Wasted efforts and solutions

Research Methodology: Beyond the RCT?

Malcolm Macleod

Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies and University of Edinburgh

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“Deregulation has become a major activity e.g. by means of developing Codes of Conduct together with a legal expert. This is a necessity in an era of abundant and overlapping regulation of biomedical science, especially when EU-guidelines aim at harmonisation.”

2010 global spend on biomedical research ~US$240bn

With regard to research methodology,
- Does biomedical research need regulation at all?
- How well do our systems of self regulation perform?
Disclosures

• Member

  – UK Commission for Human Medicines
  – EMA Neurology SAG

  – UK Animals in Science Committee

  – Independent Statistical Standing Committee, CHDI Foundation
  – Avilex Pharma Research Steering Group (on behalf of Wellcome Trust)
I am not in the office at the moment. Send any work to be translated.
Neural Correlates of Interspecies Perspective Taking in the Post-Mortem Atlantic Salmon: An Argument For Proper Multiple Comparisons Correction

Craig M. Bennett\textsuperscript{1*}, Abigail A. Baird\textsuperscript{2}, Michael B. Miller\textsuperscript{1} and George L. Wolford\textsuperscript{3}

One mature Atlantic Salmon (Salmo salar) participated in the fMRI study. The salmon measured approximately 18 inches long, weighed 3.8 lbs, and was not alive at the time of scanning. It is not known if the salmon was male or female, but given the post-mortem state of the subject this was not thought to be a critical variable.

The task administered to the salmon involved completing an open-ended mentalizing task. The salmon was shown a series of photographs depicting human individuals in social situations with a specified emotional valence, either socially inclusive or socially exclusive. The salmon was asked to determine which emotion the individual in the photo must have been experiencing.

Several active voxels were observed in a cluster located within the salmon’s brain cavity (see Fig. 1). The size of this cluster was 81 mm$^3$ with a cluster-level significance of $p = 0.001$.

Either we have stumbled onto a rather amazing discovery in terms of post-mortem ichthyological cognition, or there is something a bit off with regard to our uncorrected statistical approach.
Treatment of experimental stroke with low-dose glutamate and homeopathic Arnica montana

W. Jonas¹, Y. Lin², A. William³, F. Tortella³, R. Tuma³
¹ Uniformed Services University of the Health Sciences, Bethesda, Maryland
² Walter Reed Army Institute of Research, Washington, D.C.
³ Temple University, Philadelphia, PA

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Risk of bias in animal studies

- NXY059 for ischaemic stroke: Infarct Volume
  - 11 publications, 29 experiments, 408 animals
  - Improved outcome by 44% (35-53%)

Macleod et al, 2008

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You can usually find what you’re looking for …

- 12 graduate psychology students
- 5 day experiment: rats in T maze with dark arm alternating at random, and the dark arm always reinforced
- 2 groups – “Maze Bright” and “Maze dull”

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
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<td>“Maze bright”</td>
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<td>1.60</td>
<td>2.60</td>
<td>2.83</td>
<td>3.26</td>
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<tr>
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<td>2.23</td>
<td>1.83</td>
<td>1.83</td>
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<tr>
<td>Δ</td>
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Rosenthal and Fode (1963), Behav Sci 8, 183-9
Evidence from various neuroscience domains ...

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Stroke

Alzheimer’s disease

Multiple Sclerosis

Parkinson’s disease

Blinded assessment of behavioural outcome

Improvement in behavioural outcome (Standardised Effect Size)

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<table>
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<th>Parkinson’s disease</th>
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<tr>
<td>No MASI</td>
<td>No</td>
</tr>
<tr>
<td>Yes Spontaneous Activity</td>
<td>No</td>
</tr>
<tr>
<td>Yes Skilled Motor Activity</td>
<td>No</td>
</tr>
<tr>
<td>Yes Limb Asymmetry</td>
<td>No</td>
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<tr>
<td>Yes Parkinson’s Disability Rating</td>
<td>No</td>
</tr>
<tr>
<td>Yes Balance and Gait</td>
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</table>
The scale of the problem
UK Research Assessment Exercise 1173

“an outstanding contribution to the internationally excellent position of the UK in biomedical science and clinical/translational research.”

“impressed by the strength within the basic neurosciences that were returned …particular in the areas of behavioural, cellular and molecular neuroscience”

1173 publications using non human animals, published in 2009 or 2010, from 5 leading UK universities

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Reporting of risk bias items by decile of journal impact factor
Reporting of the use of the Morris Water Maze
Reaction norms (Voelkl 2016)

“Nuisance” variable

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Summary of dubious research practices

• Designs with opportunities for the investigator to influence
  – subject selection
  – conduct of experiment
  – assessment of outcome
• No prior assertion of stated (often flexible) group size
• P-hacking
• HARKing
• Confusion between exploratory research and hypothesis testing research
Why much published research is false …
Why much published research is false …

Assume:
• 20% of hypotheses in a field are correct
Why much published research is false …

Assume:

- 20% of hypotheses in a field are correct

- Power to detect a biologically important effect of 20%
Why much published research is false …

Assume:
• 20% of hypotheses in a field are correct
• Power to detect a biologically important effect of 20%
• Critical p threshold of 5%

Positive predictive value = 50%
The (polluted) research cycle
How well do our systems of regulation and self regulation perform?
Time for quiet reflection
What is to be done?

“In “What Is to Be Done?”, Lenin argues that the working class will not spontaneously become political simply by fighting economic battles with employers over wages, working hours and the like. To convert the working class to Marxism, Lenin insisted the Marxists should form a political party, or “vanguard”, of dedicated revolutionaries to spread Marxist political ideas among the workers.”

What is to be done?

… scientists will not spontaneously become rigorous … To convert scientists to rigor, we should form a “vanguard”, of dedicated revolutionaries to spread rigor ideas among scientists.
Our political tasks

In the internal politics of the Party, these methods lead …to the Party Organisation “substituting” itself for the party, the Central Committee substituting itself for the Party Organisation, and finally a dictator substituting himself for the Central Committee.
Our political tasks

In the internal politics of research, these methods lead ... to the research institution “substituting” itself for the researchers, the national research organisation substituting itself for the research institutions, and finally a dictator substituting himself for the national research organisation.

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By which I mean

1. We commit huge resources to biomedical research
2. There is no doubt that improvement is required
3. Unless we as a community can demonstrate that we can sort ourselves out, someone else will do it for us

(4. At least when reading an RCT we already know most of the things that can go wrong)
Consolidate through adding to standard care

Continuous improvement cycles

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If you are planning a systematic review or meta-analysis of animal data, CAMARADES are here to help: malcolm.macleod@ed.ac.uk