The genetics of brain structure and function

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Brisbane

(edits Sarah Medland)
Pathways from gene to disease

Franke et al., Hum. Genet. 2009
Heritability of brain structure and function and its relation to cognition

QLD Twin Imaging Study (QTIMS)

Australia
Greig de Zubicaray (UQ)
Nick Martin (QIMR)
Katie McMahon (UQ)
Margie Wright (QIMR)

USA
Paul Thompson (UCLA)
Arthur Toga (UCLA)
Xavier Castellanos (NYU)
Mike Millham (NYU)

Supported by NIH (2007-2012) and NHMRC (2008-2013)
Data Acquisition

4 Tesla MRI scanner
Wesley Hospital
Brisbane, Australia

Structural MRI
Functional MRI (fMRI) - n-back working memory task; resting state
Diffusion Tensor Imaging (DTI)
Sample

- 1089 twins/sibs from 611 families (tested 2007-12)
  - Aged 18-30yrs; 62% females; all right handed
  - Includes 401 complete twin pairs (173 MZ, 227 DZ)
  - And 287 single twins/ non-twin siblings
  - 80 twins/sibs were retested ~3 months later
  - Most participated in the cognition study at age 16y
  - All GW genotyped(Illumina 610k/core+exome 720k)

- Plus 156 younger twins
  - 36 pairs at age 12 years
  - 42 pairs at age 16 years
Cognitive Battery:

- Extensive battery of cognitive tests at 16 yrs
- 3.5 hr in-person assessment
- Short battery of cognitive tests at MRI if no cognitive testing available at 16 yrs

Psychometric IQ
- Full-scale IQ (MAB)
- Verbal ability (info, arith, vocab)
- Performance ability (spatial, obj ass)
- WAIS digit span/symb, LNS, matrix

Processing speed
- Inspection time
- Reaction time
- N200 latency
- P300 latency

Working memory (DRT, nBack)
- Performance accuracy
- P300 amplitude
- Slow wave amplitude

Relational Complexity
- N-term, Latin square, Sentence

Psychophysiological
- alpha frequency
- EEG power
- EEG coherence

Academic achievement
- Queensland Core Skills

Reading
- NART
- Schonell
- CORE reading and spelling
Genetics of brain structure
ACE Model for twin data

$P_{T1}$ $A$ $C$ $E$

$MZA=1.0 / DZA=0.5$

$P_{T2}$ $A$ $C$ $E$

e e c a a c e
For neuroimaging phenotypes we can fit the ACE model to every voxel – up to 2M. Very computer intensive!
MZ twins show greater resemblance in morphometry than DZ twins

Heritability:-
- 20% in white matter
- 75% in subcortical structures (corpus callosum, ventricles)
- 20–40% in basal ganglia, thalamus
- 50% occipital lobes
- voxelwise maps define a more detailed spatial pattern for the different influences

Neuroimage 48:37-49, 2009
3D profile of genetic influences on the hippocampus

- 81 MZ & 44 DZ twin pairs
- maps show hotspots of genetic influence
- substantial variance due to unique environment - hippocampus is highly plastic, adapting in response to individual experiences
- confirms previous studies - $h^2$ of hippocampal vol. ~40-69%

Heritability of cortical thickness (CT)

• Research has shown that patterns of cortical thinning is associated with diseases such as schizophrenia, bipolar, depression, and Alzheimer’s.

• In this study, we estimated the heritability of cortical thickness from 28 regions of interest (ROIs).

• Genome-wide association (GWA) scans were performed on each ROI in order to identify variants associated with the thickness of the cortex.
Voxel-by-voxel CT brain map for one individual
28 ROIs
Variance components estimates on CT

- Genetic component
- Common environment
- Unique environment

[Diagram showing variance components for different brain regions with percentages for each component.]
Heritability ranges by lobe

- Frontal: 24%-62%
- Parietal: 52%-61%
- Temporal: 0%-73%
- Occipital: 38%-69%
- Limbic/Insular: 0%-26%
Variance Decomposition of MRI-Based Covariance Maps Using Genetically-Informative Samples and Structural Equation Modeling

Genetics of brain connectivity
Challenges in Neuro Imaging Genetics

• Scope and scale of studies
  – Small N & candidate approaches

• Strong hypotheses re effect sizes
  – Common variants with large effects...

• Data harmonization

• Multiple testing
Neural correlates of interspecies perspective taking in the post-mortem Atlantic Salmon: An argument for multiple comparisons correction

Craig M. Bennett¹, Abigail A. Baird², Michael B. Miller¹, and George L. Wolford³

¹ Psychology Department, University of California Santa Barbara, Santa Barbara, CA; ² Department of Psychology, Vassar College, Poughkeepsie, NY; ³ Department of Psychological & Brain Sciences, Dartmouth College, Hanover, NH

Journal of Serendipitous and Unexpected Results

Neural Correlates of Interspecies Perspective Taking in the Post-Mortem Atlantic Salmon: An Argument For Proper Multiple Comparisons Correction

Craig M. Bennett¹, Abigail A. Baird², Michael B. Miller¹ and George L. Wolford³

Subject. One mature Atlantic Salmon (Salmo salar) participated in the fMRI study. The salmon was approximately 18 inches long, weighed 3.8 lbs, and was not alive at the time of scanning.

Task. The task administered to the salmon involved completing an open-ended mentalizing task. The salmon was shown a series of photographs depicting human individuals in social situations with a specified emotional valence. The salmon was asked to determine what emotion the individual in the photo must have been experiencing.

NEUROSCIENCE PRIZE: Craig Bennett, Abigail Baird, Michael Miller, and George Wolford [USA], for demonstrating that brain researchers, by using complicated instruments and simple statistics, can see meaningful brain activity anywhere — even in a dead salmon.


ATTENDING THE CEREMONY: Craig Bennett, Abigail Baird, Michael Miller, and George Wolford
White matter integrity
DTI - diffusion tensor images

i) 30 gradient directions (27 high b values and 3 b=0 repetitions)

ii) 105 gradient directions (94 high b-values and 11 b=0 repetitions)

**Fractional Anisotropy (FA)** = White Matter integrity
FA=0 – isotropic - in areas where water diffuses freely
FA=1 – anisotropic - in highly myelinated WM fibres
Genetic Influences on White Matter Integrity (FA)

- genetic factors explain 75 - 90% of the variance in FA in almost all white matter regions. *Chiang et al. 2009 J Neurosci. 29: 2212-24*

- splenium & part of CC

- L cerebral peduncle, fornix, R inf. longitudinal fasc. / inf. fronto-occipital fasc.

- Anterior internal capsule & L post. thalamic / optic radiation

- sup. longitudinal fasc.

- sup. & post. corona radiata
White matter integrity correlated with IQ

- correlated with PIQ
- \( r = 0.3 - 0.4 \)

Chiang et al. 2009

*J Neurosci.* 29: 2212-24
Genetic correlation of white matter integrity (FA) with IQ

- Genes (partly) moderate the correlation between fibre integrity and IQ common physiological mechanism

Chiang et al. 2009
J Neurosci. 29: 2212-24
BDNF Val66Met polymorphism effects on white matter

Group 1: 99M /135F (110 fam) age: 23.7±1.9 years.

Group 2: 89M /132F (128 fam) age: 23.7±2.2 years

- Val allele associated with up to 15% reduction in FA in major fiber tracts (splenium of the corpus callosum, left optic radiation)

- replicated in both samples
White matter heritability using diffusion tensor imaging in neonatal brains.

Geng X¹, Prom-Wormley EC, Perez J, Kubarych T, Styner M, Lin W, Neale MC, Gilmore JH.
Genetics of brain function
BOLD fMRI during $n$-back working memory task

**0-Back**

Response: 3 1 4 2 1

**2-Back**

Response: - - 4 2 1
MZ co-twins showing similar brain activation patterns during the N-back task
DZ co-twins showing different brain activation patterns during the N-back task

Twin 1

Twin 2
fMRI during working memory

fMRI study of 315 twins
- 74 MZ pairs (29M/45F)
- 63 DZ pairs (11M /27F /25MF)
- 41 unpaired subjects

- voxel analysis
  Blokland et al. J Neurosci. 2011

- regions of interest analysis
  (N=75 pairs)
  Blokland et al. 2008 Biol. Psychology
• significant genetic influences on WM related brain activation, especially in frontal and parietal brain regions

• genetic influences highest in the parietal lobe (60-70%)

• sizeable unique environmental effects - NOT all measurement error (reliability = 0.7 – 0.9 in most activated areas)
GWAS for neuroimaging phenotypes
GWAS of brain volumes (ADNI sample)

Alzheimer’s Disease Neuroimaging Initiative (ADNI)
- mixed sample of healthy controls, MCI, AD

N = 742 (temporal)
N = 698 (hippo)

610K Illumina SNP

Genome –wide evidence or support - chrm. 12

Lower temporal lobe vols were most assoc. with a common variant in GRIN2B.

Risk allele over-represented in AD and MCI vs elderly controls

Stein et al. Neuroimage, 2010
Enhancing Neuroimaging Genetics through Meta-Analysis
ENIGMA

• Drawing together groups conducting brain imaging studies
  • both patient and population samples
  • with MRI, DTI, fMRI, and ASL
  • with or collecting GWAS data
• Predominantly imaging groups moving into genetics
Meta not Mega analysis

• 3 main reasons (in order of increasing importance)
  • Cultural Barriers
  • Practical constraints
    • Size of data
    • Processing time
  • Scientific obstacles
    • Insurmountable phenotypic heterogeneity?
Insurmountable phenotypic heterogeneity

Measurement of MRI scanner performance with the ADNI phantom

Jeffrey L. Gunter, a) Matt A. Bernstein, Brett J. Borowski, Chadwick P. Ward, Paula J. Britson, and Joel P. Feldmane
Mayo Clinic and Foundation, Rochester, Minnesota 55902

Norbert Schuff and Michael Weiner
Department of Veterans Affairs Medical Center and Magnetic Resonance Unit (114M),
University of California, San Francisco, San Francisco, California

Clifford R. Jack
Mayo Clinic and Foundation, Rochester, Minnesota 55902

Med. Phys. 36 (6), June 2009 0094-2405/2009/36(6)/2193/13/$25.00
Fig. 8. Summary of scanner performance for more than 2200 phantom scans. A pooled-variance approach is used to estimate the stability of gradient performance factoring out discrete changes generally due to scanner recalibration. Symbols are plotted at the mean scale value over all values, and error bars indicate the square root of the pooled variance. System number is an arbitrary enumeration. R/L calibration appears less consistent across scanners for vendor 1 than for other vendors. The S/I per scanner error bars for vendor 3 are much larger than for other vendors and other directions. Scanners from vendor 2 are from two different models and the data are clustered by model in the S/I mean scale factors.
Protocols

- **FSL FIRST / FREESURFER**
- **HapMap III**
- **Full sample vs healthy controls only**
First ENIGMA project

Which genes contribute to hippocampus volume (HV) and measures of total brain volume (ICV)?
ENIGMA project: the approach

Genome-wide association to imaging phenotypes using dosage data (accounting for kinship in related samples)

Phenotypes
- Hippocampal Volume
- Brain Volume
- ICV

Covariates
- Brain Volume
- ICV
- Age
- Sex
- Age^2
- Sex*Age
- Sex*Age^2
- 4 MDS components
- Dummy covariates for acquisitions

17 sites uploaded (N=7795)

Quality Checking and Filtering (MAF < 0.01, R^2 < 0.3)

Fixed effects meta-analysis
Random effects meta-analysis

Uploaded to ENIGMA server for analysis at central site

17 sites uploaded (N=5776)

Quality Checking and Filtering (MAF < 0.01, R^2 < 0.3)

Fixed effects meta-analysis
Random effects meta-analysis

MA: sample-size weighted
Custom built QC pipelines
Add the current folder containing all of the required scripts to Matlab's path.

Select: File -> Set Path -> Add Folder -> (OK) -> (Save) -> (Close)

In the Matlab console window change directories to the folder with all of your FSL FIRST data.

cd /enigma/first/data/

Make a directory to store all of the QC output.

mkdir /enigma/first/QC/

The script we want to run is called make_pngFSL.m with the following parameters:

make_pngFSL(output_directory, subject_name, select_segmentations_image, select_ini)

We want to set 'subject_name' such that 'subject_name' + 'select_segmentations_image' is the full name of the registered segmentation label files we just made with flirt (e.g. subj1_brain_first2_all_fast_firstseg_std.nii.gz) and similarly for 'select_ini' image we use the full name of the registered MRI scan output by FIRST (e.g. subj1_brain_to_std.nii.gz).

In Matlab we can do:

a_dir = 'sub'.ni)

% Choose this so that it selects your original subject MRI files
for i = 1:size(a,1)
    [c,b,d] = fileparts(a(i).name);
    % If your original data files are in .nii.gz format you need
    % to remove both extensions
    % Uncomment this next command to do it
    % [c,b,d] = fileparts(b);
    try
        make_pngFSL('/enigma/first/QC/ b, ['/enigma/first/data/, b, 'to_std_sub.nii.gz', [' /enigma/first/data/ b, 'first2_all_fast_firstseg_std.nii.gz']);
    end
    display(['Done with subject: ', num2str(x), ' of ', num2str(size(a,1))])
end
% Note that you may have to change '_to_std_sub.nii.gz'
% or 'first2_all_fast_firstseg_std.nii.gz' if
% Your files are named following a different convention

The make_pngFSL script should take approximately 5 minutes/subject and will output a series of .png image files separated by individual subject folders.
Custom built QC pipelines
Did the consortium approach work?

- All studies underpowered
- Within ‘normals’ no sig results in any individual study
- 206 authors vs effect of 22 underpowered null papers on the literature?
First ENIGMA project: the findings

rs7294919
Hippocampal Volume

rs10784502
Intracranial Volume

N = 21,151; P = 6.70 × 10^{-16}

N = 15,782; P = 1.12 × 10^{-12}
Hippocampal Volume

- Intergenic region 12q24.22
- between *HRK* and *FBXW8*
- Significant within ENIGMA
- Reciprocal replication with the CHARGE consortium
  - \( N=20,797; P=3.43 \times 10^{-16}, MAF = .10 \)
Hippocampal Volume

- Signal present in healthy and patient samples
- Independent of brain or head size
- Variant is associated with decreased HV of 50.6 mm³ or 1.3% of the average hippocampal volume per risk allele.
**Hippocampal Volume**

- *TESC - cis eQTL in brain tissue*
- UCL resected temporal lobe
- SNPExpress
- UK Brain Expression Database
- Fetal Brain Expression
- Adult Brain Expression

- Notably tissue specific eQTLS

- *cis eQTLs for HRK and FBXW8 in blood (PBMC)*
Intracranial Volume

- **HMGA2 12q14.3**
  - rs10784502 intronic SNP near the 3’ UTR
  - high mobility group AT-hook 2 protein
  - chromatin-associated protein that regulates stem-cell renewal
  - role in neural precursor cells
  - Increase of 8637.0 mm$^3$ or 0.56% of ICV per risk allele

- Replication with the CHARGE consortium
  - $N=15,622; \ p=8.50 \times 10^{-12}, \ MAF = .48$
Pleiotropic effects?

- **HMGA2 & rs10784502** previously associated with height
Pleiotropic effects?

- $\text{rs10784502}$ is also associated with $\text{PIQ}$
  - $p=0.0044$

N ‘increasing’ risk alleles

0

1

2
Endophenotypes/Attenuated functional consequences/ Pleiotropy...

- ICV known to correlate with body size and IQ
- Height and IQ correlated $r^2 \sim 4\%$
  - $r^2_G \sim 1.4\%$
Brain regions do not act in isolation: connectivity is essential for proper communication.

ENIGMA-DTI

1. Create a common template
   - 100 healthy adult subjects from each of 4 sites around the world

2. Find mean white matter fiber integrity values in the full brain and 14 standard tracts of interest along the WM skeleton

3. Multi-site heritability analysis
   - Are heritability measures stable and reliable across cohorts in regions
   - If not, then they are not good targets for multi-site GWAS-MA

Jahanshad & Kochunov et al, NIMG 2013
GWAS to be conducted on full brain and 12 regional WM integrity values

- 20+ sites interested
- 8000+ images available

http://enigma.ini.usc.edu/ongoing/dti-working-group/
Prioritize the **most heritable** connections from a comparison of MZ and DZ twins

Carry forward the most heritable connections into a full Genome-Wide Screen (GWAS)…

Jahanshad/Thompson, *PNAS*, March 5 2013
Multi-site heritability analysis

- 5 sites DIFFERENT: **Family structures** (twins/pedigrees) / **Image acquisition** methods / **Age groups** (only children/only elderly/wide range) / **Ethnicities** (European/Mexican-American)

- Compare 2 meta-analysis approaches
  - Weight by N and SE
  - 13/15 regions found to be highly reliable and heritable in all cohorts

Kochunov & Jahanshad et al, submitted
**SPON1** influences regional brain volumes in AD

Ventricular regions, particularly surrounding the temporal lobes, were significantly reduced in size, whereas grey matter around the posterior cingulate cortex was increased with each additional copy of the minor T allele at rs2618516. Older people who carried the connectivity variant had significantly milder dementia scores and risk of AD
Genome-wide scan of healthy human connectome discovers *SPON1* gene variant influencing dementia severity

Neda Jahanshad, Priya Rajagopalan, Xue Hua, Derrek P. Hiber, Talia M. Nir, Arthur W. Toga, Clifford R. Jack
ENIGMA2

- GWASMA of subcortical region volumes - Caudate, Putamen, Pallidum, Thalamus, Accumbens, Amygdala and Hippocampus
- 29,000 brain scans from 47 centres
- Genetics protocols
  - 1000 Genomes imputation – April 2012 release – minus singletons
  - EUR or ALL-Ethnicities versions
Shared and region-specific genetic factors influence subcortical volumes: multivariate variance component analysis of 1090 twins
Genetic patterns of correlation among subcortical volumes in humans: results from a magnetic resonance imaging twin study.

ENIGMA2 preliminary results: Putamen
ENIGMA2 preliminary results: Hippocampus
CHARGE-ENIGMA HV – Manhattan plot

N=25,889; several GW-hits, $p \sim 10^{-10} - 10^{-23}$
CHARGE-ENIGMA ICV – Manhattan plot

N=26,378; several GW-hits, $p \sim 10^{-10} - 10^{-20}$
Putamen association \((KTN1, \text{chr} \; 14; \; p \sim 10^{-20})\) is a cross-species QTL. In BXD mice, the expression of this gene predicts putamen volume \((r = 0.47)\).

(collaboration: Rob Williams lab, UT Memphis)
Phenotypic Meta-Analyses of case control differences in subcortical volumes

- Schizophrenia, Bipolar, Major Depression, ADHD
- Where should we look for endo-phenotypes?
ENIGMA-Schizophrenia Working Group

- N=1,686
- Effect size is greatest for hippocampus, not ventricles (ventricles are too variable)

TROPHIC EFFECT OF ANTIPSYCHOTICS IN BASAL GANGLIA?

Hippocampus

Theo G. M. van Erp*1, Derrek P. Hitar*2, Jerod Rasmussen1, Ole A. Andreassen3, Unn K. Haukvik3,4, Ingrid Agartz3,4, Steven G. Potkin1, Hilleke Hulshoff-Pol5, Roel Ophoff6, Neeltje E. M. van Haren5, Oliver Gruber7, Bernd Krämer7, Stefan Erhlich8,9, Johanna Hase8, Lei Wang10, Kathryn Alpert10, Godfrey D. Pearlson11,12, David Glahn11,12, Paul M. Thompson*2, Jessica A. Turner*11,12, the ENIGMA-Schizophrenia Working Group, SOBP (2013).
ENIGMA-Bipolar Disorder Working Group

Oct 1 2013:
- 1149 BP patients
- 1523 CTLs

October 1, 2013:
- 12 sites participating
- Prelim. results from 4
  - 429 BPD patients
  - 484 CTLs

1. Hippocampus 2% smaller; half the SZ effect (lithium?)
2. <1% difference for other subcortical, unlike SZ
3. Ventricles 16% larger, like SZ

---

The ENIGMA Network and active Working Groups:

ENIGMA-2: Subcortical GWAS-MA
Diffusion Tensor Imaging

Shape Analysis

Schizophrenia

Bipolar Disorder

ADHD 22q11.2

Major Depressive Disorder

Addiction

Obsessive Compulsive Disorder

HIV

Arterial Spin Labeling

The ENIGMA Network with other Consortia:

ENIGMA + PGC

ENIGMA + CHARGE
...and finally, do gene variants affecting neuroimaging phenotypes also affect risk of psychiatric disease?
Alzheimer’s risk gene carriers (CLU-C) have lower fiber integrity even when young (N=398), 50 years before disease typically hits [News covered in 20 countries]

Voxels where CLU allele C (at rs11136000) is associated with lower FA after adjusting for age, sex, and kinship in 398 young adults (68 T/T; 220 C/T; 110 C/C). FDR critical $p = 0.023$. Left hem. on Right

Braskie et al., Journal of Neuroscience, May 4 2011
Some of ENIGMA’s “hippocampal” genes may be Alzheimer’s Disease risk genes

GERAD-ENIGMA-CHARGE

Perhaps you can screen images and find disease risk genes

*Genetic & Environmental Risk in AD Consortium
Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

Cross-Disorder Group of the Psychiatric Genomics Consortium

[Graph showing genetic loci on chromosomes with p-values indicated.]

www.thelancet.com Vol 381 April 20, 2013
Can PGC Cross Disorder GWAS results predict subcortical structure volumes? 

i.e. are the same SNPs that cause psychiatric disease also affecting brain volumes?

**Results**

SNPs in the most strongly associated region in PGC’s cross-disorder mega-analysis (chr3p21.1) also show low P-values for amygdala and pallidum volumes.

<table>
<thead>
<tr>
<th>SNP ID</th>
<th>Chr:Pos</th>
<th>OR</th>
<th>P-values in PGC-CD</th>
<th>Association P-values in QTIM</th>
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</tbody>
</table>

Next step: ENIGMA → PGC: can brain volume SNPs predict psychiatric disease?
Are ‘brain-related’ genes also psychiatric risk genes? If so, we could discover new psychiatric risk genes by screening images, and we’d also know what they do.

**ENIGMA-PGC2-SZ: SNPs affecting hippocampus DO affect SZ risk (p=10^{-165})**

Jason Stein for the ENIGMA-PGC2-SZ Working Group
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