC	-0.04 +/- 0.75	0.50 +/- 0.93	n.s	0.18 +/- 0.45	0.49 +/- 0.54	n.s

Supplementary Table 1: Table of volumetric and functional asymmetry values for each subregion. *p <0.05; n.s: not significant (two sample, two-tailed permutation test).

3. References

Achard, S., & Bullmore, E. (2007). Efficiency and cost of economical brain functional networks. *PLoS Computational Biology*, *3*(2), 0174–0183. http://doi.org/10.1371/journal.pcbi.0030017

Bassett, D. S., & Bullmore, E. T. (2016). Small-World Brain Networks Revisited. *The Neuroscientist*, 107385841666772. http://doi.org/10.1177/1073858416667720

Bassett, D. S., Zurn, P., & Gold, J. I. (2018). On the nature and use of models in network neuroscience. *Nature Reviews Neuroscience*, pp. 1–13. http://doi.org/10.1038/s41583-018-0038-8

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*, *10*(3), 186–198. http://doi.org/10.1038/nrn2575

Chai, X. J., Castañón, A. N., Öngür, D., & Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. *NeuroImage*, *59*(2), 1420–1428. http://doi.org/10.1016/j.neuroimage.2011.08.048

Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The Global Signal and Observed Anticorrelated Resting State Brain Networks. *Journal of Neurophysiology*, *101*(6), 3270–3283. http://doi.org/10.1152/jn.90777.2008

Latora, V., & Marchiori, M. (2001). Efficient Behavior of Small-World Networks, *87*(89). http://doi.org/10.1103/PhysRevLett.87.198701

Latora, V., & Marchiori, M. (2003). Economic small-world behavior in weighted networks. *European Physical Journal B*, *32*(2), 249–263. http://doi.org/10.1140/epjb/e2003-00095-5

Li, C., Wang, H., De Haan, W., Stam, C. J., & Mieghem, P. Van. (2011). The correlation of metrics in complex networks with applications in functional brain networks. *J. Stat. Mech.* http://doi.org/10.1088/1742-5468/2011/11/P11018

Lynall, M.-E., Bassett, D. S., Kerwin, R., McKenna, P. J., Kitzbichler, M., Muller, U., & Bullmore, E. (2010). Functional Connectivity and Brain Networks in Schizophrenia. *Journal of Neuroscience*, *30*(28), 9477–9487. http://doi.org/10.1523/JNEUROSCI.0333-10.2010

Murphy, K., & Fox, M. D. (2016). Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *NeuroImage*. http://doi.org/10.1016/j.neuroimage.2016.11.052

Onnela, J. P., Saramäki, J., Kertész, J., & Kaski, K. (2005). Intensity and coherence of motifs in weighted complex networks. *Physical Review E - Statistical, Nonlinear, and Soft Matter*

Physics, *71*(6). http://doi.org/10.1103/PhysRevE.71.065103
Rubinov, M., & Bassett, D. S. (2011). Emerging evidence of connectomic abnormalities in schizophrenia. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *31*(17), 6263–5. http://doi.org/10.1523/JNEUROSCI.0382-11.2011
Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, *52*(3), 1059–1069. http://doi.org/10.1016/j.neuroimage.2009.10.003