Optimized surgical techniques and postoperative care

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Optimized surgical techniques and postoperative care

Surgery

- Optimized anaesthesia
- Pre-emptive analgesia
- Anti-infective prophylaxis
- Experienced personnel
- Surgical skills *per se*

Postoperative care

Pain alleviation in laboratory mice

- Pain killers

Supportive measures

- warmth, fluid, housing conditions, …

Humane endpoints

The laboratory mouse

… represents probably ≥70% of laboratory animals used in biomedical research and testing

… thousands of genetically modified lines/models available

Examples for the need of surgery in research

Organ transplantation

- liver
- lung
- stem cells

Open chest surgery

- myocardial infarction

Stroke

Physiology

…

Agenda: Pain alleviation in laboratory mice

Problems

- detection of pain in mice
- treating pain in mice

Example: Use of a minor surgery model for assessing (1) post-surgical pain and (2) the efficacy of the pain relief regimen

Read-out:

- Clinicial investigation: cage-side observations, body weight, food consumption
- Telemetry: Heart rate, heart rate variability
- Natural behaviors: Nest building, burrowing

Where are we now?

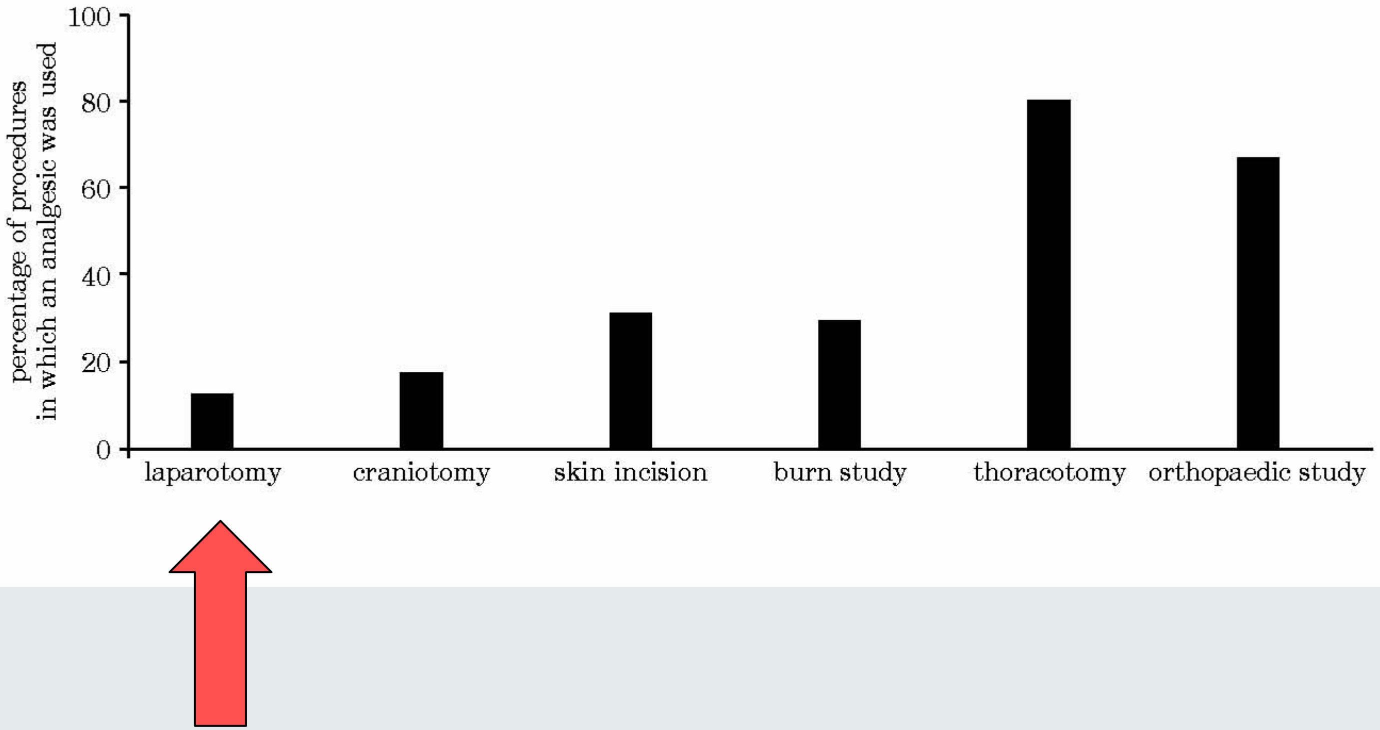
Next steps

Detection of postoperative pain in mice

Examples (video recordings):
No effect of pain killers visible by cage-side observations of typical clinical signs

Pain treatment

Figure 2: The reported use of analgesics in papers published between 2000 and 2002, according to the procedure applied



Claire A. Richardson and Paul A. Flecknell; ATLA 33, p. 119-127, 2005

Detecting ongoing pain by its effects on …

body weight?

food,

water?

pain

spontaneous

behavior?

experimental or GM

induced changes?

Clinical symptoms;

appearance?

Clinical signs

Appearance

- fur
  - rough, soiled, hair loss, piloerection
- body
  - weight loss
  - decreased food intake
  - sunken abdomen
  - hunched posture
  - sunken eyes
  - dehydration

Behavior

- aggressive
  - biting response; automutilation
- apathy
  - unresponsive; isolation from the cage mates
- increased activity
  - restlessness; sudden running movements
- prolonged times for sleeping or resting

Constraint

= fear, distress, suffering, pain, disease, …

Food intake after surgery

Decrease of **food consumption** after surgery

Alteration of body weight, water intake, wheel runing activity

Adamson 2010, Bourque 2010, Arras 2007, Bomzon 2006

Side-effects

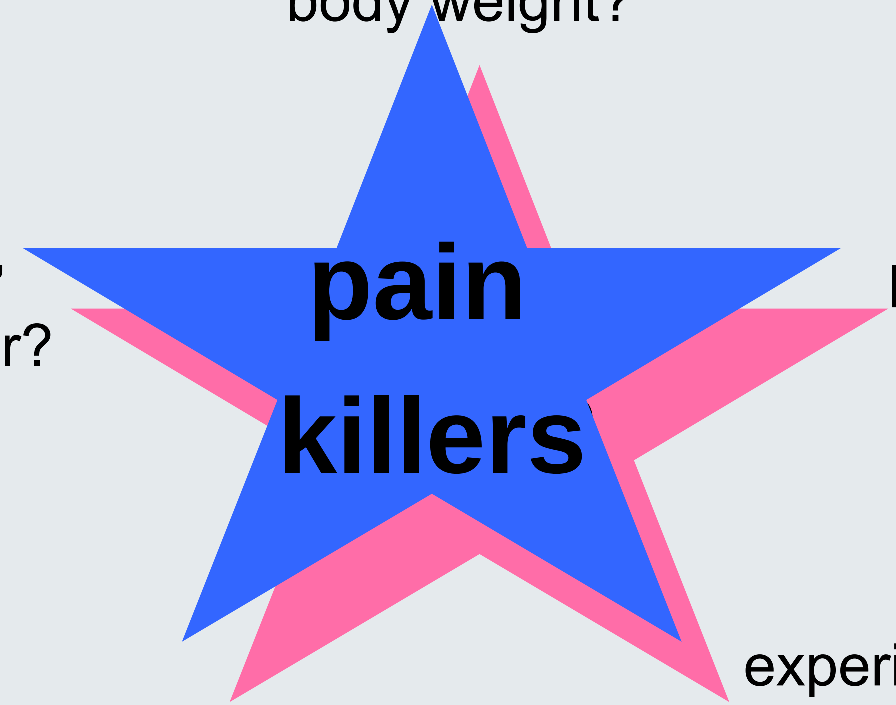
Example (picture):
Pica behaviour in the rat from Buprenorphine (Opioid) → ***high dosage?***

Detecting ongoing pain by its effects on …

body weight?

food,

water?



behavior?

appearance?

experimental or GM

induced changes?

Obstacles in pain relief regimens

Table 3: Suggested analgesic dose rates for laboratory rats and mice

	Suggested analgesic dose rate	
Analgesic	**Rat**	**Mouse**
Buprenorphine	0.01–0.05mg/kg s.c., 6–12 hourly	0.1mg/kg s.c., 6–12 hourly
Butorphanol	2.0mg/kg s.c., 4 hourly	2.0mg/kg s.c., 4 hourly
Morphine	2–5mg/kg s.c., 4 hourly	2–5mg/kg s.c., 4 hourly
Pethidine	10–20mg/kg i.m., s.c., 2–3 hourly	10–20mg/kg i.m., s.c., 2–3 hourly
Carprofen	5mg/kg s.c., ? daily	10mg/kg s.c., ? daily
Meloxicam	1–2mg/kg s.c. or 4mg/kg per os ? daily	5mg/kg s.c. ? daily
Ketoprofen	5mg/kg s.c. ? daily	10mg/kg s.c. ? daily

Dose rates are based largely on uncontrolled clinical trials and a limited range of procedures, and so are likely to be subject to revision. Whenever possible, a pain scoring scheme should be used, so that the dose rates can be adjusted according to an animal's response.

i.m. = intramuscular injection; per os = by mouth; s.c. = subcutaneous injection.

Table from Claire A. Richardson & Paul A. Flecknell, ATLA 33, p. 119-127, 2005

Pain alleviation in mice

Opioid

e.g. Burpenorphine

0.1 mg/kg BW, s.c., 2/die

NSAID

e.g.

Carprofen, Meloxicam, Metamizol, …

5 mg/kg BW, s.c., 1-2/die ?

Problems of pain alleviation

Difficulties in detecting pain in the mouse

Side-effects of analgesics → sometimes masking symptoms

No control of success → efficacy of pain treatment remains questionable

Regimens (agents, dosages, application intervals) mostly rely not on systematic studies or scientific investigations

Knowledge about efficient pain treatment in mice:
→ Evidence-based regimens
= agents, dosages and intervals
→ Animal-friendly application routes

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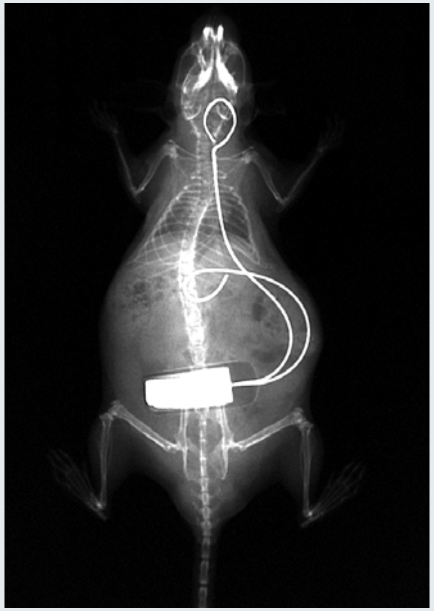
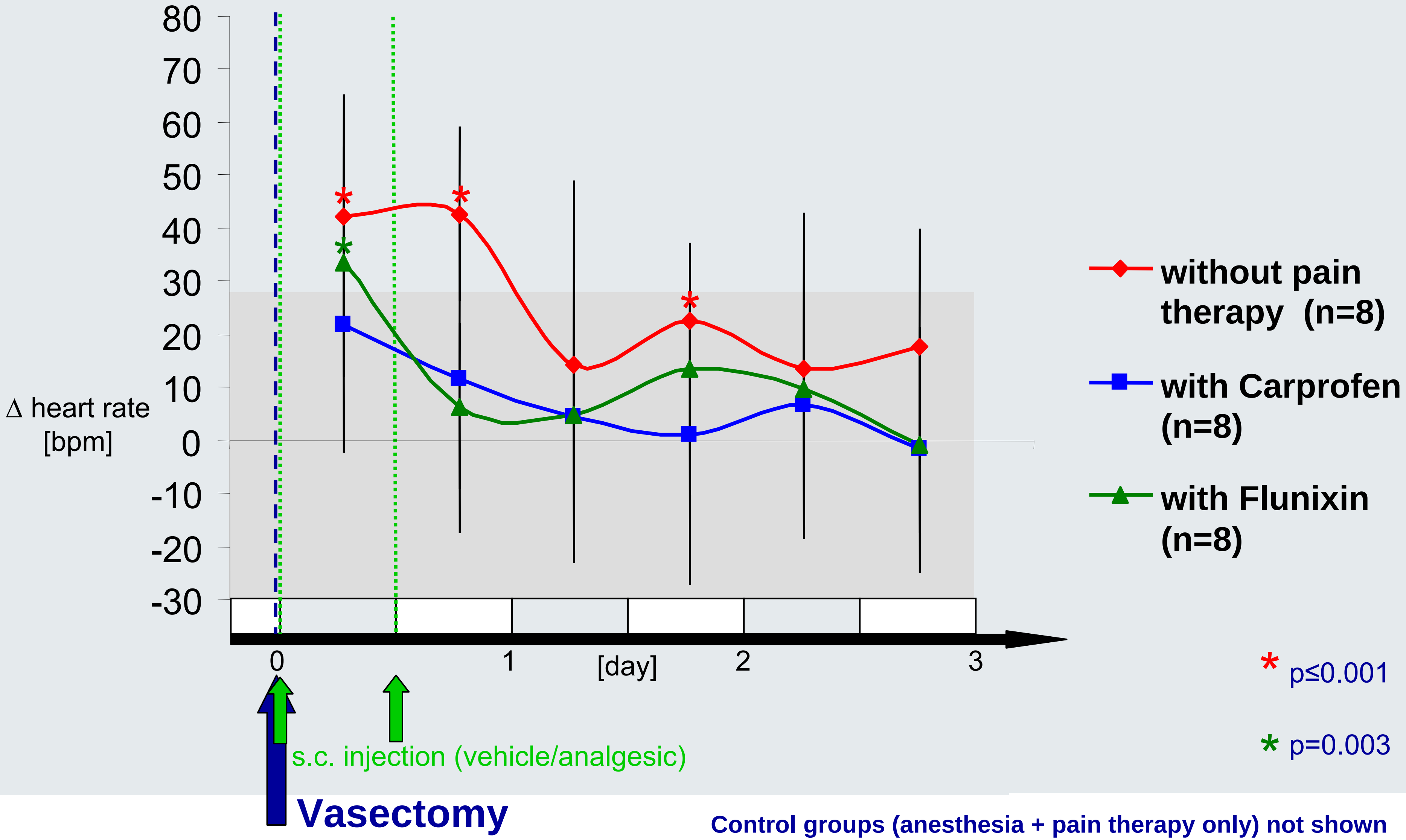
Recovery of mice after minor surgery with and without pain killers (NSAID: Carprofen, Flunixin)

Telemetric measurements → preliminary implantation of transmitters



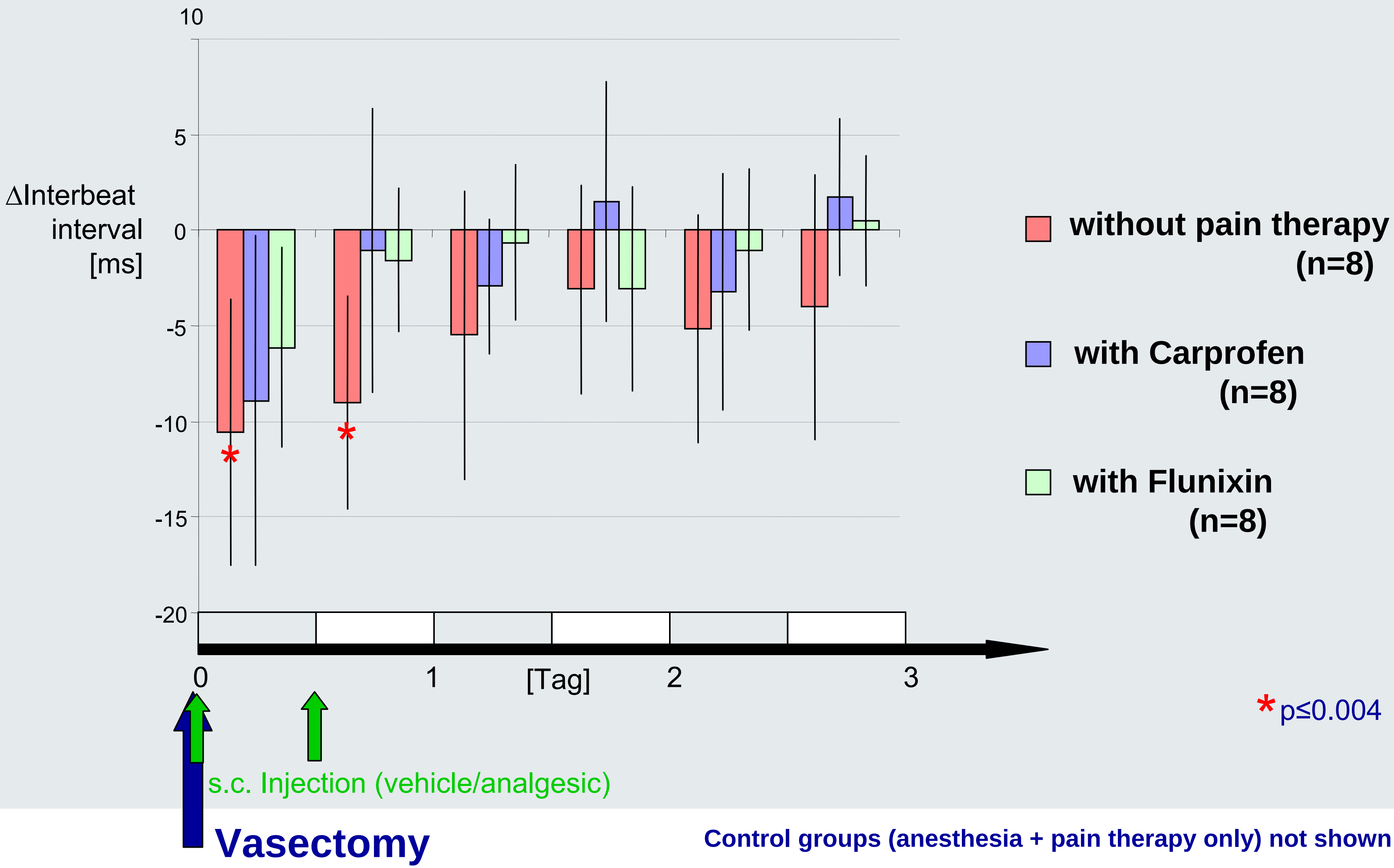
Change of heart rate



Control groups (anesthesia + pain therapy only) not shown

Arras, M. et al. BMC Vet Res; 3:16 (2007)

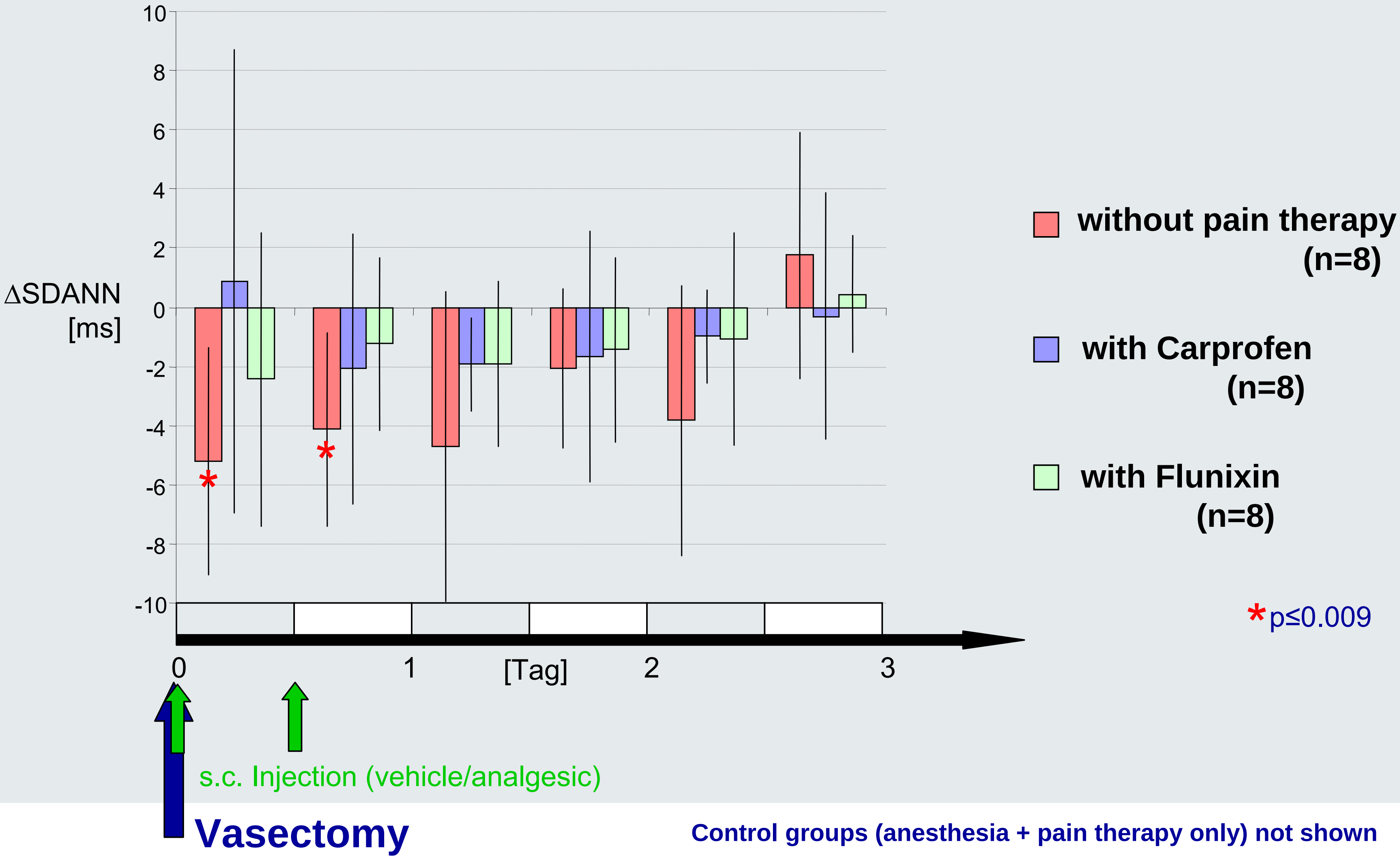
Time domain analysis of heart rate variability: IBI



Control groups (anesthesia + pain therapy only) not shown

Arras, M. et al. BMC Vet Res; 3:16 (2007)

Time domain analysis of heart rate variability: SDANN



Control groups (anesthesia + pain therapy only) not shown

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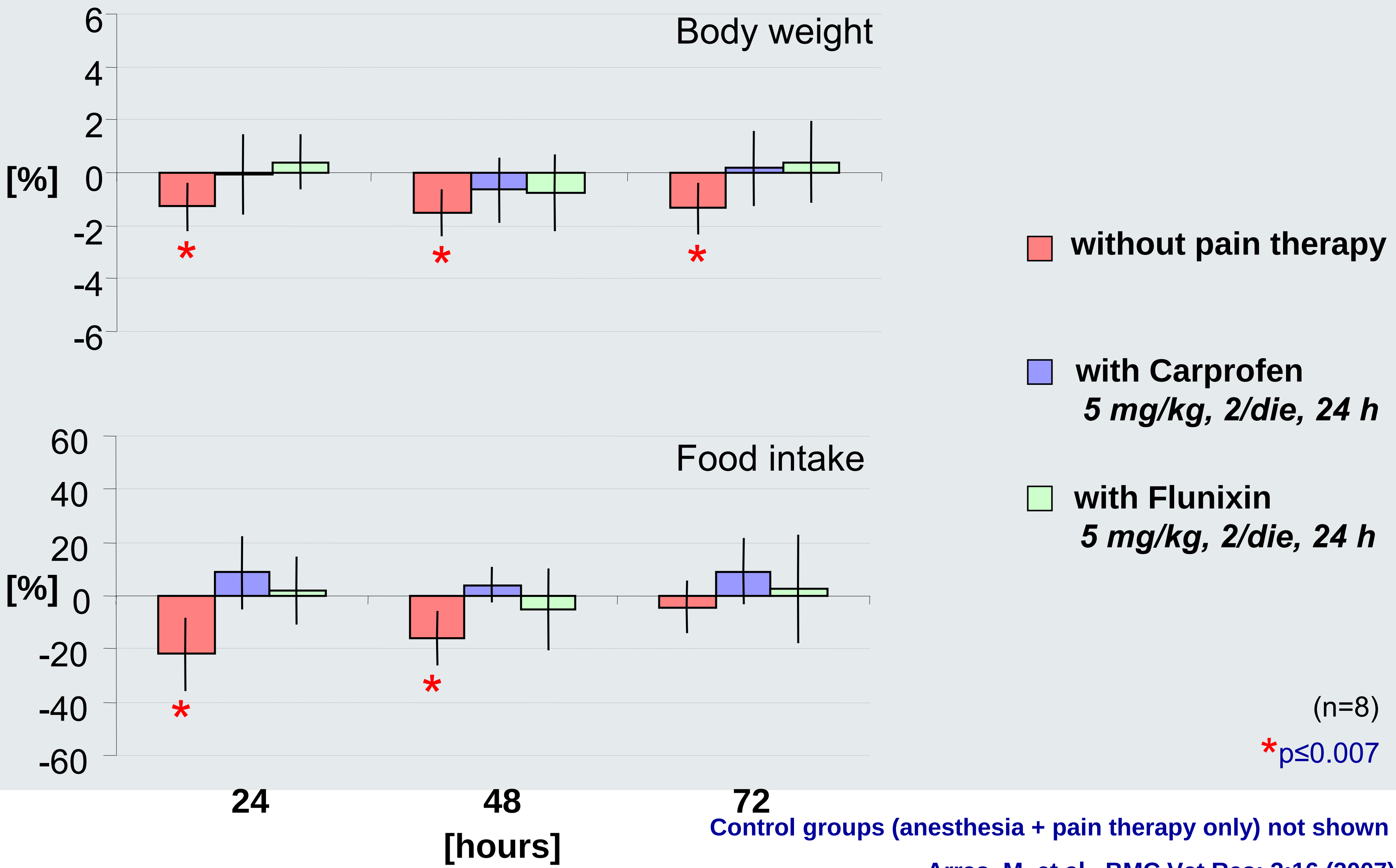
Body weight and food consumption



Control groups (anesthesia + pain therapy only) not shown

Arras, M. et al. BMC Vet Res; 3:16 (2007)

Recovery of mice after minor surgery with and without pain killers (NSAID: Carprofen, Flunixin)

Attenuation of aberrations in heart rate and heart rate variability with analgesia

Inhibition of the reduction in body weight (~2%) and food consumption (~20%) with analgesia

Clinical investigation: no difference in outer appearance, posture, spontaneous behaviors

Arras et al. 2007

Recovery of mice after minor surgery with and without pain killers (NSAID: Carprofen, Flunixin)

with pain treatment

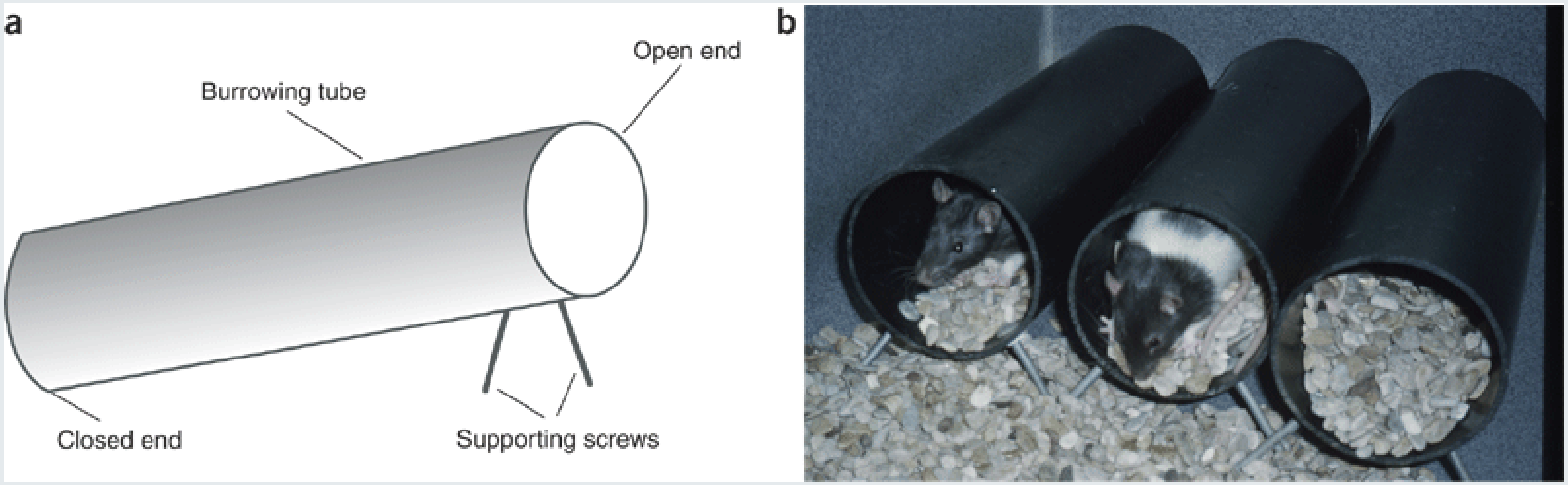
without pain treatment

Arras et al. 2007

Nature Protocols **1, - 118 - 121** (2006)

Burrowing in rodents: a sensitive method for detecting behavioral dysfunction

Robert M J Deacon



- **mice, rats, hamsters, gerbils**
- **home cage based**
- **read out: aberration of natural, highly motivated behavior**

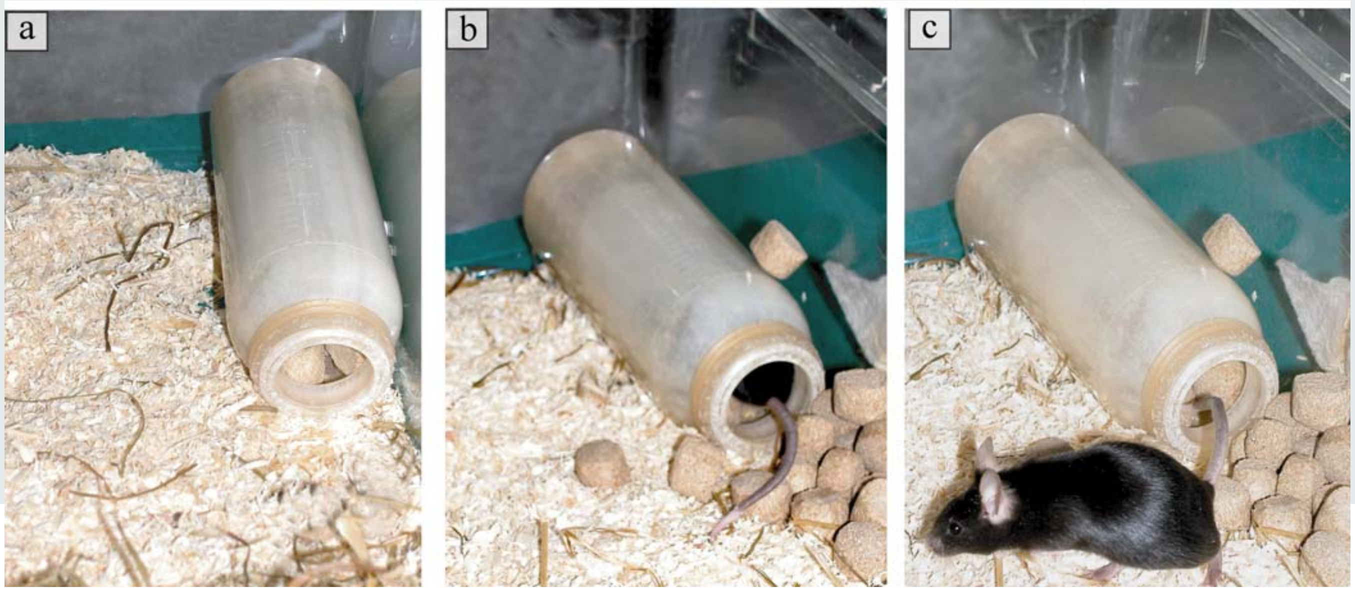
Burrowing

Species-specific, spontaneously occurring behaviour

High motivation to dig burrows persists during domestication

Deacon et al. 2001 > neurodegenerative diseases

Useful as indicator for impaired wellbeing???



Hypothesis: Abberration of a natural behavior is an indicator of pain, constraint, or impaired well-being

Aim: Changes in burrowing behavior as indicator of pain after minor surgery

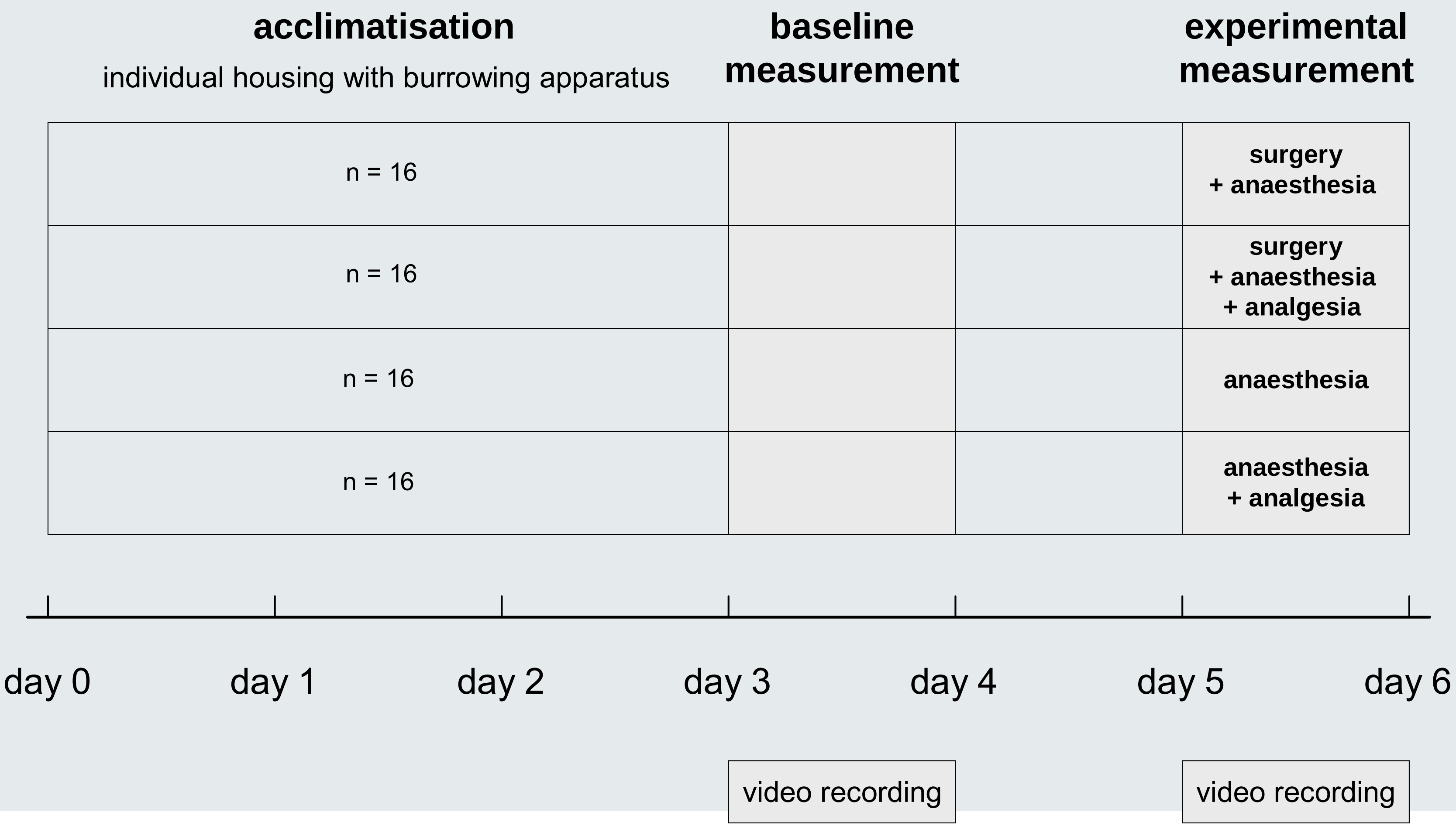
Pre-study burrowing test

Time of testing (circadian rhythm), Setup (apparatus), Sex bias, Strain bias C57BL/6J, DBA/2J, 129Sv/Ev-IFNabRtmAgt

Study design

32 male & 32 female adult C57BL/6J

Burrowing test: study design



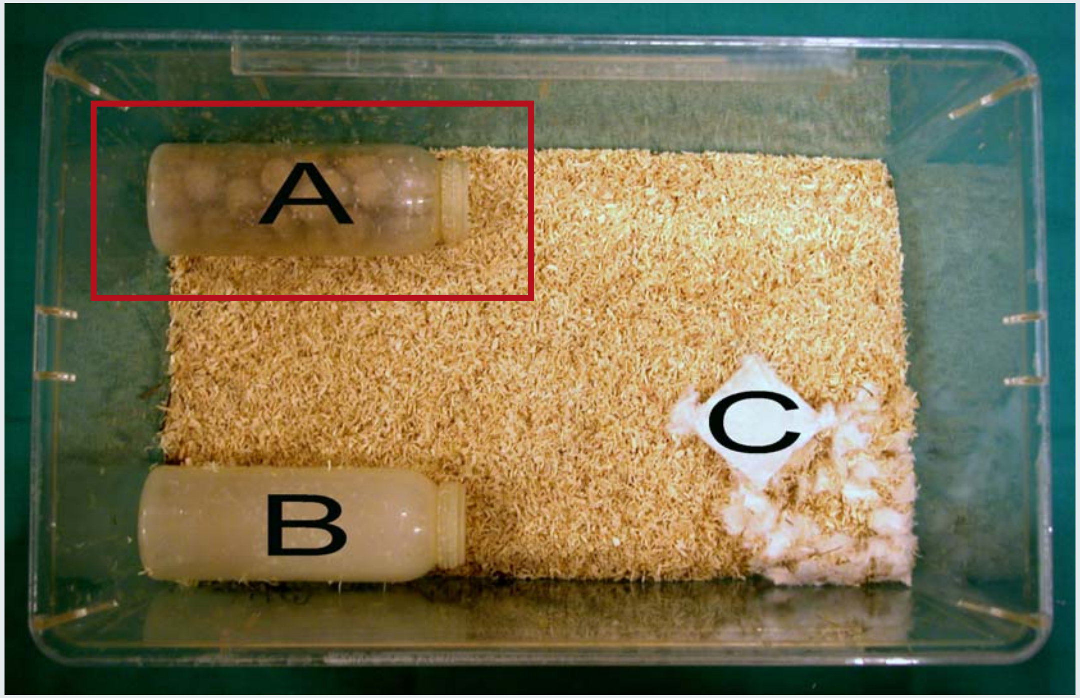
Jirkof et al. 2010

Burrowing test: study design

Surgical intervention

- Injection of analgesia
  (+/- carprofen, 5 mg/kg BW, s.c.)
- transport
  (5 min)
- inhalation anaesthesia
  (sevoflurane, 15 min)
- +/- one side minor laparotomy
- recovery on warming mat
  (at least 15 min)

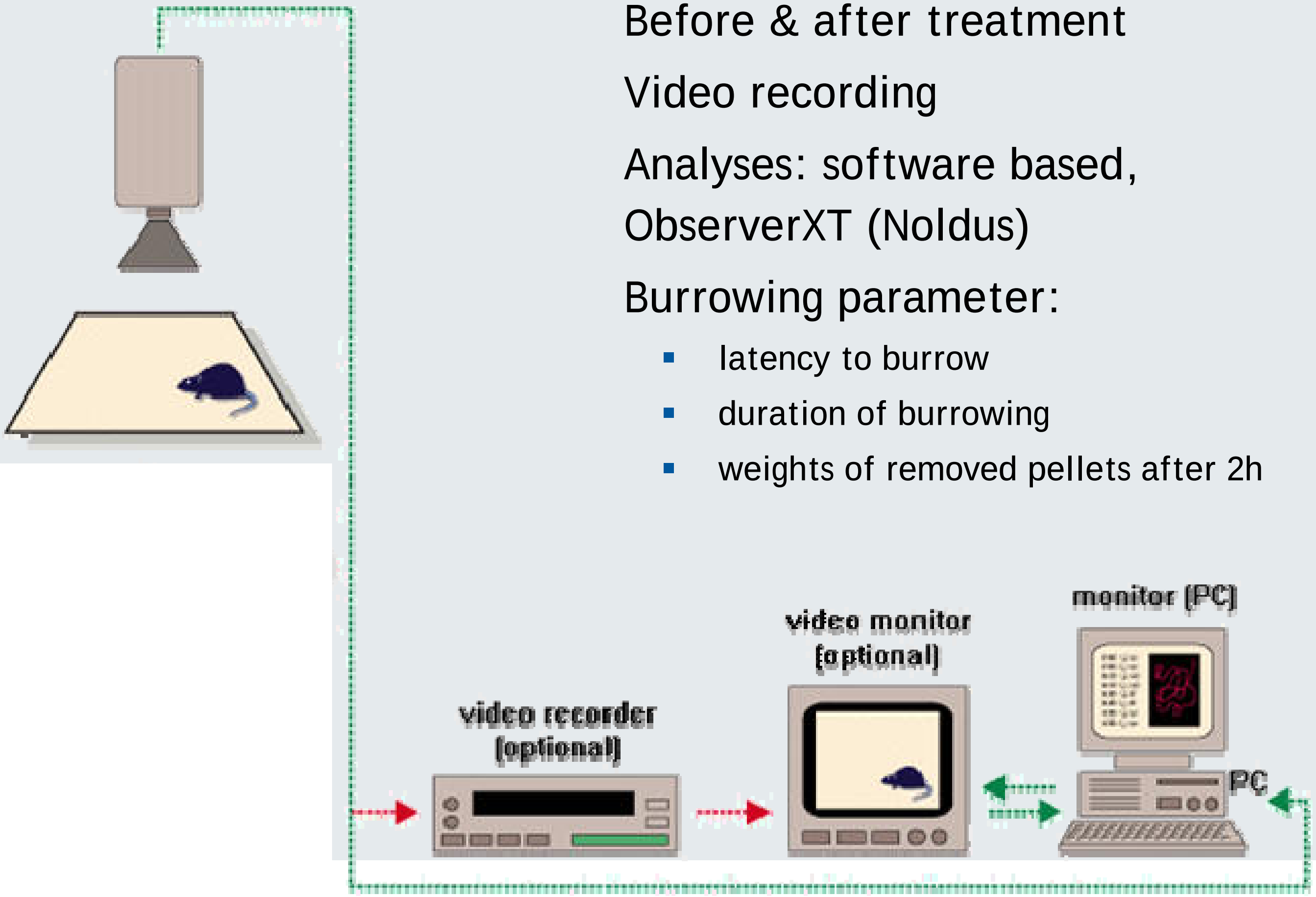
Burrowing test: set up



Experimental Setup. Burrowing test apparatus (A), shelter (B) and nesting material (C) in home cage.

Jirkof et al. 2010

Burrowing test: analysis



Before & after treatment

Video recording

Analyses: software based,
ObserverXT (Noldus)

Burrowing parameter:

- latency to burrow
- duration of burrowing
- weights of removed pellets after 2h

www.noldus.com

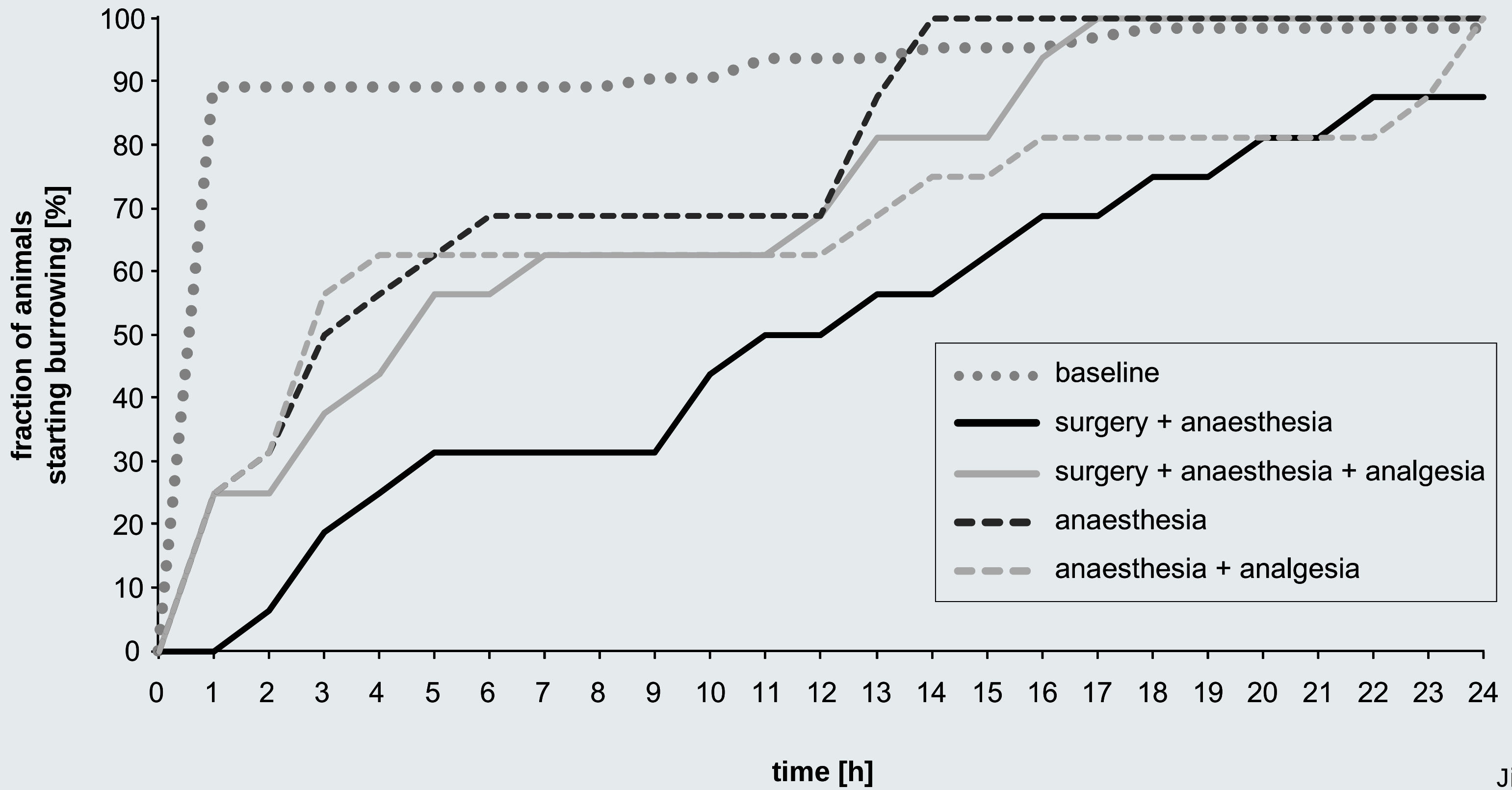
Results: burrowing performance

Almost all (98 %) healthy mice burrowed during baseline measurement

Example: infrared video recording of burrowing.

All parameters (latency to burrow, duration of burrowing, weight of removed pellets) responded to the different experimental treatments.

Results: burrowing performance

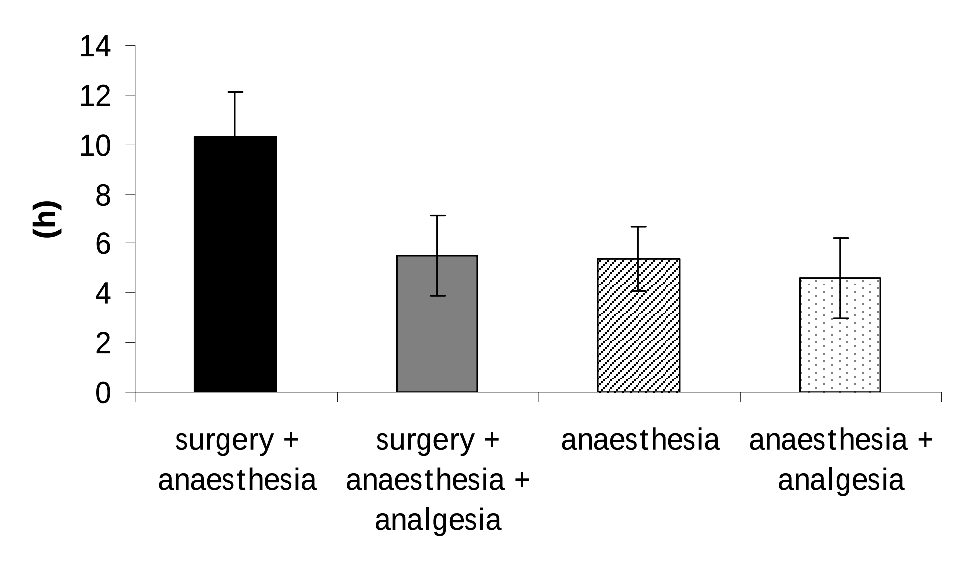


Jirkof et al. 2010

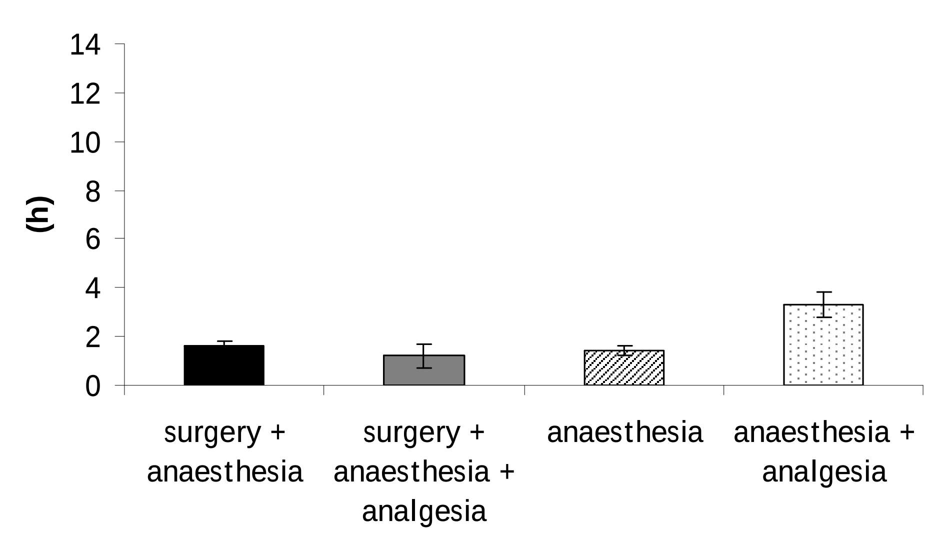
Results: baseline vs experimental

Increase in latency & duration of burrowing after treatment

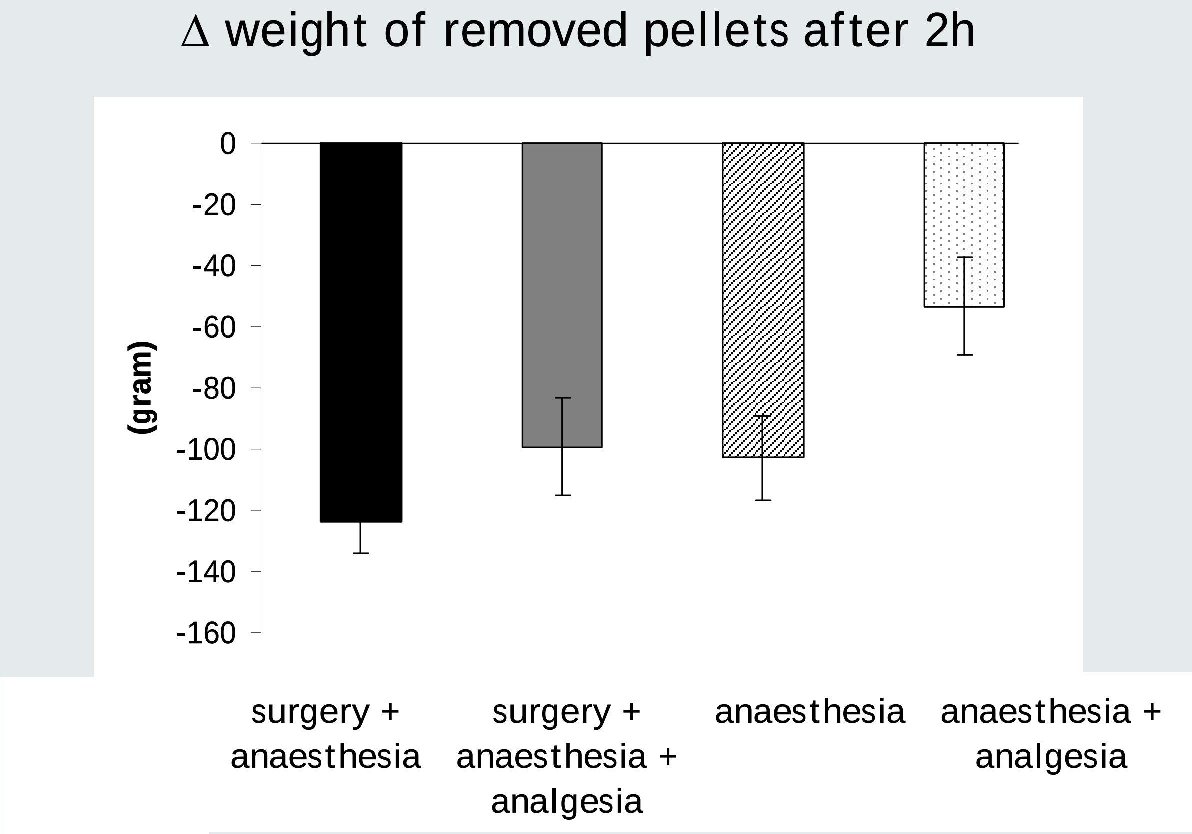
Δ latency to burrow



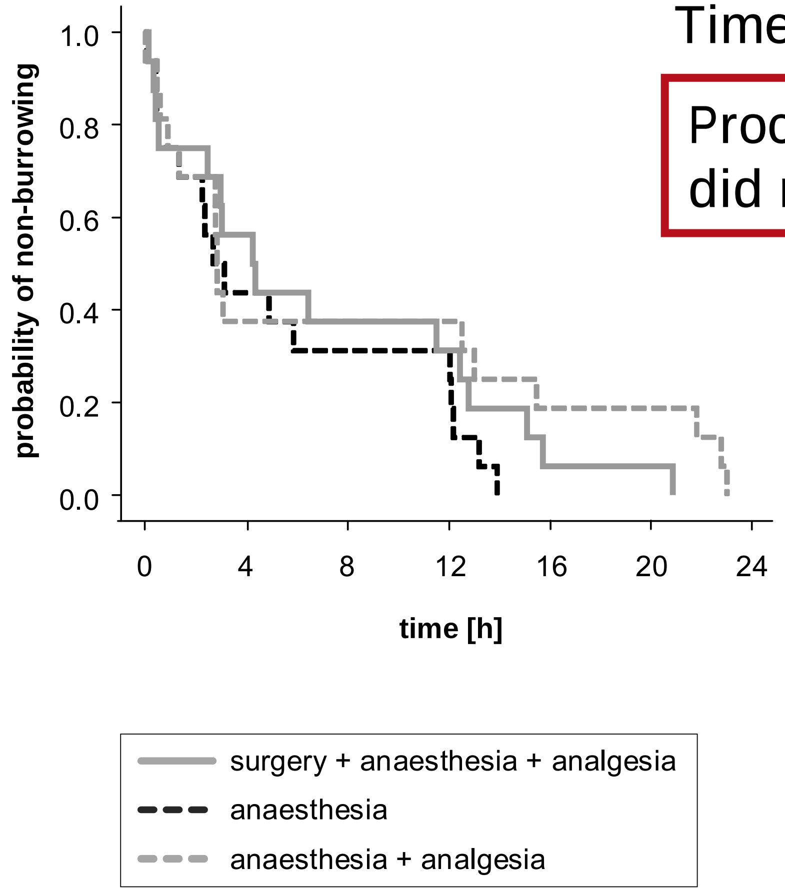
Δ duration of burrowing



Results: baseline vs experimental



Results: group comparisons

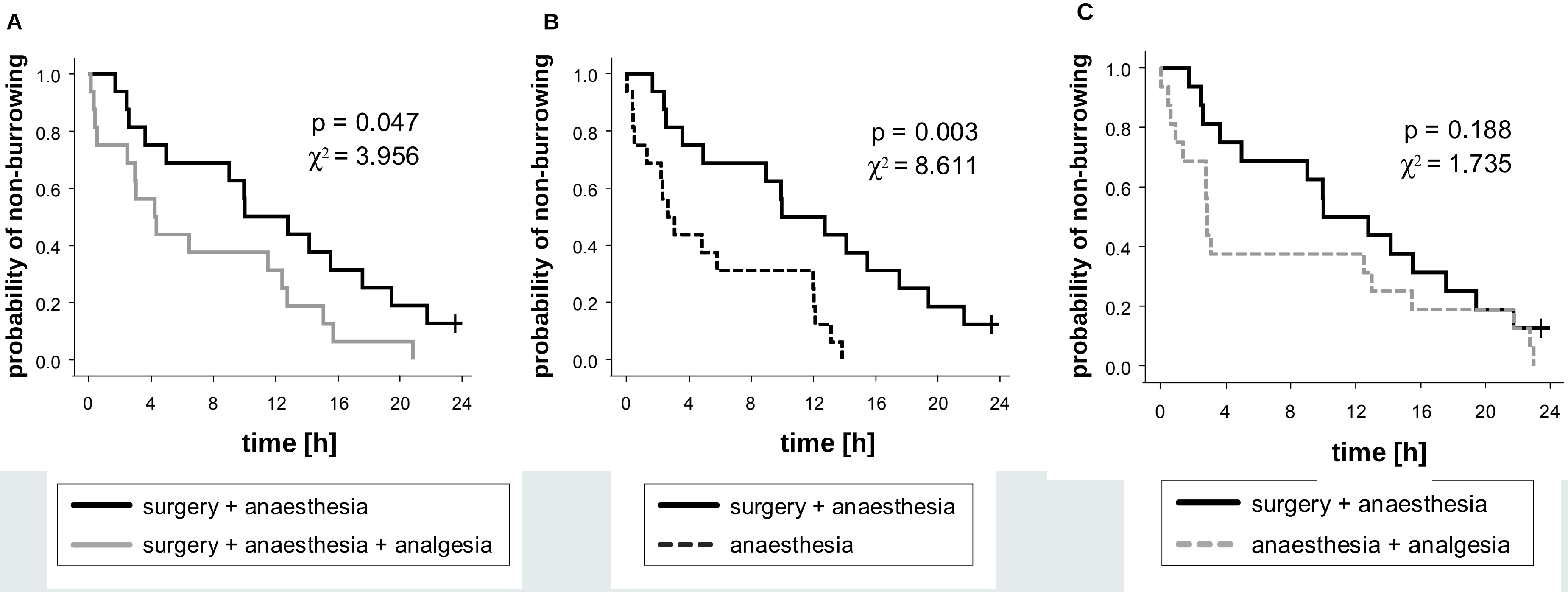


Time to effect: Kaplan-Meier analysis

Procedural control treatments did not differ in latency

Jirkof et al. 2010

Results: group comparisons



Surgery without pain treatment causes significant longer latencies

Jirkof et al. 2010

Burrowing test: summary & conclusion

- Easy to perform in the animals home cage under routine laboratory conditions
- Burrowing parameters react sensitive on treatments
- Results allow to discriminate between groups of mice that are treated with a pain killer or not before surgery
- Results imply a balance between the motivation to burrow and an individuals level of constraint experienced

In conclusion, postsurgical impairment, mainly attributable to pain, can be assessed on the basis of the burrowing test

Where are we now?

Currently: new approaches and methodologies for the assessment of pain and constraint in mice

- Conditioned place preference → Frank Porreca [King et al. 2009]
- Facial expression (mouse grimace scale) → Jeff Mogil [Langford et al. 2010]
- General changes in behaviors (rearing, climbing, etc.) → van Loo et al. 2007, Roughan et al. 2009
- Abberrant behaviors (e.g. twitching, flinching, …) → Paul Flecknell [Roughan et al. 2009]
- Drug self administration → Vera Baumans [Pham et al. 2010]
- Alterations of natural behaviors → Jirkof et al. 2010
- Sympathetic reaction (telemetry) → Arras et al. 2007
- Ultrasound vocalisations?

Feasibility, validity, benefits, limitations in routine laboratory conditions

Reliability of specific tests for estimating the efficacy of pain relief regimens

Long-term goals

Utilization of new tests for verifying pain relief regimens which are in use to-date

Establish efficient, evidence-based modern pain relief regimens

- Sustained-release drugs
  - Foley et al. 2011
- Administration of analgesia via drinking water, food, or mini-pumps
- Multimodal analgesia protocols
- …

Is there a market for analgesics or other drugs for use in mice???

Thank you for your attention

Paulin Jirkof
Andreas Rettich
Nikola Cesarovic
Thea Fleischmann

Beat Schuler
Paolo Cinelli
Robin Schneider

Kurt Bürki
Gregor Zünd

Our work was supported by

Federal Veterinary Office Switzerland; UBS Foundation; ESLAV and ECLAM foundation,

3R research foundation Switzerland

and

Central Biological Laboratory and Division of Surgical Research at University Hospital Zurich; Institute of Laboratory Animal Science, University of Zurich.