# Reproducible Preclinical Research and Medical Ethics

Culture of Care and Responsible Research, Jena 10.3.2022 (online)

@dirnagl

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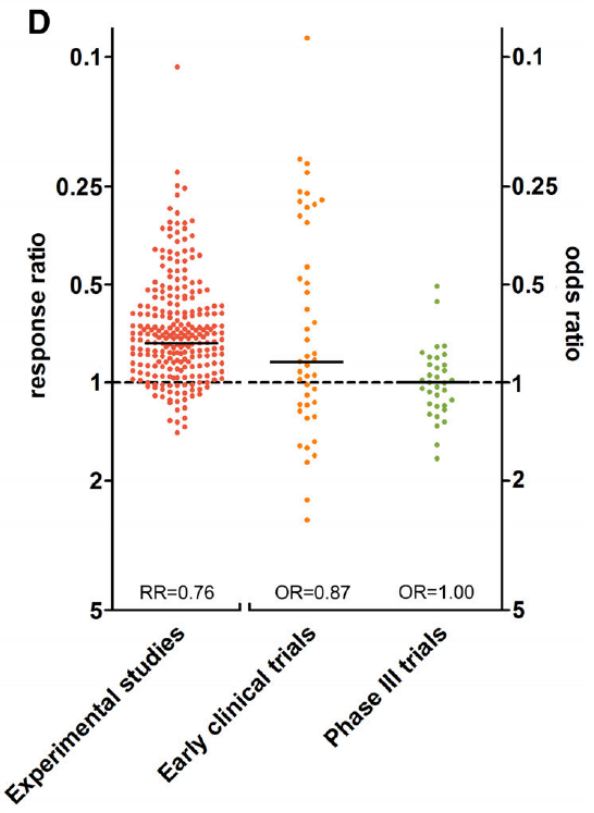
# Most novel therapies which are highly effective in preclinical models fail when tested in clinical trials. In some fields attrition = 100 %

Why Most Acute Stroke Studies Are Positive in Animals but Not in Patients: A Systematic Comparison of Preclinical, Early Phase, and Phase 3 Clinical Trials of Neuroprotective Agents

Schmidt-Pogoda A, Bonberg N, Koecke MHM, Strecker JK, Wellmann J, Bruckmann NM, Beuker C, Schäbitz WR, Meuth SG, Wiendl H, Minnerup H, Minnerup J.

ANN NEUROL 2020;87:40–51

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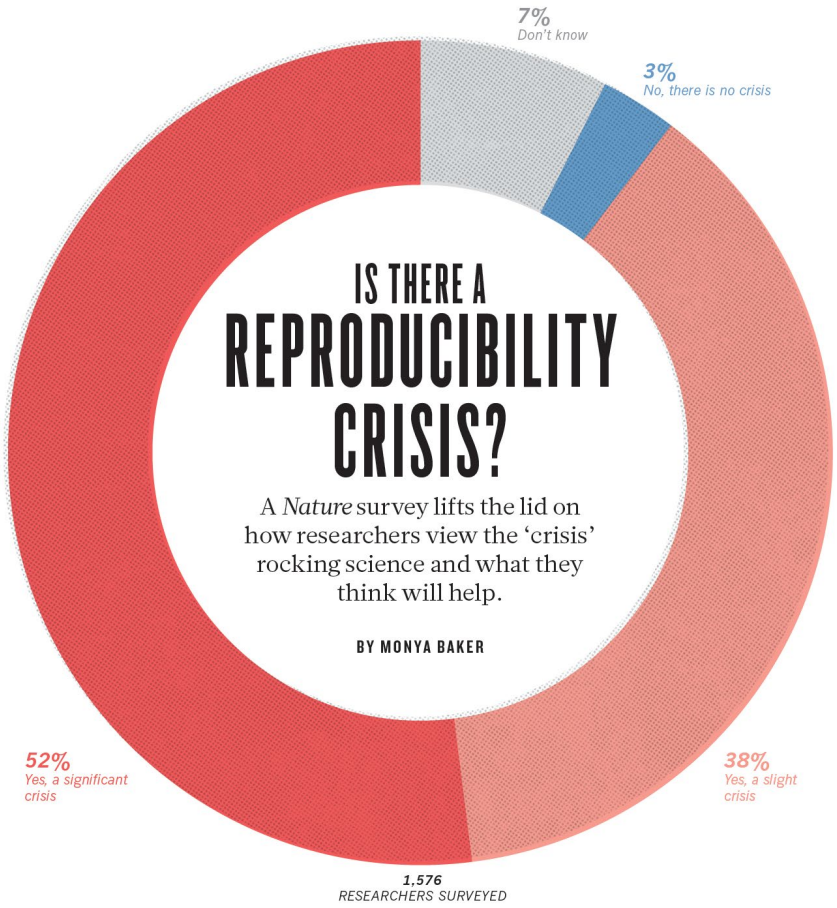
# 90 % of researchers surveyed by Nature think they are experiencing a ‚reproducibility crisis‘




**THE CAUSE**

The survey asked scientists what led to problems in reproducibility. More than 60% of respondents said that each of two factors — pressure to publish and selective reporting — always or often contributed. More than half pointed to insufficient replication in the lab, poor oversight or low statistical power.

**WHAT CAN BE DONE?**

Respondents were asked to rate 11 different approaches to improving reproducibility in science, and all got ringing endorsements. Nearly 90% — more than 1,000 people — ticked "More robust experimental design" "better statistics" and "better mentorship".



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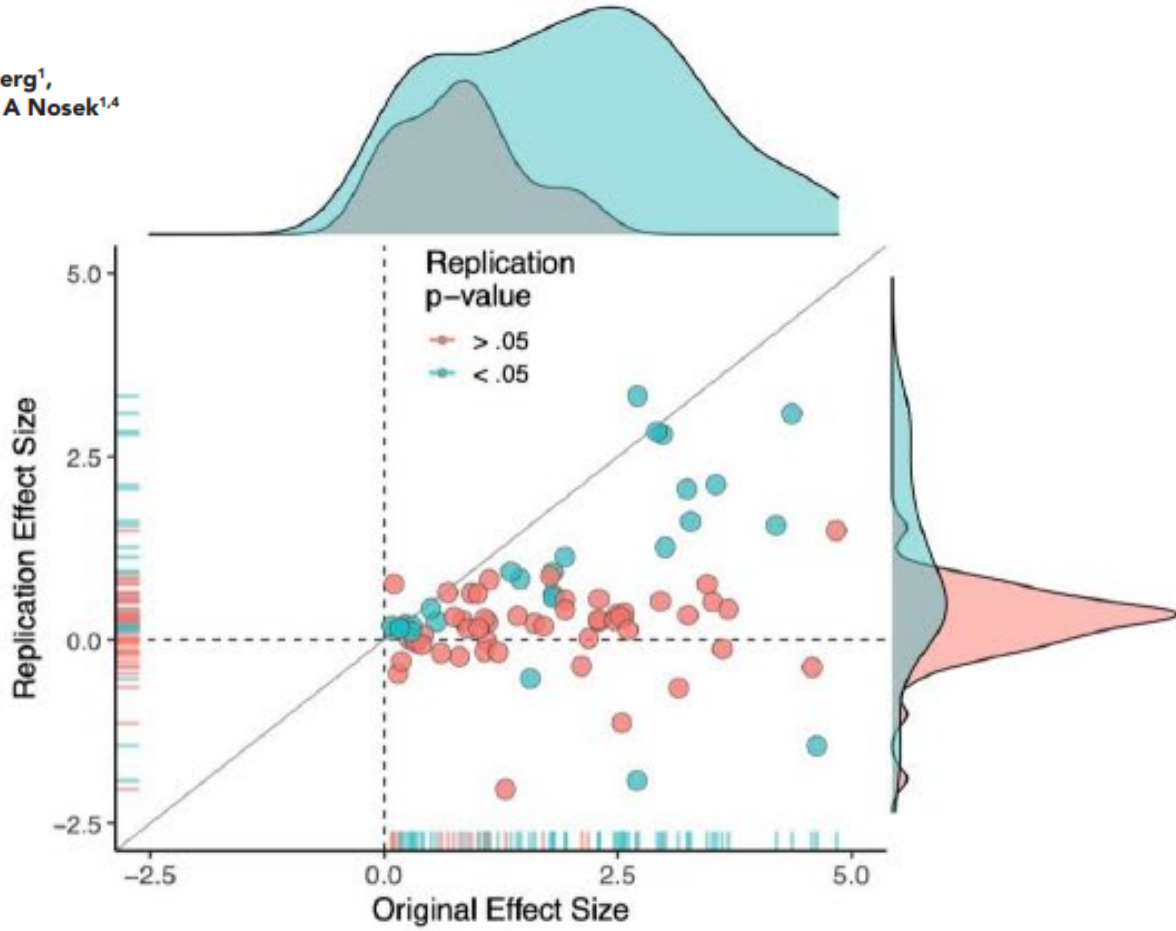
eLife

# Investigating the replicability of preclinical cancer biology

Timothy M Errington[1]*, Maya Mathur[2], Courtney K Soderberg[1], Alexandria Denis[1†], Nicole Perfito[1‡], Elizabeth Iorns[3], Brian A Nosek[1,4]

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EINSTEIN FOUNDATION AWARD

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Errington et al. https://elifesciences.org/articles/71601

# THIS WEEK

EDITORIALS

DRUGS New agreement to tackle pharmaceutical pollution p.164

WORLD VIEW Vaccination the best way to measure health care p.165

DUNG OVER Rolling b fooled by look-ali seeds p.167

## Let's think about cognitive bias

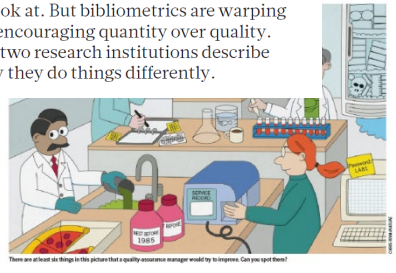
*The human brain's habit of finding what it wants to find is a key problem for research. Establishing robust methods to avoid such bias will make results more reproducible.*

"...ver since I first learned about confirmation bias I've been see-

Some researchers already do this well, so one relatively simple strategy

## Fewer numbers, better science

Scientific quality is hard to define, and numbers are easy to look at. But bibliometrics are warping science — encouraging quantity over quality. Leaders at two research institutions describe how they do things differently.



There are at least six things in this picture that a quality-assurance manager would try to improve. Can you spot them?

## QUALITY TIME

IT MAY NOT BE SEXY, BUT QUALITY ASSURANCE IS BECOMING A CRUCIAL PART OF LAB LIFE.

BY MONYA BAKER

## Acknowledging and Overcoming Nonrepr in Basic and Preclinical Research

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COMMENT

6 Cl, ( of th

nature International weekly journal of science

Home | News & Comment | Research | Careers & Jobs | Current Issue | Archive | Audio & V

News & Comment › News › 2016 › May › Article

NATURE | NEWS

## Missing mice: gaps in data plague animal resea

Reports of hundreds of biomedical experiments lack essential information.

## Reproducibility: Seek out stronger science

nature

Monya Baker

*Nature* **537**, 703–704

DATA SHARING

## An open mind on open data

*The move to make scientific findings transparent can be a major boon to research, but it can be tricky to embrace the change.*

## Power failure: why small sample size undermines the reliability of neuroscience

WORKPLACE CLIMATE

## Metrics for ethics

*Focus on perceived working conditions could help graduate schools to train responsible researchers.*

## Hide results to seek the truth

More fields should, like particle physics, adopt blind analysis to thwart bias, urge **Robert MacCoun** and **Saul Perlmutter**.

## Believe it or not: how much ... rely on published data on po... drug targets?

...ience

Current Issue | A...

Article

# THIS WEEK

EDITORIALS

POSTDOCS More pay but fewer jobs on the way p.438

WORLD VIEW Treat antibiotic resistance as an ecological crisis p.439

DRONES Tiny flying robots with power to stick around p.441

## Reality check on reproducibility

A survey of Nat... results. Resear...

NATURE | NEWS

Muddled meanings hamper efforts to fix reproducibility crisis

Is there a reprodu... the readers of *Nat*... researchers who r... current levels of repro...

The ability to repro...

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rsos.royalsocietypublishing.org

Research

Check for updates

## Low statistical power in biomedical science: a review of three human research domains

Scientific method: Statistical errors

***P* values, the 'gold standard' of statistical validity, are not as reliabl... assume.**

## Repetitive flaws

*Strict guidelines to improve the reproducib... of experiments are a welcome move.*

From next week, scientists who submit grant applications to National Institutes of Health (NIH) will be asked to take more care. As part of an increasing drive to boost the rel... of research, the NIH will require applicants to explain the sci... premise behind their proposals and defend the quality of their ... mental designs. They must also account for biological variabi... example, by including both male and female mice in planned s... and describe how they will authenticate experimental materia... as cell lines and antibodies.

These demands are timely, sensible and, if researchers hav... following the advice of their scientific societies, will sound fa... Over the past year, a string of organizations have published the ...

## Confidence in preclinical research

...decades, model organisms have provided an ...portant reductionist approach for understanding ...mechanistic basis of human diseases. With

making strides in their efforts to understand and ... for the complexity of the microbiome in rodent mo... (see page 114)

## Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

...works, and ...hers to uphold t...

532 | NATURE | VOL 483 | 29 MARCH 2012

256 | NATURE | VOL 529 | 21 JANUARY 2016

# THE LANCET

Research: increasing value, reducing waste · January, 2014

**"85% of health research is wasted."**

## DUE DILIGENCE, OVERDUE

Results of rigorous animal tests by the Amyotrophic Lateral Sclerosis Therapy Development Institute (ALS T... are less promising than those published. All these compounds have disappointed in human testing.

Perrin S (2014) Nature 407:423-...

# Preclinical studies often are not robust, key findings can not be reproduced, and translation into effective therapies in patients fails

1. Internal validity is low, bias is rampant
2. Statistical power is exceedingly low
3. Questionable statistical practices are frequent
4. Only ‚positive' resultats are published (‚Publication bias')

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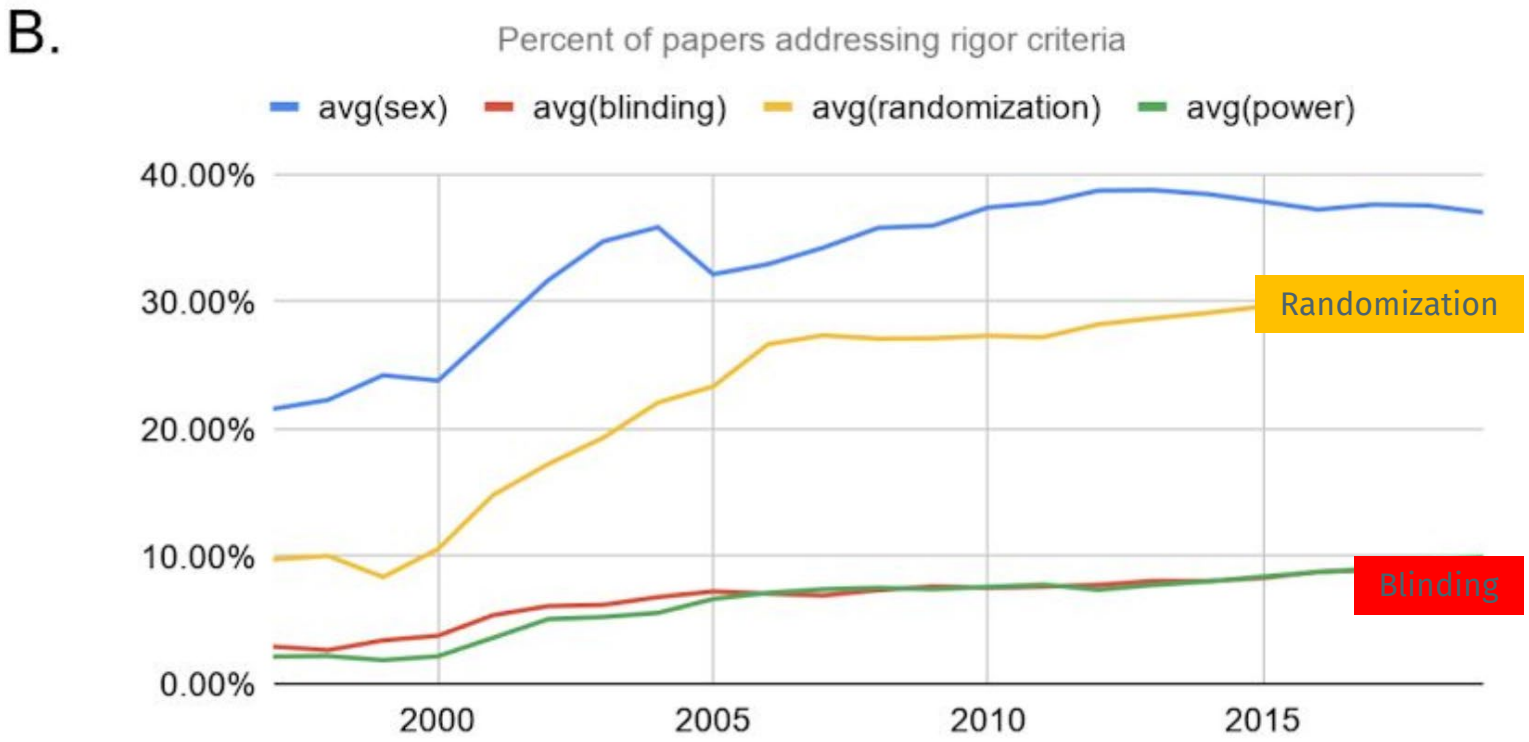
# Preclinical studies have low internal validity (Selection-, performance-, attrition- und and many other biases are insufficiently controlled)




Rigor and transparency in reporting of preclinical research
(Analysis of 1.6 million papers 1997 – 2019)

iScience. 2020 Oct 20;23(11):101698. doi: 10.1016/j.isci.2020.101698.

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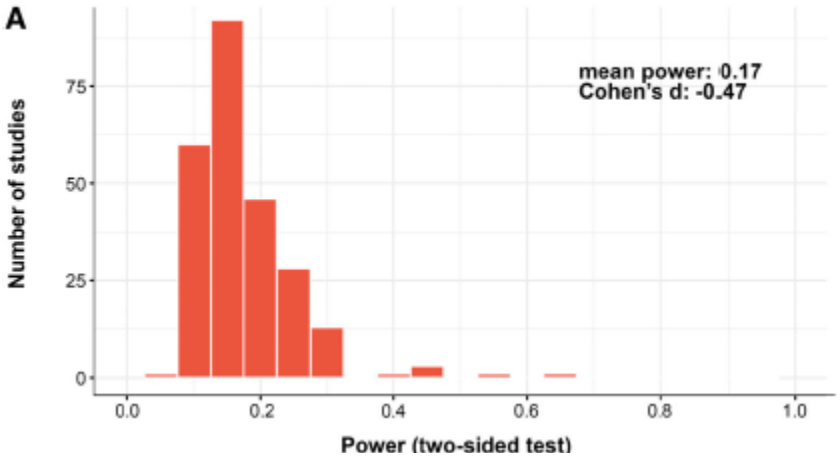
# Preclinical studies have exceedingly low statistical power, hence false positive and false negative results are frequent, and effect sizes are overestimated (if there there is a true effect)

Schmidt-Pogoda A, Bonberg N, Koecke MHM, Strecker JK, Wellmann J, Bruckmann NM, Beuker C, Schäbitz WR, Meuth SG, Wiendl H, Minnerup H, Minnerup J.

**ANN NEUROL 2020;87:40–51**
doi: 10.1002/ana.25643.

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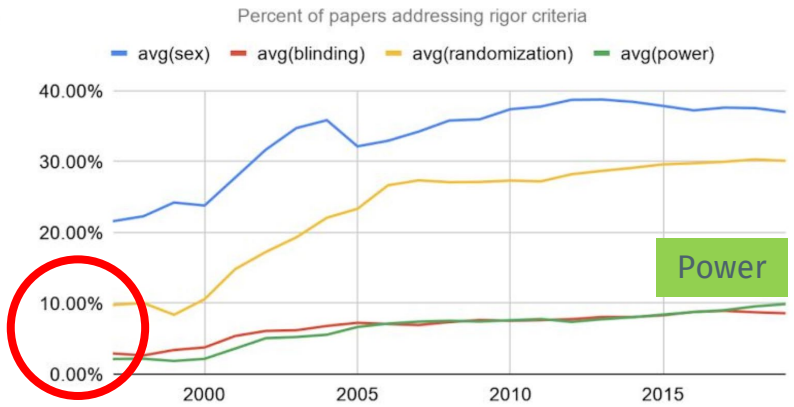


doi: 10.1016/j.isci.2020.101698

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# Questionable but frequent statistical practices: p-Hacking

Researchers try out several statistical analyses and/or data eligibility specifications and then selectively report those that produce significant results.

E.g. by

- conducting analyses midway through experiments to decide whether to continue collecting data
- recording many response variables and deciding which to re-port post analysis,
- deciding whether to include or drop outliers postanalyses
- ex-cluding, combining, or splitting treatment groups postanalysis
- including or excluding covariates postanalysis
- stopping data exploration if an analysis yields a significant p-value
- Perfoming multiple statistical tests without prespecification and reporting only the significant one(s)

"If you torture the data long enough, it will confess to anything "
Darrell Huff *How to Lie With Statistics* (1954).

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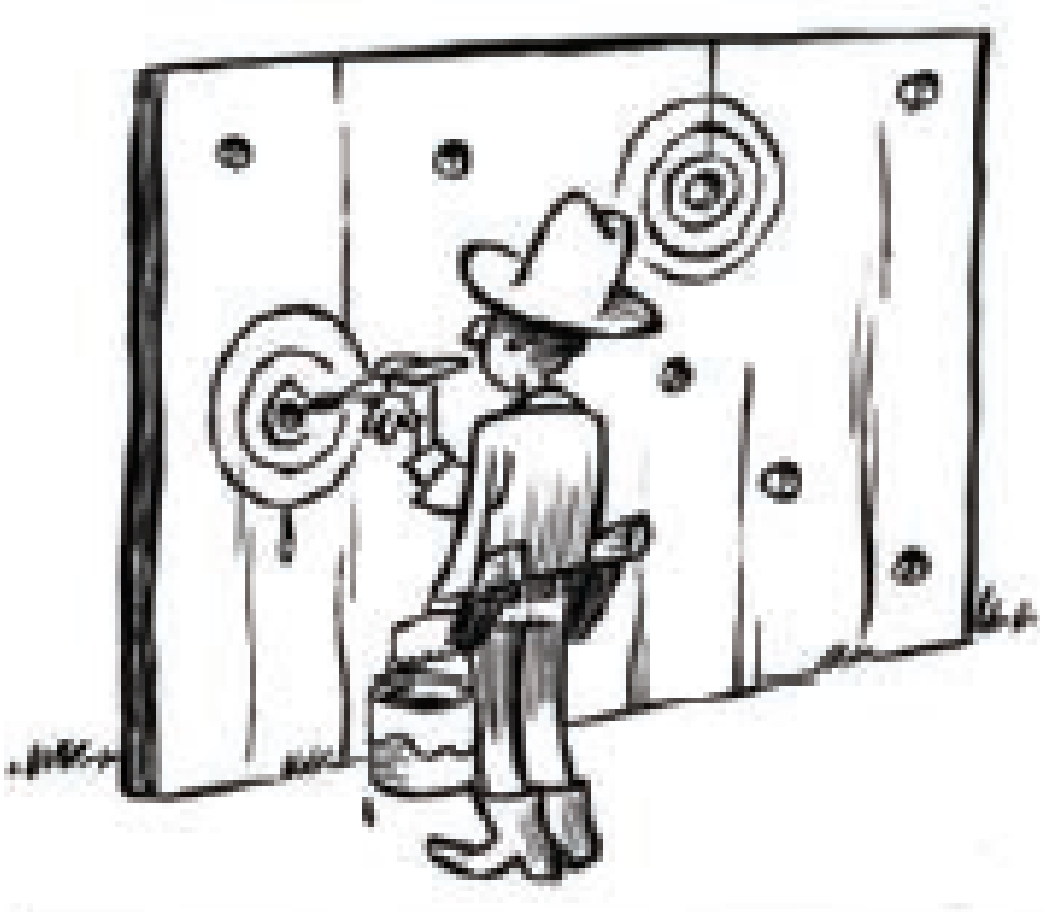
# Questionable but frequent statistical practices:
## *Hypothesizing after the results are known (HARKING)*



**An Agenda for Purely Confirmatory Research**

**Eric-Jan Wagenmakers, Ruud Wetzels, Denny Borsboom, Han L. J. van der Maas, and Rogier A. Kievit**
University of Amsterdam, The Netherlands

Perspectives on Psychological Science
7(6) 632–638

DOI: 10.1177/1745691612463078

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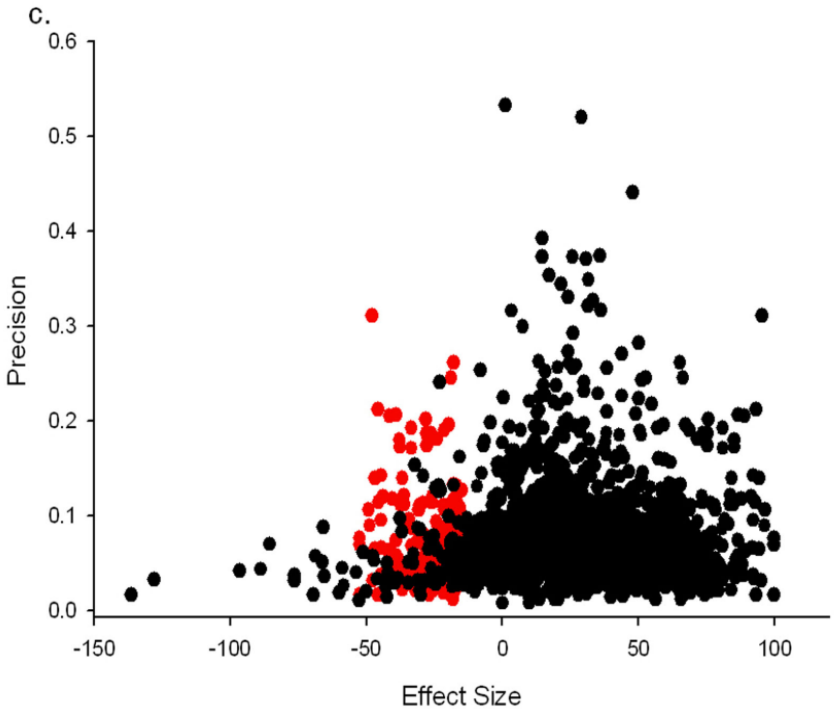
# Publication bias: 'positive' results are overrepresented in the literature

OPEN ACCESS Freely available online

PLoS BIOLOGY

## Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy

Emily S. Sena[1,2,3], H. Bart van der Worp[4], Philip M. W. Bath[5], David W. Howells[2,3], Malcolm R. Macleod[1,6]*




"Only ten publications (2%) [of 525] reported no significant effects on infarct volume and only six (1.2%) did not report at least one significant finding."

PLoS Biol. 2010; 8 e1000344

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# Preclinical research of low scientific quality is unethical (with respect to animals AND humans!)

PLOS BIOLOGY

PLoS Biol. 2018;16:e2006343. doi: 10.1371/journal.pbio.2006343

PERSPECTIVE

## The bench is closer to the bedside than we think: Uncovering the ethical ties between preclinical researchers in translational neuroscience and patients in clinical trials

**Mark Yarborough[1]*, Annelien Bredenoord[2], Flavio D'Abramo[3,4], Nanette C. Joyce[1,5], Jonathan Kimmelman[6], Ubaka Ogbogu[7], Emily Sena[8], Daniel Strech[9,10,11], Ulrich Dirnagl[10,11]**

nature

Preclinical research: Meet patients to sharpen up research

Mark Yarborough & Ulrich Dirnagl

Shoddy preclinical research is not just bad science – it is unethical. It stalls cures and exposes people to drug trials that cannot work (see, for example, G. Cossu *et al. The Lancet* http://doi.org/cf29; 2017). Researchers need a better appreciation of the connection between sloppy results and the consequences to people who have a disease.

PDF version

SUBJECTS

DISEASES

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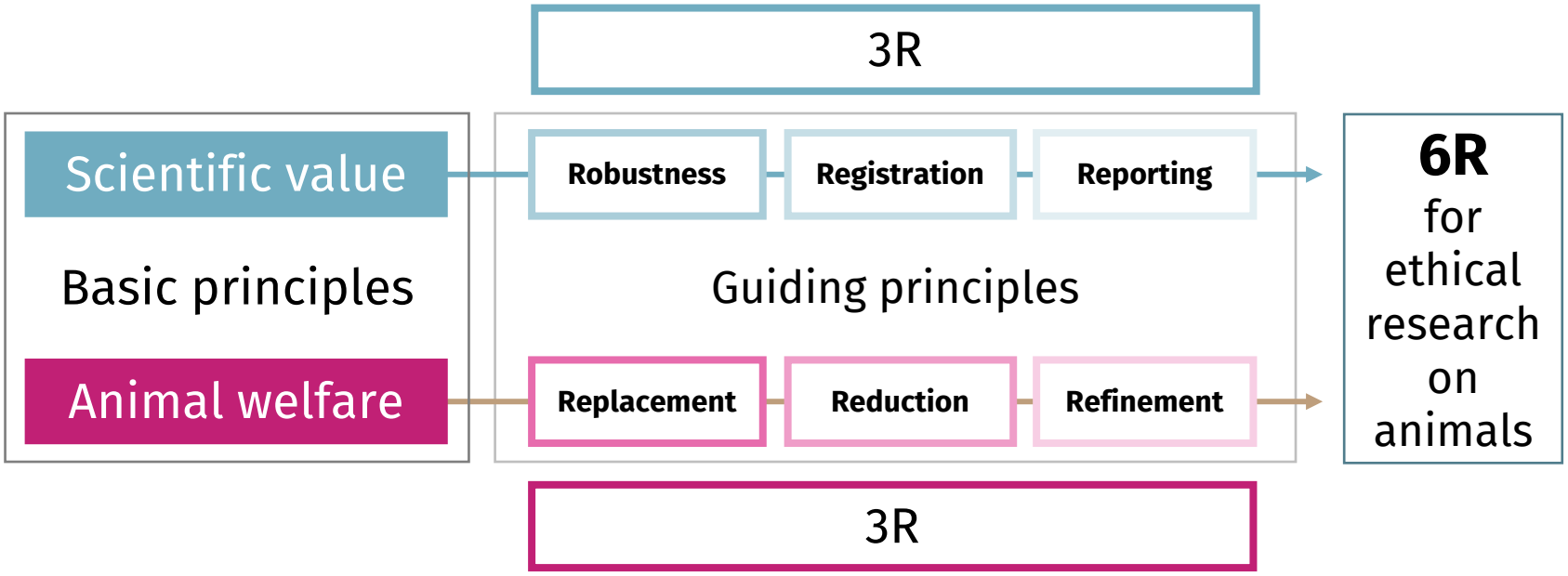
# 3 Rs are conspicuously incomplete

- animal welfare alone does not suffice to make animal research ethical if the research does not have sufficient scientific value
- The scientific value of animal studies strongly decreases if they are not sufficiently robust, if their questions have already been sufficiently addressed or if the results are selectively reported

# Conclusion: From 3R to 6R

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