Rigor & Reproducibility in Research

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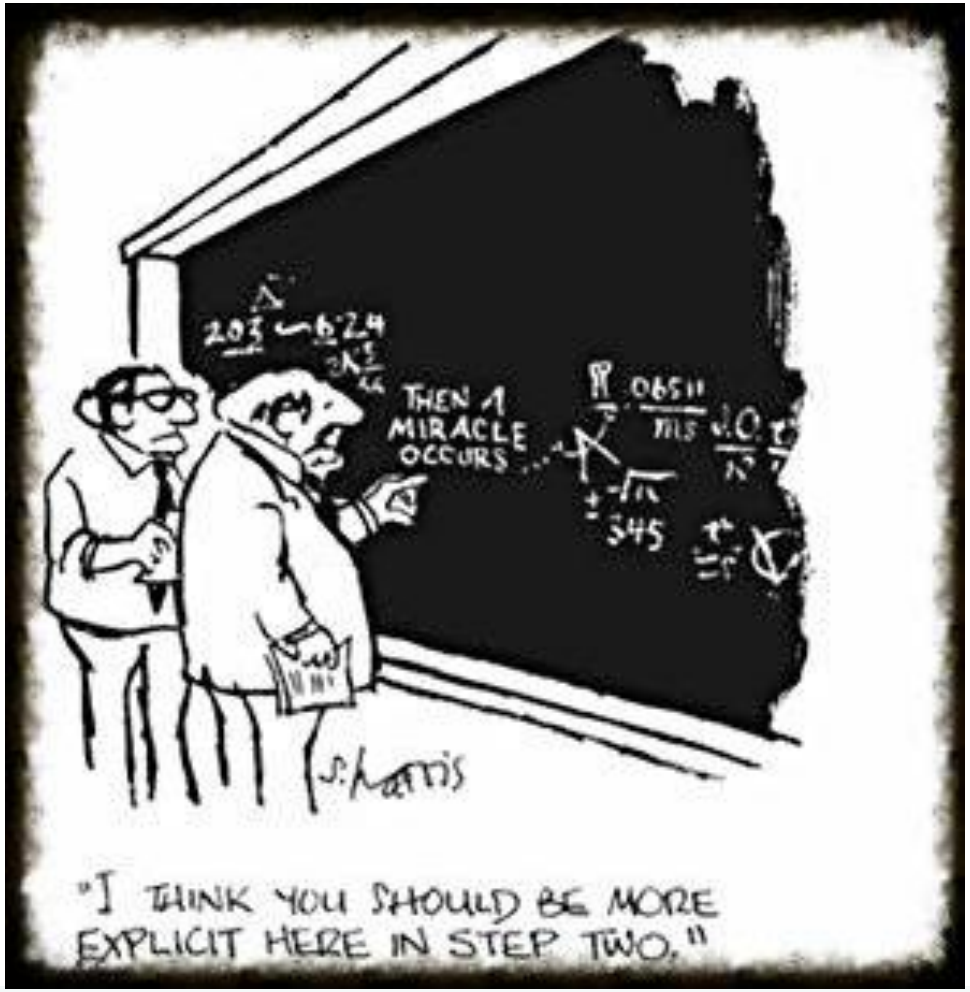
Defining Key Concepts



Reproducibility: Ability to achieve consistent results using the same data and methods

Replicability: Ability to achieve consistent results using new data but similar methods

Rigor: Strict application of the scientific method to ensure robust and unbiased results

R&R Challenges

Publish or perish

Statistical misuse

No negative data

Insufficient reporting

Deadlines

Poor Time management

Bias

Poor data management

Historical Context

Early Milestones (2005-2019)

2005 – "Why Most Published Research Findings Are False." John Ioannidis' PLOS Medicine essay puts the issue on the map and sparks a decade-long debate about statistical power, bias and false positives. https://doi.org/10.1371/journal.pmed.0020124

2011 – Bayer audit. Company finds just **14/67 (≈21 %)** high-profile target-validation papers reproducible. Nat Rev Drug Discovery calls it a "wake-up call." https://www.nature.com/articles/nrd3439-c1

2012 – Amgen/Begley & Ellis replication attempt. Amgen scientists can confirm findings in only **6/53 (11 %)** landmark oncology papers; commentary in *Nature* urges tougher standards. https://www.nature.com/articles/483531a

2015 – Economic scale revealed. Freedman et al. estimate **US *$28 B/year*** wasted on irreproducible U.S. pre-clinical work; *Nature* news story amplifies to policymakers and media. https://journals.plos.org/plosbiology/article?id=10.1371%2Fjournal.pbio.1002165

2019 – National Academies Report. Landmark consensus study ("Reproducibility and Replicability in Science") urges agencies to fund confirmatory studies, reward open data and reform incentives.
https://nap.nationalacademies.org/catalog/25303/reproducibility-and-replicability-in-science

Historical Context

Growing Federal Emphasis & Policy Action(2013-2023)

2013 – First OSTP Public-Access Directive. Obama-era memo tells ≥$100 M R&D agencies to draft free-access plans, laying the groundwork for transparency and data-sharing norms. https://www.wired.com/2013/03/want-to-know-what-scientists-are-doing-with-your-money-soon-you-will-be-able-to/

2014 – "Principles & Guidelines for Reporting Pre-clinical Research." NIH, Nature, *Science* and 30+ journals adopt common check-lists for blinding, randomization, power calculations and full-methods sections. https://grants.nih.gov/policy-and-compliance/policy-topics/reproducibility/principles-guidelines-reporting-preclinical-research

2016 – NIH "Rigor & Transparency" Rule (NOT-OD-16-011). Grant reviewers must score study design rigor, sex-as-a-biological-variable, and authentication plans; new attachment required in every application. https://grants.nih.gov/grants/guide/notice-files/not-od-16-011.html

2023 – NIH Data Management & Sharing Policy. All NIH-funded projects must budget for, and deposit, FAIR data; compliance is a term-of-award requirement. https://sharing.nih.gov/data-management-and-sharing-policy/about-data-management-and-sharing-policies/data-management-and-sharing-policy-overview#after

2022 – OSTP "Nelson Memo." Requires *immediate* open-access to every federally-funded article and its underlying data by 2026, reinforcing transparency as a cornerstone of rigor. https://www.axios.com/2022/08/25/white-house-federal-funded-research-public

Scope of the problem

Scope of Estimate	Figure	What is counted	Source
U.S. pre-clinical life-science research	~ $28 B/yr	Direct spending on animal & cell-based discovery work whose findings later prove irreproducible (≈50 % failure rate model)	https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002165
Global health & medical research (all stages)	~$170 B/yr	85 % of the ≈ $200 billion world-wide health-research budget lost through poorly chosen questions, avoidable design flaws, non-publication and unusable reports	https://blogs.bmj.com/bmj/2016/01/14/paul-glasziou-and-iain-chalmers-is-85-of-health-research-really-wasted/
Biomedical R&D – industry perspective	~ $38 B/year (£28B/yr)	Company spending diverted by irreproducible academic findings that seed drug programs later abandoned in pre-clinical or Phase I	https://www.ddw-online.com/spotlight-tackling-the-issue-of-scientific-data-waste-15522-202202/
Bad research antibodies (U.S. subset)	~ $350 M/yr	Reagents that fail specificity/validation tests, producing misleading data and cascading experimental waste	https://www.tandfonline.com/doi/full/10.1080/19420862.2024.2323706

Consequences

Economic costs

Human impact

Erosion of Public Trust

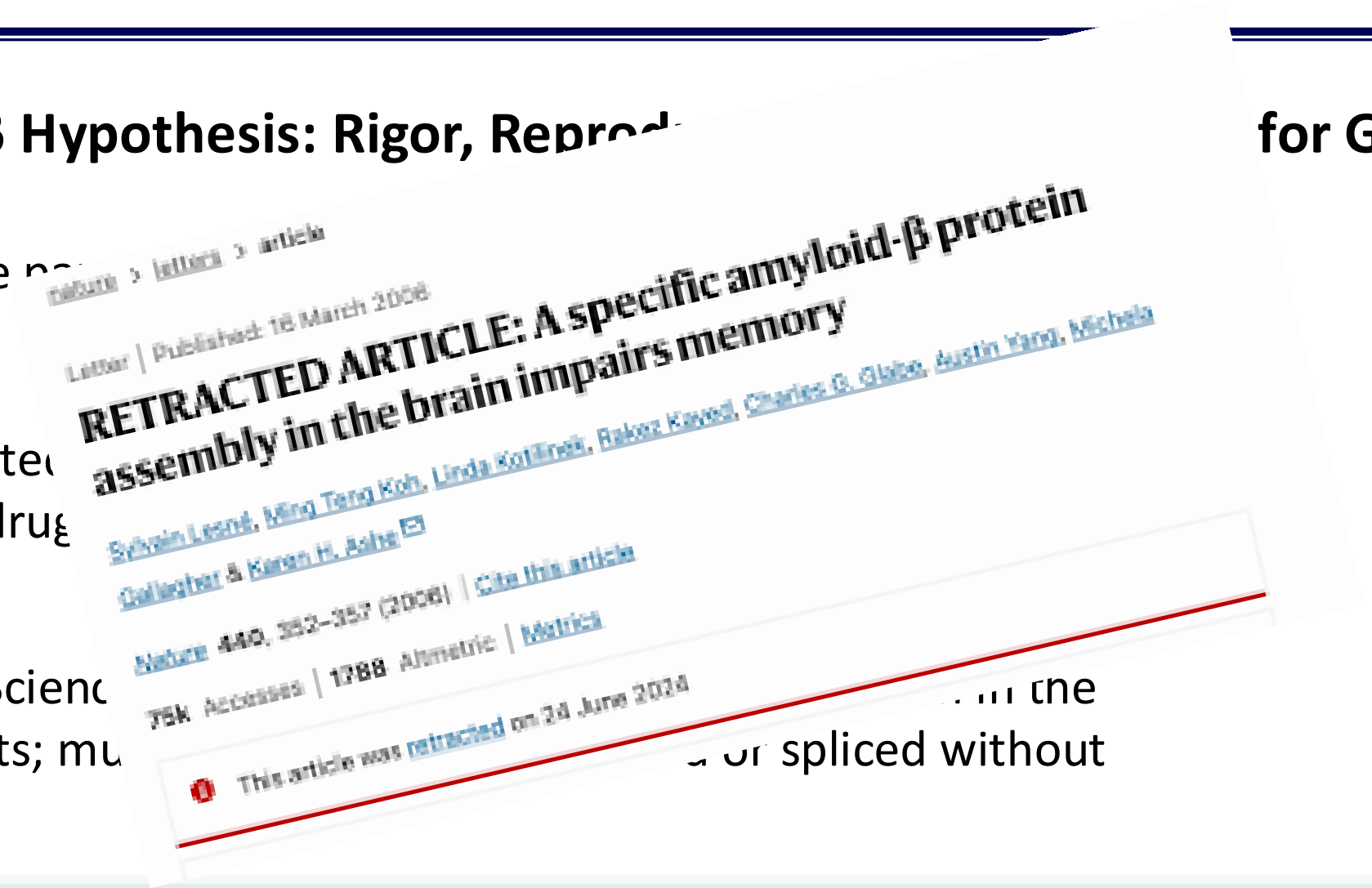
Case Stud -Questionable data

Amyloid-β Hypothesis: Rigor, Repro… … for Getting It Wrong

2006 Nature pa…
in mice

study was cite…
grants and drug…

July 2022 - Scienc… … in the
western blots; mu… … or spliced without
disclosure


Letter | Published: 16 March 2006

RETRACTED ARTICLE: A specific amyloid-β protein assembly in the brain impairs memory

Sylvain Lesné, Ming Tang Koh, Linda Kotilinek, Rakez Kayed, Charles G. Glabe, Austin Yang, Michela Gallagher & Karen H. Ashe

Nature 440, 352–357 (2006) | Cite this article

75k Accesses | 1788 Altmetric | Metrics

This article was retracted on 24 June 2024

Cascade of failed clinical trials

Amyloid-β Hypothesis: Rigor, Reproducibility — and the Bill for Getting It Wrong

1995-2022 ≥ 250 amyloid-targeting agents entered the clinic; ~95 % failed in Phase II/III. Private out-of-pocket expense is estimated at $42.5 billion (1995-2021), exclusive of public funding

Each late-stage failure consumes 5-10 years, thousands of human participants, and hundreds of millions of dollars, and diverts attention from alternative hypotheses (tau, neuroinflammation, vascular)

Ongoing public funding skew

Amyloid-β Hypothesis: Rigor, Reproducibility — and the Bill for Getting It Wrong

FY 2022 NIH investment that mentioned “amyloid” ≈ **$1.6 billion**—~40 % of the institute’s Alzheimer’s portfolio.

Heavy reliance on one mechanistic model distorts federal priorities; other avenues receive comparatively little rigor testing or seed support

Gatekeeping and publication bias

Amyloid-β Hypothesis: Rigor, Reproducibility — and the Bill for Getting It Wrong

Investigative reports describe a tight network of reviewers steering journals and study sections toward amyloid work and rejecting dissenting results
https://www.statnews.com/2019/06/25/alzheimers-cabal-thwarted-progress-toward-cure/

Lack of viewpoint diversity reduces the self-correcting power of science, letting weak data propagate unchecked

Opportunity cost to patients

Amyloid-β Hypothesis: Rigor, Reproducibility — and the Bill for Getting It Wrong

Two monoclonal antibodies (aducanumab, lecanemab) have gained restricted FDA approval; aducanumab withdrawn Nov 1, 2024; per Biogen clinical study results, no confirmatory benefit – development terminated

Clinical benefit is modest and safety controversial

Treatments aimed at symptom relief, prevention

Non-amyloid targets lag years behind

Lessons for R&R

Amyloid-β Hypothesis: Rigor, Reproducibility — and the Bill for Getting It Wrong

Single high-impact paper can set an entire field's agenda — robust image-forensics and routine replication of "too-good-to-be-true" animal data are essential before large-scale translation

Portfolio diversity mitigates systematic error - funding agencies need explicit balance tests so no hypothesis dominates solely through legacy momentum

Transparent raw data & blots. Had original images been openly archived, the fabrication might have been caught before billions were spent

Erosion of Trust

Modern Medical Science Conspiracies that Conflict with Evidence

mRNA vaccines change your DNA." CDC states they do not alter DNA; https://archive.cdc.gov/www_cdc_gov/coronavirus/2019-ncov/vaccines/facts.html

"Ivermectin cures COVID-19." Updated Cochrane review: no evidence supporting prevention or treatment benefit. https://pubmed.ncbi.nlm.nih.gov/35726131/

"COVID vaccines cause infertility." Multiple health bodies and reviews refute this recurring claim. https://www.sciencedirect.com/science/article/pii/S0264410X24000562

"Hydroxychloroquine works for COVID-19." NIH halted its trial for lack of benefit, and FDA revoked EUA. https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine

Gulf Coast Consortia

Characterization of Research Grant Terminations at the National Institutes of Health

Michael Liu, MPhil[1]; Kushal T. Kadakia, MSc[1]; Vishal R. Patel, MD, MPH[1,2]; et alHarlan M. Krumholz, MD, SM[3,4]

Author Affiliations Article Information

JAMA. Published online May 8, 2025. doi:10.1001/jama.2025.7707

~ $1,8B

Weekly terminated NIH Grants Report

~3,000 grants terminated (at any point) → ~7.5B (5/20/25) - $9.5B (6/30/25

~1,900 remain terminated → ~$2.15B

https://grant-witness.us/

~ $2,15B

Where are we now?

- Reorganization of HHS (FDA/CDC/NIH)

- Some HHS policies reduced public-comment/transparency requirements

https://www.cbsnews.com/news/rfk-jr-transparency-policy-medicaid-nih/

- So far, NIH's Rigor and Transparency policy framework (scientific premise, rigorous design, sex as a biological variable, authentication of key resources) remains in force and is reflected in current CSR reviewer guidance

Threats to R&R Moving Forward

- Industrialized fraud (paper mills) & rising retractions
- Generative-AI fabrication (text, images, “data”)
- Publication bias (over-representation of positive results) & p-hacking incentives
- Policy/organizational instability; Large-scale staffing cuts/reorganizations and reduced transparency may erode scientific capacity, oversight, and morale—indirect risks to rigor
- Opaque/proprietary methods, data, and code; Even with Nelson-memo-driven access to publications/data, uneven methods/code sharing and privacy/IP constraints still limit reproducibility


WE MUST DO BETTER.
How?

The DOGE Rigor & Reproducibility Innovation Challenge

You've been appointed to lead DOGE's Biomedical Research Efficiency Task Force. In this high-stakes mission, you must:

1.Turbocharge Rigor: Design a low-cost pilot program that directly tackles a reproducibility or transparency gap (e.g. centralized raw-data repositories, peer-to-peer protocol audits).

3. Submit your strategy by email to anm15@rice.edu

The University Rigor & Reproducibility Innovation Challenge

You've been tapped by your academic institution's leadership to spearhead a new Research Excellence Task Force. In this campus-wide competition, your mission is to:

1.Elevate Research Rigor: Propose a low-cost pilot initiative (≤ $50 K/year) that tackles a specific reproducibility or transparency gap on campus

3. Submit your two-pronged strategy by email to anm15@rice.edu