

Introduction to Reproducibility in the Life Sciences

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HWNI, UC Berkeley

Part I: Reproducibility: background

Part II : Etiology of Irreproducibility

Part III : Epistemology and statistics

Part IV :Some therapeutic proposals

Part I: Reproducibility: background

Part II : Etiology of Irreproducibility

Part III : Epistemology and statistics

Part IV :Some therapeutic proposals

- 53 papers examined at Amgen in preclinical cancer research
- Papers were selected that described something completely new and in very high impact factor journals
- **Scientific findings were confirmed in only 6 (11%)**

Begley and Ellis, Nature, 2012

Altered Brain Activity in Unipolar Depression Revisited Meta analyses of Neuroimaging Studies

Veronika I. Müller, PhD, Edna C. Cieslik, PhD, Ilinca Serbanescu, MSc, Angela R. Laird, PhD, Peter T. Fox, MD, and Simon B. Eickhoff, MD

RESULTS—In total, 57 studies with 99 individual neuroimaging experiments comprising in total 1058 patients were included; 34 of them tested cognitive and 65 emotional processing. Overall analyses across cognitive processing experiments ($P > .29$) and across emotional processing experiments ($P > .47$) revealed no significant results. Similarly, no convergence was found in analyses investigating positive (all $P > .15$), negative (all $P > .76$), or memory (all $P > .48$) processes. Analyses that restricted inclusion of confounds (eg, medication, comorbidity, age) did not change the results.

Stein et al., 2012, Nature Genetics, study of the hippocampal volume in more than 10k+7k subjects

Previously identified candidate polymorphisms associated with hippocampal volume in general showed little association within our meta-analysis :(

Stein et al, Nat. Gen. 2013

Credibility Crisis

Los Angeles Times | BUSINESS

LOCAL U.S. WORLD BUSINESS SPORTS ENTERTAINMENT HEALTH STYLE TRAVEL

Science has lost its way, at a big cost to humanity

Researchers are rewarded for splashy findings, not for double-checking accuracy. So many scientists looking for cures to diseases have been building on ideas that aren't even true.

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Home > Science Magazine > 17 January 2014 > McNutt, 343 (6168): 229

Article Views Science 17 January 2014:
Vol. 343 no. 6168 p. 229
DOI: 10.1126/science.1250475

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Reproducibility
Marcia McNutt

» Marcia McNutt is Editor-in-Chief of Science.
Science advances on a foundation of trusted data. But the scientific method, the approach that scientists use to gain confidence in their results, is under threat. The scientific community was shaken by reports that a troubling number of studies in the field are not reproducible. Because confidence in results is fundamental to the credibility of science, we are announcing new initiatives to address this problem. In this week's issue of *Science*, for preclinical studies (one of the targets of the new initiatives), the National Institutes of Health is calling for increased transparency. Authors will indicate how they handled data (such as how to deal with outliers), what statistical methods were used, and whether the experimenter was blind to the conduct of the experiments. These changes will help ensure a sufficient signal-to-noise ratio, which is critical for reproducibility. We encourage authors to follow these guidelines.

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TheScientist
EXPLORING LIFE. INSPIRING INNOVATION

NIH Tackles Irreproducibility

The federal agency speaks out about how to improve the quality of scientific research.

By Jef Akst | January 28, 2014

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NATURE | EDITORIAL

Announcement: Reducing our irreproducibility

24 April 2013

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Over the past year, *Nature* has published a string of articles that highlight the need to improve the reliability and reproducibility of published research (collected and discussed in this editorial). The problem is not unique to *Nature*; it is a concern across all fields of science. The recent statement from the US National Institutes of Health (NIH) is a welcome step towards addressing this issue. It is clear that the scientific community must take action to ensure that the results of our research are reliable and reproducible. This is crucial for the credibility of science and for the advancement of knowledge.

nature International weekly journal of science

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NATURE | EDITORIAL

Must try harder

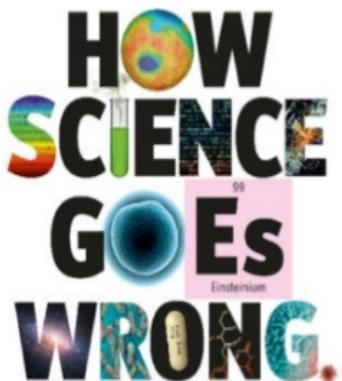
Nature 483, 509 (29 March 2012) | doi:10.1038/483509a
Published online 28 March 2012

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Too many sloppy mistakes are creeping into scientific papers. Lab heads must look more rigorously at the data — and at themselves.

The Economist

Washington's lawyer surplus
How to do a nuclear deal with Iran
Investment tips from Nobel economists
Junk bonds are back
The meaning of Sachin Tendulkar



NIH plans to enhance reproducibility

Francis S. Collins and **Lawrence A. Tabak** discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

Collins and Tabak. 2014. Nature 505: 612–13.

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

2005. *PLoS Medicine*, 2(8), e124. doi:
10.1371/journal.pmed.0020124

“There is increasing concern about the reliability of biomedical research, with recent articles suggesting that up to 85% of research funding is wasted.”

Bustin, S. A. (2015). The reproducibility of biomedical research: Sleepers awake!
Biomolecular Detection and Quantification

THE LANCET

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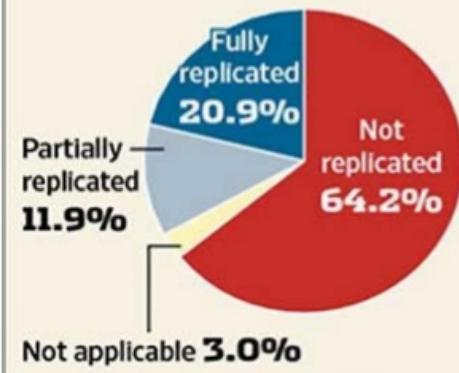
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Research: increasing value, reducing waste

No Cure

When Bayer tried to replicate results of 67 studies published in academic journals, nearly two-thirds failed.



Source: Nature Reviews Drug Discovery

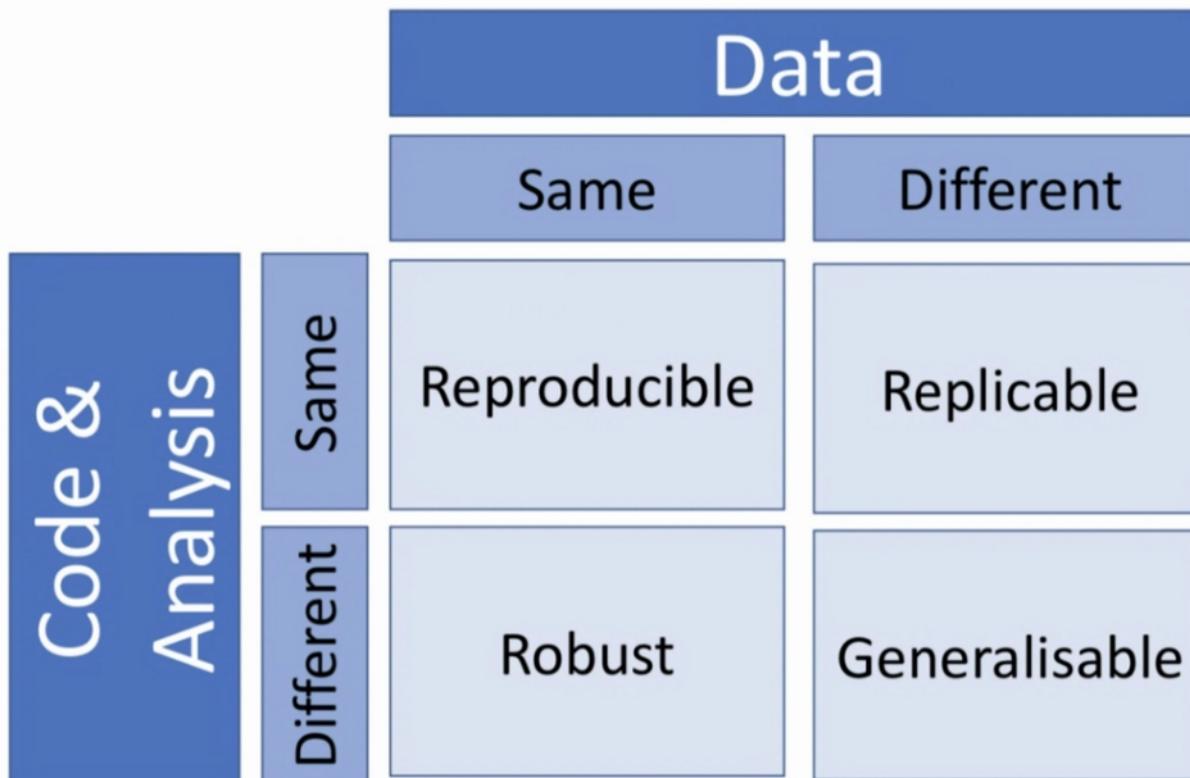
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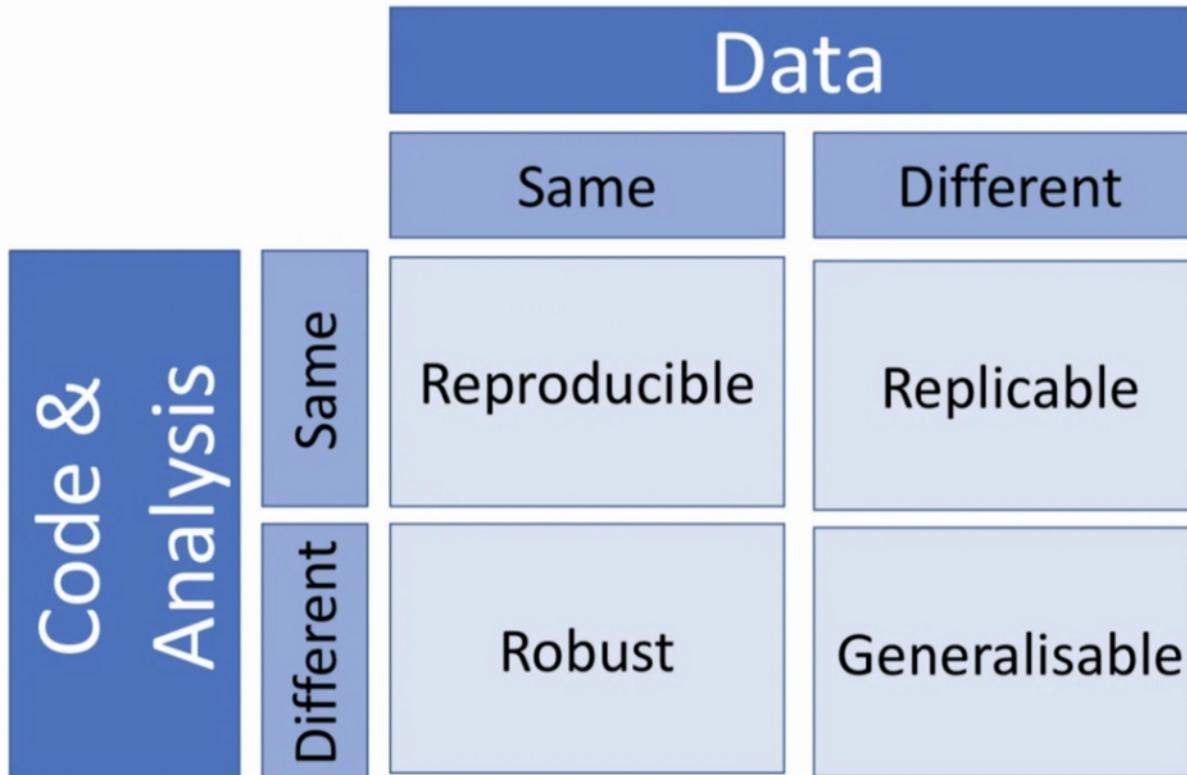
NATURE | NEWS

First results from psychology's largest reproducibility test



Credit: J.Pineau

- My (preferred) way of thinking about reproducibility: **only talk about generalizability** across ... (Data, Software, Time, Scanner, Stimuli, ... etc)



Credit: J.Pineau

- My (preferred) way of thinking about reproducibility: **only talk about generalizability** across ... (Data, Software, Time, Scanner, Stimuli, ... etc)

Part I: Reproducibility: background

Part II : Etiology of Irreproducibility

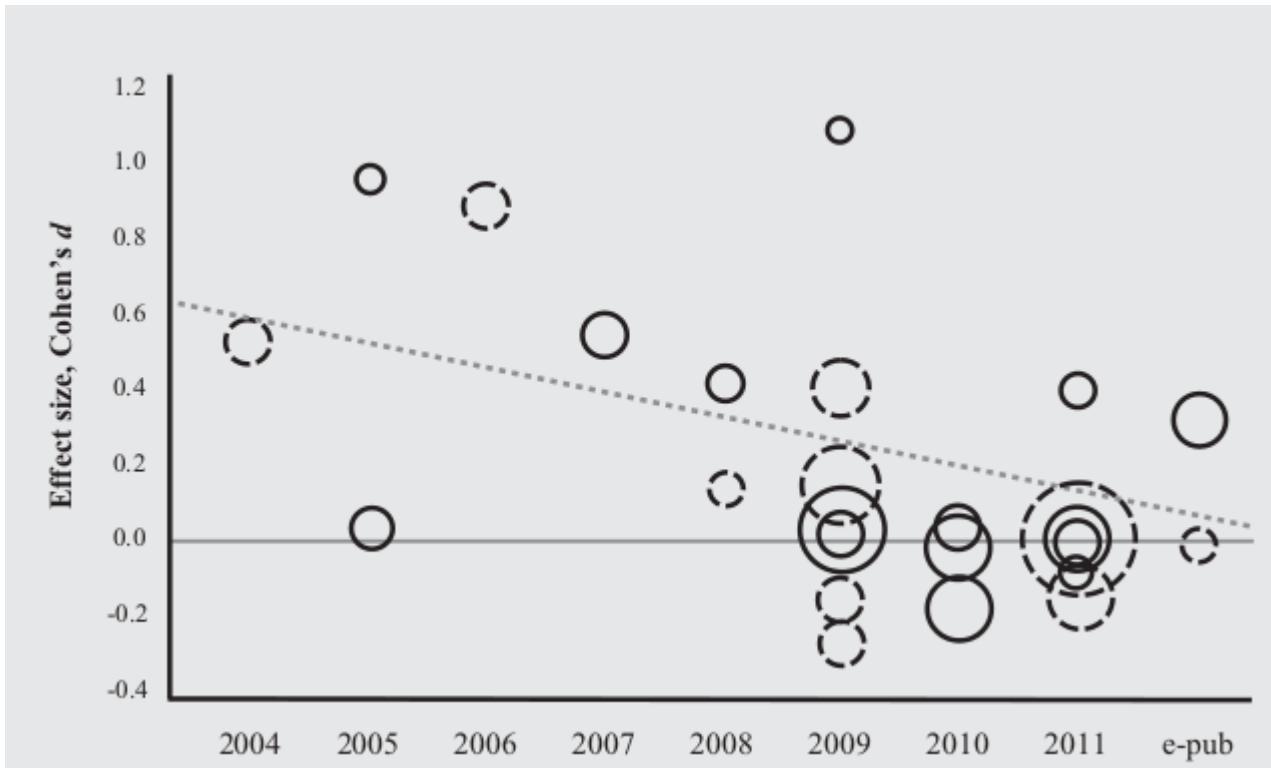
Part III : Epistemology and statistics

Part IV :Some therapeutic proposals

Three causes

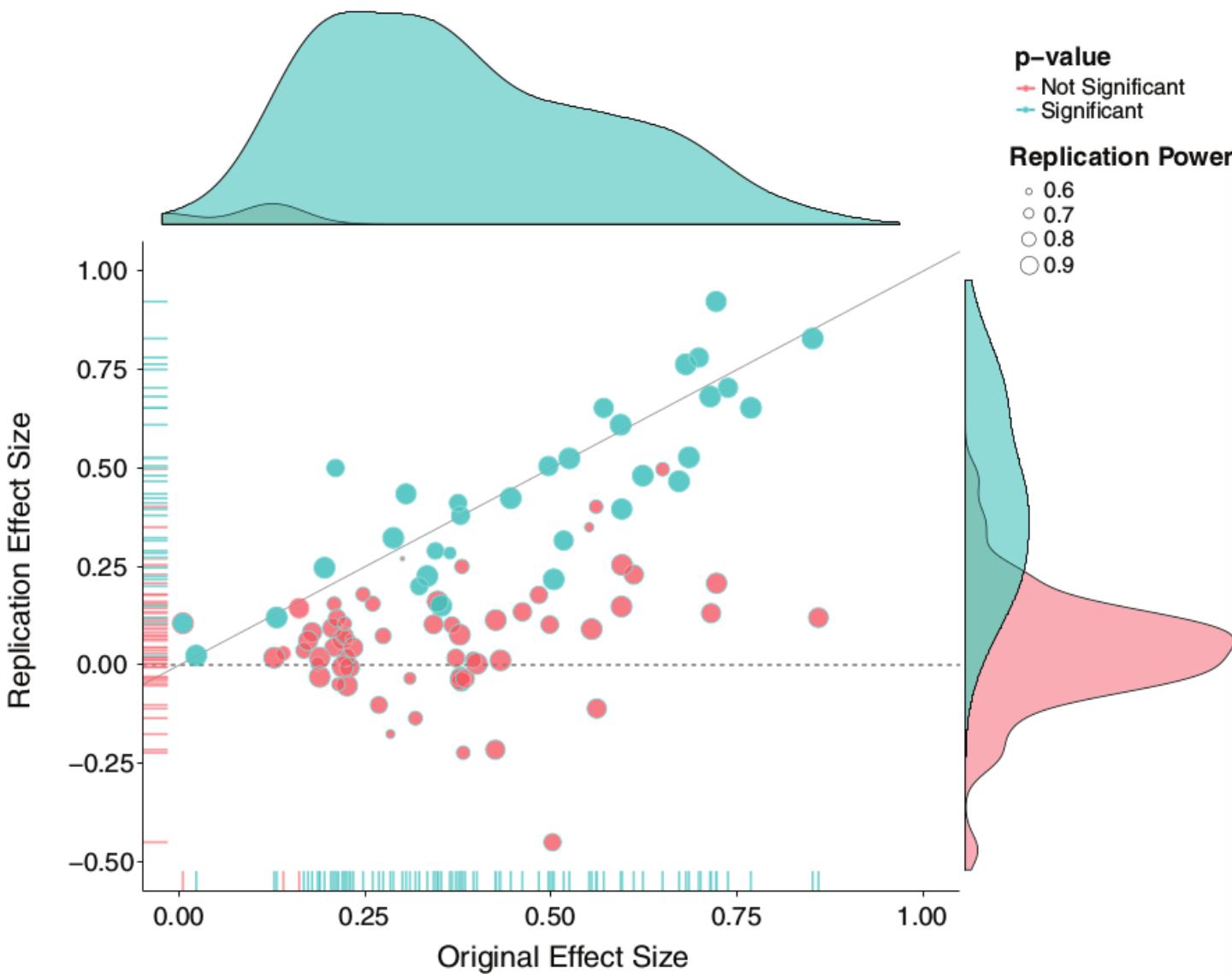
1. Poor statistical procedures
2. Issues in data and software
3. A cultural issue: Publication practices and research incentives

1. Poor statistical procedures
 - Small Ns and effect sizes
 - Power issues
 - P-hacking
2. Issues in data and software
3. A cultural issue: Publication practices and research incentives



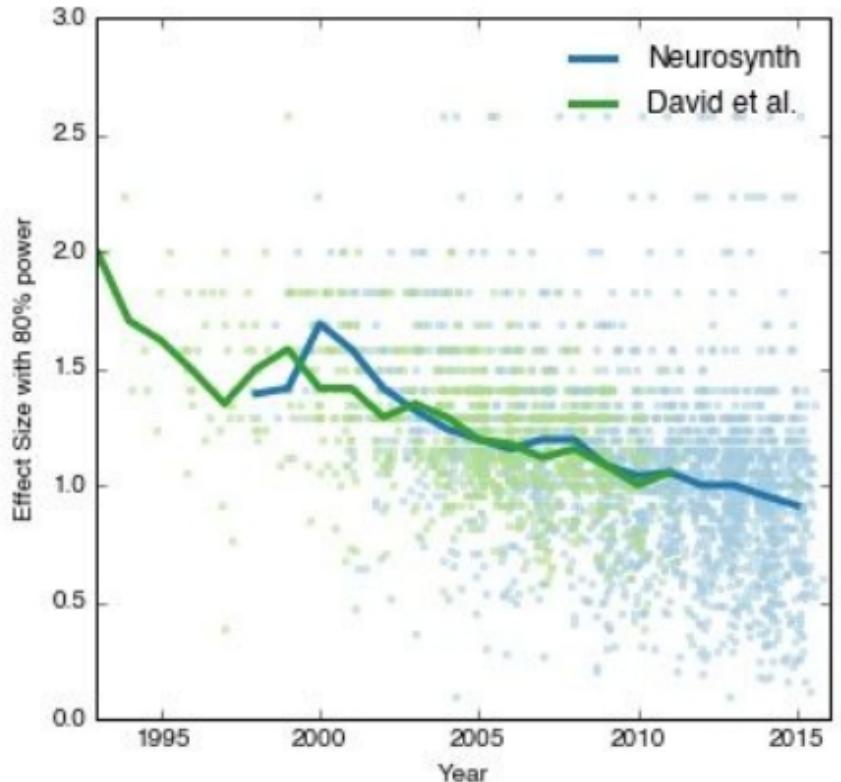
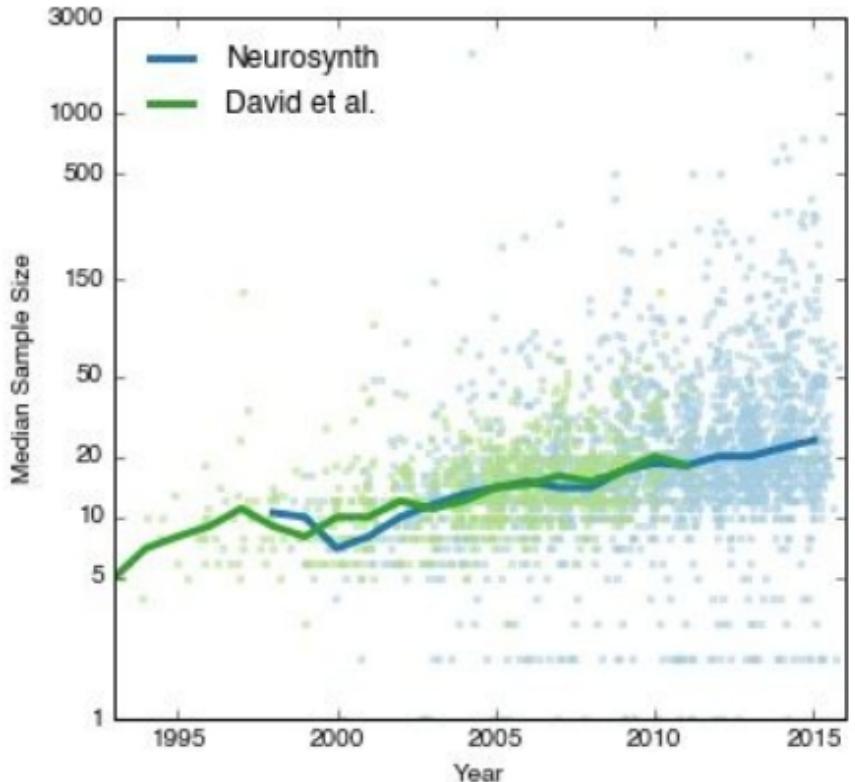
Molendijk, 2012: BDNF and hippocampal volume

See also : Mier, 2009: COMT and DLPFC



* The mean **effect size** (r) of the replication effects ($M r = 0.197$, $SD = 0.257$) was **half the magnitude** of the mean effect size of the original effects ($M r = 0.403$, $SD = 0.188$)

* **39%** of effects were rated to have replicated the original effect



Poldrack et al., PNAS, 2016

Paradigm	Intersection mask	mask size (vox)	Cohen D			BOLD		
			P10	median	P90	P10	median	P90
MOTOR	Bilateral Precentral Gyrus	12894	0.158	0.628	1.070	0.505	2.707	8.582
	Bilateral Supplementary motor cortex	3418	0.211	0.716	1.197	0.911	4.033	12.510
	Left putamen	1532	0.114	0.513	0.864	0.586	2.388	4.318
	Right putamen	1437	-0.008	0.369	0.749	-0.045	1.696	3.609
WM	Bilateral Middle frontal gyrus	7116	0.101	0.474	0.837	0.130	0.986	2.504
EMOTION	Left amygdala	1133	0.265	0.534	1.065	0.516	1.198	3.379
	Right amygdala	1082	0.308	0.645	1.140	0.581	1.350	3.557
GAMBLING	Left accumbens	455	0.138	0.310	0.461	0.369	0.849	1.440
	Right accumbens	417	0.141	0.332	0.488	0.373	0.981	1.618

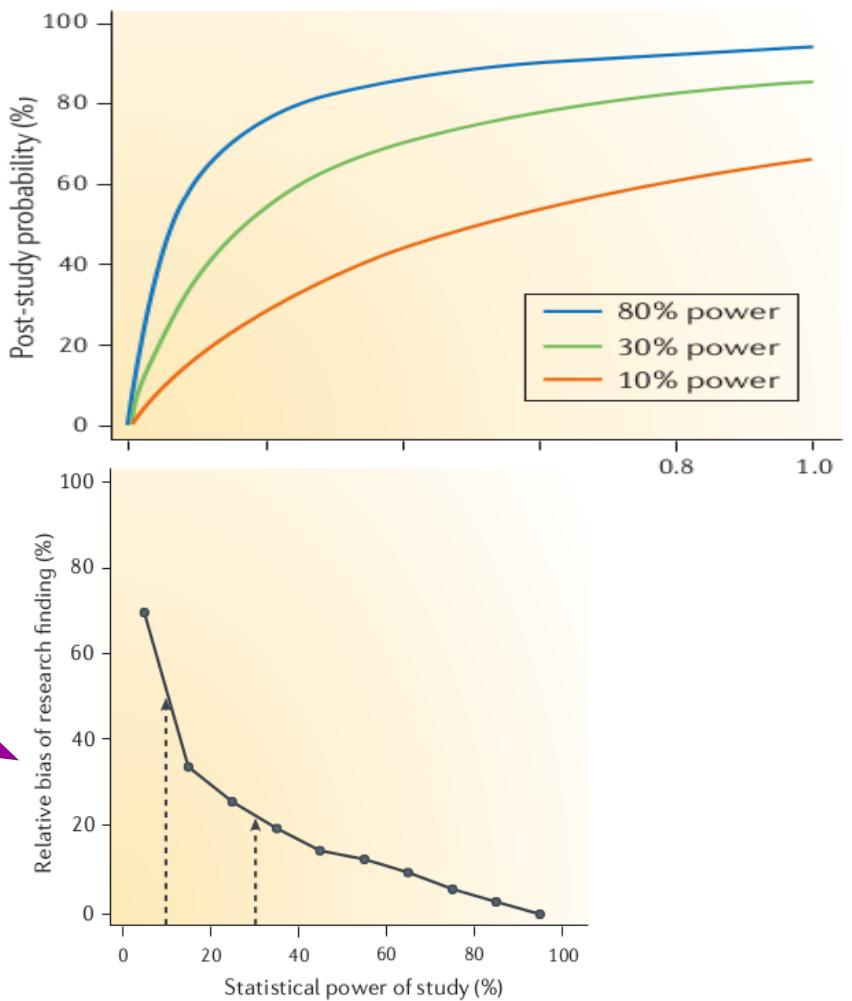
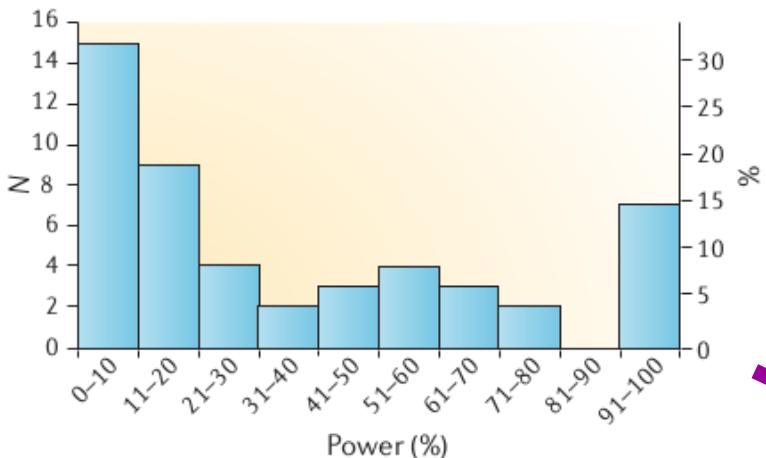
With effect size = 0.5 => Power ~ 30%

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Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis



Button et al., NNR, 2013

Open access, freely available online

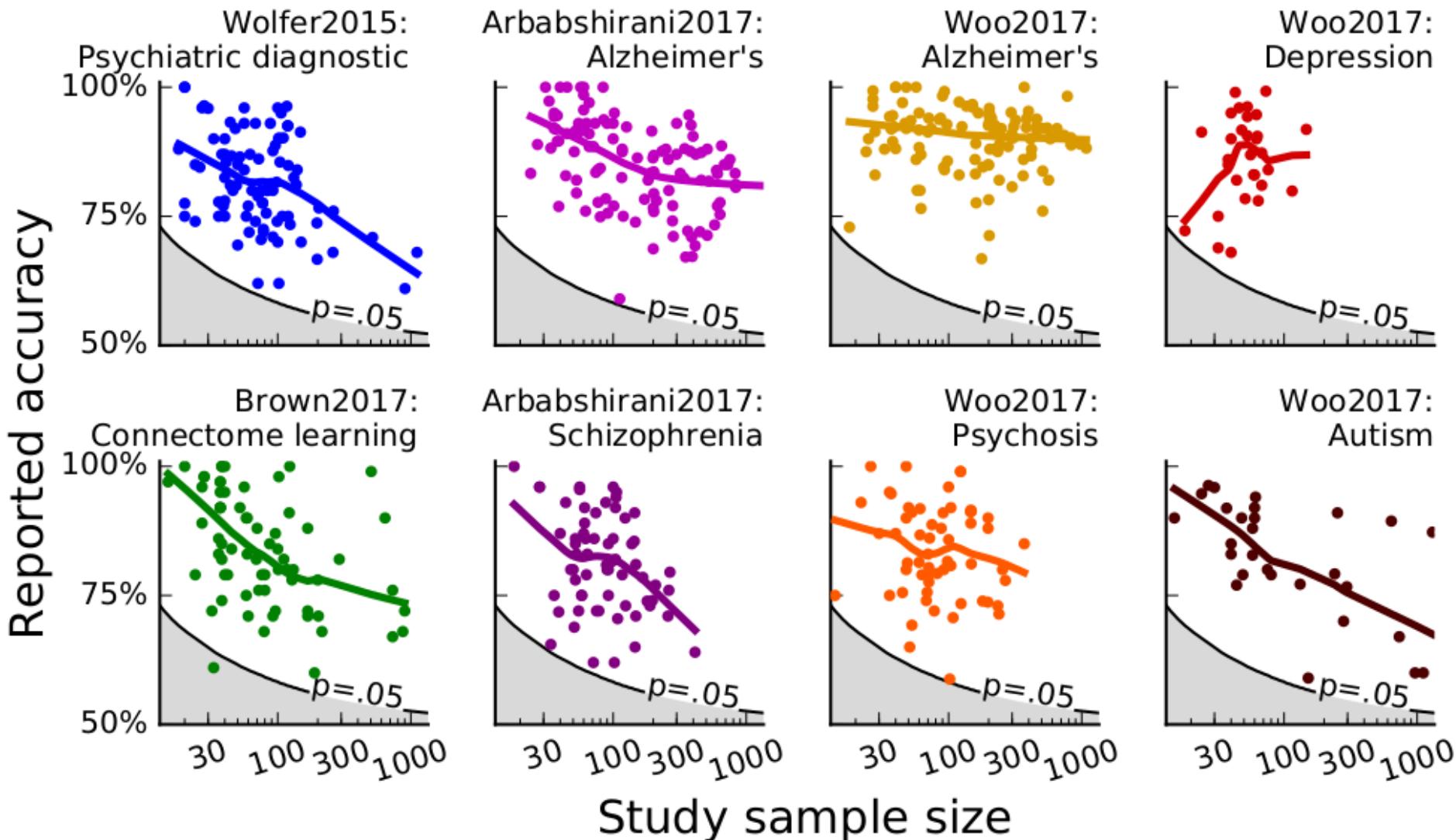
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John P. A. Ioannidis

- Positive Predictive Value : The probability that the alternative hypothesis is true knowing that the test is significant

Sample size issue in ML



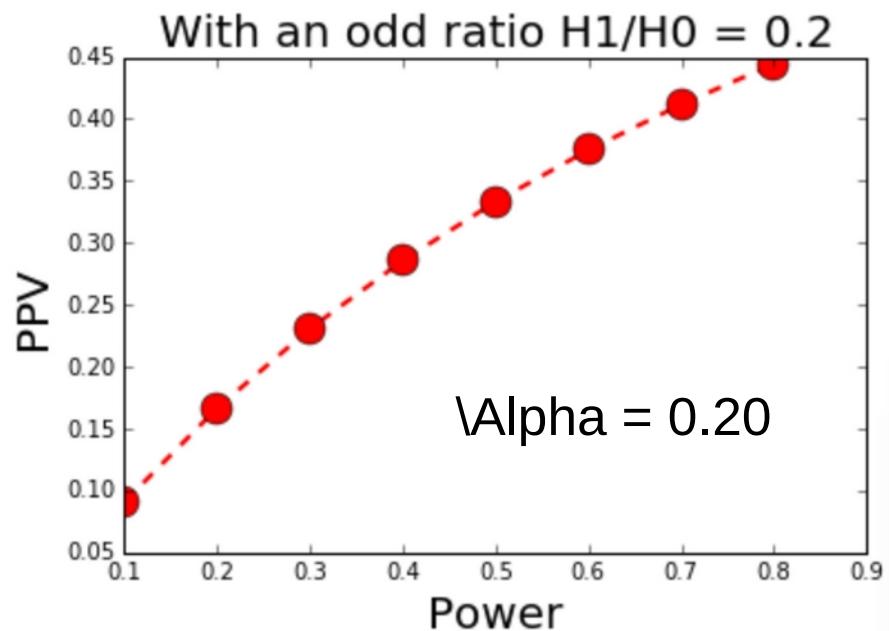
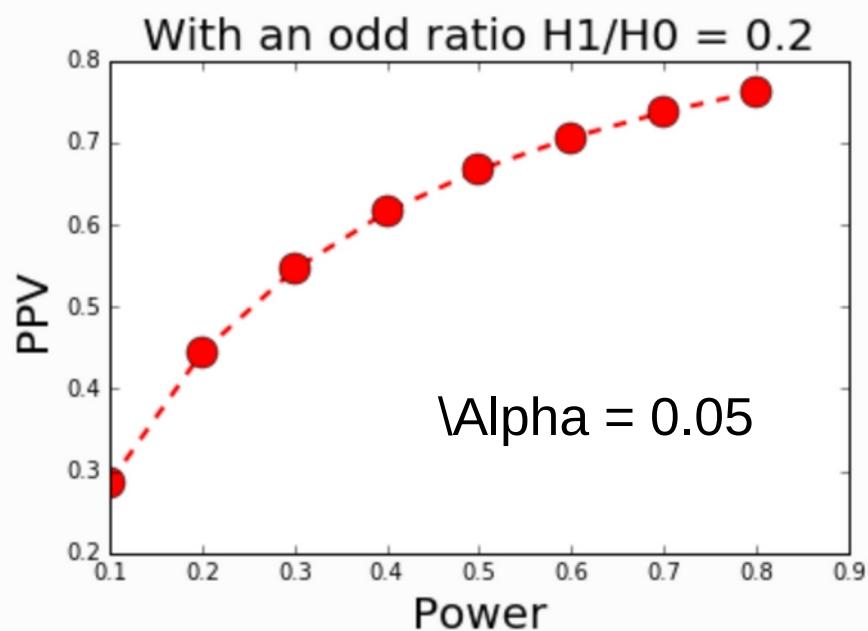
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Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

$$P(H_A \mid T_S) = \frac{WR}{WR + \alpha}$$



False-Positive Psychology: Undisclosed Flexibility in Data Collection and Analysis Allows Presenting Anything as Significant

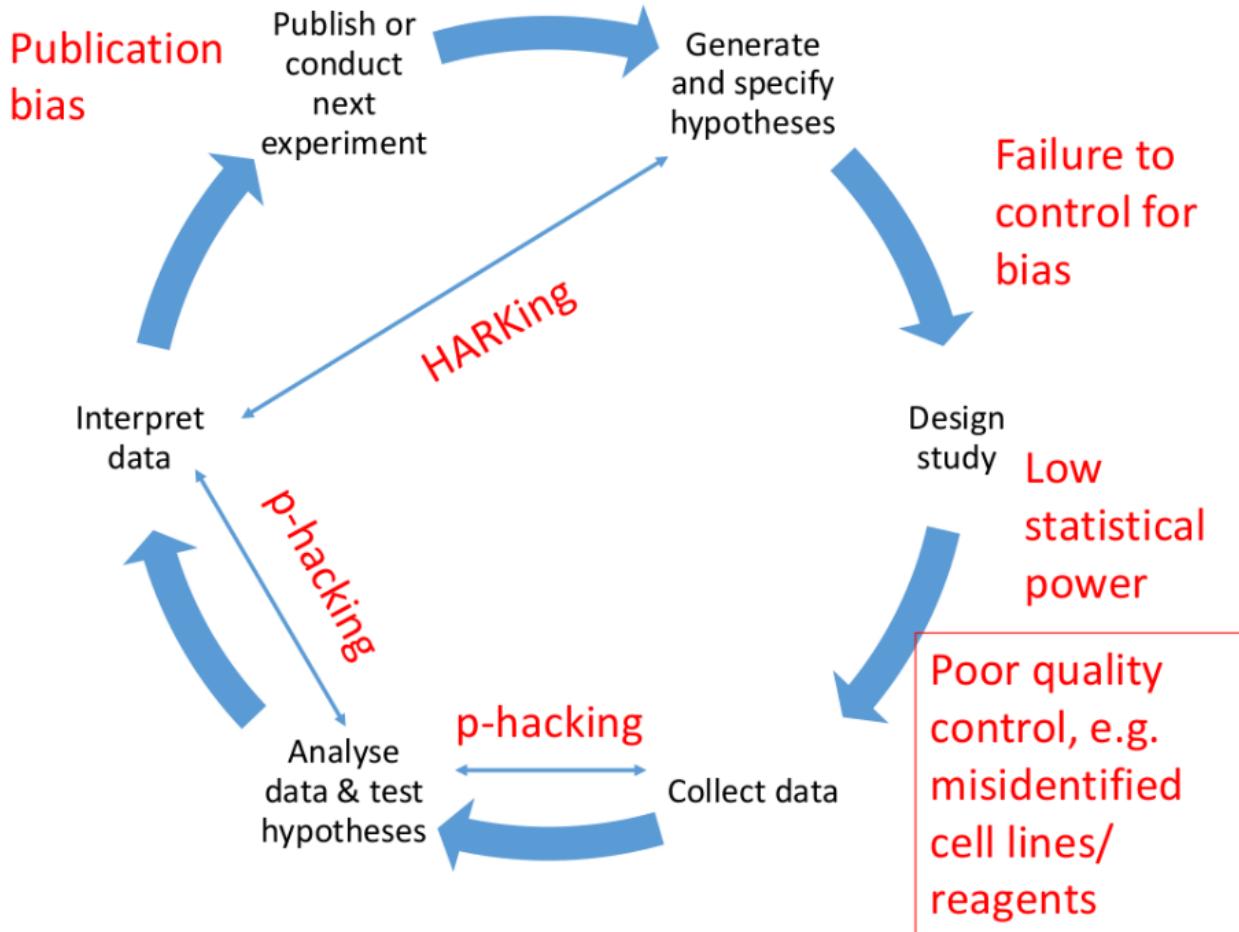
Joseph P. Simmons¹, Leif D. Nelson², and Uri Simonsohn¹

¹The Wharton School, University of Pennsylvania, and ²Haas School of Business, University of California, Berkeley

Table I. Likelihood of Obtaining a False-Positive Result

Researcher degrees of freedom	Significance level		
	$p < .1$	$p < .05$	$p < .01$
Situation A: two dependent variables ($r = .50$)	17.8%	9.5%	2.2%
Situation B: addition of 10 more observations per cell	14.5%	7.7%	1.6%
Situation C: controlling for gender or interaction of gender with treatment	21.6%	11.7%	2.7%
Situation D: dropping (or not dropping) one of three conditions	23.2%	12.6%	2.8%
Combine Situations A and B	26.0%	14.4%	3.3%
Combine Situations A, B, and C	50.9%	30.9%	8.4%
Combine Situations A, B, C, and D	81.5%	60.7%	21.5%

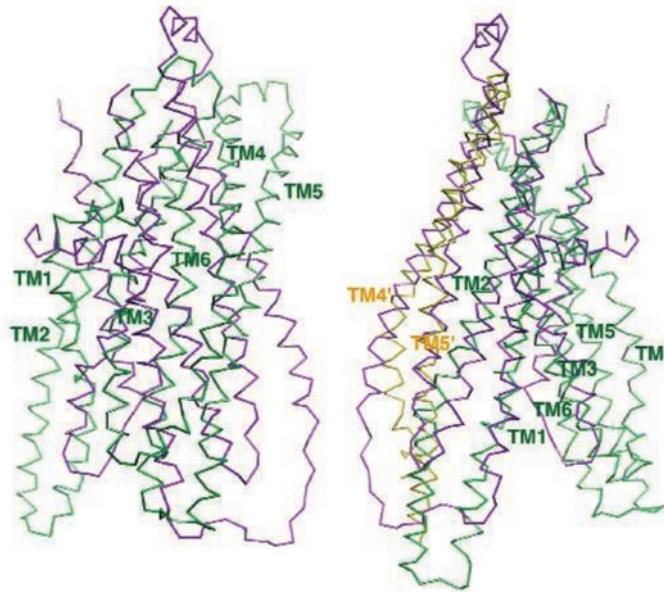
- Usually performed “in good faith”
 - I have forgotten a covariate
 - I haven’t excluded some outliers
 - I should have included an interaction
 - I should only test subjects with X
 - ...
- The “cost of seeing data”
 - Proper statistical test for inference require that you are “blind” to the data



- D. Bishop 2015

Three causes

1. Poor statistical procedures
2. Issues in data and software
3. A cultural issue: Publication practices and research incentives



Flipping fiasco. The structures of MsbA (purple) and Sav1866 (green) overlap little (left) until MsbA is inverted (right).

- G. Chang: 3 Science, 1 PNAS, 1 J Mol Biol retracted
- “... a homemade data-analysis program had flipped two columns of data...”
- “... inherited from another lab...”
- The code was distributed and used by others

- Potti et al., Nat. Med. 2006, 2008 vs Baggerly and Coombes, “Forensic analysis”, Annals of applied Stat., 2009
- Choose cell lines that are most sensitive / resistant to a drug, use expression profiles to build a model that predicts patient response

Baggerly and Coombes Forensic:

“with poor documentation and irreproducibility even well meaning investigator may argue for drug that are contraindicated to some patients”

“the most common errors are simple (e.g., row or column offsets); conversely, the most simple errors are common.”

Across OS Across implementations

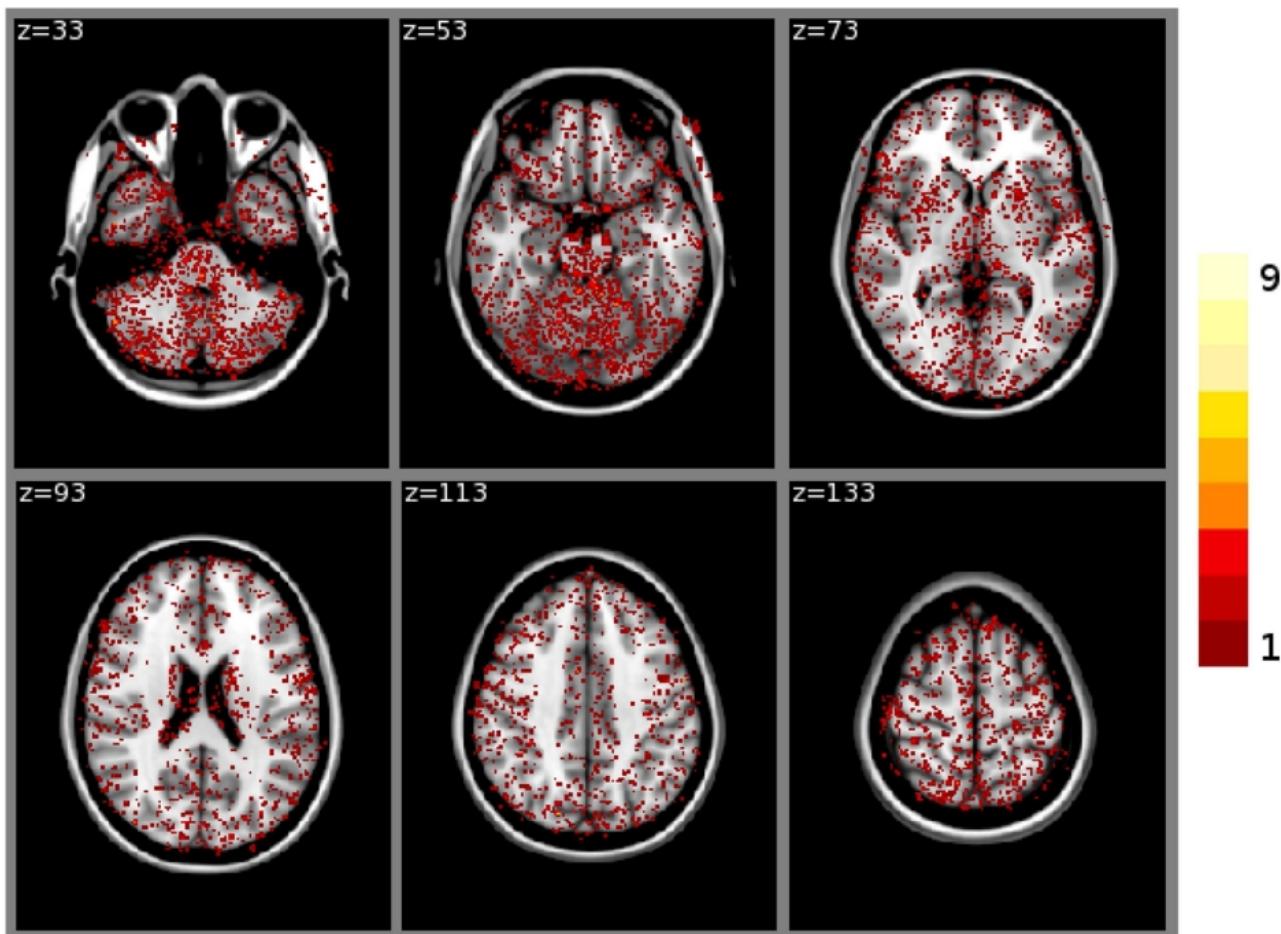
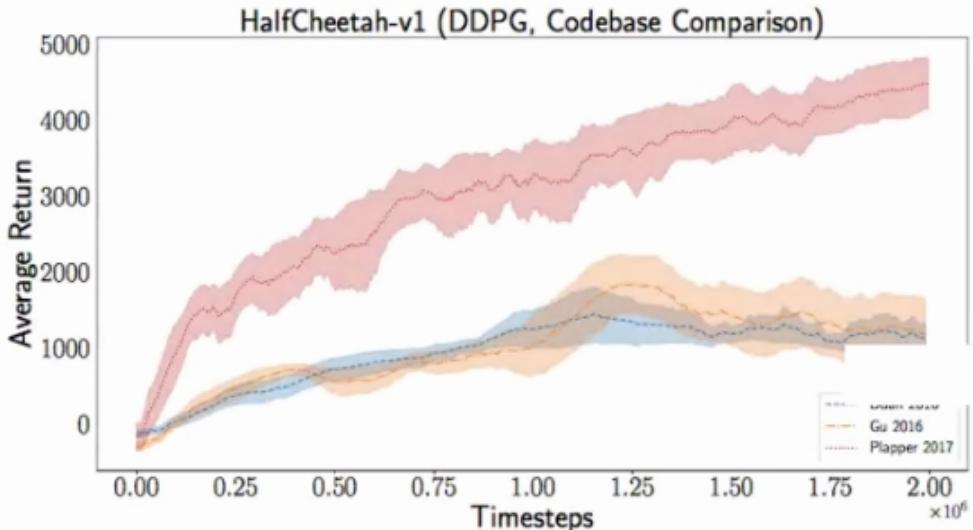
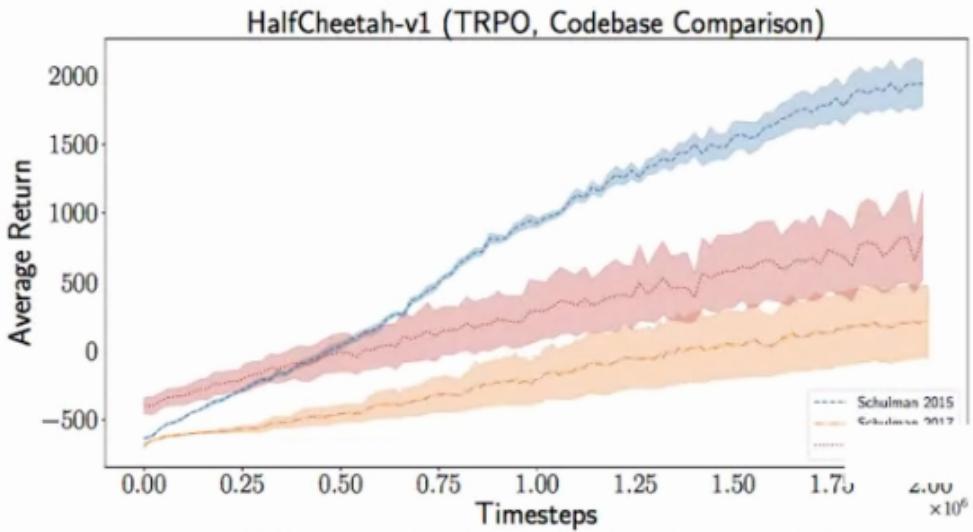


FIGURE 2 | Sum of binarized differences between cortical tissue classifications obtained on cluster A and cluster B (FSL FAST, build 1, $n = 150$ subjects). All binarized differences were resampled to the default MNI152 volume template.

Glatard et al, 2015, F. in Neuroinformatics

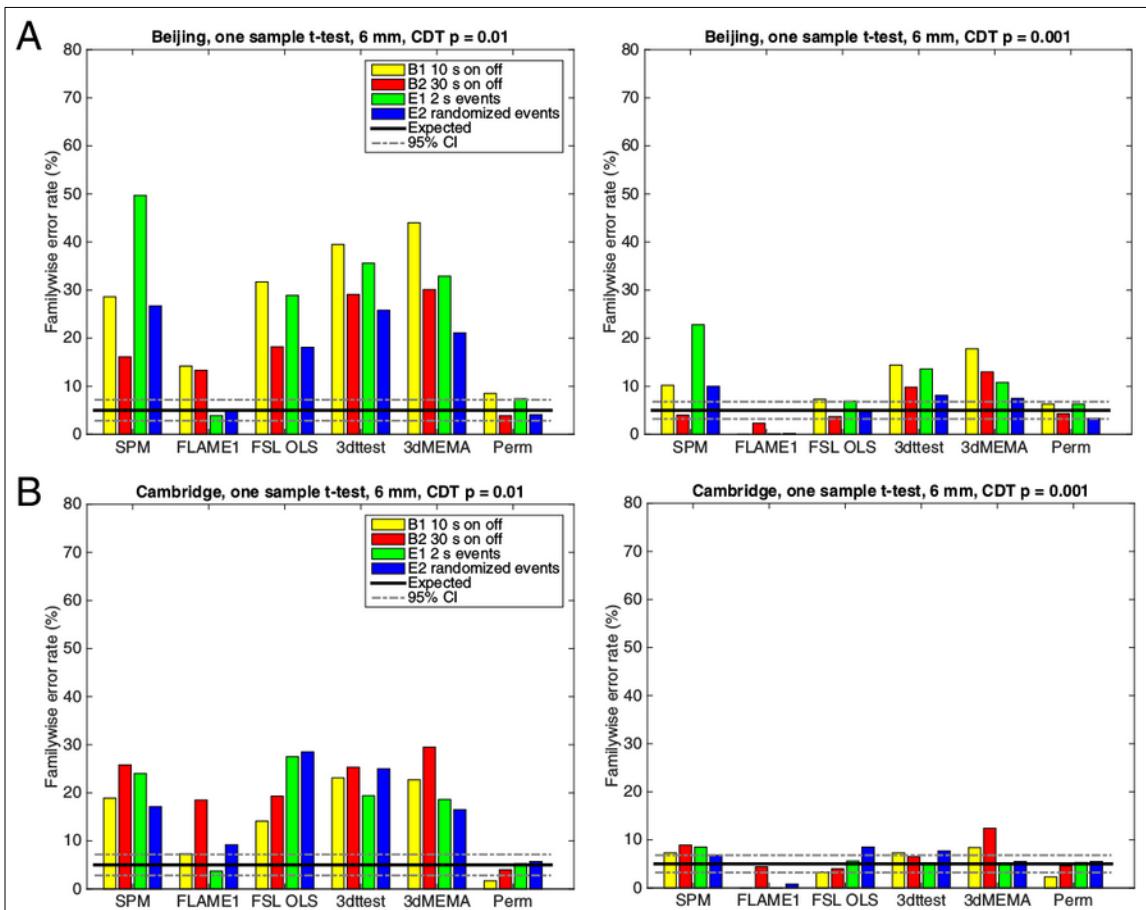
- Same algorithm
 - Top graph: TRPO
 - Bottom graph: DDPG
- Same domain
- Simulation environment
- Different implementations



Credit : Joelle Pineau

Across parametrizations of software

and across software

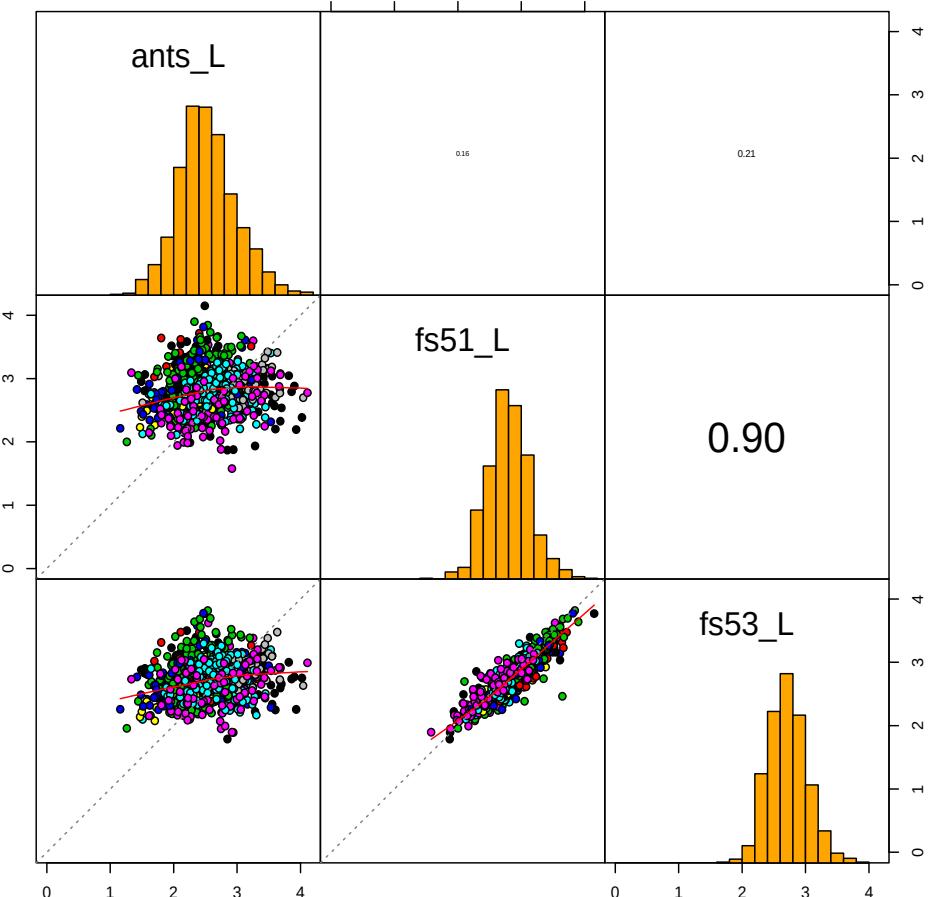


Eklund et al., PNAS, 2016 :

- Low threshold issue
- High threshold issue with Paradigm E1 ?
- Ad hoc procedure leads to around 70% FPR

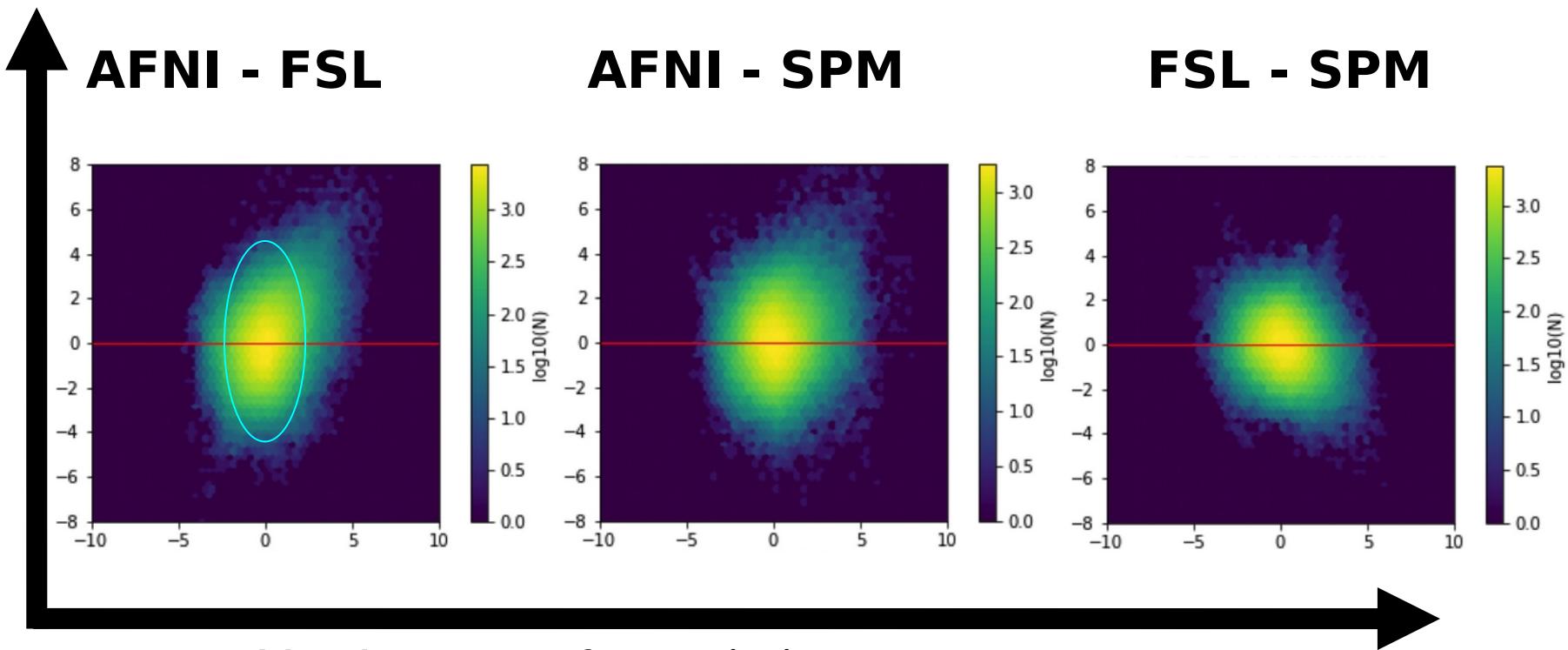
- Estimated 3,500 papers affected by low threshold ?
- But 13000 w/o multiple comparisons ?

Size of the left caudal anterior Cingulate



Dickie E et al., 2017

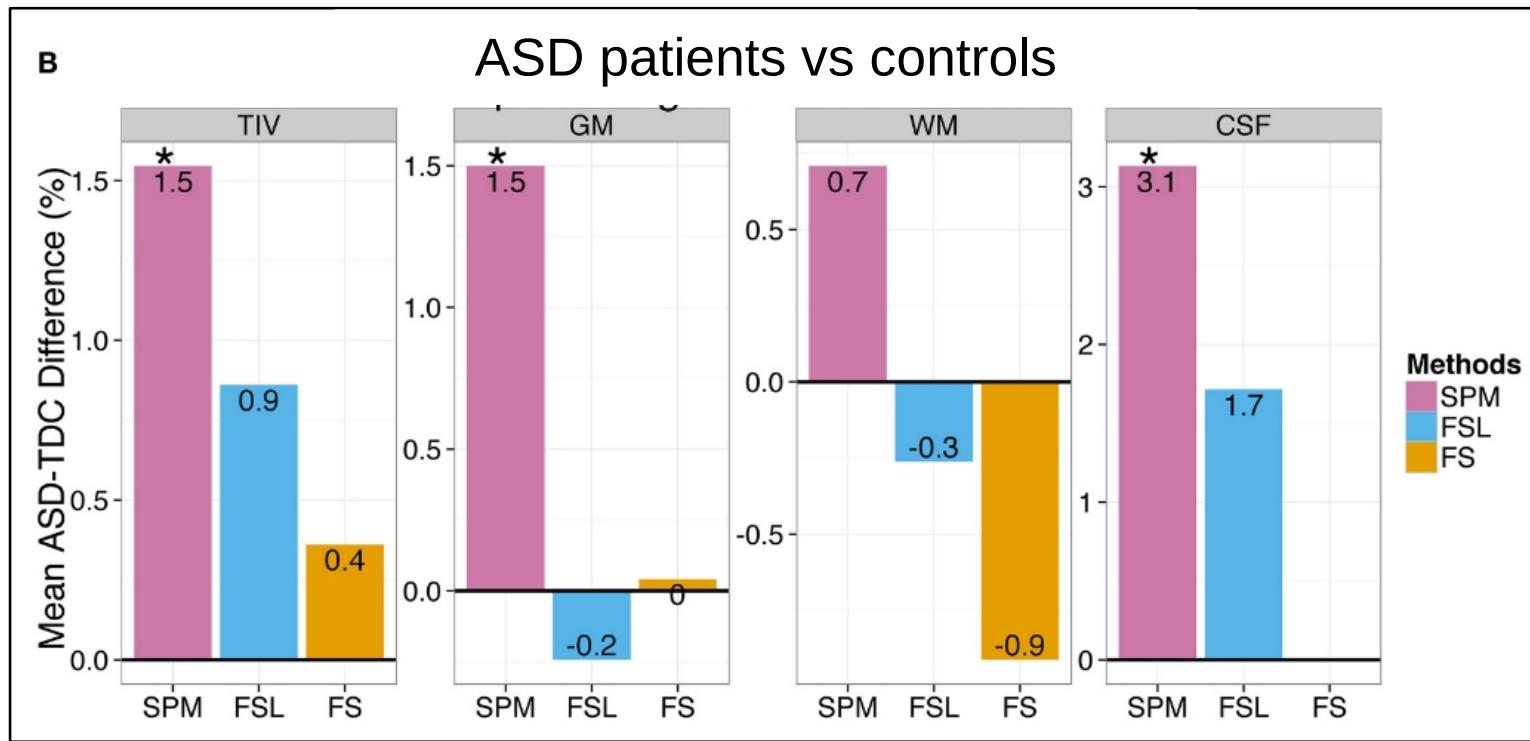
Y = Diff. of t-statistics



- ▷ Plots similar to expected variation if **independent** was fed into each package

Alex Bowring, Camille Maumet, Thomas Nichols

G. Katuwal, f. in Brain Imaging Methods, 2016

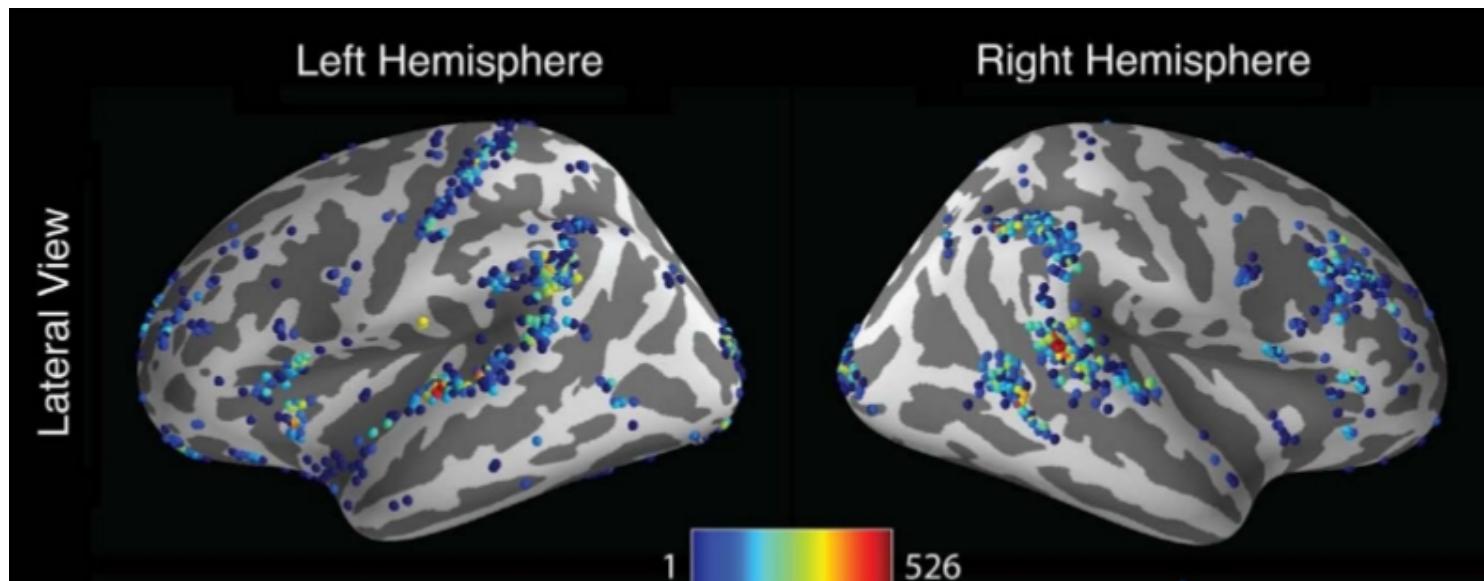


- Change from FSL to SPM?
- Change from v.1.12 to v.2.1 ?
- Change from cluster A to cluster B? Glatard et. al., finsc, 2015

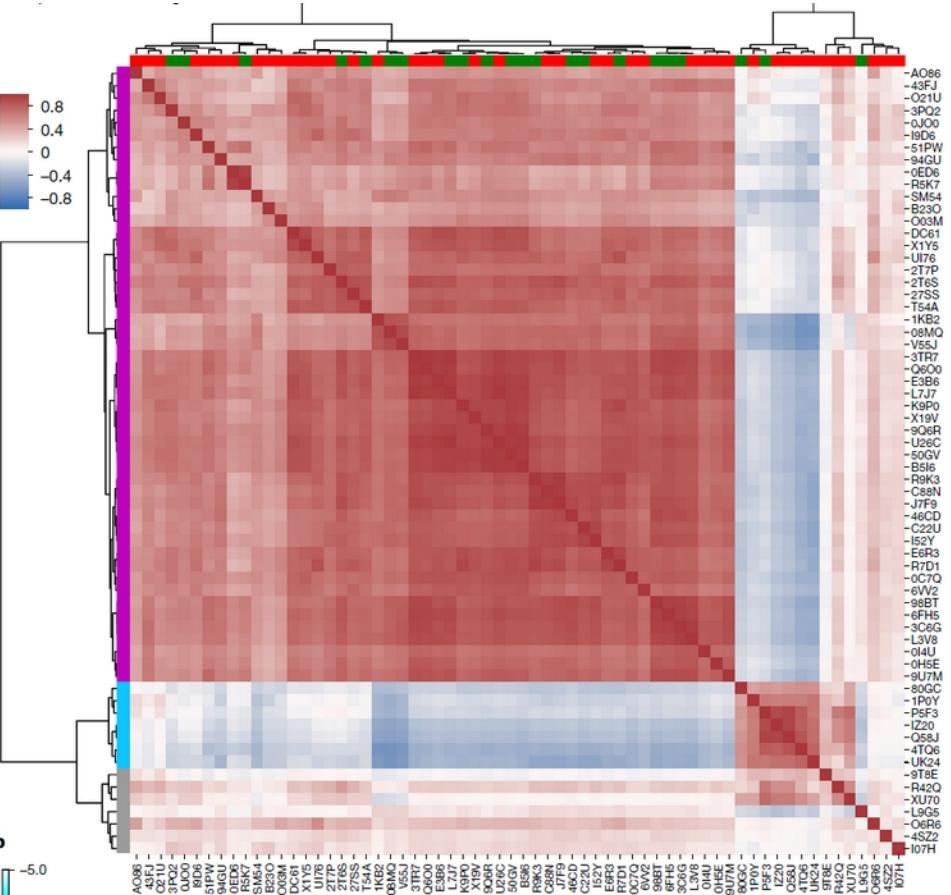
Across possible pipelines

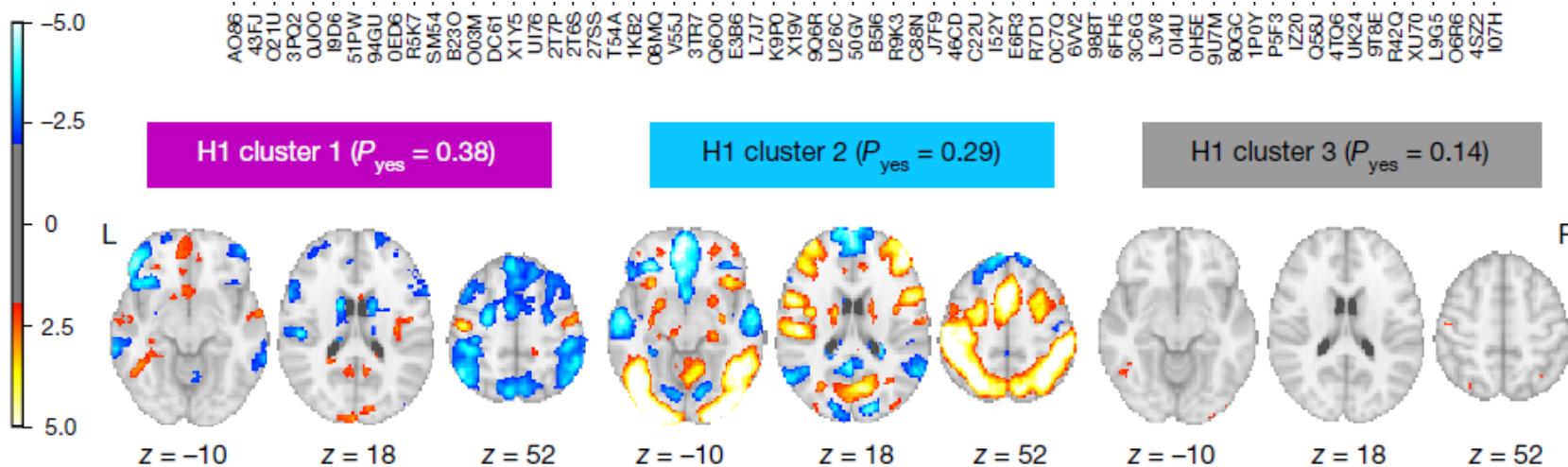
J. Carp, *f. Neuroscience*, 2012

- A **single** event-related fMRI experiment to a large number of unique analysis procedures
- Ten analysis steps for which multiple strategies appear in the literature : **6,912 pipelines**
- Plotting the maximum peak

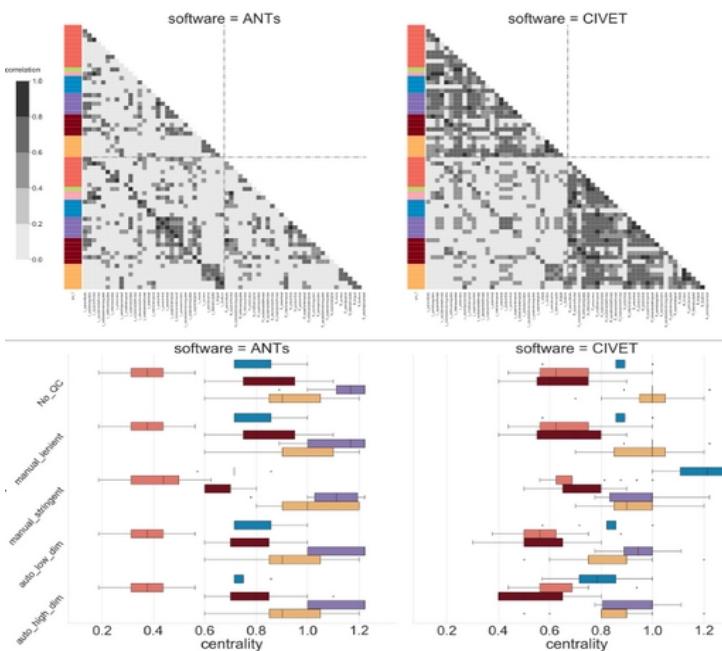


- 70 independent teams analyzing the same fMRI dataset
- No team had the same pipeline
- Results show three “clusters”
- Even within clusters decision to reject H0 varies





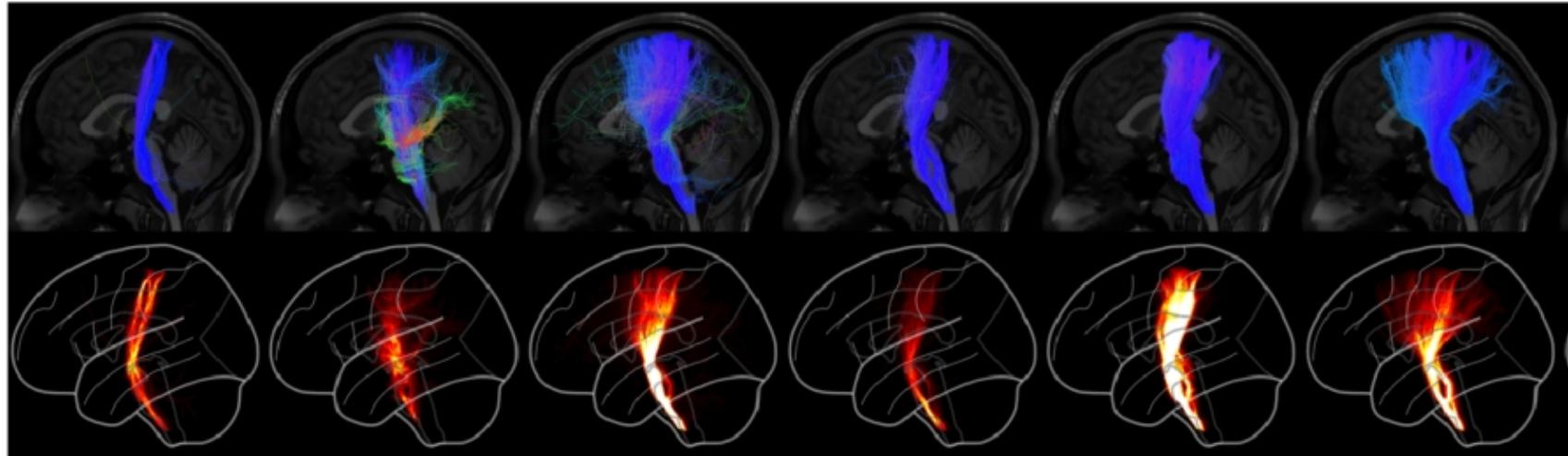
Analytical flexibility: N. Bhagwat, 2020



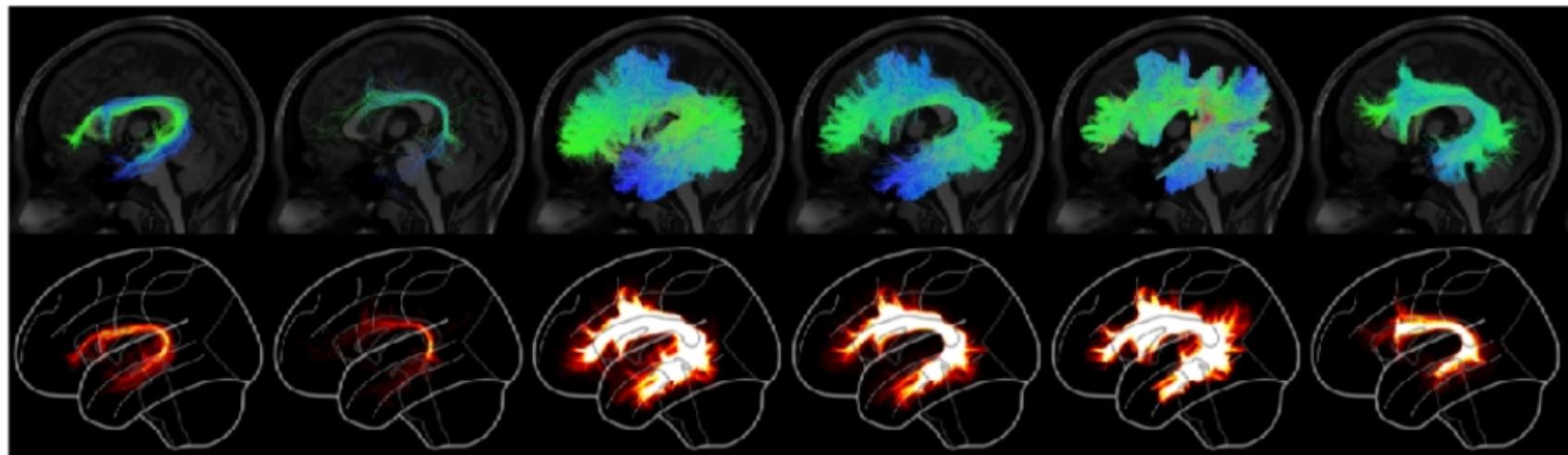
What happens when 42 groups dissect 14 white matter bundles on the same dataset?

KG Schilling ... M Descoteaux 2020 (~150 authors)

CST



AF



- A less rare case than usually thought !
- No license
- Database not containing what it describes
- Wrong QC – QC unreliable
- Headers of files are not correct (cf the Left/Right issue)
- Provenance of data is lost
- **SAM1 SAM2 SAM3:**
<https://www.youtube.com/watch?v=N2zK3sAtr-4>

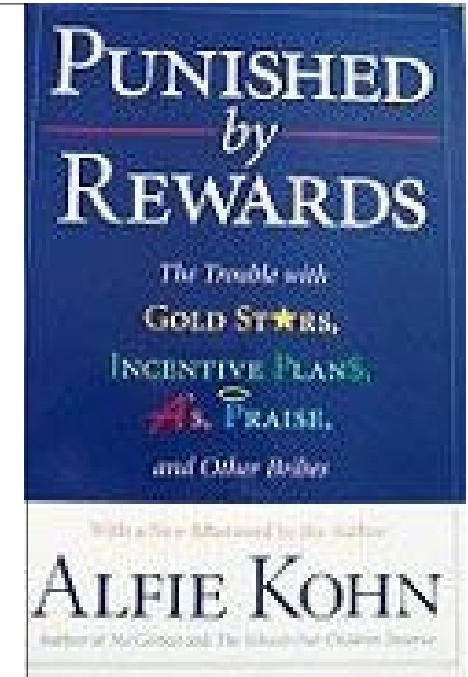
- From HCP:

"With the releases of FreeSurfer 7.X, there have been some regressions in surface placement performance when running FreeSurfer inside the HCP Pipelines. At this time, *I would recommend sticking with FreeSurfer 6.0* while we get these issues sorted out."

Three causes

1. Poor statistical procedures
2. Issues in data and software
3. A cultural issue: Publication practices and research incentives

- Publication = the only “currency” for researchers, universities
- The high competition incites researchers to keep data and code as “assets” and to get as many authorships as possible
- The current incentive system promotes poorly reproducible research



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Research



The natural selection
of bad science

Paul E. Smaldino¹ and Richard McElreath²

¹Cognitive and Information Sciences, University of California, Merced, CA 95343, USA

²Department of Human Behavior, Ecology, and Culture, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

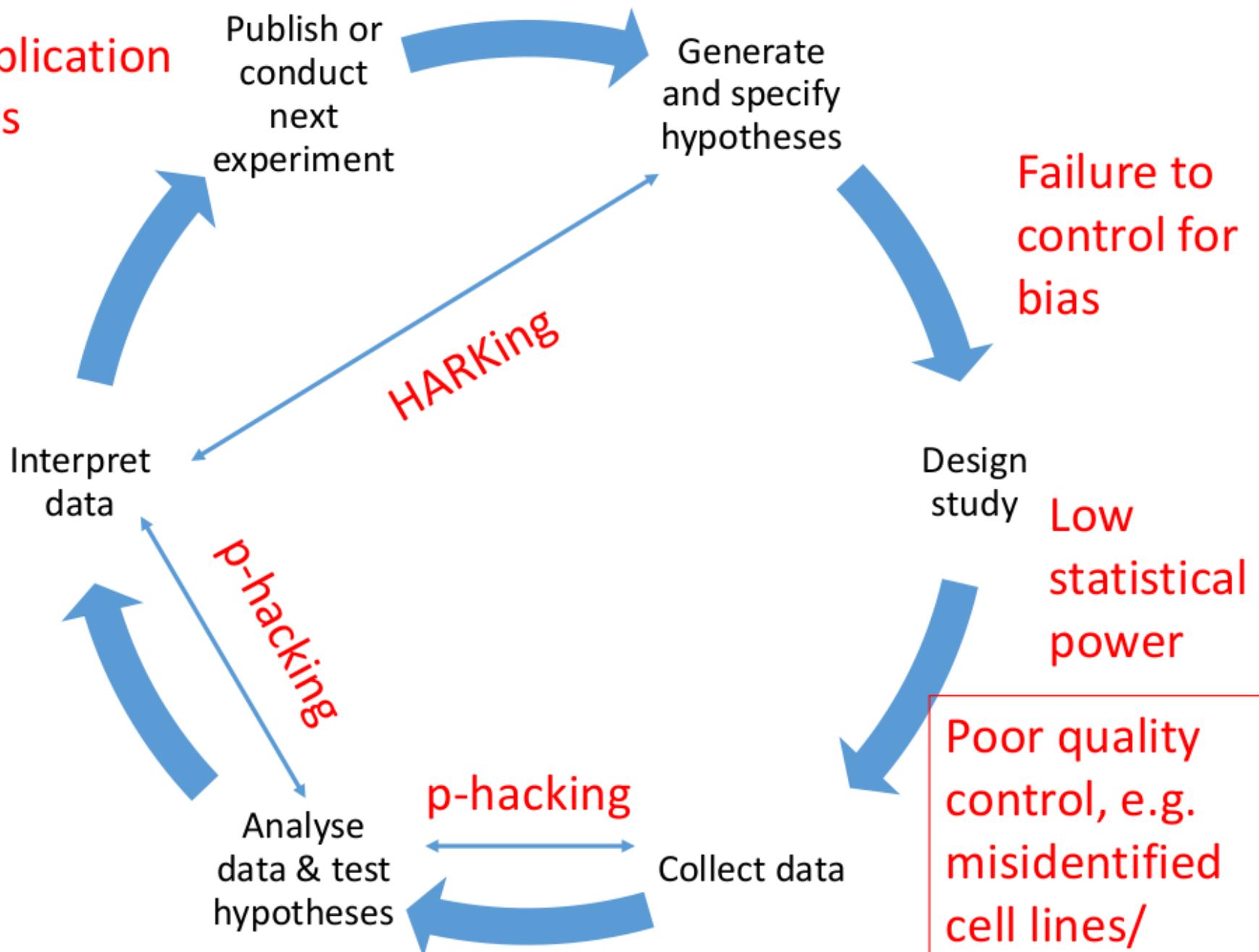
Objectives US national pilot study to

- (1) test the feasibility of online administration of the Bioethical Issues in Biostatistical Consulting (BIBC) Questionnaire
- (2) determine the prevalence and relative severity of a broad array of bioethical violations requests that are presented to biostatisticians by investigators seeking biostatistical consultations; and
- (3) establish the sample size needed for a full-size phase II study.

Conclusion: **clear evidence** that researchers make requests of their biostatistical consultants that are rated as severe violations and occur frequently

Wang et al. 2017. BMJ Open 7 (11): 2017.

Publication bias



Part I: Reproducibility: background

Part II : Etiology of Irreproducibility

Part III : Epistemology and statistics

Part IV : Some therapeutic proposals

- Improve training
- Develop better tools and standards – make these tools that could change the culture
- Change the incentives

- Pre-registration
- Ban p-values
- Change α
- Complement with other statistics

Significance

The lack of reproducibility of scientific research undermines public confidence in science and leads to the misuse of resources when researchers attempt to replicate and extend fallacious research findings. Using recent developments in Bayesian hypothesis testing, a root cause of nonreproducibility is traced to the conduct of significance tests at inappropriately high levels of significance. Modifications of common standards of evidence are proposed to reduce the rate of nonreproducibility of scientific research by a factor of 5 or greater.

Johnson, V.E. (2013). Revised standards for statistical evidence. PNAS 110, 19313–19317.

- Promoted by many, in particular Chris Chambers
- Simple: explain in details your methods and hypotheses, what you will test
- This is reviewed, and if accepted results will be published
- This does not preclude exploratory analyses
- Do it for yourself - eg use OSF (time stamped)
- There is almost no reason to not do it

There's a better way to manage your research

OSF is a free, open platform to support your research and enable collaboration.

COMMENT · 10 SEPTEMBER 2019

What's next for Registered Reports?

Reviewing and accepting study plans before results are known can counter perverse incentives. Chris Chambers sets out three ways to improve the approach.

Chris Chambers 

- The rise of Git (GitHub, GitLab, ...) repositories
 - Many are open, collaborative
 - Ex: from FSL to nilearn
- The rise of “FAIR” containers
 - Standards descriptor
- The (slow) rise of standardized provenance information

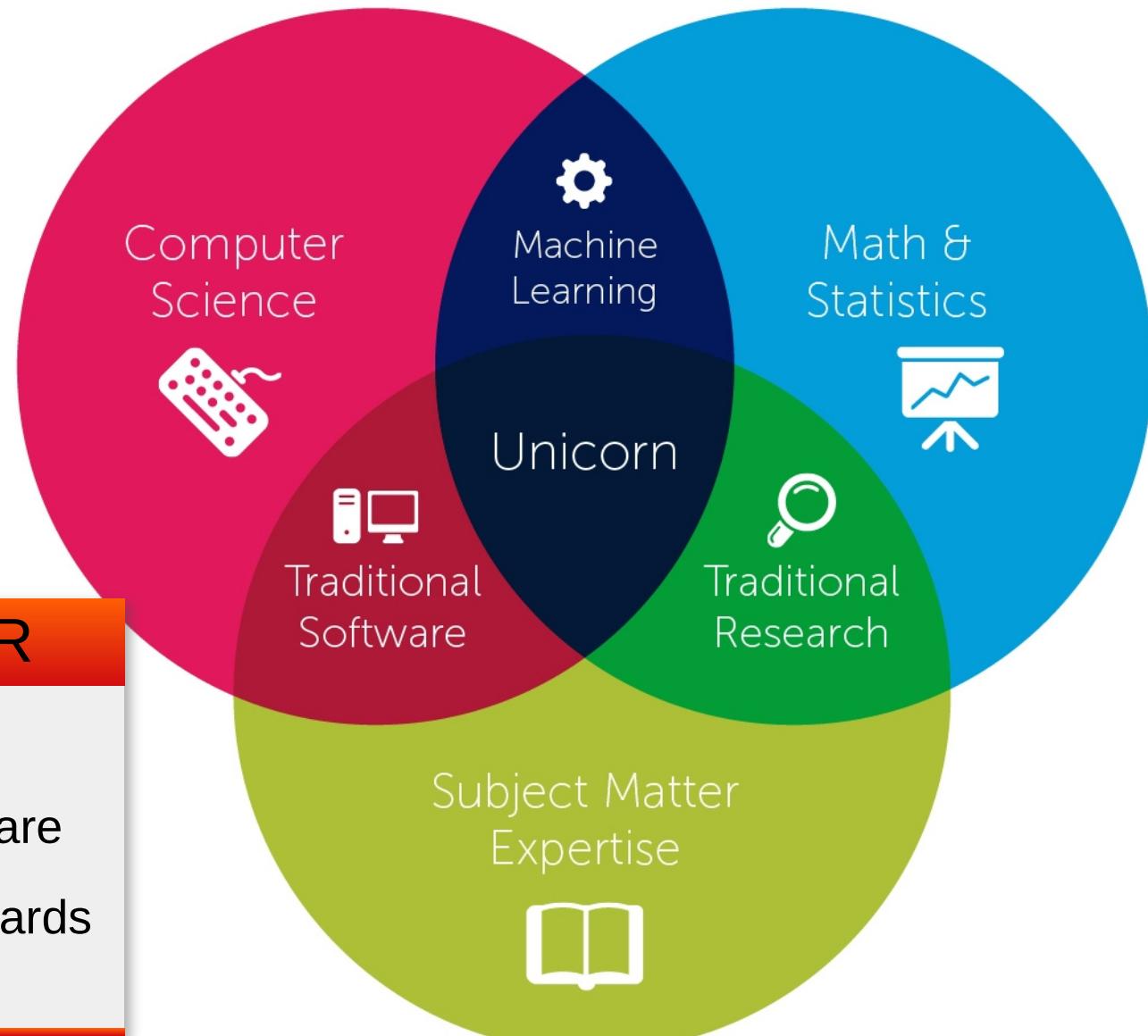
Data Science

Ethical Scholarly communications
Epistemology / lessons from the past
How to collaborate and teach

Research

FAIR

- Data
- Software
- Standards
- reuse



Science and Technology

ReproNim

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ReproNim: A Center for Reproducible Neuroimaging Computation

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ReproNim module 0: Reproducible basics

Prerequisites

Depending on your level of competence in any particular topic, you might like to go through additional materials which will be referenced in each particular lesson. Even if you feel that you are very proficient in all of those topics, we hope you would still learn some new "tricks" or would recommend or contribute some new materials to the lessons.

This lesson is based on lesson templates used in [ReproNim](#) training modules, and [Neurohackweek](#), [Data Carpentry](#) and [Software Carpentry](#) workshops.

Schedule

09:00	Command line/shell	Why and how does using the command line/shell efficiently increase reproducibility of neuroimaging studies? How can we assure that our scripts do the right thing?
12:00	Version control systems	How do version control systems help reproducibility, and which systems should be used?
16:10	Package managers and distributions	How can we establish and control computation environments using available package managers and distributions?
18:10	'Right to share'	Q1
21:10	Other day-to-day reproducible practices	How does reproducibility help in fixing bugs? What can you do to be ready to share your studies and have them be reproducible?
21:35	Wrap-Up	What have we learned?
21:50	Finish	

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ReproNim module for dataprocessing

This lesson is a template for creating [ReproNim](#) lessons.

It is based on the lesson template used in [Neurohackweek](#), [Data Carpentry](#) and [Software Carpentry](#) workshops.

Schedule

09:00	Module overview	What do we need to know to conduct reproducible analysis?
09:10	Lesson 1: Core concepts using an analysis example	What are the different considerations for reproducible analysis?
09:55	Lesson 2: Annotate, harmonize, clean, and version data	How to work with and preserve data of different types?
10:40	Lesson 3: Create and maintain reproducible computational environments	Why and how to use containers and Virtual Machines?
11:40	Lesson 4: Create reusable and composable dataflow tools	How to use dataflow tools?
11:55	Lesson 5: Use integration testing to revalidate analyses as data and software change	Why and how do we use continuous integration?
11:55	Lesson 6: Track provenance from data to results	Can we represent the history of an entire analysis? Can we use this history to repeat the analysis?
12:40	Finish	



Reproducibility: A tragedy of errors, Allison et al, 2016, Nature

SCIENTIFIC DATA 

OPEN

Comment: High-quality science requires high-quality open data infrastructure

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Resources for data management, discovery and (re)use are numerous and diverse, and more specifically we need data resources that enable the FAIR principles¹ of Findability, Accessibility, Interoperability and Reusability of data.

My paper concludes:

- Increase in resting state connectivity between Right Superior Temporal Gyrus and the Right Superior Frontal Gyrus in subjects with autism, and this connectivity correlated with diagnostic severity.

What statistic? (covariates, corrections)

What data? (MR parameters)
What analysis? (software and parameters)

My paper concludes:

- Increase in resting state connectivity between Right Superior Temporal Gyrus and the Right Superior Frontal Gyrus in subjects with autism, and this connectivity correlated with diagnostic severity.

What subject characteristics?
(age, gender, SES, genetics, environment, etc.)

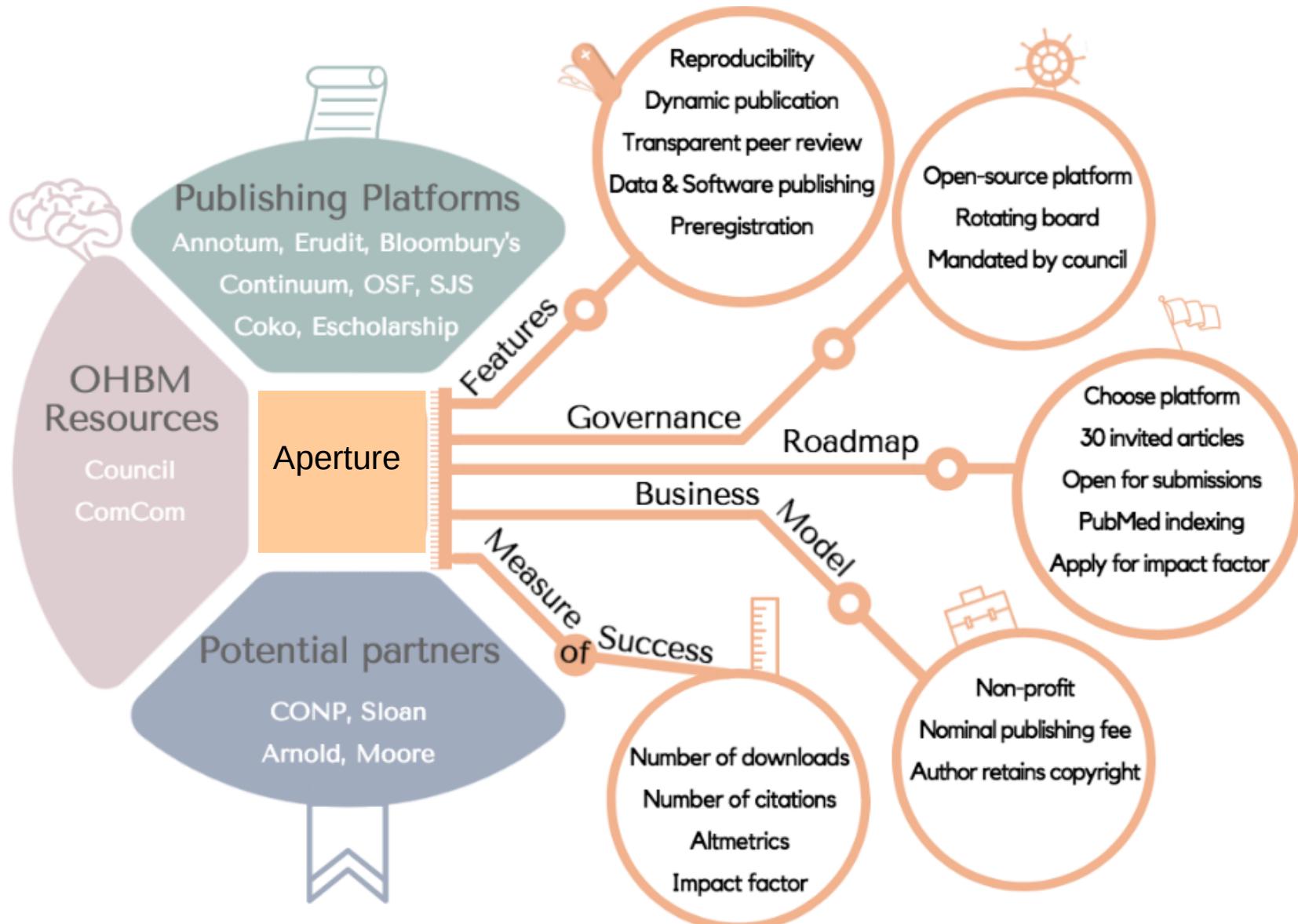
What measure?

What anatomic framework? (atlas)

My paper actually concludes:

- Using a paired T-test, covarying for age, gender and handedness using cluster-size FWE correction, we saw an increase ($P<.01$) in regional seed-based using CONN resting state connectivity between AAL regions of the Right Superior Temporal Gyrus and the Right Superior Frontal Gyrus in 40 subjects with autism (age 14+-5, 19M/11F, IQ 90+- 10, ADOS 20+-5), and this connectivity correlated (Pearson, $P<.05$) with diagnostic severity as measured by the social subscale of the ADI.

- Publish reusable research objects
 - Data first !
 - Software, workflow, analyses
 - Jupyter notebooks, hybrid objects
 - Pre-registered report
- Vetting objects
 - By experts
 - By community based (alt)metrics
- Make published research object machine readable as much as possible



Thank you

- Lab@McGill: <https://neurodatascience.github.io/>
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