The problems associated with the use of p-values in brain imaging and their effects on reproducibility

A reproducibility perspective

JB Poline

McGill University, UC Berkeley

Aug 2nd 2018

Plan

- Definition
- A quick historical perspective

Plan

- Definition
- A quick historical perspective
- Was Ioannidis right?

Plan

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- A quick historical perspective
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- What is/are the problems?
  - technical
  - sociological

Plan

- Definition
- A quick historical perspective
- Was Ioannidis right?
- What is/are the problems?
  - technical
  - sociological
- Is there a solution?

Definition

Probability of observing a statistic equal to the one seen in the data, or one that is more “extreme”, when the null hypothesis is true

Requires:

- Knowledge of the null hypothesis

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- Choice of a statistic

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- Concept of repeating the whole study in the same way
    - Same study design

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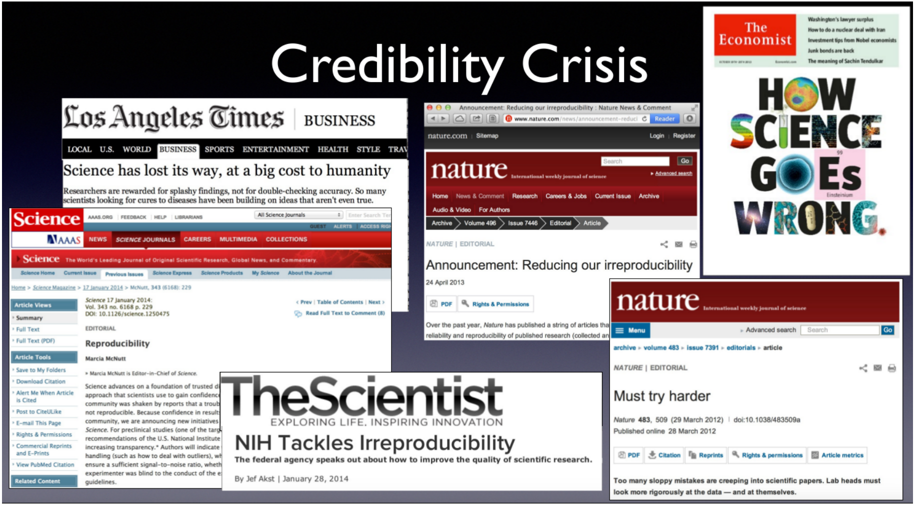
- Concept of repeating the whole study in the same way
    - Same study design
    - Same sampling scheme
    - Same definition of the statistic

Issues of reproducibility in science



Credibility Crisis

Los Angeles Times | BUSINESS

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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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EDITORIAL

Reproducibility

Marcia McNutt

» Marcia McNutt is Editor-in-Chief of *Science*.

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community was shaken by reports that a troub
not reproducible. Because confidence in result
community, we are announcing new initiatives
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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 tha
reliability and reproducibility of published research (collected an

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HOW SCIENCE GOES WRONG

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

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.

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- Reproducibility a *computational* issue, Replicability *a statistical issue*

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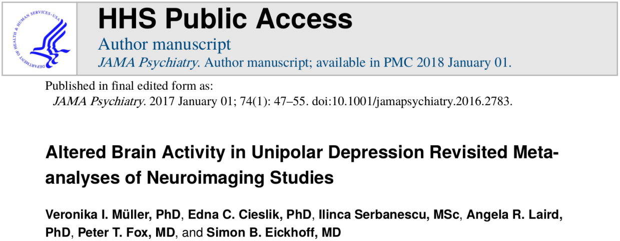
- Statistics is about the **practice** of statistics
- Study on the statistical practices
  - Simmons and Simonsohn in psychology
  - Wang et al., 2018 in biomedical research

Anecdotal evidence 1



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Author manuscript

JAMA Psychiatry. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

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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**

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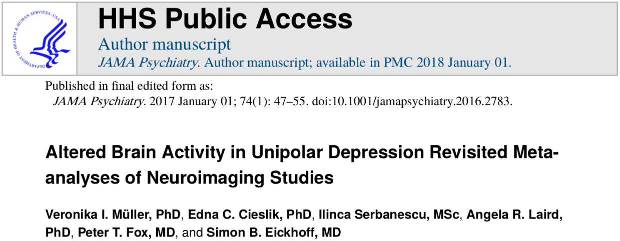

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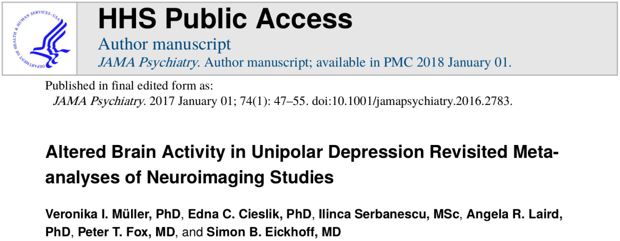

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$>$ During the past 20 years, numerous neuroimaging experiments have investigated aberrant brain activation during cognitive and emotional processing in patients with unipolar depression.

> *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.***

Anecdotal evidence 2: All foods cause cancer ? Schoenfeld 2013

- Of 264 single-study assessments, 191 (72%) concluded that the tested food was associated with an increased (n = 103) or a decreased (n = 88) risk;

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- 75% of the risk estimates had weak ($0.05 > P > 0.001$) or no statistical ($P > 0.05$) significance.
- Meta-analyses presented more conservative results; only 13 (26%) reported an increased ($n = 4$) or a decreased ($n = 9$) risk

Historical perspective

- When did we start to talk of the problem?
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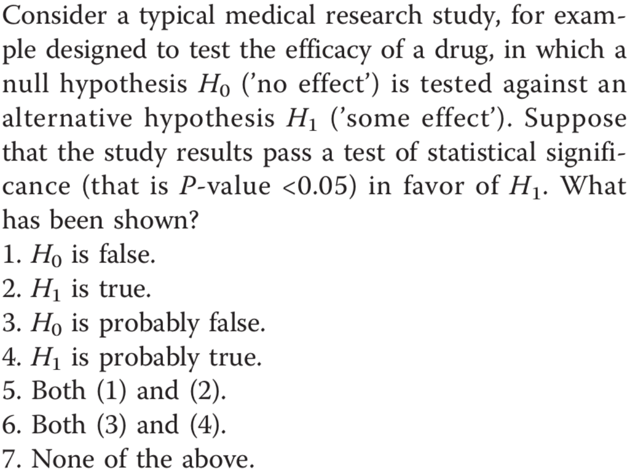
Historical perspective

- When did we start to talk of the problem?
  - almost as soon as the time of the p-value was defined, 1925
- Fisher conception:
  - an indication of something about the data under H0
- Neyman-Pearson conception:
  - a decision making rule
- Which one is used today ?

Significance testing as perverse probabilistic reasoning



Consider a typical medical research study, for example designed to test the efficacy of a drug, in which a null hypothesis H_0 ('no effect') is tested against an alternative hypothesis H_1 ('some effect'). Suppose that the study results pass a test of statistical significance (that is P-value <0.05) in favor of H_1. What has been shown?

1. H_0 is false.
2. H_1 is true.
3. H_0 is probably false.
4. H_1 is probably true.
5. Both (1) and (2).
6. Both (3) and (4).
7. None of the above.

# Significance testing as perverse probabilistic reasoning

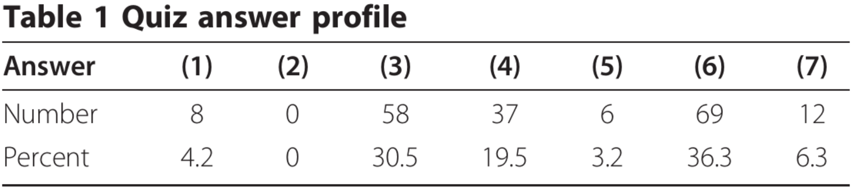


Table 1 Quiz answer profile

Answer	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Number	8	0	58	37	6	69	12
Percent	4.2	0	30.5	19.5	3.2	36.3	6.3

- Westover, 2014

# What happens if . . . p is “significant” but study power is low ?

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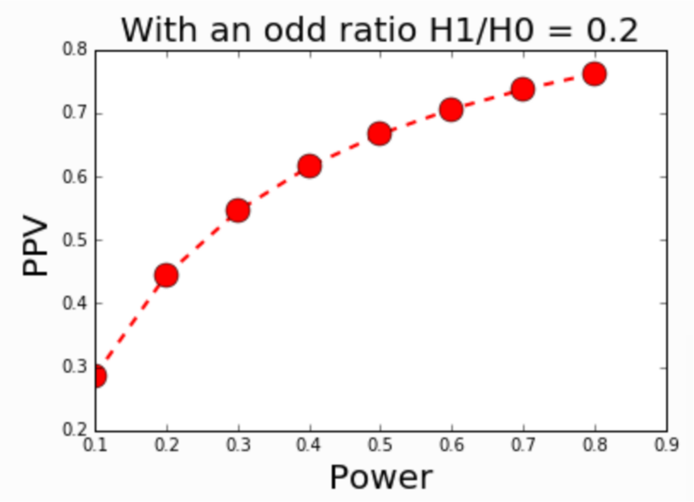
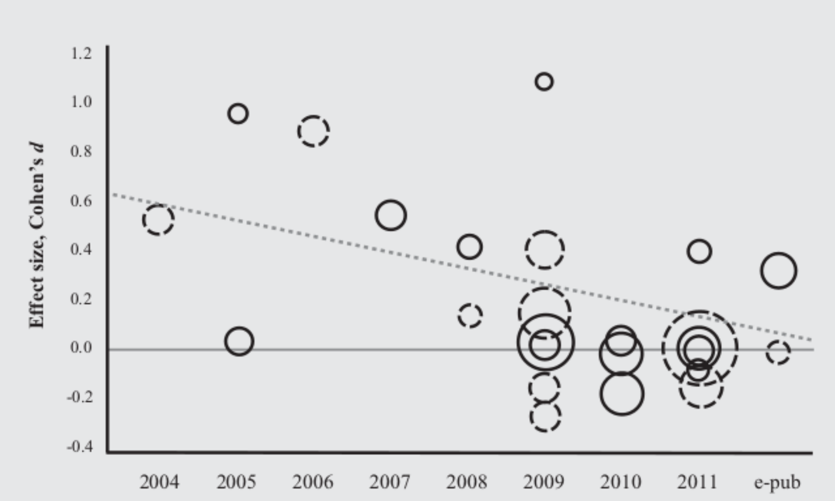
- Study in Button et al, 2013, more than half of the studies have less than 30% power
- Low Positive Predictive Value P(H_A true | test significant)
- Inflated effect size
- Depends on the prior probability of H_A and H_0

# Low Positive Predictive Value : P(H_A is true | test is significant)



# Inflated effect size Effect-size = f(years, sample, . . .)



Molendijk, 2012, BDNF and hippocampal volume

Not everybody believes in power

- Grant reviewer quote (grant on power rejected)

  "... I am skeptical that searches of existing studies have information that's relevant and targeted enough to assessing power or reproducibility for scientifically interesting new designs."

Do we know how to compute some effect sizes ?

- often *very hard* to find in the paper

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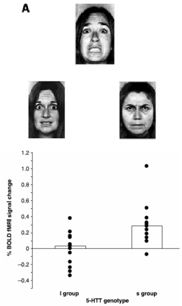
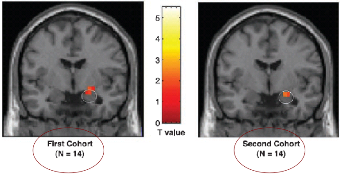


Serotonin Transporter Genetic Variation and the Response of the Human Amygdala

Ahmad R. Hariri,[1] Venkata S. Mattay,[1] Alessandro Tessitore,[1]
Bhaskar Kolachana,[1] Francesco Fera,[1] David Goldman,[2]
Michael F. Egan,[1] Daniel R. Weinberger[1]*

19 JULY 2002 VOL 297 SCIENCE

Amygdala Response: s Group > l Group



- Authors report
  $m_1 = .28, m_2 = .03, \mathrm{SDM}_1 = 0.08, \mathrm{SDM}_2 = 0.05, N_1 = N_2 = 14$
- How do we compute the effect size ?

Computing Effect size: practice

- First, compute the standard deviation of the data from the SDM

Computing Effect size: practice

- First, compute the standard deviation of the data from the SDM - get σ from SDM : $\sigma = \sqrt{14-1} \times \mathrm{SDM}$
  - Combine the σ to have one estimation across the groups
    - formula easy to recompute or find
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  - Write the estimated model: $Y = [1 \dots 1]^t [m_1 - m_2] + \mathrm{residual}$
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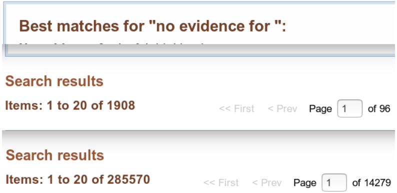
  - Compute the total sum of square $Y^t Y$, then the proportion:
  - $V_e = \frac{(n_1 + n_2)(m_1 - m_2)^2}{n_1 s_1^2 + n_2 s_2^2 + (n_1 + n_2)(m_1 - m_2)^2} > 40\%$

What happens if . . . p is not significant? File drawer effect

- Described first by Rosenthal in **1979**
- Most publications accepted only with $p < .05$
- Hard to publish null results

“. . . whether you would be able to review the manuscript”No Evidence for an Effect of XXX on Hippocampal Volume in a YYY Sample“, by some-authors, submited for consideration in . . . ”



Best matches for "no evidence for ":

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Search results

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Wait - are we always testing/publishing at p=0.05 ? Incentive perversion

- Implies P-Hacking and Harking
  - Simmons and Simonsohn 2011, P-curves

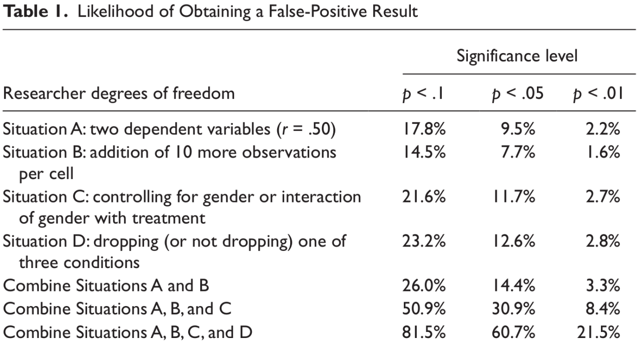
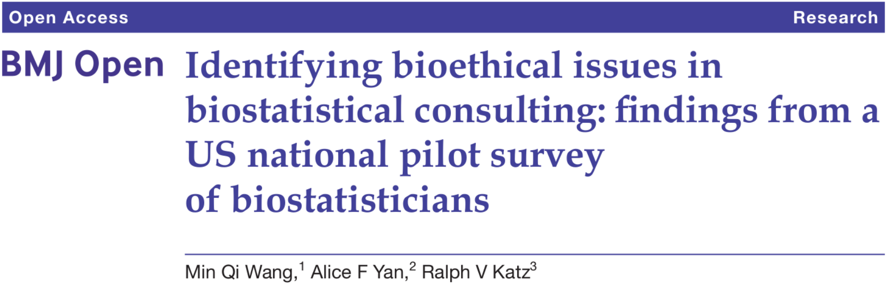


Table 1. Likelihood of Obtaining a False-Positive Result

	Significance level		
Researcher degrees of freedom	$p < .1$	$p < .05$	$p < .01$
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%

Is p-hacking really happening ?



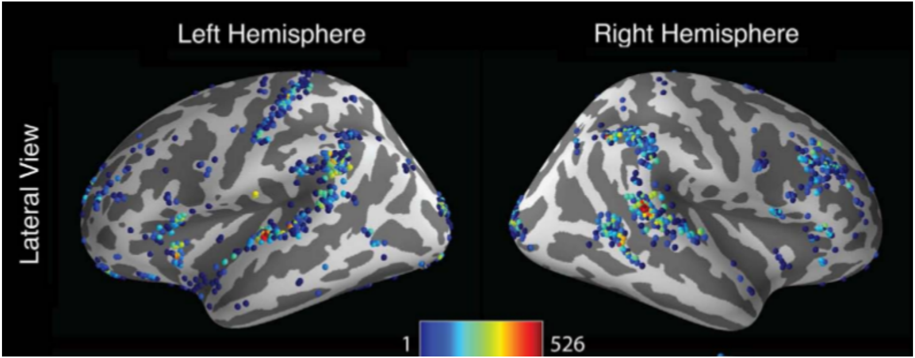
Open Access Research

BMJ Open Identifying bioethical issues in biostatistical consulting: findings from a US national pilot survey of biostatisticians

Min Qi Wang,[1] Alice F Yan,[2] Ralph V Katz[3]

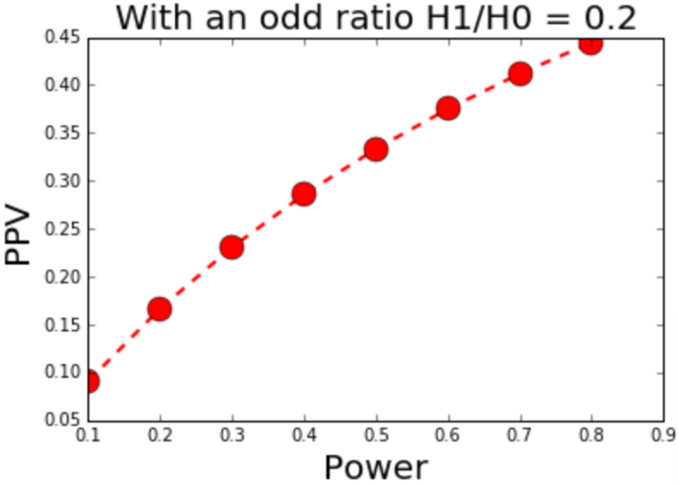
- study gives **clear evidence** that researchers make requests of their biostatistical consultants that are not only rated as **severe violations**, but further that these requests occur quite **frequently**.

Wait - are we always testing/publishing at p=0.05 ? Incentive perversion

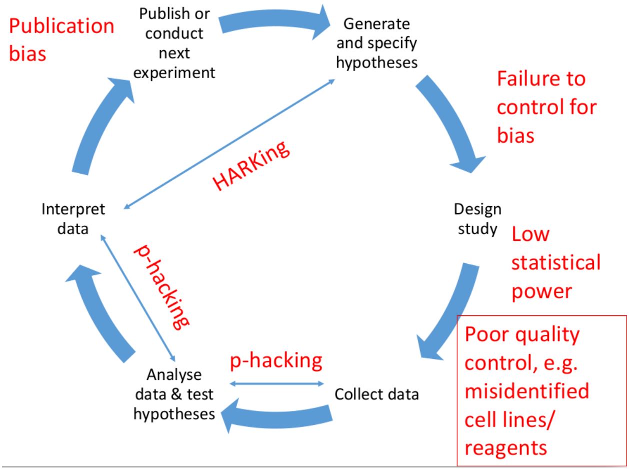


- Carp 2012

Low Positive Predictive Value : P(H_A is true | test is significant)



A possibly quite dire situation


Publication bias
Publish or conduct next experiment
Generate and specify hypotheses
Failure to control for bias
HARKing
Interpret data
Design study
Low statistical power
p-hacking
Poor quality control, e.g. misidentified cell lines/ reagents
p-hacking
Analyse data & test hypotheses
Collect data

- D. Bishop 2015

The reactions - the solutions?

- Technical:
  - Redefine significance
  - Use Bayesian framework
  - Prediction framework

The reactions - the solutions?

- Technical:
  - Redefine significance
  - Use Bayesian framework
  - Prediction framework
- Social: work with the journals
  - Ban p-values
  - Long list of checkboxes in nature publications - Cobidas
  - Nature statistician review
  - Registered Reports

Solutions - technical - redefine significance

- 70 prominent scientists worked on a google document ...

"We propose to change the default P-value threshold for statistical significance for claims of new discoveries from 0.05 to 0.005."

- move BF from **weak 2-3 to strong 12-26 evidence** (under many H1)

Daniel J. Benjamin 1 *, James O. Berger 2 , Magnus Johannesson 3 *, Brian A. Nose k 4, 5 , E. - J. W agenma k er s 6 , Richard Ber k 7, 1 0 , K enneth A. Bollen 8 , Björn Bremb s 9 , Lawrence Brown 10 , Colin Camerer 11 , David Cesarini 12, 13 , Christopher D. Chambers 14 , Merlise Clyde 2 , Thomas D. Cook 15,16 , Paul De Boeck 17 , Zoltan Dienes 18 , Anna Dreber 3 , Kenny Easwaran 19 , Charles Efferson 20 , Ernst Fehr 21 , Fiona Fidler 22 , Andy P. Field 18 , Malcolm Forster 23 , Edward I. George 10 , Richard Gonzalez 24 , Steven Goodman 25 , Edwin Green 26 , Donald P. Green 27 , Anthony Greenwald 28 , Jarrod D. Hadfield 29 , Larry V. Hedges 30 , Leonhard Held 31 , Teck Hua Ho 32 , Herbert Hoijtink 33 , James Holland Jones 39,40 , Daniel J. Hruschka 34 , Kosuke Imai 35 , Guido I mbens 36 , John P.A. Ioannidis 37 , Minjeong Jeon 38 , Michael Kirchler 41 , David Laibson 42 , John List 43 , Roderick Little 44 , Arthur Lupia 45 , Edouard Machery 46 , Scott E. Maxwell 47 , Michael McCarthy 48 , Don Moore 49 , Stephen L. Morgan 50 , Marcus Munafó 51, 52 , Shinichi Nakagawa 53 , Brendan Nyhan 54 , Timothy H. Parker 55 , Luis Pericchi 56 , Marco Perugini 57 , Jeff Rouder 58 , Judith Rousseau 59 , Victoria Savalei 60 , Felix D. Schönbrodt 61 , Thomas Sellke 62 , Betsy Sinclair 6 3 , Dustin Tingley 6 4 , Trisha Van Zandt 6 5 , Simine Vazire 6 6 , Duncan J. Watts 6 7 , Christopher Winship 6 8 , Robert L. Wolpert 2 , Yu Xie 69 , Cristobal Young 7 0 , Jonathan Zinman 7 1 , Valen E. Johnson 7 2 *

Solutions: is it a solution, really?

- 88 non less prominent scientists declare that this is not a solution !

Abstract: In response to recommendations to redefine statistical significance to $p \leq .005$, we propose that researchers should transparently *report and justify* all choices they make when designing a study, *including the alpha level*.

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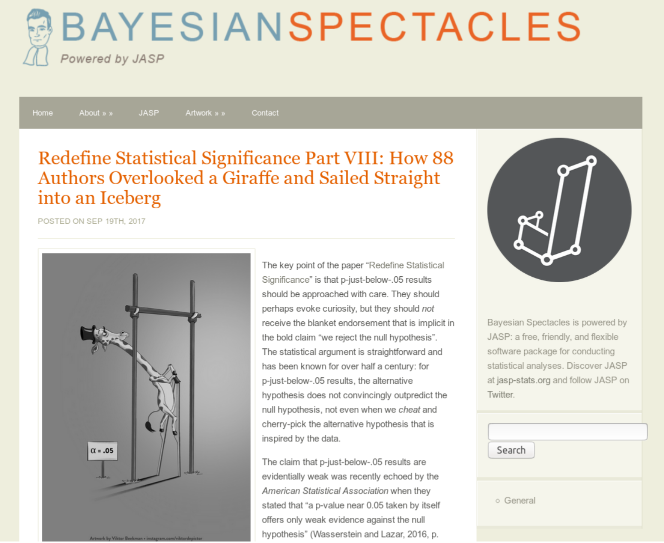
Abstract: In response to recommendations to redefine statistical significance to p $\leq$ .005, we propose that researchers should transparently *report and justify* all choices they make when designing a study, *including the alpha level*.

- results depend on power and prior
- results depend on H1
- priors are really hard to estimate
- may make science more costly and analyses lose sensitivity

# Original authors fight back !



BAYESIANSPECTACLES

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Redefine Statistical Significance Part VIII: How 88 Authors Overlooked a Giraffe and Sailed Straight into an Iceberg

POSTED ON SEP 19TH, 2017

The key point of the paper "Redefine Statistical Significance" is that p-just-below-.05 results should be approached with care. They should perhaps evoke curiosity, but they should *not* receive the blanket endorsement that is implicit in the bold claim "we reject the null hypothesis". The statistical argument is straightforward and has been known for over half a century: for p-just-below-.05 results, the alternative hypothesis does not convincingly outpredict the null hypothesis, not even when we *cheat* and cherry-pick the alternative hypothesis that is inspired by the data.

The claim that p-just-below-.05 results are evidentially weak was recently echoed by the *American Statistical Association* when they stated that "a p-value near 0.05 taken by itself offers only weak evidence against the null hypothesis" (Wasserstein and Lazar, 2016, p.

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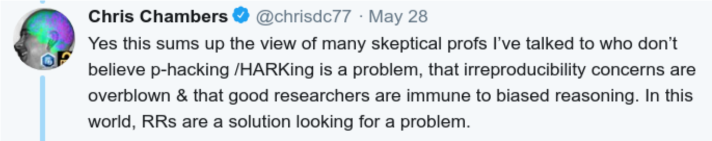
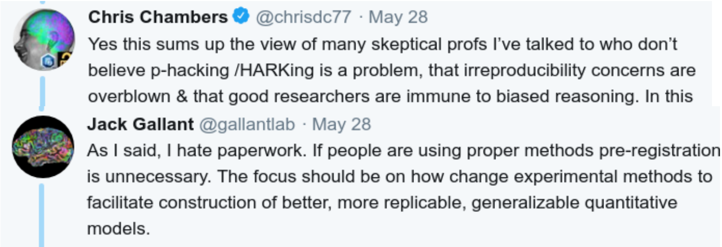


Chris Chambers @chrisdc77 · May 28

Yes this sums up the view of many skeptical profs I’ve talked to who don’t believe p-hacking /HARKing is a problem, that irreproducibility concerns are overblown & that good researchers are immune to biased reasoning. In this world, RRs are a solution looking for a problem.

Registered reports



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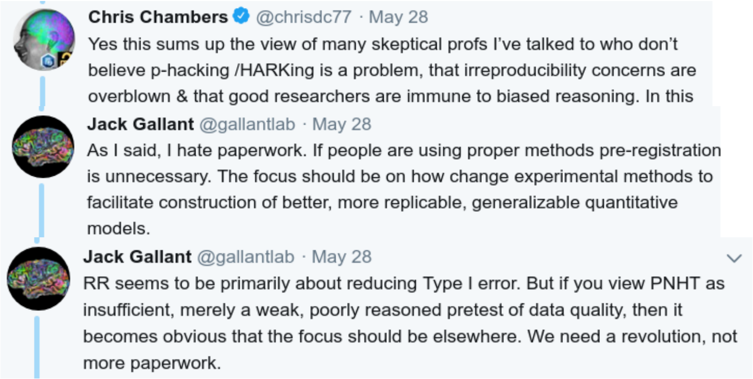

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RR seems to be primarily about reducing Type I error. But if you view PNHT as insufficient, merely a weak, poorly reasoned pretest of data quality, then it becomes obvious that the focus should be elsewhere. We need a revolution, not more paperwork.

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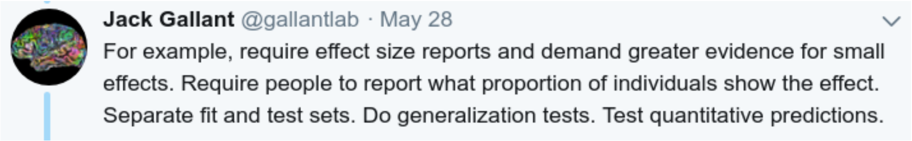

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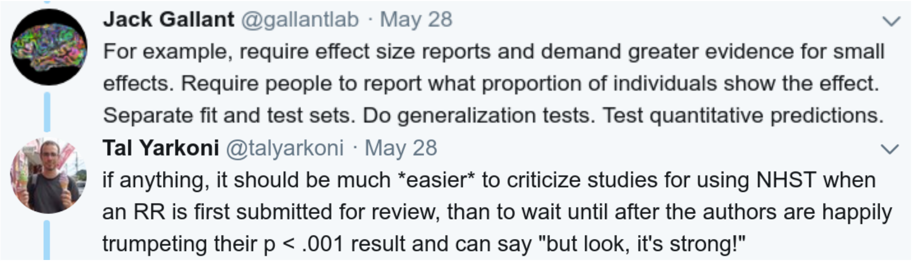

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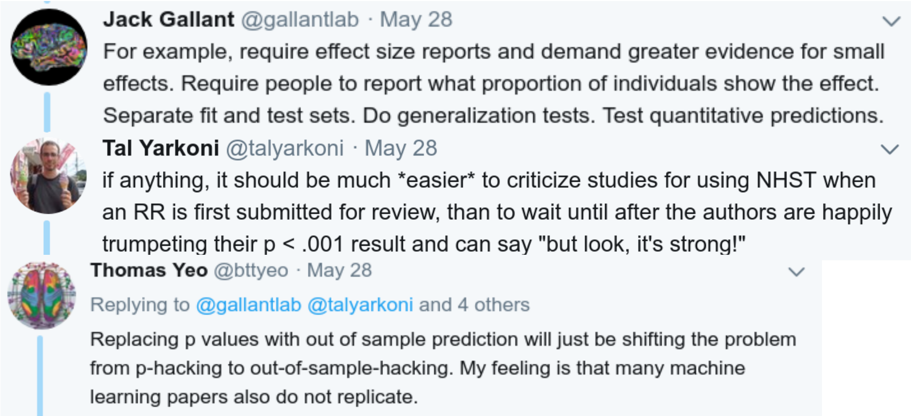

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Thomas Yeo @bttyeo · May 28

Replying to @gallantlab @talyarkoni and 4 others

Replacing p values with out of sample prediction will just be shifting the problem from p-hacking to out-of-sample-hacking. My feeling is that many machine learning papers also do not replicate.

Solutions - others

- Ban p-values sounds a little extreme (BASP)
  - Btw: Nature editorial stated :
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- Cobidas and reporting best practices
  - community education and publishing efforts
  - standards for easing reuse of data (INCF-BIDS)

Conclusion 1: Ioannidis again

- Young fields tend to have less stringent criteria
- Ioannidis 2005: When are results more likely to be false?
  - The smaller the studies ...
  - The smaller the effect size ...
  - The larger the number of tests ...
  - The more flexibility in the analyses
  - The more trendy ...
  - The more financial interest ...

Acknowledgements

- Repronim: D. Kennedy, S. Ghosh, Y. Halchenko, D. Keator, D. Jarecka, J. Grethe, M. Martone, etc. . .
- McGill: Celia Greenwood, Bettina Kemme, Samir Das, Shawn Brown, Alan Evans, Bratislav Misic
- Berkeley: M. D'Esposito, M. Brett, S. Van der Walt, J.Millman
- Pasteur: G. Dumas, R. Toro, T. Bourgeron, A. Beggiato
- Neurospin: B. Thirion, G. Varoquaux, V. Frouin, others

- **Hiring on reproducibility and neuroinformatics projects !**

Thank you for your attention - Questions ?