Neuroimaging Statistics for Population Scale Data: Effective DF for Pearson's r, & Confidence Sets

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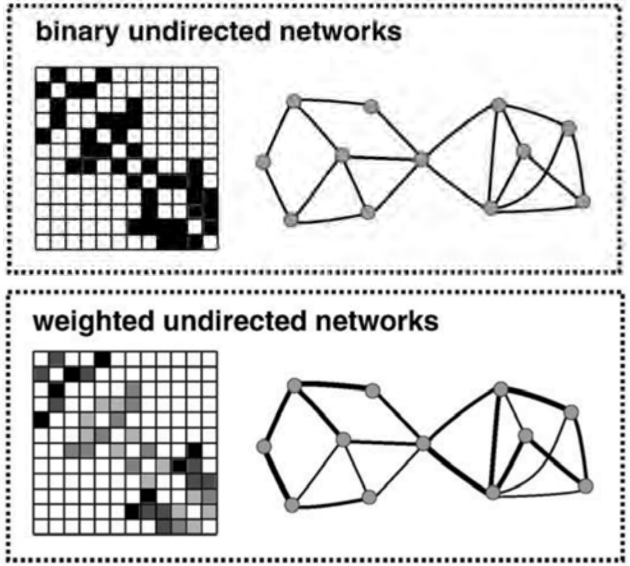
University of Cambridge

***feat.* Alex Bowring**
University of Oxford

Plan

- Effective DF for Inference on Correlation
  - Afyouni, S., Smith, S. M., & Nichols, T. E. (2019). Effective degrees of freedom of the Pearson's correlation coefficient under autocorrelation. NeuroImage, 199, 609–625.
- Spatial Confidence Sets
  - Bowring, A., Telschow, F., Schwartzman, A., & Nichols, T. E. (2019). Spatial confidence sets for raw effect size images. NeuroImage, 203(September), 116187.
  - Bowring, A., Telschow, F. J. E., Schwartzman, A., & Nichols, T. E. (2021). Confidence Sets for Cohen's d effect size images. NeuroImage, 226(May 2020), 117477.

So many correlations



- Typical graph theory application
  - Compute correlation matrix, threshold
  - Compute graph characteristics
    - Degree
      - Number of edges per node
    - Betweeness
      - ×��W !"#$%&'()*+,-./0123456789:;�ÿ��<=�>��?@ABCDEFGHIJ�KLMN�O nodes
    - Local Efficiency
      - Measure of clustering
      - Measures topological distance between two neighbours of a node
  - Compute for each node, average over nodes
  - Compare between populations, or correlate with covariate

Rubinov & Sporns (2009). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, *52*(3), 1059–1069.

Correlations & Sample Size

- As every one knows, more data, lower variance

$$\rho = 0: \mathrm{Var}(r) \approx 1/N$$

Simulation

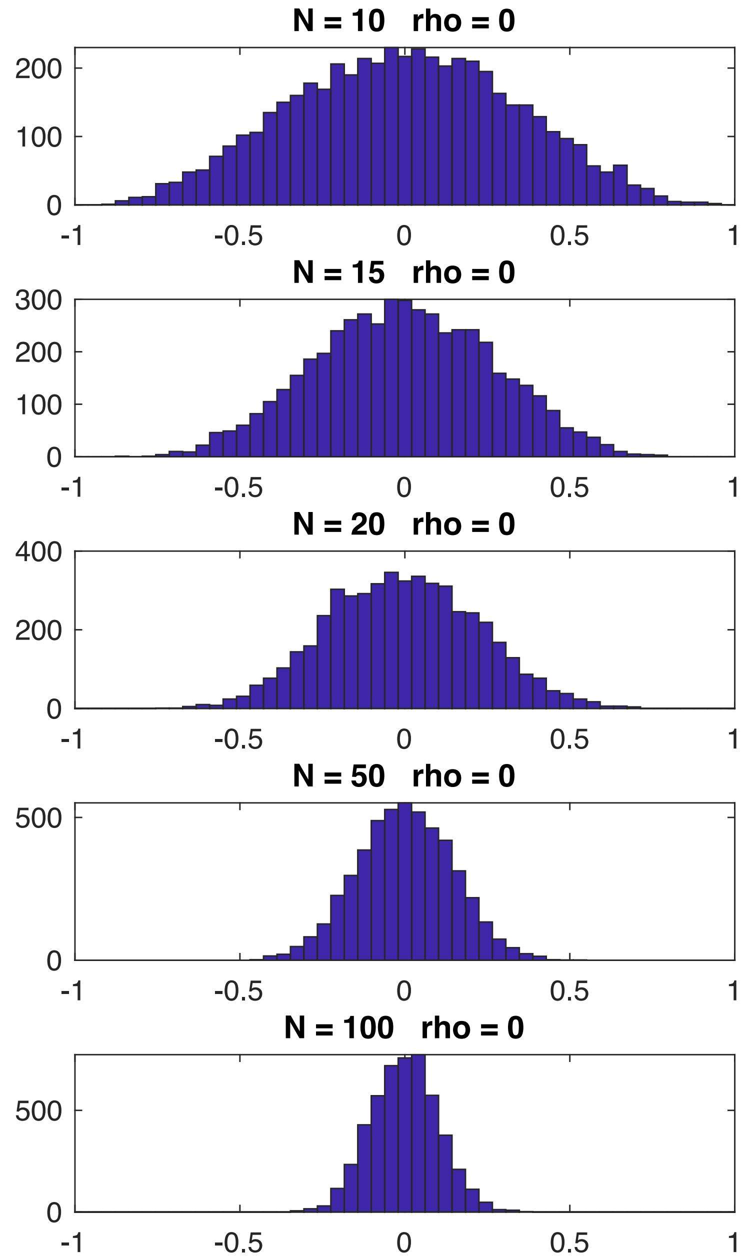
Generate length-N r.v. A,B,C ~N(0,1)

$$X = A + \sqrt{\frac{\rho}{1-\rho}}C$$

$$Y = B + \sqrt{\frac{\rho}{1-\rho}}C$$

r = corrcoef(X,Y)

Simulated Correlations: r

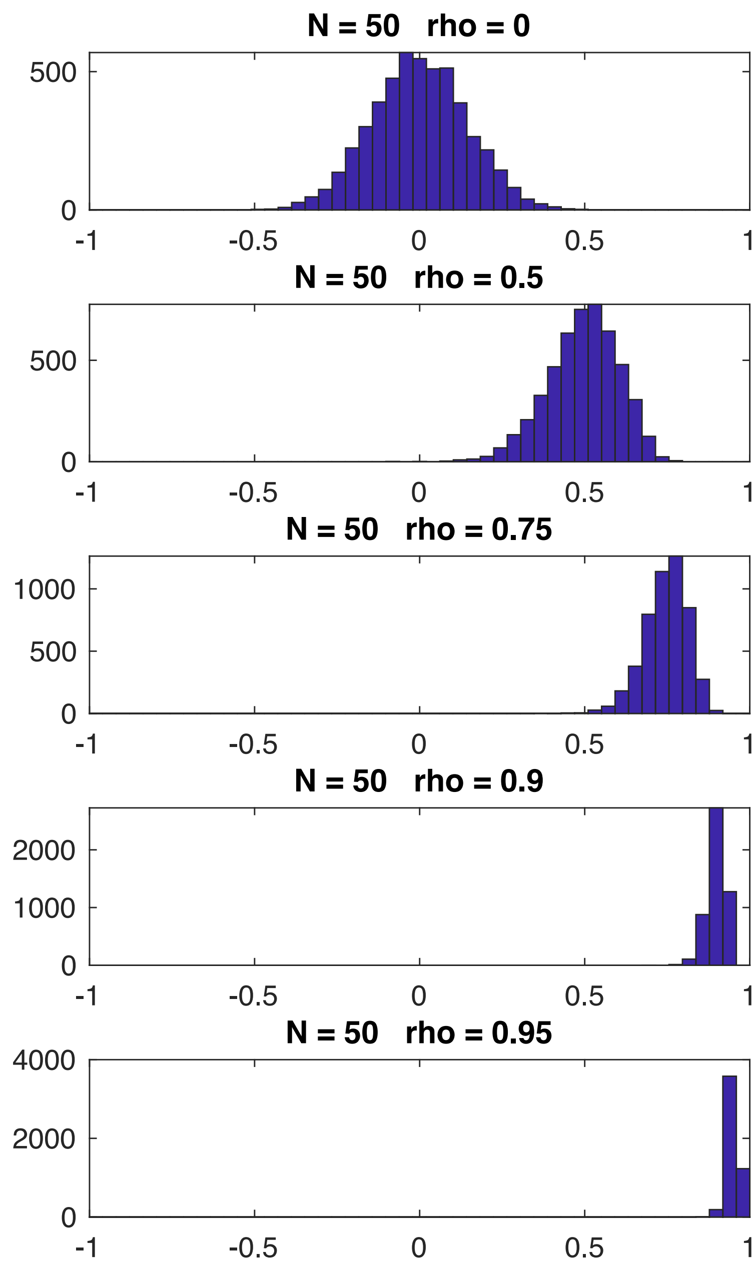


Correlations & true ρ

- And as every statistician knows, the more extreme correlation, the, the lower variance

$$\mathrm{Var}(r) \approx (1-\rho^2)^2/N$$

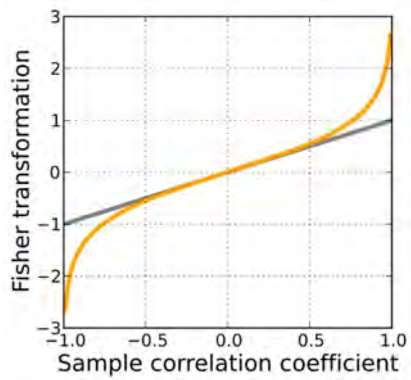
Simulated Correlations: r



Fisher's Transformed Corr. & True ρ

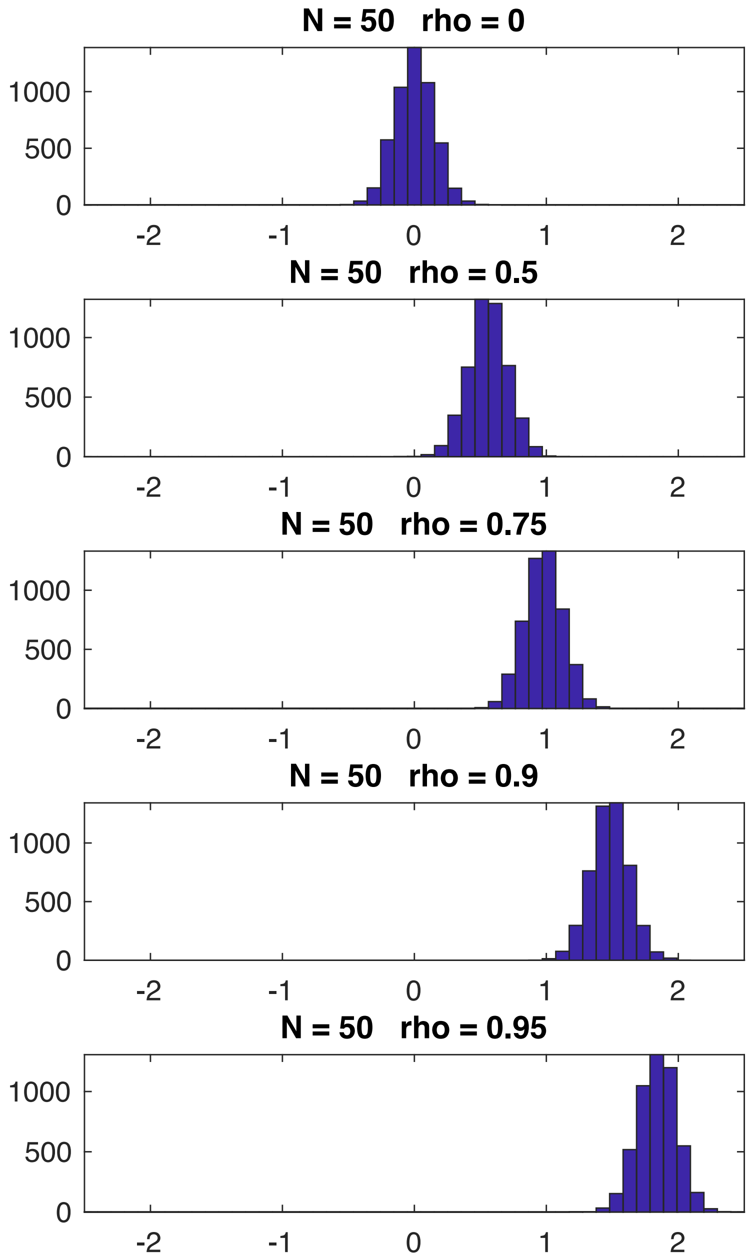
- That's why we use Fisher's Transformation

$$\text{atanh}(r) = \frac{1}{2}\log\left(\frac{1+r}{1-r}\right)$$



- Magically stabilises the variance
- Reduces skew, too

Simulated Correlations: $\text{atanh}(r)$



Correlation & Serial Correlation

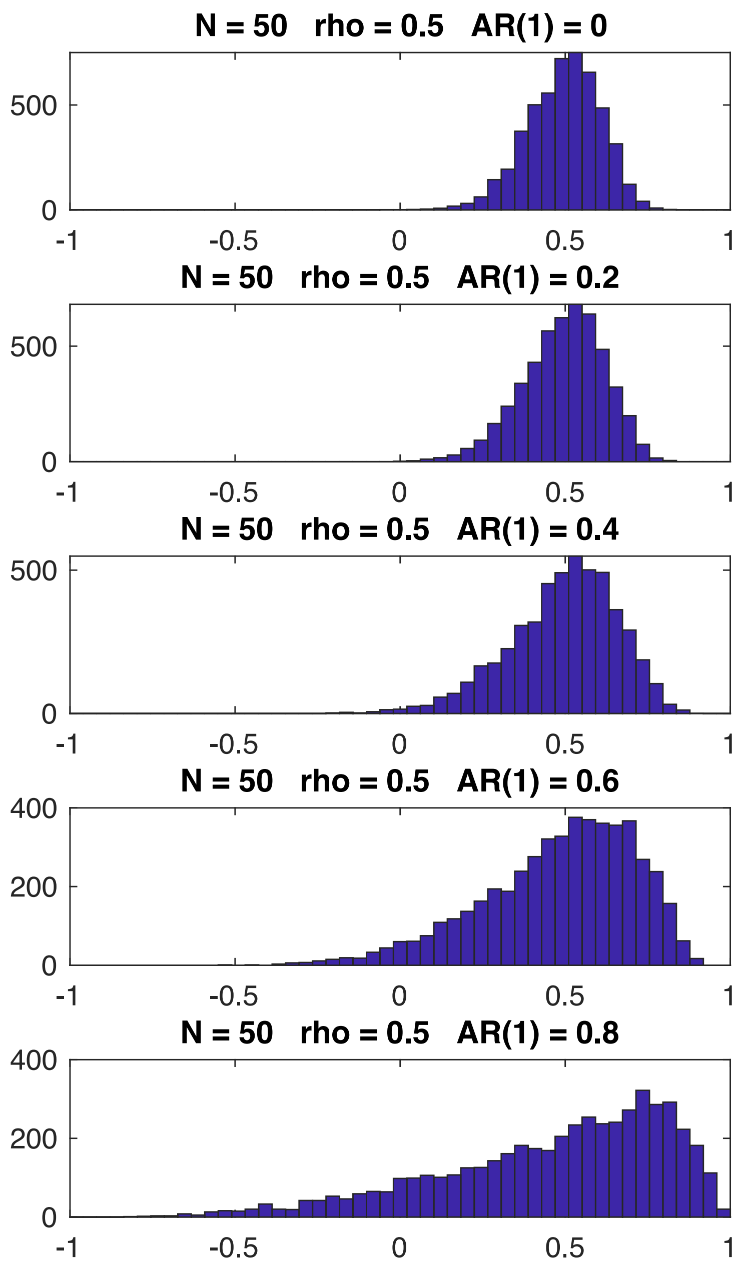
- However, what happens when respective variables have temporal autocorrelation?
- Very serious impact!
  - Though still roughly unbiased
- Does Fisher's transformation help?

Simulation: A,B,C ~AR(1), unit marginal variance

$$X = A + \sqrt{\frac{\rho}{1-\rho}}\,C, \quad Y = B + \sqrt{\frac{\rho}{1-\rho}}\,C$$

r = corrcoef(X,Y)

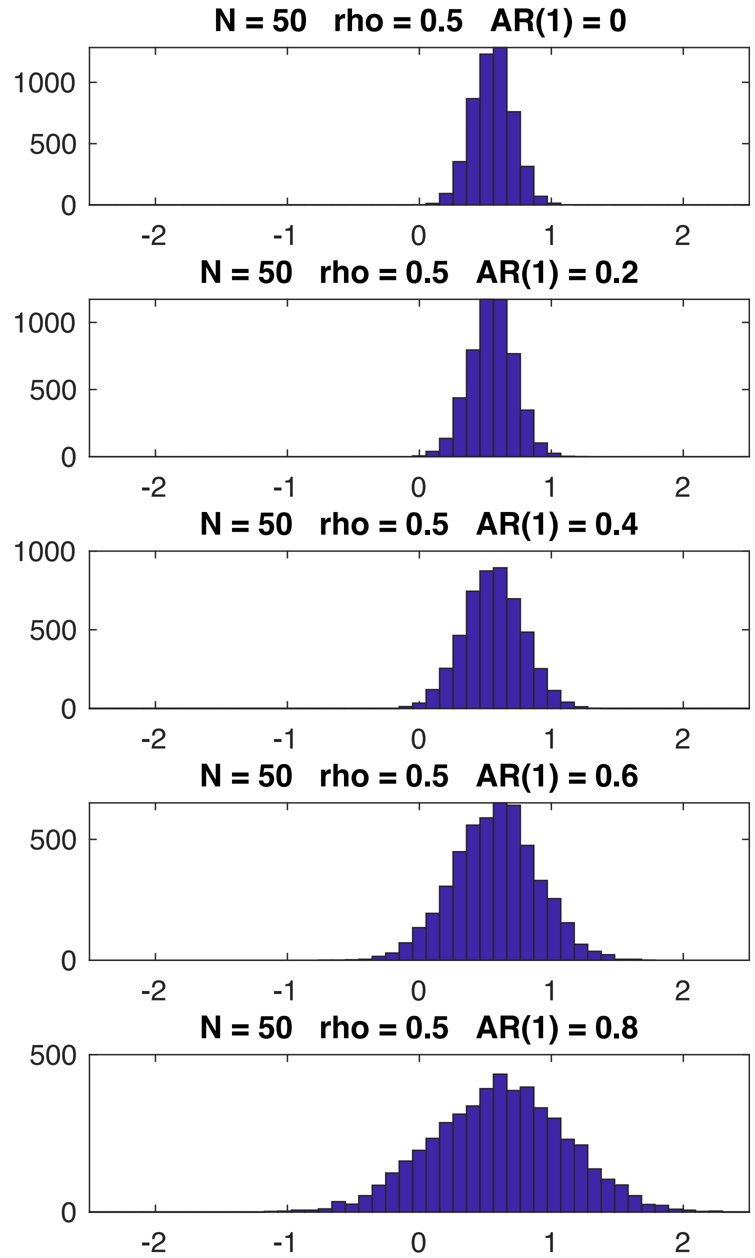
Simulated Correlations: r



Fisher's Trans. & Serial Correlation

- Fisher's Transformation reduces skew
- But variance remains dependent on severity of correlation

Simulated Correlations: $\text{atanh}(r)$



Are Neuroscientists Aware of the Issue?

- Bartlett’s Theory

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *PNAS*, *102*(27), 9673–9678.

of freedom in the measurement. Because individual time points in the BOLD signal are not statistically independent, the degrees of freedom must be corrected according to Bartlett’s theory (25).

25. Jenkins, G. M. & Watts, D. G. (1968) *Spectral Analysis and Its Applications*

  - Bartlett’s correction to asymptotic confidence intervals??

- ACF Integral

Van Dijk, K. R. A., Hedden, T., Venkataraman, A., Evans, K. C., Lazar, S. W., & Buckner, R. L. (2010). Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. *Journal of Neurophysiology*, *103*(1), 297–321.

1968). The Bartlett correction factor (BCF) was applied when statistical significance was dependent on temporal degrees of freedom as is the case in our calculation of power to detect correlations with varying run length (dataset 3b). The BCF is not necessary when performing second-level random effects tests on group data, where degrees of freedom is determined by the number of subjects. The BCF for dataset 3b, computed as the integral across time of the square of the autocorrelation function, was 1.62. The *t*-value corresponding to the correla-

  - $\int \rho^2(k) dk$??
  - Or is that $\sum_{k=1}^{N} \rho^2(k)$
  - Or $\sum_{k=-N}^{N} \rho^2(k)$
  - And, *really*, all lags?

Variance of Sample Correlation Coefficients

- Functional connectivity, ROIs X and Y, r_{xy}.

$$\mathbb{V}(\hat{\rho}_{xy,0}) = \frac{1}{N-3}$$

Fisher 1917

Bartlett 1935

$$\mathbb{V}(\hat{\rho}_{xy,0}) \approx \frac{1}{N}\frac{1+\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}{1-\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}$$

$$\mathbb{V}(\hat{\rho}_{xy,0}) = N^{-1}\sum_{i=-\infty}^{i=+\infty}\rho^2_{xx,i}$$

Bartlett 1946

Clifford, Richardson & Hemon 1989

$$\mathbb{V}(\hat{\rho}_{xy,0}) = N^{-2}\,\mathrm{tr}(\mathbf{\Sigma}_X\,\mathbf{\Sigma}_Y)$$

×W !"#$%&'(

$$\mathbb{V}(\hat{\rho}_{xy,0}) = N^{-1}\sum_{i=-\infty}^{i=+\infty}\rho_{xx,i}\rho_{yy,i}$$

$$\mathbb{V}(\hat{\rho}_{xy,0}) = N^{-1} + 2N^{-2}\sum_{i=1}^{N-1}(N-i)\hat{\rho}_{xx,i}\hat{\rho}_{yy,i}$$

×W !"#$%&'()*+,-./0

Effective Degree of Freedom in Resting-state Functional Connectivity

Assumptions:

- Equal autocorrelation in X & Y
- Zero cross-correlation

Fisher 1917

$$\mathbb{V}(\hat{\rho}_{xy,0}) = \frac{1}{N-3}$$

Bartlett 1935

$$\mathbb{V}(\hat{\rho}_{xy,0}) \approx \frac{1}{N} \frac{1 + \hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}{1 - \hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}$$

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Effective Degree of Freedom in Resting-state Functional Connectivity

"integral across time of the square of the autocorrelation function"

"Bartlett's th

The human bra
dynamic, antic

Michael D. Fox*†, Abraham Z. Snyder*‡, Justin L. Vincent*, Maurizio Corbetta‡, David C. Van Essen§, and Marcus E. Raichle*‡§¶

J Neurophysiol 103: 297–321, 2010.
First published November 4, 2009; doi:10.1152/jn.00783.2009.

Intrinsic Functional Connectivity As a Tool For Human Connectomics: Theory, Properties, and Optimization

Koene R. A. Van Dijk,[1,2,3] Trey Hedden,[1,2] Archana Venkataraman,[4] Karleyton C. Evans,[5] Sara W. Lazar,[5] and Randy L. Buckner[1,2,5,6]

$$N^{-1}\left(1+2\sum_{i}^{N}\rho_{xx,i}^{2}\right)$$

In practice ?

$$\mathbb{V}(\hat{\rho}_{xy,0}) = \frac{1}{N-3}$$

Fisher 1917

Bartlett 1935

$$\mathbb{V}(\hat{\rho}_{xy,0}) \approx \frac{1}{N}\frac{1+\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}{1-\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}$$

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×W !"#$%&'()*+,-./0

Effective Degree of Freedom in Resting-state Functional Connectivity

- Other more advanced results have followed
  - Haven't been used much in neuroimaging
  - And these assume $\rho_{xy,i}$ = 0 for all lags i
    - Zero instantaneous (cross) correlation ($\rho = \rho_{xy,i} = 0$)
    - Zero lagged cross-correlation

Fisher 1917

$$\mathbb{V}(\hat{\rho}_{xy,0}) = \frac{1}{N-3}$$

Bartlett 1935

$$\mathbb{V}(\hat{\rho}_{xy,0}) \approx \frac{1}{N}\frac{1+\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}{1-\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}$$

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Bailey & Hammersley (1946)

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Effective Degree of Freedom in Resting-state Functional Connectivity

Monte-Carlo Simulations (e.g. FSLNets)

- Simulation approaches
  - FSLNets:
    - Assume all time series share a common AR(1) structure
    - Simulate
    - Compute variance of simulated null correlations

xDF: Variance of r Accounting for Auto- and cross-correlation

Roy 1989

"xDF"
Afyouni 2019

$$\mathbb{V}(\hat{\rho}_{xy,0}) = N^{-2}\Big[(N-2)(1-\rho^2)^2 + \rho^2 \sum_i^M w_i(\rho_{xx,i}^2 + \rho_{yy,i}^2 + \rho_{xy,+i}^2 + \rho_{xy,-i}^2) - 2\rho \sum_i^M w_i(\rho_{xx,i} + \rho_{yy,i})(\rho_{xy,+i} + \rho_{xy,-i}) + 2 \sum_i^M w_i(\rho_{xx,i}\rho_{yy,i} + \rho_{xy,+i}\rho_{xy,-i})\Big],$$

Roy. Asymptotic covariance structure of serial correlations in multivariate time series. *Biometrika*, 76(4): 824–827, 1989.
Afyouni, Smith, Nichols (2019). Effective degrees of freedom of the Pearson's correlation coefficient under autocorrelation. *NeuroImage*, *199*(May), 609–625.

Fisher's Z-scores?

- If you know/trust variance or Pearson's, you can then get Fisher's variance as:

$$\mathbb{V}(\text{arctanh}(\hat{\rho})) = \mathbb{V}(\hat{\rho})(1 - \hat{\rho}^2)^{-2}$$

- … and *then* make z-scores

$$z_{XY} = \frac{\text{arctanh}(\hat{\rho})}{\sqrt{\mathbb{V}(\hat{\rho})(1 - \rho^2)^{-2}}}.$$

Recall iid var…

$$\mathbb{V}(\hat{\rho}_{xy,0}) \approx \frac{(1 - \rho_{xy}^2)^2}{N}$$

… reduces to usual result

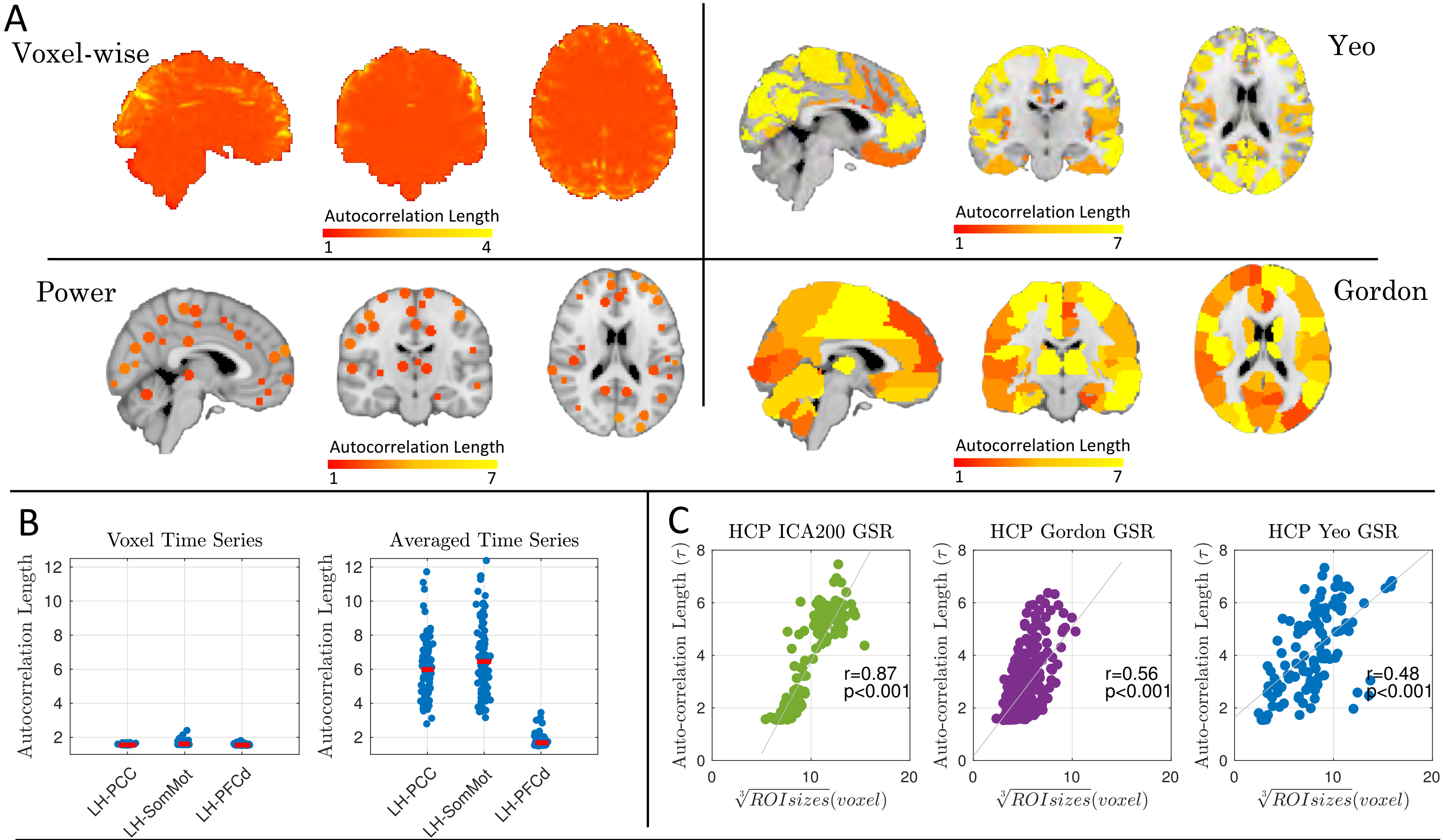
- In terms of effective DF, you can calculate

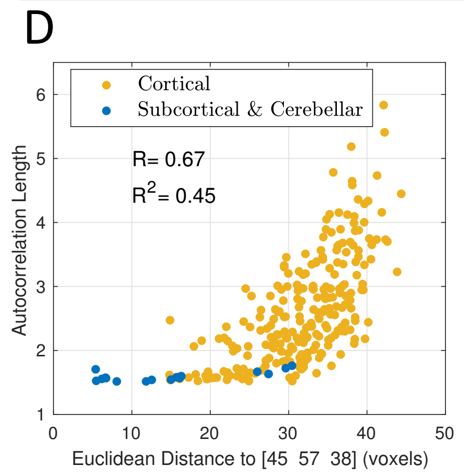
$$eDF = 1 \,/\, \sqrt{\mathbb{V}(\hat{\rho})(1 - \rho^2)^{-2}}$$

How to estimate the ACFs?

- To use Roy/xDF result we need
  $\rho_{xx,k}, k = 1, \ldots, N$
  $\rho_{yy,k}, k = 1, \ldots, N$
  $\rho_{xy,k}, k = -N, \ldots, N$
- Various rules of thumb
  - Truncate at k=N/4, k=N/5
  - Tapering, zero for k>M; $\mathrm{M} = \sqrt{N}$ or $2\sqrt{N}$
- All seem arbitrary, so we proposed
  - Test H_0: $\rho_{xx,k} = 0$ at 5% uncorrected, k=1,2,…
  - First non-significant test k_0; set $\rho_{xx,k} = 0, k \geq k_0$
  - Repeat for ρ_{yy}
  - For ρ_{xy}, use the larger k_0 from either of ρ_{xx} and ρ_{yy}

But Does Autocorrelation Vary Much?





Strength of correlation matters!

But varies…

- Increases with avg. w/in ROI
- Increases ROI size
- Varies with anatomy/location

$$\tau_x = \sum_{i=0}^{N-1} \rho_{xx,i}^2$$

Autocorrelation Length

Monte-Carlo Simulations: Bias of $V(\hat{\rho})$, Non-null ρ & various ACFs

Clifford, et al. 1989

Bartlett 1935

×W !"#$%&'(

Bailey & Hammersley (1946)

Settings

T=100

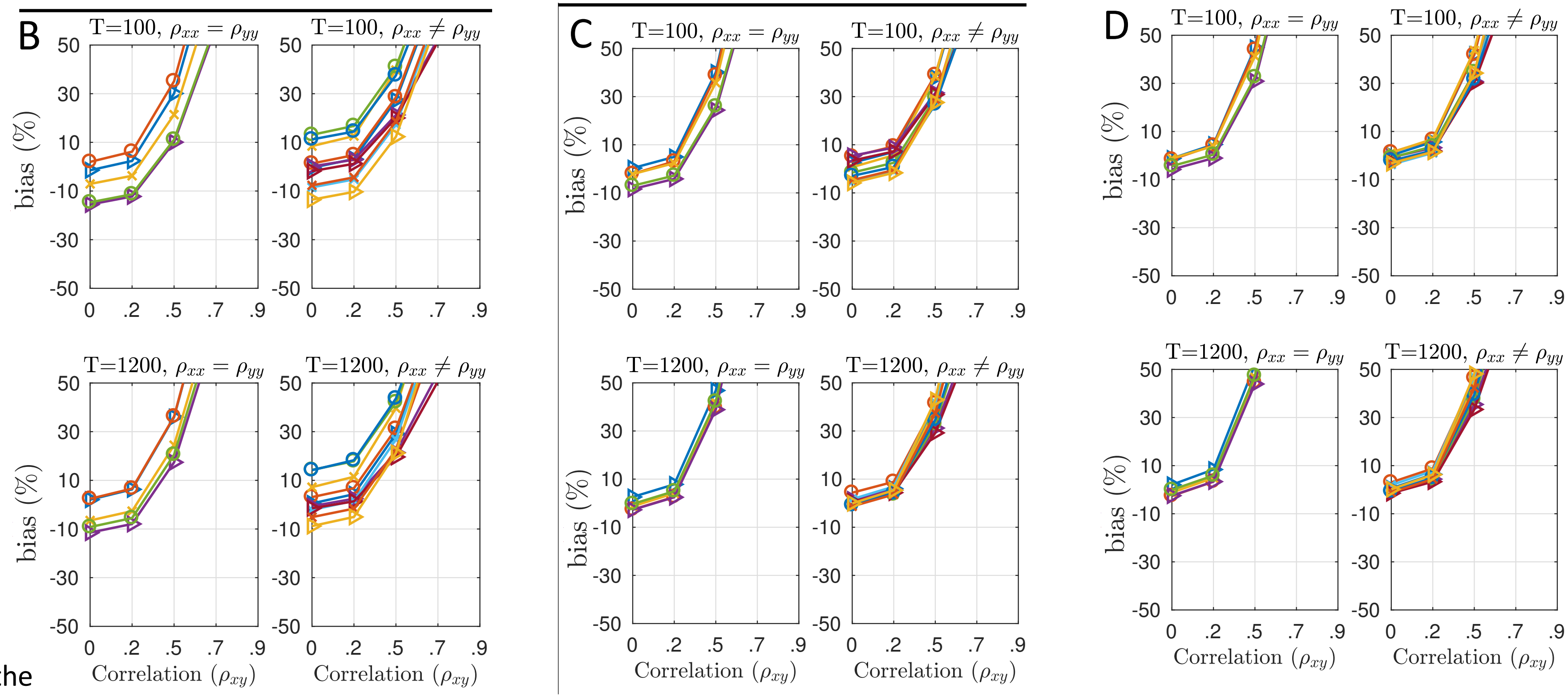
T=1200

$$\mathbb{V}(\hat{\rho}_{xy,0}) \approx \frac{1}{N}\frac{1+\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}{1-\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}$$

$$\mathbb{V}(\hat{\rho}_{xy,0}) = N^{-1}(1+2\sum_{i=1}^{N-1}\rho_{xx,i}\rho_{yy,i})$$

$$\mathbb{V}(\hat{\rho}_{xy,0}) = N^{-2}\,\mathrm{tr}(\mathbf{\Sigma}_X\,\mathbf{\Sigma}_Y)$$

Equal & Unequal ACFs



All methods go off the rails as ρ grows

Not surprising as all assume ρ = 0…

Even with W-W

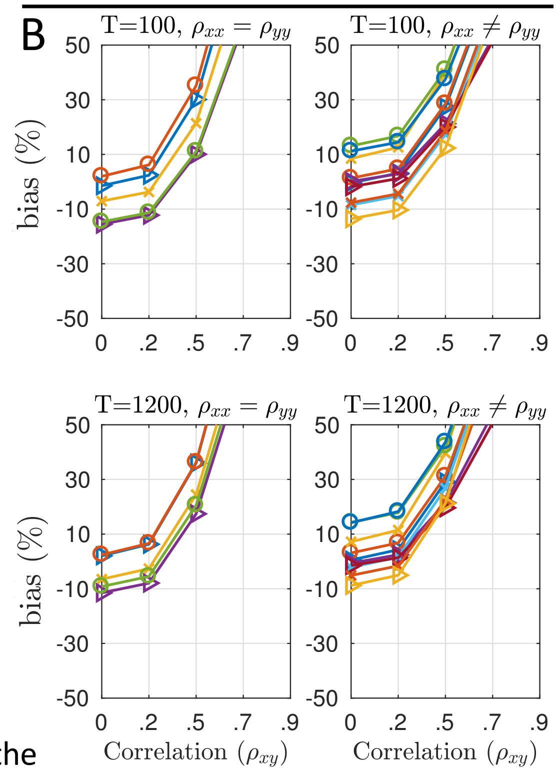
Monte-Carlo Simulations: Bias of $V(\hat{\rho})$, Non-null ρ & various ACFs

Settings
T=100
T=1200

Equal & Unequal ACFs

Bartlett 1935

$$\mathbb{V}(\hat{\rho}_{xy,0}) \approx \frac{1}{N}\frac{1+\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}{1-\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}$$



×W !"#$%&'(

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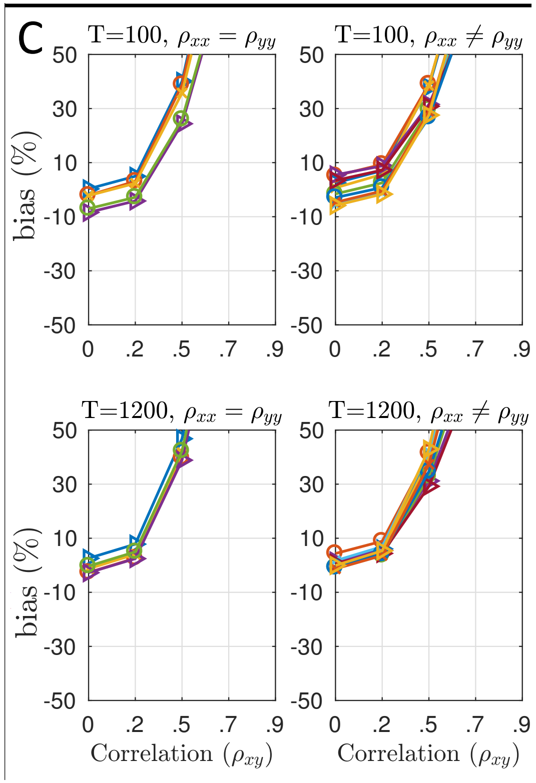
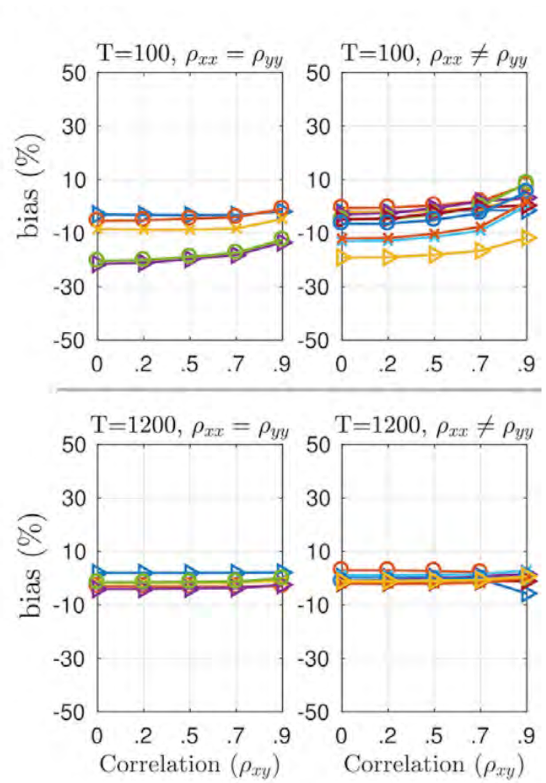


Afyouni et al (2019)

xDF



All methods go off the rails as ρ grows

Not surprising as all assume ρ = 0…

Even with W-W

Why do Bartlett &co do so bad even for White-White Simulations?

- Aliasing
  - Product of ACFs is aliased with square of the correlation!

$$\rho_{xx,k}\rho_{yy,k} = \sum_t x_t x_{t+i} \times \; y_t y_{t+i}$$

$$= \sum_t x_t y_t \times x_{t+i} y_{t+i}$$

$$E(\rho_{xx,k}\rho_{yy,k}) = \sum_t E(x_t y_t) \times E(x_{t+i} y_{t+i})$$

$$= \sum_t \rho_{xy,0}^2 = \sum_t \rho^2$$

Bartlett 1935

$$\mathbb{V}(\hat{\rho}_{xy,0}) \approx \frac{1}{N}\frac{1+\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}{1-\hat{\rho}_{xx,1}\hat{\rho}_{yy,1}}$$

Bartlett 1946

$$\mathbb{V}(\hat{\rho}_{xy,0}) = N^{-1}(1+2\sum_{i=1}^{N-1}\rho_{xx,i}\rho_{yy,i})$$

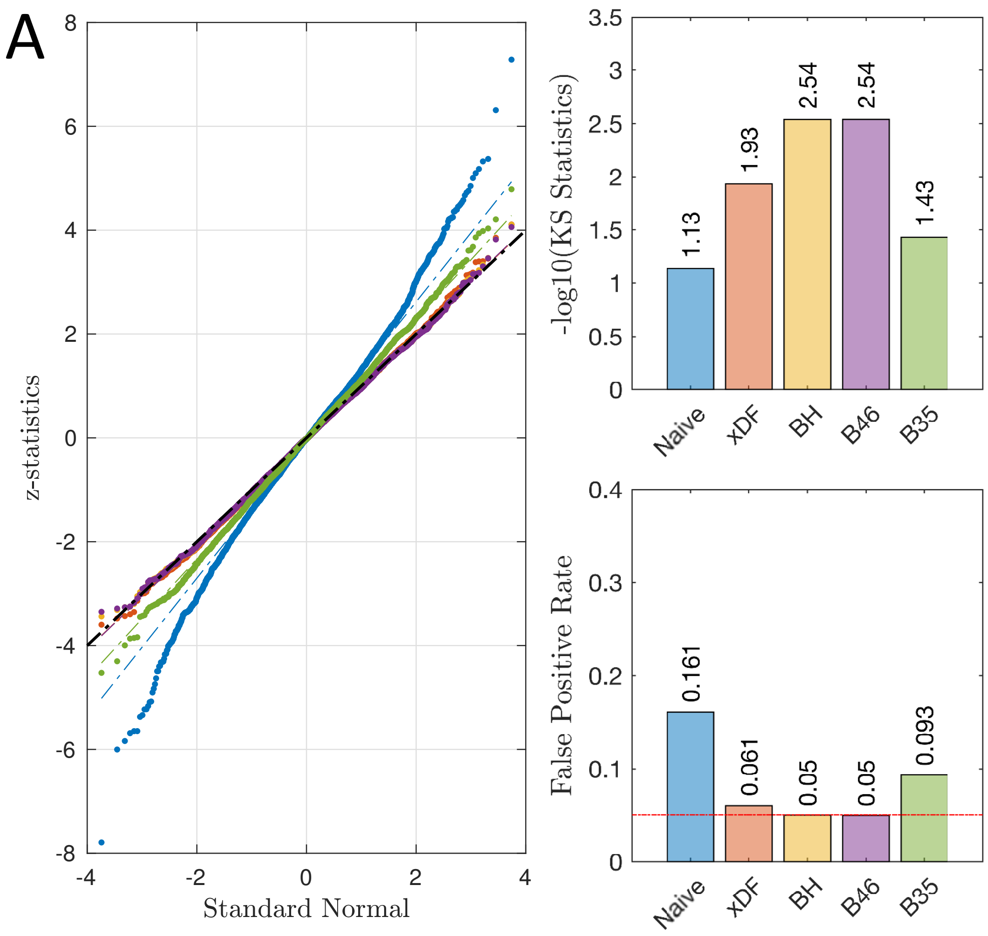
Clifford et al (1989), Bailey & Hammersley (1946)

$$\mathbb{V}(\hat{\rho}_{xy,0}) = N^{-1} + 2N^{-2}\sum_{i=1}^{N-1}(N-i)\hat{\rho}_{xx,i}\hat{\rho}_{yy,i}$$

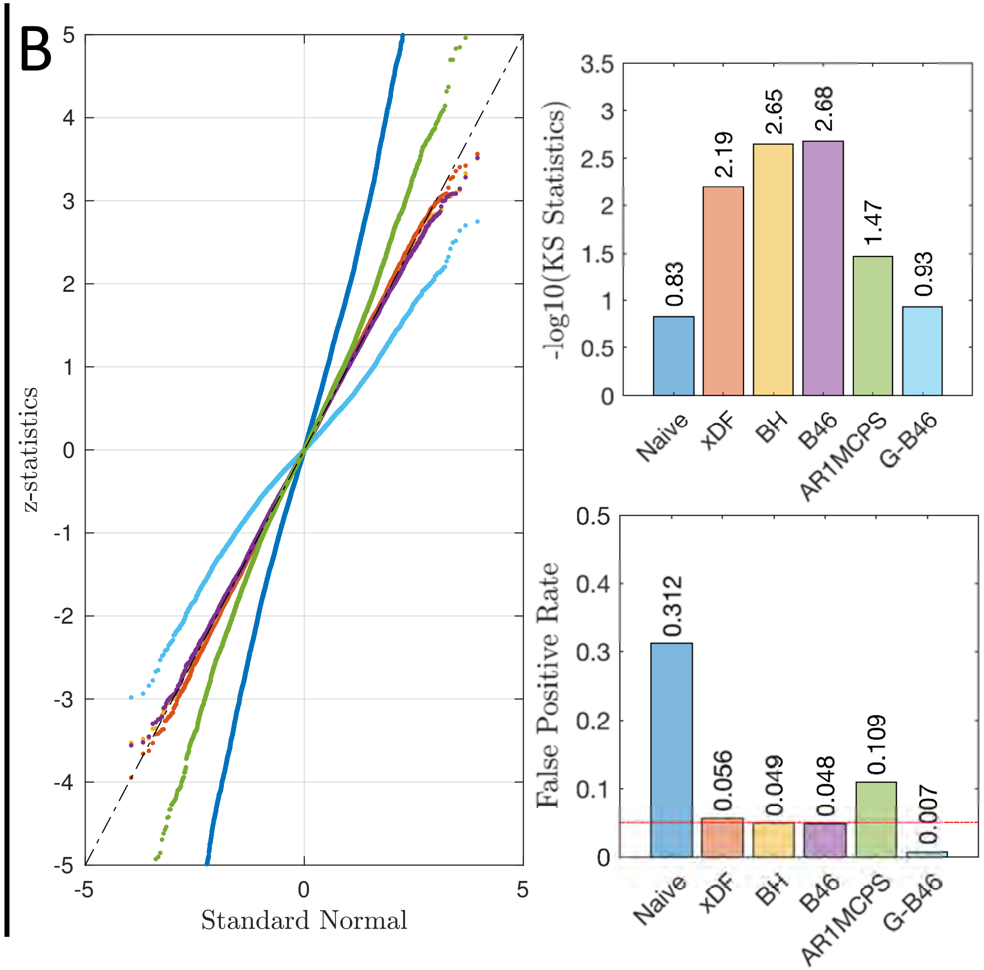
Null Evaluations

- Only xDF controls FPR under all settings considered

Null Real Data
Intersubject Scrambling



Null Simulated Data
True correlation set from data



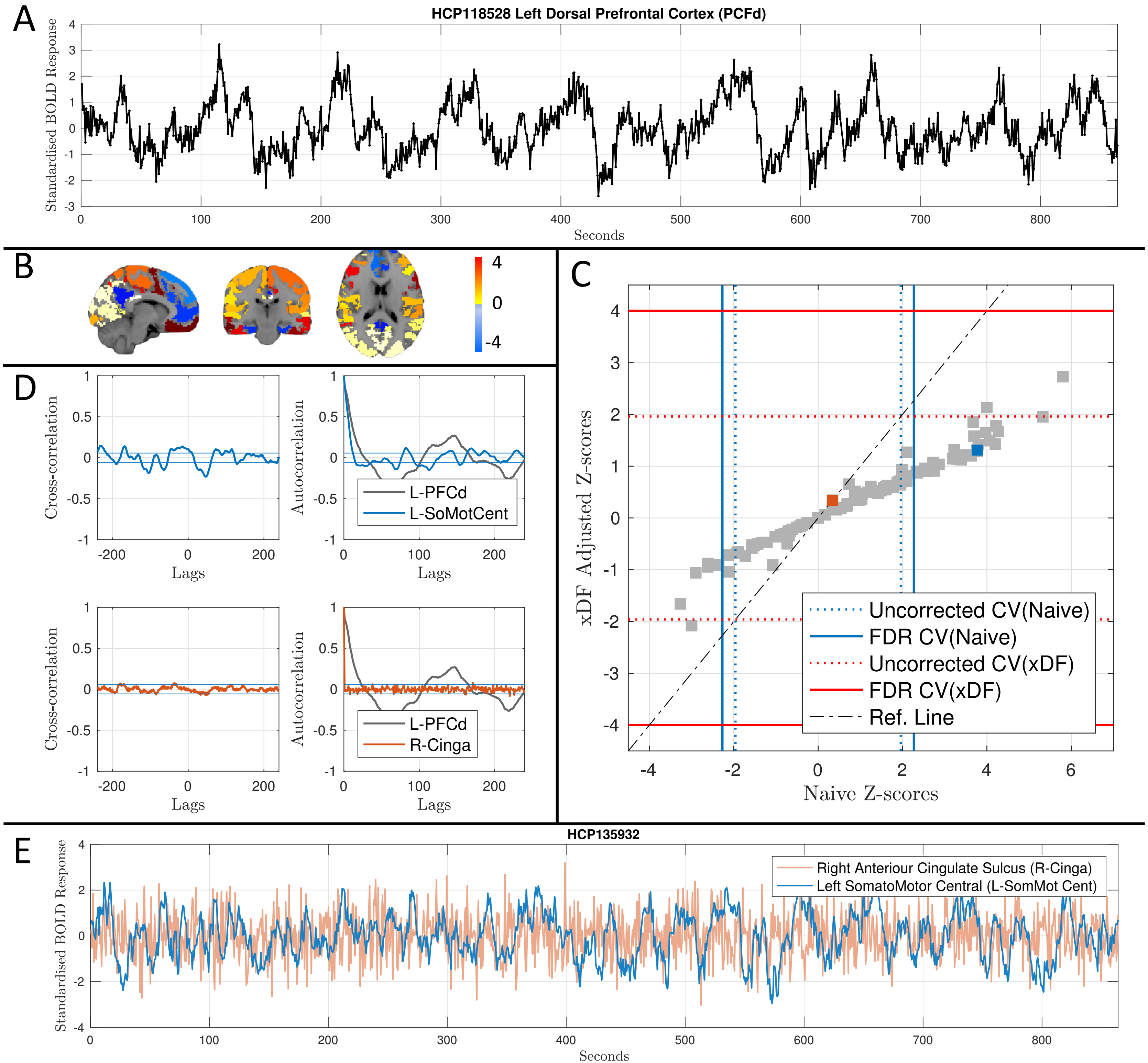
HCP Demo

From one subject: PFCd

From a different subject: SoMotCent Cinga

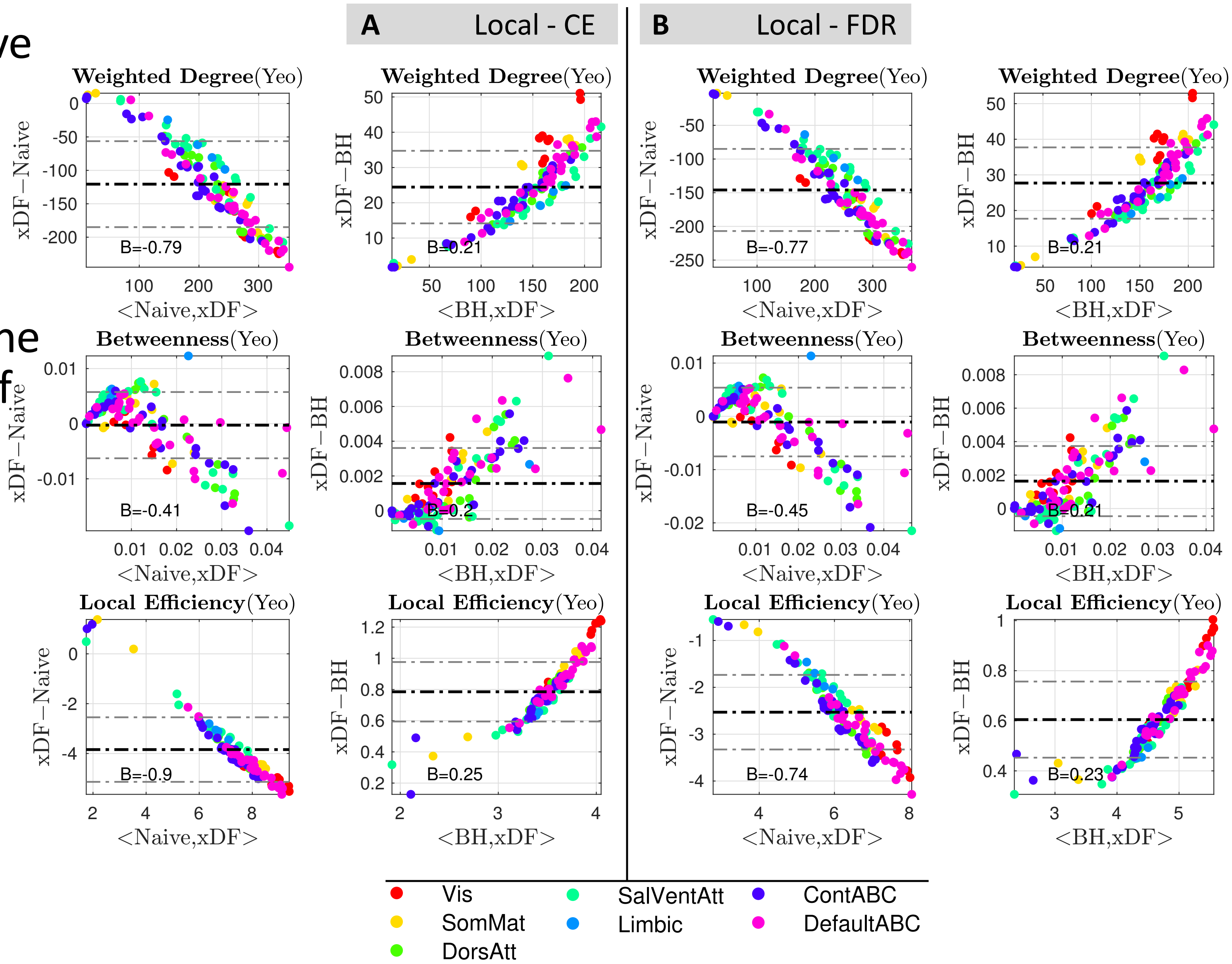
Null is true!

Yet huge Z's observed!



Topological Measures: Naïve vs xDF matters

- Thresholding naïve r/Z gives very different results
- Discipline must decide: What is the ‘right’ measure of connectivity strength?
  - r?
  - Z (SNR)
- (HCP U100)



Toolbox & Reproducibility

- xDF:
  - https://github.com/asoroosh/xDF

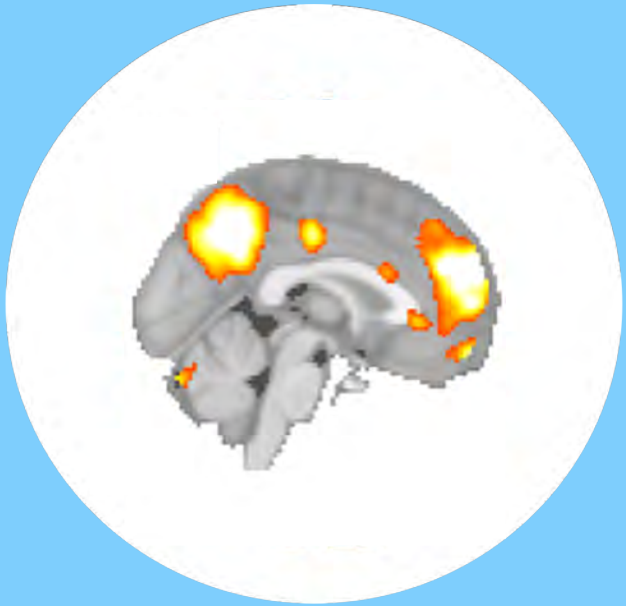
xDF Take Aways

- Var of r=corr(X,Y) & atanh(r) depends on
  (1) Autocorr(X), (2) Autocorr(Y) & (3) Crosscorr(X,Y)
- Impact of Autocorrelation on Correlation
  – Underappreciated in neuroscience
  – Better methods, reporting of methods needed
- If don't need inference, *r* or atanh(*r*) is fine
- If need z-scores
  – Must use Roy/xDF stderrs
  – But appreciate variation in stderrs & diff from *r*

Spatial Confidence Sets for Raw Effect Size Images

Beyond Null Hypothesis Testing of Cluster Size

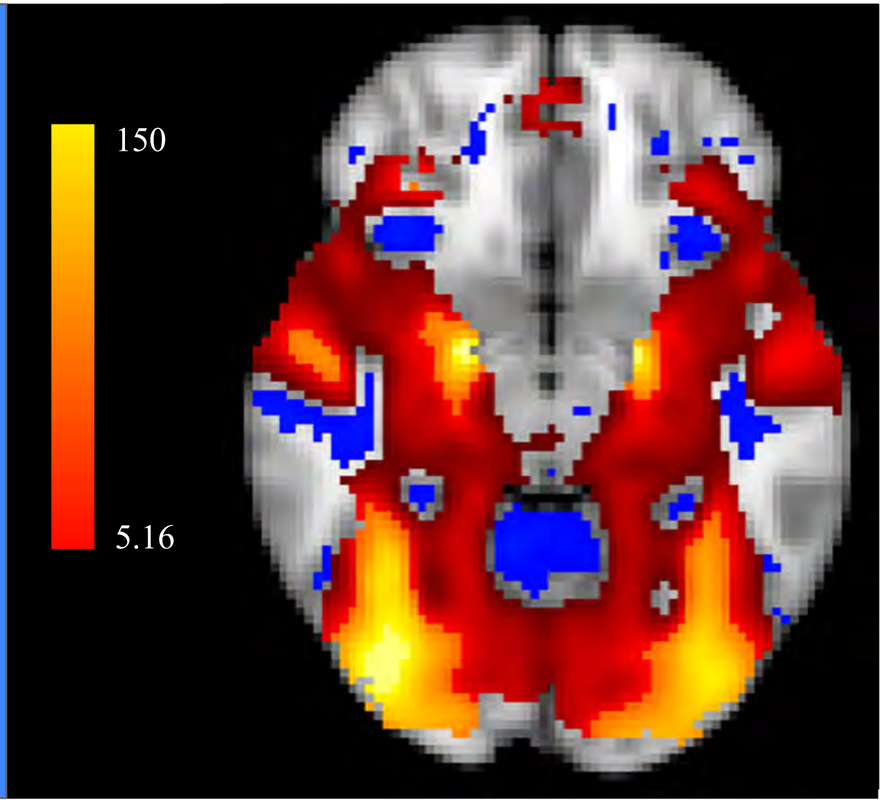
Alex Bowring, Fabian Telschow, Armin Schwarzman, Thomas Nichols

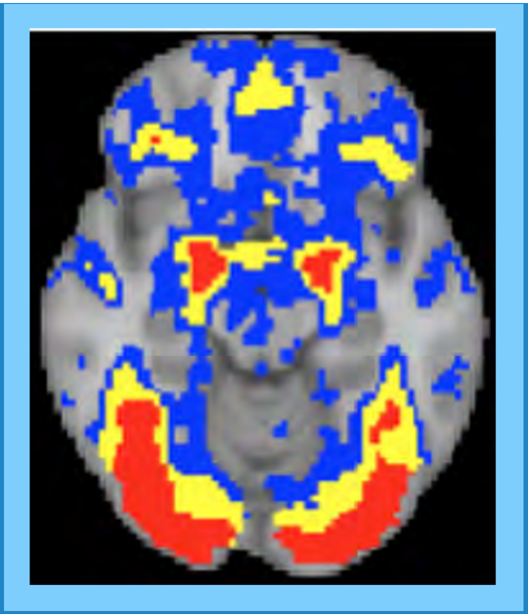


Background

The Fallacy of the Null Hypothesis

- UK Biobank
  - Faces - Shapes
  - N = 8569
- Thresholded t-statistic
  - $p_{FWE} < 0.05$ (Bonferroni)





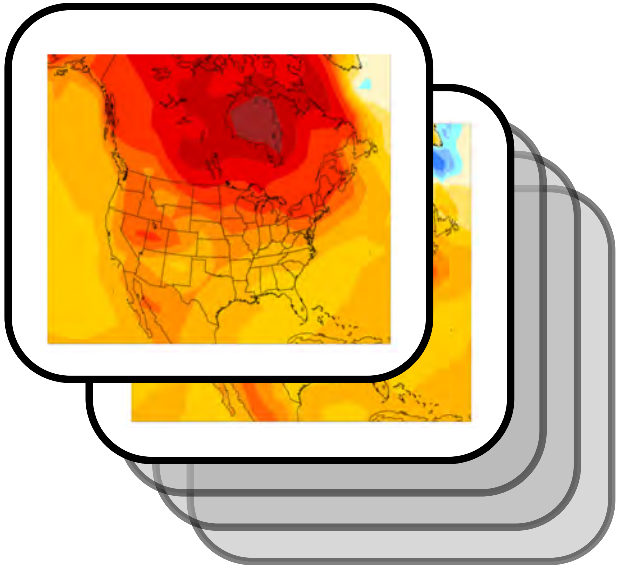
- With enough statistical power, can **always** reject null

- Solution:
  - Stop testing, start estimating non-zero effects (%BOLD change)
  - Univariate: Point estimate + confidence interval
  - **Multivariate: Cluster + spatial Confidence Set**

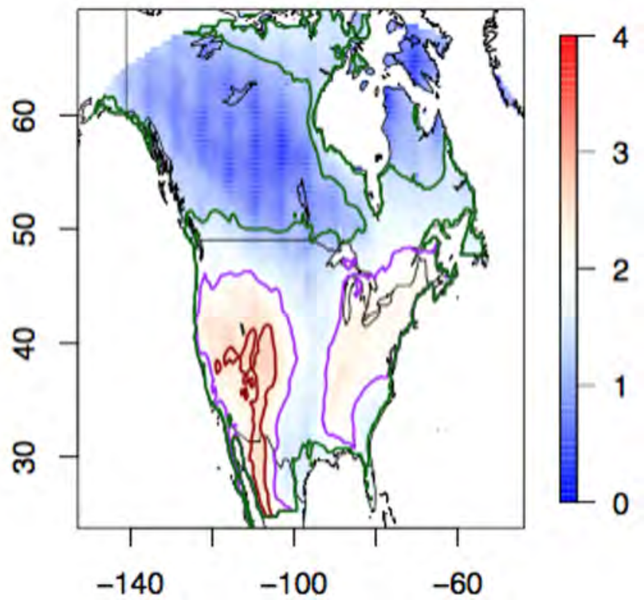
Spatial Confidence Sets

Spatial Confidence Sets Method

- ▷ Method Conceived by *Sommerfeld, Sain, Schwartzman (2015)*
  - ○ Used for geospatial data
  - ○ Regions in the USA at risk of climate change, *c* = 2℃



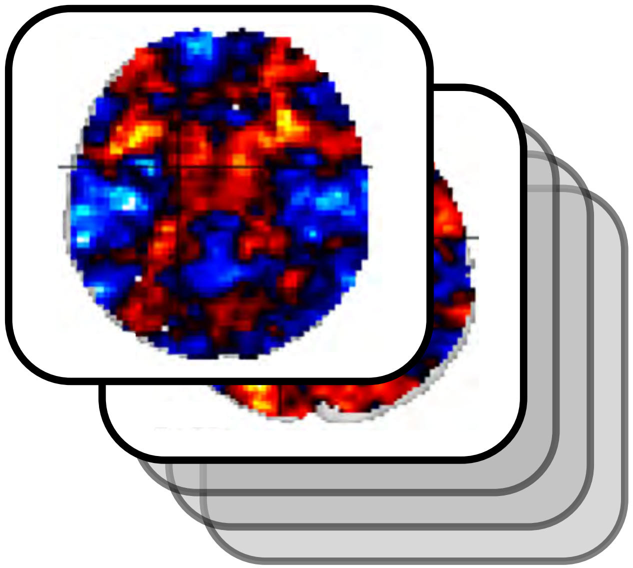
Year-on-year temperature data

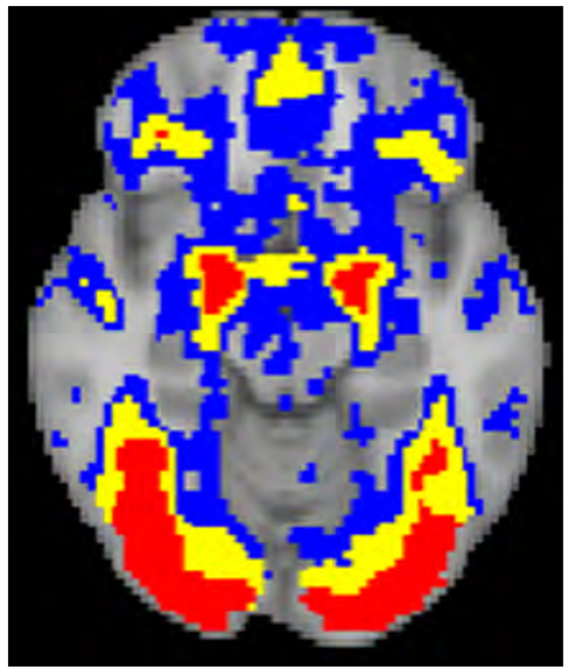


Spatial confidents sets estimating 2℃ temperature change

Sommerfeld, Sain, Schwartzman (2018). Confidence Regions for Spatial Excursion Sets From Repeated Random Field Observations, With an Application to Climate. *JASA*, *113*(523), 1327–1340.

Spatial Confidence Sets Method



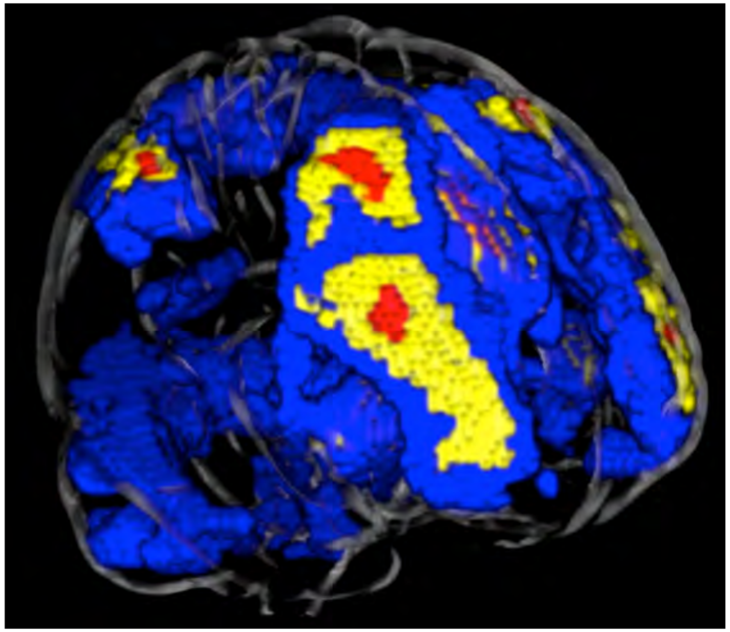


fMRI subject-level data

Spatial Confidents Sets estimating
1% BOLD change

Confidence Sets

Interpreting the Confidence Sets for a c = 1.0% BOLD change



RED VOXELS
The Upper Confidence Set
We are 95% confident over the whole brain these voxels have a true %BOLD > 1.0%

YELLOW VOXELS (Overlapped by red)
Obtained by thresholding the data at 1.0%
The best guess from your data voxels where %BOLD > 1.0%

BLUES VOXELS (Overlapped by yellow + red)
The Lower Confidence Set
We are 95% confident over the whole brain that voxels *outside* this set (background voxels) have a true %BOLD < 1.0%

A 1D Intuition

Signal + Noise Model

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

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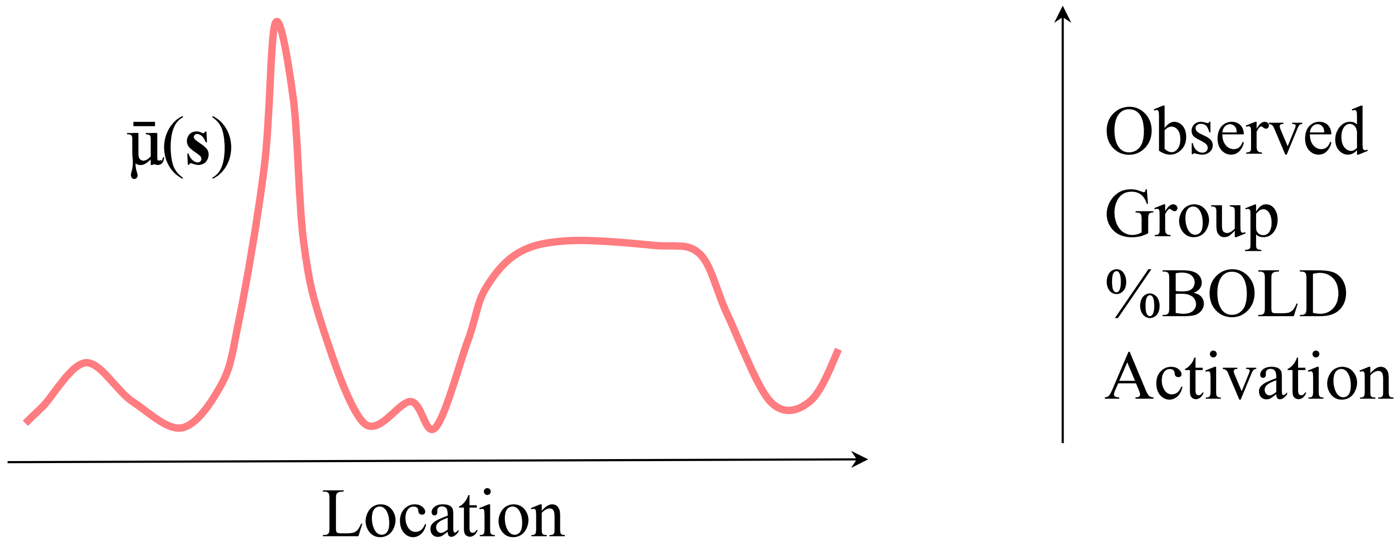

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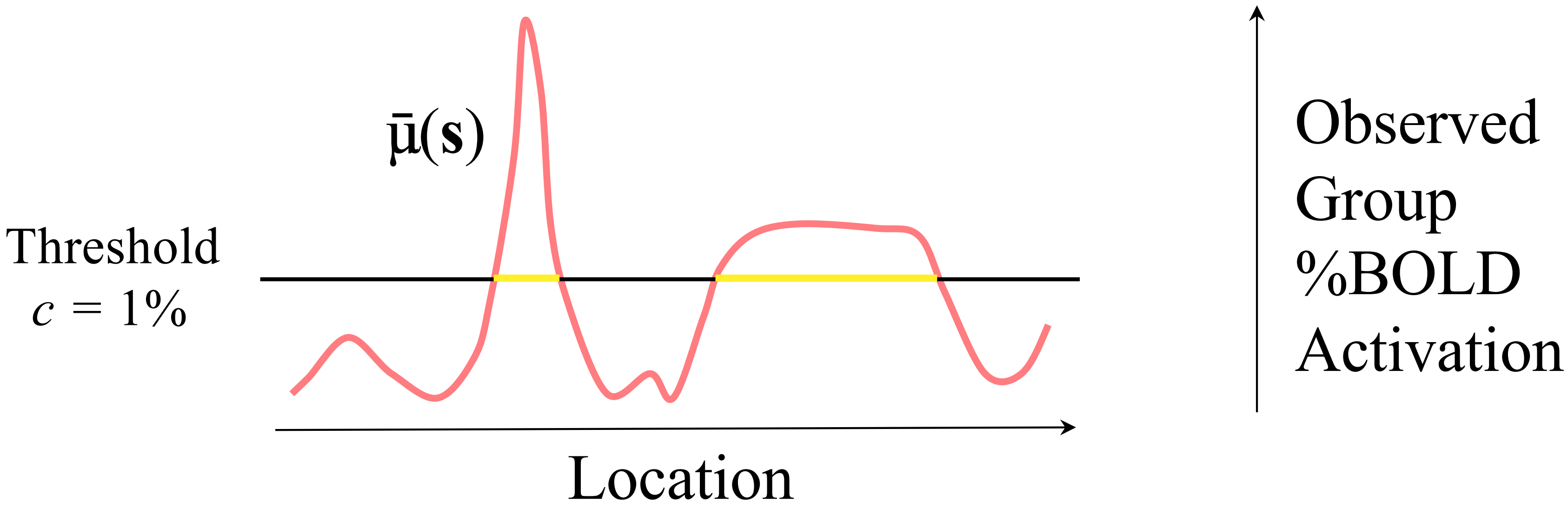

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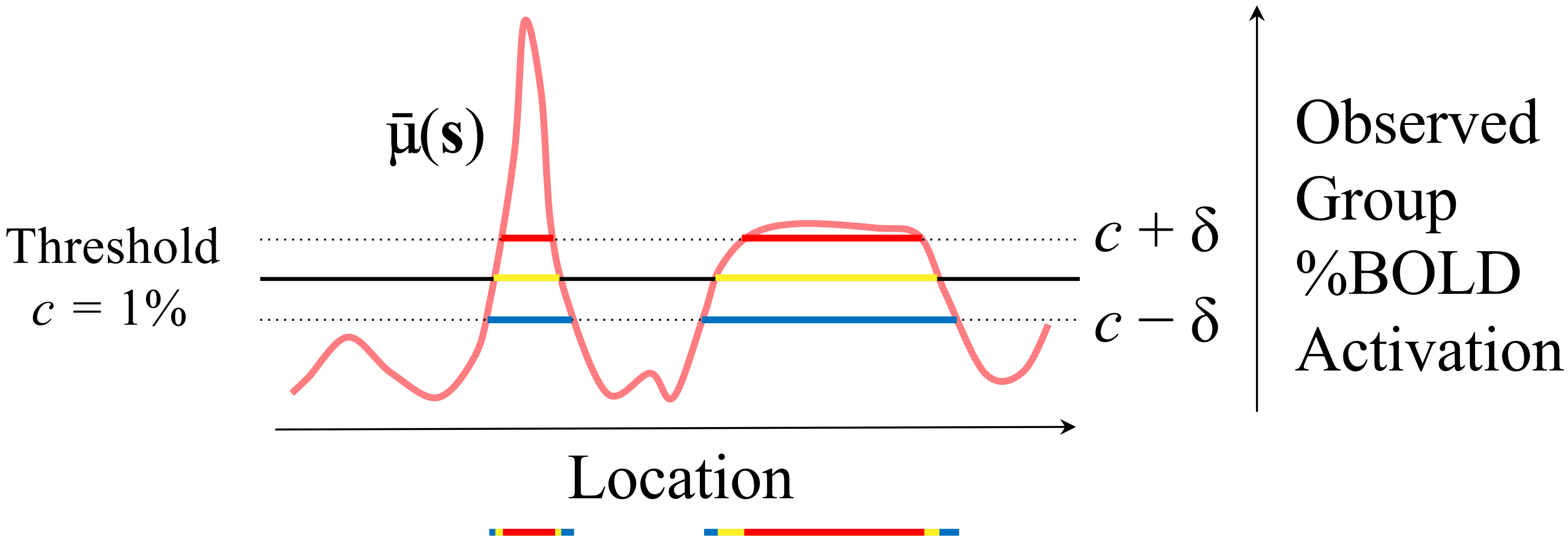

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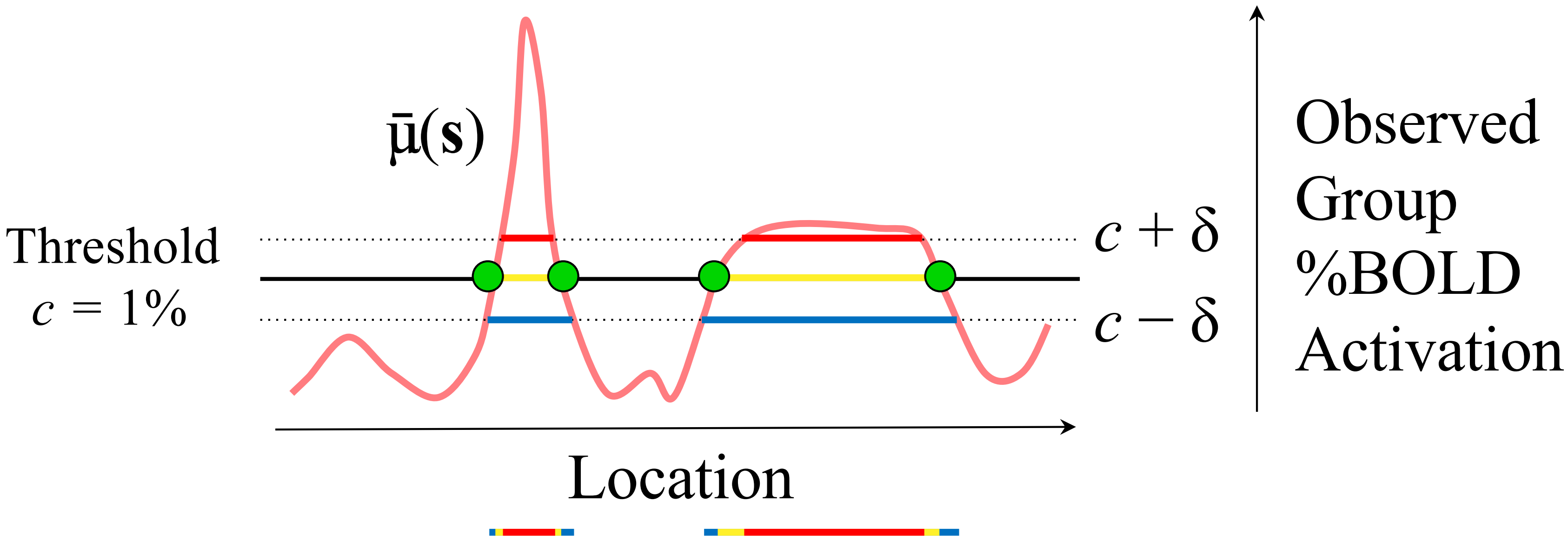


Estimate the max distribution of $\varepsilon(\mathbf{s})$ on the boundary $\bar{\mu}(\mathbf{s})$ = 1% BOLD

- ▷ Bootstrap the residuals along the boundary

Compute δ using the 95%-ile of the max distribution of $\varepsilon(\mathbf{s})$

The Wild Bootstrap Scheme

- Compute each subjects residual field on the boundary $\hat{\mu}(\mathbf{s}) = 1\%$ BOLD
  - $(R_1(\mathbf{s}), \ldots, R_N(\mathbf{s})) = \mathbf{R(s)} = \mathbf{Y(s)} - \hat{\mu}(\mathbf{s})$

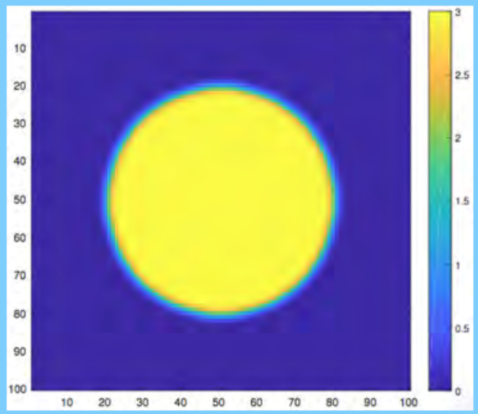
- Standardize the residuals to have unit variance
  - $\bar{\mathbf{R}}(\mathbf{s}) = \sqrt{N}\, \mathbf{R(s)} / \hat{\sigma}(\mathbf{s})$

- Multiply each $\bar{R}_i(\mathbf{s})$ by a Rademacher random variable $r_i(s)$
  - $r_i(s) = +1$ or -1 with probability 0.5

- Estimate the distribution of $\varepsilon(\mathbf{s})$ with the field:

  $\bar{G}(\mathbf{s}) = 1/N \times \sum r_i(s)\bar{R}_i(\mathbf{s})$
  - Obtain one estimate of the maximum $m = \max[\bar{G}(\mathbf{s})]$

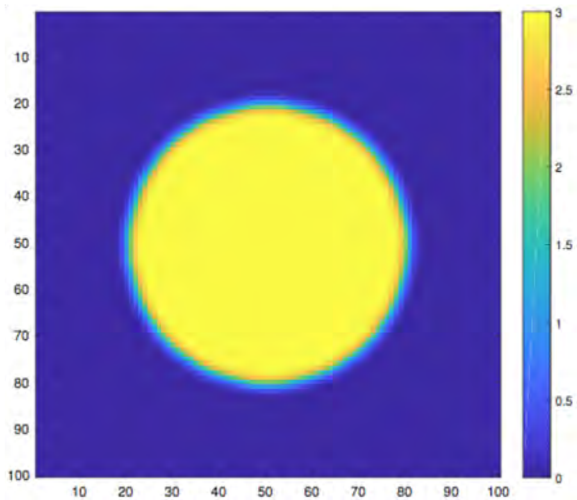
- Repeat steps 3 and 4 many times to obtain many copies $\bar{G}_1(\mathbf{s}), \ldots, \bar{G}_B(\mathbf{s})$ and construct the empirical max distribution $m_1, \ldots, m_B$
  - Compute δ by calculating the 95%-ile of the m_i



▷ In simulating the Confidence Sets, we discovered some hiccups with the method

Simulations and Further Developments

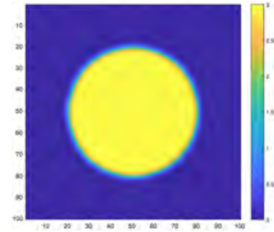
Simulation Set-up

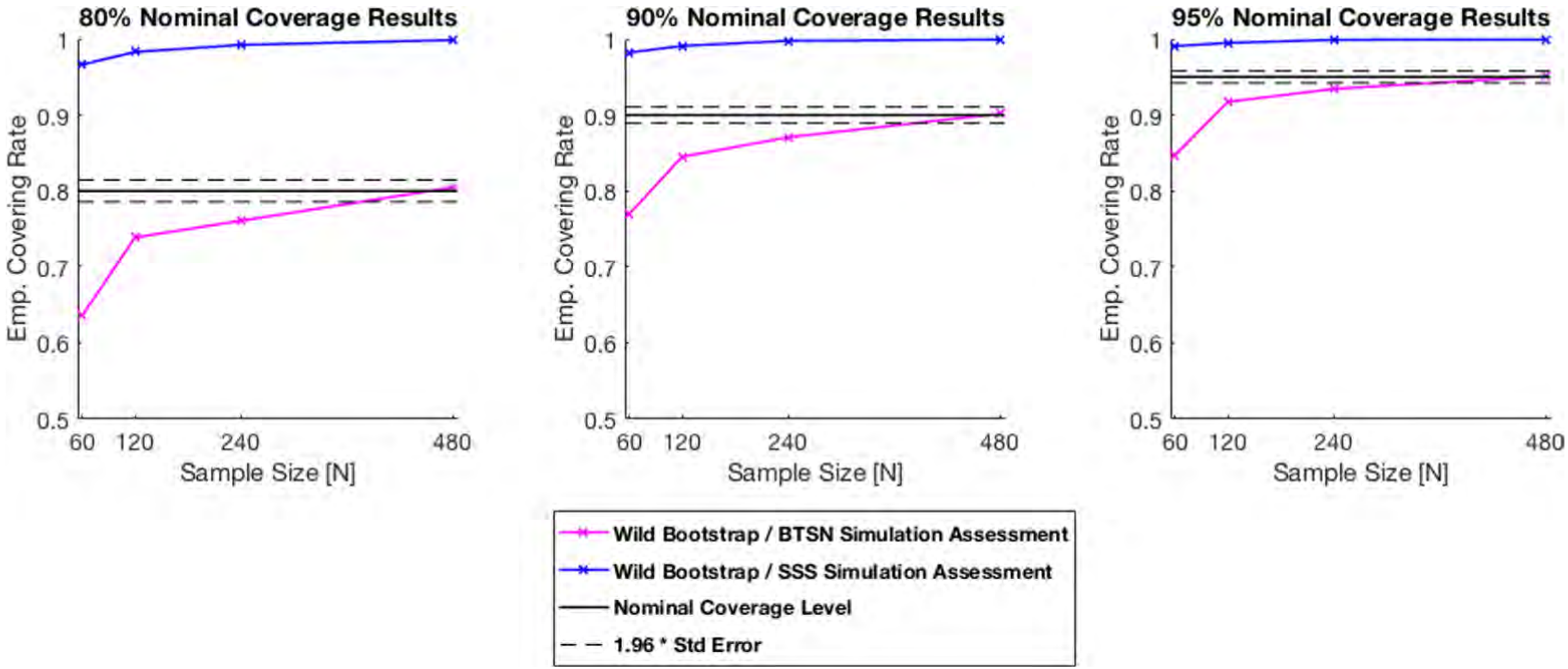


- ▷ Number of Subjects (N) = 60, 120, 240, 480
- ▷ Number of Realisations = 3000
- ▷ True Signal $\mu(\mathbf{s})$:
  - ○ Circle, magnitude 3, radius 30
  - ○ 3mm Gaussian FWHM
- ▷ Noise $\varepsilon_i(\mathbf{s})$:
  - ○ Homogeneous Gaussian Noise
  - ○ 3mm Gaussian FWHM
- ▷ Threshold c = 2
- ▷ Confidence 1 - α = 80%, 90%, 95%

Upper Conf. Set $\subset$ {True Signal > 2} $\subset$ Lower Conf. Set

Results A





Coverage reduced using new simulation assessment!

Asymptotic nominal coverage, can we do better for small samples?

The Wild Bootstrap Scheme

- Compute each subjects residual field on the boundary $\hat{\mu}(\mathbf{s}) = 1\%$ BOLD
  - $(R_1(\mathbf{s}), \ldots, R_N(\mathbf{s})) = \mathbf{R}(\mathbf{s}) = \mathbf{Y}(\mathbf{s}) - \hat{\mu}(\mathbf{s})$

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  - $\tilde{\mathbf{R}}(\mathbf{s}) = \sqrt{N}\, \mathbf{R}(\mathbf{s}) / \hat{\boldsymbol{\sigma}}(\mathbf{s})$

Asymptotically Gaussian
But t-distributed for finite N

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- Estimate the distribution of ... $(\mathbf{s})$ with the field:

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▷ Estimate the distribution of $\varepsilon(\mathbf{s})$ with the field:

$\bar{G}(\mathbf{s}) = 1/N * \sum r_i(s)\bar{R}_i(\mathbf{s})$

○ Obtain one estimate of the maximum $m = \max[\bar{G}(\mathbf{s})]$

Conditional on $\bar{R}$,
$\bar{G}$ is Gaussian

▷ Repeat steps 3 and 4 many times to obtain many copies $\bar{G}_1(\mathbf{s}), \ldots, \bar{G}_B(\mathbf{s})$ and construct the empirical max distribution $m_1, \ldots, m_B$

○ Compute "c" by calculating the 95%-ile of the m_i

The Wild Bootstrap Scheme

- Compute each subjects residual field on the boundary $\hat{\mu}(\mathbf{s})$ = 1% BOLD
  - $(R_1(\mathbf{s}), \ldots, R_N(\mathbf{s})) = \mathbf{R}(\mathbf{s}) = \mathbf{Y}(\mathbf{s}) - \hat{\mu}(\mathbf{s})$
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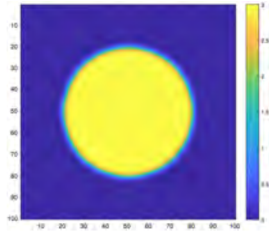
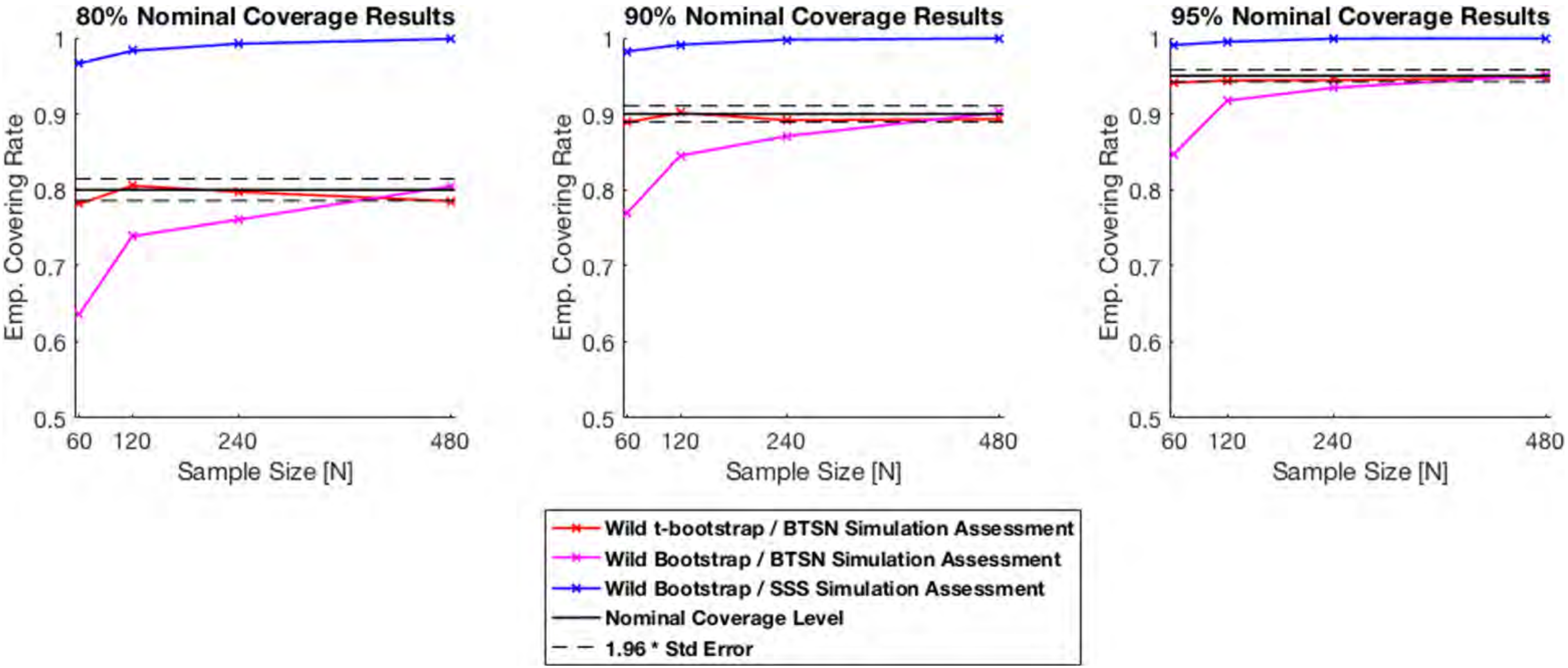
- Estimate the distribution of $\varepsilon(\mathbf{s})$ with the field:

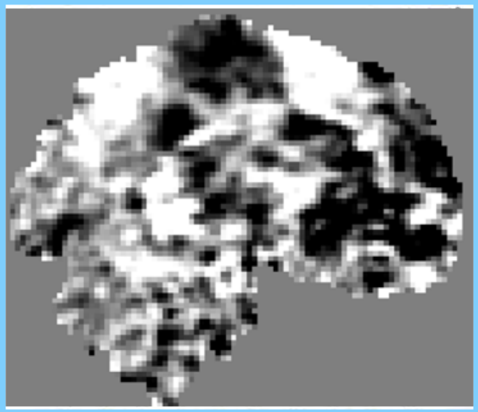
  $\tilde{G}(\mathbf{s}) = 1/N * \sum r_i(s)\tilde{R}_i(\mathbf{s}) / \hat{\sigma}^*(\mathbf{s})$
  - Obtain one estimate of the maximum $m = \max[\tilde{G}(\mathbf{s})]$
- Repeat steps [illegible] and 4 many times to obtain many copies $\tilde{G}_1(\mathbf{s}), \ldots, \tilde{G}_B(\mathbf{s})$ and construct the empirical max distribution $m_1, \ldots, m_B$
  - Compute $\hat{c}$ by calculating the 95%-ile of the m_i

Conditional on $\tilde{R}$,
$\tilde{G}$ is Gaussian

Results B




80% Nominal Coverage Results
90% Nominal Coverage Results
95% Nominal Coverage Results
Emp. Covering Rate
1
0.9
0.8
0.7
0.6
0.5
60
120
240
480
Sample Size [N]
Wild t-bootstrap / BTSN Simulation Assessment
Wild Bootstrap / BTSN Simulation Assessment
Wild Bootstrap / SSS Simulation Assessment
Nominal Coverage Level
1.96 * Std Error



▷ We obtain Confidence Sets for 80 subjects %BOLD data from the Human Connectome Project

Real Data demonstration

Human Connectome Project

- 80 Subjects

- Working Memory Task:
  - Participants presented with pics of places, tools, faces, body parts:

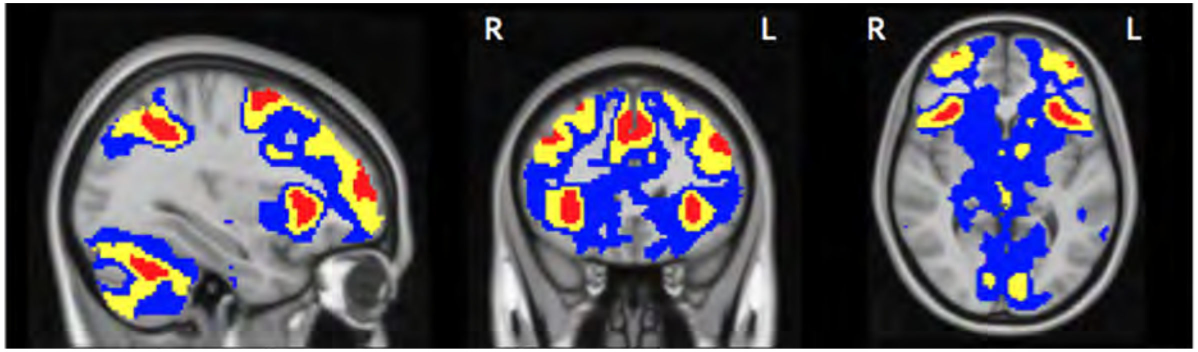
  - 2-back Task
    - Press button when you saw same image 2 stimuli ago
  - 0-back Task
    - Press button when you see a particular image

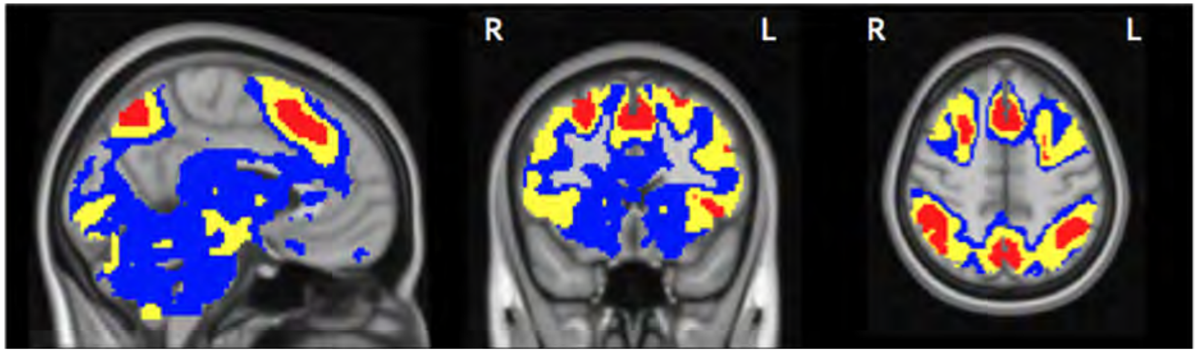
- Two runs, Eight task blocks (25 seconds per block)

- We obtain Confidence Sets on subject-level %BOLD maps contrasting 2-back vs 0-back tasks
  - Inference on 1.0% and 2.0% BOLD change

Results

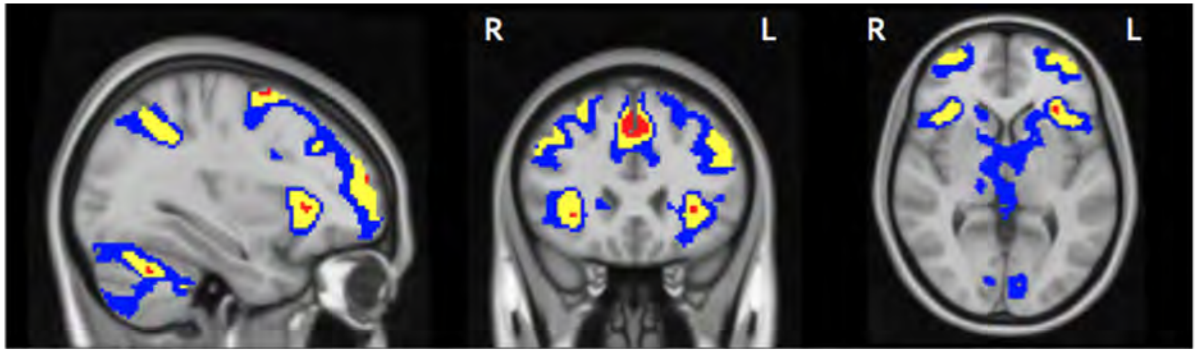
1.0%
BOLD change

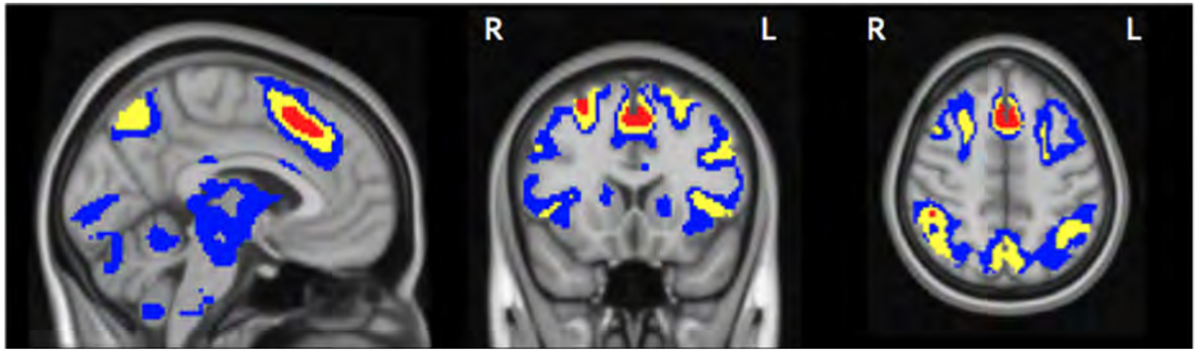




Results

2.0%
BOLD change



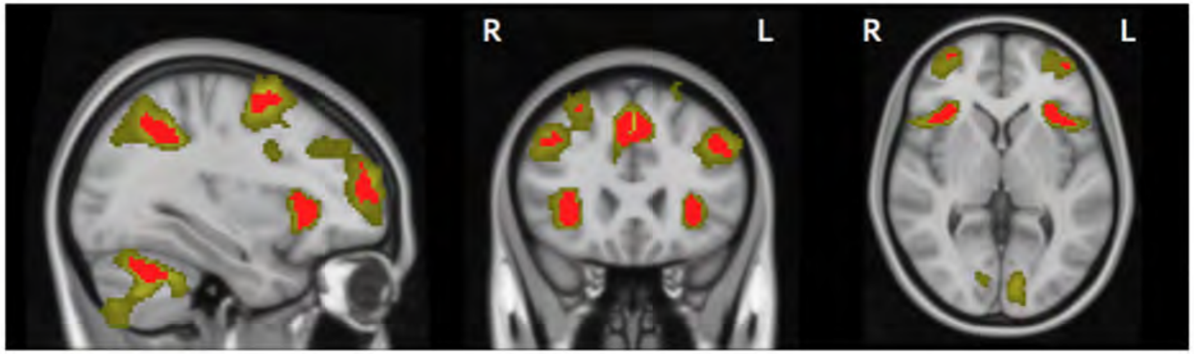


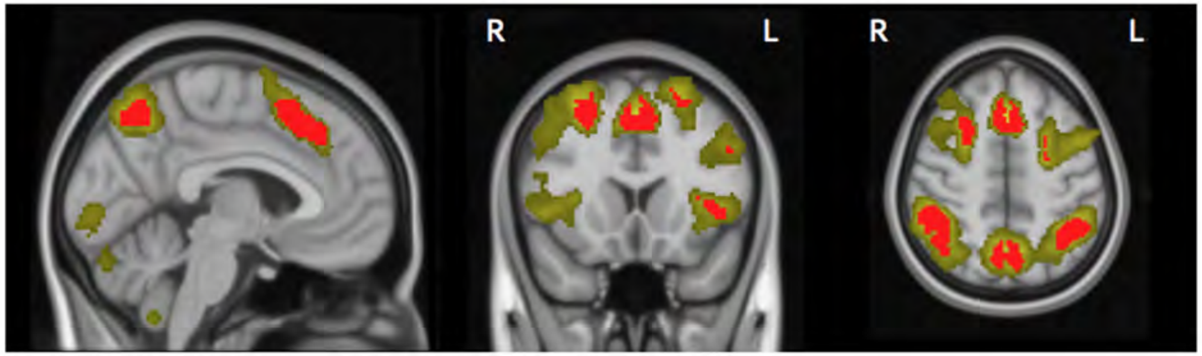
Results

1.0%
BOLD change

vs

Voxelwise p<0.05 FWE (permutation)





From %BOLD to Cohen's *d*

Signal + Noise Model

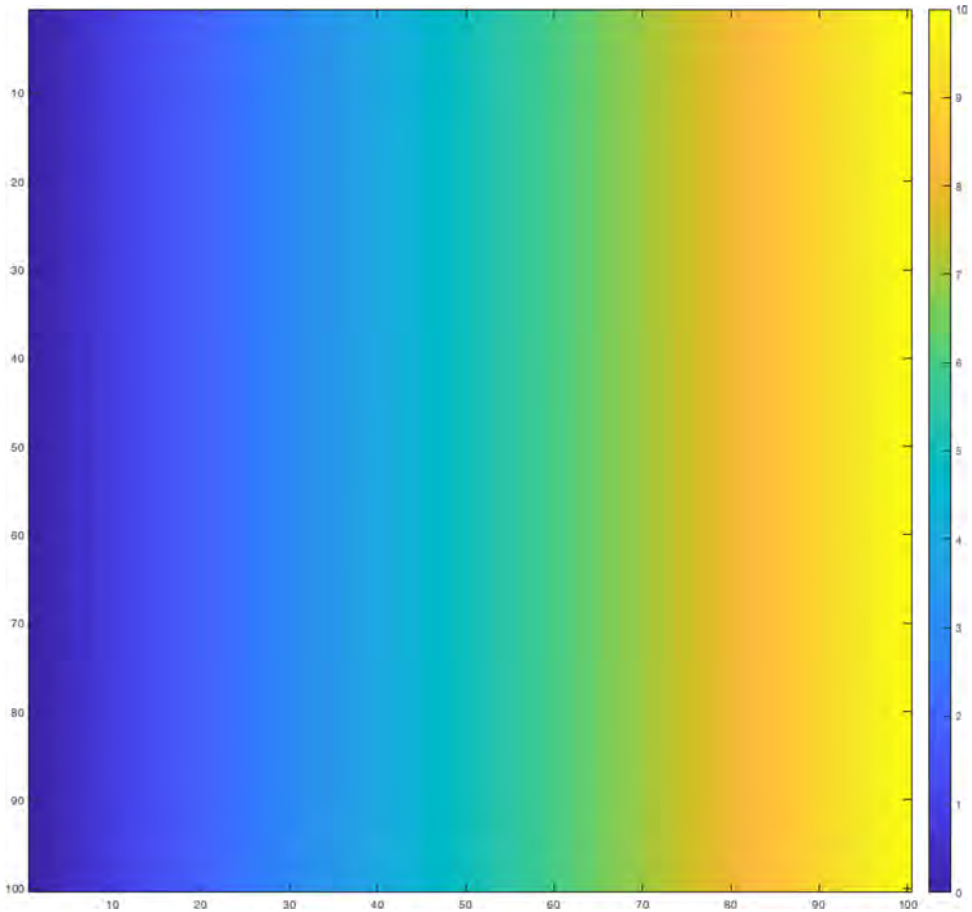
$$Y_i(\mathbf{s}) = \mu(\mathbf{s}) + \varepsilon_i(\mathbf{s}) \qquad i = 1, \ldots, N$$

%BOLD: Inference on $\mu(\mathbf{s})$

⬇

Cohen's *d*: Inference on $d(\mathbf{s}) = \mu(\mathbf{s})/\boldsymbol{\sigma}(\mathbf{s})$

From %BOLD to Cohen's *d*

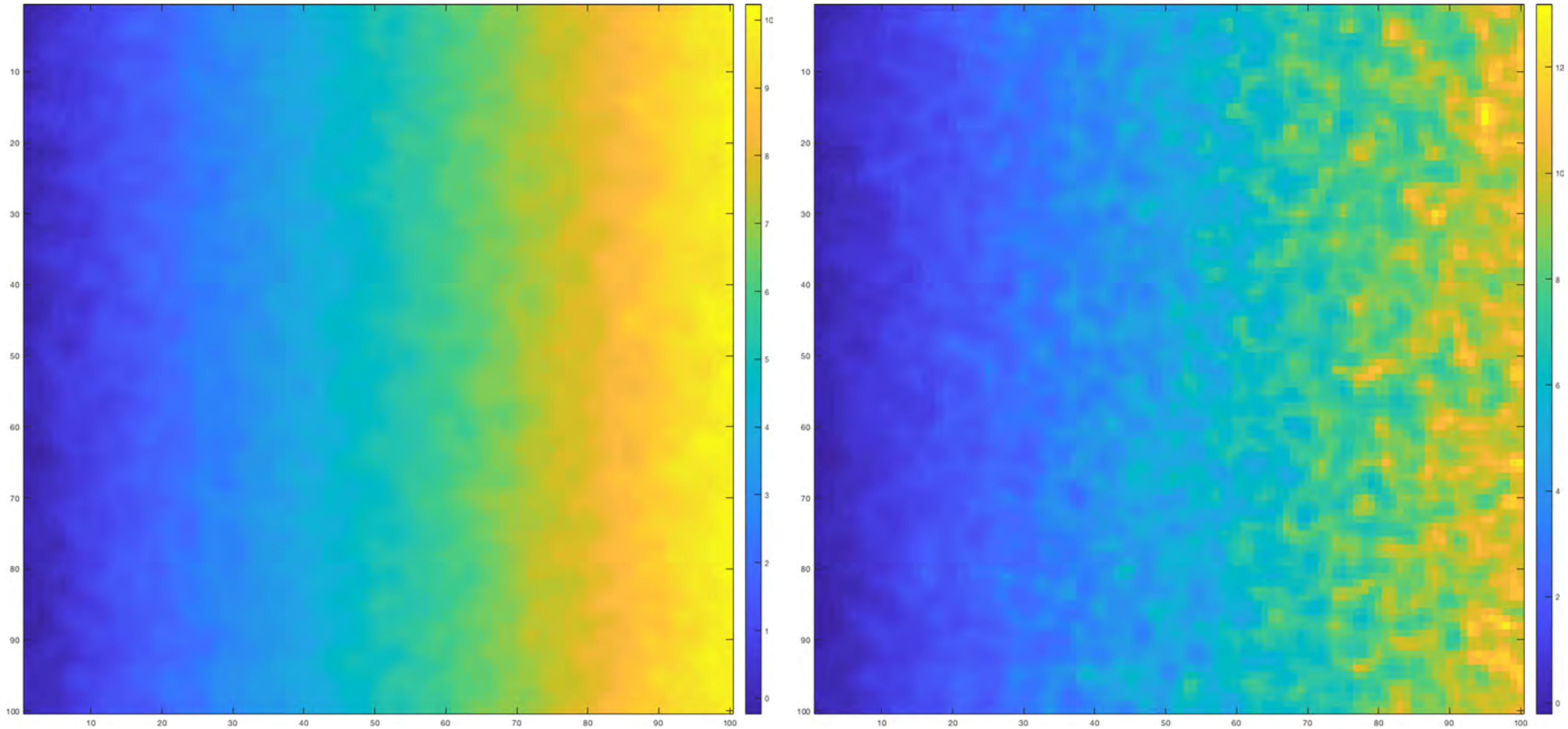


Ramp of signal μ(**s**) from 0 to 10

(Each subject, signal + noise of variance 1 everywhere, so μ = *d*)

From %BOLD to Cohen's *d*

For N = 60



$\bar{\mu}(s)$ $\qquad$ $\bar{\mu}(s)/\bar{\sigma}(s)$

From %BOLD to Cohen's *d*

What's going on?

▷ $\bar{\mu} \sim N(\mu, \boldsymbol{\sigma}/\sqrt{N})$

▷ Cohen's *d* estimator can be written:

$$\hat{d}(\boldsymbol{s}) = \frac{\hat{\mu}(\boldsymbol{s})}{\hat{\sigma}(\boldsymbol{s})} = \frac{1}{\sqrt{N}} \cdot \frac{\hat{\mu}(\boldsymbol{s})}{\hat{\sigma}(\boldsymbol{s})/\sqrt{N}} = \frac{1}{\sqrt{N}} \cdot \frac{\frac{\hat{\mu}-\mu}{\sigma/\sqrt{N}} + \frac{\mu}{\sigma/\sqrt{N}}}{\sqrt{\left(\frac{\hat{\sigma}^2}{\sigma/(N-1)}\right)/(N-1)}}$$

From RHS, $\hat{d}$ distributed by $1/\sqrt{N}$ times a noncentral-t distribution with noncentrality parameter $\sqrt{N} \times \mu/\boldsymbol{\sigma}$ and N - 1 degrees of freedom

From %BOLD to Cohen's *d*

Moments of the Cohen's *d* estimator

$\sqrt{N}\hat{d}$ is noncentral t-distributed, with expectatio

$$\mathbb{E}\left[\sqrt{N}\hat{d}\right] = \left(\frac{1}{2}(N-1)\right)^{1/2} \sqrt{N}\frac{\mu}{\sigma}\frac{\Gamma(\frac{1}{2}(N-1)-\frac{1}{2})}{\Gamma(\frac{1}{2}(N-1))}$$

$$\approx \sqrt{N}\frac{\mu}{\sigma}\left(1-\frac{3}{4N-5}\right)^{-1}$$

So…

Expectation of $\bar{\mu}$ is μ

$$\hat{d} = \frac{\hat{\mu}}{\hat{\sigma}} \qquad \frac{\mu}{\sigma}\left(1-\frac{3}{4N-5}\right)^{-1}$$

But expectation of is

From %BOLD to Cohen's *d*

Moments of the Cohen's *d* estimator

$\sqrt{N}\hat{d}$ is noncentral t-distributed, variance:

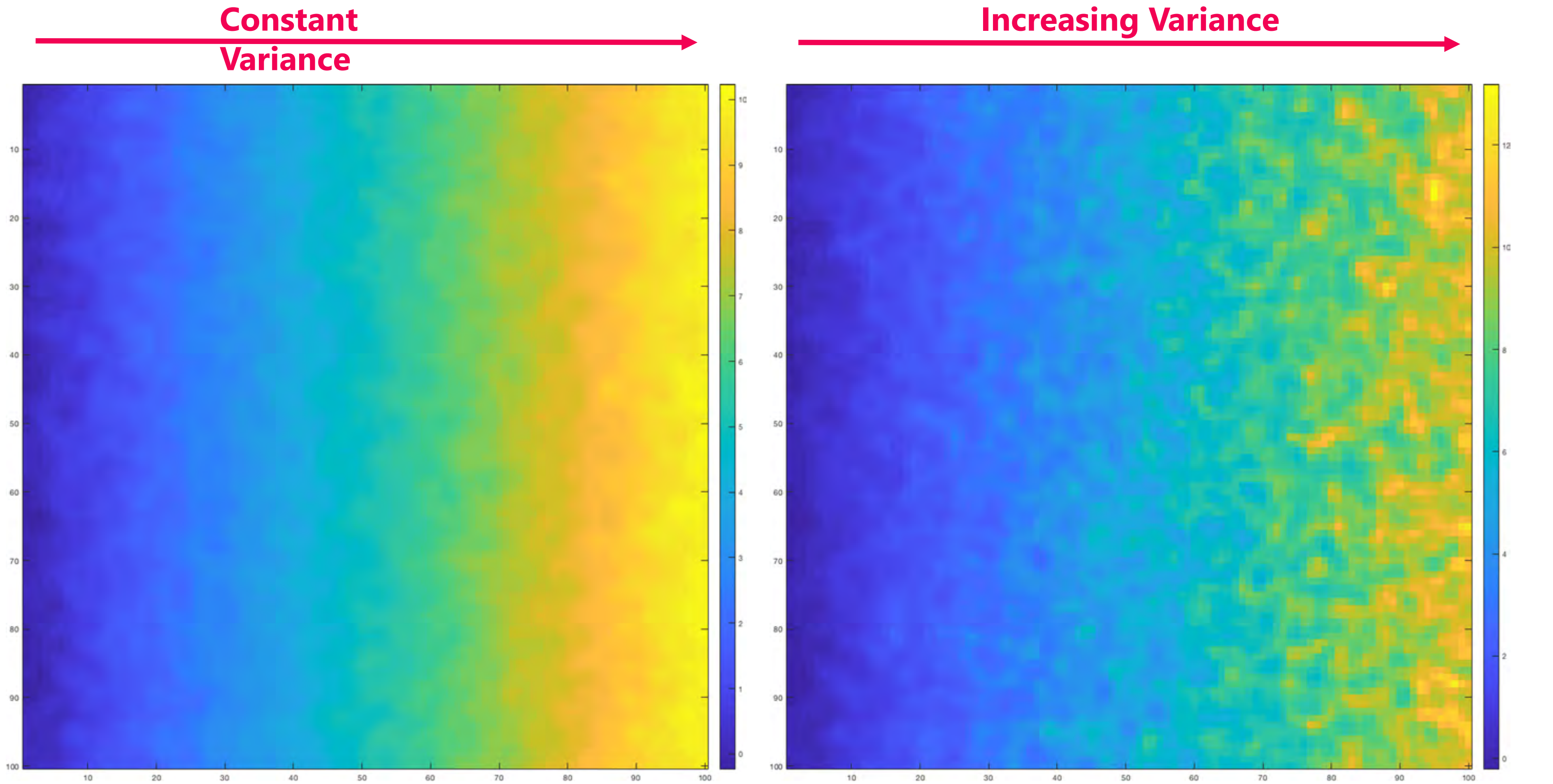
$$\begin{aligned}\mathrm{Var}\left[\sqrt{N}\hat{d}\right] &= \frac{(N-1)(1+N\frac{\mu^2}{\sigma^2})}{N-3} - m_1^2 \\ &\approx \frac{N-1}{N-3} + N\frac{\mu^2}{\sigma^2}\left(\frac{N-1}{N-3} - \left(1 - \frac{3}{4N-5}\right)^{-2}\right) \\ &= \frac{N-1}{N-3} + N\frac{\mu^2}{\sigma^2}\left(\frac{8N^2-17N+11}{16(N-3)(N-2)^2}\right)\end{aligned}$$

NOTE

Variance is dependent on the effect size:

Larger effect size -> Larger variance

From %BOLD to Cohen's *d*



$\bar{\mu}(s)$ $\quad$ $\bar{\mu}(s)/\bar{\sigma}(s)$

A Covariance problem

Signal + Noise Model

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

$\mathrm{Cov}[\varepsilon(\mathbf{s}), \varepsilon(\mathbf{t})] = \boldsymbol{\sigma}(\mathrm{s})\boldsymbol{\sigma}(\mathrm{t})\,\mathfrak{c}(s,t)$

Where $\mathfrak{c}(s,t)$ is the correlation between the observations at voxels s and t.

A Covariance problem

Multivariate Central limit theorem:

$$\sqrt{N}\Big(\big(\hat{\mu}(s),\hat{\sigma}^2(s),\hat{\mu}(t),\hat{\sigma}^2(t)\big)-\big(\mu(s),\sigma^2(s),\mu(t),\sigma^2(t)\big)\Big)\Rightarrow\mathcal{N}\Big(0,\Sigma(s,t)\Big)$$

With covariance matrix:

$$\Sigma(s,t)=\begin{pmatrix}\sigma^2(s) & 0 & \sigma(s)\sigma(t)\mathfrak{c}(s,t) & 0\\ 0 & 2\sigma^4(s) & 0 & 2\sigma^2(s)\sigma^2(t)\mathfrak{c}(s,t)^2\\ \sigma(s)\sigma(t)\mathfrak{c}(s,t) & 0 & \sigma^2(t) & 0\\ 0 & 2\sigma^2(s)\sigma^2(t)\mathfrak{c}(s,t)^2 & 0 & 2\sigma^4(t)\end{pmatrix}$$

A Covariance problem

Applying the delta method, with g(x, y) = x/√y :

$$\sqrt{N}\left(\left(\hat{d}(s),\hat{d}(t)\right)-\left(d(s),d(t)\right)\right)\to\mathcal{N}\left(0,\Sigma^*(s,t)\right)$$

With covariance matrix:

$$\Sigma^*(s,t)=\begin{pmatrix} 1+\frac{\mu^2(s)}{2\sigma^2(s)} & \mathfrak{c}(s,t)+\mathfrak{c}(s,t)^2\frac{\mu(s)\mu(t)}{2\sigma(s)\sigma(t)} \\ \mathfrak{c}(s,t)+\mathfrak{c}(s,t)^2\frac{\mu(s)\mu(t)}{2\sigma(s)\sigma(t)} & 1+\frac{\mu^2(t)}{2\sigma^2(t)} \end{pmatrix}$$

Asymptotic covariance of estimated Cohen's d field

The Wild Bootstrap Scheme:

μ

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The Wild Bootstrap Scheme: d

$$\hat{d}(\mathbf{s}) = c\left(1 - \frac{3}{4N-5}\right)^{-1}$$

- ▷ Compute each subjects residual field on the boundary
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A Covariance problem

$$\mathrm{Cov}\left[\tilde{G}(s), \tilde{G}(t)\right] = \frac{1}{n} \sum_{i,j=1}^{n} \tilde{R}_i(s)\tilde{R}_j(t)$$

$$= \frac{1}{n} \cdot \frac{1}{\hat{\sigma}(s)\,\hat{\sigma}(t)} \sum_{i,j=1}^{n} (Y_j(s) - \hat{\mu}(s))(Y_j(t) - \hat{\mu}(t))$$

$$\to \mathfrak{c}(s,t)$$

$$< \mathfrak{c}(s,t) + \mathfrak{c}(s,t)^2 \frac{\mu(s)\mu(t)}{2\sigma(s)\sigma(t)}$$

Asymptotic covar. of bootstrap residuals is wrong!

The Taylor Expansion Trick

Inspired by the delta method, take a first order Taylor expansion of g(x, y) = x/√y about ($\bar{\mu}$, $\bar{\sigma}$), approximate the residuals as:

$$g(Y_i, (Y_i - \hat{\mu})^2) - g(\hat{\mu}, \hat{\sigma}^2) \approx \nabla g(\hat{\mu}, \hat{\sigma}^2)\Big((Y_i, (Y_i - \hat{\mu})^2 - (\hat{\mu}, \hat{\sigma}^2))\Big)$$

$$= \frac{Y_i - \hat{\mu}}{\hat{\sigma}} - \frac{\hat{\mu}}{2\hat{\sigma}}\left(\frac{(Y_i - \hat{\mu})^2}{\hat{\sigma}^2} - 1\right)$$

$$= \mathcal{R}_i$$

The Taylor Expansion Trick

For

$$\mathcal{R}(s) = \nabla g(\mu(s), \sigma^2(s))(\epsilon(s), \epsilon^2(s) - \sigma^s(s))$$

We can show,

$$a.s. - lim_{N\to\infty} \mathcal{R}_i(s) = \mathcal{R}(s), \quad with \ \ \mathrm{Cov}\left[(\mathcal{R}(s), \mathcal{R}(t))\right] = \Sigma^*(s,t)$$

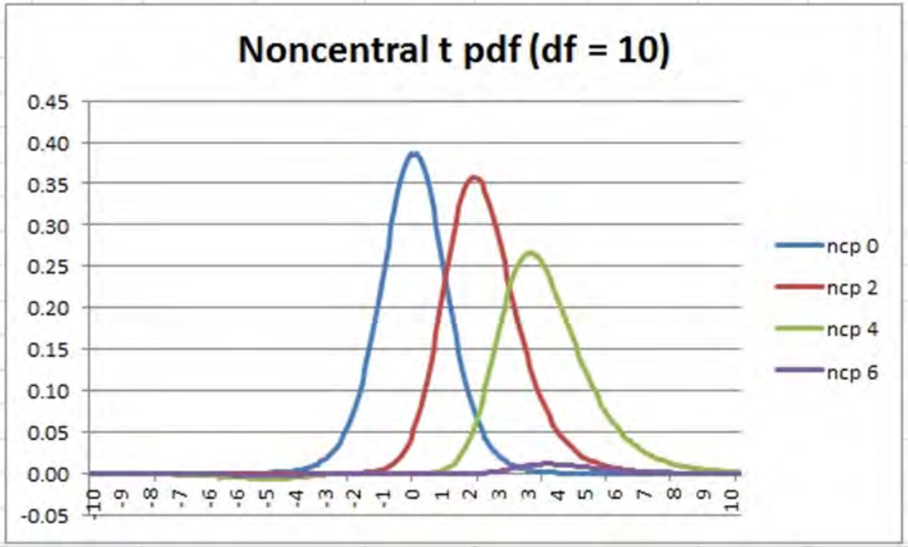
In particular

$$N^{-1} \sum_{i=1}^{N} \mathcal{R}_i(s) = 0$$

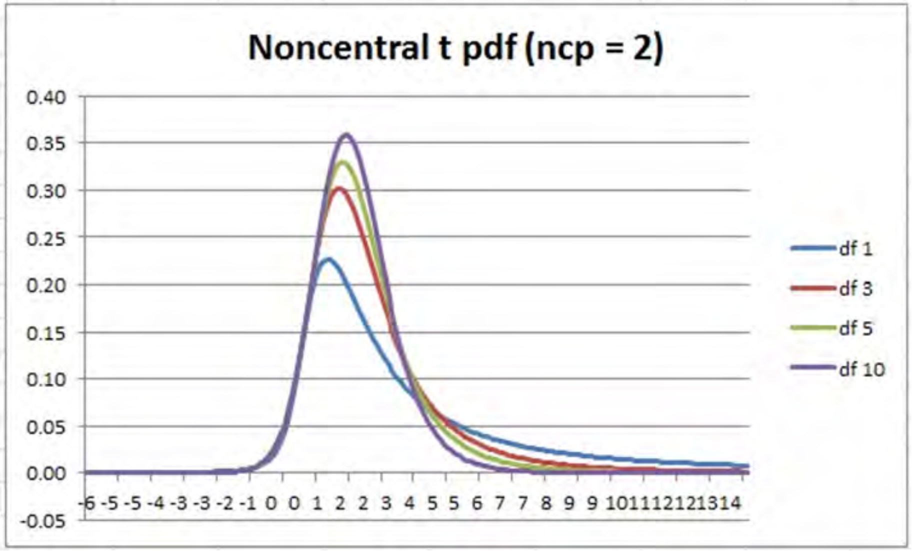
$$a.s. - lim_{N\to\infty} \frac{1}{N-1} \sum_{i=1}^{N} \mathcal{R}_i(s) R_i(t) = \mathfrak{c}(s,t) + \mathfrak{c}(s,t)^2 \frac{\mu(s)\mu(t)}{2\sigma(s)\sigma(t)}$$

I.e. mean zero residuals, with correct covariance!

Skew of the noncentral t



fixed degrees of freedom, increasing ncp



fixed ncp, increasing degrees of freedom

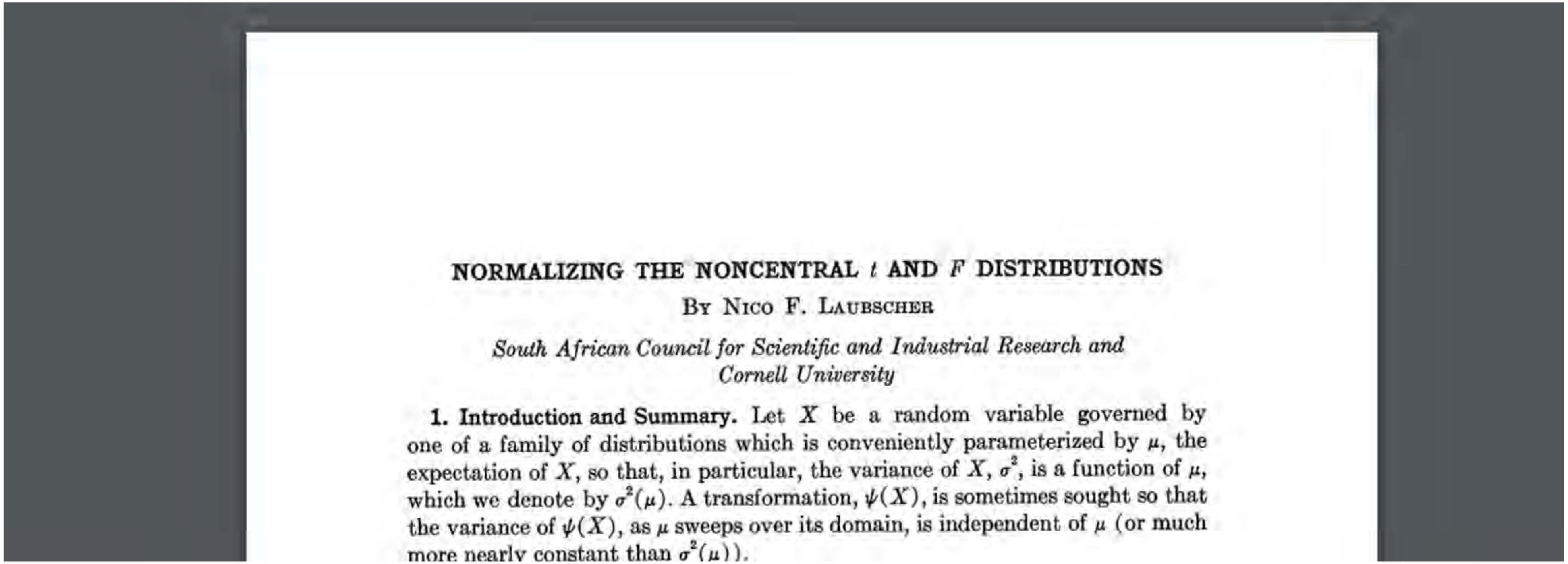
Noncentral t more skew for large NCP, small DOF

Construction of the Conf. Sets

	Upper Conf. Set	Lower Conf. Set
%BOLD:	$\{ \bar{\mu}(s) > c + \delta \}$	$\{ \bar{\mu}(s) > c - \delta \}$
Cohen's d:	$\left\{ \frac{\hat{\mu}(s)}{\hat{\sigma}(s)} > c\left(1 - \frac{3}{4N-5}\right)^{-1} + \delta \right\}$	$\left\{ \frac{\hat{\mu}(s)}{\hat{\sigma}(s)} > c\left(1 - \frac{3}{4N-5}\right)^{-1} - \delta \right\}$

Symmetric construction... but Cohen's d is skew

Normalizing the noncentral t



NORMALIZING THE NONCENTRAL t AND F DISTRIBUTIONS

BY NICO F. LAUBSCHER

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1. Introduction and Summary. Let X be a random variable governed by one of a family of distributions which is conveniently parameterized by μ, the expectation of X, so that, in particular, the variance of X, σ^2, is a function of μ, which we denote by $\sigma^2(\mu)$. A transformation, $\psi(X)$, is sometimes sought so that the variance of $\psi(X)$, as μ sweeps over its domain, is independent of μ (or much more nearly constant than $\sigma^2(\mu)$).

Laubscher (1960)

Suggests arsinh transformation to reduce skew

Normalizing the noncentral t

Laubscher's Machinery

Applying the Laubscher machinery to the non central t-distributed $\sqrt{N}\hat{d}$ ɔle , we obtain

$$\sqrt{N}\left(\alpha^* \operatorname{arcsinh}\left(\beta^* \hat{d}\right) - \alpha^* \operatorname{arcsinh}\left(\beta^* d\left(1 - \frac{3}{4N-5}\right)^{-1}\right)\right)$$

is approximately N(0,1), for α^* and β^* constants depending on N

Construction of the Conf. Sets

Upper Conf. Set **Lower Conf. Set**

Cohen's d:

$$\left\{ \frac{\hat{\mu}(s)}{\hat{\sigma}(s)} > c\left(1 - \frac{3}{4N-5}\right)^{-1} + \delta \right\} \qquad \left\{ \frac{\hat{\mu}(s)}{\hat{\sigma}(s)} > c\left(1 - \frac{3}{4N-5}\right)^{-1} - \delta \right\}$$

By monotonicity of the transformation

$$\left\{ \alpha^* \operatorname{arcsinh}\left(\beta^* \frac{\hat{\mu}}{\hat{\sigma}}\right) \geq \alpha^* \operatorname{arcsinh}\left(\beta^* c\left(1 - \frac{3}{4N-5}\right)^{-1}\right) \pm \delta \right\}$$

The Wild Bootstrap Scheme

- Compute each subject's Taylor residual $\mathcal{R}_i$ on the boundary $\hat{d}$ = c by doing a first-order Taylor expansion of the normalizing function $g(x, y) = \alpha^* \operatorname{arcsinh}\left(\beta^* \frac{x}{\sqrt{y}}\right)$ about the $(\hat{\mu}, \hat{\sigma})$

- Multiply each Taylor residual $R_i(\mathbf{s})$ by a Rademacher random variable $r_i(s)$
  - $r_i(s)$ = +1 or -1 with probability 0.5

- Estimate the distribution of the normalized noise with the field:

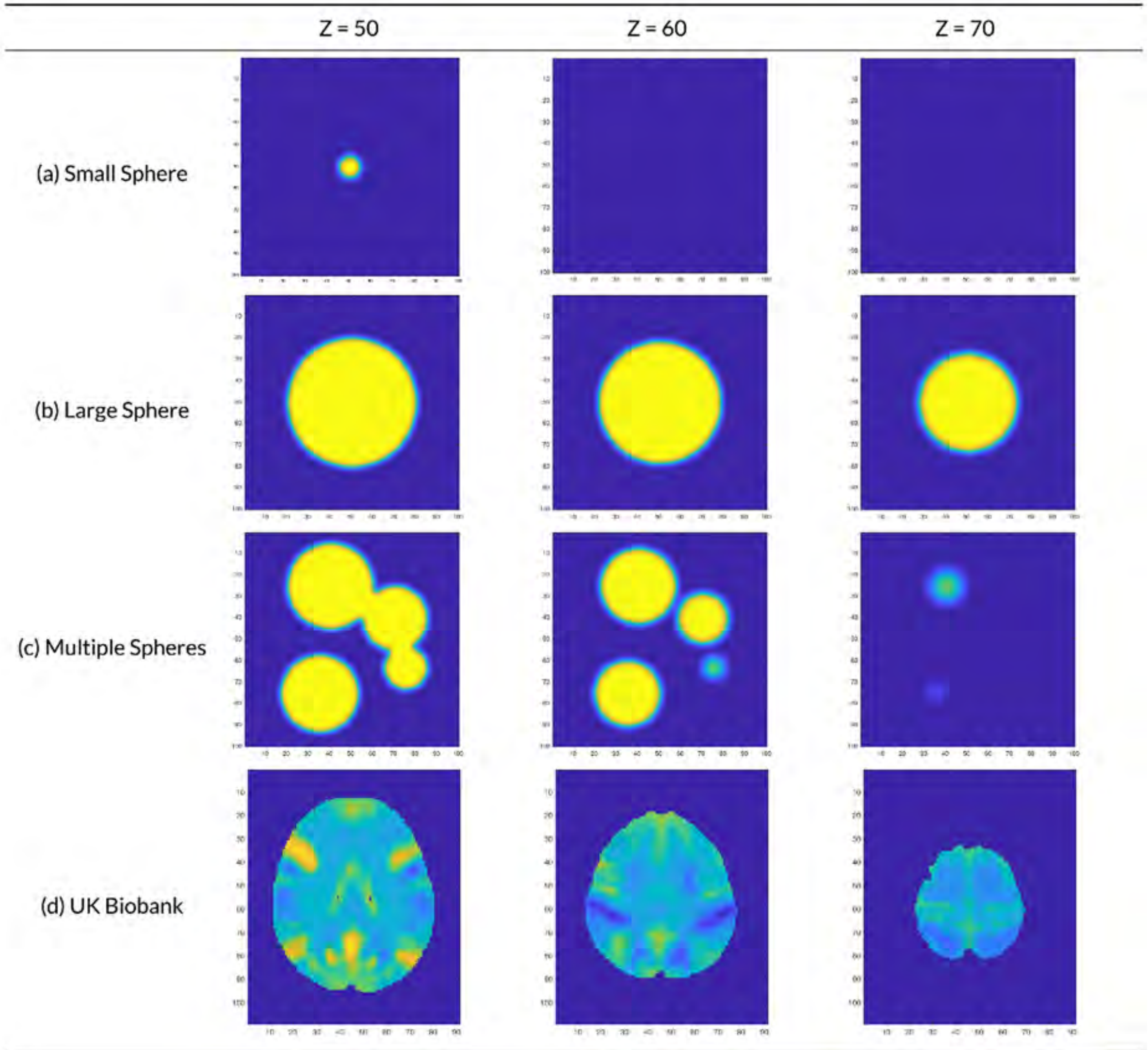
  $\bar{G}(\mathbf{s}) = 1/N * \sum r_i(s) R_i(\mathbf{s}) / \boldsymbol{\sigma}^*(\mathbf{s})$
  - Obtain one estimate of the maximum m = max[$\bar{G}(\mathbf{s})$]

- Repeat steps 3 and 4 many times to obtain many copies $\bar{G}_1(\mathbf{s})$, …, $\bar{G}_B(\mathbf{s})$ and construct the empirical max distribution m_1, …, m_B
  - Compute δ by calculating the 95%-ile of the m_i

- Construct Confidence Sets in the standardized space

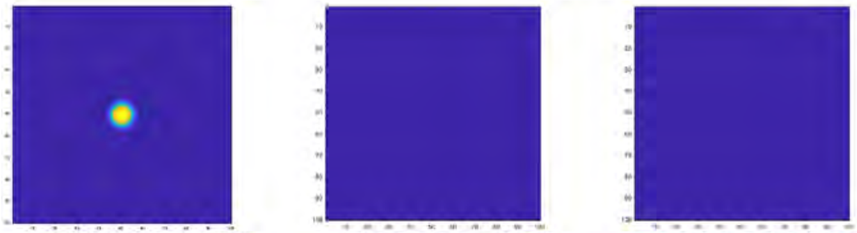
3D Simulations

In all simulations, inference on where *d* > 0.8

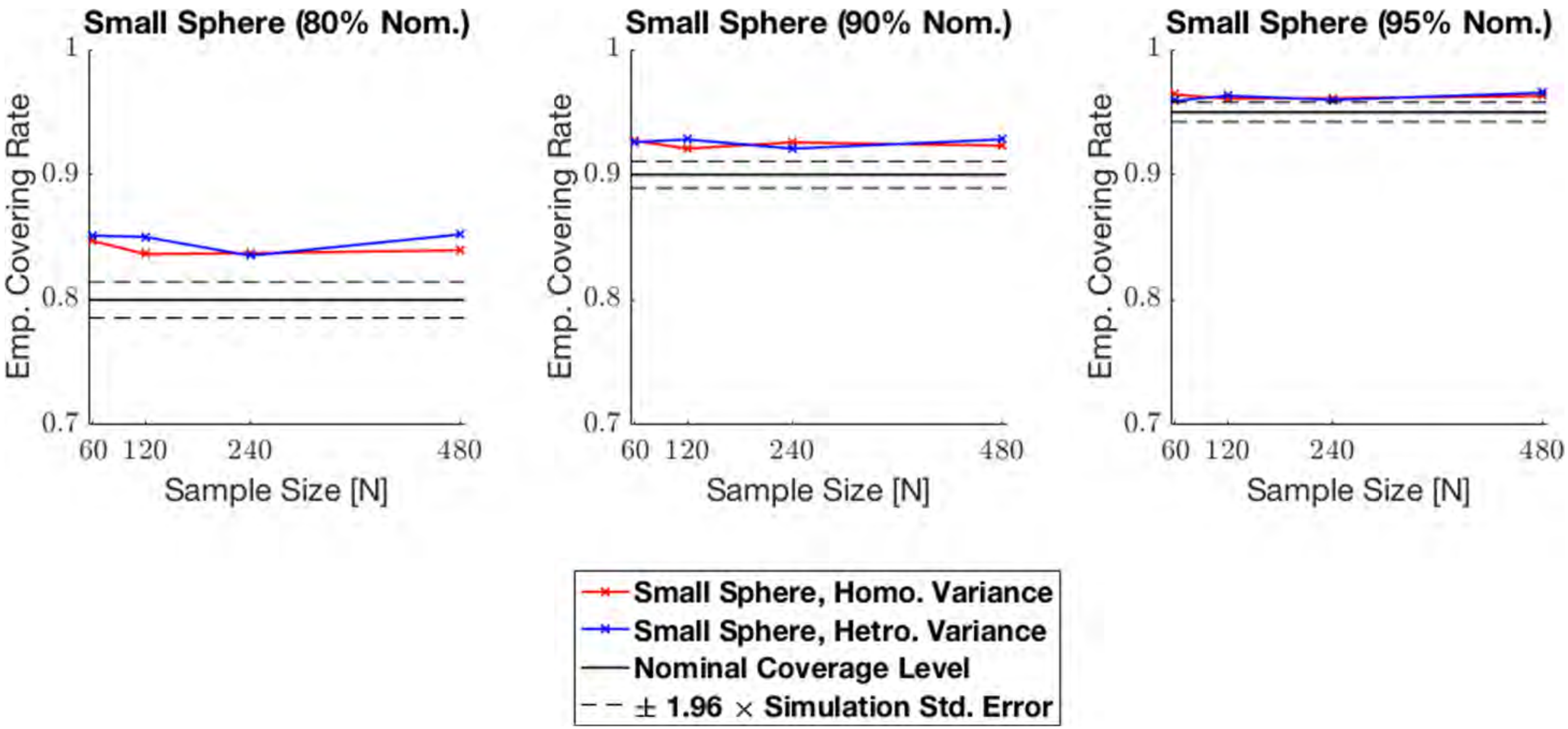


Signal	Noise
Small Sphere Large Sphere Multi Sphere	Homo- and Heterogeneous Noise
UK Biobank Mean	Heterogeneous Noise (UK Biobank Variance)

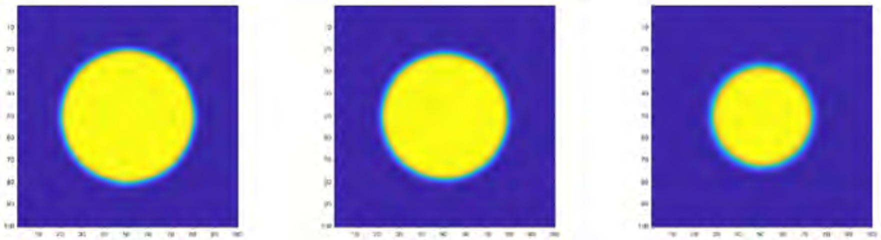
3D Simulation Results



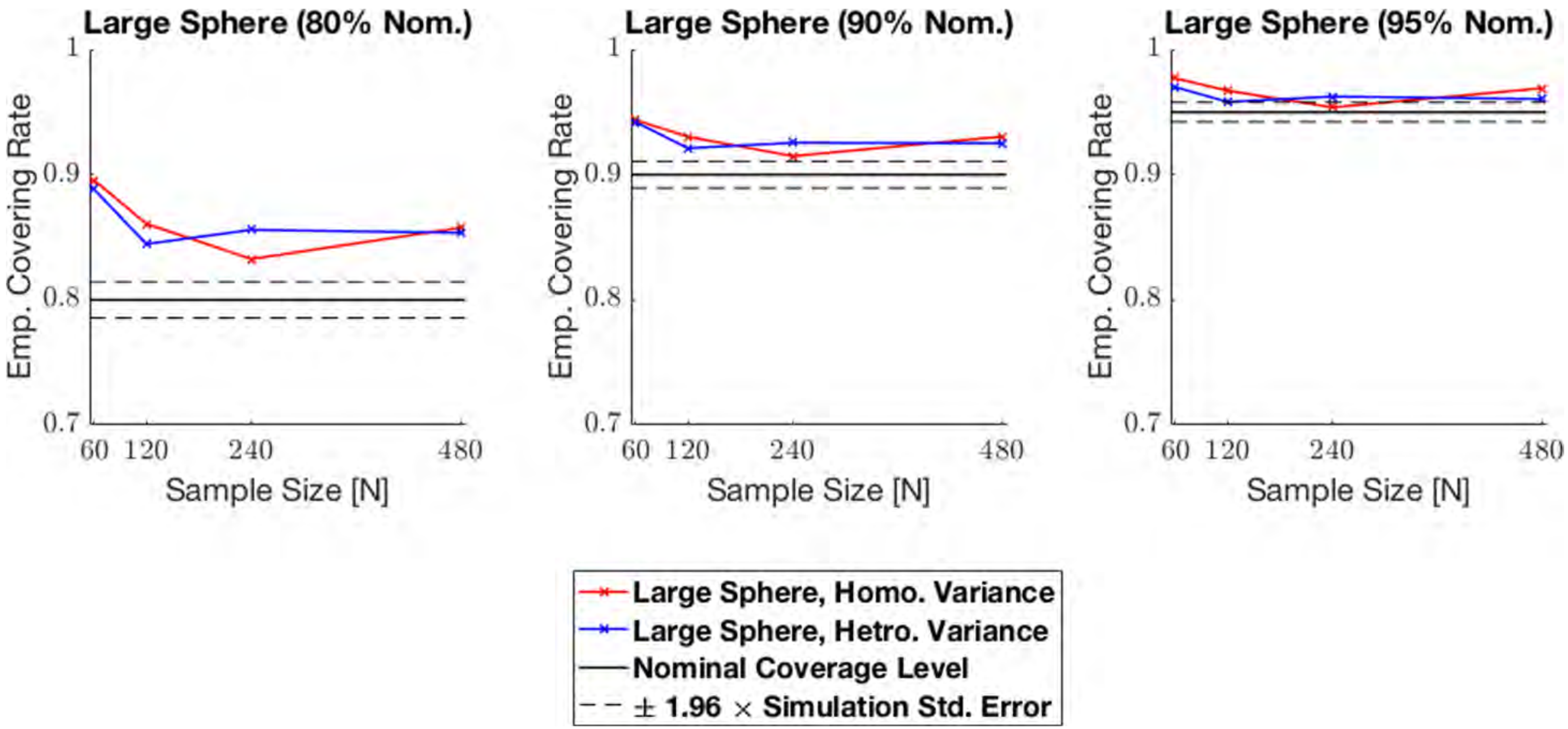
Small Sphere



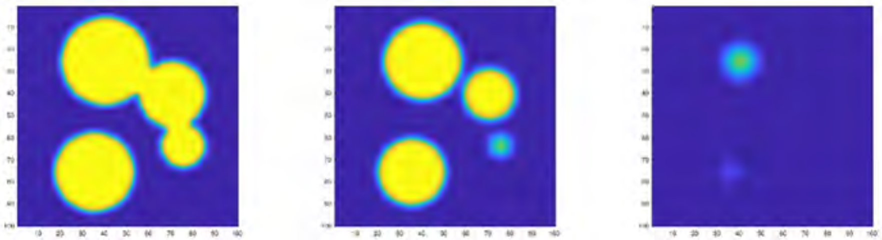
3D Simulation Results



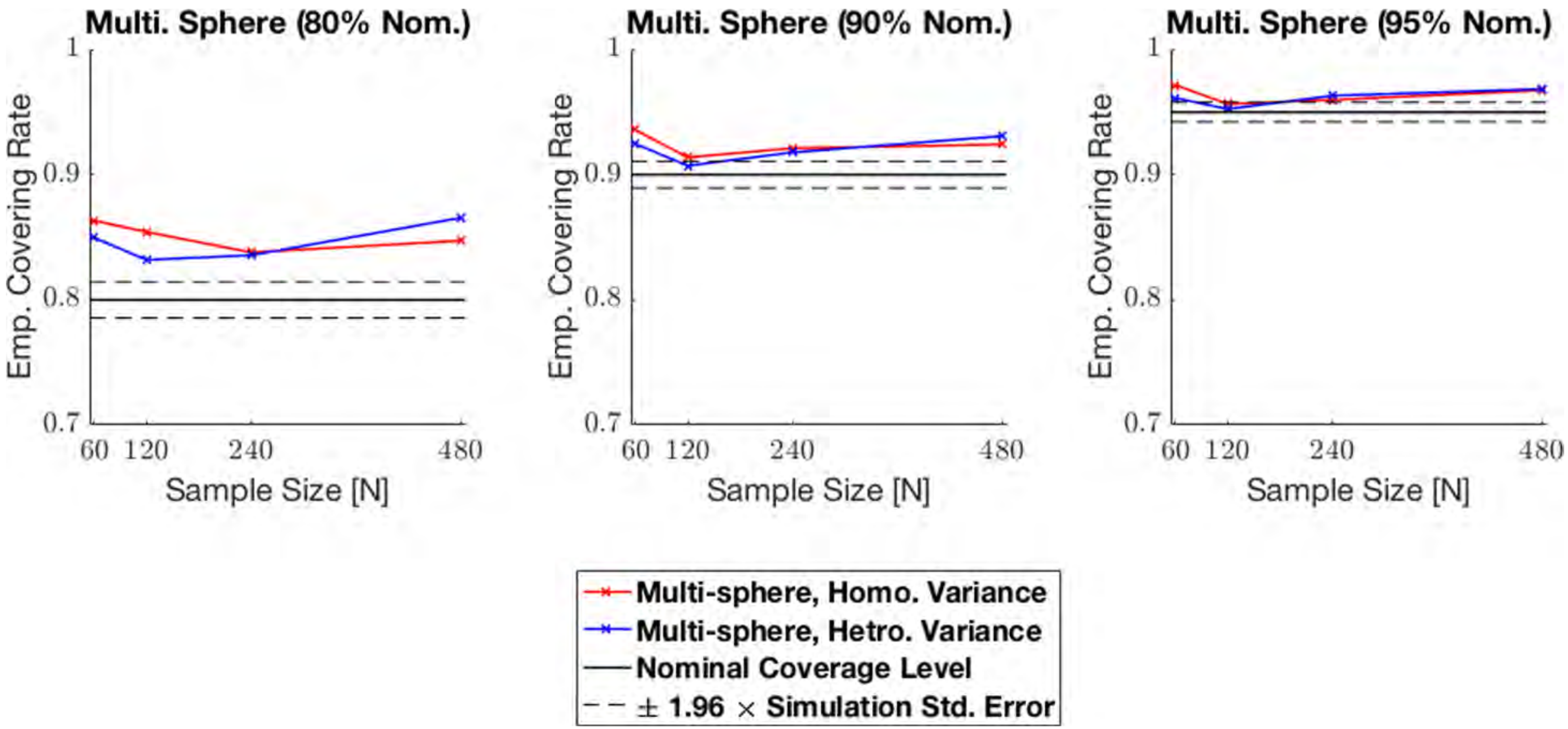
Large Sphere



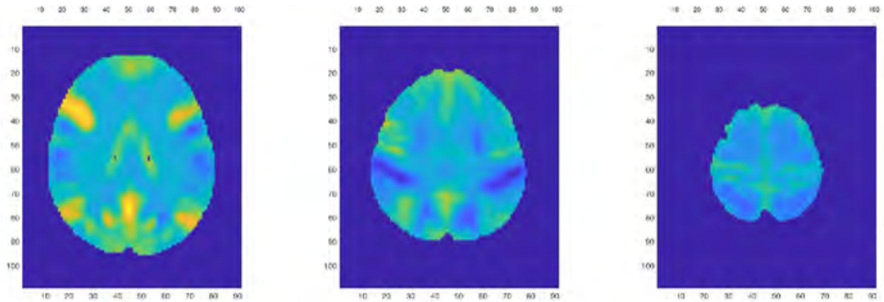
3D Simulation Results



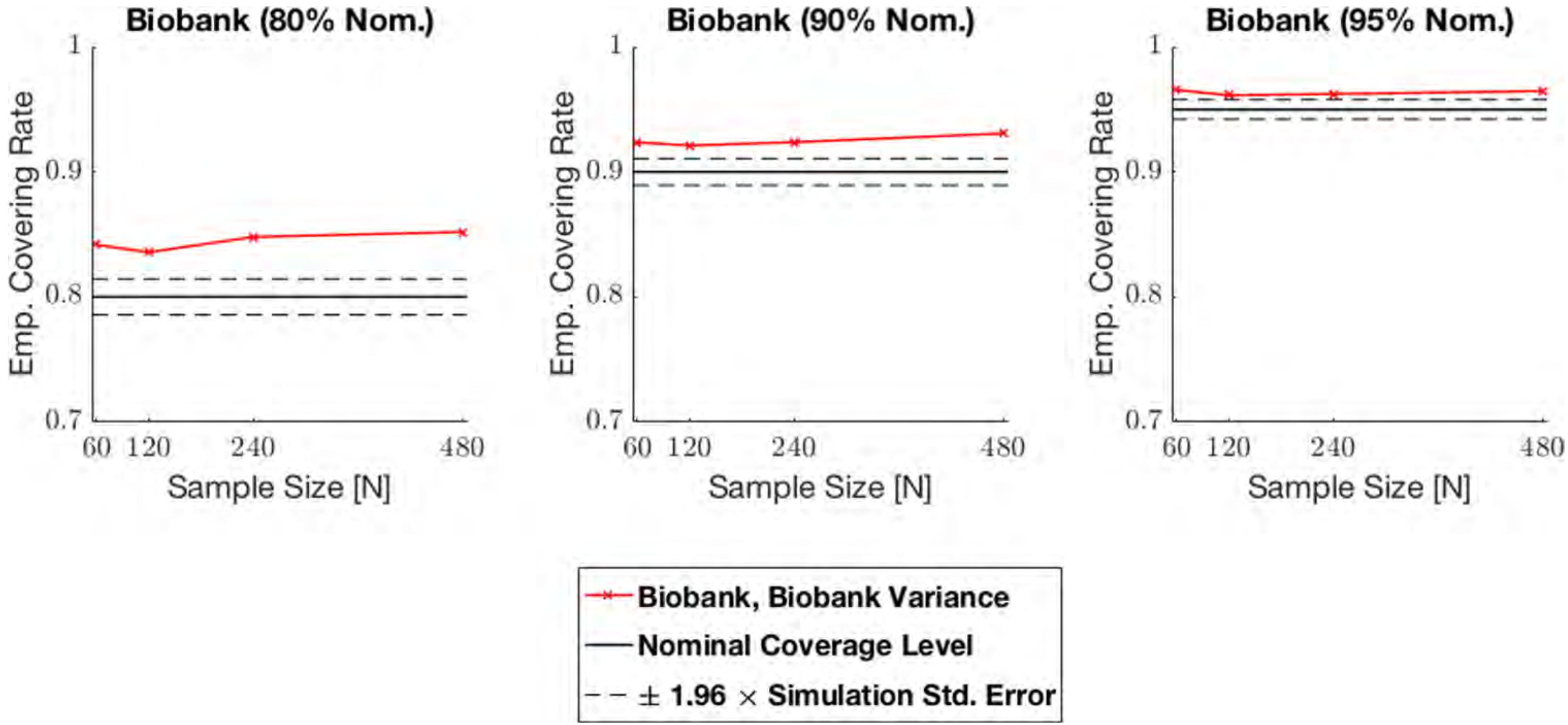
Multi Sphere



3D Simulation Results



UK Biobank
Cohen's d



Human Connectome Project

- 80 Subjects

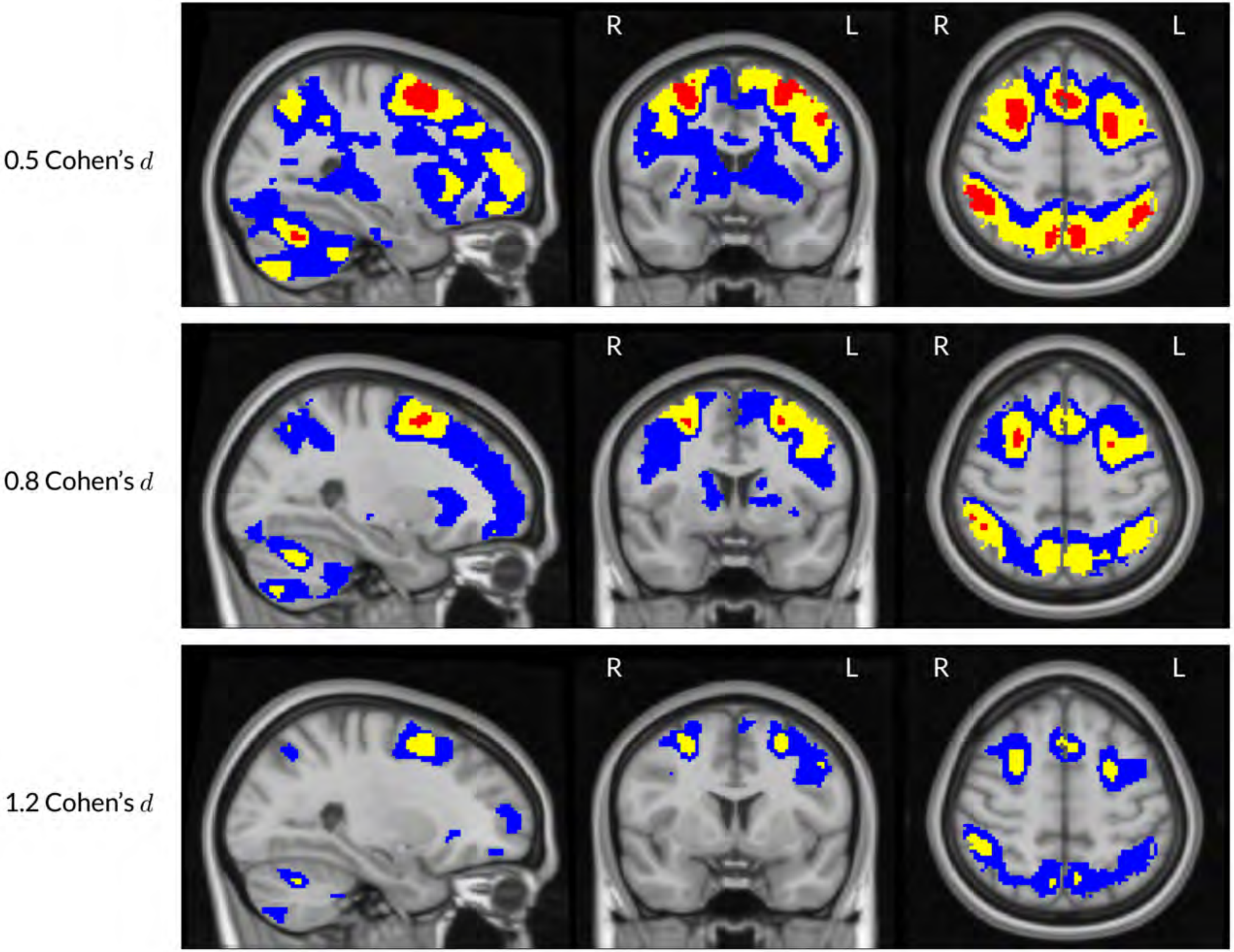
- Working Memory Task:
  - Participants presented with pics of places, tools, faces, body parts:

  - 2-back Task
    - Press button when you saw same image 2 stimuli ago
  - 0-back Task
    - Press button when you see a particular image

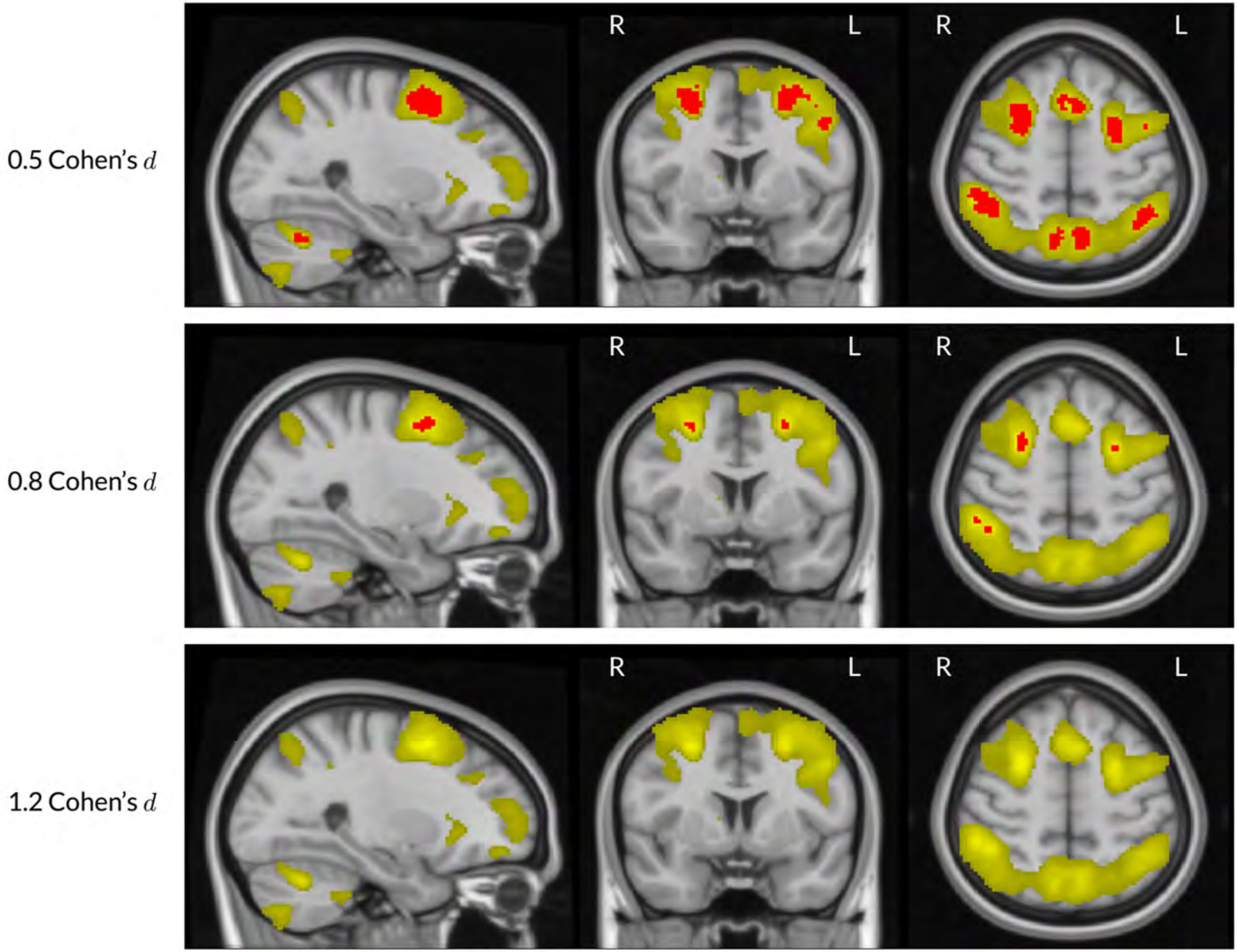
- Two runs, Eight task blocks (25 seconds per block)

- We obtain Confidence Sets on subject-level **Cohen's *d* maps** contrasting 2-back vs 0-back tasks
  - Inference on 0.5, 0.8 and 1.2 Cohen's *d* effect size

Results



Results



Confidence Set Conclusion

- Standard fMRI t-statistic inference procedures:
  - Do not account for spatial variation of the results
  - For large N, universal activation
- Confidence sets provide inference on non-zero effect sizes
  - Localization of regions we are 95% confident have exceeded a positive meaningful %BOLD threshold
- We have proposed theoretical and practical advancements to the original method
  - Rademacher variables, wild t-bootstrap method
  - Interpolation method for obtaining boundary + assessing simulations
  - For Cohen's d
    - Modified residuals to match Bootstrapped spatial ACF
    - Transformation to reduce skew