Plan

- issues of reproducibility in science, historical perspective

Plan

- issues of reproducibility in science, historical perspective - Was Ioannidis right?

Plan

- issues of reproducibility in science, historical perspective - Was Ioannidis right? - Annecdotal evidence

Plan

- issues of reproducibility in science, historical perspective - Was Ioannidis right? - Annecdotal evidence
- where is the problem coming from?
  - computations, stats, sociology
  - cf everything matters
- emphasis on statistical issues

Plan

- issues of reproducibility in science, historical perspective - Was Ioannidis right? - Annecdotal evidence
- where is the problem coming from?
  - computations, stats, sociology
  - cf everything matters
- emphasis on statistical issues
- Are there solutions ?

Issues of reproducibility in science

Issues of reproducibility in science

Issues of reproducibility in science

Issues of reproducibility in science

Issues of reproducibility in science

Issues of reproducibility in science

Anecdotal evidence 1

Published in final edited form as:

JAMA Psychiatry. 2017 January 01; 74(1): 47–55. doi:10.1001/jamapsychiatry.2016.2783.

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**

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

Anecdotal evidence 1

Published in final edited form as:
JAMA Psychiatry. 2017 January 01; 74(1): 47–55. doi:10.1001/jamapsychiatry.2016.2783.

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**

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;

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;
- 75% of the risk estimates had weak ($0.05 > P > 0.001$) or no statistical ($P > 0.05$) significance.

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;
- 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

Computational problems

- OS can be a problem (same container, different segementation)
  - Glatard et al, 2015
- Version of librairies and software
- Algorithms initialization
- Algorithms sensitivity to noise (Kiar et al)
- Software variation

Evil p-values: 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

P-value 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

P-value requires:

- Knowledge of the null hypothesis

P-value requires:

- Knowledge of the null hypothesis
- Choice of a statistic

P-value requires:

- Knowledge of the null hypothesis
- Choice of a statistic
- Concept of repeating the whole study in the same way
    - Same study design

P-value requires:

- Knowledge of the null hypothesis
- Choice of a statistic
- Concept of repeating the whole study in the same way
    - Same study design
    - Same sampling scheme

P-value requires:

- Knowledge of the null hypothesis
- Choice of a statistic
- Concept of repeating the whole study in the same way
  - Same study design
  - Same sampling scheme
  - Same definition of the statistic

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

- Power : the probability of finding a significant p-value under H1
- Study in Button et al, 2013, more than half of the studies have less than 30% power

What happens if ... p is "significant" but study power is low ?

- Power : the probability of finding a significant p-value under H1
- 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)

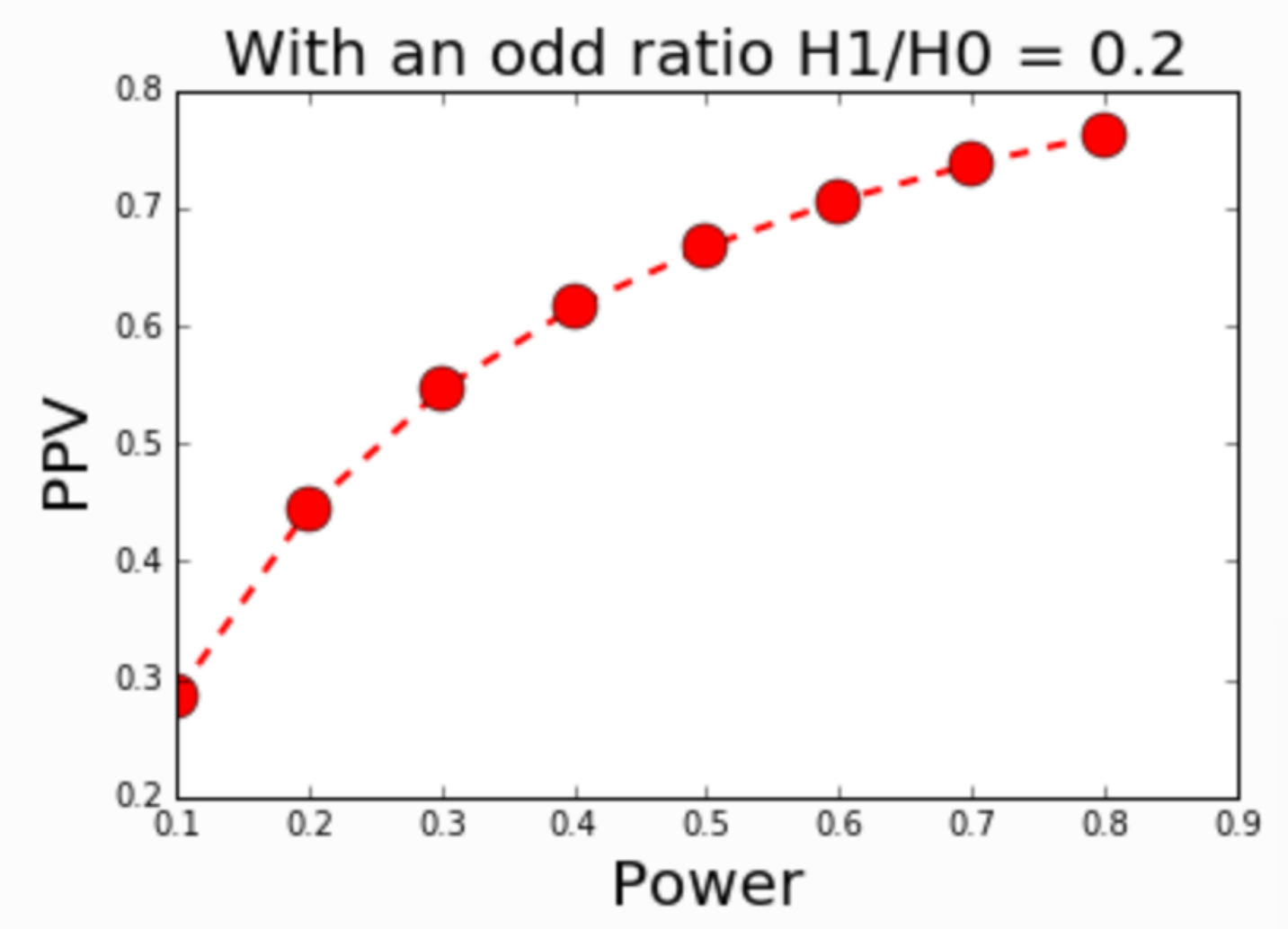
What happens if ... p is "significant" but study power is low ?

- Power : the probability of finding a significant p-value under H1
- 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

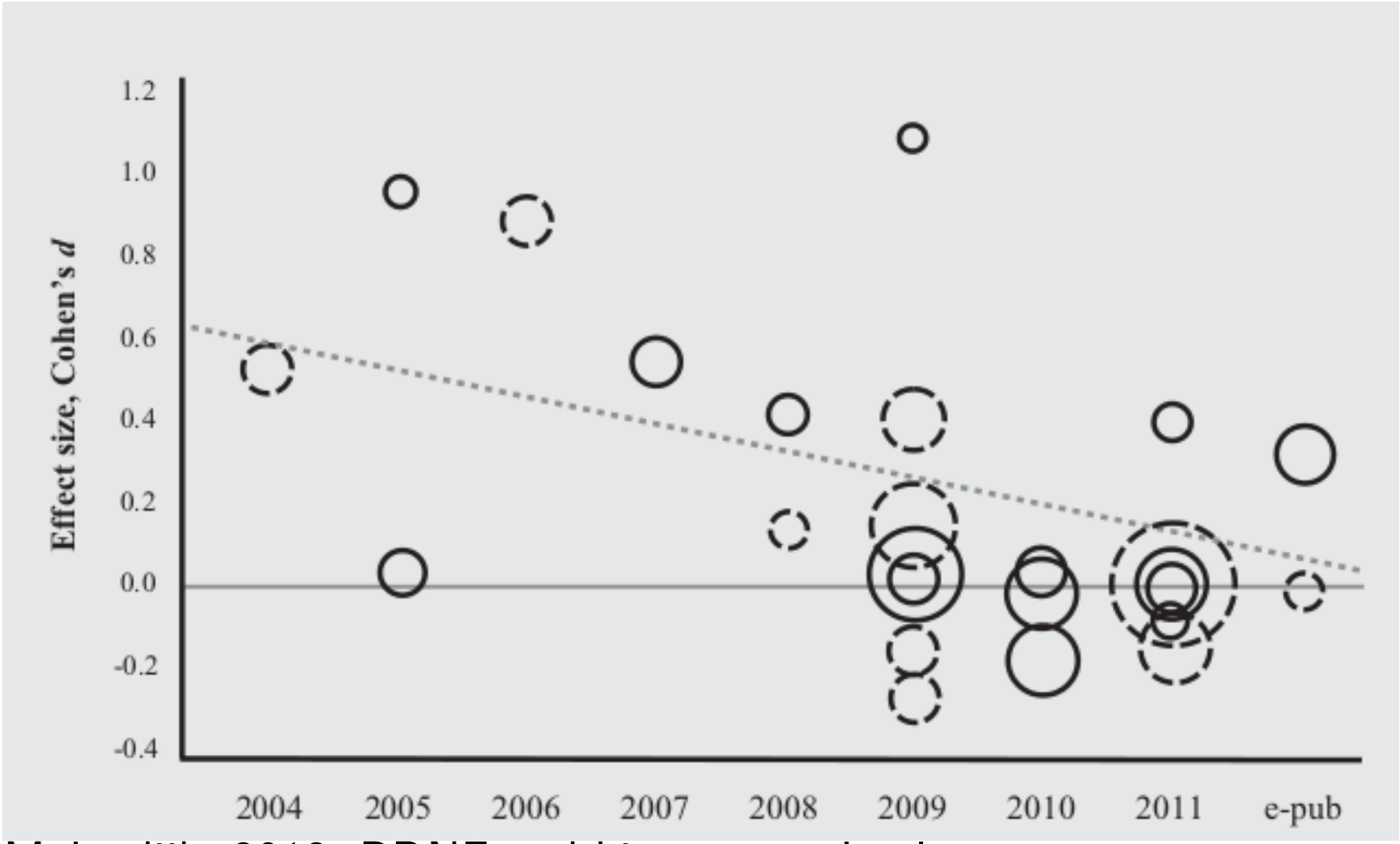
What happens if ... p is "significant" but study power is low ?

- Power : the probability of finding a significant p-value under H1
- 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, . . .)

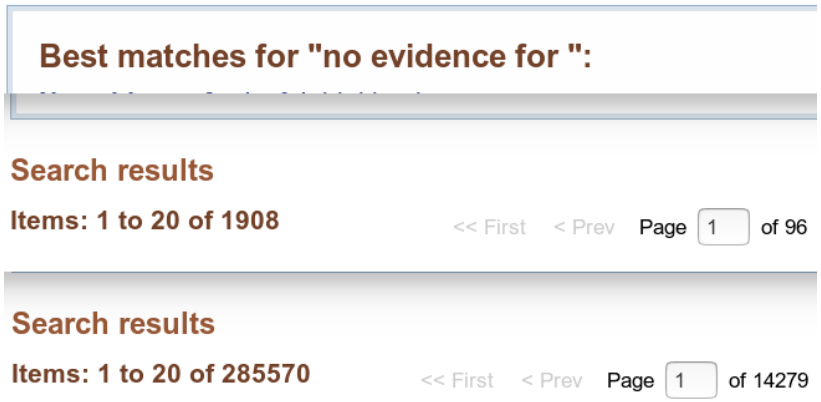


Molendijk, 2012, BDNF and hippocampal volume

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

- Described by Rosenthal in **1979**
- Most publications accepted if 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 . . . "



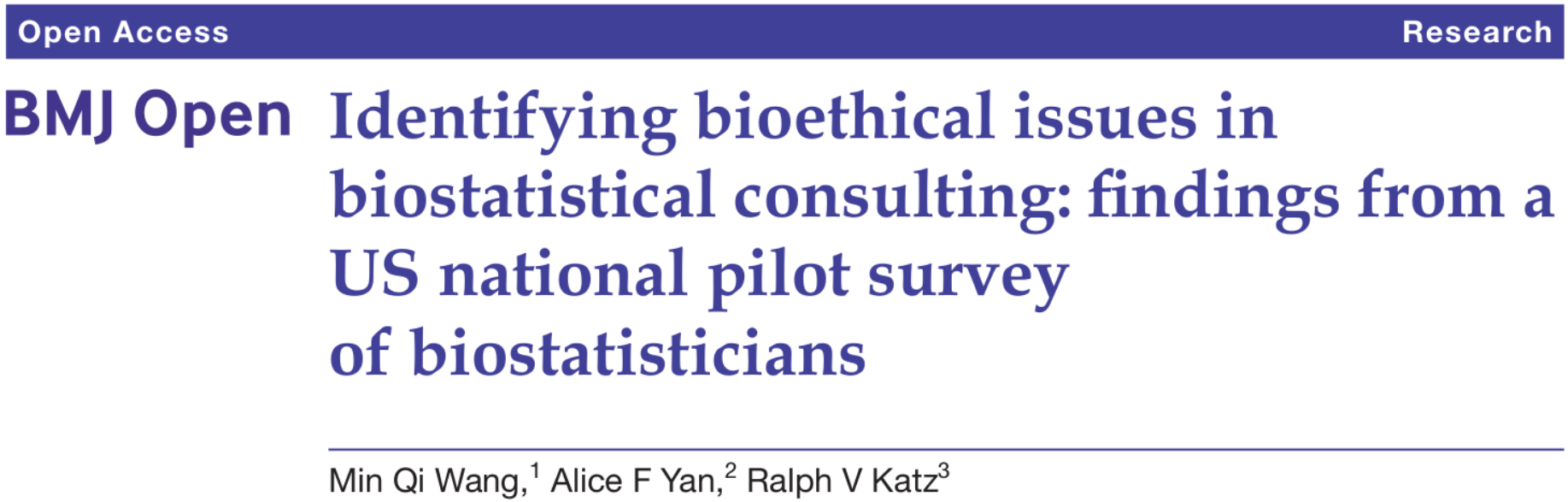
Are we always testing/publishing at p=0.05 ? Incentive perversion

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

Table 1. Likelihood of Obtaining a False-Positive Result

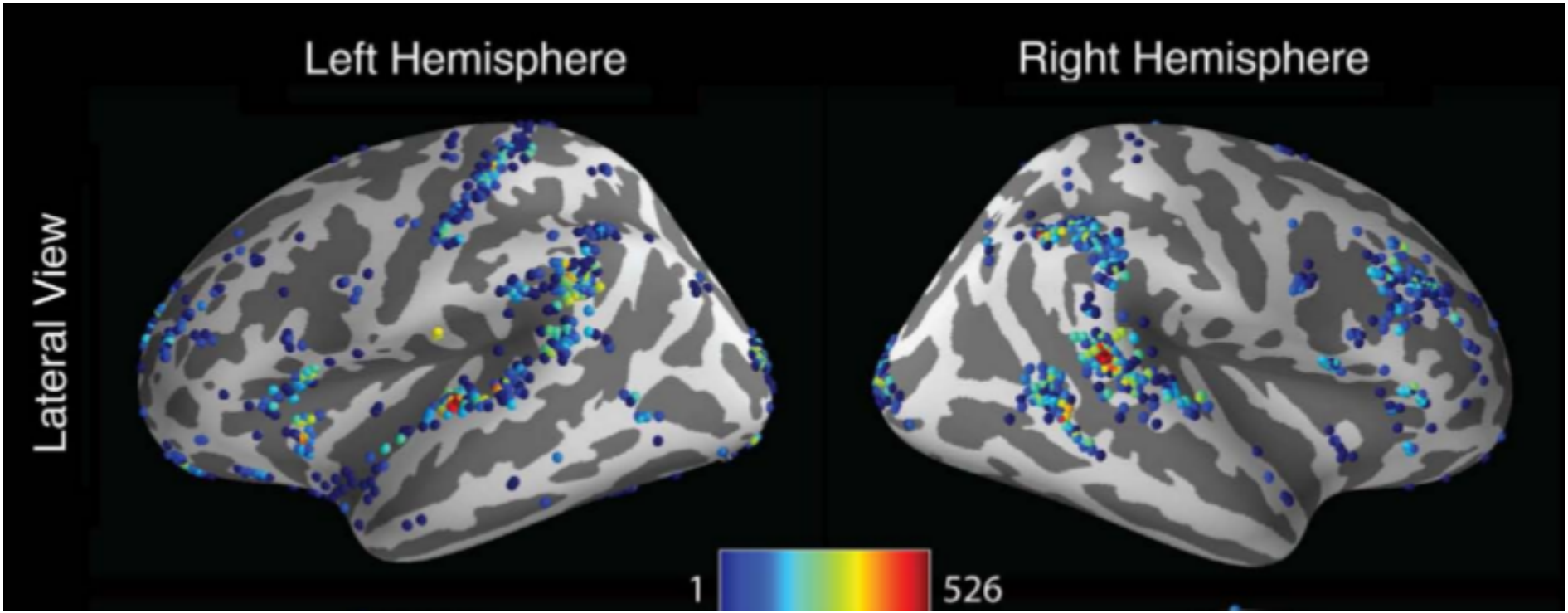
	Significance level		
Researcher degrees of freedom	$p < .1$	$p < .05$	$p < .01$
Situation A: two dependent variables ($r = .50$)	17.8%	9.5%	2.2%
Situation B: addition of 10 more observations per cell	14.5%	7.7%	1.6%
Situation C: controlling for gender or interaction of gender with treatment	21.6%	11.7%	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 ?



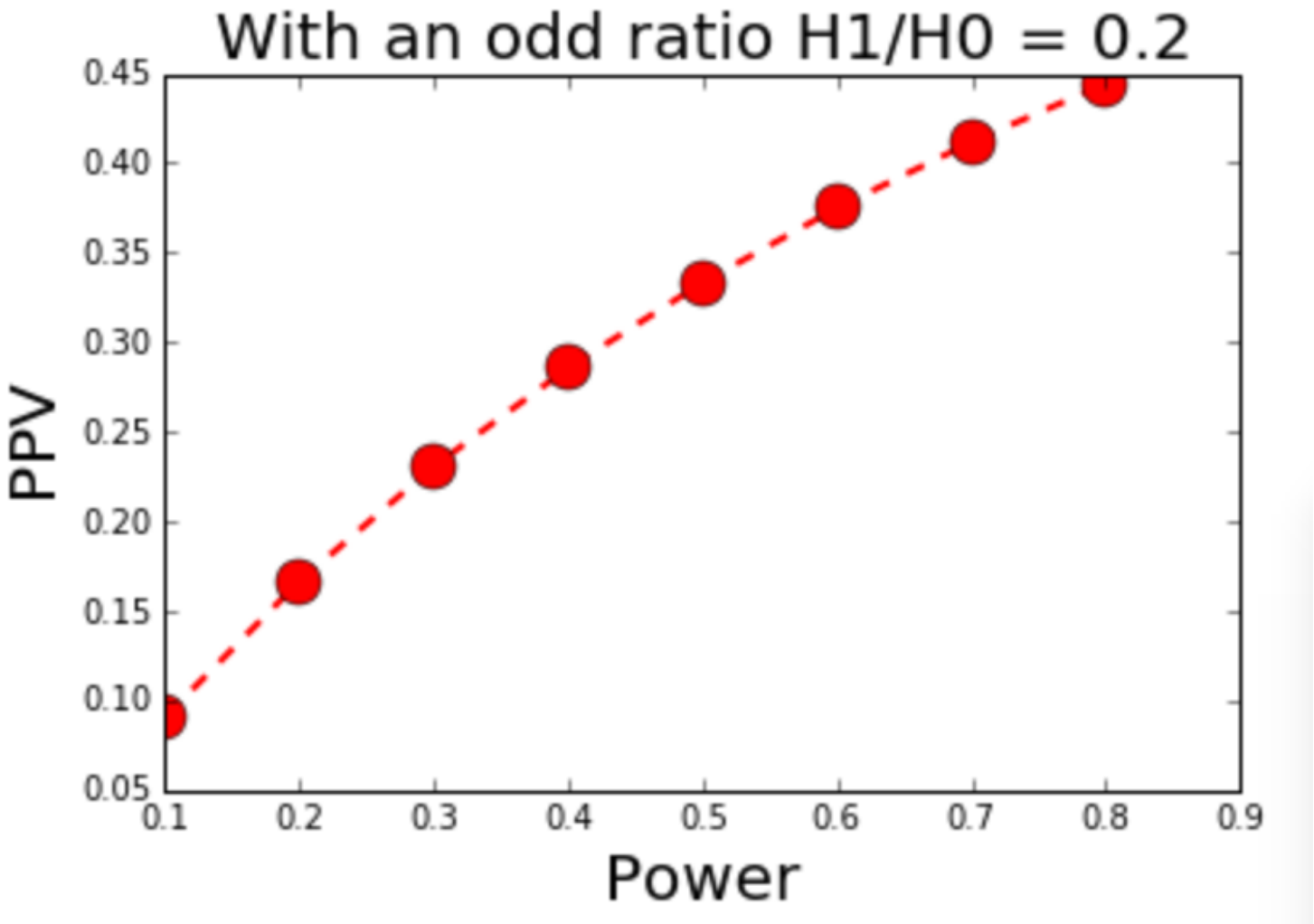
- study gives **clear evidence** that researchers make requests of their biostatistical consultants that are not only rated as **severe violations**, but further that these requests occur quite **frequently**.
- P-curve: Simonsohn, U., Nelson, L.D., Simmons, J.P., 2014.
  - Principle: literature should not have that many p close to .05
  - p-values are uniformely distributed (how do you show that?)

Are we always testing/publishing at p=0.05 ? Incentive perversion

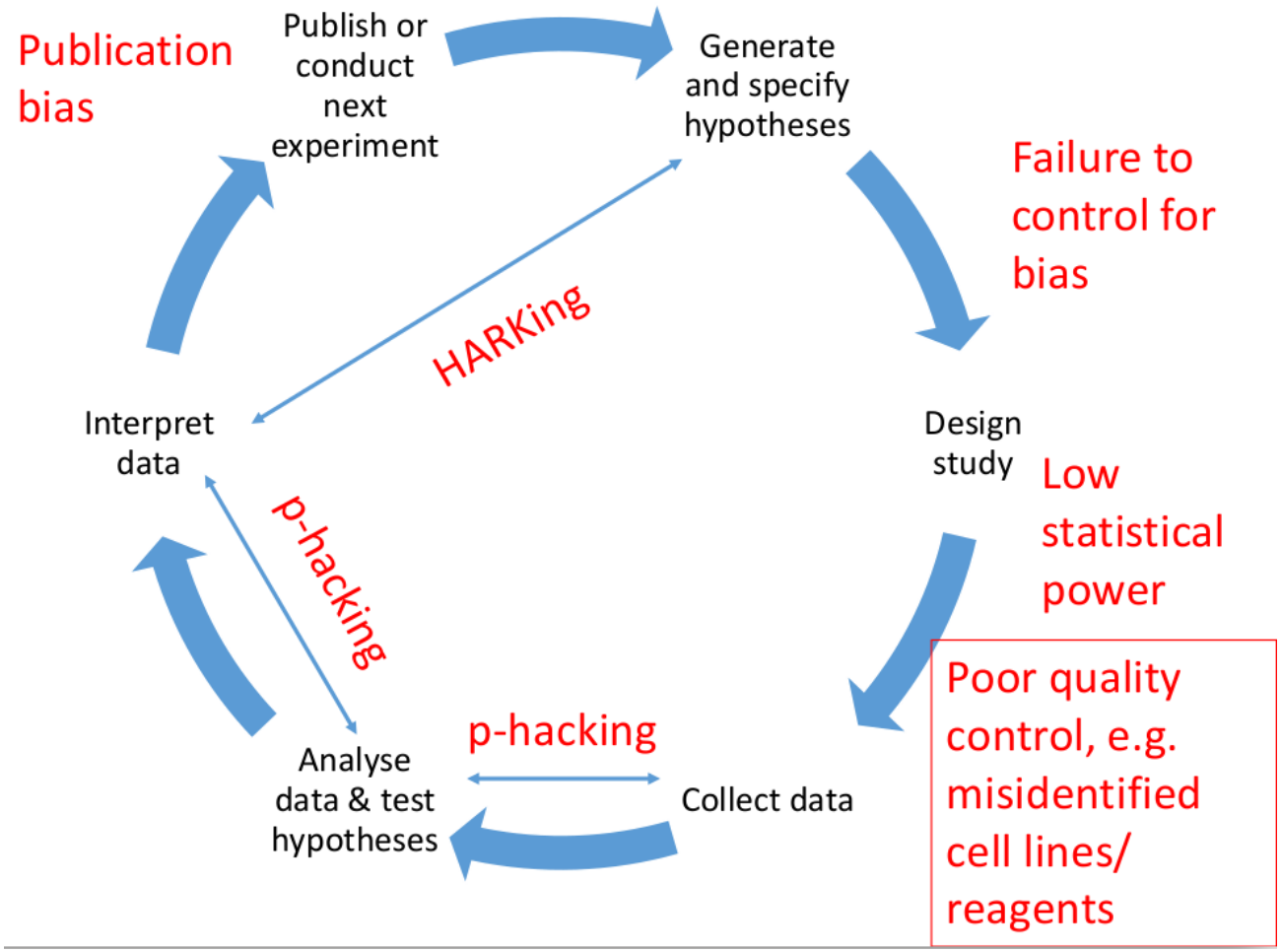


- Carp 2012

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



A possibly quite dire situation



- D. Bishop 2015

Solutions

- Ban p-values sounds a little extreme (BASP)
  - Btw: Nature editorial stated :
    "The closer to zero the P value gets, the greater the chance the null hypothesis is false."

Solutions

- Ban p-values sounds a little extreme (BASP)
  - Btw: Nature editorial stated :
    "The closer to zero the P value gets, the greater the chance the null hypothesis is false."
- Registered Reports
  - Seems a good solution in many cases: can implement a culture shift: worth the paper work !

Solutions

- Ban p-values sounds a little extreme (BASP)
  - Btw: Nature editorial stated :
    "The closer to zero the P value gets, the greater the chance the null hypothesis is false."
- Registered Reports
  - Seems a good solution in many cases: can implement a culture shift: worth the paper work !
- Cobidas and reporting best practices
  - community education and publishing efforts
  - standards for easing reuse of data (INCF, BIDS)

Solutions?

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

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

Conclusion: Is machine learning (prediction / classification) going to save us?

- Yes: Why ?
- No: Why ?

Conclusion: rephrase reproducibility into generalizability

- What do I generalize on ?
  - datasets ?
  - software ?
  - algorithms ? - initializations ?
  - populations ? . . .
- where is the biggest varation ?

Conclusion: 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 ?