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Non-reproducibility is an integral part of a productive and efficient scientific enterprise

- A key task for biomedical research is to scan a large number of hypotheses
- Efficient scanning of a large number of candidates requires fast and frugal methodologies, like use of small sample sizes and surrogate endpoints.
- By their very nature, however, fast and frugal methods are prone to producing false positive signals of activity.
- Drugs that look promising in preclinical studies but fail conceptual reproduction in phase 2 trials are to some degree a byproduct of rational decision-making across a sequence of investigations rather than poor study design.
- Failed conceptual reproduction maps the boundaries of a theory.
- Observation of phenomena in one experimental system, but not in another, often leads to deeper understandings of processes and of experimental systems. It defines the boundaries of a theory's explanatory power.

see also: London and Kimmelman. Why clinical translation cannot succeed without failure eLife 2015;4:e12844.

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'Replication' - Speed dating

- Falsch Positive und Inflation von Effektgrössen
- Publikationsbias
- Exploration vs. Konfirmation
- Gründe für 'Nicht-Replizierbarkeit'
- Probleme
- Quo vadis

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Falsch Positive und Inflation der Effektgrösse

- Fraud
- Niedrige prior probabilities (=low base rates)
- Bias
- p-Hacking
- Hypothesizing after the results are known
- Verwechslung von p-Wert mit positiv prädiktivem Wert
- Power niedrig
- 'Winner's curse'
- Regression to the mean

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Falsch Positive und Inflation der Effektgrösse

- Betrug

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Falsch Positive und Inflation der Effektgrösse

- Niedrige prior probabilities (=low base rates)

The low 'low hanging fruits' are already harvested....

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Falsch Positive und Inflation der Effektgrösse

- Bias

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Falsch Positive und Inflation der Effektgrösse

- p-Hacking

THE QUARTERLY JOURNAL OF EXPERIMENTAL PSYCHOLOGY
2012, i*First*, 1–9

Psychology Press
Taylor & Francis Group

A peculiar prevalence of *p* values just below .05

E. J. Masicampo[1], and Daniel R. Lalande[2]

[1]Department of Psychology, Wake Forest University, Winston-Salem, NC, USA
[2]Department of Health Sciences, Université du Québec à Chicoutimi, Chicoutimi, QC, Canada

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Falsch Positive und Inflation der Effektgrösse

- Hypothesizing after the results are known ('Hark-ing')

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Falsch Positive und Inflation der Effektgrösse

- Verwechslung von p-Wert mit positiv prädiktivem Wert

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Falsch Positive und Inflation der Effektgrösse

Positive predictive value (PPV)

$$PPV = ([1 - \beta] \times R) / ([1 - \beta] \times R + \alpha)$$

PPV = (Power x Prestudy odds) / (Power x prestudy odds + alpha)

power	0,5
prestudy odds	0,2
alpha	0,05
PPV	0,66

power	0,8
prestudy odds	0,2
alpha	0,01
PPV	0,94

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Falsch Positive und Inflation der Effektgrösse

- Power niedrig

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

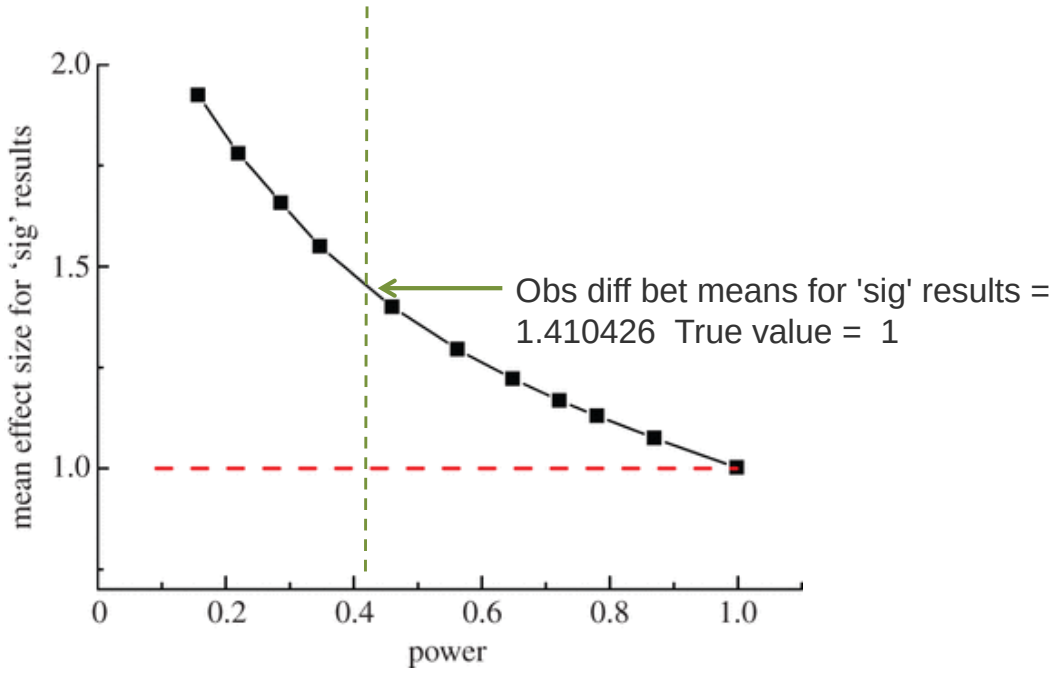
Katherine S. Button[1,2], John P. A. Ioannidis[3], Claire Mokrysz[1], Brian A. Nosek[4], Jonathan Flint[5], Emma S. J. Robinson[6] and Marcus R. Munafò[1]

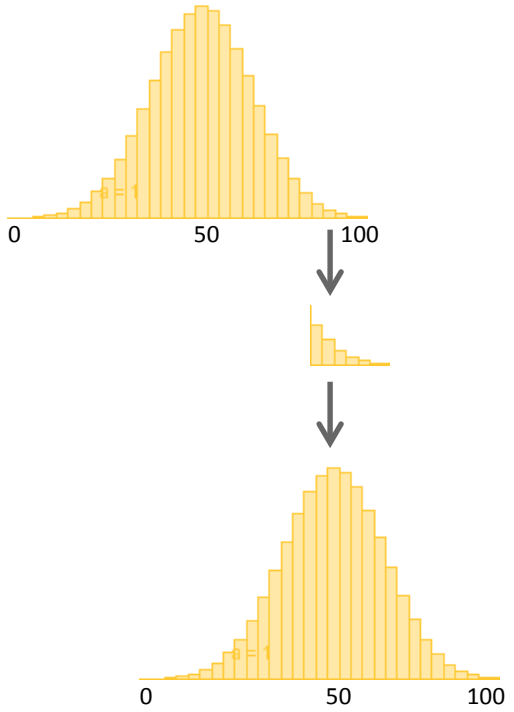
Nature Reviews Neuroscience | AOP, published online 10 April 2013; doi:10.1038/nrn3475

Overall median power of 730 primary neuroscience studies: 21 %

Falsch Positive und Inflation der Effektgrösse

- 'Winner's curse' , Regression to the mean





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Publication bias

"Publication bias is highly prevalent (present in the literature describing the efficacy of at least 16 of 18 interventions) and accounts for around 30% of the reported efficacy of candidate neuroprotective interventions."

Publication bias in reports of animal stroke studies leads to major overstatement of efficacy

Emily S Sena, H. Bart van der Worp, Philip M.W. Bath, David W Howells, and Malcolm R Macleod (PLoS Biol. 2010 Mar 30;8(3):e1000344)

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Exploratory vs confirmatory research

OPEN ACCESS Freely available online

PLOS | BIOLOGY

Perspective

Distinguishing between Exploratory and Confirmatory Preclinical Research Will Improve Translation

Jonathan Kimmelman[1]*, Jeffrey S. Mogil[2], Ulrich Dirnagl[3,4,5]

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Exploratory vs confirmatory research

In **exploratory investigation**, researchers should aim at generating robust pathophysiological theories of disease.

In **confirmatory investigation**, researchers should aim at demonstrating strong and reproducible treatment effects in relevant animal models.

Protocols and publications should pre-specify whether they are ‘‘exploratory’’ or ‘‘confirmatory’’ studies, with the latter category reserved for studies that aim at demonstrating promise of clinical utility for an intervention.

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Exploratory vs confirmatory research

	Exploratory 'Discovery'	Confirmatory
Hypothesis	(+)	+++
Establish pathophysiology	+++	(+)
Sequence and details of experiments established at onset	(+)	+++
Primary endpoint	-	++
Sample size calculation	(+)	+++
Blinding	+++	+++
Randomization	+++	+++
External validity (aging, comorbidities, etc.)	-	++
In/Exclusion criteria	++	+++
Test statistics	+	+++
Preregistration	(-)	++
Find what might work: Sensitivity (accept Type I errors)	+++	+
Weed out false positives: Specificity (accept Type II errors)	+	+++

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Ursachen für Nichtreplizierbarkeit

- Fraud
- False positive (Replication = true Null result)
- Methodical (Incompetence, biased study design, low power, etc.)
- Poor reporting (incl. 'tacit knowledge')
- Random variation

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Replicating a statistically significant finding

$p = 0.049$ ($p < \alpha = 0.05$)

Assume that the experimental result is correct, i.e. measured difference equals (unknown) treatment effect.

Repeat experiment under identical conditions.

What is the probability to replicate the significant findings?

50 %!

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Randomisierte multicenter präklinische Studien

RESEARCH ARTICLE

STROKE

Results of a preclinical randomized controlled multicenter trial (pRCT): Anti-CD49d treatment for acute brain ischemia

Gemma Llovera,[1,2] Kerstin Hofmann,[1,2] Stefan Roth,[1,2] Angelica Salas-Pérdomo,[3,4] Maura Ferrer-Ferrer,[3,4] Carlo Perego,[5] Elisa R. Zanier,[5] Uta Mamrak,[1,2] Andre Rex,[6] Hélène Party,[7] Véronique Agin,[7] Claudine Fauchon,[8] Cyrille Orset,[7,8] Benoît Haelewyn,[7,8] Maria-Grazia De Simoni,[5] Ulrich Dirnagl,[6] Ulrike Grittner,[9] Anna M. Planas,[3,4] Nikolaus Plesnila,[1,2] Denis Vivien,[7,8] Arthur Liesz[1,2]*

Science Translational Medicine
AAAS

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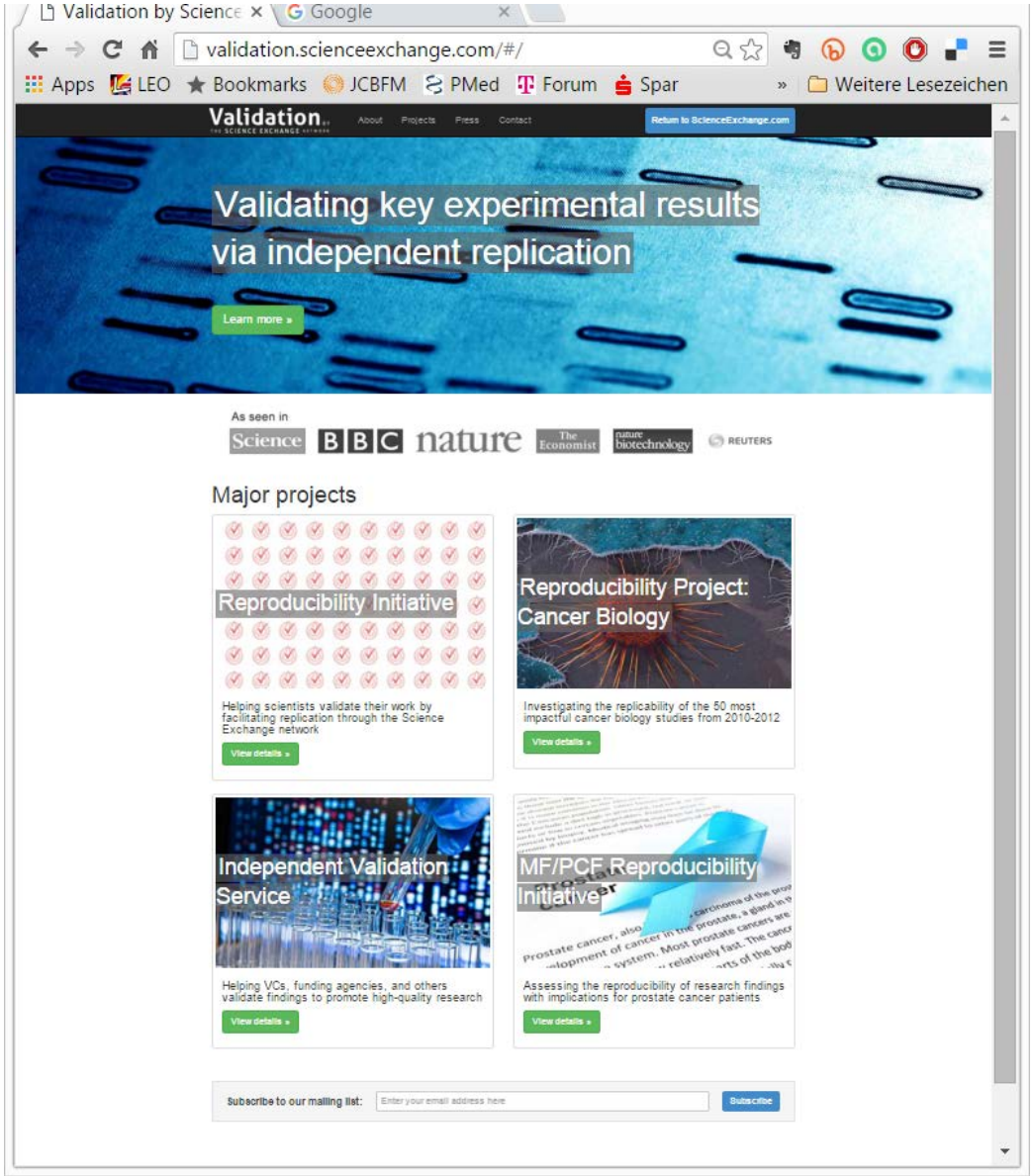
Strukturierte Initiativen



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Probleme

- Finanzierung
- Fehlende Incentivierung; Kultur (Replikation nicht gleich Innovation)
- Regulatorisch (Erkenntnisgewinn?)

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Quo vadis?

- Methodischer Rigor (Ausbildung, auch von PIs!)
- Präregistrierung
- Unterscheidung Exploration / Konfirmation
- Replikation 'kritischer' Befunde
- Internationale Initiativen
- Funding
- Wertschätzung ('Incentivierung')

http://bit.ly/dirnaglreplication

Button Power failure Nat Neuros...	Adobe Acrobat-Dokument	515 KB
Colquhoun False dicsovery rate ...	Adobe Acrobat-Dokument	383 KB
Dirnagl Sind die meisten publizi...	Adobe Acrobat-Dokument	1.387 KB
Dirrnagl DFG Replication Slides....	Adobe Acrobat-Dokument	1.840 KB
Good Institutional Practice Natu...	Adobe Acrobat-Dokument	584 KB
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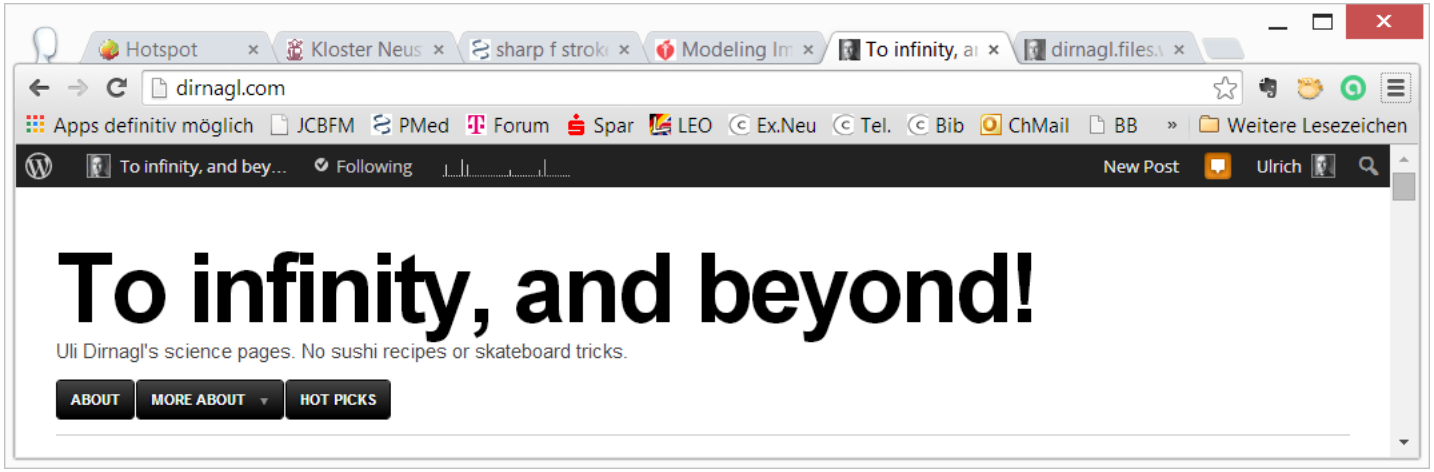
Kimmelman Mogil Dirnagl Expl...	Adobe Acrobat-Dokument	89 KB
Open Science Collaboration Psy...	Adobe Acrobat-Dokument	559 KB

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