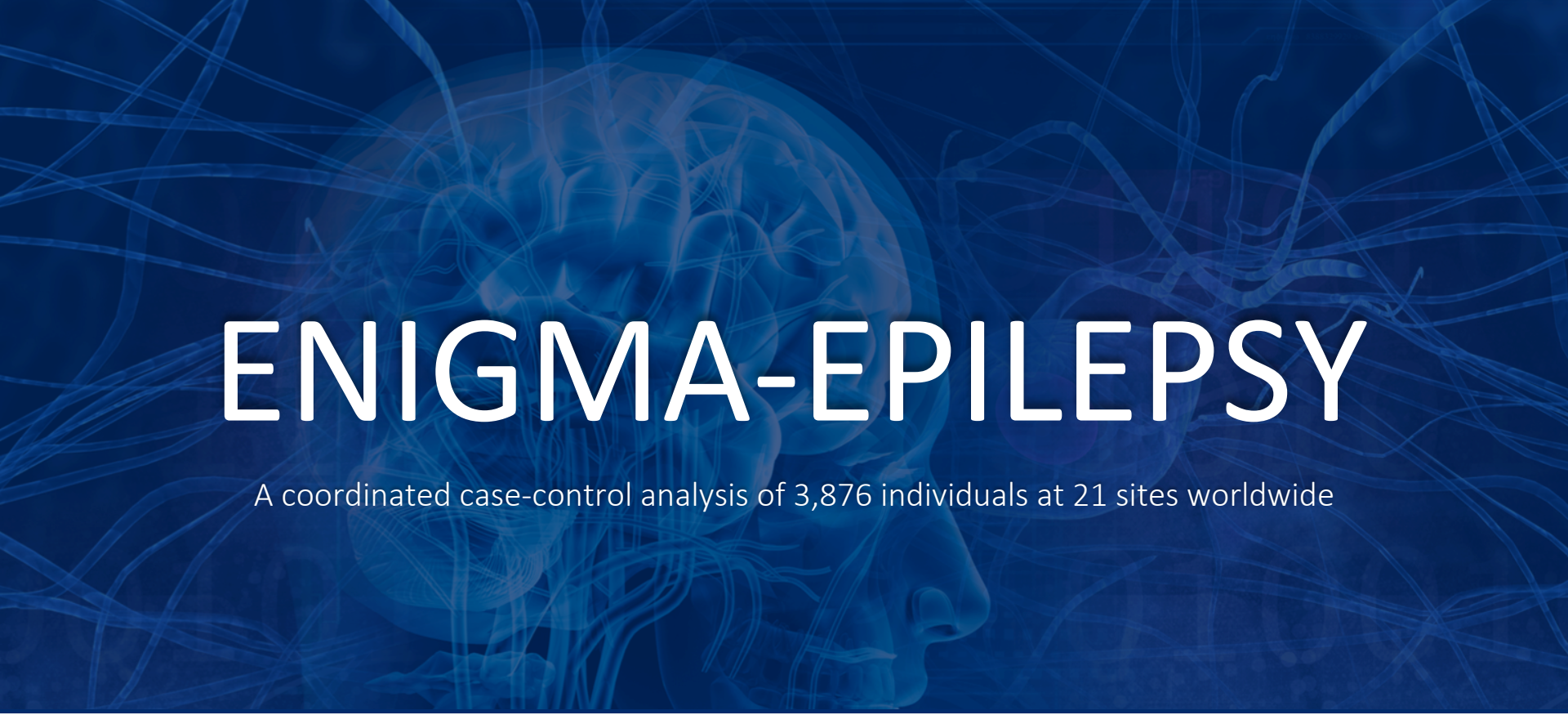


ENIGMA-EPILEPSY

A coordinated case-control analysis of 3,876 individuals at 21 sites worldwide

CHRISTOPHER WHELAN, PHD

UNIVERSITY OF SOUTHERN CALIFORNIA

EPILEPSY

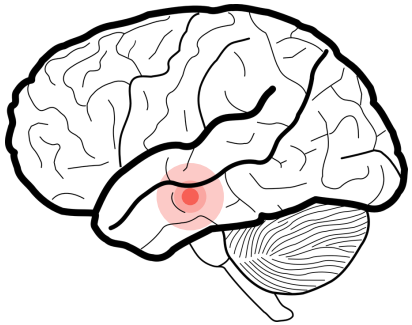
“A history of deities and demons, of spirits and curses… thus a history of human suffering and medical ignorance.”

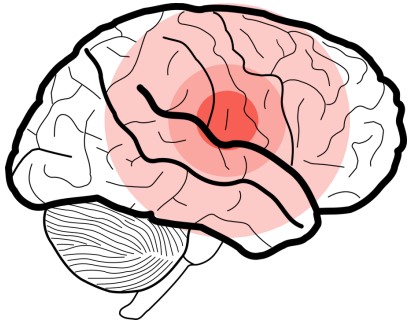
- Donald F. Weaver

MRI in epilepsy: Unanswered questions

Temporal lobe epilepsy (MTLE)…

- What is the extent of extrahippocampal atrophy, associated with **mesial temporal sclerosis (MTS)?**
- Are abnormalities more pronounced in **left** vs. **right** MTLE?





Genetic generalized epilepsy (GGE)

- Which brain regions are affected? Thalamo-cortical circuitry?[1]

1.Bernhardt, Rozen, Worsley, Evans. *NeuroImage* 2009, 46: 373-81.

MRI in epilepsy: Unanswered questions

- Small, cross-sectional neuroimaging studies are underpowered to detect subtle effects, and may over-inflate other effects.

nature REVIEWS NEUROSCIENCE

ANALYSIS

Power failure: why small sample size undermines the reliability of neuroscience

Katherine S. Button[1,2], John P. A. Ioannidis[3], Claire Mokrysz[1], Brian A. Nosek[4], Jonathan Flint[5], Emma S. J. Robinson[6] and Marcus R. Munafò[1]

Abstract | A study with low statistical power has a reduced chance of detecting a true effect, but it is less well appreciated that low power also reduces the likelihood that a statistically significant result reflects a true effect. Here, we show that the average statistical power of

PNAS

Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates

Anders Eklund[a,b,c,1], Thomas E. Nichols[d,e], and Hans Knutsson[a,c]

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Edited by Emery N. Brown, Massachusetts General Hospital, Boston, MA, and approved May 17, 2016 (received for review February 12, 2016)

The most widely used task functional magnetic resonance imaging (fMRI) analyses use parametric statistical methods that depend on a variety of assumptions. In this work, we use real resting-state data and a total of 3 million random task group analyses to compute empirical FSL, and A nominal methods and inval principal lation fur comparison, the nonparametric permutation test is found to produce nominal results for voxelwise as well as clusterwise inference. These findings speak to the need of validating the statistical methods being used in the field of neuroimaging.

fMRI | statistics | false positives | cluster inference | permutation test

Since its beginning more than 20 years ago, functional magnetic resonance imaging (fMRI) (1, 2) has become a popular tool for understanding the human brain, with some 40,000 published papers according to PubMed. Despite the popularity of fMRI as a tool for studying brain function, the statistical methods used have rarely been validated using real data. Validations have instead

(FWE), the chance of one or more false positives, and empirically measure the FWE as the proportion of analyses that give rise to any significant results. Here, we consider both two-sample and

each voxel, and clusterwise inference (19–21), where significance is assessed on clusters formed with an arbitrary threshold.

In brief, we find that all three packages have conservative voxelwise inference and invalid clusterwise inference, for both one- and two-sample *t* tests. Alarmingly, the parametric methods can give a very high degree of false positives (up to 70%, compared with the nominal 5%) for clusterwise inference. By comparison, the nonparametric permutation test (22–25) is found to produce nominal results for both voxelwise and clusterwise inference for two-sample *t* tests, and nearly nominal results for one-sample *t* tests. We explore why the methods fail to appropriately control the false-positive risk.

"...the most common software packages... (SPM, FSL, AFNI)... can result in false-positive rates of up to 70%"

ENIGMA
EPILEPSY

3,876 MRI scans

- **21** research centers
- **14** countries
- **50+** scientists

Formed: March 2015
Royal Society, London
International League Against Epilepsy
Consortium on Complex Epilepsies Meeting

The epilepsy working group of the Enhancing Neuro Imaging Genetics through Meta-Analysis Consortium

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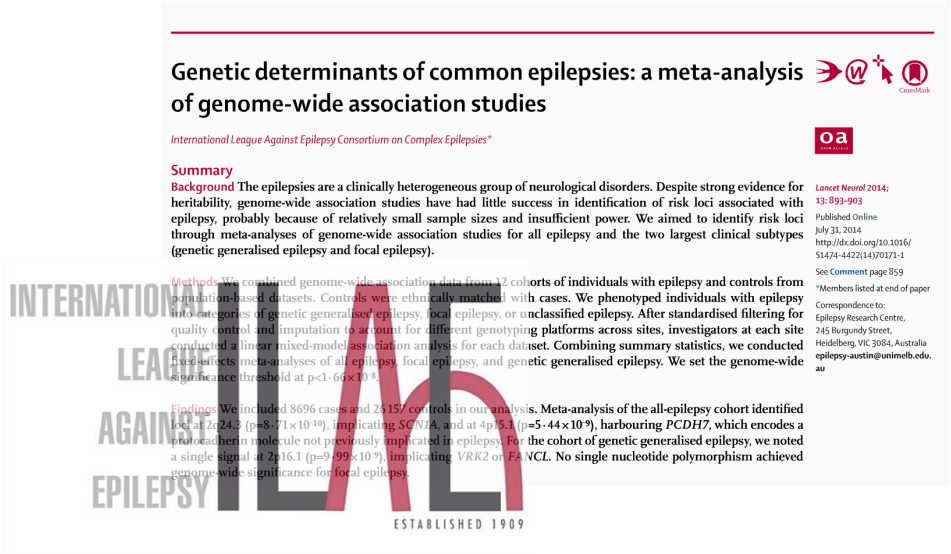
Study design

Phenotypes:

- MTLE with left MTS • **N= 415**
- MTLE with right MTS • **N= 339**
- GGE • **N = 367**
- ‘All epilepsies’ • **N = 2,149**
- Healthy controls • **N= 1,727**



Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies

International League Against Epilepsy Consortium on Complex Epilepsies*

Summary

Background The epilepsies are a clinically heterogeneous group of neurological disorders. Despite strong evidence for heritability, genome-wide association studies have had little success in identification of risk loci associated with epilepsy, probably because of relatively small sample sizes and insufficient power. We aimed to identify risk loci through meta-analyses of genome-wide association studies for all epilepsy and the two largest clinical subtypes (genetic generalised epilepsy and focal epilepsy).

Methods We combined genome-wide association data from 12 cohorts of individuals with epilepsy and controls from population-based datasets. Controls were ethnically matched with cases. We phenotyped individuals with epilepsy into categories of genetic generalised epilepsy, focal epilepsy, or unclassified epilepsy. After standardised filtering for quality control and imputation to account for different genotyping platforms across sites, investigators at each site conducted a linear mixed-model association analysis for each dataset. Combining summary statistics, we conducted fixed-effects meta-analyses of all epilepsy, focal epilepsy, and genetic generalised epilepsy. We set the genome-wide significance threshold at $p<1{\cdot}66\times10^{-8}$.

Findings We included 8696 cases and 26 157 controls in our analysis. Meta-analysis of the all-epilepsy cohort identified loci at 2q24.3 ($p=8{\cdot}71\times10^{-10}$), implicating *SCN1A*, and at 4p15.1 ($p=5{\cdot}44\times10^{-9}$), harbouring *PCDH7*, which encodes a protocadherin molecule not previously implicated in epilepsy. For the cohort of genetic generalised epilepsy, we noted a single signal at 2p16.1 ($p=9{\cdot}99\times10^{-9}$), implicating *VRK2* or *FANCL*. No single nucleotide polymorphism achieved genome-wide significance for focal epilepsy.

Lancet Neurol 2014; 13: 893-903
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http://dx.doi.org/10.1016/S1474-4422(14)70171-1
See Comment page 859
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epilepsy-austin@unimelb.edu.au

Inclusion criteria:

- Aged 18-55 years
- No strokes, infarcts, tumors
- No neurosurgery
- No neurological co-morbidities, or progressive syndromes (e.g. FCDs, PMEs)

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Methods • Overview

Run post-processing on MRI data
(FreeSurfer v5.3.0)

Perform image QC
(standardized ENIGMA QA guidelines)

Conduct linear regression
(R, *lm;* covariates = AGE, SEX, ICV)

Upload [anon.] summary statistics to ENIGMA server
cranium.ini.usc.edu

Run random-effects meta-analysis
(R, *metafor,* $p<1.84x10^{-4}$)

For protocols, see: **http://enigma.ini.usc.edu/protocols/**

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Subcortical results

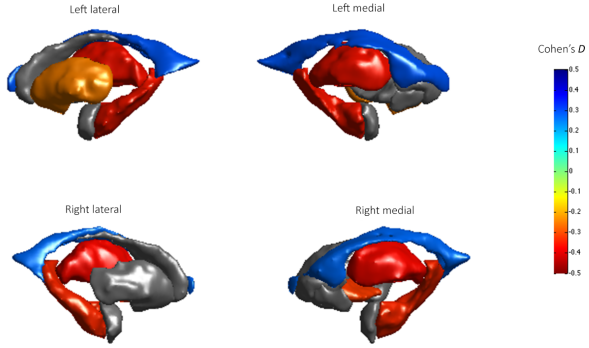
(A) ALL EPILEPSIES:
- **Bilateral thalamus** (*d*≤ −0.348; *P*≤1.31×10−6)
- **Bilateral hippocampi (***d*≤ −0.336; *P*≤3.04× 10−7)
- **Right pallidum** (*d*= -0.316; *P*=8.32×10−9),
- **Bilateral lat. ventricles (***d*< 0.268; *P*≤2.14×10−12)

(B) TLE-MTS-L:
- **ipsilateral hippocampus** (d= -1.73; P=1.35x10-19),
- **bilateral thalamus** (d≤ −0.462; P≤ 8.12x10-5),
- **contralateral pallidum** (d= -0.45; P=5.48x10-7)
- **ipsilateral putamen** (d= -0.385; P=1.07x10-6),
- **bilateral lat. ventricles** (d≥ 0.36; P≤8.95x10-5)

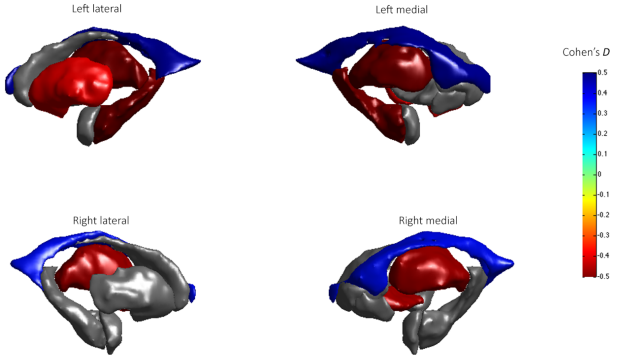
(C) TLE-MTS-R:
- **ipsilateral hippocampus** (*d*=-1.906; *P*=6.36x10^{-37})
- **ipsilateral thalamus** (*d*= −0.727; *P*=1.60x10-12)
- **ipsilateral putamen** (*d*= -0.47; *P*=4.94x10-4)
- **ipsilateral pallidum** (*d*= −0.451; *P*=3.96x10-7)
- **bilateral lat. ventricles** (d≥ 0.39; *P*≤1.52x10-6)

(D) GGE:
- **right thalamus** (*d*= −0.403; *P*=3.6x10-6)
- **right pallidum** (*d*= −0.35; *P*=3.37x10-4)

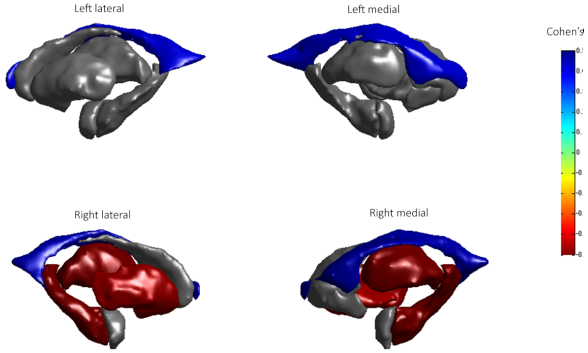
A. All epilepsies



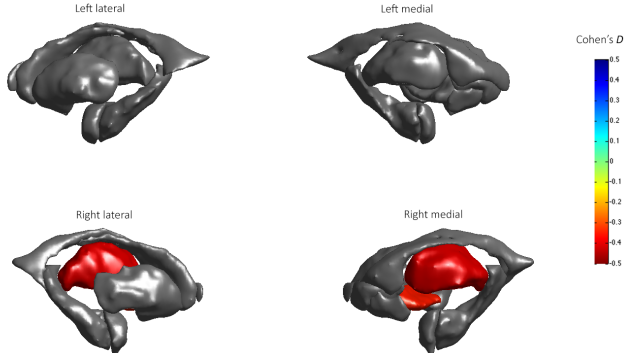
B. Temporal lobe epilepsy with left MTS



C. Temporal lobe epilepsy with right MTS



D. Genetic generalized epilepsies



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Cortical results

(A) ALL EPILEPSIES:

BILATERAL changes in…

- precentral gyri (d≤-0.384; P≤1.82x10-18),
- caudal middle frontal gyri (d≤-0.307; P≤2.09x10-9),
- paracentral gyri (d≤-0.311; P≤2.05x10-6),
- pars triangularis (d≤-0.192; P≤1.29x10-4),
- superior frontal gyri (d≤−0.342; P≤1.44x10-9),
- transverse temporal gyri (d≤−0.342; P≤1.29x10-4),
- supramarginal gyri (d≤-0.232; P≤9.87x10-5).

UNILATERAL changes in…

- right cuneus (d=-0.204; P=9.68x10-8),
- right pars opercularis (d= -0.177; P= 6.48x10-7),
- right precuneus (d= -0.275; P= 2.7x10-5)
- left entorhinal gyrus (d=-0.264; P= 2.04x10-5)

(B) TLE-MTS-L:

BILATERAL changes in…

- caudal middle frontal gyri (d≤-0.403; P≤7.07x10-9),
- paracentral gyri (d≤-0.378; P≤1.61x10-5),
- precentral gyri (d≤-0.466; P≤8.64x10-9)
- superior frontal gyri (d≤-0.365; P≤1.44x10-9)

UNILATERAL changes in…

- ipsi. entorhinal cortex (d=-0.445; P=7.35x10-10)
- ipsi. fusiform gyrus (d=-0.359; P=2.19x10-7),
- ipsi. temporal pole (d=-0.315; P=3.33x10-6),
- contra precuneus (d=-0.473; P=5.16x10-6)
- contra pars triangularis (d=-0.285; P=2.16x10-6)

A

(C) TLE-MTS-R:

BILATERAL changes in…

- paracentral gyri (d≤-0.421; P≤7.67x10-7),
- precentral gyri (d≤-0.415; P≤4.31x10-6),

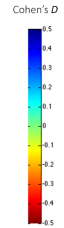
UNILATERAL changes in…

- ipsi. lateral occipital gyrus (d=-0.366; P=1.79x10-4)
- ipsi. pars opercularis (d=-0.271; P=1.45x10-4)
- contra. superior frontal gyrus (d=-0.355; P=1.59x10-4)
- contra. transverse temporal gyrus (d=-0.312; P=2.15x10-5)

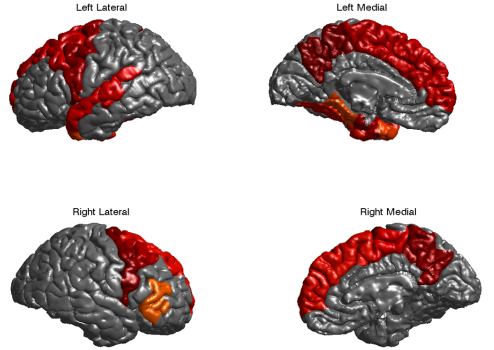
(D) GGE:

BILATERAL changes in…

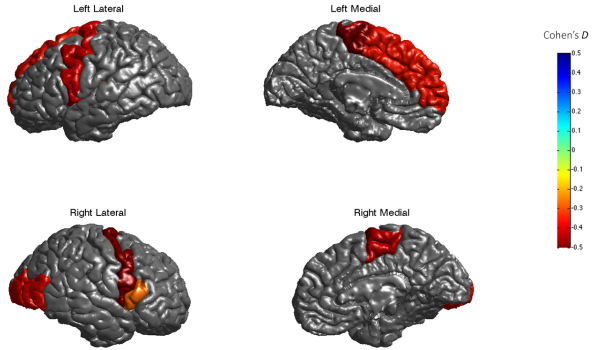
- precentral gyri (d≤−0.342; P≤1.75x10-6)



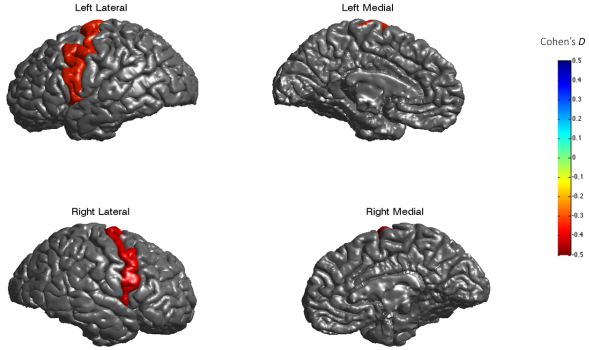
B. Temporal lobe epilepsy with left MTS



C. Temporal lobe epilepsy with right MTS



D. Genetic generalized epilepsies



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Results • Effects of duration, age at onset, age*Dx

Duration effects…

- Observed in ‘all epilepsies’ and MTLE-MTS-R groups.
- *Precentral gyri, thalamus, hippocampus, pars triangularis, superior frontal gyri.*

Age at onset effects…

- Observed in ‘all epilepsies’ group only.
- *Superior frontal gyri, pars triangularis, transverse temporal gyrus.*

Age*Diagnosis effects…

- None observed after correction for multiple comparisons.

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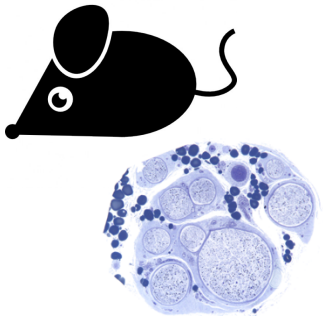
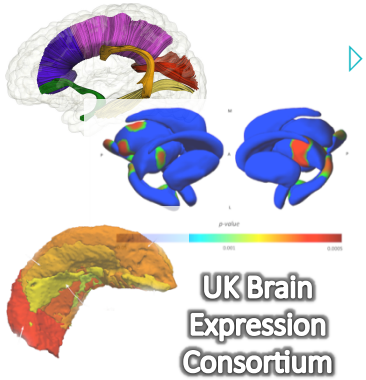
Discussion



- Specific functional implications cannot be inferred from GM changes alone.
- How, then, can our findings help?
  - Confirm / refute prior reports from smaller studies
  - ROI prioritization, e.g. neuropathology • animal models • gene expression

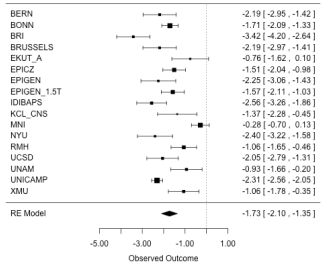


- Many other ENIGMA-Epilepsy groups are active, or will soon form…
  - ENIGMA-Epilepsy **DTI (ongoing)**
  - ENIGMA-Epilepsy Subcortical Shape
  - ENIGMA-Epilepsy Hippocampal Subfields
  - Sulcal/gyrification measures
  - Expression studies, in collab w/ UKBEC
  - Eventual imaging genetics in epilepsy

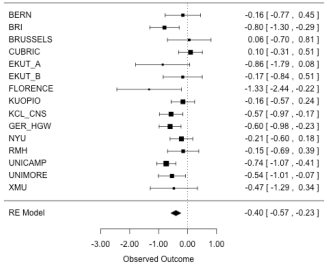
ENIGMA-EPILEPSY

- Largest neuroimaging study of epilepsy to date.
- Shows profound, robust, and consistent effects across and within syndromes.
- Must be wary of limitations: Cross-sectional design, omission of certain covariates.
- An open, collaborative network aiming to identify structural biomarkers.

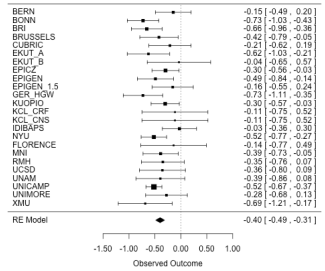
Hippocampus (left) • MTLE-MTS-L



Thalamus (right) • GGE



Precentral gyrus (right) • All epilepsies



THANK YOU!



NIH Big Data to Knowledge (BD2K)

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