Nociception and pain in animal models: von Frey and its difficulties

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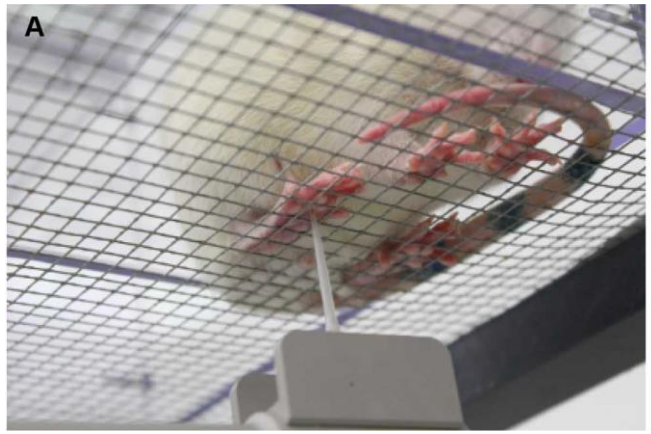
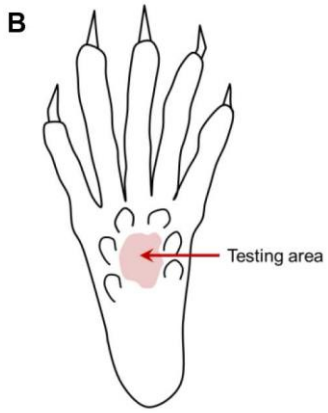
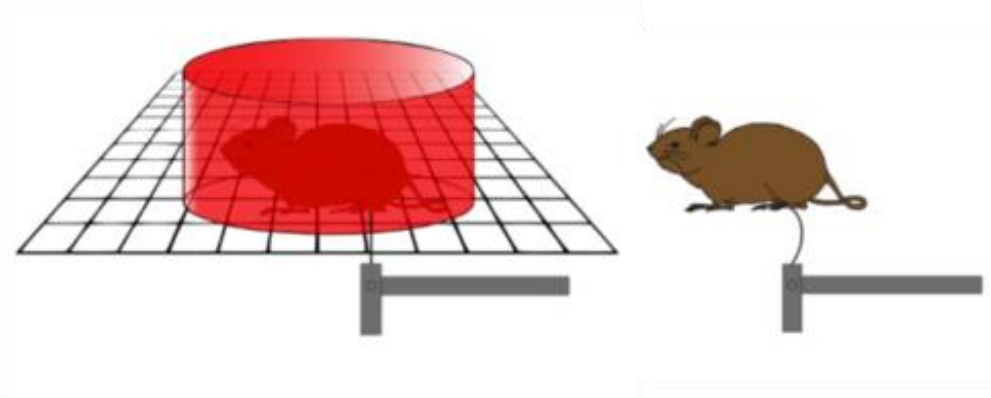
Nociception and pain in pre-clinical research

- Common in various indications and performed in different animal models
- Outcome: Determination of a paw withdrawal reaction upon a mechanical stimulus at the animals' feet







- Over time a huge variety of sophisticated and detailed measurement protocols comprising complex sequential testing specifications have been developed.

Available recommendations regarding statistical data analysis are lacking precision

Measurement and Outcome

Most prominent measurement protocol described in Chaplan *et al*. (1994)

- Sophisticated sequential testing of von Frey filaments:
  Via a lookup-table the yes/no-coding of reactions can be translated into a force [g] which describes the paw withdrawal threshold

$$50\%\ response\ threshold\ [g] = (10^{(Xf+k\delta)})/10000$$

Xf = value (in log units) of the final von Frey filament used
k = tabular value for the pattern of positive/negative responses (Chaplan et al. 1994, appendix 1, p. 62)
δ = mean difference (in log units) between stimuli

S.R. Chaplan, F.W. Bach, J.W. Pogrel, J.M. Chung, T.L. Yaksh (1994) Journal of Neuroscience Methods 53: 55-63.

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Main Difficulties

- Limited set of possible outcome values often with lower and upper limit of detection
  - **Pseudo-continuous outcome variable**

- Experimental design adds levels of complexity to the statistical model
  - Repeated measurements at the same animal and/or at different time points
  - Large set of treatment groups with complex set of group comparisons of interest

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Modelling approaches

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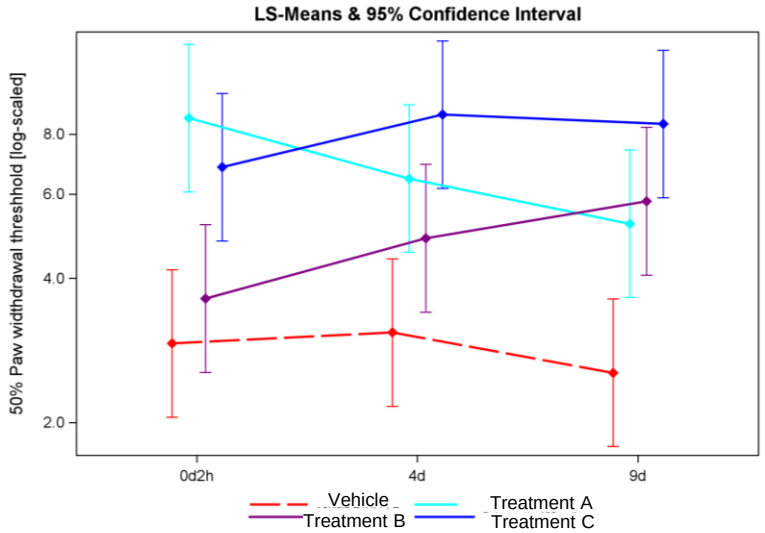
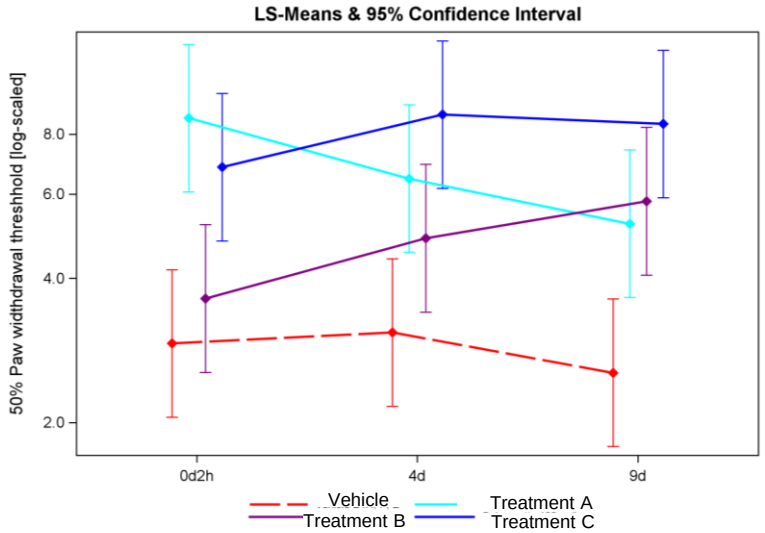
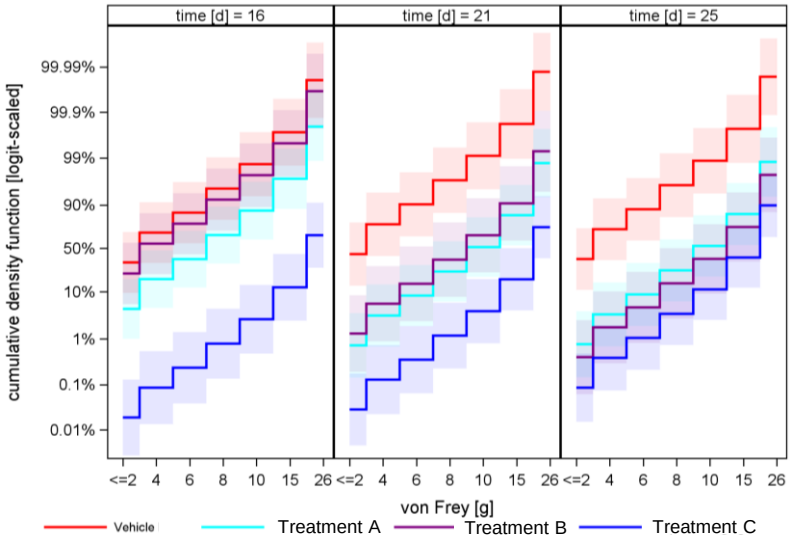


Model I: log-transformed von Frey values as continuous variable

- Does not account for censored scale
  - ➢ Confidence limits can exceed the actual range of tested von Frey-filaments
- Straight-forward group mean comparisons and (pseudo-) continuous effect sizes available

Modelling approaches





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Model II: raw von Frey values as categorical variable – Modelling of cumulative density

- With low sample size only simple models estimable
  - ➢ Model with group specific intercepts & von Frey filament specific probabilities
- More intuitive to interpret

Summary

- No one-fits-all solution available
- Choice of statistical analysis strategy depends, among other parameters (Bradman et al. (2015)), on
  - selected experimental procedure
  - animal model used
- Typically small sample sizes severely restrict applicable model fitting

Outlook

- Technical refinement and improved lab-equipment is supposed to lead to
  - Continuous measurements of von Frey as *50% response threshold [g]*
  - Automated measurement shall lead to better reproducibility

M. J.G. Bradman, F. Ferrini, C. Salio, A. Merighi (2015) Journal of Neuroscience Methods 255: 92–103.

Thank you!