# Discovering Pathophysiologic Networks of Temporal Lobe Epilepsy using the BrainMap Community Portal through the Texas Advanced Computing Center

**Jonathan M. Towne[1,2], Vahid Eslami[3], P Mickle Fox[1], José E. Cavazos[2], Peter T. Fox[1,2]**

[1]Research Imaging Institute, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[2]South Texas Medical Scientist Training Program, University of Texas Health San Antonio, San Antonio, TX, USA
[3]Department of Neurology, UCLA Health, Los Angeles, CA, USA

## Introduction

Medial temporal lobe epilepsy (MTLE) seizures cause regional damage (Barron et al., 2013), detectable on imaging of brain structure (VBM; Ashburner et al., 2000) and function (VBP; Deng et al., 2022). Damage is mediated by aberrant neuronal activity propagating along existing network architecture (Barron et al., 2014). However, MTLE disease networks remain ill-defined and are of great interest to diagnostic and therapeutic development.

Independent component analysis (ICA; Beckmann et a., 2004) can detect neural-networks by computing multi-variate co-occurrence patterns across a volume and is validated for coordinate-based meta-analysis (CBMA/Meta-ICA; Fox et al., 2014; Vanasse et al., 2021). Meta-ICA is methodologically distinct from mass-univariate meta-analytics (Activation Likelihood Estimation (ALE); Eickhoff et al., 2016) that simply detect robust regions/hubs of pathology. Although meta-ICA is typically used to extract many (>20) healthy canonical networks (Smith et al., 2009), **we applied low-dimensional meta-ICA to VBM/VBP reports of MTLE-pathology, to infer TLE-specific network anomalies.**

## Canonical vs. Disease Networks

Neural networks derived from imaging have revolutionized the field of neuroscience, a field relying increasingly on high performance computing. (Bassett & Sporns 2017 - *Nature neuroscience*). The intrinsic connectivity of the brain (Seeley et al., 2007) presents a robust functional architecture, with networks that are detectable both in resting-state and task-based neuroimaging (Smith et al., 2009 – *PNAS*), and are consistent across analytic modalities (Crossley et al., 2013 – *PNAS*).

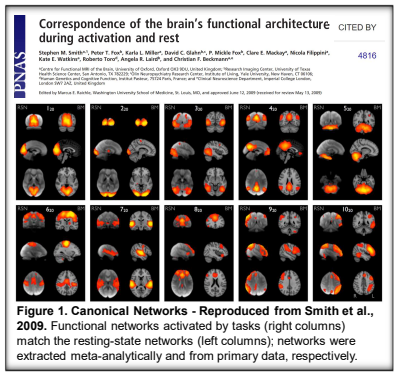


**Figure 1. Canonical Networks - Reproduced from Smith et al., 2009.** Functional networks activated by tasks (right columns) match the resting-state networks (left columns); networks were extracted meta-analytically and from primary data, respectively.

These "canonical" networks also independently emerge from structural imaging of diseases, as shown by a transdiagnostic meta-analysis of coordinate data (Vanasse et al., 2021 – *Communications Biology*), supporting the Network Degeneration Hypothesis (Seeley et al., 2009 – *Neuron*). Canonical networks have immensely enhanced our overall understanding of neurophysiology and neuropathology; however, no diseases map to just a single canonical network and no such network is affected by only one disease (Vanasse et al., 2021).

**Canonical networks are therefore inadequate to explain the effects of individual diseases. In order to fully understand the pathophysiology of a neurologic condition, disease-specific networks must be defined.**

## Materials and Methods

1. 74 neuroimaging experiments assessing MTLE disease effects (contrasting patients vs. healthy controls) were obtained from the BrainMap database using Sleuth. All BrainMap Portal applications are shown in **Figure 7**.
   - 45 structural experiments (voxel-based morphometry; VBM)
   - 29 functional experiments (voxel-based pathophysiology; VBP)
   - 588 foci of pathology were reported, collectively representing 1599 MTLE subjects
2. Coordinate data were modeled as spatial probability maps per-experiment (weighted by sample size) using GingerALE commands.
3. Maximally discrete networks were extracted as spatial component-maps by computing spatial co-occurrences within and between experiments in a voxel-wise manner, using FSL Melodic as implemented in Meta-ICA (**Figure 2**).
   - Spatial cross-correlations and the $\chi^2$ Test for Homogeneity were used to compare results.
4. Component maps were interpreted using the Behavioral Analysis Plugin from Mango and compared with MTLE pathology hubs that were established in a prior analysis (Towne et al., 2022; cf. **Figure 5**).

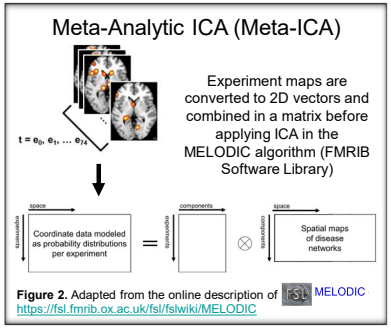


**Figure 2.** Adapted from the online description of MELODIC https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC

## Results

1. Two non-canonical networks are specifically affected by MTLE pathology.

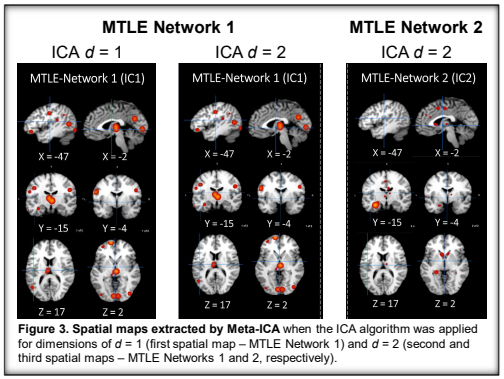


**Figure 3. Spatial maps extracted by Meta-ICA** when the ICA algorithm was applied for dimensions of $d = 1$ (first spatial map – MTLE Network 1) and $d = 2$ (second and third spatial maps – MTLE Networks 1 and 2, respectively).

2. Both MTLE networks are congruent with separate subsets of symptoms associated with the disease, as shown by analysis of behavioral meta-data in the BrainMap database
   - Network 1 (verbal/motor/visual) explains symptoms of impaired communication, involuntary movements, and visual hallucinosis
   - Network 2 (limbic-attentional) explains symptoms of impaired awareness, social-emotional deficits, transient amnesia

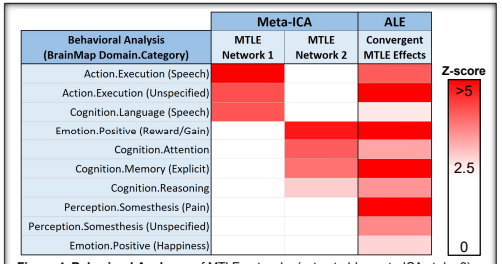


**Figure 4. Behavioral Analyses** of MTLE-networks (extracted by meta-ICA at $d = 2$), compared with that of the regions of spatial convergence among all imaging studies of MTLE disease effects (computed by activation/anatomic likelihood estimation; ALE).

3. MTLE-networks are spatially distinct beyond the main hubs of disease.
   - Spatial cross correlation between Network 1 and Network 2 was minimal (R = 0.042).
   - Network 1 was stable, showing congruence (R = 0.890) between analyses performed at $d = 1$ and $d = 2$

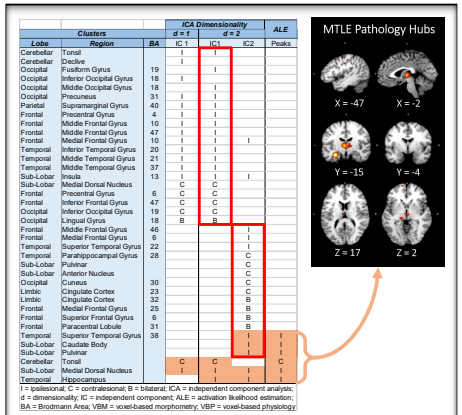


**Figure 5. ICA Comparison with Activation Likelihood Estimation (ALE).** MTLE-networks (IC1 & IC2) only overlap at two MTLE-hubs: hippocampus and medial dorsal nucleus (MDN) thalamus. Previously identified (Towne et al., 2022) hubs of MTLE pathology are highlighted in the table in orange.

4. Spatial separation between the two networks is not attributable to structural-functional effect modification.
   - The distribution of VBM and VBP experiments to each component network was shown to be homogenous by the $\chi^2$ Test for Homogeneity

| Distribution of VBM and VBP Experiments | | |
|---|---|---|
| | VBM | VBP |
| Experiment Count | 45 | 29 |
| Percent of Total | 60.8% | 39.2% |

| Observed Percent Contribution to Each Network (independent component) | | |
|---|---|---|
| | VBM | VBP |
| Network 1 | 74.3% | 25.7% |
| Network 2 | 67.5% | 32.5% |

| $\chi^2$ Test for Homogeneity | | |
|---|---|---|
| p-value | 0.0695 | > 0.05 |

**Figure 6.** We fail to reject the null hypothesis ($\chi^2$ test for homogeneity) that the distribution of VBM versus VBP experiments is homogenous for the identified networks.

## BrainMap Community Portal on TACC

- A web-based platform for meta-analysis in human brain mapping
- This neuroimaging research resource aspires to make cognitive neuroscience and disease-biomarker discovery via coordinate-based meta-analysis (CBMA) widely accessible to the research community
- The database contains >20% of structural/functional imaging literature
  - 25k+ experiments
  - 200k+ subjects

Check out BrainMap on TACC!

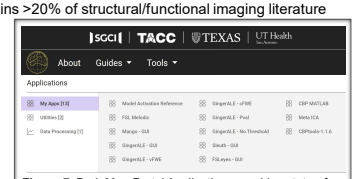


**Figure 7.** BrainMap Portal Applications combine state-of-the-art neuroimaging analytics with high-performance computing on TACC's Stampede 2 & Maverick 2 systems.

## Conclusion

- Meta-ICA identified two physiologically meaningful networks that bear little resemblance to canonical networks and are specific to MTLE pathology.
- These MTLE-networks likely represent discrete seizure-propagation routes that originate in the two most significant disease hubs.
- Meta-ICA is only one of the many tools that will soon be available to Big Data Neuroscience researchers on the BrainMap Community Portal (portal.brainmap.org). This resource will continue to enable rapid, novel discoveries and serve as the modern encyclopedia of the brain.

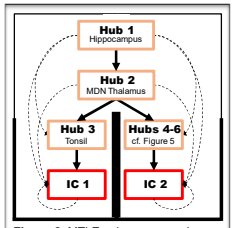


**Figure 8.** MTLE seizures spread beyond the hippocampus and MDN thalamus in two distinct networks

## Future Directions

- Primary resting-state imaging in MTLE patients should be pursued to determine the diagnostic and prognostic potential of these MTLE networks in per-subject prediction.
  - MTLE-associated brain changes in individual patients may be biased toward one network or the other and should be correlated with clinical markers.
- Low-d meta-ICA has the potential to elucidate neurodegenerative sub-networks
  - This method should be tested in the other 100+ neurologic diseases cataloged in the BrainMap database (brainmap.org/taxonomy/icd.html).
- No optimization statistics are established for ICA at low dimensions; it will be critical to validate a method for determining the optimal number of disease sub-networks.

## References

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry--the methods. *NeuroImage*, *11*(6 Pt 1), 805–821.
Barron, D. S., Fox, P. M., Laird, A. R., Robinson, J. L., & Fox, P. T. (2013). Thalamic medial dorsal nucleus atrophy in medial temporal lobe epilepsy: A VBM meta-analysis. *Neuroimage. Clinical*, *2*, 25–32.
Barron, D. S., Fox, P. T., Pardoe, H., Lancaster, J., Price, L. R., Blackmon, K., Berry, K., Cavazos, J. E., Kuzniecky, R., Devinsky, O., & Thesen, T. (2014). Thalamic functional connectivity predicts seizure laterality in individual TLE patients: application of a biomarker development strategy. *Neuroimage. Clinical*, *7*, 273–280.
Bassett DS, Sporns O. Network neuroscience. *Nat Neurosci*. 2017;20(3):353-364.
Beckmann, C. F., & Smith, S. M. (2004). Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Transactions on medical imaging*, *23*(2), 137–152.
Crossley NA, Mechelli A, Vértes PE, et al. Cognitive relevance of the community structure of the human brain functional coactivation network [published correction appears in Proc Natl Acad Sci U S A. 2013 Sep 17;110(38):15502]. *Proc Natl Acad Sci U S A*. 2013;110(28):11583-11588.
Deng, S., Franklin, C. G., O'Boyle, M., Zhang, W., Helq, B. L., Jerabek, P. A., Lu, H., & Fox, P. T. (2022). Hemodynamic and metabolic correspondence of resting-state voxel-based physiological metrics in healthy adults. *NeuroImage*, *250*, 118923.
Eickhoff, S. B., Nichols, T. E., Laird, A. R., Hoffstaedter, F., Amunts, K., Fox, P. T., Bzdok, D., & Eickhoff, C. R. (2016). Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation. *NeuroImage*, *137*, 70–85.
Fox, P. T., Lancaster, J. L., Laird, A. R., & Eickhoff, S. B. (2014). Meta-analysis in human neuroimaging: computational modeling of large-scale databases. *Annual review of neuroscience*, *37*, 409–434.
Müller, V. I., Cieslik, E. C., Serbanescu, I., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2017). Altered Brain Activity in Unipolar Depression Revisited: Meta-analyses of Neuroimaging Studies. *JAMA psychiatry*, *74*(1), 47–55.
Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007;27(9):2349-2356.
Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron*. 2009;62(1):42-52.
Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., Watkins, K. E., Toro, R., Laird, A. R., & Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(31), 13040–13045.
Towne, J., Eickes, Y., and Fox, P. T. (2021). Sub-cortical structural change and network involvement in medial temporal lobe epilepsy: a VBM meta-analysis. [Abstract 114]. *Annals of Neurology: 144th Annual Meeting of the American Neurological Association*. 90(S27), S105-S106. PMID: 34622980. doi:10.1002/ana.26180
Towne, J. M., Eickes, Y., Cavazos, J. E., and Fox, P. T. (2022). Resting-state voxel-based pathophysiologic changes in medial temporal lobe epilepsy. [Abstract 3643]. Neurology, 98(18S), 3643. https://n.neurology.org/content/98/18_Supplement/3643
Vanasse, T. J., Fox, P. T., Fox, P. M., Cano, S., Costa, T., Smith, S. M., Eickhoff, S. B., & Lancaster, J. L. (2021). Brain pathology recapitulates physiology: A network meta-analysis. *Communications Biology*, *4*(1), 341.

This study was funded by R01MH074457 and T32GM113896

More information on brainmap.org