ENIGMA-EPILEPSY

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

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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

MRI in epilepsy: Unanswered questions

Small, cross-sectional neuroimaging studies are underpowered to detect subtle effects, and may over-inflrate other effects.
The epilepsy working group of the Enhancing Neuro Imaging Genetics through Meta-Analysis Consortium

**ENIGMA**

- 21 research centers
- 14 countries
- 50+ scientists

**ENIGMA** Epilepsy Group: Formed March 2015 by Royal Society, London International League Against Epilepsy

**ENIGMA** is a global neuroimaging research organization with 49 research centers from 14 countries and 250 scientists. It focuses on complex epilepsies, with 3,876 MRI scans from various sites around the world.

**ENIGMA** has led to significant breakthroughs in understanding epileptic conditions and advancing therapeutic options.

**ENIGMA** is an ongoing collaborative effort that aims to advance our understanding of epilepsy through integration of neuroimaging and genomics data.
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

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

(A) ALL EPILEPSIES:
- Bilateral thalamus ($d = -0.348; P = 1.33 \times 10^{-6}$)
- Bilateral hippocampi ($d = -0.336; P < 3.04 \times 10^{-7}$)
- Right pallidum ($d = -0.316; P = 3.12 \times 10^{-9}$)
- Bilateral lat. ventricles ($d = 0.268; P = 2.14 \times 10^{-12}$)

(B) TLE-MTS-L:
- Ipsilateral hippocampus ($d = -0.73; P = 1.35 \times 10^{-19}$)
- Bilateral thalamus ($d \leq -0.462; P = 8.12 \times 10^{-5}$)
- Contralateral pallidum ($d = -0.45; P = 5.84 \times 10^{-7}$)
- Ipsilateral putamen ($d = -0.385; P = 1.07 \times 10^{-6}$)
- Bilateral lat. ventricles ($d \geq 0.36; P = 8.95 \times 10^{-5}$)

(C) TLE-MTS-R:
- Ipsilateral hippocampus ($d = -1.906; P = 6.36 \times 10^{-37}$)
- Ipsilateral thalamus ($d = -0.727; P = 1.60 \times 10^{-12}$)
- Ipsilateral putamen ($d = -0.47; P = 4.94 \times 10^{-4}$)
- Ipsilateral pallidum ($d = -0.451; P = 3.96 \times 10^{-7}$)
- Bilateral lat. ventricles ($d \geq 0.39; P = 1.52 \times 10^{-5}$)

(D) GGE:
- Right thalamus ($d = -0.403; P = 3.62 \times 10^{-6}$)
- Right pallidum ($d = -0.35; P = 3.37 \times 10^{-4}$)
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≤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≤1.44x10^{-9}),
- superior frontal gyri (d≤0.365; P≤3.33x10^{-6}).

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=3.13x10^{-6}),
- contra precuneus (d=0.472; P=5.16x10^{-6}),
- contra pars triangularis (d=0.285; P=2.16x10^{-6}).

(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=1.5x10^{-4}),
- contra. superior frontal gyrus (d=0.355; P=1.5x10^{-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})

UNILATERAL changes in:

- ipsi. lateral occipital gyrus (d=0.366; P=1.79x10^{-4}),
- ipsi. pars opercularis (d=0.271; P=1.5x10^{-4}),
- contra. superior frontal gyrus (d=0.355; P=1.5x10^{-4}),
- contra. transverse temporal gyrus (d=0.312; P=2.15x10^{-5}).
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.
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
CONCLUSIONS

- 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.

**ENIGMA-EPILEPSY**
THANK YOU!

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