Challenges and Opportunities in Population Neuroimaging

Thomas E. Nichols

Oxford Big Data Institute
Li Ka Shing Centre for Health Information and Discovery
Nuffield Department of Population Health
University of Oxford

Biomedical big data potential

Screening programmes

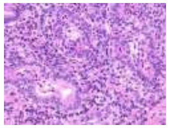
Death registries

Imaging

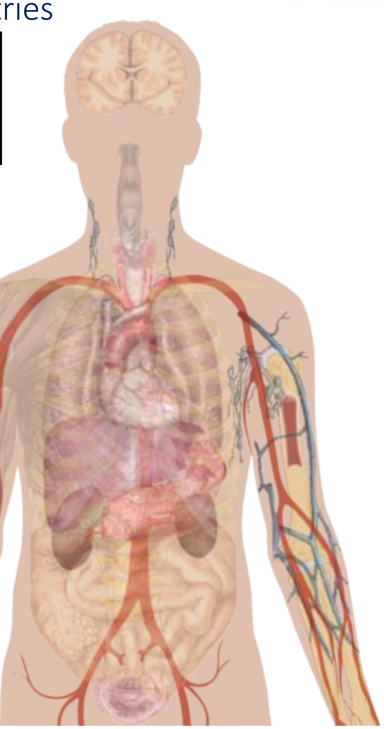
Environmental data

Genetic data

Cancer registries



Pathology records



Hospital records

Employment records

Pharmacy records

Primary care data

Built environment

The Oxford Big Data Institute

Interdisciplinary research institute of 350 researchers working on the acquisition and analysis of population-scale data resources linking detailed biological measurement with longitudinal information on health, treatment and outcome.

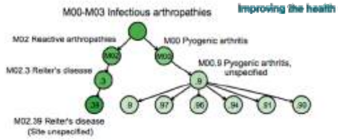
Gil McVean FRS FMedSci Director

Cohorts

UK Biobank
China Kadoorie Biobank
Genomics England 100,000 Genomes
Local partnerships within BRC
Tropical medicine overseas centres

Measurement technologies

Genomics and other 'omics
Neuroimaging
Sensors
Electronic healthcare records
Mobile data



biobank uk
Improving the health of future generations

Integrative analysis methods

Statistics
Epidemiology
Meta-analysis
Machine learning
Software development

Data access and sharing

Consent
Privacy and security
Information governance
Intellectual property
Standards and protocols

http://bdi.ox.ac.uk

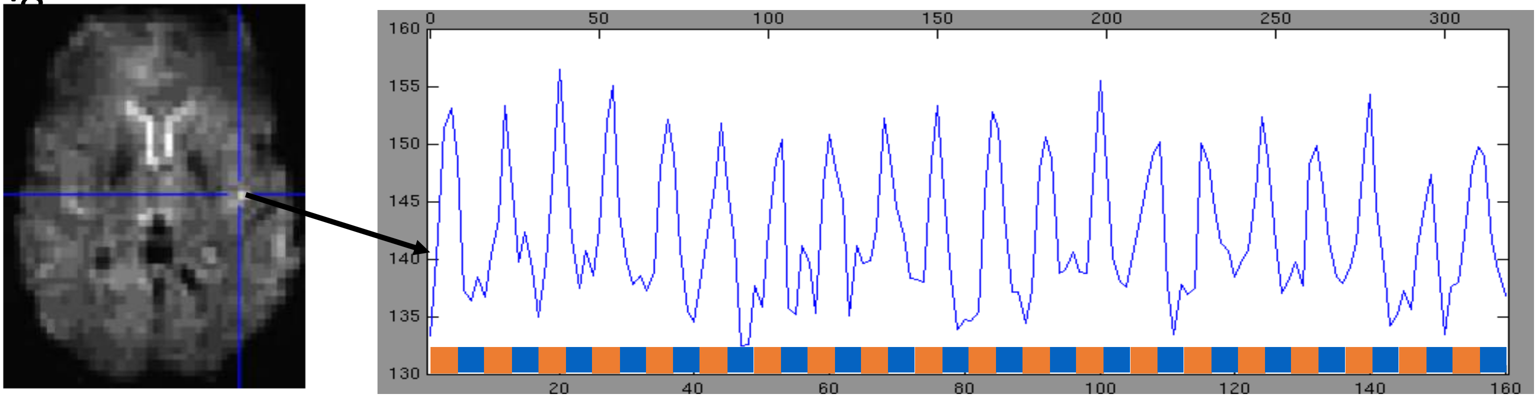
Intro to BOLD fMRI

Blood Oxygenation Level-Dependent Effect
Red blood → Blue blood
Diamagnetic → Paramagnetic

- Finger Tapping

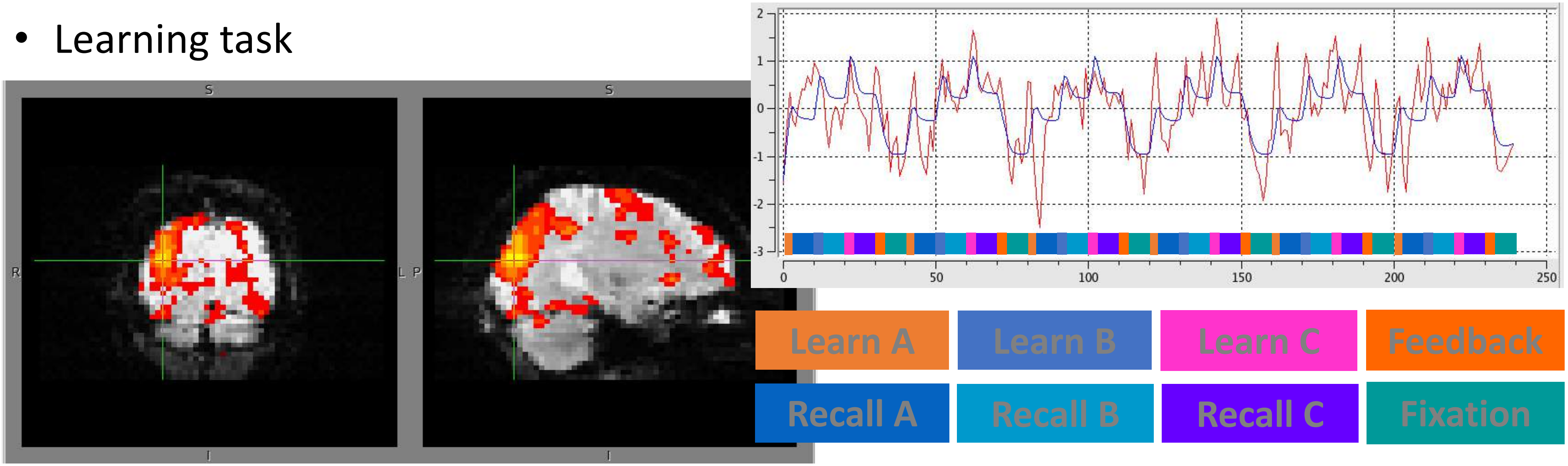
Tap fingers

Rest



Single fMRI Image

- Learning task



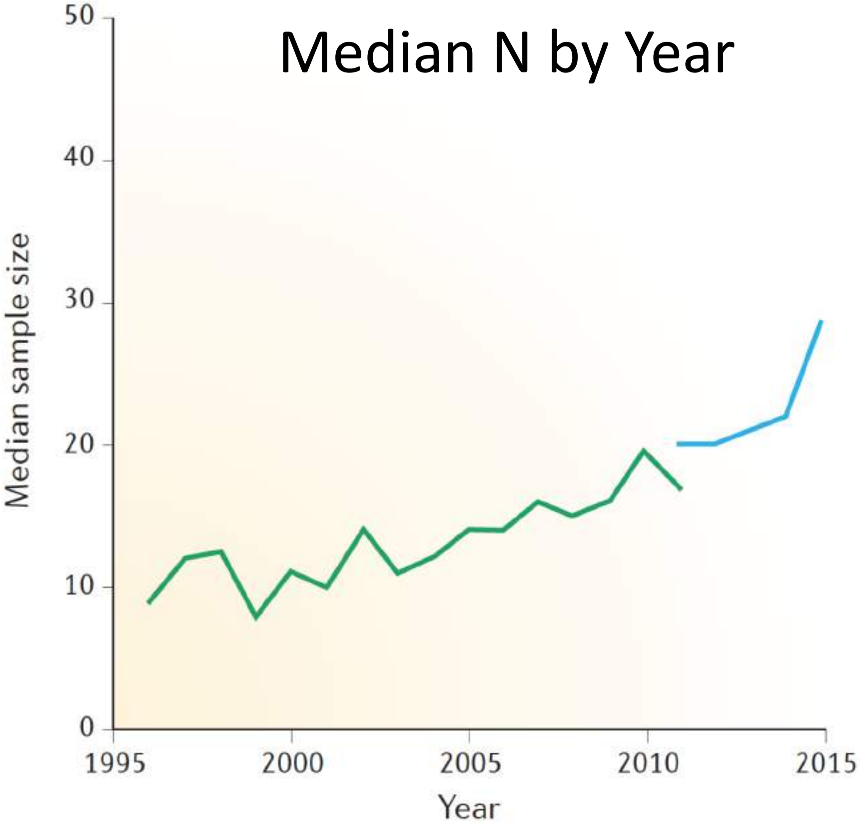
Learn A | Learn B | Learn C | Feedback

Recall A | Recall B | Recall C | Fixation

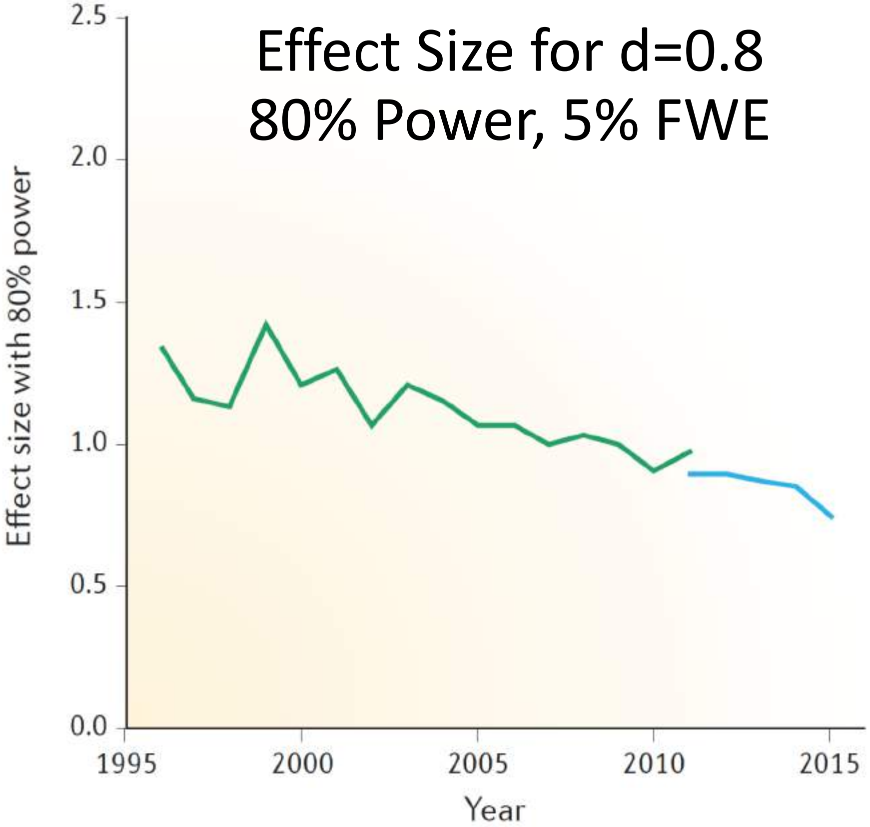
Thresholded T statistic image overlaid on single fMRI image

- Mass Univariate Model:
  Actually, just a simple regression model at each voxel

Neuroimaging: Big Data?



Median N by Year



Effect Size for d=0.8
80% Power, 5% FWE

Typical fMRI sizes break the N=20 barrier only recently

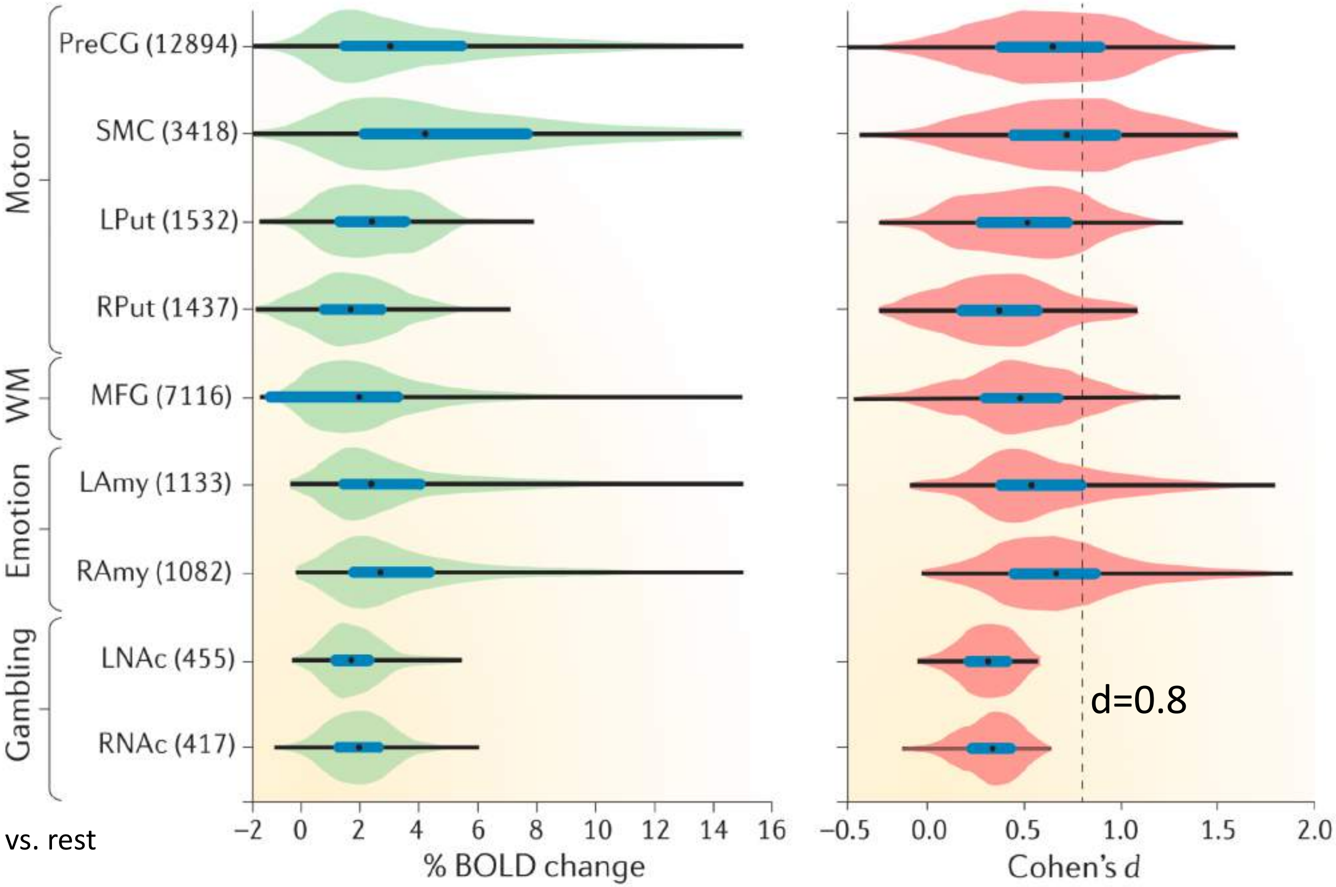
Poldrack, et al. (2017). *Nature Reviews. Neuroscience*.

Neuroimaging: Big Effects?

- Main effects in fMRI strong - designed experiment
- d=0.8 ≈ r^2=13%
- But interest is rather in subtle modulations, r^2<1%
- Big N needed

% BOLD change

Cohen's d

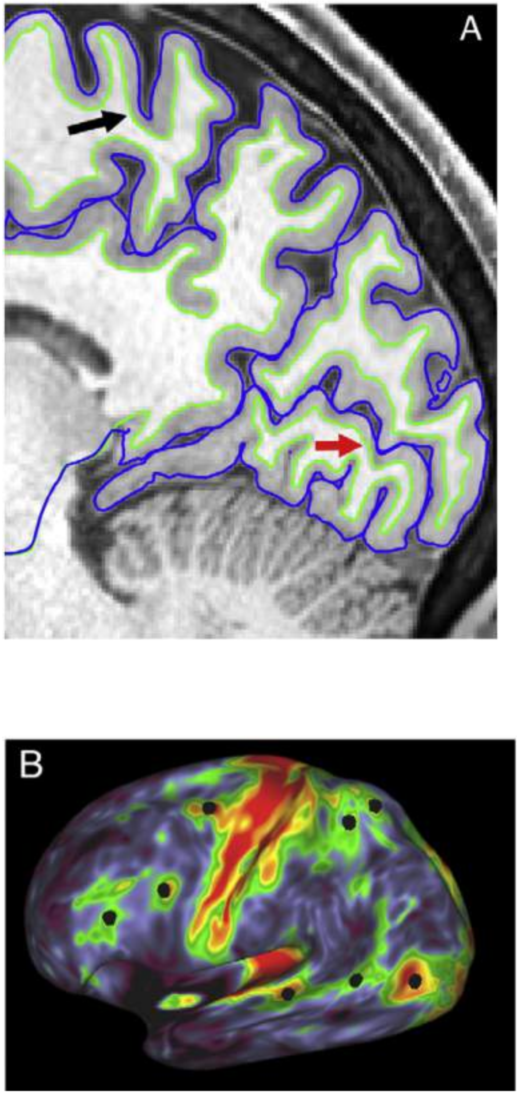


Motor: tongue, hand and foot movements vs. rest
Working memory: '2-back' vs.'0-back'
Emotion: fearful faces vs. neutral faces
Gambling: monetary reward vs. punishment

Poldrack, et al. (2017). *Nature Reviews. Neuroscience*.

Big(ger) Imaging Data:
The Human Connectome Project

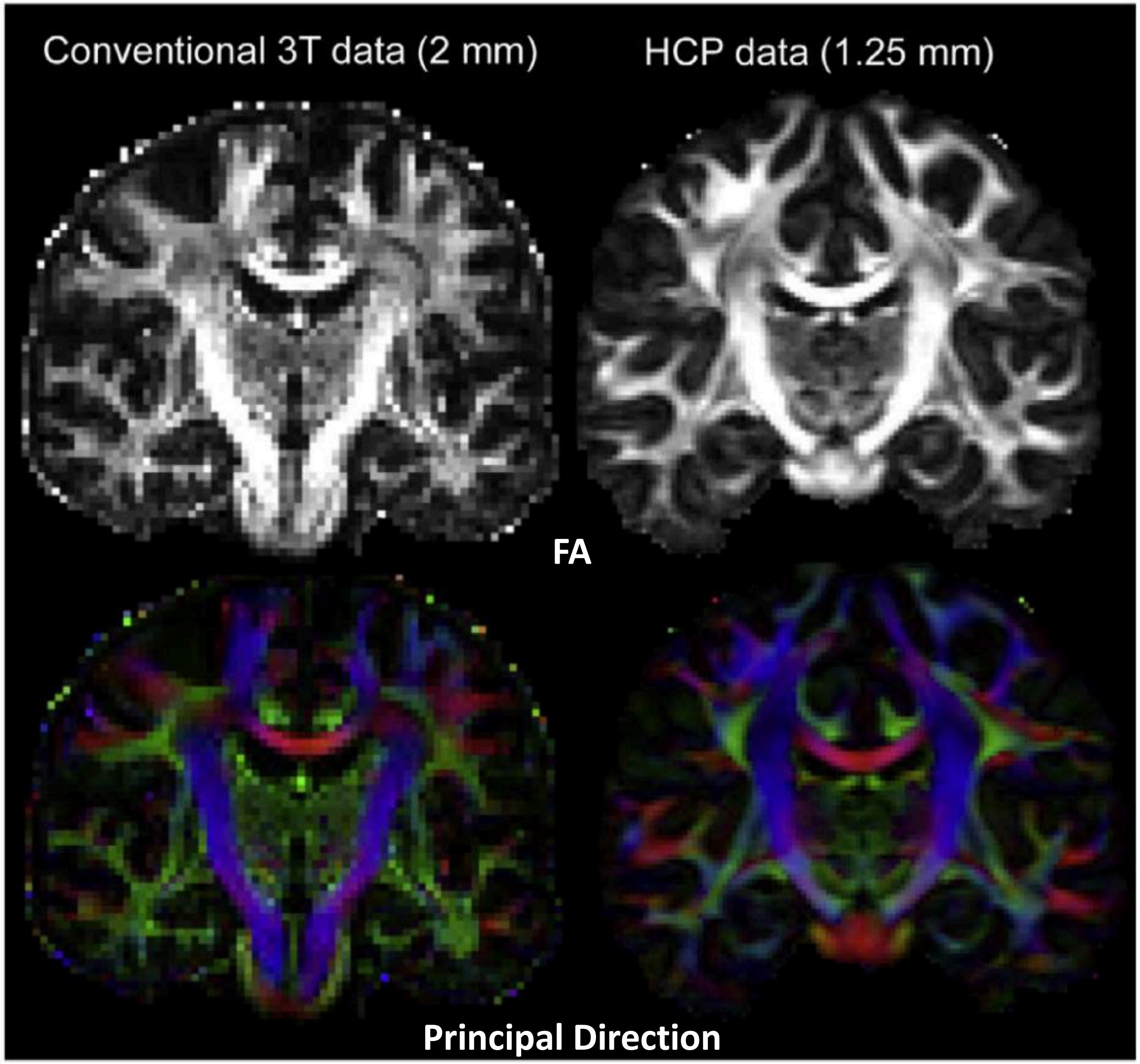
- 1,200 subjects
  - Population sample
  - Subjects drawn from state birth records
  - Twins+siblings design, ≈300 families of ≈4
- Cutting edge MRI
  - fMRI + rs-fMRI + dMRI
- Extensive non-imaging
  - 478 variables on behavior, health, medical history
- All data openly shared
- Allows unprecedented methodological development



Van Essen et al. (2013). The WU-Minn Human Connectome Project:
An overview. *NeuroImage*, 80, 62–79.

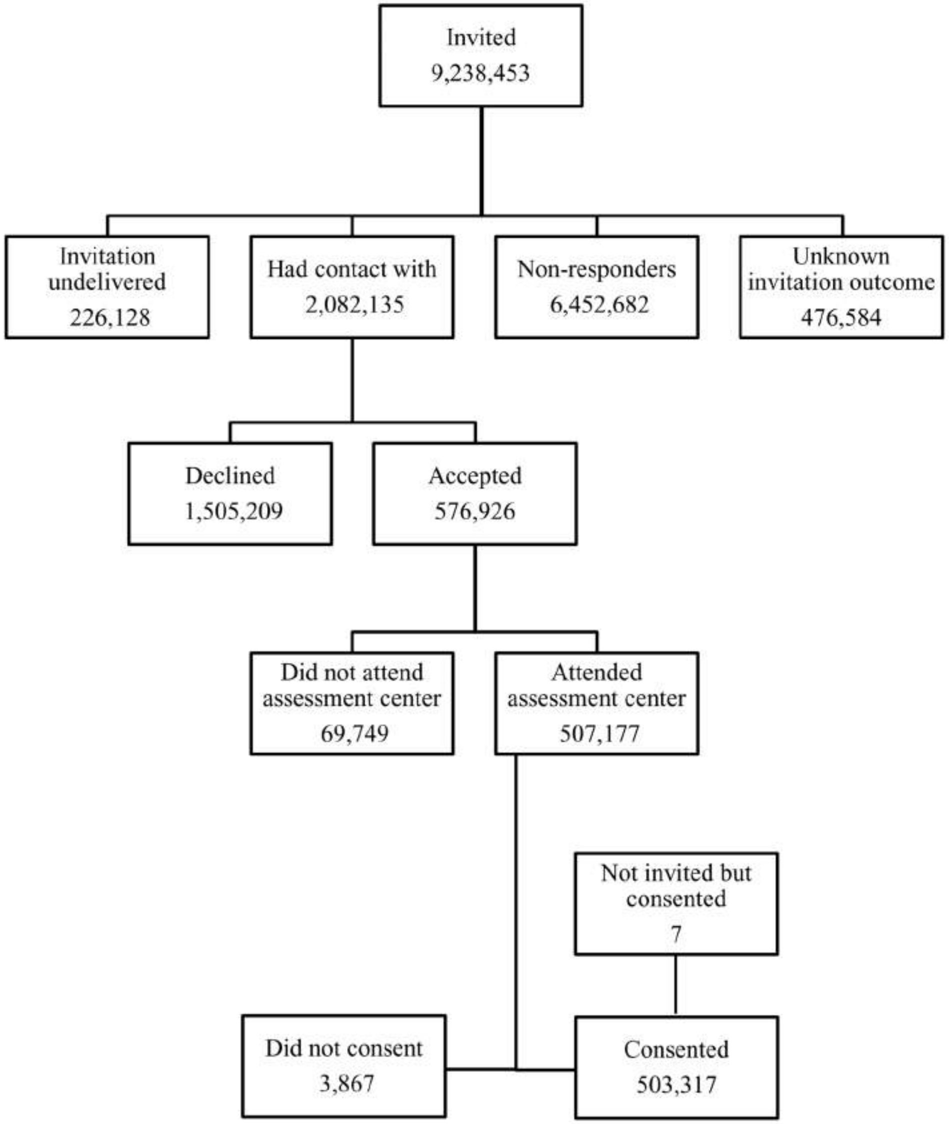
Human Connectome Project

- All data freely available
  - ‘1-click’ authorization
    - All imaging data
    - Coarsened age
    - No sensitive medical history
    - No family structure.
  - With signed authorization
    - All variables



UK Biobank: Sampling Design

- 2006-2010: 9.2 million individuals contacted
  - Drawn from NHS registers
  - Aged 40–69 years
  - Living within 40 km of one of 22 assessment centres in England, Wales, and Scotland
- 503,317 consented & had baseline assessment
  - 5.5% response rate



Fry et al. (2017). *Am. J of Epid*, *186*, 1-9. http://doi.org/10.1093/aje/kwx246

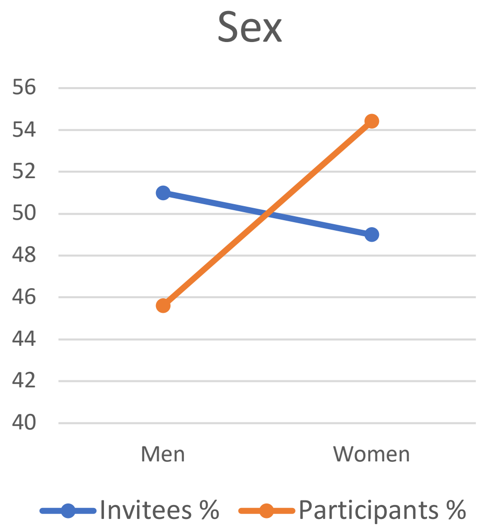
UK Biobank: The Sample

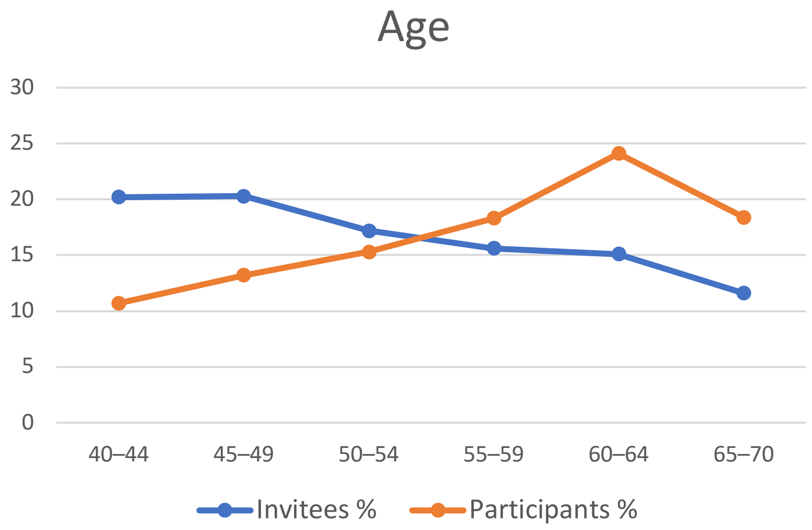
- Basic demographics on 9.2 million
  - For 95% of those contacted (8.8m), have:
    - Sex
    - Birth month & year
    - Townsend deprivation index (socioeconomic status) of the post code of residence
- UK census data also available
- Fry et al. (2017) used this to to assess characteristics of 500k subjects in UKB sample

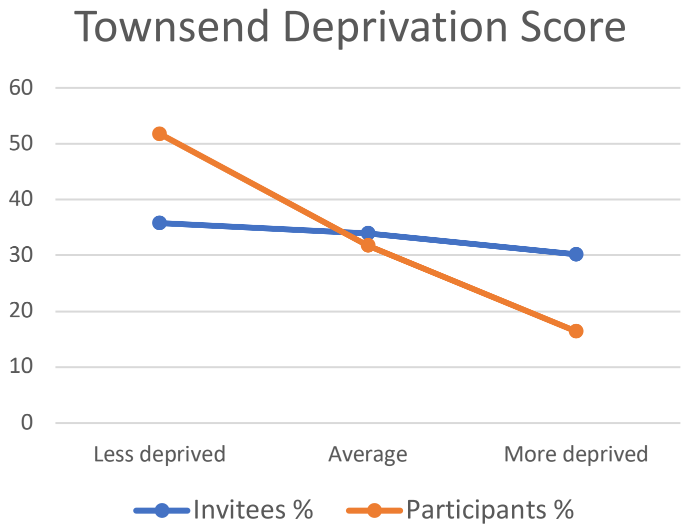
Fry et al. (2017). *Am. J of Epid*, *186*, 1-9. http://doi.org/10.1093/aje/kwx246

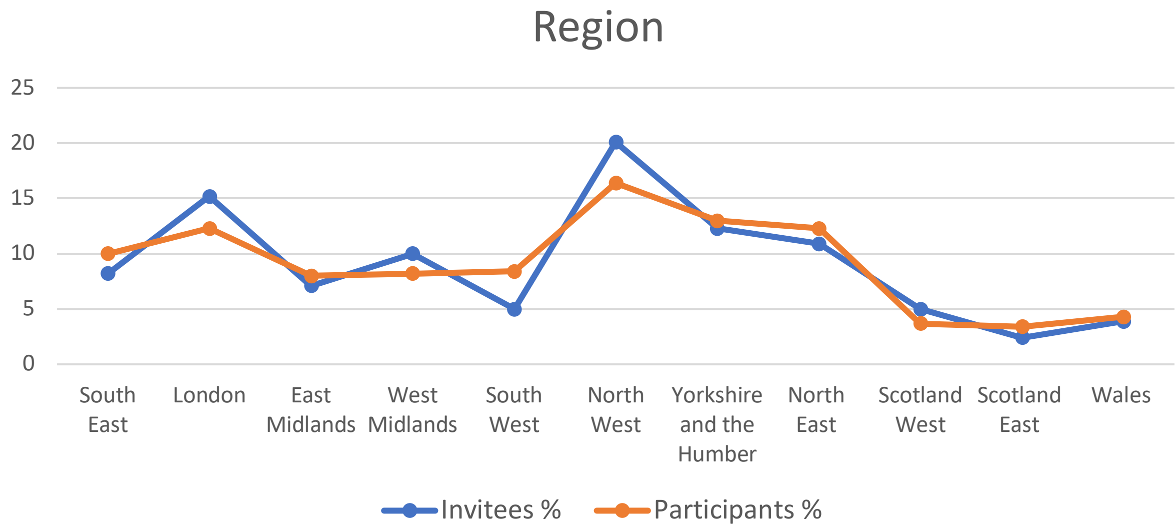
UK Biobank: Response Rates (%)

- UKB Sample: More women, older & better SES than all invitees


Sex


Age

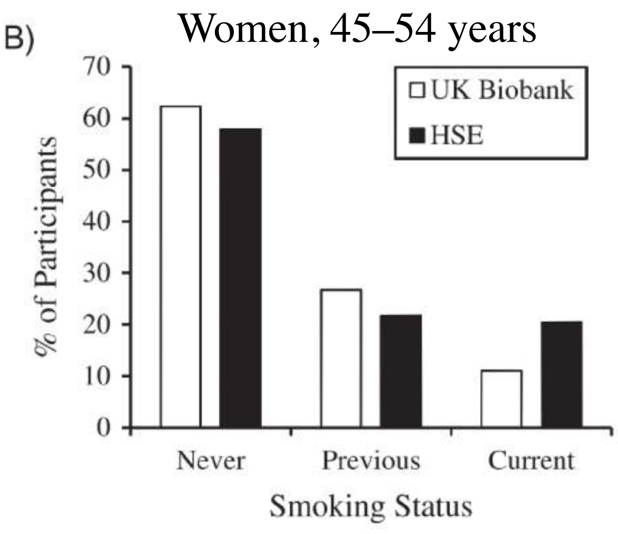

Townsend Deprivation Score


Region

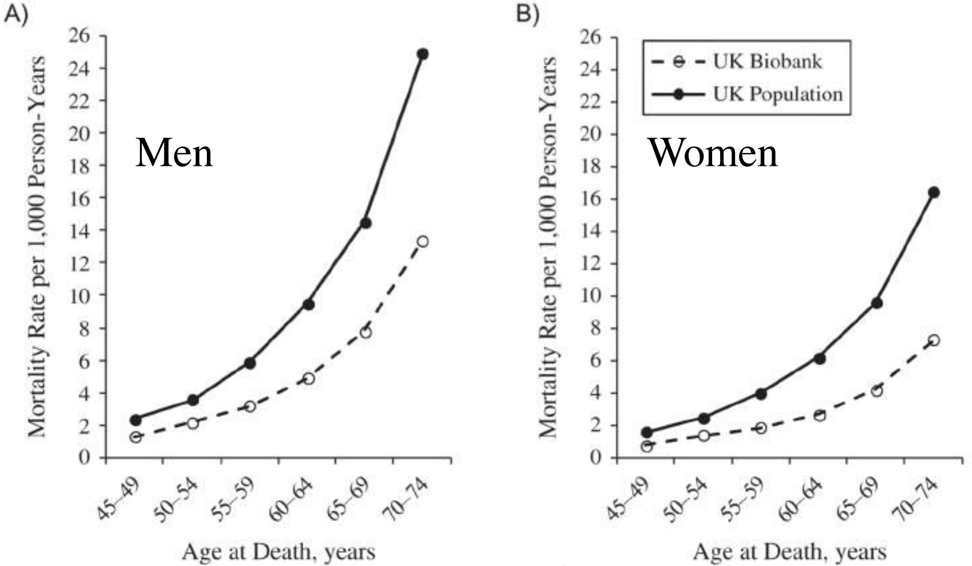
Fry et al. (2017). *Am. J of Epid*, *186*, 1-9. http://doi.org/10.1093/aje/kwx246

UK Biobank: Representitive(ish)

- UKB sample slightly more white, more affluent,
  - **94.6%** white in UKB, vs. **91.3%** in 2011 UK Census
  - **90.6%** own a home in UKB, vs **80.2%** in 2001 UK Census
- UKB sample slightly more healthy
  - Lower disease burden, smokes less than UK population
  - Well-established "healthy volunteer" effect



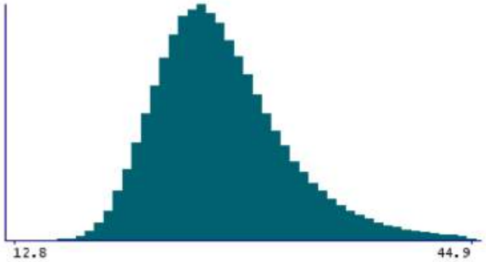
Smoking



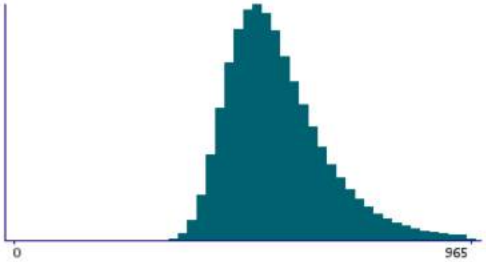
Fry et al. (2017).

Mortality

UK Biobank: 1000+ variables



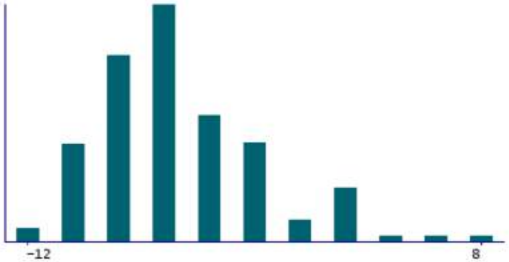
Body Mass Index
(N=492,753)



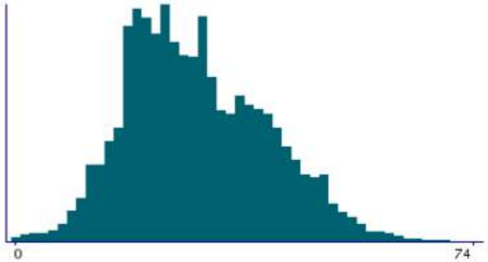
Processing speed (RT)
(N=496,898)

Fluid Intelligence
(N=190,387)

Spirometry, FEV1
(N=353,384)



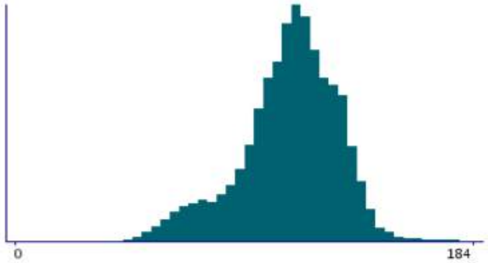
Hearing test, SNR
(N=192,164)



Grip strength
(N=499,305)

Vision, logMAR
(N=132,026)

Systolic BP
(N=473,723)



Max heart rate during fitness test (N=95,138)

http://www.ukbiobank.ac.uk/data-showcase/

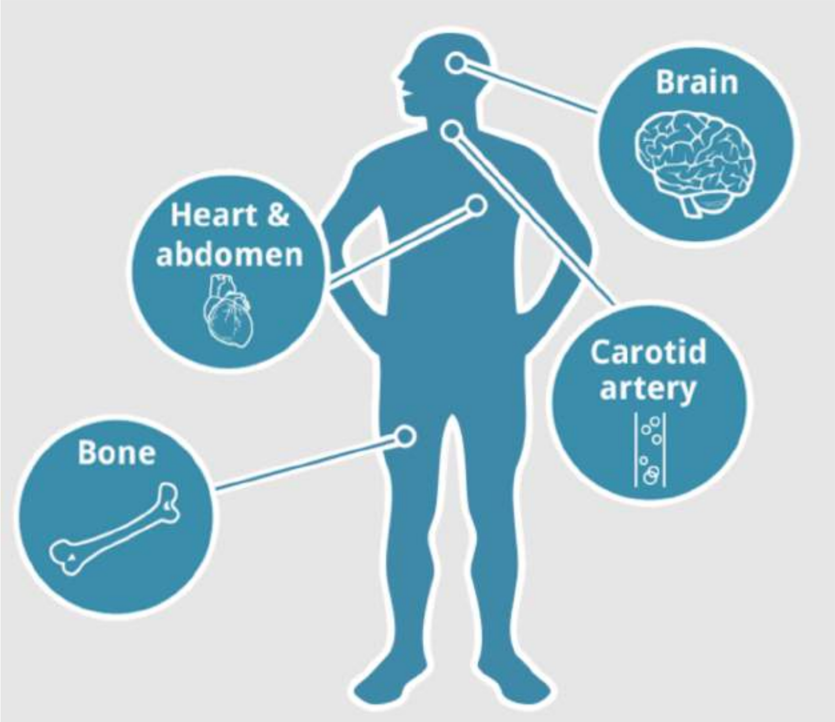
Big Data in UK Biobank

- Genetics
  - Genotyping: 11,734,353 SNPs (all subjects)
  - Sequencing (planned)

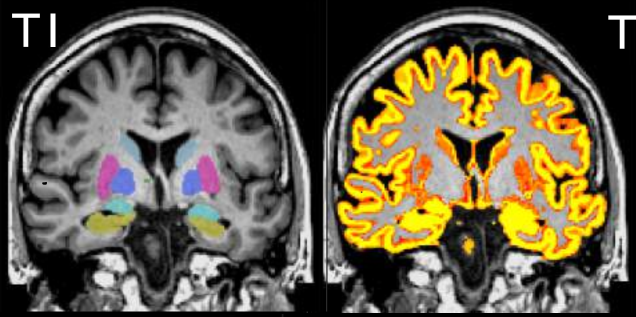
- Imaging
  - 100,000 planned, ~20k so far
  - MRI: T1, T2 FLAIR, SWI, dMRI, rs-fMRI t-fMRI
    - Distilled into 3,144 “Image-Derived Phenotypes” IDP

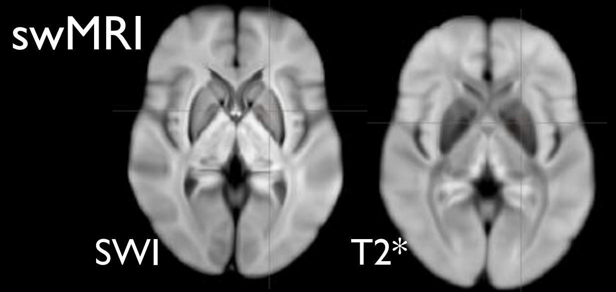
SKIP

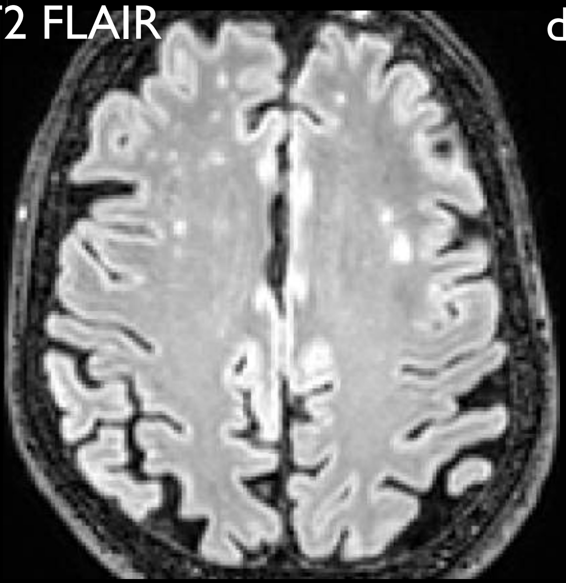
UK Biobank: Imaging Extension

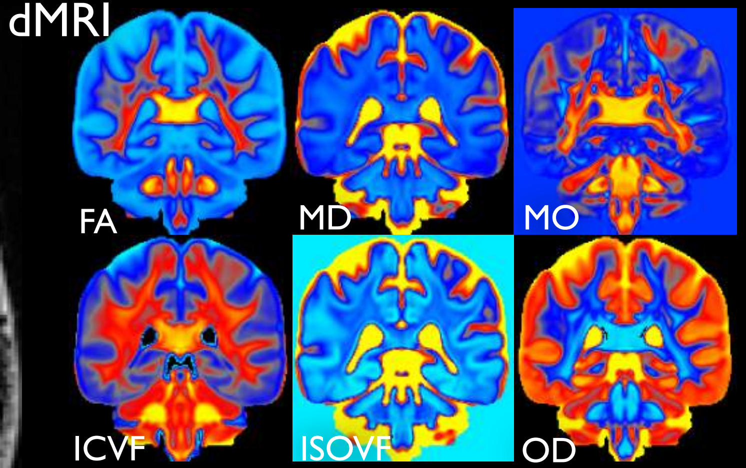


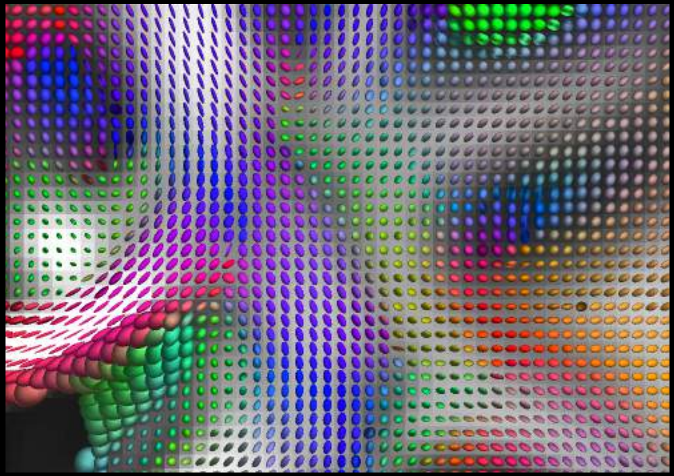
- 2006-2010
  - Baseline assessment of 500,000
- 2014-
  - Imaging of 100,000 UKB subjects
  - Brain MRI, Heart MRI, Carotid ultrasound, Dexa
- Brain MRI
  - T1, T2 FLAIR, T2*, r-fMRI, t-fMRI, dMRI & SWI
  - Customised FSL pipeline by S. Smith, F. Alfaro-Almagro et al.
  - Generates 1000’s of “Image-Derived Phenotypes” (IDPs)

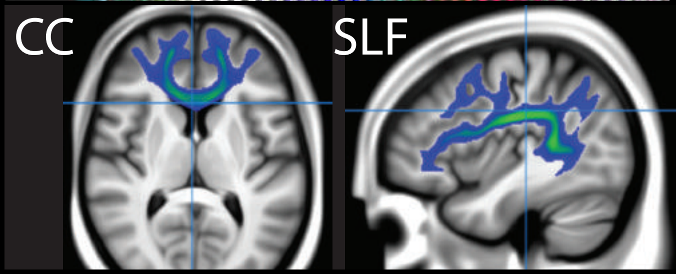


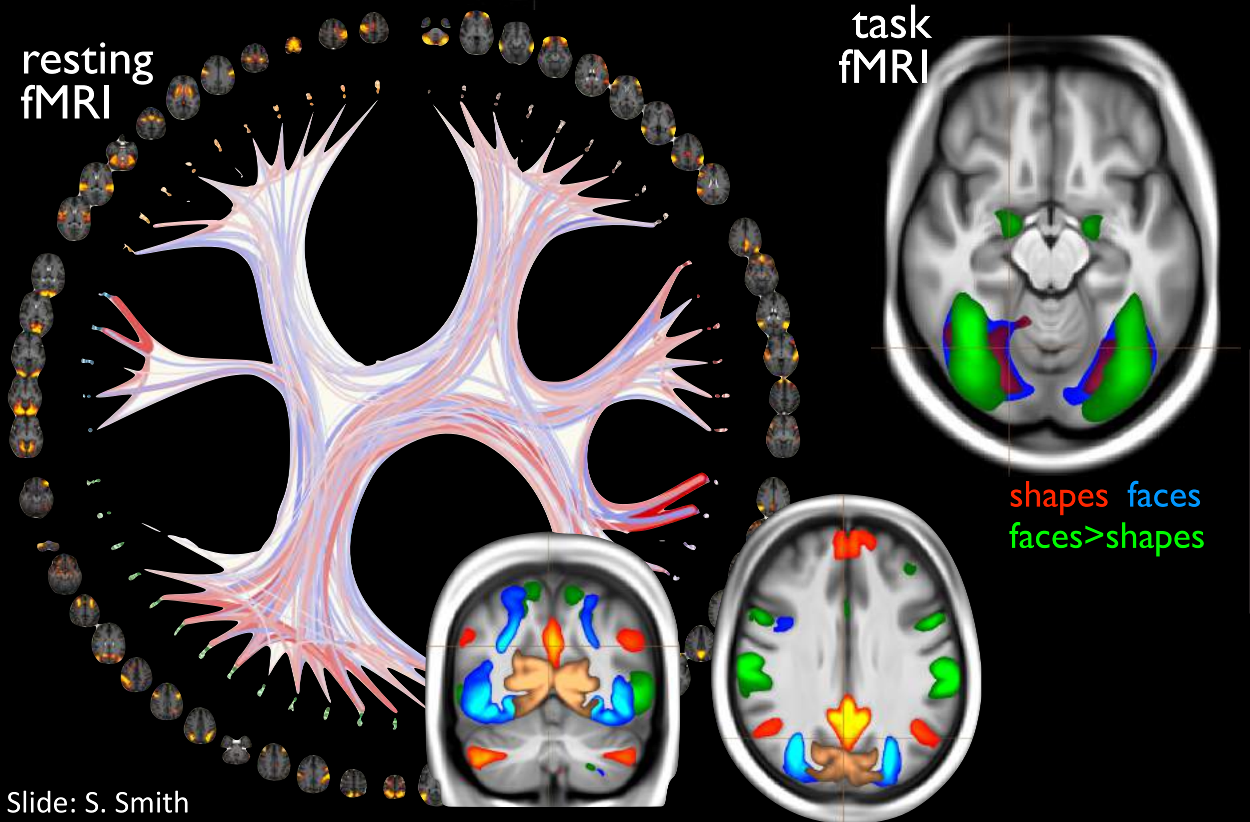










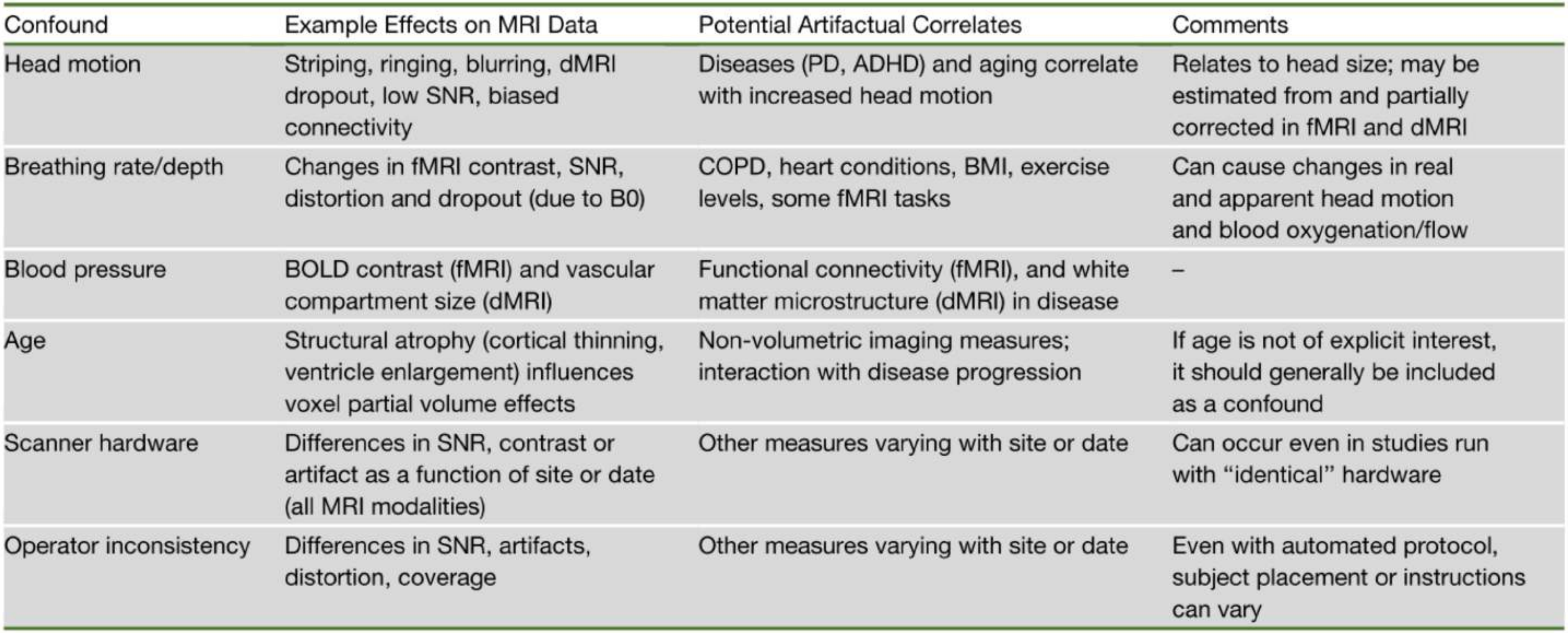


Slide: S. Smith

biobank uk
Imaging study

Concern:
Big Imaging Data Confounds

- Just a few sources of (confound) imaging effects



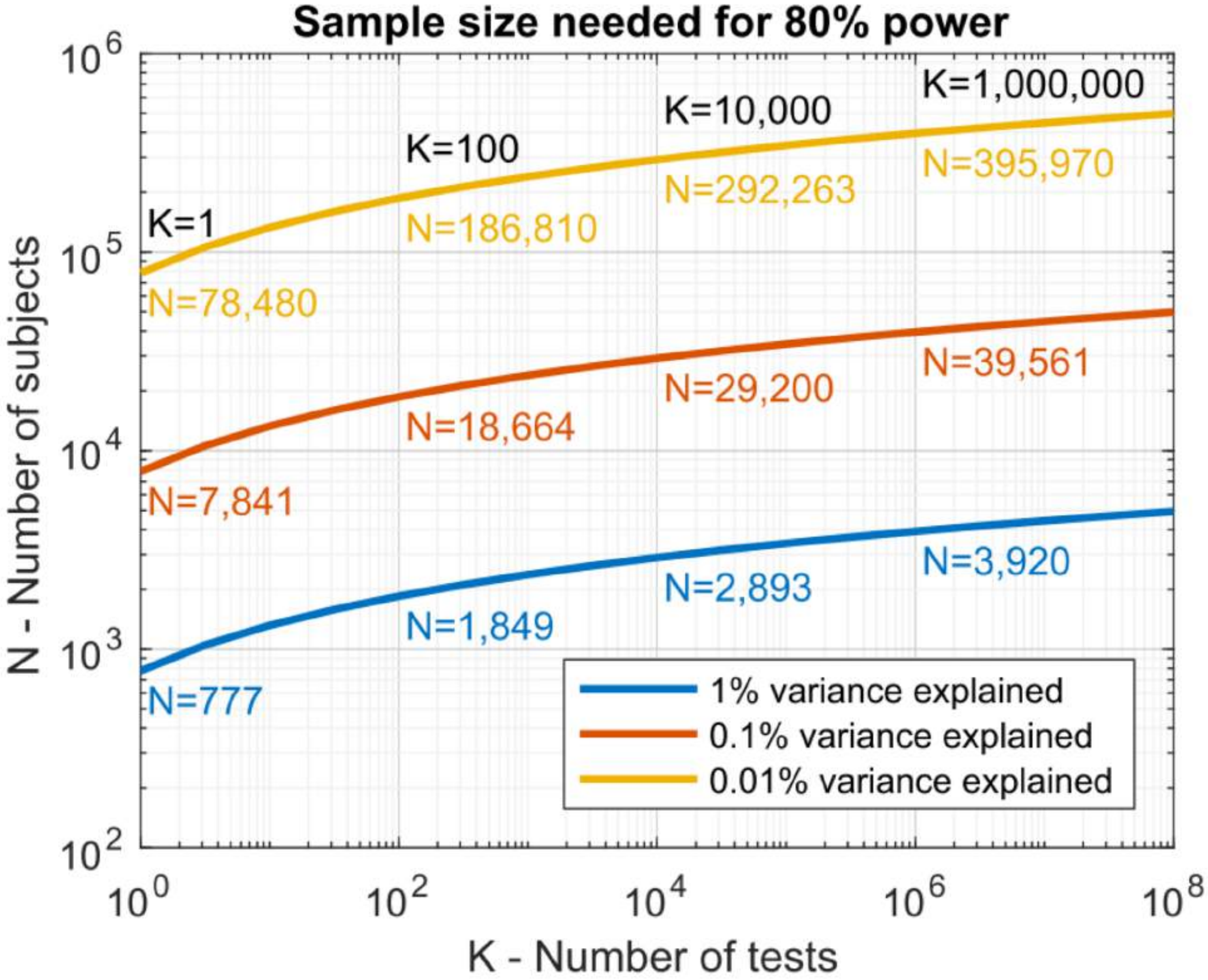
Confound	Example Effects on MRI Data	Potential Artifactual Correlates	Comments
Head motion	Striping, ringing, blurring, dMRI dropout, low SNR, biased connectivity	Diseases (PD, ADHD) and aging correlate with increased head motion	Relates to head size; may be estimated from and partially corrected in fMRI and dMRI
Breathing rate/depth	Changes in fMRI contrast, SNR, distortion and dropout (due to B0)	COPD, heart conditions, BMI, exercise levels, some fMRI tasks	Can cause changes in real and apparent head motion and blood oxygenation/flow
Blood pressure	BOLD contrast (fMRI) and vascular compartment size (dMRI)	Functional connectivity (fMRI), and white matter microstructure (dMRI) in disease	–
Age	Structural atrophy (cortical thinning, ventricle enlargement) influences voxel partial volume effects	Non-volumetric imaging measures; interaction with disease progression	If age is not of explicit interest, it should generally be included as a confound
Scanner hardware	Differences in SNR, contrast or artifact as a function of site or date (all MRI modalities)	Other measures varying with site or date	Can occur even in studies run with “identical” hardware
Operator inconsistency	Differences in SNR, artifacts, distortion, coverage	Other measures varying with site or date	Even with automated protocol, subject placement or instructions can vary

Smith & Nichols (2018). Statistical Challenges in “Big Data” Human Neuroimaging. *Neuron, 97*(2), 263–268.

Non-concern: Big Data Power - N (sample size) beats K (number of tests)

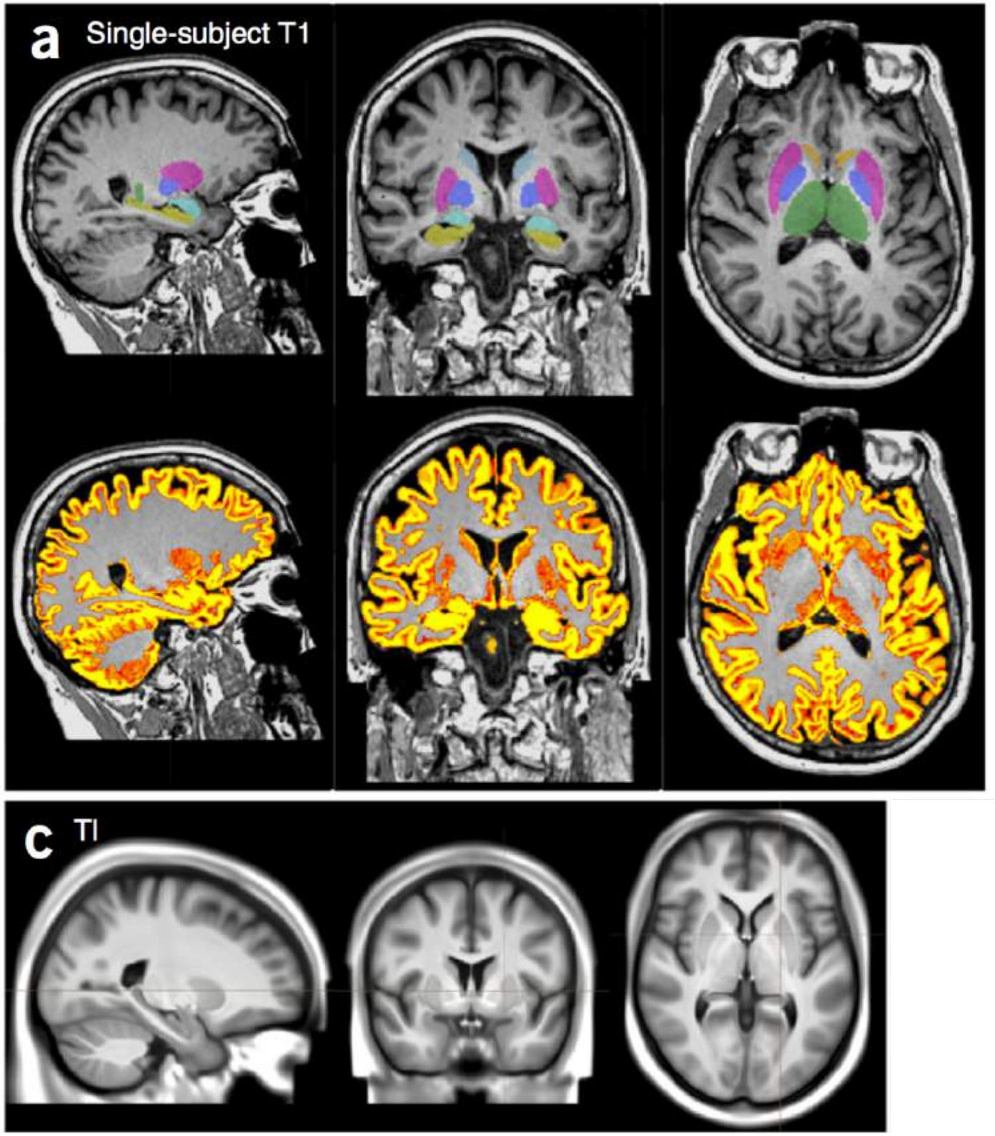
- N subjects
  K tests
  1 effect, K-1 null
- To retain same power, roughly:

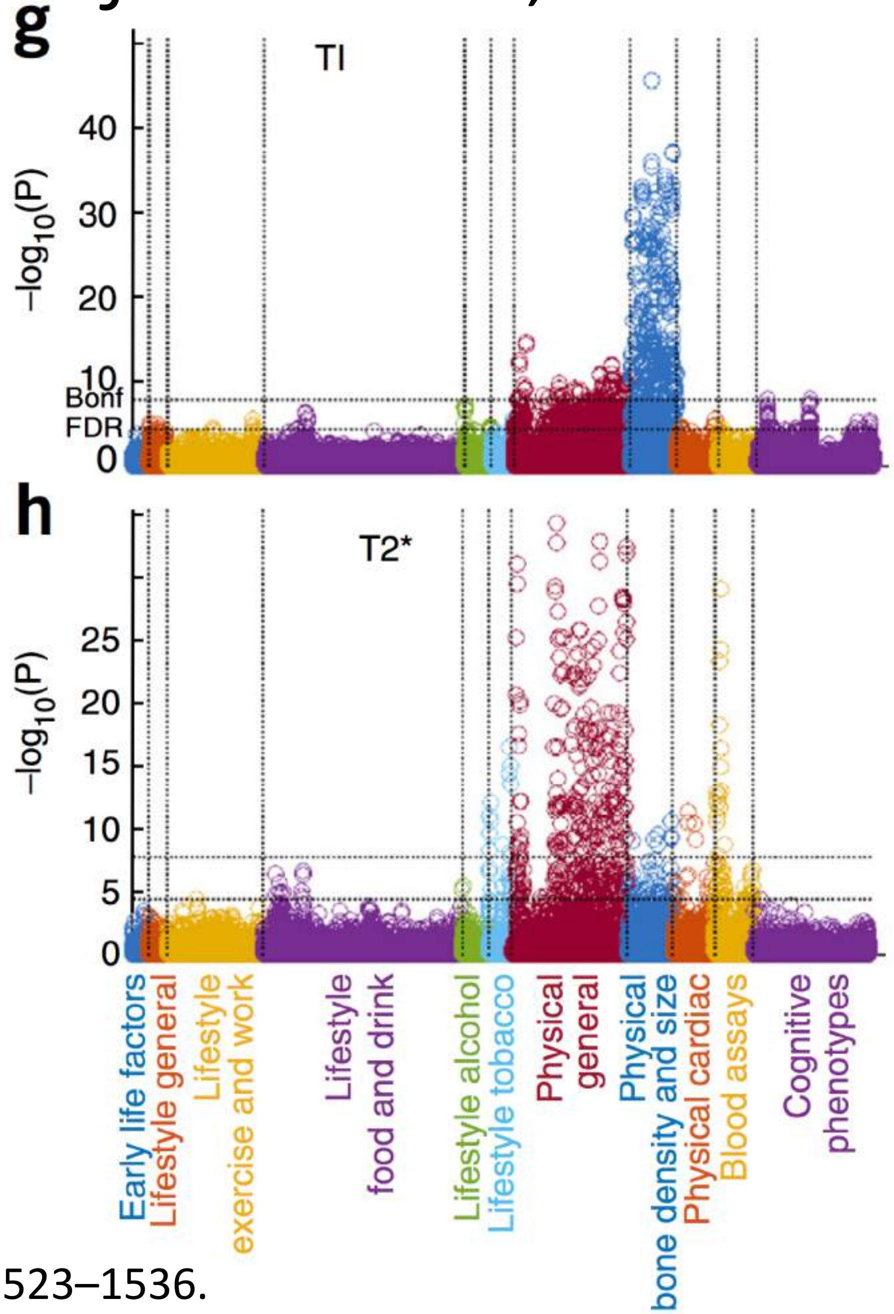
  Square the number of tests
  ->
  Only double the sample size



Smith & Nichols (2018). Statistical Challenges in “Big Data” Human Neuroimaging. *Neuron*, *97*(2), 263–268.

Powerful even with ‘just’ N=8,000

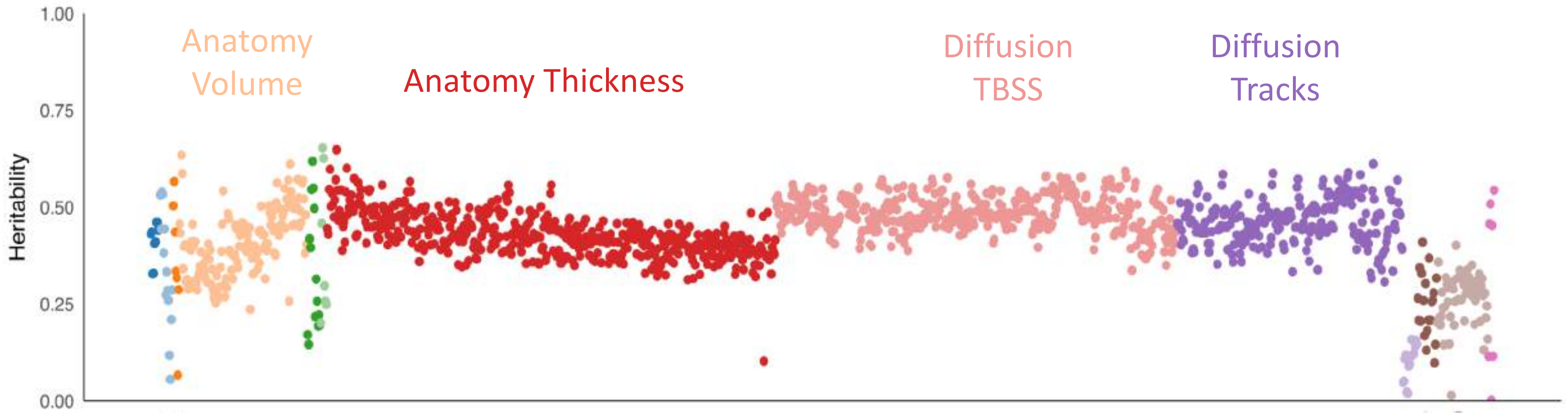




Miller, et al. (2016). *Nature Neuroscience*, *19*(11), 1523–1536.

UK Biobank: Imaging-Genetics Association

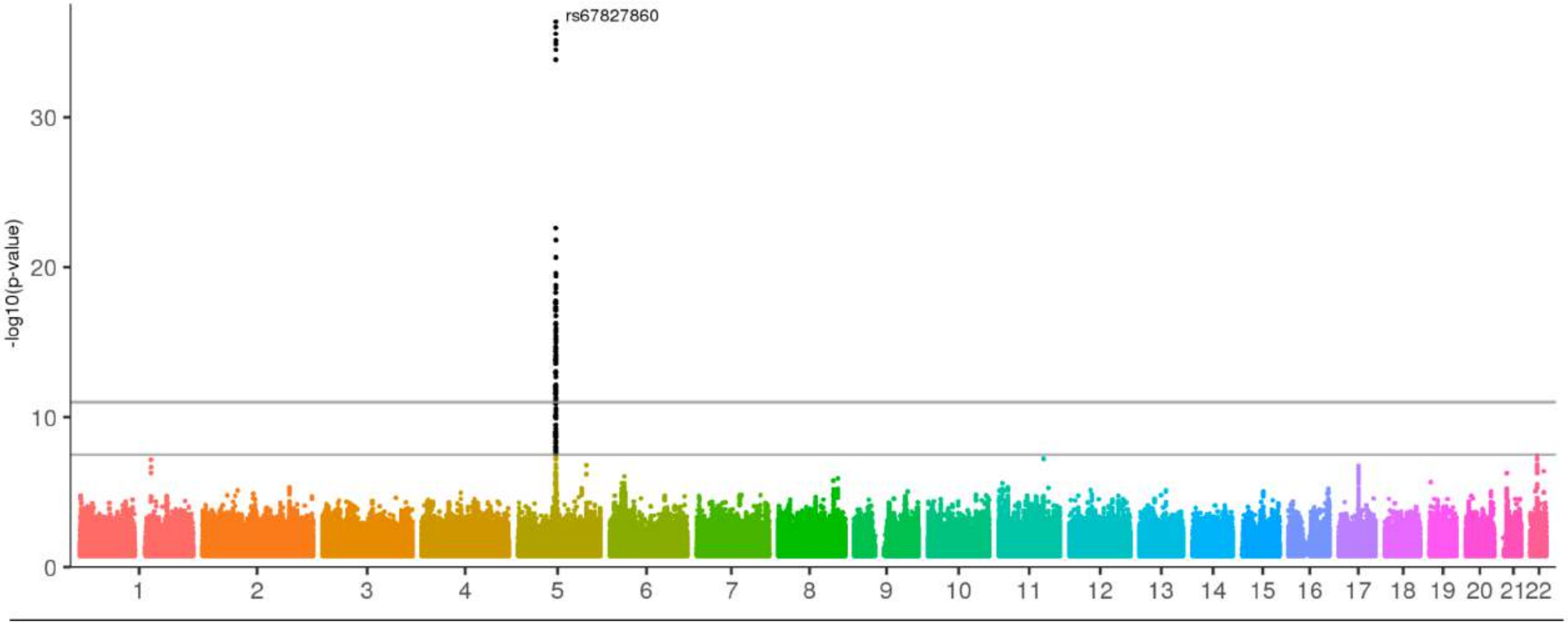
- Imaging+Genetics
  - Genetics
    - 11,734,353 SNPs (all 500k subjects)
  - Imaging
    - MRI: T1, T2 FLAIR, SWI, dMRI, rs-fMRI t-fMRI
    - Distilled into 3,144 “Image-Derived Phenotypes” IDP
  - N=8,428 have both in Elliot et al. (2017)



Elliott et al. (2017). The genetic basis of human brain structure and function … bioRxiv. http://doi.org/10.1101/178806

UK Biobank: Imaging-Genetics Association

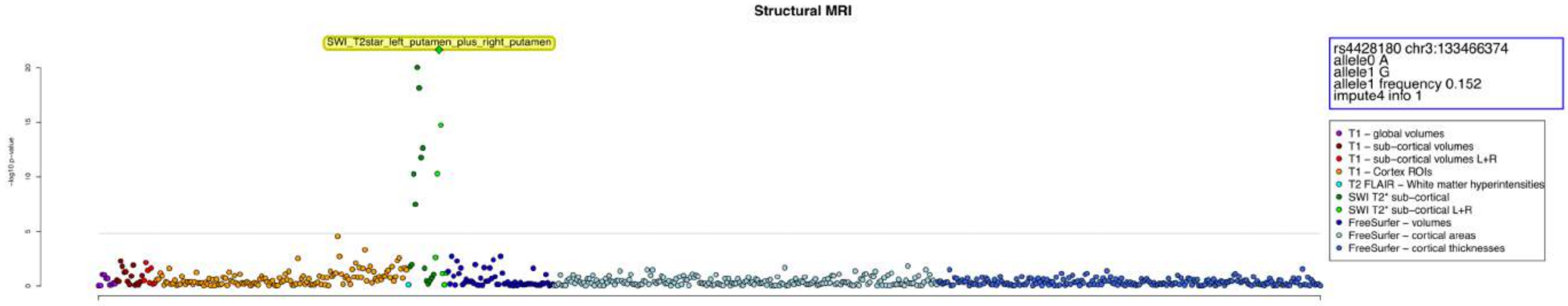
- Strong gene-brain associations discovered
  - $P<10^{-30}$!
  - Diffusion MRI measure: intra-cellular volume fraction

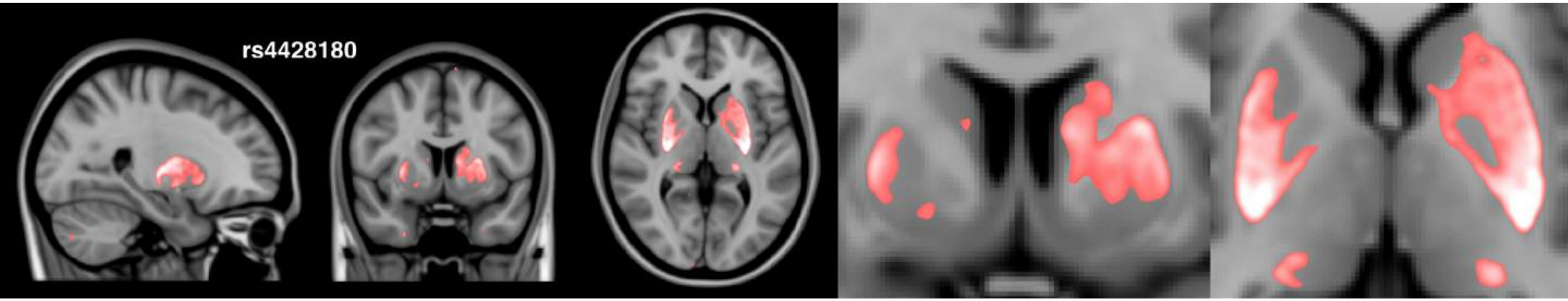


Elliott et al. (2017). The genetic basis of human brain structure and function … bioRxiv. http://doi.org/10.1101/178806

UK Biobank: Imaging-Genetics Association

- Association between T2* in Putamen & iron transport genes





Elliott et al. (2017). The genetic basis of human brain structure and function … bioRxiv. http://doi.org/10.1101/178806

Progress on two problems

- Dependence (not spatial)

- Spatial Inference Under the Alternative

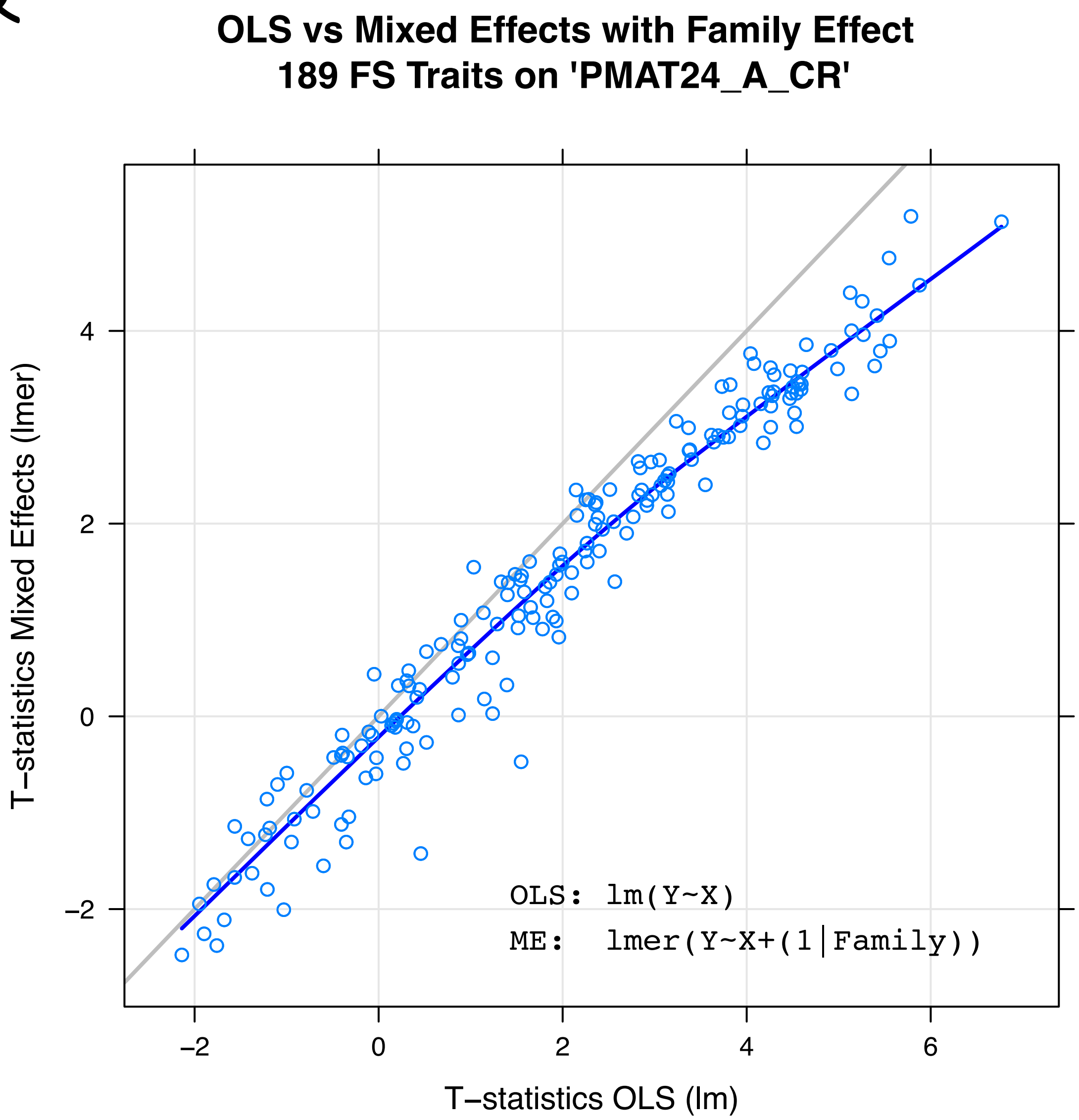
Related Individuals

- HCP subjects clustered in families
  - Twins + siblings
- UK Biobank – relatedness varies
  - “Unrelated” can mean sharing 0.0001%-0.01% of DNA
  - This is small, but if effect highly heritability, some dependence induced

- Neglected dependence = inflated FPR
  - But neuroimaging software can’t accommodate complex dependence
  - Modelling dependence can also improve sensitivity

Example of Inference Bias: HCP Data, Anatomy on IQ

- 523 subjects
- 189 Freesurfer traits
- Compare
  - Naïve OLS
  - Mixed Effects, random Family effect
- OLS inflates significance



Modeling Relatedness

- Structured variance component model
  - Neglecting common environment

$$Y = X\beta + \epsilon \quad \mathrm{Var}(\epsilon) = \Sigma = \sigma_A^2(2\Phi) + \sigma_E^2 I$$

    - Φ is kinship matrix
  - Jointly estimate β and σ^2_A and σ^2_E
  - Inference on H_0: $\beta = 0$ accounting for $\sigma^2_A \neq 0$, or may also want
  - Inference on H_0: $\sigma^2_A = 0$ (no heritability)

Kinship Matrix
$2\Phi_{ij} = 1$: Subj *i* & *j* MZ twins
$2\Phi_{ij} = 1/2$: Subj *i* & *j* DZ twins or sibs.

- Eigen-simplification

$$\Phi = S D_g S'$$

$$S'Y = S'X\beta + S'g + S'\epsilon \quad \Rightarrow Y^* = X^*\beta + \epsilon^*$$

- This turns a **correlated-data** problem into an **independent but heteroscedastic** one

Ganjgahi, et al. (2015). NeuroImage Fast and powerful heritability inference for family-based … *NeuroImage*.

Nonparametric INference for Genetic Analysis (NINGA)

- Initial, OLS estimate of regression

$$\hat{\beta}_{\mathrm{OLS}} = \left(X^{*\prime}X^{*}\right)^{-1} X^{*\prime}Y^{*}$$

- Make squared residuals f^*_{OLS}, regress on Φ eigenvalues

$$\hat{\theta}_{\mathrm{OLS}} = \max\left\{0,\ \left(U^{\prime}U\right)^{-1} U^{\prime}f^{*}_{\mathrm{OLS}}\right\}$$

U=[1 diag(D_g)]
$\theta = (\sigma^2_E\ \sigma^2_A)'$

- 1-step GLS of β

$$\hat{\beta}_{\mathrm{WLS}} = \left(X^{*\prime}(\hat{\Sigma}^{*}_{\mathrm{OLS}})^{-1}X^{*}\right)^{-1} X^{*\prime}(\hat{\Sigma}^{*}_{\mathrm{OLS}})^{-1}Y^{*}$$

- 1-step ML of $\theta = (\sigma^2_E\ \sigma^2_A)'$

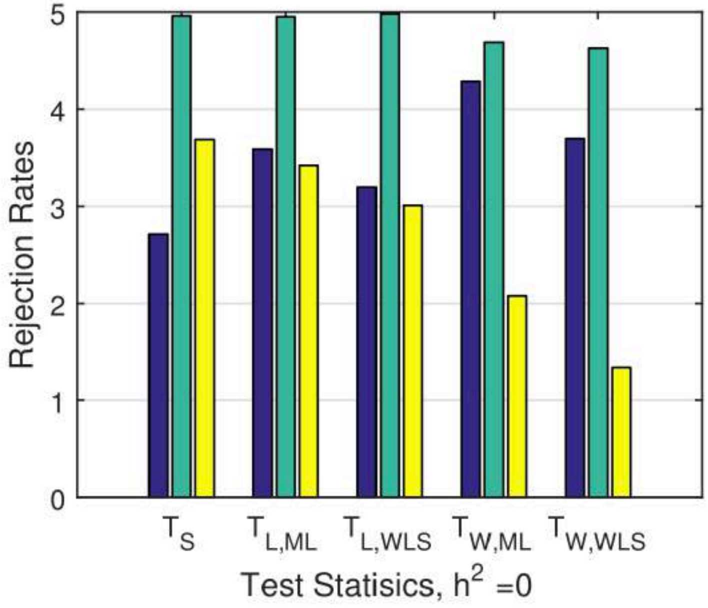
$$\hat{\theta}_{\mathrm{WLS}} = \max\left\{0,\ \left(U^{\prime}(\hat{\Sigma}^{*2}_{\mathrm{OLS}})^{-1}U\right)^{-1} U^{\prime}(\hat{\Sigma}^{*2}_{\mathrm{OLS}})^{-1}f^{*}_{\mathrm{OLS}}\right\}$$

Ganjgahi, et al. (2015). NeuroImage Fast and powerful heritability inference for family-based … *NeuroImage*.

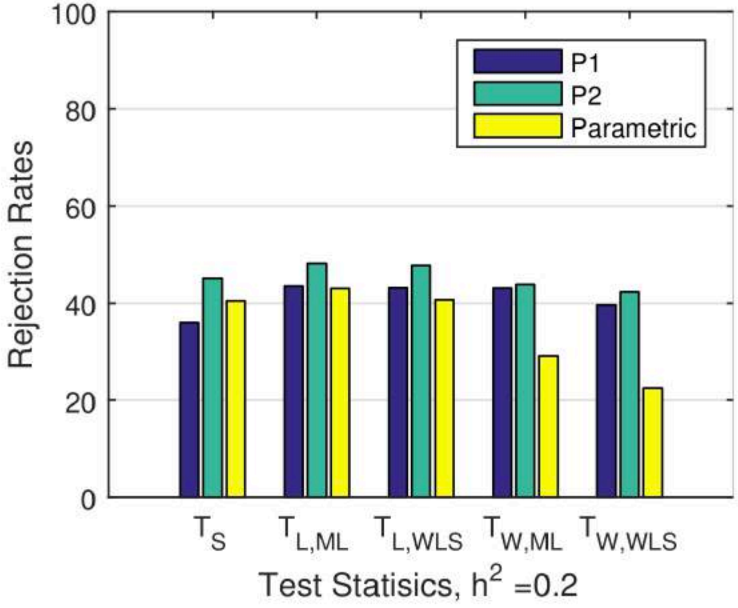
NINGA Evaluations: Inference on h^2

- Heritability
  - $h^2 = \sigma^2_A / (\sigma^2_A + \sigma^2_E)$ …. test with H_0: $\sigma^2_A = 0$
- Despite 1-step optimization
  - Valid FPR control with score test
    - Better than ML due to inaccuracies of 50:50 χ^2_0:χ^2_1 null

False Positive Rates



Power



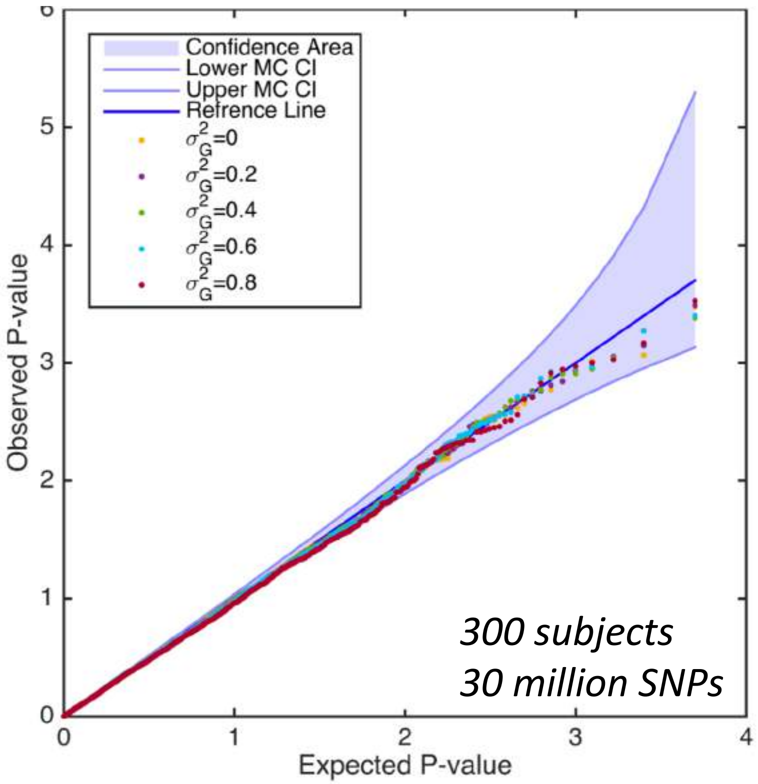
- Comparable power to ML

Simulation: 138 subjects, 2 families from GAW10, 5000 realisations and 500 permutation each

NINGA Evaluations: Inference on β

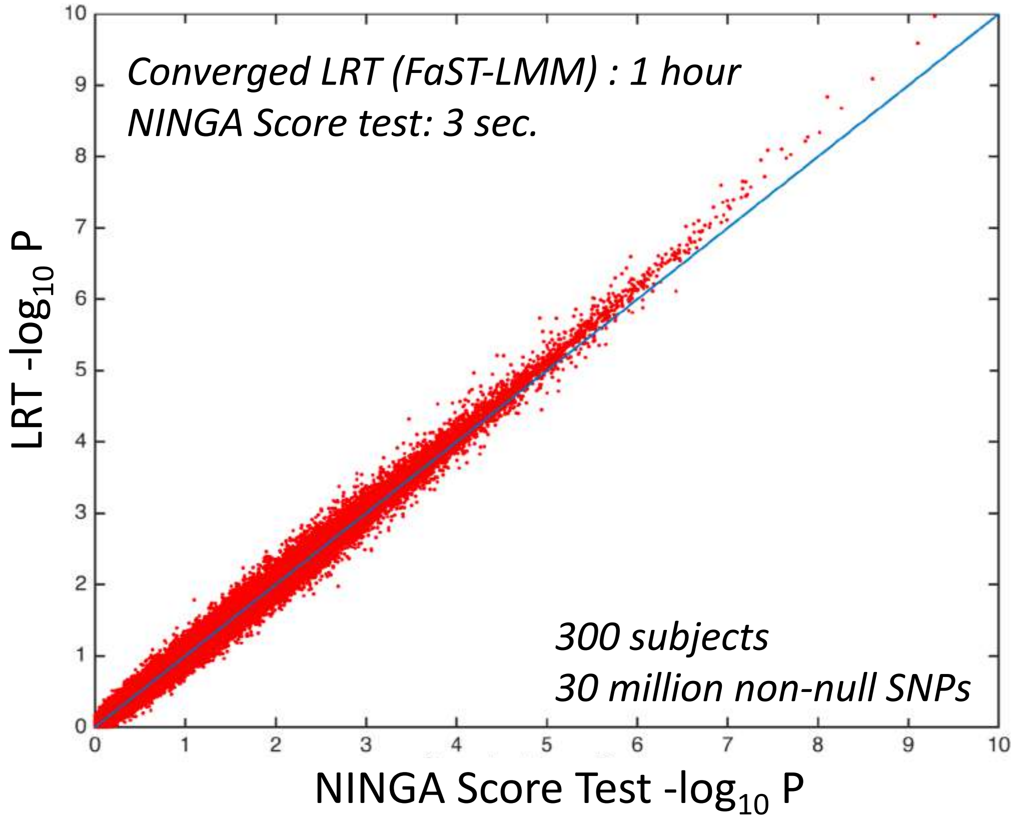
- Typically regression application: Genome-Wide Association Study (GWAS)
  - X has one column for allele dose {0,1,2} for SNP
- Valid, nearly as powerful as fully converged LRT

1-Step WLS+Score Test: Null



300 subjects
30 million SNPs

Fully Converged ML/LRT vs NINGA Score Test



Converged LRT (FaST-LMM) : 1 hour
NINGA Score test: 3 sec.

300 subjects
30 million non-null SNPs

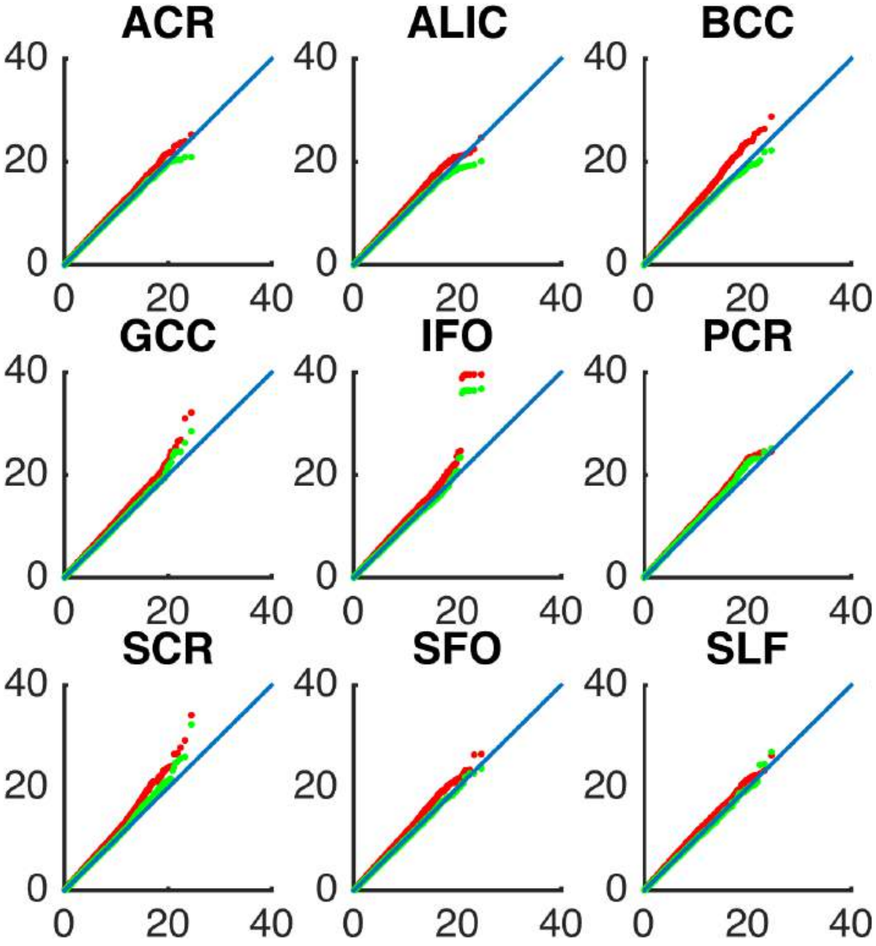
NINGA Association Example

- Maryland Psychiatric Research Center study
  - 332 subjects of European ancestry (CEU)
  - Diffusion MRI collected
    - Fractional Anisotropy computed
  - 2.5 M marker, 20 ROIs of Fractional Anisotropy
  - “Unrelated” subjects
    - But genetic relationship matrix to account for population structure
- Running time, all ROIs, all markers
  - NINGA: 2 mins, FastLMM: 6.5 hours

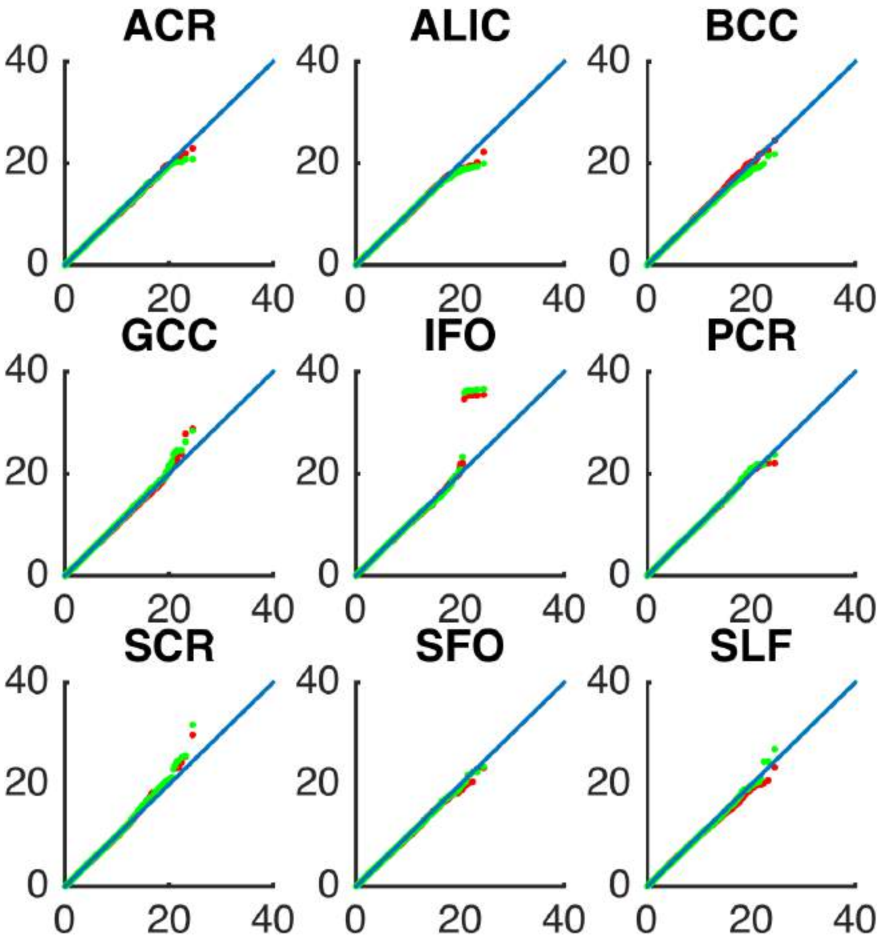
NINGA Association Example

- CEU sample, but mixed effect gives cleaner PP, comparable power after G.C.

PP plot (raw)



PP plot – After Genomic Control



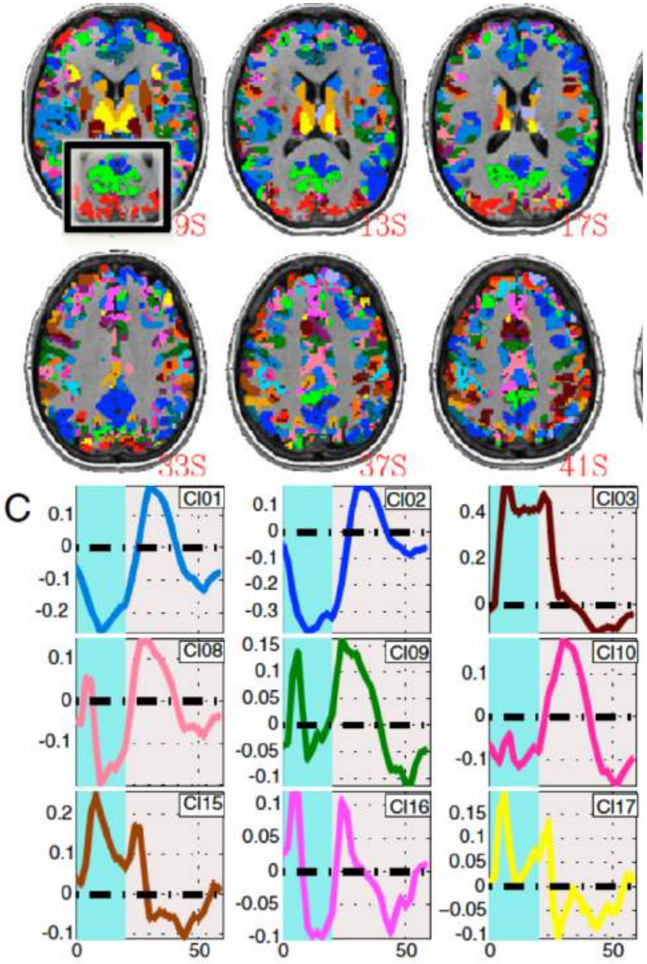
Progress on two problems

- Dependence (not spatial)

- Spatial Inference Under the Alternative

Big Neuro Data:
Beyond Null Hypothesis Testing

- Task fMRI:
  Scan a subject 100 times
  - 99% brain active (FDR), or
    80% brain active (FWE)
  - Null hypothesis testing fallacy
    - With enough N, can reject null everywhere
- Task fMRI:
  Scan 100,000 subjects
  - Null hypothesis testing fallacy will strike hard



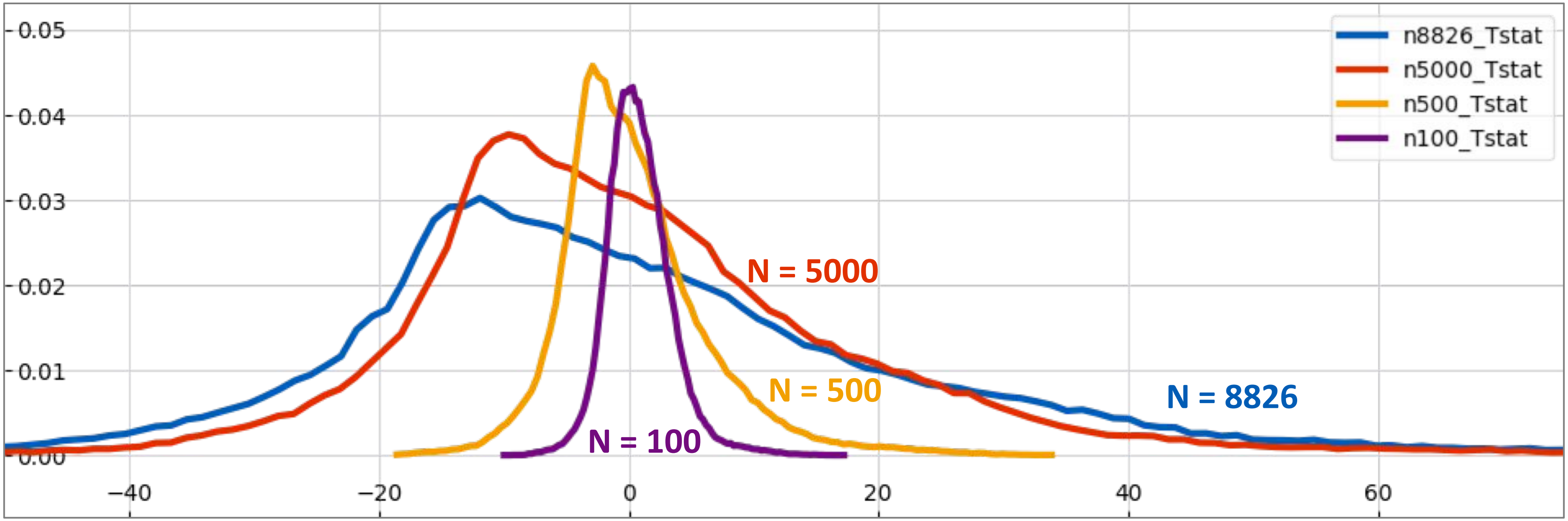
Gonzalez-Castillo et al. (2012). PNAS 109(14), 5487–92.

UK Biobank: Task fMRI
Faces Task (Faces - Shapes)

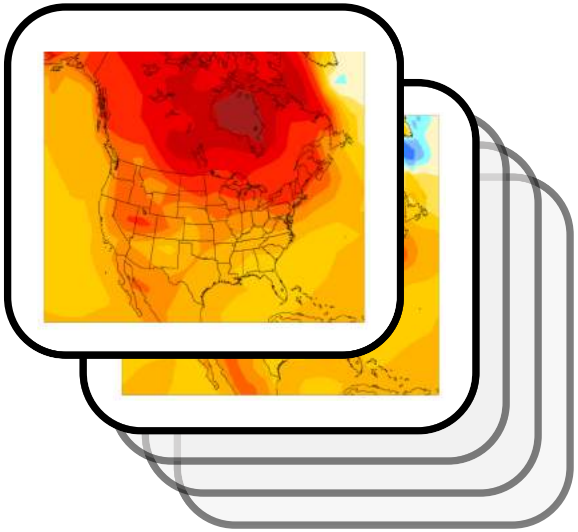
- T-statistics grow with N
  - “N beats K” or “H_0 fallacy”
  - Both at work

N	Max T
100	17.36
500	34.11
1000	52.10
5000	109.05
8569	144.87

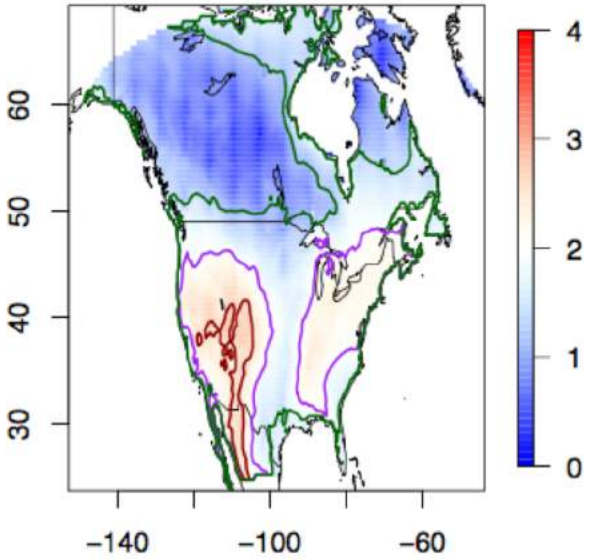
T-Statistics over brain, Faces – Shapes task



Geospatial method



Year-on-year temperature data



Spatial confidents sets estimating
2°C temperature change

Sommerfeld, Sain, Schwartzman (2017). Confidence regions for spatial excursion sets from repeated random field observations, with an application to climate. *JASA*, *1459*

Goal: Estimate a spatial set of activation, and its uncertainty

$$A_c = \{s : \mu(s) \geq c\}$$

”Point estimate” set of where mean exceeds c

$$A_c^- = \{s : \mu(s) \geq c - \delta\}$$

$$A_c^+ = \{s : \mu(s) \geq c + \delta\}$$

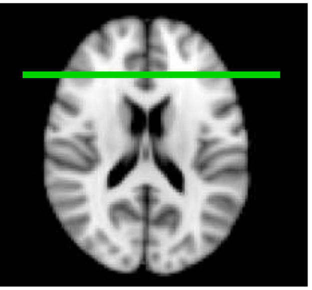
“Envelope” sets that cover A_c, with δ chosen …

$$P\left[\hat{A}_c^- \subset A_c \subset \hat{A}_c^+\right] = 1 - \alpha$$

to control confidence (e.g. 1- α = 95%) that true set is covered

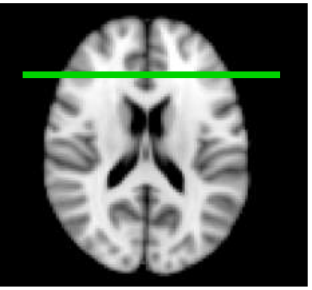
Alex Bowring (Warwick->Oxford)
Armin Schwartzman, Fabian Telschow (UC Irvine)
Max Sommerfeld (Göttingen)

1-D Intuition



$Y_i(\mathbf{s}) = \mu(\mathbf{s}) + \varepsilon_i(\mathbf{s}) \qquad i = 1, \ldots, n$

1-D Intuition



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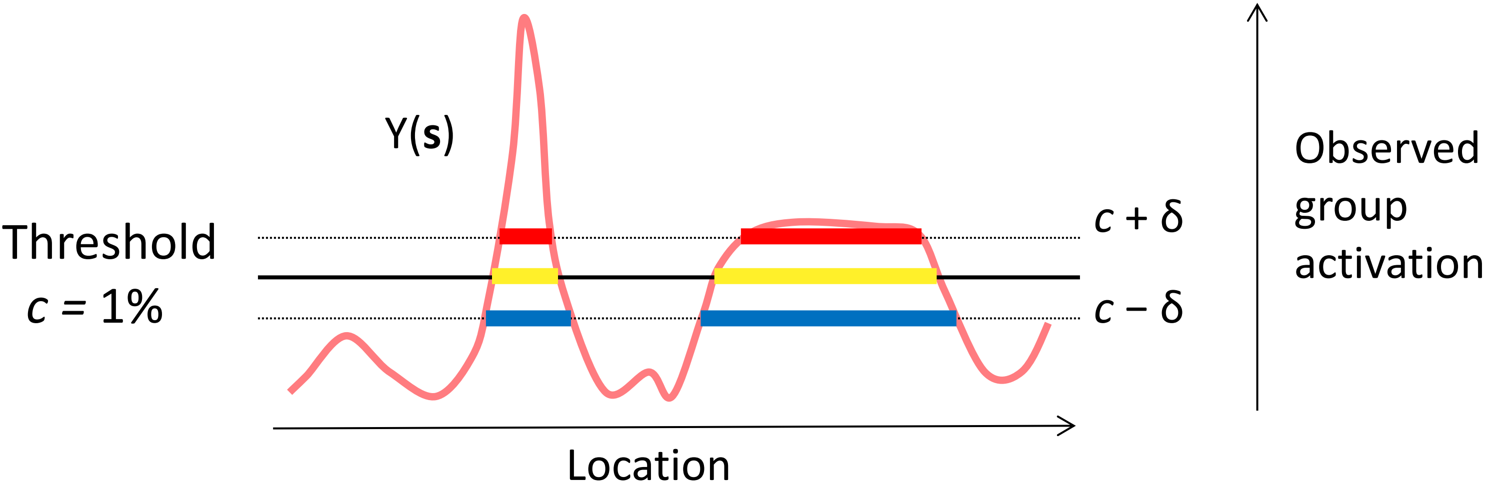

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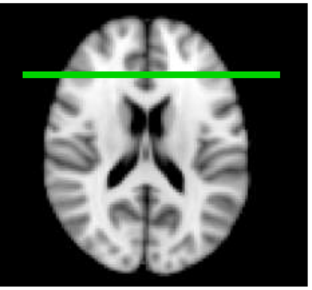

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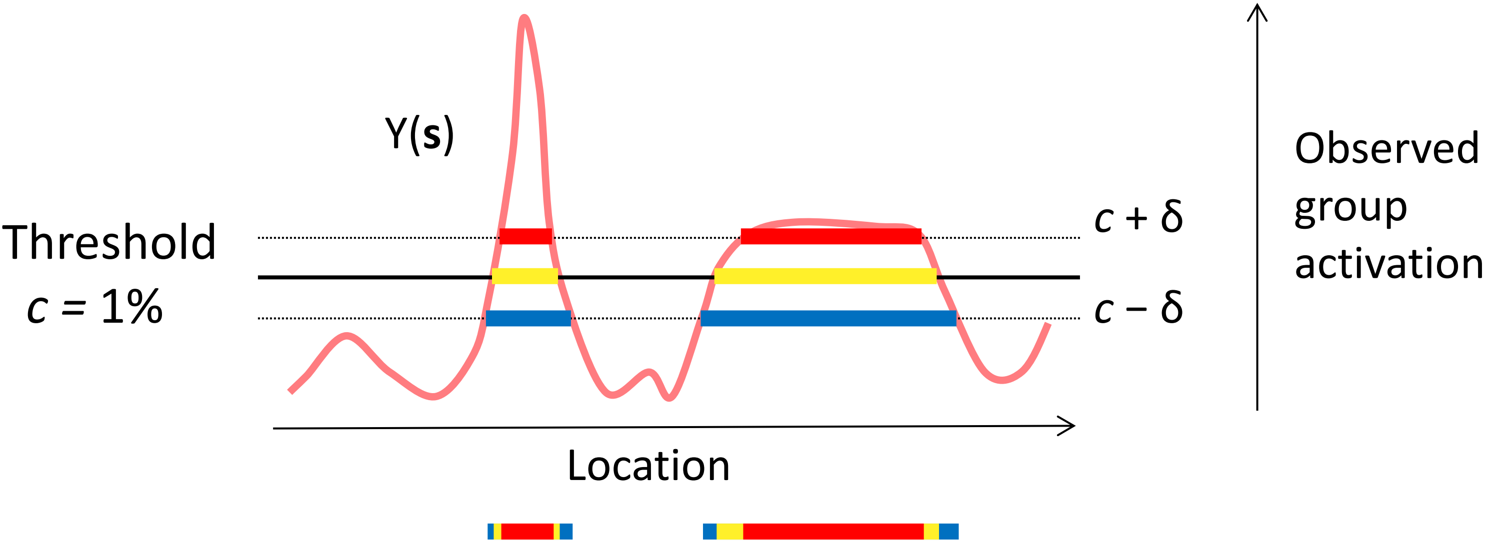

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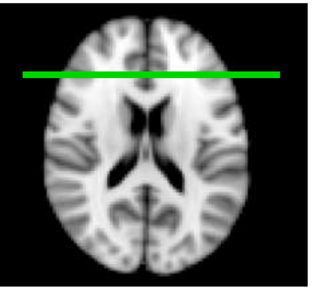

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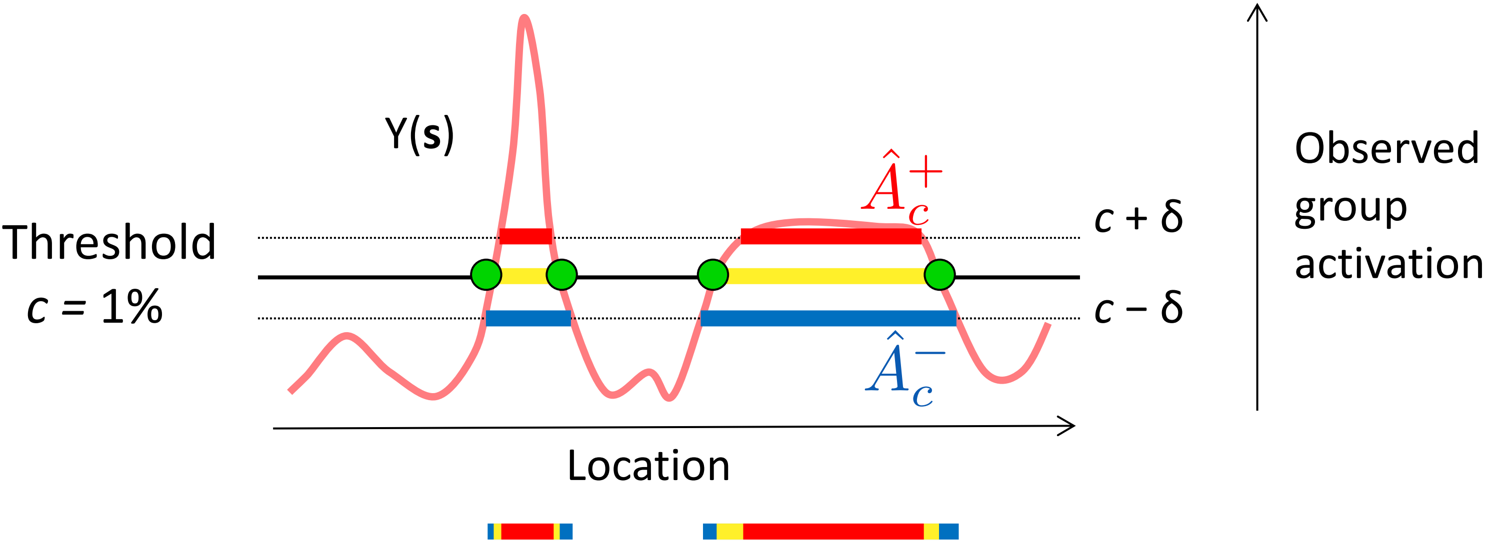


$Y(\mathbf{s})$

$\hat{A}_c^{+}$

Threshold

$c = 1\%$

$c + \delta$

$c - \delta$

$\hat{A}_c^{-}$

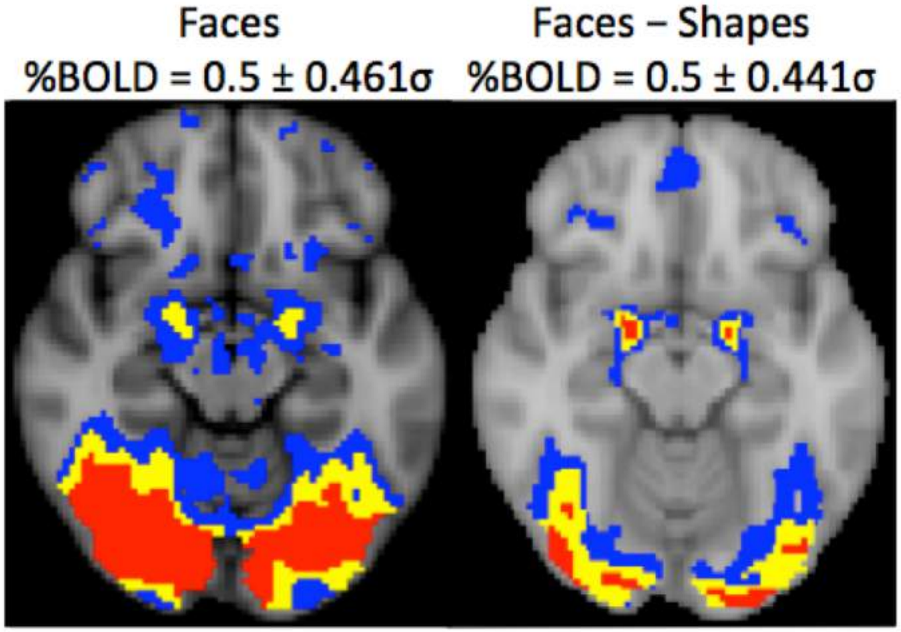
Observed group activation

Location

Use bootstrap to estimate the maximum distribution of $|\varepsilon(\mathbf{s})|$ on the boundary $\mu(\mathbf{s}) = c$

δ estimated as $(1-\alpha)100$%ile of this max dist^n

Results: HCP fMRI



Faces

$\%BOLD = 0.5 \pm 0.461\sigma$

Faces – Shapes

$\%BOLD = 0.5 \pm 0.441\sigma$

Red conf. set ⊂ Yellow set ⊂ Blue conf. Set

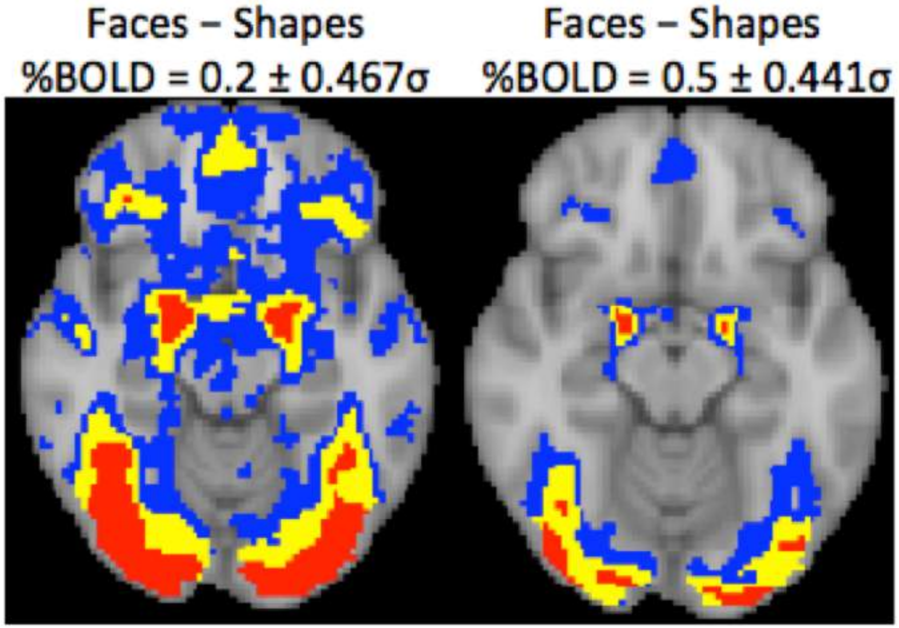
Confidence Sets:
Red ‘inner’ confidence set:
95% confidence have activation > 0.5%.

Blue ‘outer’ Confidence Set:
95% confidence have activation < 0.5%.

Confdience statements simultaneous over brain.

- Human Connectome Project
  - Unrelated 80 dataset.
- Task fMRI block paradigm
  - Participants match faces, or match shapes.
- ‘Faces’ and ‘Faces – Shapes’ contrasts

Results: HCP fMRI



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Confdience statements simultaneous over brain.

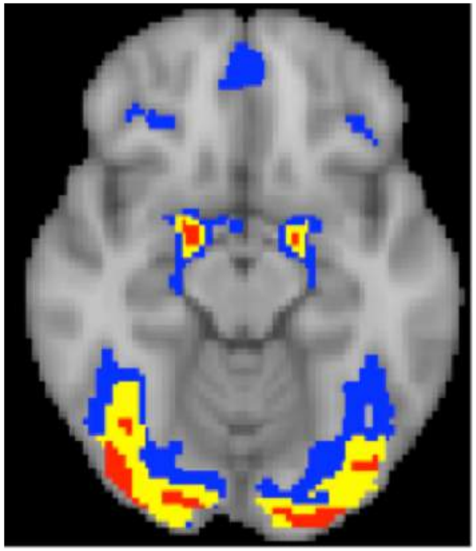
- Human Connectome Project
    - Unrelated 80 dataset.
- Task fMRI block paradigm
    - Participants match faces, or match shapes.
- 'Faces' and 'Faces – Shapes' contrasts
- Comparison of 0.2% and 0.5% threshold

Beyond Null Hypothesis Testing

- Spatial confidence sets
- Given threshold on % effect find confidence sets…
  - Inside red: 95% confident true signal greater
  - Outside blue: 95% confident true signal smaller

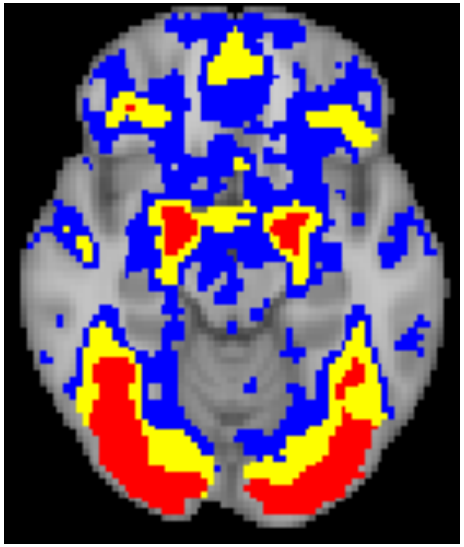
    … in FWE/simultaneous sense

- Human Connectome Project data
- N=80 subjects
- Task fMRI, Faces>Shapes
  - Threshold at 0.5% (left) 0.2% (right)



Faces − Shapes

$\%\text{BOLD} = 0.5 \pm 0.441\sigma$



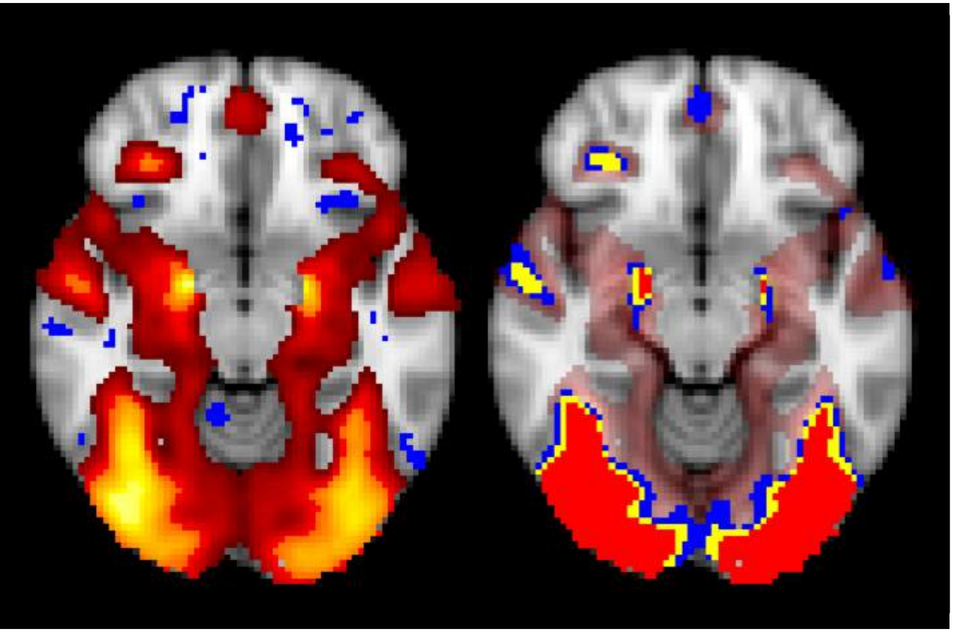
Faces − Shapes

$\%\text{BOLD} = 0.2 \pm 0.467\sigma$

Alex Bowring (Warwick->Oxford)
Armin Schwartzman (UC Irvine)
Max Sommerfeld (Göttingen)

UK Biobank: Faces-Shapes

Faces – Shapes
N = 1000

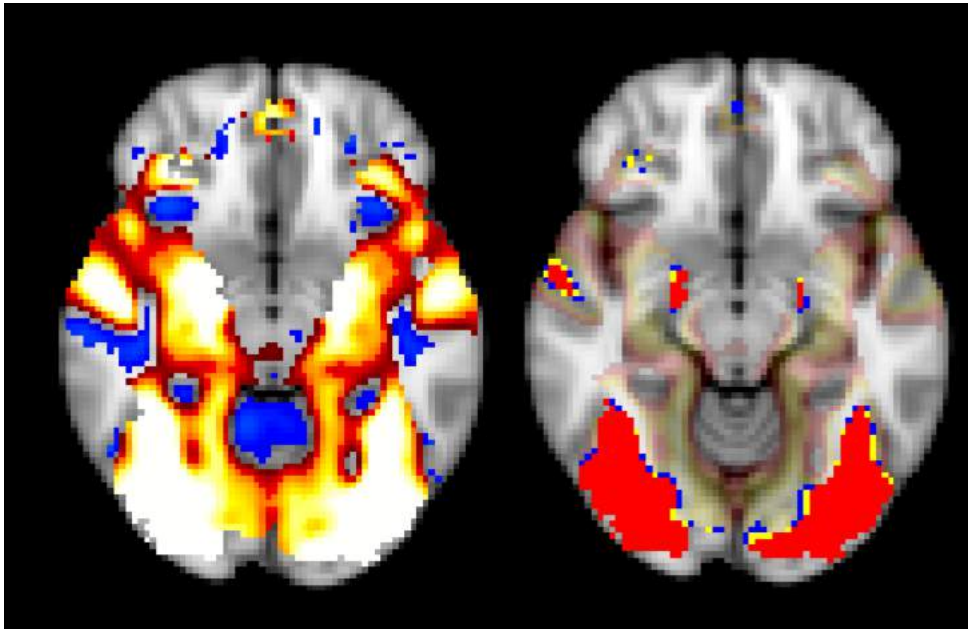


T-statistic,
Bonferroni
FWE $p < 0.05$

Contour Inference,
$c = 0.2\%$

Volume between
confidence sets:
12,791

Faces – Shapes
N = 5000



T-statistic,
Bonferroni
FWE $p < 0.05$

Contour Inference,
$c = 0.2\%$

Volume between
confidence sets:
2,621

Next steps

- Developing method for use on standardized ‘Cohen’s d’ effects
    - %BOLD change divided by standard deviation of the data.
- Extend to confidence statements on ‘peaks’
    - E.g. ellipsoidal confidence regions

Population Neuroimaging Conclusions

- Most neuroimaging ‘small’ big data
- Still presents enormous challenges
  - Must deal with dependence
    - Due to family or even distant relations
  - Move from null hypothesis testing to estimation
    - NIH: Please fund Schwartzman H_1-RFT grant
  - Epidemiological concerns
    - Understand sample bias
    - Account for confounds

Acknowledgments

- Neuroimaging Statistics Oxford (NISOx) group
- Collaborators near and far
  - Steve Smith, FMRIB
  - Tim Johnson, U Michigan
  - Tor Wager, U Colorado
  - Tal Yarkoni, San Antonio
  - Armin Schwartzman, UC San Diego