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

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. Ioannidis³, Claire Mokrysz¹, Brian A. Nosek⁴, Jonathan Flint⁵, Emma S. J. Robinson⁶ and Marcus R. Munafo¹

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

estimates of Cluster failure: Why fMRI inferences for spatial extent to this have inflated false-positive rates

ibility in en ianored

Anders Eklund^{a,b,c,1}, Thomas E. Nichols^{d,e}, and Hans Knutsson^{a,c}

"Division of Medical Informatics, Department of Biomedical Engineering, Linköping University, S-581 85 Linköping, Sweden; "Division of Statistics and Machine Learning, Department of Computer and Information Science, Linköping University, S-581 83 Linköping, Sweden: Center for Medical Image Science and Visualization, Linköping University, 5-581 83 Linköping, Sweden: "Department of Statistics, University of Warwick, Coventry CV4 7AL, United Kingdom; and "WMG, University of Warwick, Coventry CV4 7AL, United Kingdom

s or both) neganally statistically ie effect. We dis-

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 (FWE), the chance of one or more false positives, and empirically and a total of 2 million random task group analyzes to empirical

(fMRI) analyses use parametric statistical methods that depend on a measure the FWE as the proportion of analyses that give rise to variety of assumptions. In this work, we use real resting-state data any significant results. Here, we consider both two-sample and

FSL, and "...the most common software packages... (SPM, FSL, nominal methods and inva AFNI)... can result in false-positive rates of up to 70%" principal lation fu

comparison, the nonparametric permutation test is round 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

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 onesample t tests. We explore why the methods fail to appropriately control the false-positive risk.



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

3,876 MRI scans

21 research centers .

KCL

Molecular Psychiatry (2015), 1-7

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ondon

14 countries

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50+ scientists

Formed: March 2015 Royal Society, London

International League Against Epilepsy **Consortium on Complex Epilepsies Meeting**

Identification of common variants associated with human hippocampal and intracranial volumes

Identifying genetic variants influencing human brain structures may reveal new biological mechanisms underlying cognition and neuropsychiatric illness. The volume of the hippocampus is a biomarker of incipient Alzheimer's disease^{1,2} and is reduced in schizophrenia3, major depression4 and mesial temporal lobe epilepsy⁵. Whereas many brain imaging phenotypes are highly heritable^{6,7}, identifying and replicating genetic influences has been difficult, as small effects and the high costs of magnetic resonance imaging (MRI) have led to underpowered studies Here we report genome-wide association meta-analyses and replication for mean bilateral hippocampal, total brain and intracranial volumes from a large multinational consortium. The intergenic variant rs7294919 was associated with hippocampal volume (12q24.22; N = 21,151; P = 6.70 × 10⁻¹⁶) and the expression levels of the positional candidate gene TESC in brain tissue, Additionally, rs10784502, located within HMGA2, was associated with intracranial volume (12q14.3; $N = 15,782; P = 1.12 \times 10^{-12}$). We also identified a suggestive association with total brain volume at rs10494373 within DDR2 (1g23.3: N = 6.500: P = 5.81 × 10⁻⁷).

LETTERS

LETTER

Common genetic variants influence human subcortical brain structures

A list of authors and their affiliations appears at the OPEN

The highly complex structure of the human brain is stro by genetic influences'. Subcortical brain regions form c cortical areas to coordinate movement², learning, m motivation⁴, and altered circuits can lead to abnorma and disease². To investigate how common genetic variar structure of these brain regions, here we conduct genom

clation studies of the volume of seven subcortical regi intracranial volume derived from magnetic resonant 30,717 individuals from 50 cohorts. We identify five n variants influencing the volumes of the putamen and cauce with schizophrenia and 25. Verlados find stronger evidence for three loci with previ lished influences on hippocampal volume' and intracran ENIGMA consortium Inser uniants show specific volumetric effects on brain rather than global effects across structures. The strongest TGM van Erp^{1,39}, DP Hibar^{2,39}, JM Rasmussen³, DC Glahr

rahler fangehal effekt annes internies. The dronget ToMA van Ep⁻¹⁷, OP Hisher³⁴, Mithael¹⁴, Mithael¹⁴

development, and may help to determine mechanism chiatric dysfunction.

At the individual level, genetic variations evert lasting is



ORIGINAL ARTICLE

doi:10.1038/asture14101

Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder

BONN

Ronn German

The profile of brain structural abnormalities in schizoph working group scans. To validate a prospective meta-analysis approach

L Schmaal¹, DJ Veltman¹, TGM van Erp², PG Sämann³, T Frodl^{4,5}, N Jahans MW Vernooj^{7,9}, MA Ikram^{7,9,11}, K Wittfeld^{1,2}, HJ Grabe^{12,13,14}, A Block¹³, K J Lagopoulos¹⁷, SN Hatton¹⁷, IB Hickle¹⁷, R Goya-Maldonado¹⁸, B Krämer¹ from 2028 schizophrenia patients and 2540 healthy coidentified subcortical brain volumes that differentiated Compared with healthy controls, patients with schizoph thalamus (d = -0.31), accumbens (d = -0.25) and intrac LT Strike^{19,20,21}, NT Mills^{22,23}, GI de Zubicaray²⁰, KL McMahon²¹, SE Media ventricle volumes (d = 0.37). Putamen and pallidum voli GM MacQueen²⁷, EM Frey⁴, A Carballedo³⁸, LS van Velzen¹, MJ van Tol²⁹ hippocampal deficits scaled with the proportion of unr E Schramm³⁴, C Normann³⁴, D Schoepf³⁵, C Konrad³⁶, B Zurowski³⁷, T Ni JE Sussmann³⁸, BR Godlewska⁴⁰, PJ Cowen⁴⁰, FH Fischer^{41,42}, M Rose^{41,43} ort a profile of subcortical abnormalities in schizor approaches. This first ENIGMA Schizophrenia Working (ENIGMA-Major Depressive Disorder Working Group44 across brain phenotypes and disorders and encourage

> The pattern of structural brain alterations associated with major depressiv small sample sizes of neuroimaging studies resulting in limited statistical p between clinical characteristics and brain morphology. To address this, w resonance imaging data from 1728 MDD patients and 7199 controls from volumes that robustly discriminate MDD patients from healthy controls. hippocampal volumes (Cohen's d = -0.14, % difference = -1.24). This effe d = - 0.17, % difference = - 1.44), and we detected no differences between associated with a smaller hippocampus (Cohen's d = -0.20, % difference d = -0.11, % difference = -1.23) and larger lateral ventricles (Cohen's d= inclusion was not associated with any regional brain volumes. Sample cha users and proportion of remitted patients, and methodological character



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Kiamen, China

ORIGINAL ARTICLE

GREIFSWALD

1ORE

Molecular Psychiatry (2015), 1-7

wald Germany

Subcortical volumetric abnormalities in bipolar disorder

DP Hibar¹, LT Westlye^{2,3}, TGM van Erp⁴, J Rasmussen⁴, CD Leonardo¹, J Faskowitz¹, UK Haukvik^{2,5}, CB Hartberg², NT Doan², I Agartz^{2,5} AM Dale^{6,7}, O Gruber^{8,9}, B Krämer⁸, S Trost⁸, B Liberg¹⁰, C Abé¹¹, CJ Ekman¹⁰, M Ingvar^{11,12,13}, M Landen^{14,15}, SC Fears^{16,17}, NB Freimer¹⁷ CE Bearden^{12/18/9}, the Costa Bica/Colombia Costartium for Genetic Investigation of Bioplar Endonhenotypes, E Spropten²⁵. DC Glahn^{20,21}, GD Pearlson^{20,21,22}, L Emsell²³, J Kenney²³, C Scanlon²³, C McDonald²³, DM Cannon²³, J Almeida²⁴, A Versace²⁵ De claimini, Job Presidovili, J. Cermider, J. Nermiley, J. Scalandini, F. Chuckonaldi, L. Michani, J. Zhinghou, A. Versade, B. X. Caserasi, N. C. Lawrenczi, M. Hallinghi, D. Diametri, J. Schwartz, J. B. Versade, B. S. Schwartz, J. K. Shanghou, J. S. Schwartz, J. K. Shanghou, J. Schwartz, J. K. Shanghou, J. Schwartz, J. K. Shanghou, J. Schwartz, J. Schwartz, J. Bener, J. Schwartz, J. Bener, J. Schwartz, J. Bener, J. Schwartz, J. T Hajek^{40,47}, B Mwangi⁴⁸, JC Soares⁴⁸, T Nickson⁴⁹, R Dimitrova⁴⁹, JE Sussmann⁴⁹, S Hagenaars⁴⁹, HC Whalley⁴⁹, AM McIntosh⁴ PM Thompson^{1,18}, OA Andreassen² for the ENIGMA Bipolar Disorder Working Group

Considerable uncertainty exists about the defining brain changes associated with bipolar disorder (BD). Understanding and quantifying the sources of uncertainty can help generate novel clinical hypotheses about etiology and assist in the development of biomarkers for indexing disease progression and prognosis. Here we were interested in quantifying case-control differences in intracranial volume (ICV) and each of eight subcortical brain measures nucleus accumbens, anwordala, caudate, hippocampus, globus pallidus, putamen, thalamus, lateral ventricles. In a large study of 1710 BD patients and 2594 healthy controls, we found sistent volumetric reductions in BD patients for mean hippocampus (Cohen's d = -0.232; $P = 3.50 \times 10^{-7}$) and thalamus

1H stralia

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 $\gg @$ 🍾 🕕 of genome-wide association studies

International League Against Epilepsy Consortium on Complex Epilepsies*

Summarv

Background The epilepsies are a clinically heterogeneous group of neurological disorders. Despite strong evidence for Lancet Neurol 2014; 13:893-903 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).

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oa



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

ENIGMA

EPILEPSY

ENIGMA EPILEPSY

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

Cohen's

C. Temporal lobe epilepsy with right MTS

B. Temporal lobe epilepsy with left MTS

D. Genetic generalized epilepsies

ENIGMA EPILEPSY

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≤1.29x10-3),
- 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)

(C) TLE-MTS-R:

Α

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)

C. Temporal lobe epilepsy with right MTS

Cohen's D

Cohen's D

Left Medial

Cohen's D

D. Genetic generalized epilepsies

ENIGMA EPILEPSY 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.

ENIGMA 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

BERN BONN BRI BRUSSELS EKUT_A EPIGEN EPIGEN_1.5T IDIBAPS KCL_CNS MNI NYU RMH UCSD		$\begin{array}{c} -2.19 \left[-2.95 \right] , -1.42 \left] \\ -1.71 \left[-2.09 \right] , -1.33 \right] \\ -3.42 \left[-4.20 \right] , -2.64 \right] \\ -3.42 \left[-4.20 \right] , -2.64 \right] \\ -2.97 \\ -1.41 \left[-2.97 \right] , -1.41 \right] \\ -0.76 \left[-1.62 \right] , -0.98 \right] \\ -2.25 \left[-3.06 \right] , -1.43 \right] \\ -1.51 \left[-2.04 \right] , -0.98 \right] \\ -2.25 \left[-3.06 \right] , -1.43 \right] \\ -1.57 \left[-2.11 \right] , -1.03 \\ -2.56 \left[-3.26 \right] , -1.88 \right] \\ -1.37 \left[-2.28 \right] , -0.0 \\ -0.28 \left[-0.70 \right] , 0.13 \\ -2.40 \left[-3.22 \right] , -1.58 \\ -1.06 \left[-1.65 \right] , -0.46 \right] \\ -2.05 \left[-2.79 \right] , -1.31 \right] \end{array}$
UCSD UNAM		-2.05 [-2.79, -1.31] -0.93 [-1.66, -0.20] -2.31 [-2.66, -0.20]
XMU		-1.06 [-1.78 , -0.35]
RE Model	+	-1.73 [-2.10 , -1.35]
	-5.00 -3.00 -1.00 1.0	0
	Ubserved Outcome	

Thalamus (right) • GGE

BERN		-0.16[-0.77.0.45
BRI	—	-0.80[-1.300.29]
BRUSSELS		0.06 [-0.70 , 0.81
CUBRIC		0.10[-0.31, 0.51]
EKUT_A		-0.86[-1.79, 0.08]
EKUT_B		-0.17 [-0.84 , 0.51]
FLORENCE	·	-1.33 [-2.44 , -0.22]
KUOPIO		-0.16 [-0.57 , 0.24]
KCL_CNS		-0.57 [-0.97 , -0.17]
GER_HGW		-0.60 [-0.98 , -0.23]
NYU	H	-0.21 [-0.60 , 0.18]
RMH		-0.15[-0.69, 0.39]
UNICAMP		-0.74 [-1.07 , -0.41]
UNIMORE		-0.54 [-1.01 , -0.07]
XMU	·•	-0.47 [-1.29 , 0.34]
RE Model	•	-0.40 [-0.57 , -0.23]
	-3.00 -2.00 -1.00 0.00 1.00	
	Observed Outcome	

Precentral gyrus (right) • All epilepsies

THANK YOU!

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Maria C Covorino