Why are systematic reviews important for good science and the 3Rs?

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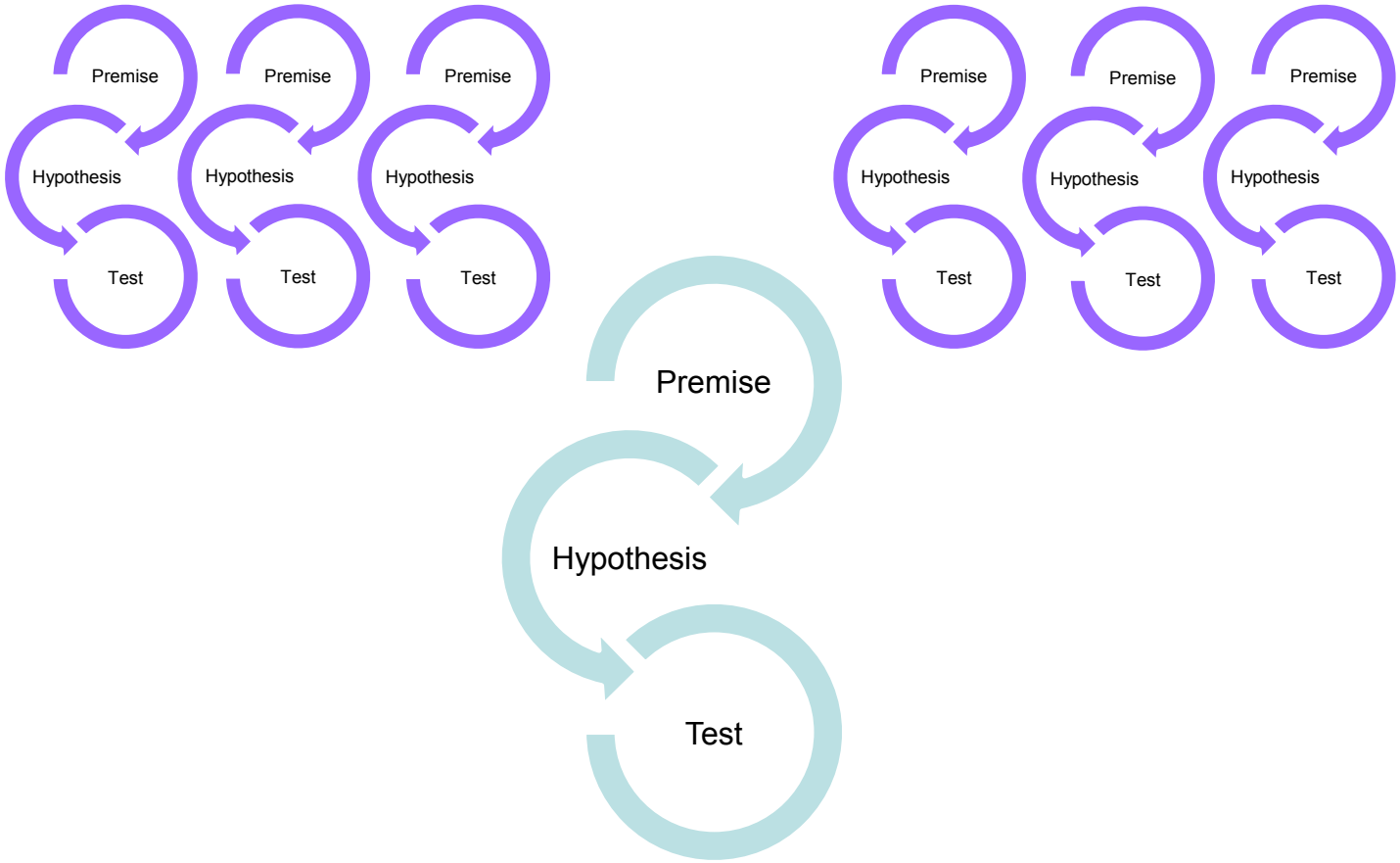
The research cycle



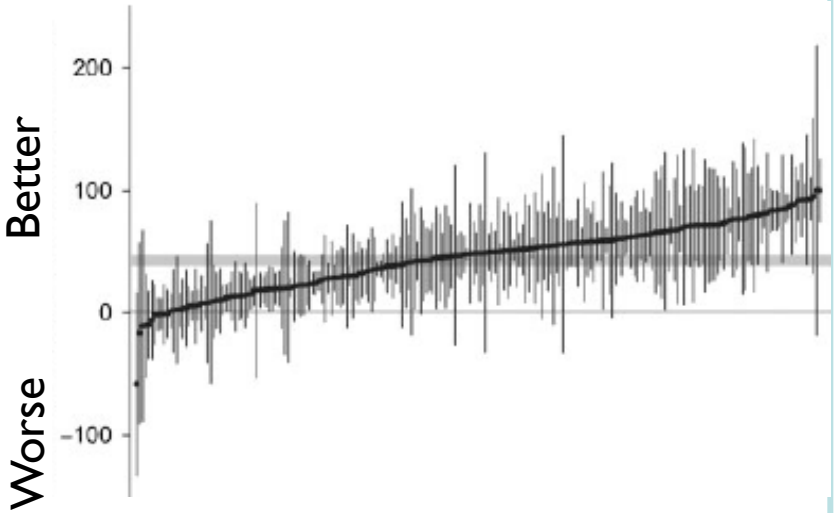
Why do we do meta-analysis of animal studies?

- Animal models are generally performed to inform human health but when should you be convinced to move to the next step?
- Systematic reviews & meta-analyses:
  - assess the quality and range of evidence
  - identify gaps in the field
  - quantify relative utility of outcome measures
  - inform power/sample size calculations
  - assess for publication bias
  - try to explain discrepancies between preclinical and clinical trial results
  - inform clinical trial design

Data from *in vivo* studies

- There are huge amounts of often confusing data
- Systematic review can help to make sense of it
- If you select extreme bits of the evidence you can "prove" either harm or substantial benefit
- Investigating the sources behind this variation may be helpful in translation

Hypothermia: a systematic search identified 222 experiments in 3353 animals



Van der Worp *et al Brain* 2007

Good science

- Examples from different reviews describing
  - Knowing what has been done already
  - Confidence in the cause-effect relationship
  - Generalisability of findings
  - Presence & impact of publication bias

What has been done already?

Chemotherapy-induced peripheral neuropathy publications

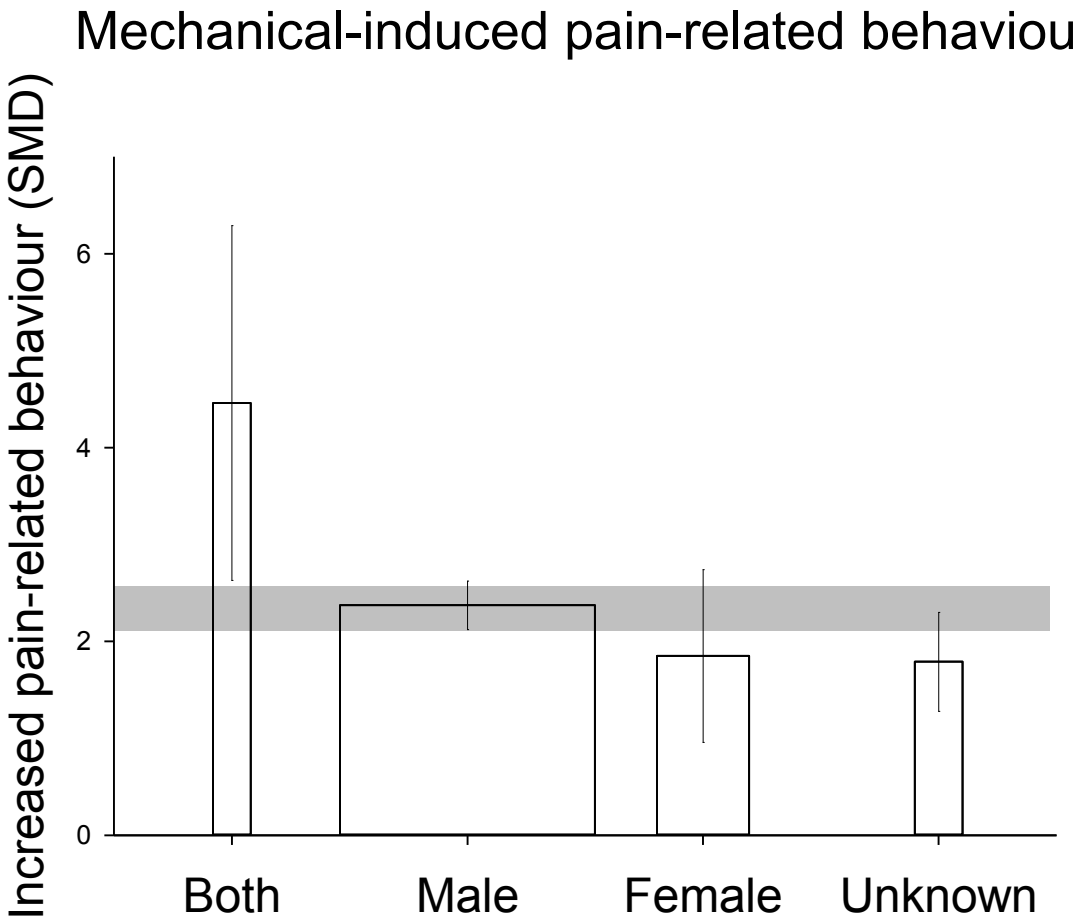
Chemotherapy drug used to induce model	Number of publications (/176)
Paclitaxel	67
Vincristine	61
Oxaliplatin	38
Cisplatin	25
Bortezomib	5
Docetaxel	2

Quality
- confidence in in cause-effect

Chemotherapy-induced peripheral neuropathy publications

	%	No. of publications /Total
Blinded Assessment of Outcome	**46**	80/176
Allocation concealment	**0**	0
Randomisation - Drug	**18**	25/125
Animal Welfare Regulations	**92**	163/176
Potential Conflicts of Interest	**28**	50/176
Animal exclusions	**9**	15/176
Sample Size Calculation	**2**	3/176

Impact of study characteristics - generalisability



Choice of strain - generalisability

	Early Gestation		Midgestation		Late Gestation	
	WR	SDR	R	SDR	WR	SDR
Vasodilator						
Gq_{EC}	•	•	•	=	=	↑
Flow-mediated vasodilation	•	•	↑	•	↑	↑
Vascular compliance	•	↑	=	↑	=	↑
Gs_{SMC}	•	•	↑	•	↓	↑
Vasoconstrictor						
Gq_{SMC}	•	•	=	=	=	↓
Myogenic reactivity	•	=	=	=	=	?

Pregnancy-induced vascular function: increase (↑), decrease (↓), no change (=), inconsistent effects (?), and no effects reported (•).

Van Drongelen et al. 2012 – vascular function during pregnancy

The umbrella of reporting bias

Not all outcomes and *a priori* analyses are reported

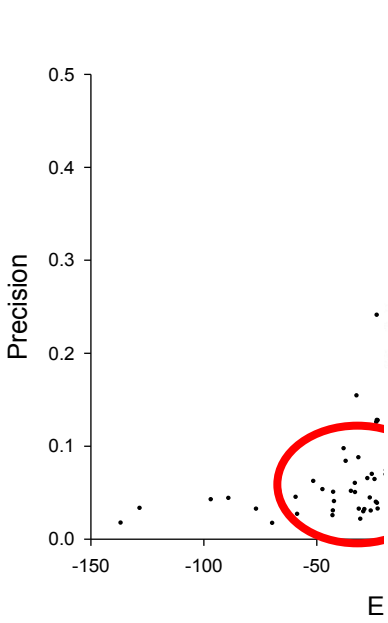
- Publication bias
  - Neutral and negative studies
  - Time lag/remain unpublished
  - Less likely to be identified
- Selective analysis reporting
- Selective outcome reporting

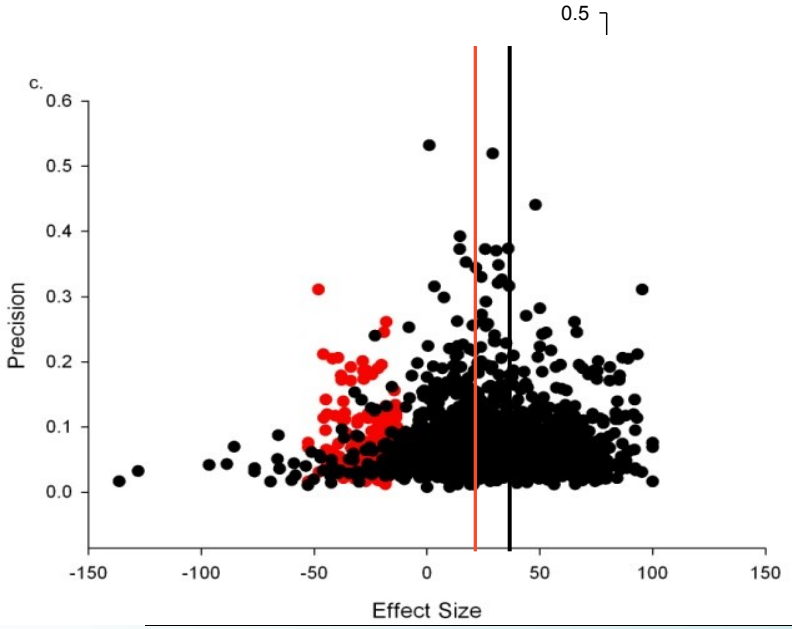
Mouse image stolen from: Jessehirt.shutterfly.com

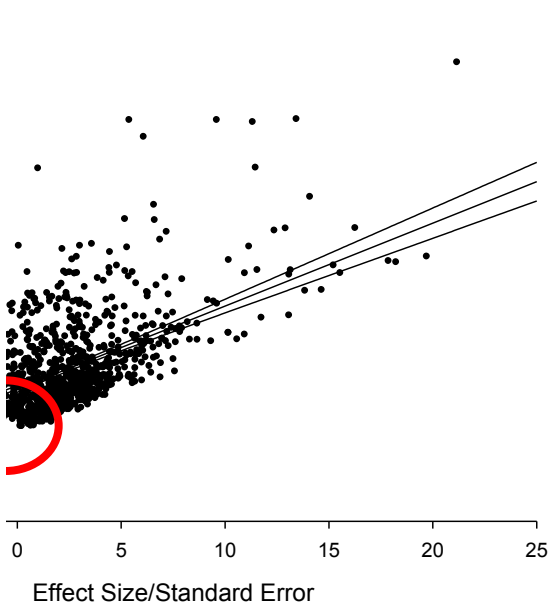
Is the File-Drawer Infested With Mice?

How to assess for publication bias?

- To assess for its presence
  - Funnel plot/Egger regression
- Estimate efficacy in the absence of publication bias
  - Trim and Fill







3Rs

- Examples describing
  - Assess whether less noxious tests are as predictive as more severe alternatives
  - Robust sample size calculations
  - Assess whether multiple tests are necessary
  - Refine duration of experiments

Indicative Power Calculations

Mechanical induced outcomes

Behavioural Test	No. of experiments	Median N	Calculated power	Median Effect Size (IQRs)	Calculated sample size (power=0.8)
von Frey (electronic)	48	9	0.3	1.3 (0.9-1.8)	11
von Frey (filaments)	369	11	0.5	1.5 (0.8-2.4)	9
Pin prick	12	11	0.6	1.6 (0.3-8.3)	8
Randall-Selitto paw pressure	156	10	0.8	1.9 (1.0-3.8)	6

Separation-induced anxiety - multiple testing?

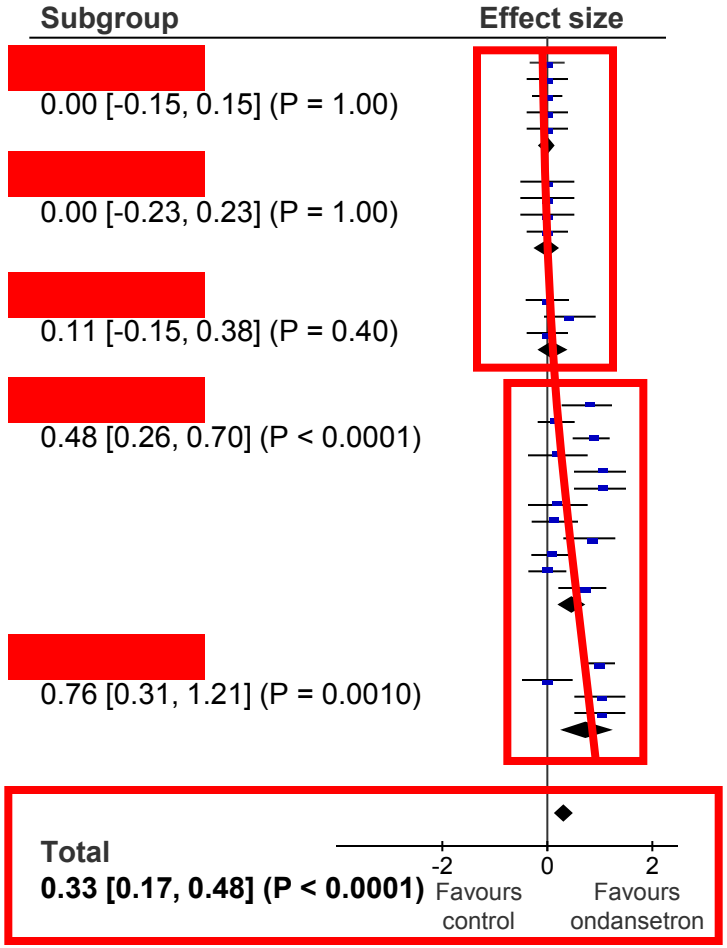
Table 5
Subgroup statistics for total number of vocalizations.

Subgroup	# Articles	# Experiments	# Animals	SMD[CI]
Repeated testing				
Test for subgroup differences $P < 0.00001$				
Once	3	9	233	−1.16 [−1.61, −0.70]
2-3 times	3	5	102	−2.41 [−3.32, −1.50]
4 or more times	6	24	540	−2.35 [−2.88, −1.81]
Not reported	3	5	102	−1.63 [−2.34, −0.92]

NA not applicable; NS not significant; # number; SMD standardized mean difference; CI confidence interval; Subgroups consisting of less than three experiments and/or less than three articles were excluded from between subgroup analyses.

Anti-emetic research
- refine duration of experiments

- Ondansetron protects 50% of the patients treated with Cisplatin
- Ondansetron reduced the number of animal developing emesis
- Efficacy was dependent on dosage and duration of the observation period
- Supporting evidence to improve the model
- Provides evidence supporting refinement of the model (4h instead of 24h)



Percie du Sert N *et al* (2011) Cancer Chemother Pharmacol 67(3): 667-686.

In Summary

- Why systematic reviews are important for…….
  - Good Science
    - Knowing what has been done already
    - Confidence in the cause-effect relationship
    - Generalisability of findings
    - Presence & impact of publication bias
  - 3Rs
    - Assess whether less noxious tests are as predictive as more severe alternatives
    - Robust sample size calculations
    - Assess whether multiple tests are necessary
    - Refine duration of experiments

Thanks to……

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