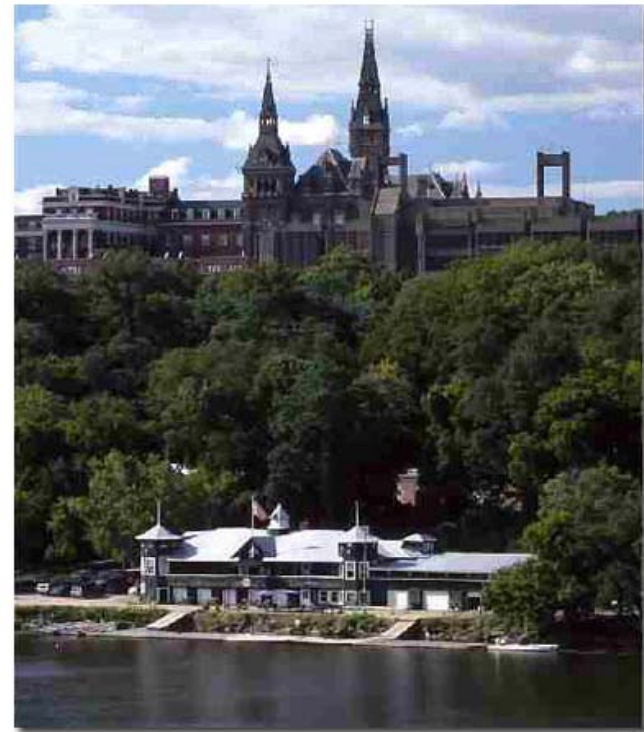# Macro- and micro-behaviors in animal modeling of neuropsychiatric disorders

Allan V. Kalueff
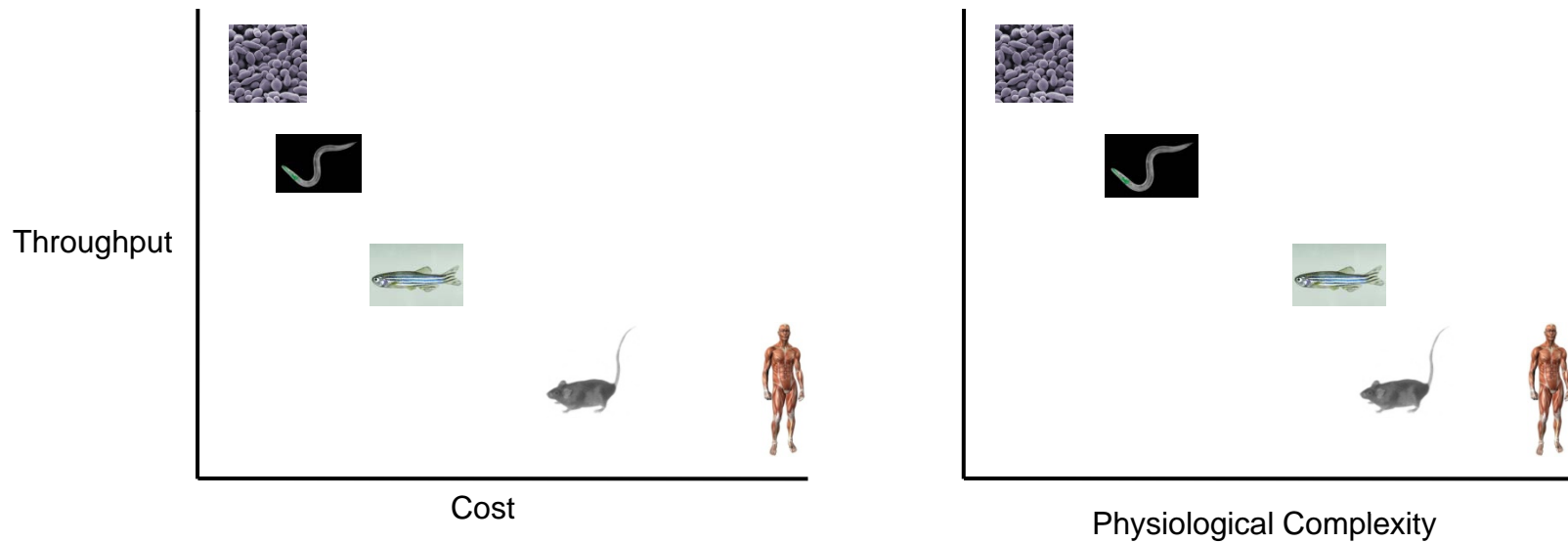Peter C. Hart, Amanda N. Smolinsky,
Carisa L. Bergner, Justin L. LaPorte,
and Rupert J. Egan

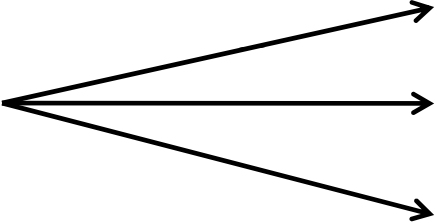**Department of Physiology and Biophysics, Georgetown University Washington, DC**

November 17, 2008
SFN Satellite Symposium

Current Challenges in Phenotyping Research
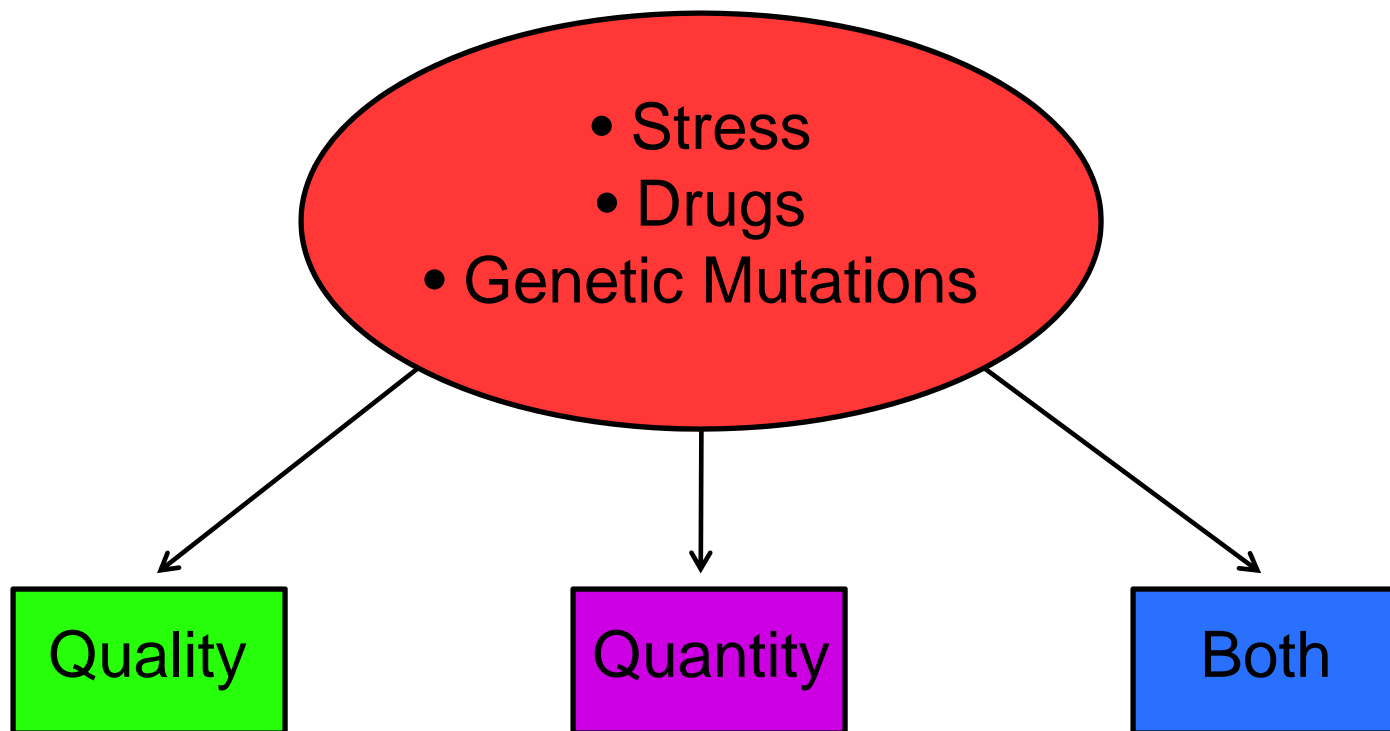

Throughput

Cost

Physiological Complexity

Modified from Kokel and Peterson, 2008

Macro-behavioral and Micro-behavioral Levels of Analysis

Character of Behaviors	Endpoints
Quantity	• Frequency • Duration • Latency
Quality	• Sequencing A → B → C vs. C → A → B

Macro-behavioral and Micro-behavioral Levels of Analysis

- Stress
- Drugs
- Genetic Mutations

Quality

Quantity

Both

Macro-behavioral Video Tracking

Video tracking systems have been used in animal models of neuropsychiatric disorders

Until recently, this was to the extent of simple behaviors, such as movement and place preference
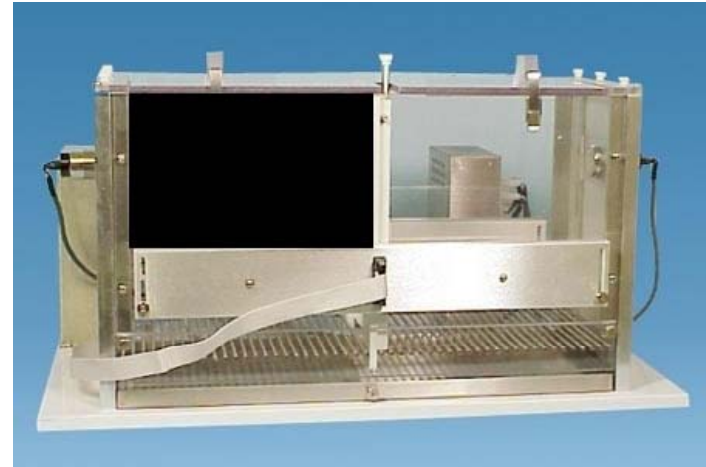

www.bioseb.com
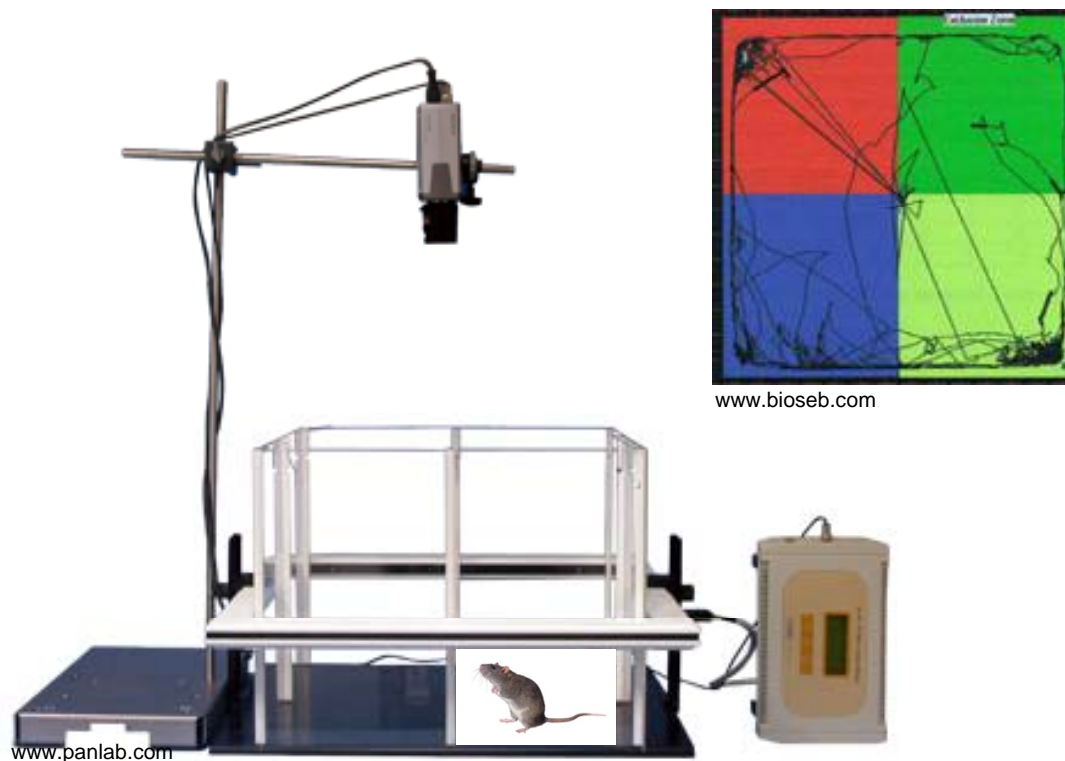
Conventional video tracking records movement of an animal as a single point-based entity

These systems analyze the macro-behavioral levels in animals

www.panlab.com

Current Challenges in Phenotyping Research

It is time consuming and expensive to perform a battery of behavioral testing subsequently macro- and micro-behaviors

abdellab.sunderland.ac.uk

Micro-behavioral level video tracking can assess many behaviors simultaneously, quantify actions, and analyze sequences of actions
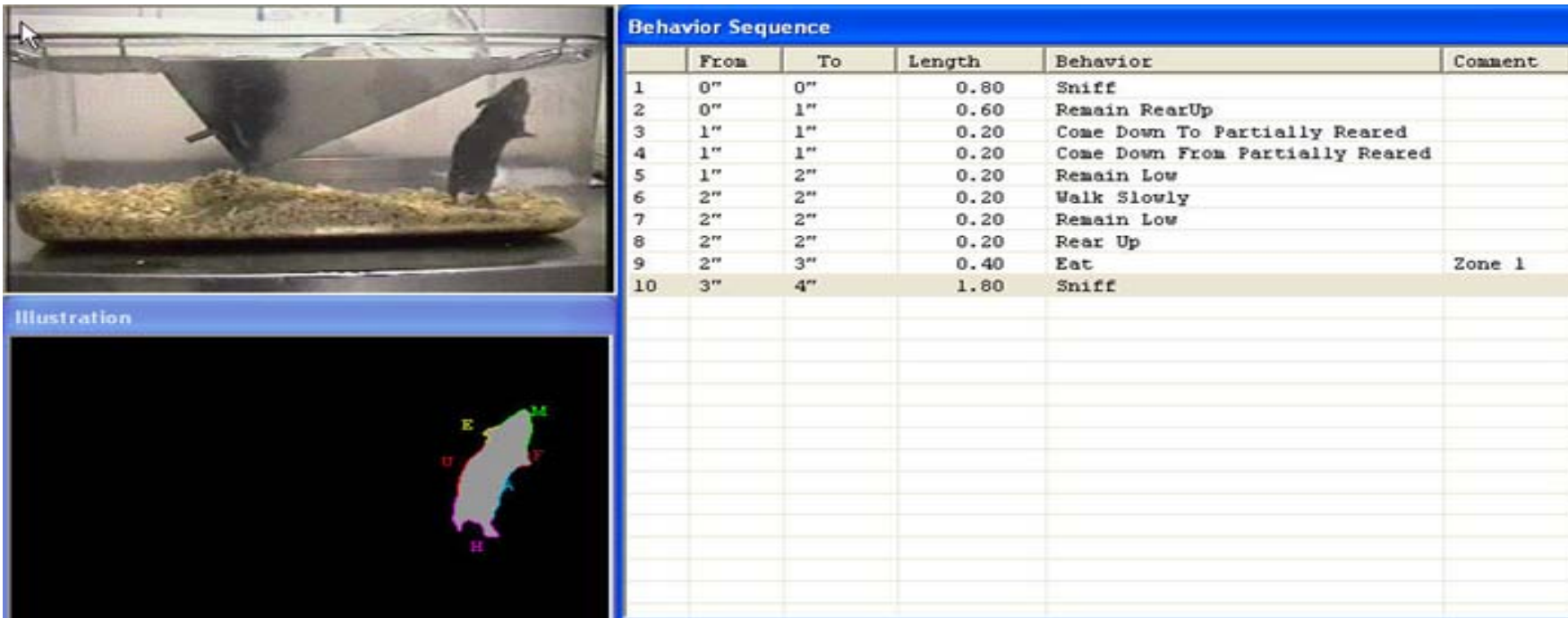

www.lsa.umich.edu

www.med-associates.com

Micro-behavioral Video Tracking

Modern tracking systems can analyze an individual animal in a full spectrum, recording the movement of specified body parts
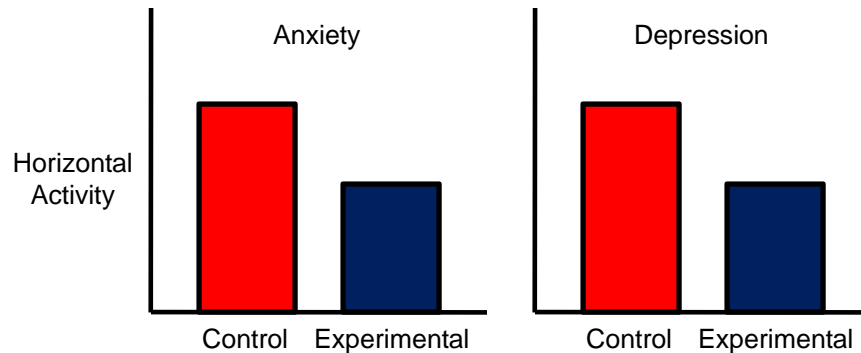
It is also possible to assess regional distribution of physiological markers, such as regional body temperature

www.cleversysinc.com

Why Use Micro-behavioral Levels of Analysis?

Behavioral Domains

Solutions

• Test in more specific models
(Do we have them?)

• Challenge with a drug
(Do we always want drugs to be used?)
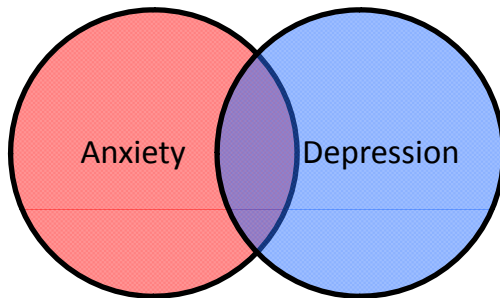
Macro-behavioral assessment yields unclear results

• Micro-behavioral Analysis

Advantages of Micro-behavioral Analyses
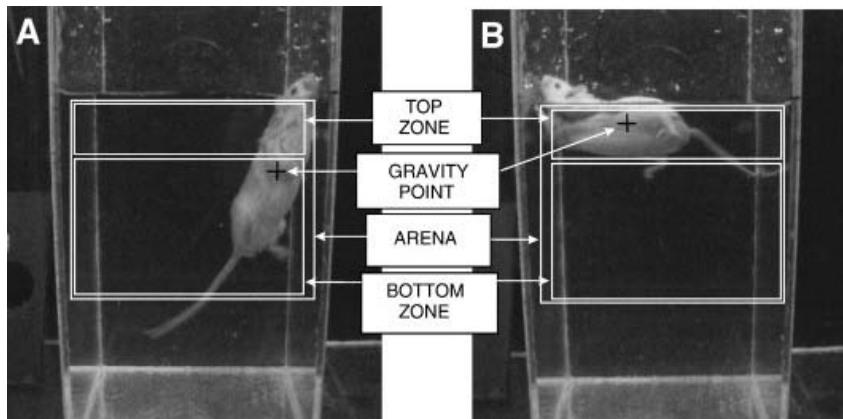
- Certain abnormal behaviors can be detected, such as differences in swimming pattern in the Forced Swim Test

- Video-tracking algorithmic computation reduces effects of manual scoring on reproducibility of data
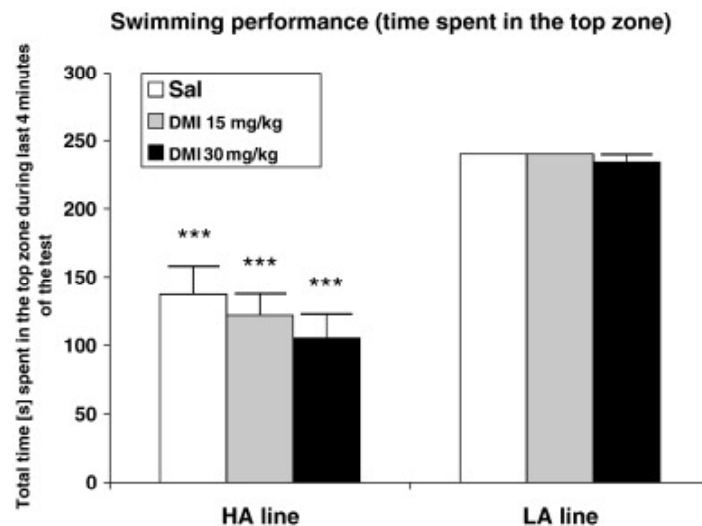
- Micro-behavioral analysis complements macro-behavioral endpoints, resulting in higher throughput models

Juszczak et al., 2008

Advantages of Micro-behavioral Analyses

www.aps.uoguelph.ca/~gmason/StereotypicAnimalBehaviour

www.nc3rs.org.uk

Commonly seen behavioral perseverations:

- Barbering
- Repetitive Jumping
- Bar-Mouthing
- Cage-Top Twirling
- Excessive Licking
- Excessive Grooming

This allows the first automated video assessment of OCD-like behaviors in rodents, to determine possible OCD-like phenotypes

Advantages of Micro-behavioral Analyses

User-defined regions (head, forepaws, body, hind legs, tail) are monitored

www.lsa.umich.edu

Complex behaviors, such as grooming, can be isolated and quantified in the assessment of anxiety

Grooming Behavior

- Ancient, innate behavior, common in rodents

- Represents 30-50% of waking time

- Most represented behavior after sleep

- Seen in low-stress "comfort" conditions

- May be experimentally triggered by stress
  - Novelty
  - Predator stress
  - Water misting
  - Various drugs and hormones
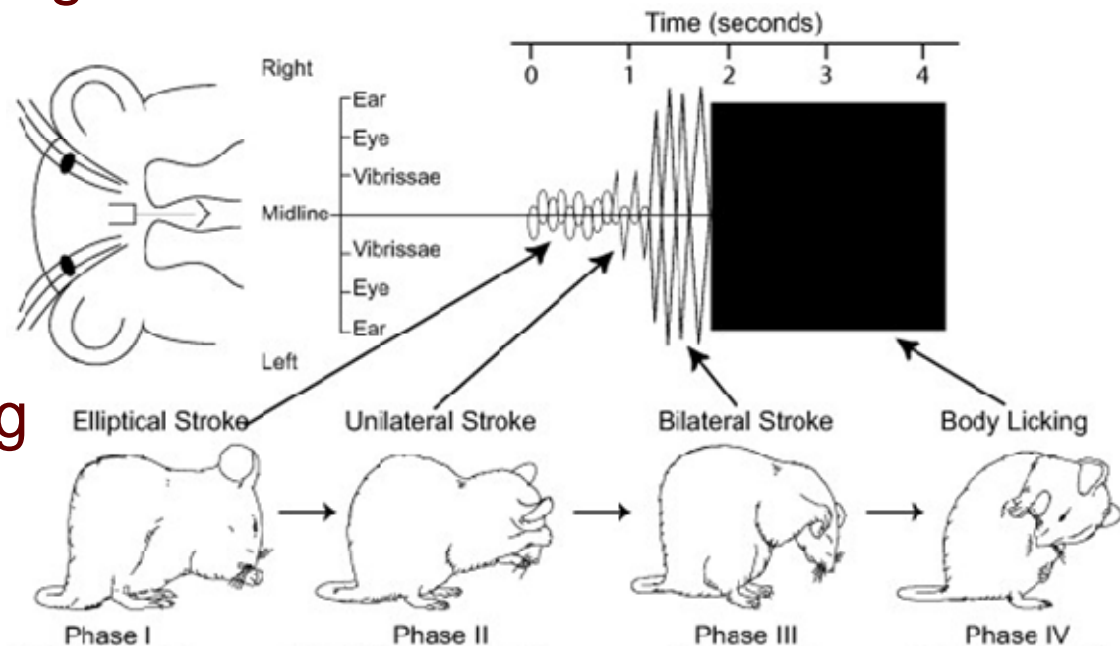

http://www.lsa.umich.edu/psych.html

http://www.instablogsimages.com/images/

Measurements

- Traditional scores: the "amount" of grooming
  - Latency
  - Duration
  - Frequency

- Complex patterning (microstructure)

Berridge et al. 2005

Grooming Analysis Algorithm
(Kalueff et al., 2000, 2005, 2007)

- Quantifies grooming behavior
  - Examines all grooming behaviors globally
  - Assesses adherence to the cephalo-caudal progression
  - Evaluates interruptions and regional distribution

- **Found that stress usually disorganizes grooming**
  - Disrupts cephalo-caudal patterning & regional distribution
  - Increases incorrect transitions
  - Increases number of incomplete & interrupted bouts

Kalueff et al. 2007

Grooming Patterning Measures

- Induce grooming through novelty or social stress
- Record pattern and transitions of each bout:
    - 0- No grooming
    - 1- Paw licking
    - 2- Nose/face/head washing
    - 3- Body grooming
    - 4- Leg licking
    - 5- Tail/genitals grooming

- Correct transitions: 0-1, 1-2, 2-3, 3-4, 4-5, 5-0
- Incorrect transitions: e.g., 2-5, 1-4, 3-2, 4-0
- Complete bout: 0-1-2-3-4-5-0

- Three main ethological measures:
    - % incorrect transitions (of total transitions)
    - % of interrupted bouts
   - % incomplete bouts

Kalueff et al., 2007

Example of stress-evoked alterations in grooming sequencing in rats (using GAA)
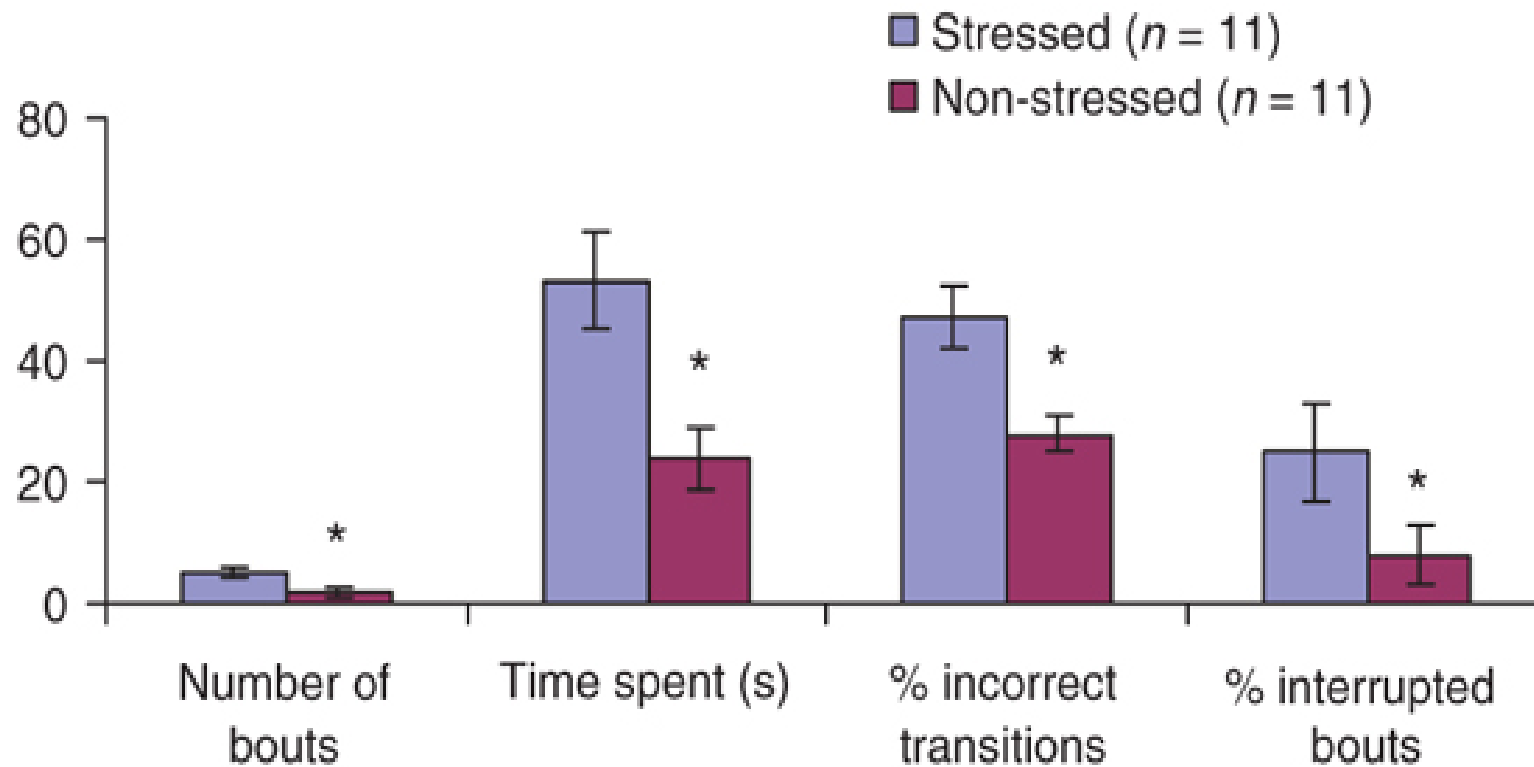
Rats have been stressed by exposure to a brightly illuminated novel environment for 5 min.

Kalueff et al., 2007

Regional Distribution of Grooming Patterns
# in Vitamin D Receptor Knock-out Mice

- Novelty-induced grooming: knockout mice displayed significantly higher percentages of forepaw, head and hind leg grooming, and less caudal grooming than wild type

- Artificial swim-induced grooming: no genotype differences between the groups

Novelty-induced (%)

Swim-induced (%)

Kalueff et al., 2005
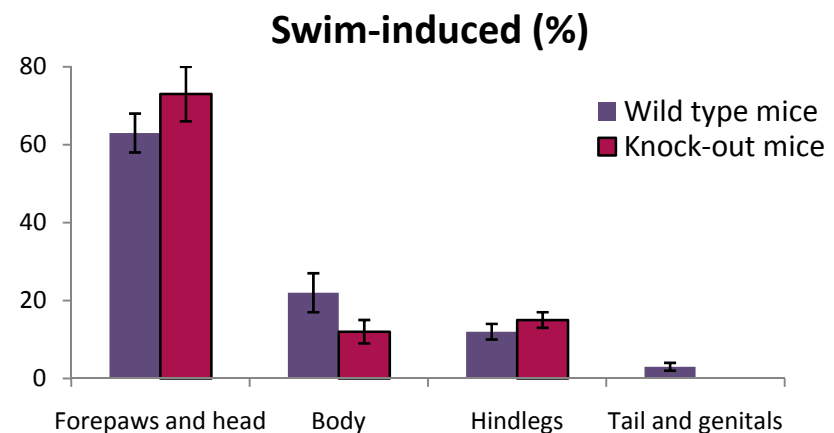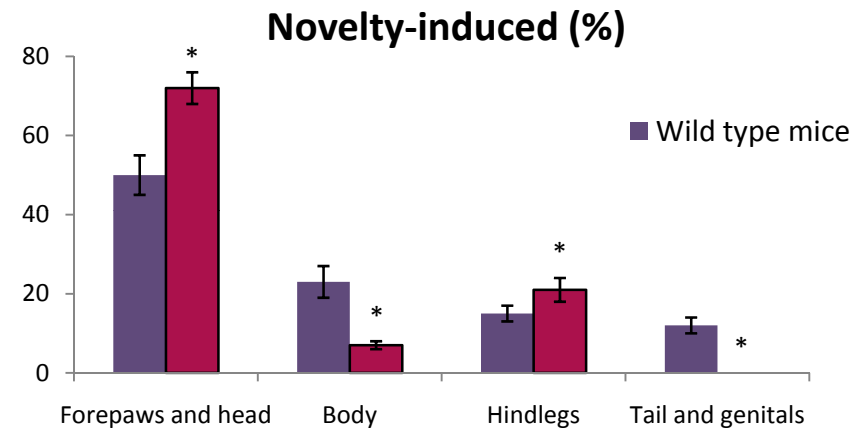
Sensitivity of Mouse Grooming Behaviors to Anxiolytic and Anxiogenic Drugs
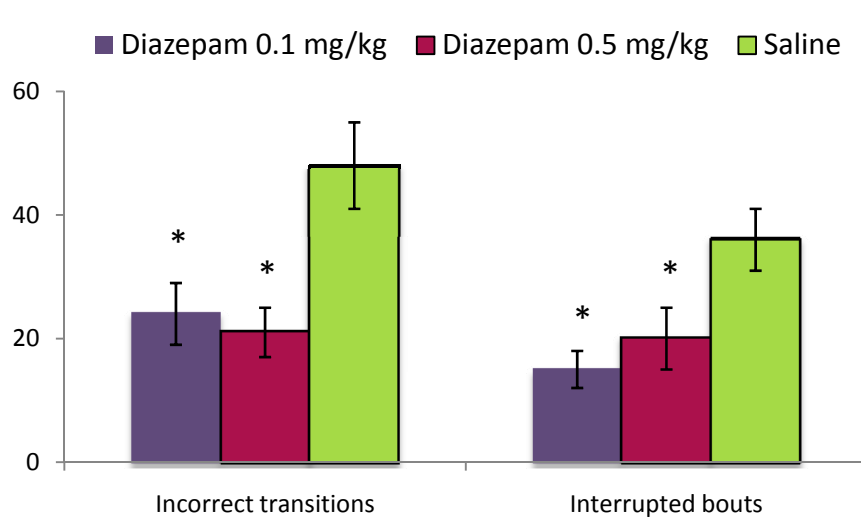
Anxiolytic diazepam lowers percentage of incorrect transitions and incorrect bouts
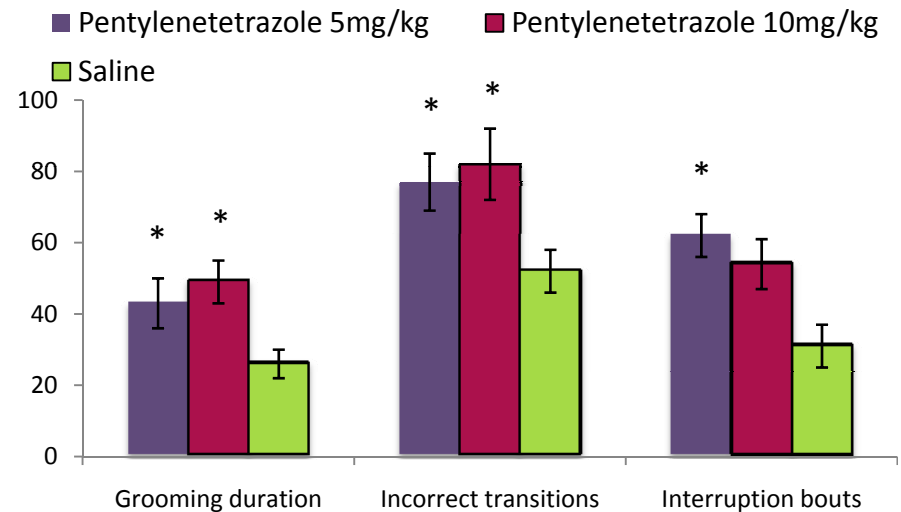
Anxiogenic pentylenetetrazole increases duration of grooming, with higher percentages of incorrect transitions and interrupted bouts

Kalueff et al., 2005

Pharmacological Uses

- Grooming microstructure in rodents is sensitive to acute anxiogenic, anxiolytic, antidepressant, and chronic anxiolytic drugs

Studies	Drug
Kalueff et al., 2005	Diazepam, Pentylenetetrazole
Audet et al., 2006	Phencyclidine
Enginar et al., 2007	Amitriptyline, Fluoxetine
Dronjak et al., 2007	Diazepam (chronic)

Application to Biological Psychiatry

- (**a**) Relevance to human brain/behavioral disorders

- (**b**) Activity-patterning plotting of grooming data and their relevance to corresponding disorders
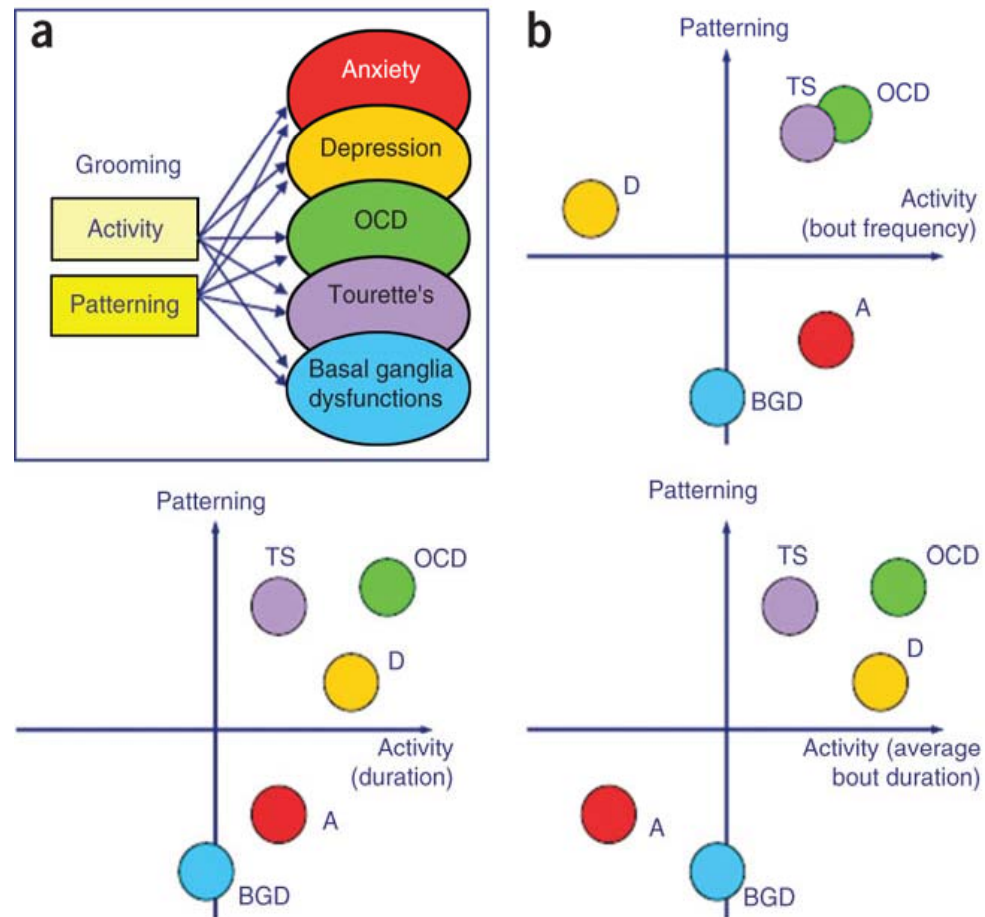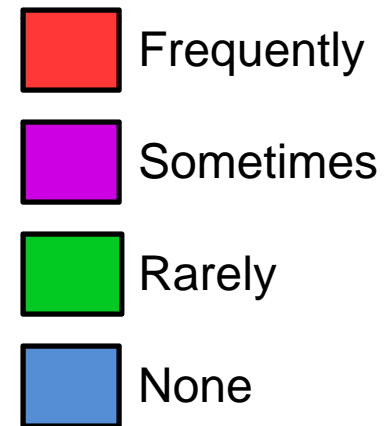
A-Anxiety; BGD-Basal Ganglia Dysfunction; D-Depression
OCD-Obsessive Compulsive Disorder; TS-Tourette's Syndrome

Animal Models of Psychiatric Disorders

	Macro-	Micro-
Anxiety	🟥	🟩
OCSD	🟪	🟥
Depression	🟥	🟦
Schizophrenia	🟥	🟦
Epilepsy	🟩	🟥
Serotonin Syndrome	🟪	🟥
Tourette's Syndrome	🟦	🟥
Rett Syndrome	🟦	🟥

Use

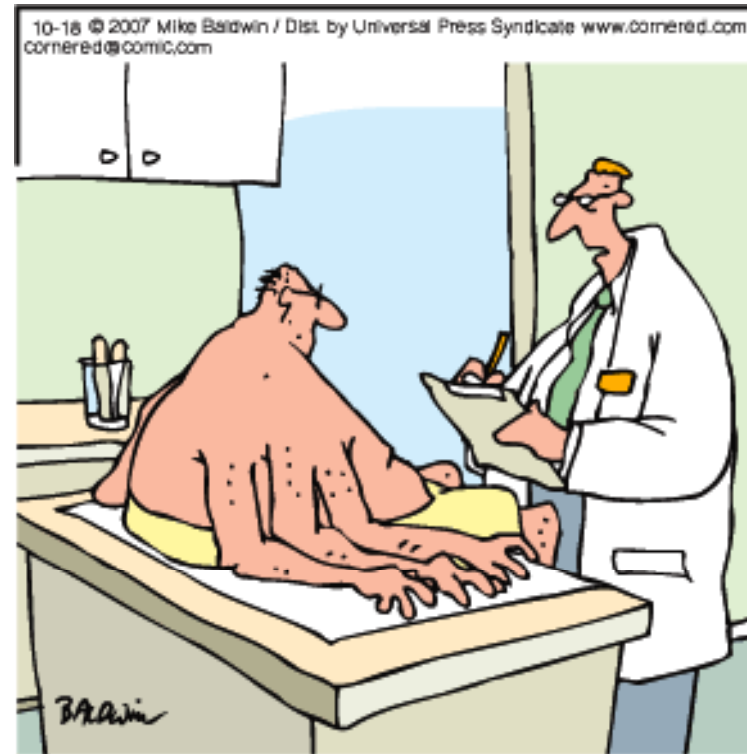🟥 Frequently

🟪 Sometimes

🟩 Rarely

🟦 None

Conclusions

- Micro-behavioral analyses are as important as macro-behavioral analyses

- These approaches are complementary, and will be able to generate high-throughput biological data

Acknowledgements

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cornered@comic.com

Sounds like an OCD. Normal people don't spend that much time washing their hands.

Thank You!