

Automated Multi-Dimensional Phenotyping of Mouse and Rat Models of Human Diseases

From PhenoMaster to PhenoWorld Cage Concept

Metabolic & Behavioral & Physiological & Social Phenotyping

November 13th, 2014

IMPC / Infrafrontier – Industry Liaison Meeting

Lars.Breuer@TSE-Systems.com

Outline

- **TSE Systems – European Projects**
- **PhenoMaster**
Concept – Technology – Metabolism – Behavior
- **IntelliCage**
- **PhenoWorld Concept & Examples**
- **PhenoTower**
- **Stellar – Innovative Telemetry**
- **PhenoWorld Projects 2014**

TSE Systems

- **Complete solutions in hardware & software** for in-vivo research
- Very different hardware technologies applied
- Coverage of broad variety of established paradigms
- **Certified quality** / German engineering
- Worldwide Scientific Network
- **Premium Service incl. worldwide 24/7 Technical Hotline**
- Leading manufacturer in Europe
- Founded in 1886 (**>125 years**)

EU Project: **RATstream™** (2007 - 2010)

European project on the characterization of **transgenic rat models** for **neurodegenerative and psychiatric diseases**:

Automated home cage analyses, live imaging and treatment

TSE & NewBehavior = Technology Partners

PhenoMaster & IntelliCage for Rats

www.RATstream.eu
www.PhenoMaster.com

EU Project: **PhenoScale** (2009 - 2012)

**TSE Systems is proud to be the technological partner within the
EU Project PhenoScale**

Development of a **new high-throughput automated phenotyping** platform using home cage monitoring; establishing Standard Operation Procedures for the **phenotyping of mouse models** at different phenotyping centers.

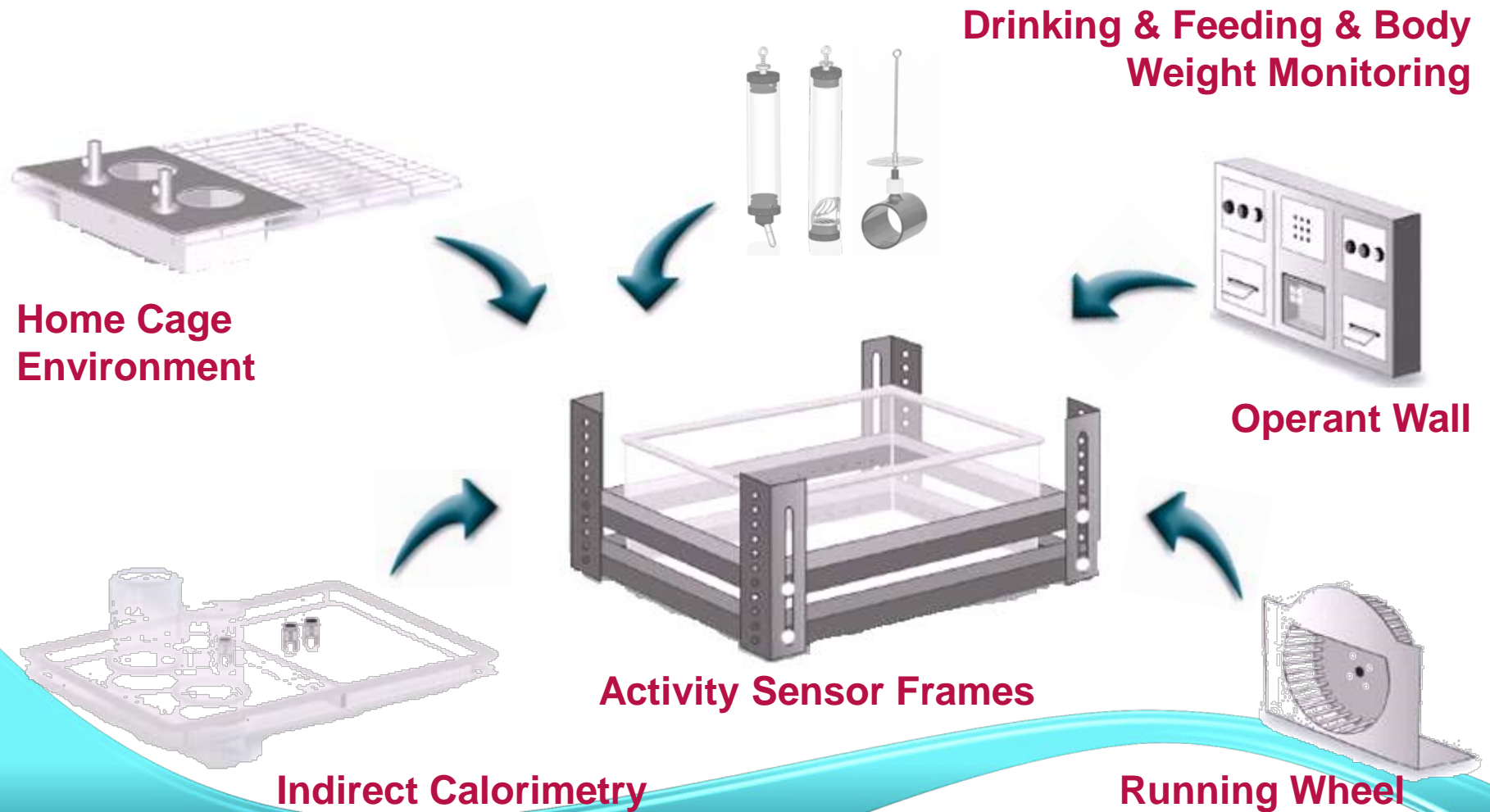
Scientific Partners:

- MRC Harwell, UK (Coordinator)
- German Mouse Clinic, GMC, Munich, GER
- Italian Institute of Technology, IIT, Genova, IT
- Institute of Cell Biology, IBC, Monterotondo, IT



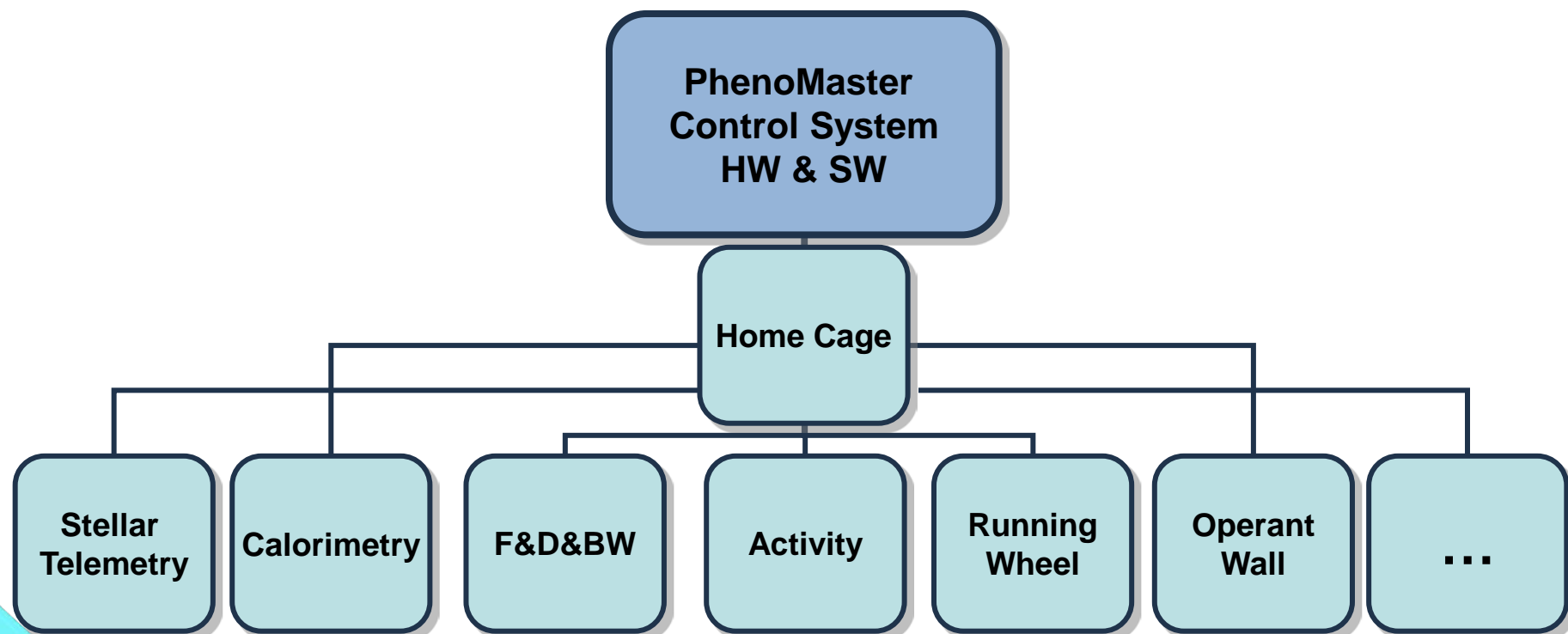
PhenoMaster
Automated Home Cage Battery
for Mice / Rats
Metabolism & Behavior & Physiology

PhenoMaster – Modular Concept

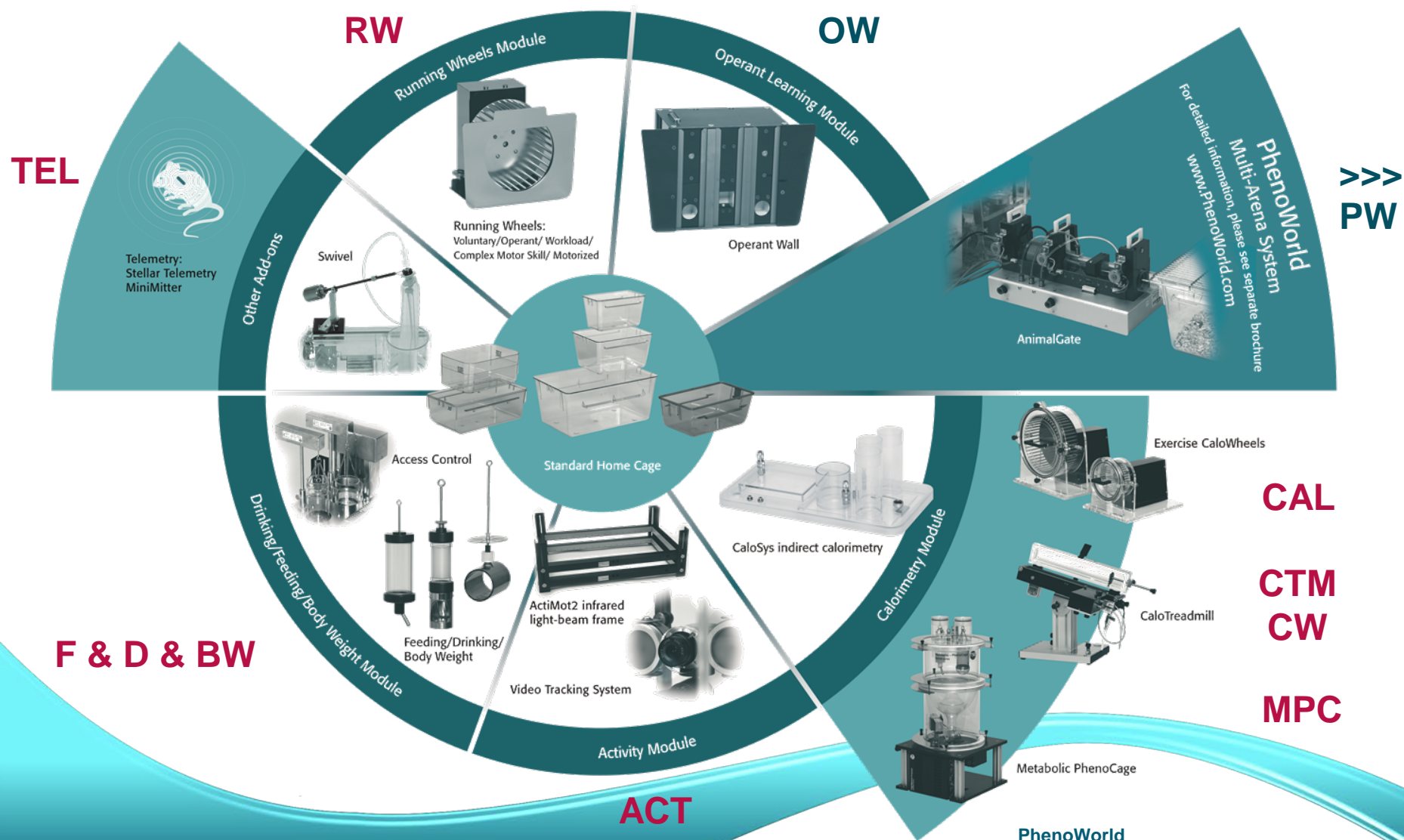


PhenoMaster – OPEN System Structure

(Hardware & Software – many Home Cages in parallel)



PhenoMaster – Modules (Metabolic)



PhenoMaster – Combinable Modules / Functions

Behavior

- **Food & Liquid** Intake Monitoring
- Food / Liquid Access (Operant) Control
- Automated Body Weight Monitoring
- Home Cage **Activity XYZ**
- **Running Wheel** Activity
(Voluntary, Operant Control, Forced)
- **Operant Wall** (Learning & Memory)
- **NeuroLogger** (4*EEG, Act)

Metabolism

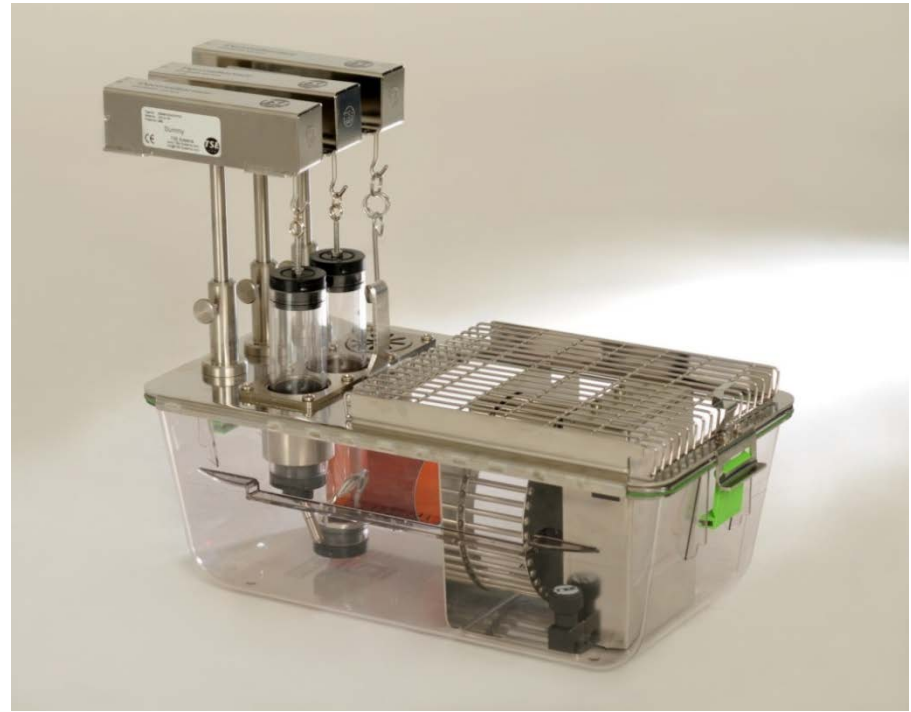
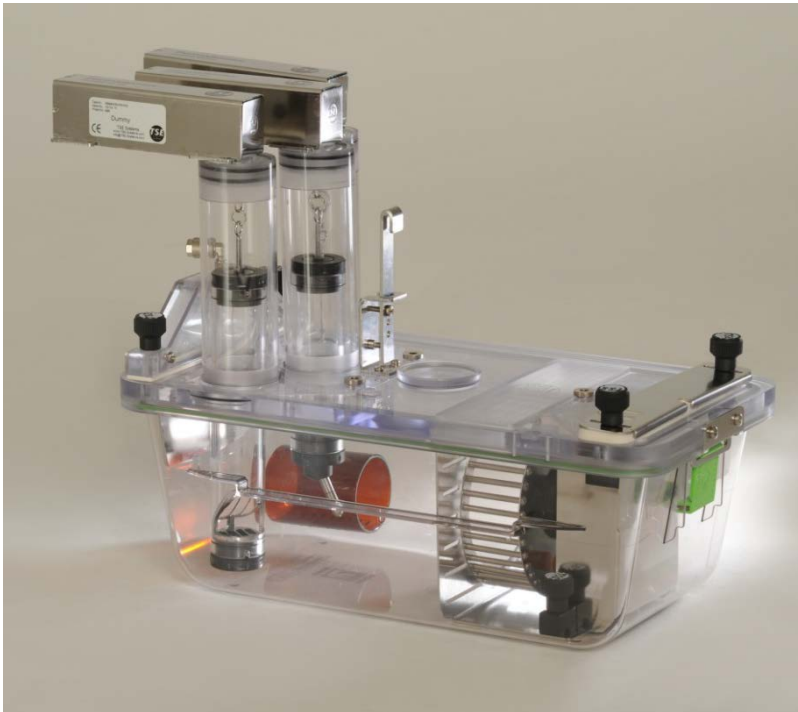
- **Metabolic Performance** by Indirect Gas **Calorimetry** – CaloSys (Continuous)
- **CaloTreadmill** / **CaloWheel** for Exercise Calorimetry
- Metabolic PhenoCages – **Urine & Feces** Separation & Quantification

Physiology

- **Telemetry:** Stellar / Mini Mitter
BP, ECG, HR, T

Mouse Cages “Tecniplast Greenline IVC”: Standard “GL”

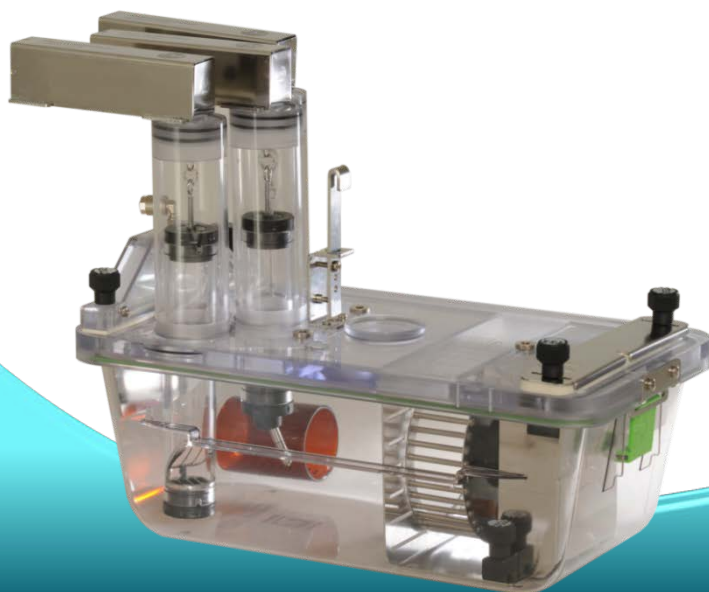
- METABOLISM: CaloCages “GL”
- BEHAVIOR: Open Wires Lid Cages “GL”

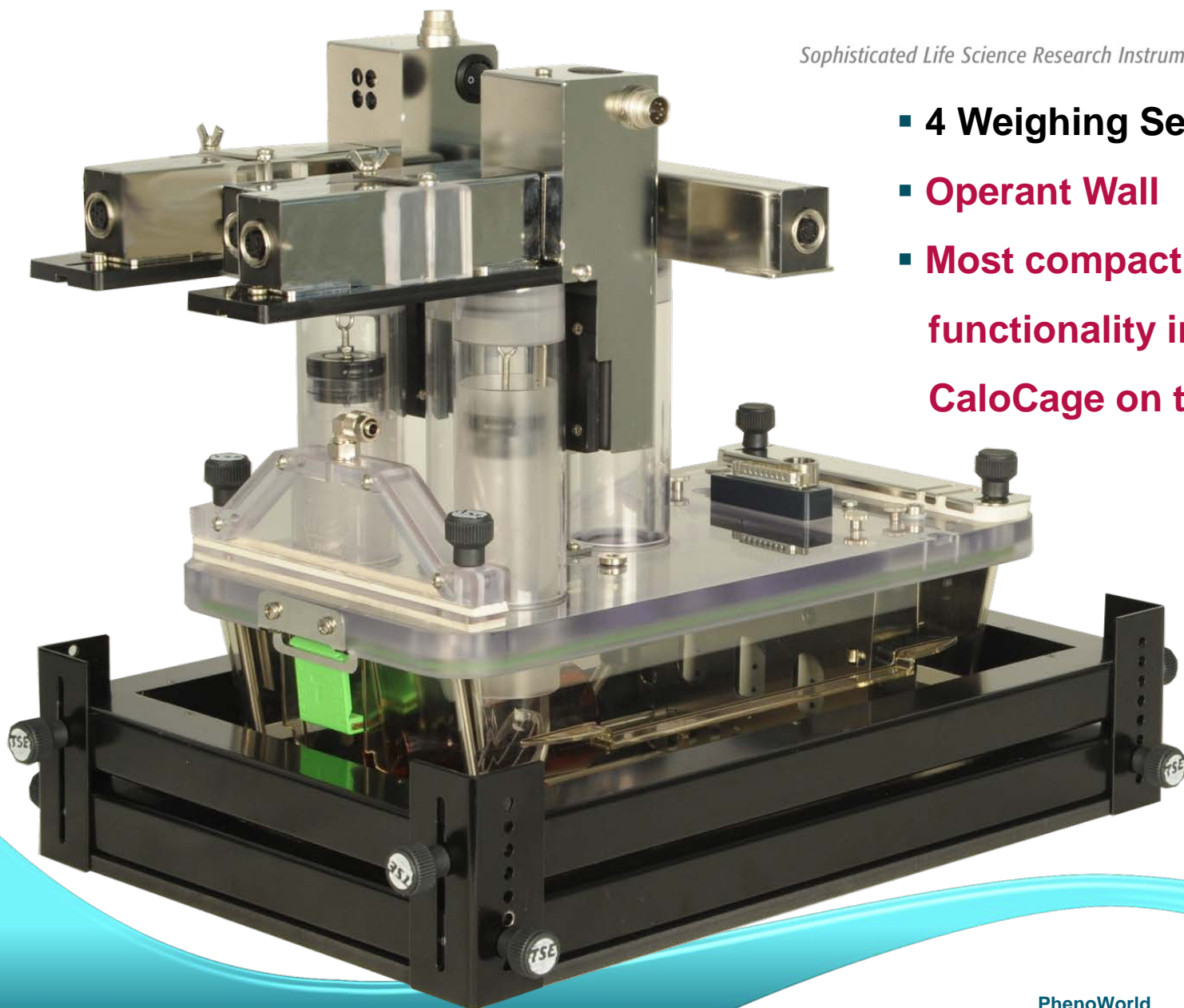


PhenoMaster – Calorimetry Module

CaloSys / CaloCages

- Small volumes - suited for mice/rats
- Indirect Calorimetry
 - ⇒ O₂ & CO₂ concentration measurements
 - ⇒ VO₂ Consumption, VCO₂ Production
 - ⇒ RER (Respiratory Exchange Ratio)
- BUT :**
- Reasonable dimensions for **Activity**
- Maximum functionalities (**Add-Ins**)
 - Add-In: **D & F & BW (4 Sensors, 3*AC)**
 - Add-In: Modular **Running Wheel**
 - Add-In: Modular **Operant Wall**
 - Add-In: Calo **IntelliCage Corner**
 - Add-In: **Swivel Technologies**



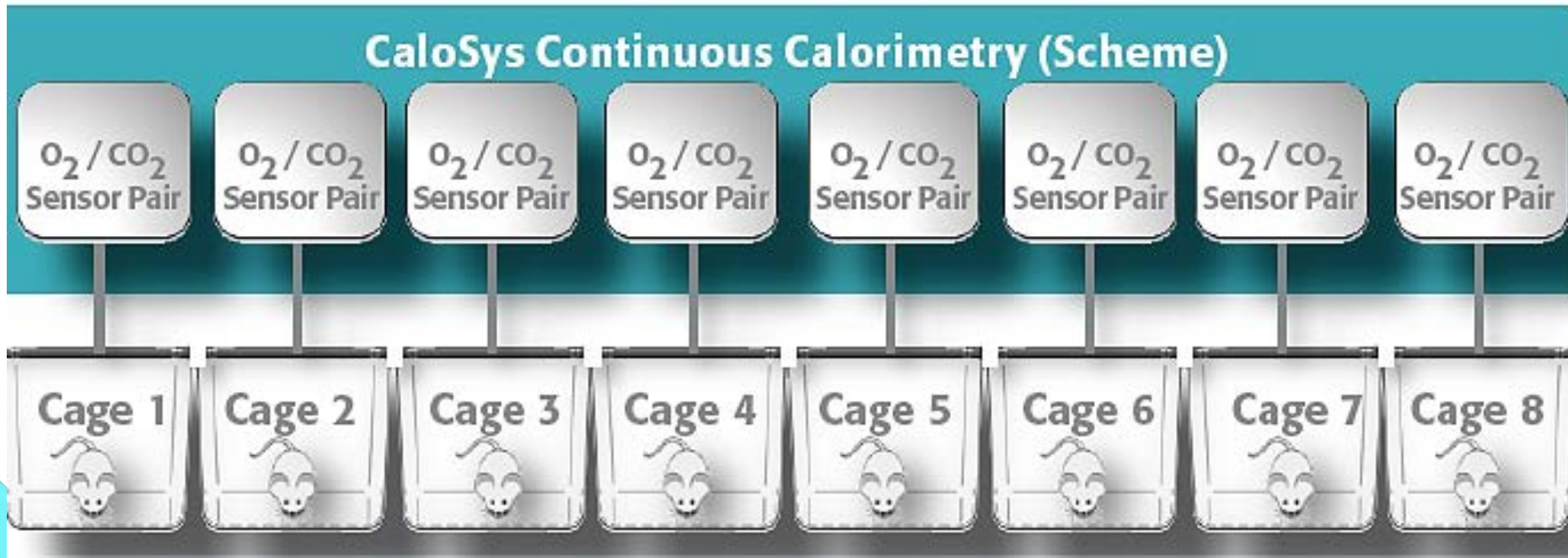


- **4 Weighing Sensors**
- **Operant Wall**
- **Most compact and rich functionality inside Mouse CaloCage on the market**

PhenoMaster – CaloSys Continuous

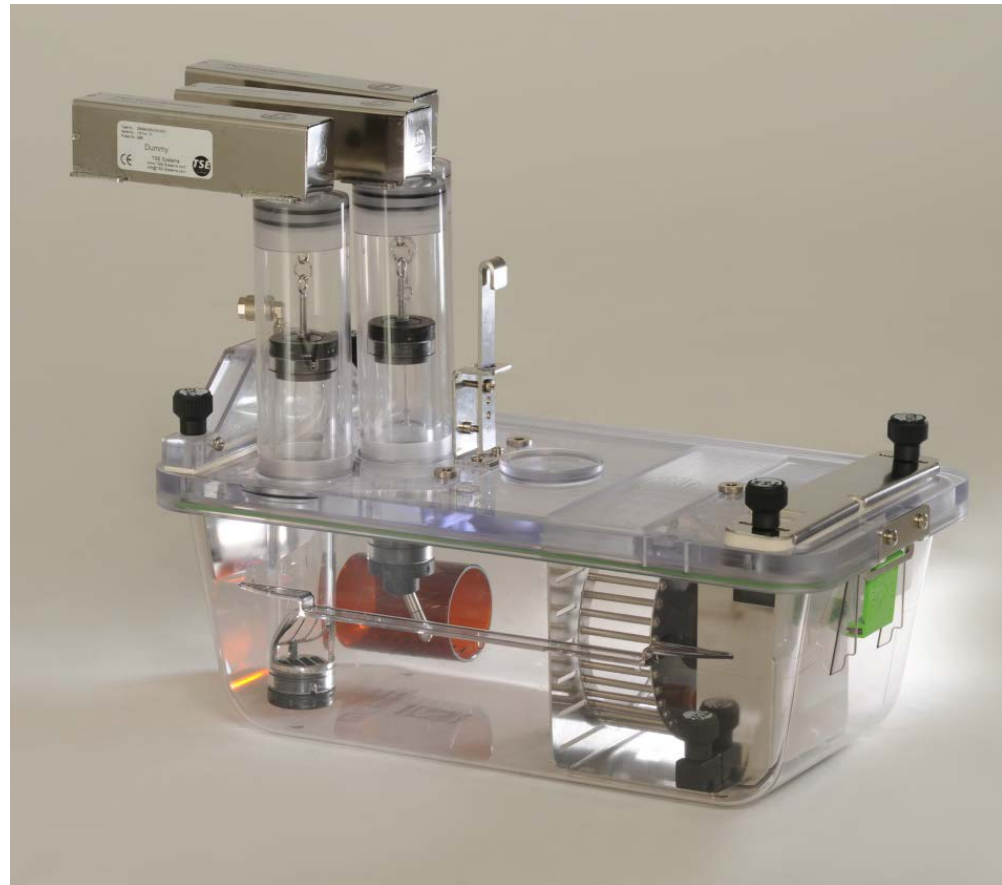
IDEALLY: For each animal ONE (O_2 & CO_2) Sensor Pair

>>> measurement samples each second for ALL animals in parallel – if wanted

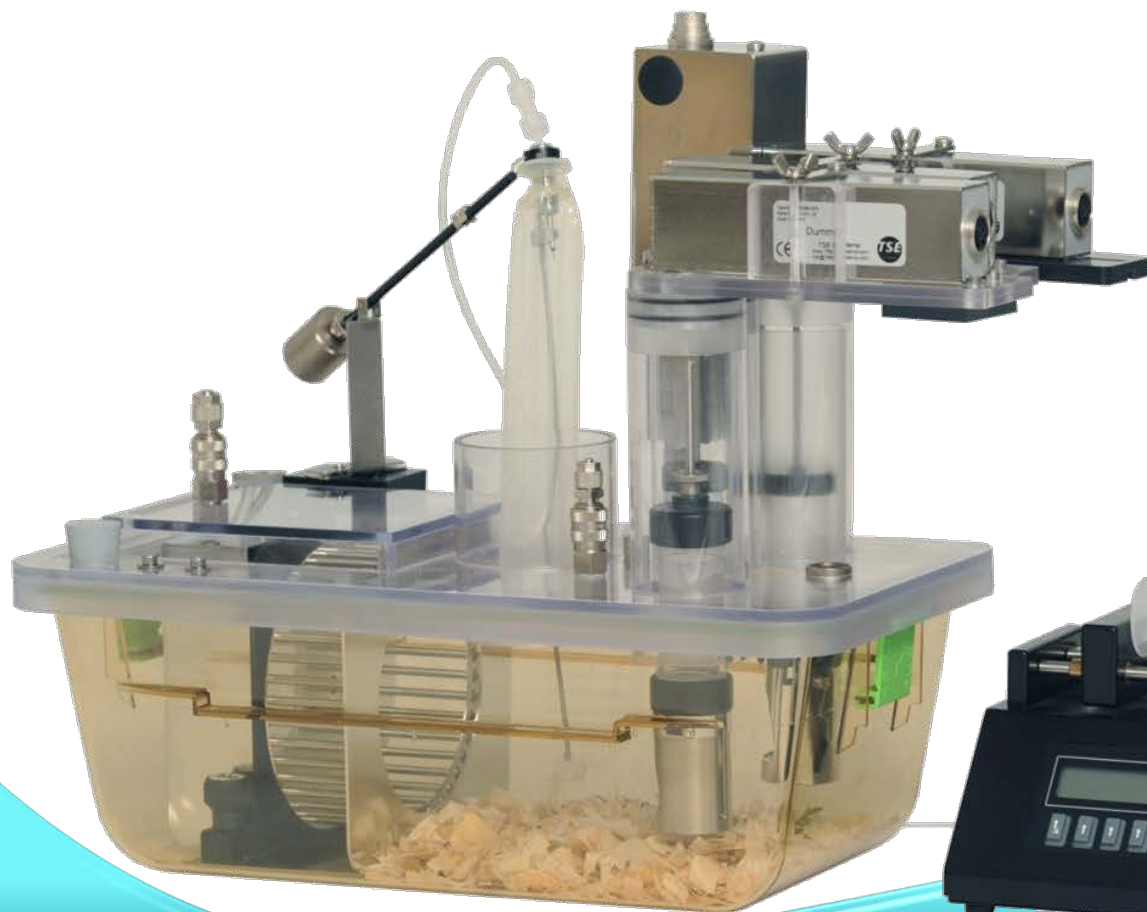


CaloCage with integrated Voluntary Running Wheel:

- Enabled / Disabled (Time & Distance Control on Running)
- Workload Control
- Paired Running
- Operant Control
- Running for Food
- Running for Liquid
- ...



PhenoMaster – Swivel Applications with Operant Control



- Automated Infusion by Syringe Pump
- Optogenetics
- Blood Sampling
- Microdialysis
- Electrophysiology
- Electrostimulation
- ...



PhenoWorld

ORIGINAL ARTICLE

Dietary triglycerides act on mesolimbic structures to regulate

the rewarding and motivational aspects of feeding

C Cansell¹, J Castel¹, RGP Denis¹, C Rouch¹, A-S Delbes¹, S Martinez¹, D Mestivier², B Finan³, JG Maldonado-Aviles⁴, M Rijnsburger⁵,

MH Tschöp^{3,6}, RJ DiLeone⁴, RH Eckel⁷, SE la Fleur⁵, C Magnan¹, TS Hnasko⁸ and S Luquet¹

Circulating triglycerides (TGs) normally increase after a meal but are altered in pathophysiological conditions, such as obesity.

Although TG metabolism in the brain remains poorly understood, several brain structures express enzymes that process TG-enriched

particles, including mesolimbic structures. For this reason, and because consumption of high-fat diet alters dopamine signaling, we tested the hypothesis that TG might directly target mesolimbic reward circuits to control reward-seeking behaviors.

PhenoMaster – Metabolism & Optogenetics (UNIQUE)

Sophisticated Life Science Research Instrumentation



- CaloCage Mouse:**
- Swivel Integration for**
- **Optogenetics**
 - **Automated Infusion**
 - **Blood Sampling**
 - **Microdialysis**
 - **Electrophysiology**
 - **Electrostimulation**
 - ...



PhenoWorld

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PhenoMaster – Metabolism & Cognition (UNIQUE)

Sophisticated Life Science Research Instrumentation



CaloCage Mouse:

- Indirect Calorimetry
- **Operant Wall** (Liquid Reward)
- Automated Liquid Restriction by Access Control



PhenoWorld

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PhenoMaster

Metabolism – Exercise Calorimetry

Dedicated Equipment – Temporary Experiments

PhenoMaster – CaloTreadmill Mouse



- PC Control
- Sealed housing – connected to Calorimetry CaloSys
- Speed profile editor
- Light-beam detection
- Electric shocker
- Mechanical pushing device



PhenoWorld

PhenoMaster – Metabolic PhenoCages

- Separation of urine & feces
- Quantification of urine & feces – weighing technology
- Monitoring of urine & feces by amount & time
- Urine freezing unit
- Feeding & drinking Monitoring
- Sealed construction – indirect calorimetry
- Activity monitoring
- Mouse: Special construction from glass
- For mouse / rat – different sizes



PhenoWorld

Metabolic PhenoCages



Urine Freezing Unit

PhenoWorld

Metabolic PhenoCages



**Urine:
Weighing &
Freezing Unit**



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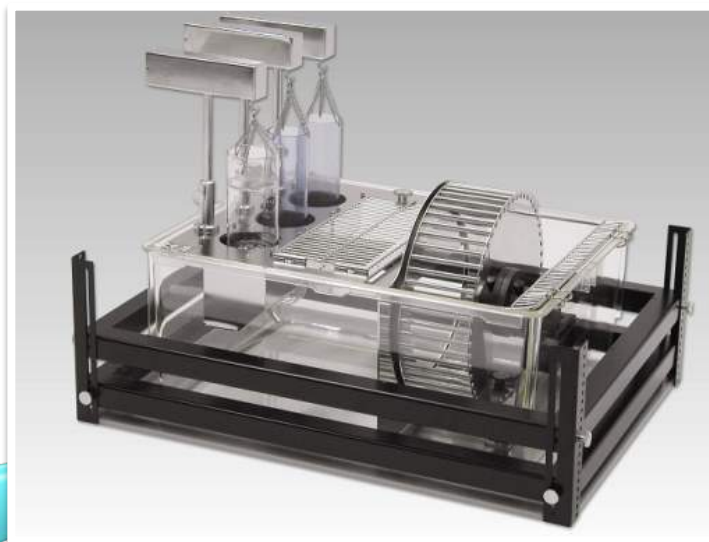
PhenoMaster

Modular Running Wheels

PhenoMaster – Modular Operant Running Wheels

Voluntary / Passive Wheel (software controlled)

- Registration of revolutions (90°)
- Left / Right Turns
- Enabled / Disabled Function
- Time Control
- Distance Control
- Workload Control
- Operant Control



PhenoMaster

Operant Walls – Learning & Memory

PhenoMaster – Cognition: Operant Wall (Mice or Rats)

- Learning & Memory acc. to Skinner
- Variety of operant behavioral tasks within home cage environment
- **Fully automated Operant Conditioning experiments**
- Feeding / Drinking with access control >>>
Automated food / liquid deprivation
- Pellets / liquid as rewards
- **Wheel running as reward**



PhenoWorld

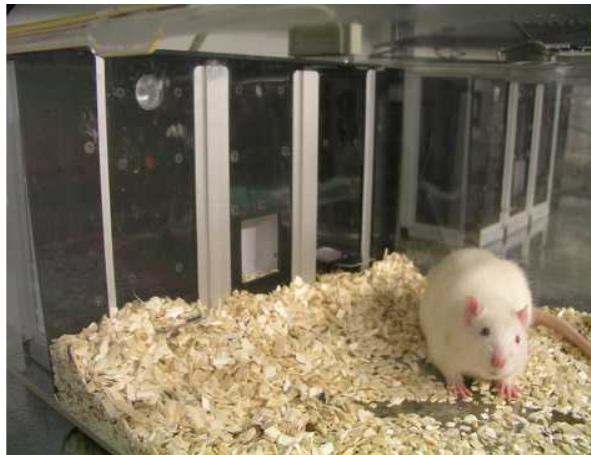
PhenoMaster – Cognition: Operant Wall Rat / Mouse

Operant Wall Rat with:

- 2 Stimulus lights
- 2 Levers (retractable)
- 1 Pellet dispenser (reward, centrally)
- House light

PhenoCage with (example):

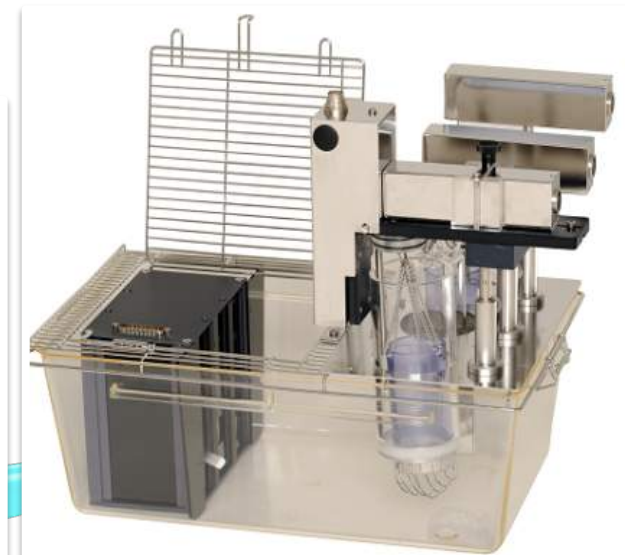
- Feeding with food access control
- Automated food deprivation



Rat



Mouse

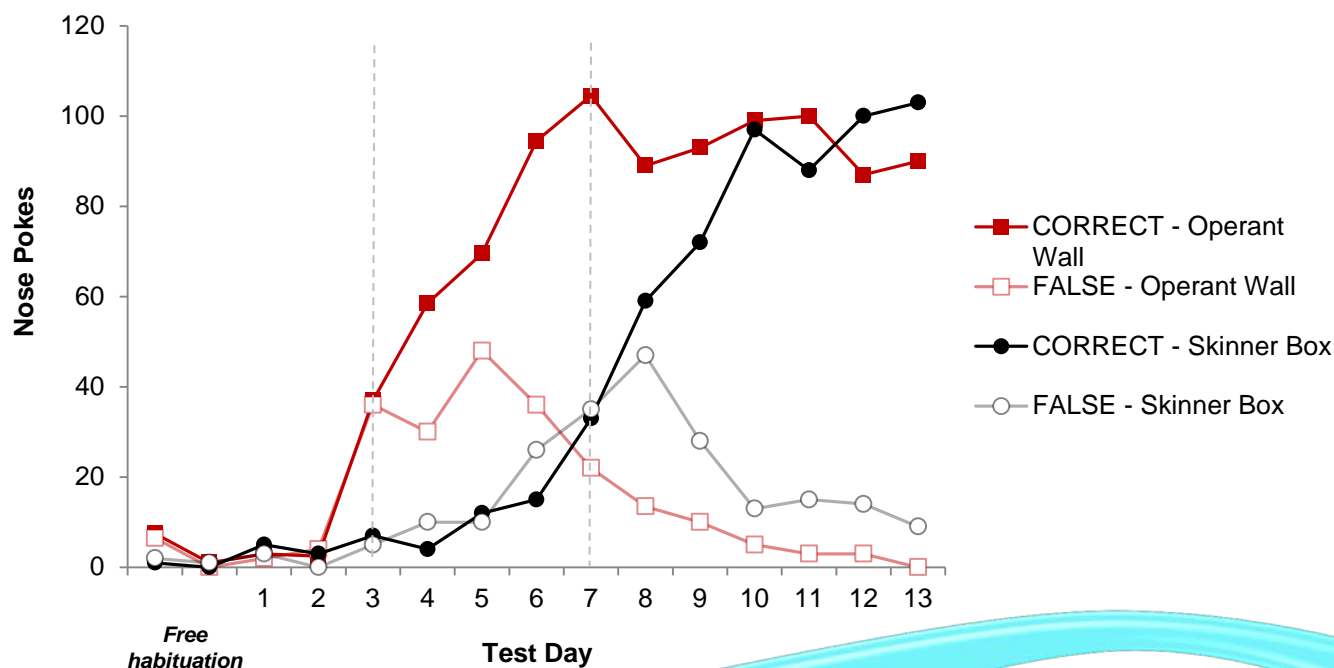


PhenoWorld

PhenoMaster – Cognition: Operant Wall (Mice or Rats)

- Variety of operant behavioral tasks within home cage environment
- Fully automated Operant Conditioning experiments

Operant Response Learning



PhenoMaster – High-Throughput (e.g. 64 Cages) Dedicated Racks with easy-to-handle lid fixation



PhenoWorld

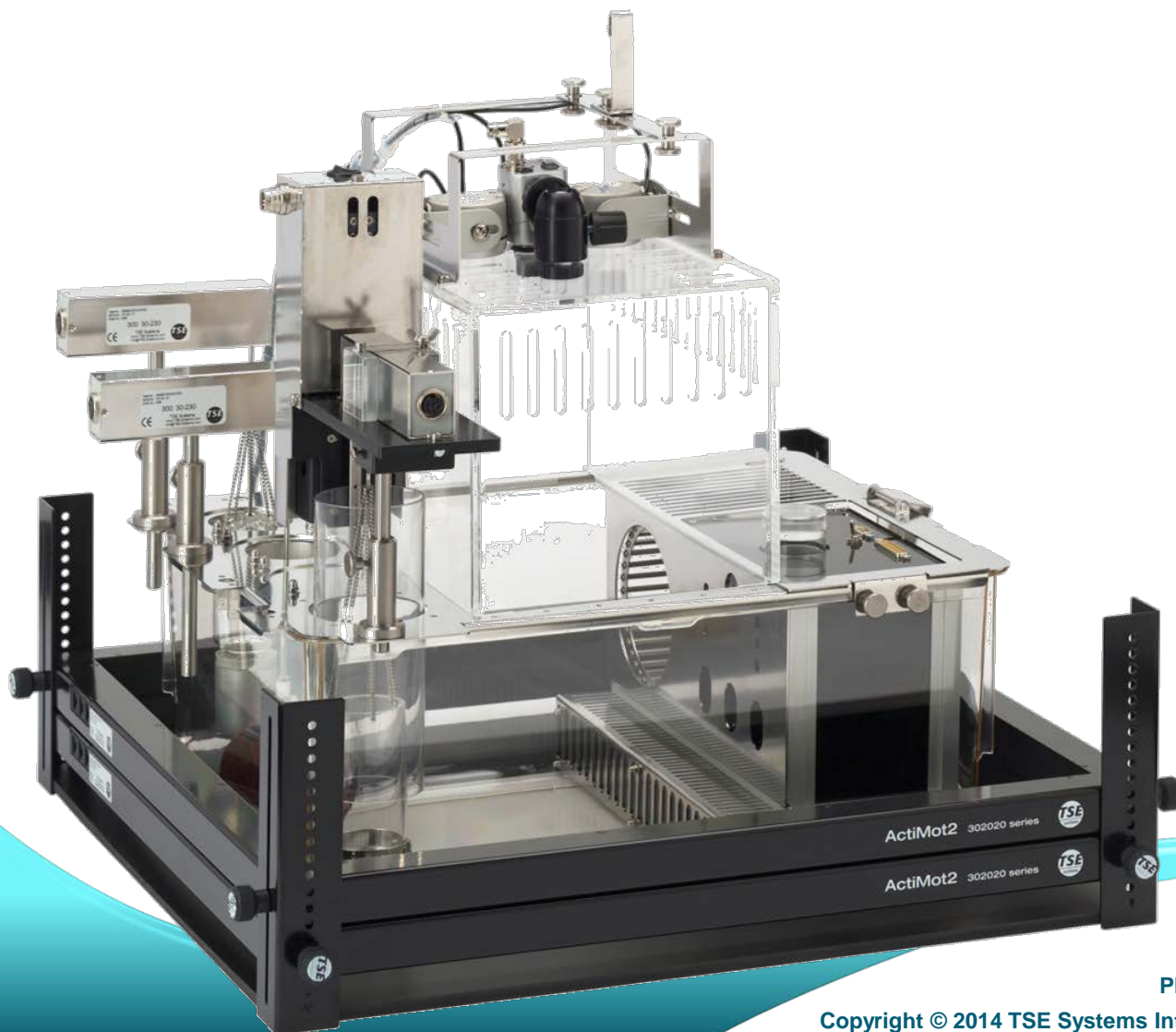
PhenoMaster – Metabolism: **Climate Chambers**

Thermoneutrality / Temperature Challenges

Light-Control



PhenoMaster „Mouse Studio Behavior & Physiology“

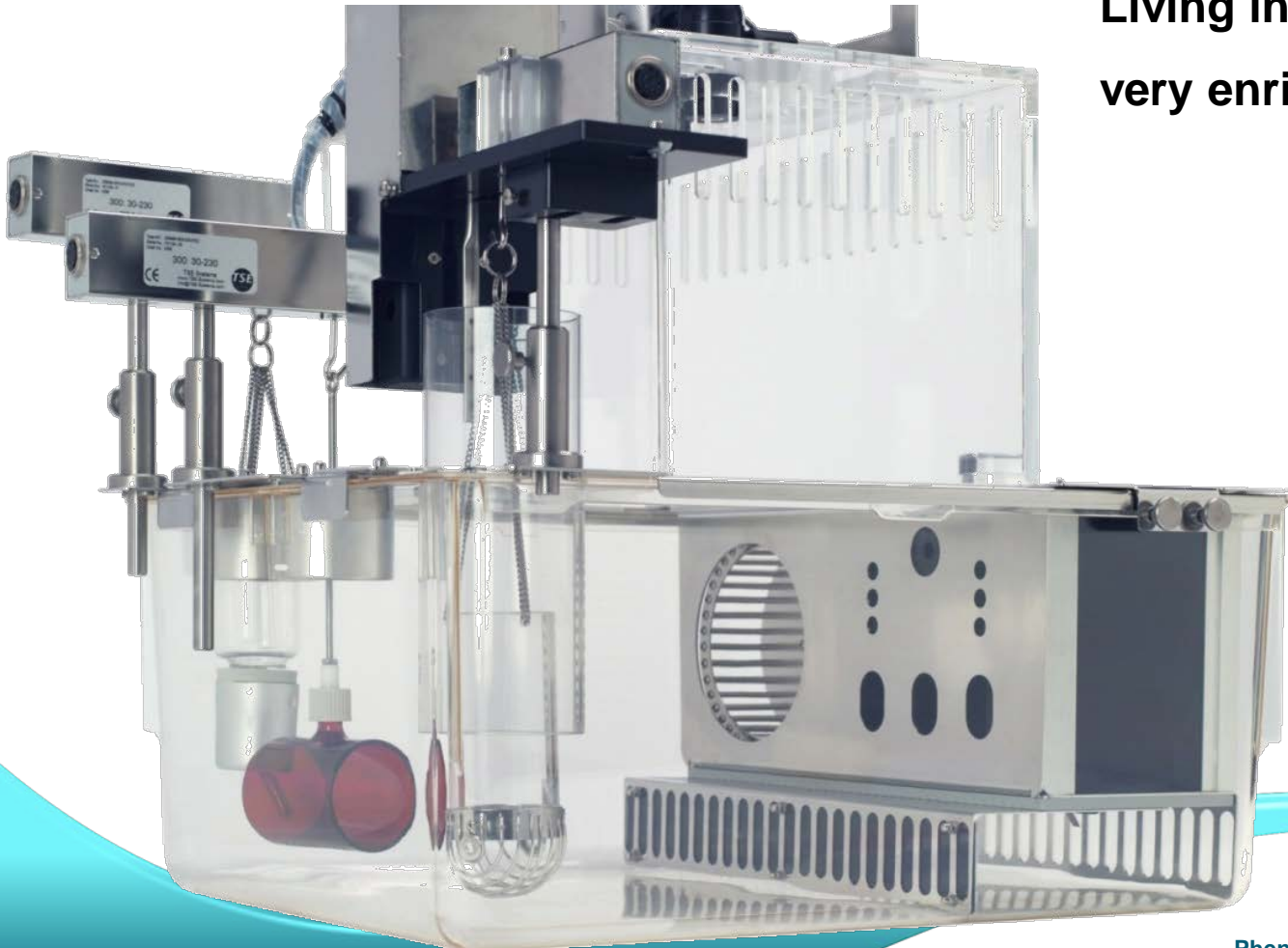


PhenoWorld

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PhenoMaster „Mouse Studio Behavior & Physiology“

Living in a functionally
very enriched environment

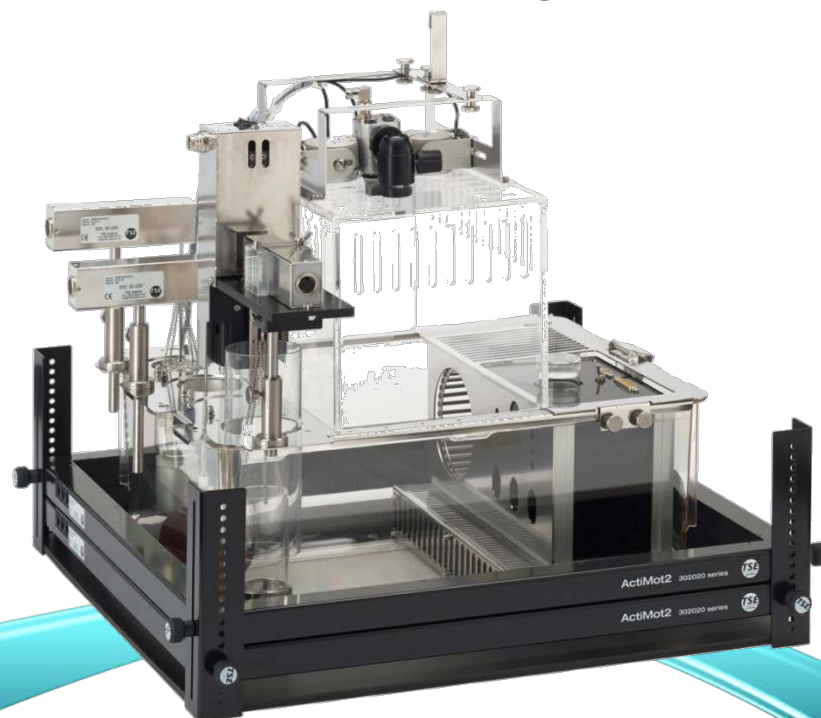


PhenoWorld

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PhenoMaster – Behavioral PhenoCage for Rodents

- Activity XYZ & IR Video
- Drinking & Feeding Monitoring up to 4-fold
- Liquid Choice & Access Control to Food
- Learning & Memory: by Operant Wall
- Fully Automated Operant Conditioning
- Automated Food / Liquid Deprivation
- Variety of Operant Behavioral Tasks
- Rewards: Pellets / Liquid / Wheel
- Anxiety “Vogel Test” Paradigm
- Fine Movements (from IR Video Tracking)
- Telemetry (BP&ECG&T)
- NeuroLogger (4*EEG&Act)
- Openings for AnimalGates
- Swivel Technologies



PhenoWorld

PhenoMaster – Video !

IntelliCage for Mice / Rats

Automated Cognitive Screening with Social Interaction

IntelliCage

A unique solution for automated monitoring of animal cognitive behavior in **social groups**

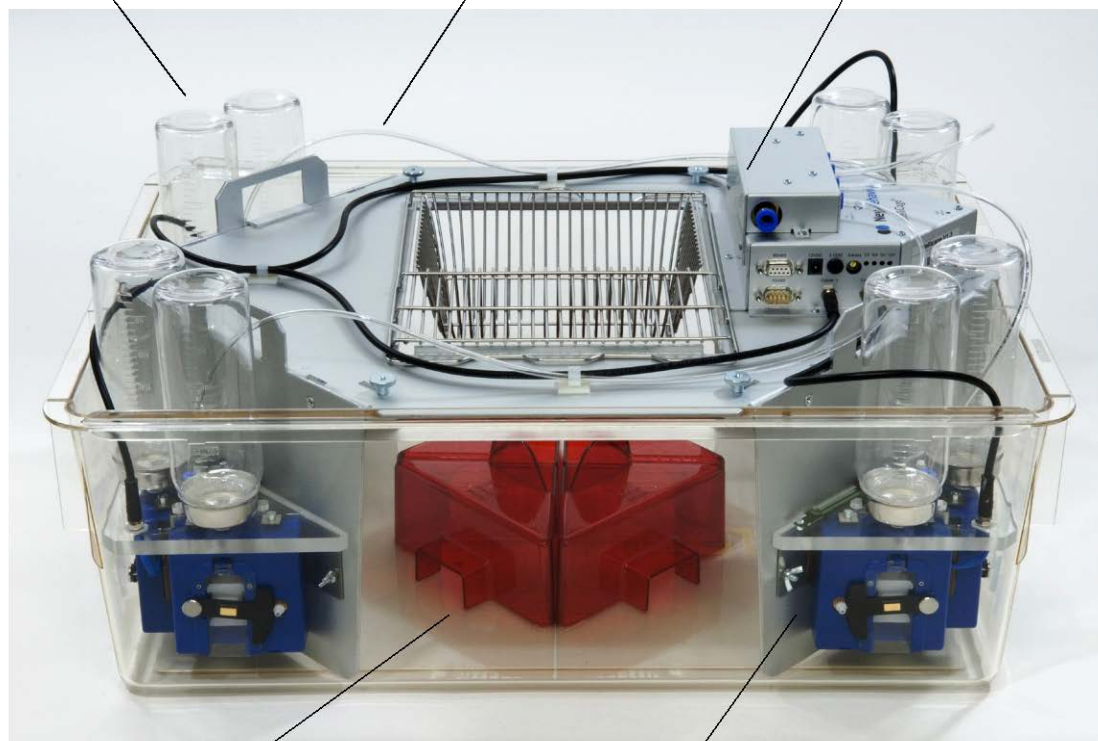
- Home cage approach, **group of transponderized animals**
- Continuously: **16 mice at the same time in ONE cage**
- To be run even with **two groups of each 8 mice** together
- **Animals not stressed**, fully automated behavioral testing
- Long-term data collection possible 24h/7d/weeks
- Combination of **spatial learning tasks and operant conditioning**
- Several paradigms subsequently without removal of animals
- **High throughput**: 8 IntelliCages at one PC (128 mice)

IntelliCage Mice – Overview

liquid bottles

air-puff tubing

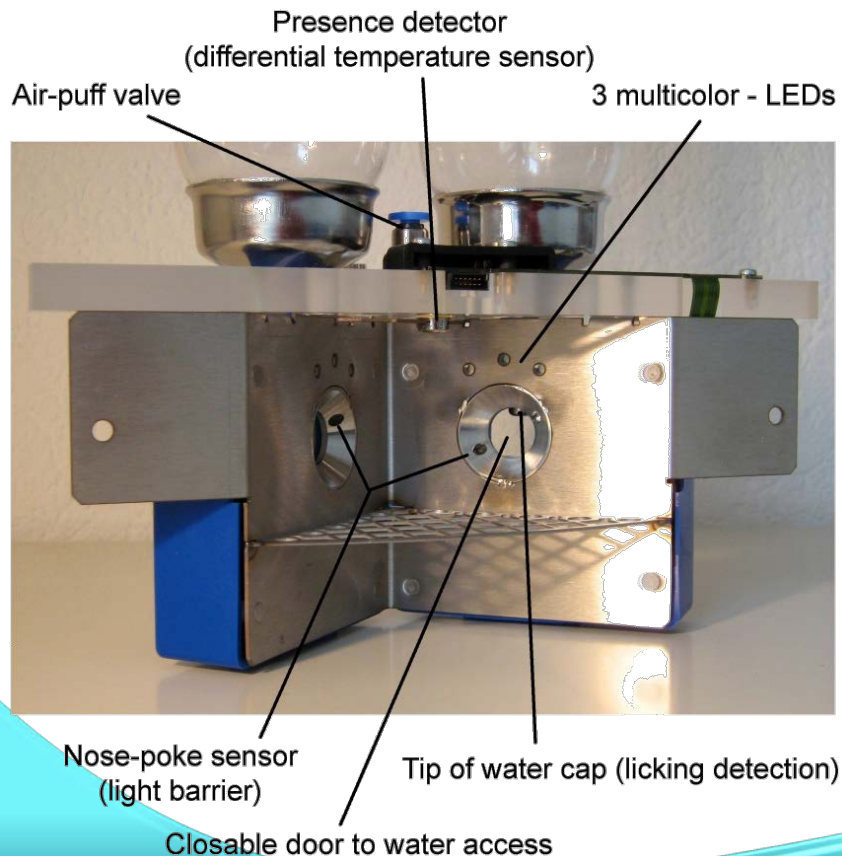
microprocessor



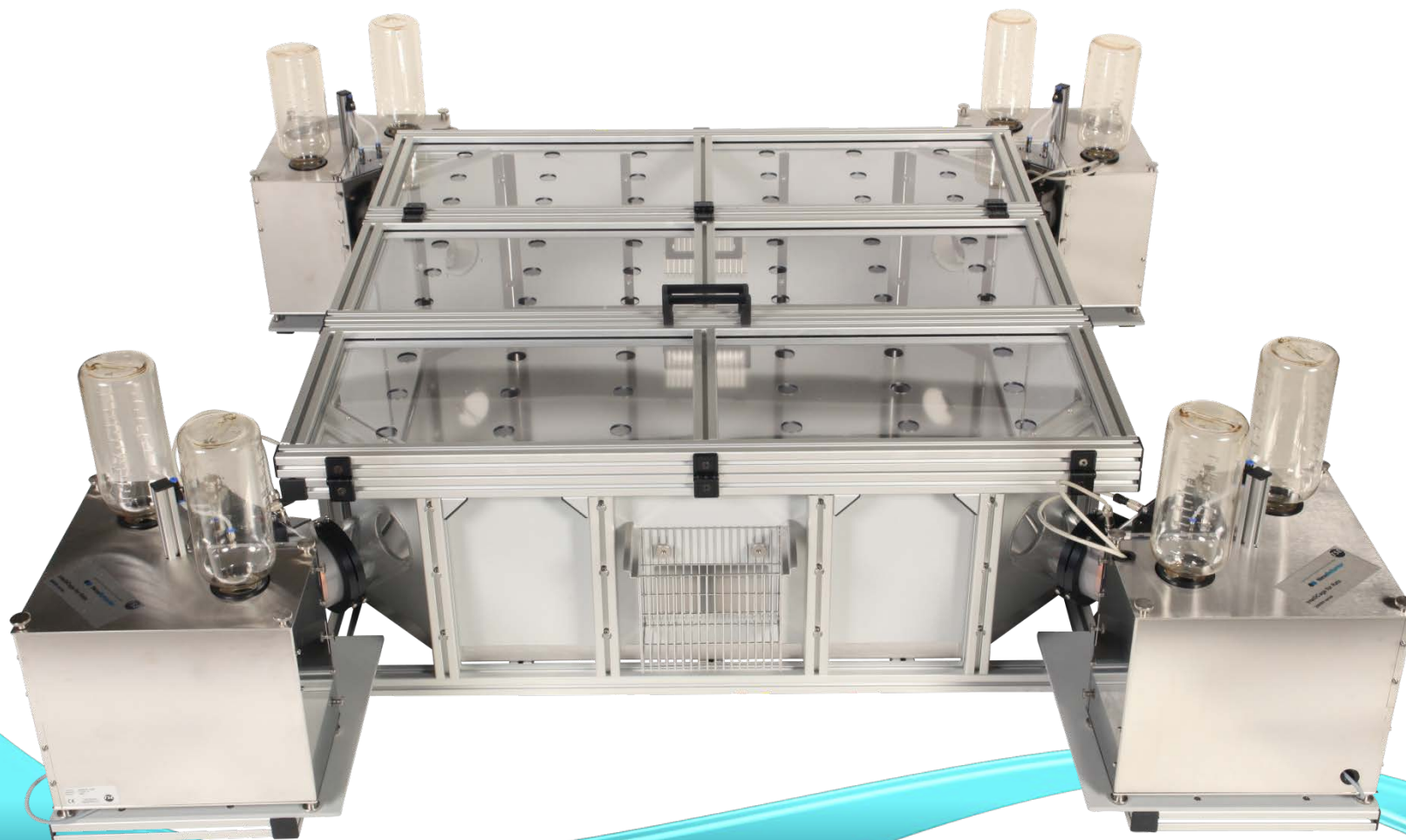
mouse houses

4 learning corners with dual liquid reward

IntelliCage Mice – 4 Operant conditioning corners



IntelliCage Rats – 4 Operant conditioning corners



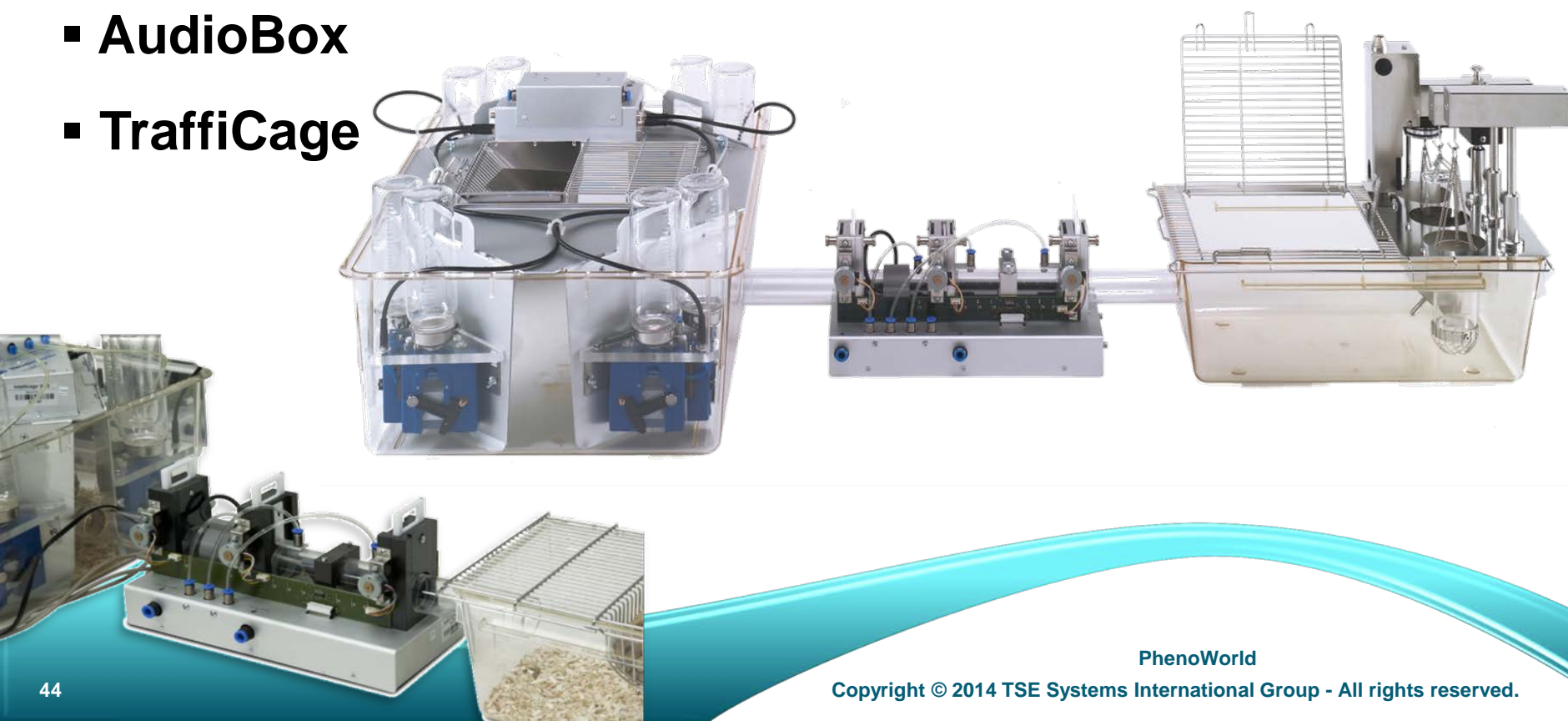
IntelliCage – Main benefits

- high level of standardization
- high level of accuracy
- minimal level of stress
- minimal supervision by experimenter
- increased efficiency and throughput
- high animal welfare
- reduction of routine work for technicians and scientists
- Multitude of different paradigms with only ONE system

IntelliCage – Video !

IntelliCage – Add-Ons:

- AnimalGate >>> PhenoCages etc.
- SocialBox
- AudioBox
- TraffiCage



PhenoWorld

Multi-Arena Combinatorial Approach

**A unique system approach
to equip connected home cages / test compartments / environments with
a variety of distributed functional modules**

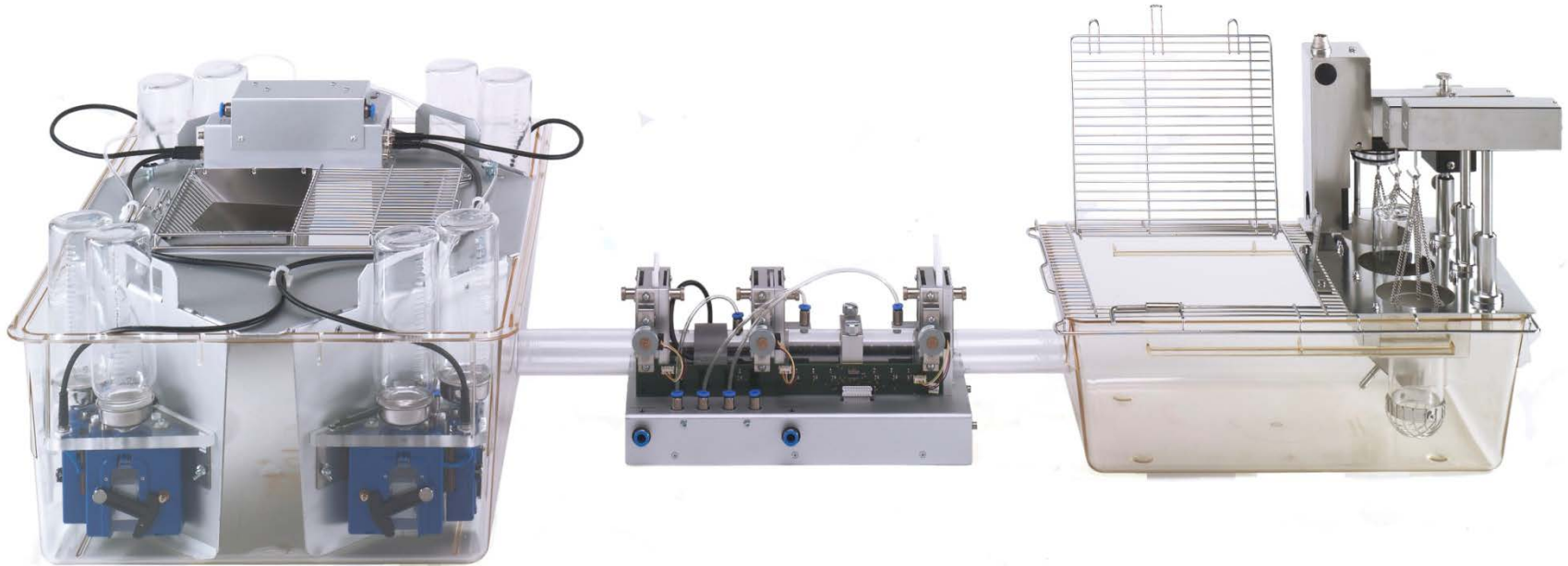
**Automated Multi-Arena In-vivo Analysis
of Rodents
Including Social Interaction**

PhenoWorld – Multi-Arena Combinatorial Approach

Selected Hardware Components from

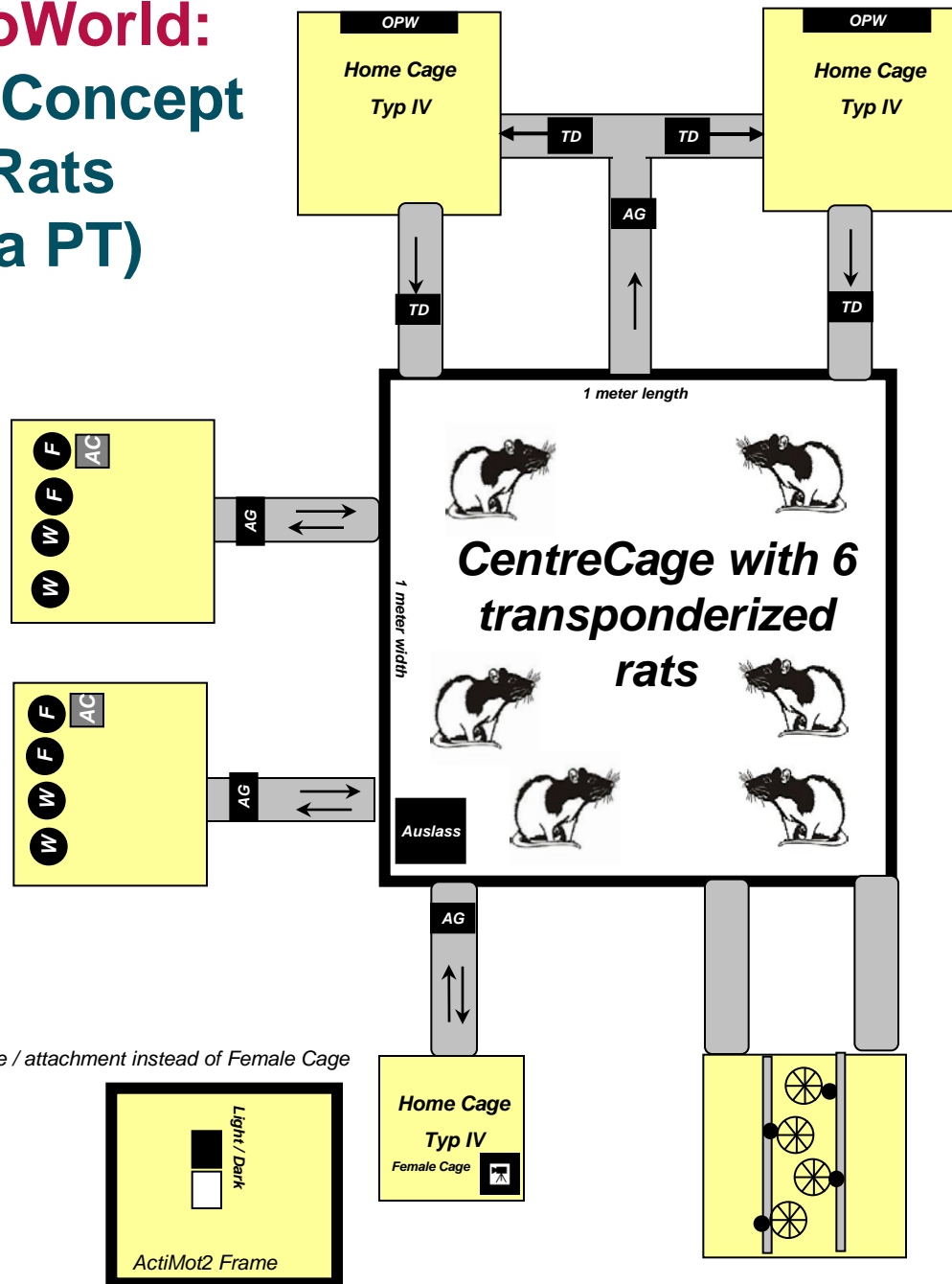
- **PhenoMaster**
- **IntelliCage & Add-Ons**
- **Multi Conditioning**
- **TraffiCage / SocioMot**
- **Mazes & Classical Behavior Systems**
- **Transponder Technologies**
- **Telemetry: Stellar (BP, ECG, HR, T) / NeuroLogger (4*EEG, Act)**










Combinatorial Approach



IntelliCage < > AnimalGate < > PhenoMaster

PhenoWorld: Cage Concept for 6 Rats (Braga PT)



-  Running Wheel
-  USB-Cam
-  Feeding Sensor
-  Drinking Sensor
-  Automated Access Control
-  Operant Wall
-  Light / Dark Box
-  Animal Gate (without balance)
-  Trapdoors

For alternative use / attachment instead of Female Cage

Entrances to wheels with antennas

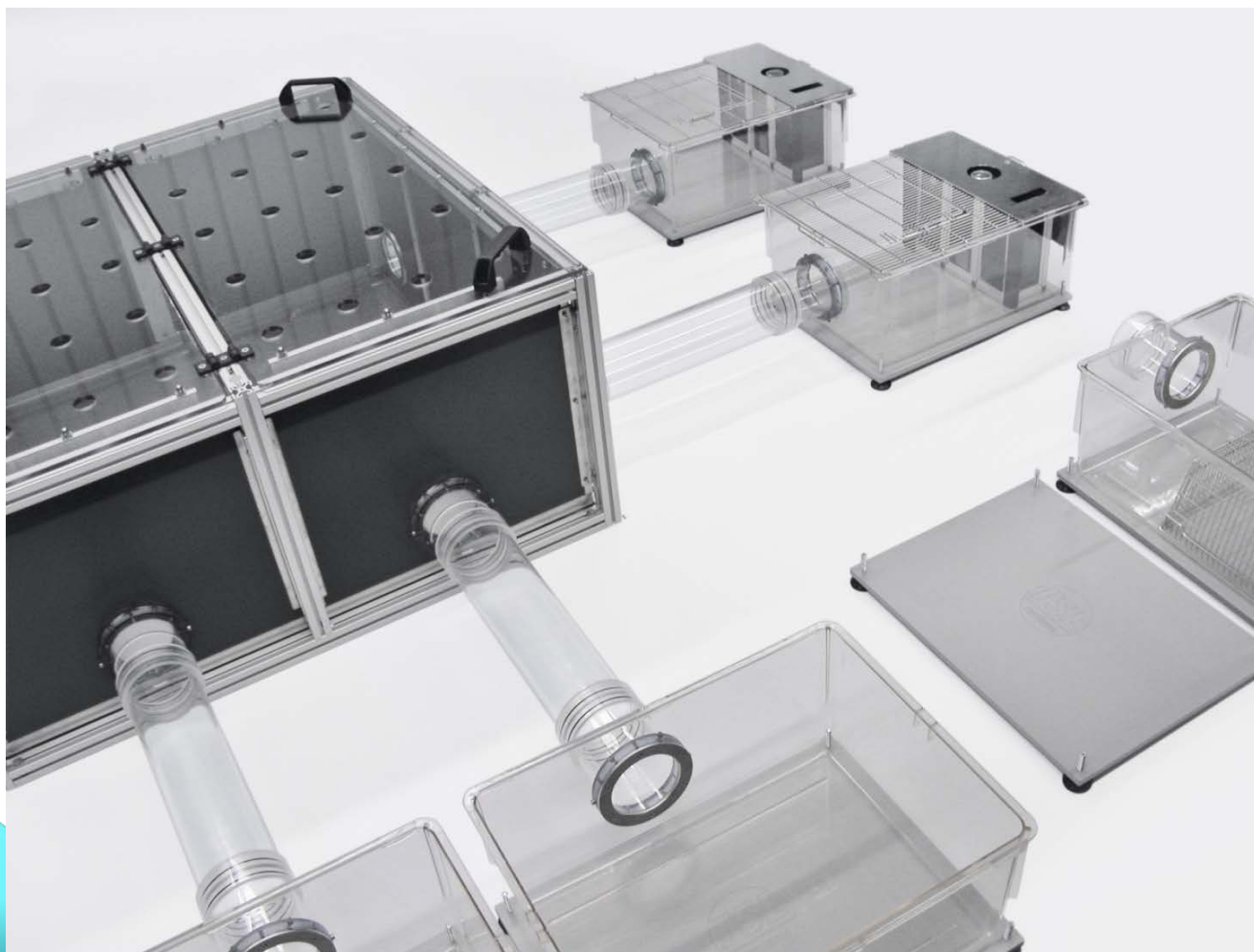
PhenoWorld “SocioBehavior” 6 Rats

Sophisticated Life Science Research Instrumentation



PhenoWorld “SocioBehavior” 6 Rats

Sophisticated Life Science Research Instrumentation



PhenoWorld

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PhenoWorld – Publication June 2014

Prof. Nuno Sousa, Braga / PT

OPEN

Citation: *Transl Psychiatry* (2014) **4**, e399; doi:10.1038/tp.2014.40
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www.nature.com/tp



ORIGINAL ARTICLE

PhenoWorld: a new paradigm to screen rodent behavior

M Castelhana-Carlos^{1,2}, PS Costa^{1,2}, H Russig³ and N Sousa^{1,2}

Modeling depression in animals has inherent complexities that are augmented by intrinsic difficulties to measure the characteristic features of the disorder. Herein, we describe the PhenoWorld (PhW), a new setting in which groups of six rats lived in an ethological enriched environment, and have their feeding, locomotor activity, sleeping and social behavior automatically monitored. A battery of emotional and cognitive tests was used to characterize the behavioral phenotype of animals living in the PhW and in standard conditions (in groups of six and two rats), after exposure to an unpredictable chronic mild stress paradigm (uCMS) and antidepressants. Data reveal that animals living in the PhW displayed similar, but more striking, behavioral differences when exposed to uCMS, such as increased behavioral despair shown in the forced swimming test, resting/sleep behavior disturbances and reduced social interactions. Moreover, several PhW-cage behaviors, such as spontaneous will to go for food or exercise in running wheels, proved to be sensitive indicators of depressive-like behavior. In summary, this new ethological enriched paradigm adds significant discriminative power to screen depressive-like behavior, in particularly rodent's hedonic behavior.

Translational Psychiatry (2014) **4**, e399; doi:10.1038/tp.2014.40; published online 10 June 2014



Prof. Nuno Sousa, Braga / PT: Poster FENS 2014

PhenoWorld: a new paradigm to screen rodent behavior

Magda J. Castelhamo-Carlos^{1,2}, Patricio S. Costa^{1,2}, Holger Russig³, Nuno Sousa^{1,2}

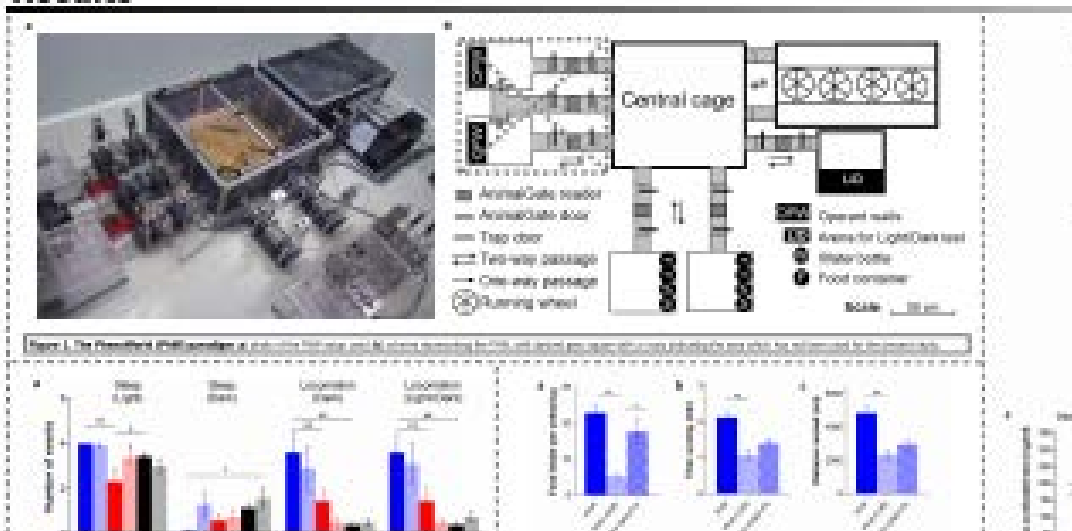
¹Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Campus Gualtar, 4710-057 Braga, Portugal; ²ICVS/3B's - PT Government Associate Laboratory, Braga/Gaia, Portugal; ³TSE Systems GmbH, TSE Systems International Group, Bad Homburg vor der Höhe, Germany

Introduction

Depression is a chronic complex multidimensional recurring disorder, involving several signs and symptoms, and affecting around 25% of the population around the globe^{1,2}. Identifying such a complex disorder in non-human species is remarkably difficult both from the conceptual perspective of how to reproduce mood disorders in such species, but also from an operational perspective of what to measure. The field has evolved to produce several animal models of the disorder³, but also in the development of several behavioral tests that can measure different behavioral dimensions^{4,5} known to be relevant to depression. However, there are still limitations in our assessment of rodent's depressive-like behavior⁶⁻¹⁰. One of the most obvious limitation is the fact that, so far, the tests we have to measure antidepressant behavior are based on the ratio of alternative choices and, in most cases, imply animal's isolation. Moreover, depressive-like behavioral tests are typically performed in different arenas than those where the animals live, creating confounding effects of novel environment. Finally, in almost all testing conditions, the complexity of social interactions of living in large groups is lost as the animals are tested either individually or in small cohort interactive contexts.

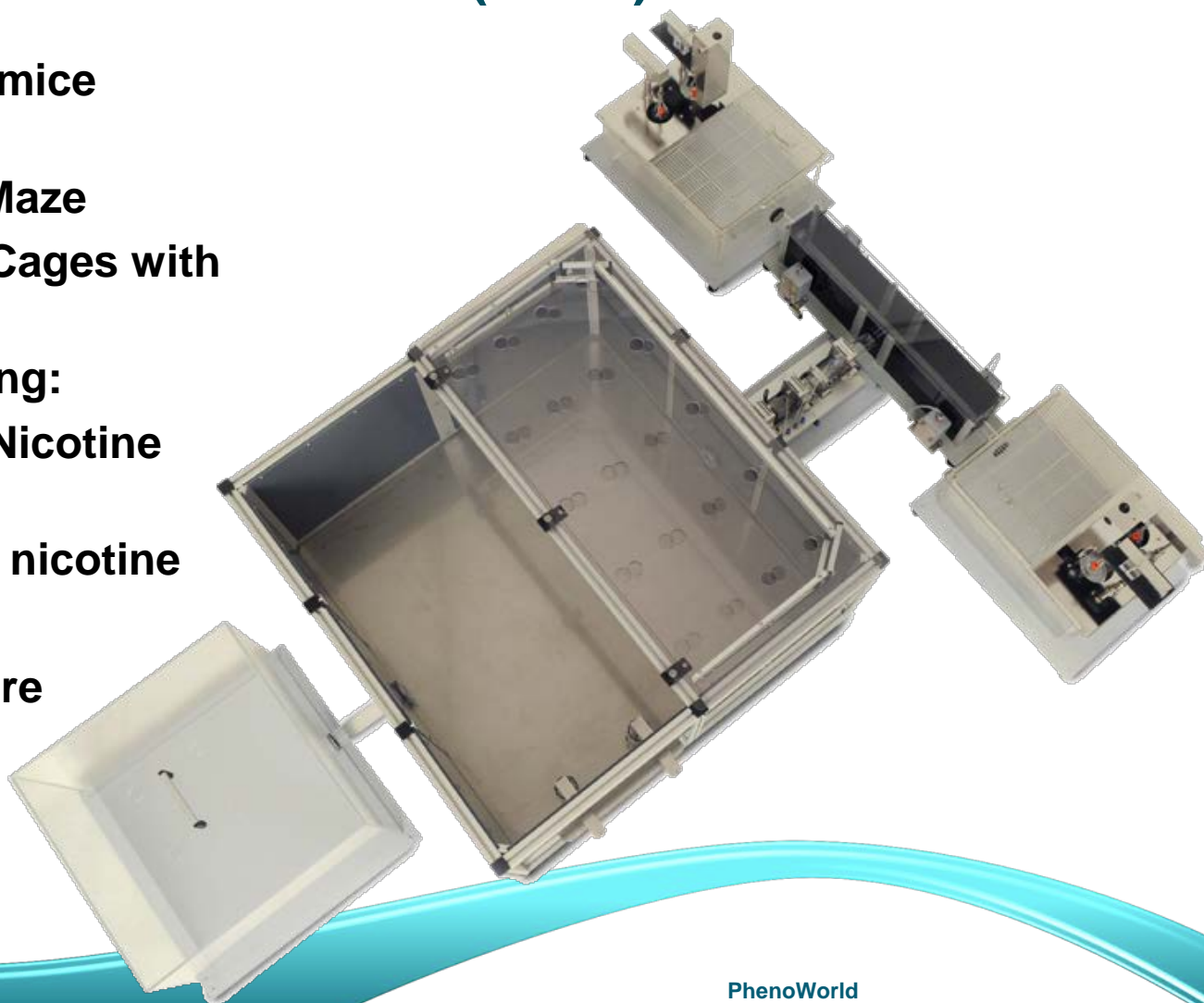
We have conceptualized the PhenoWorld (PHW), a new paradigm to analyze rodents' behavior, where groups of 6 rats with implanted RFID transponders lived in an ethologically enriched setting and had their feeding, locomotor activity, resting and social behavior automatically monitored. To validate the ability of this paradigm to screen depressive-like behavior, we have compared their depressive-like behavior in standard tests to that of animals living in standard conditions after exposure to unpredictable Chronic Mild Stress (CMS), a validated animal model of depression¹¹⁻¹³ and following antidepressant therapy.

Results



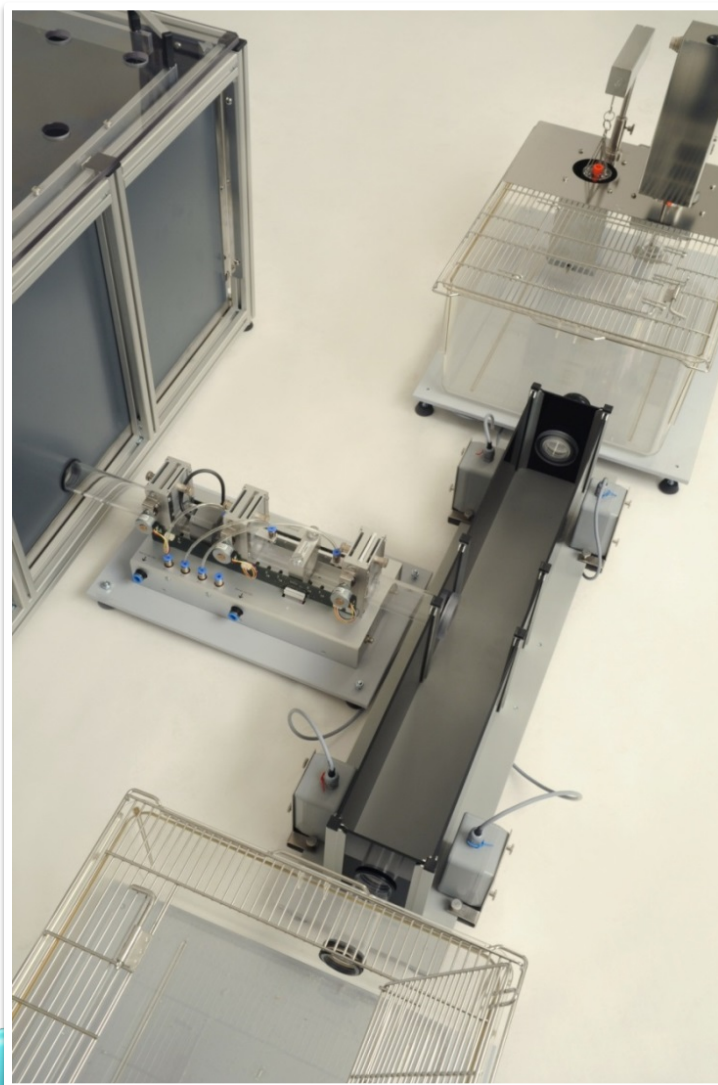
PhenoWorld “Addiction” 5 Mice (Paris)

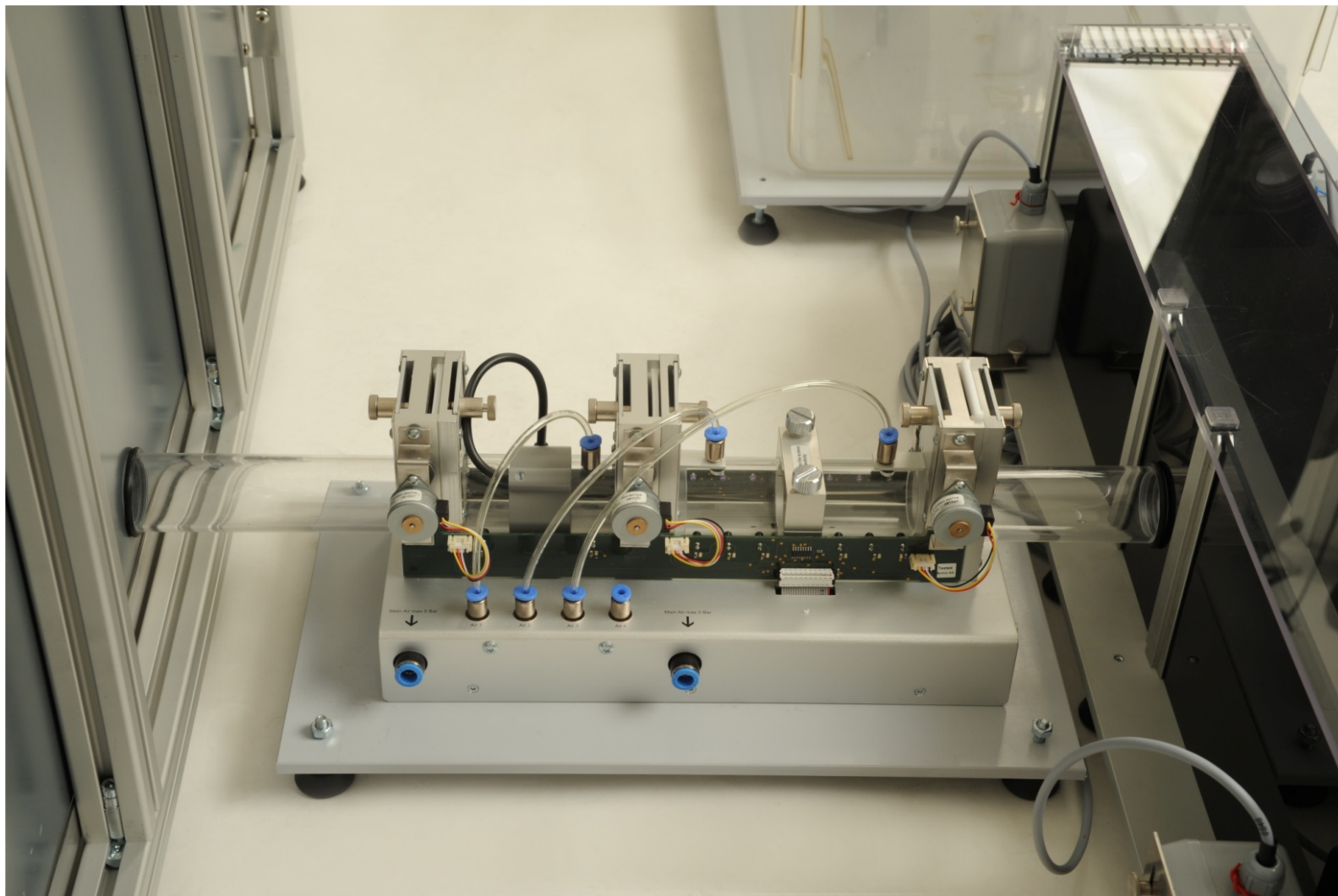
- CenterCage for 5 mice (transponderized)
- AnimalGate to T-Maze
- Reward: 2 PhenoCages with each 2 liquids
- Drinking Monitoring: Choice - Water & Nicotine in water
- Access control to nicotine
- Fully automated
- High animal welfare



PhenoWorld “Addiction” 5 Mice

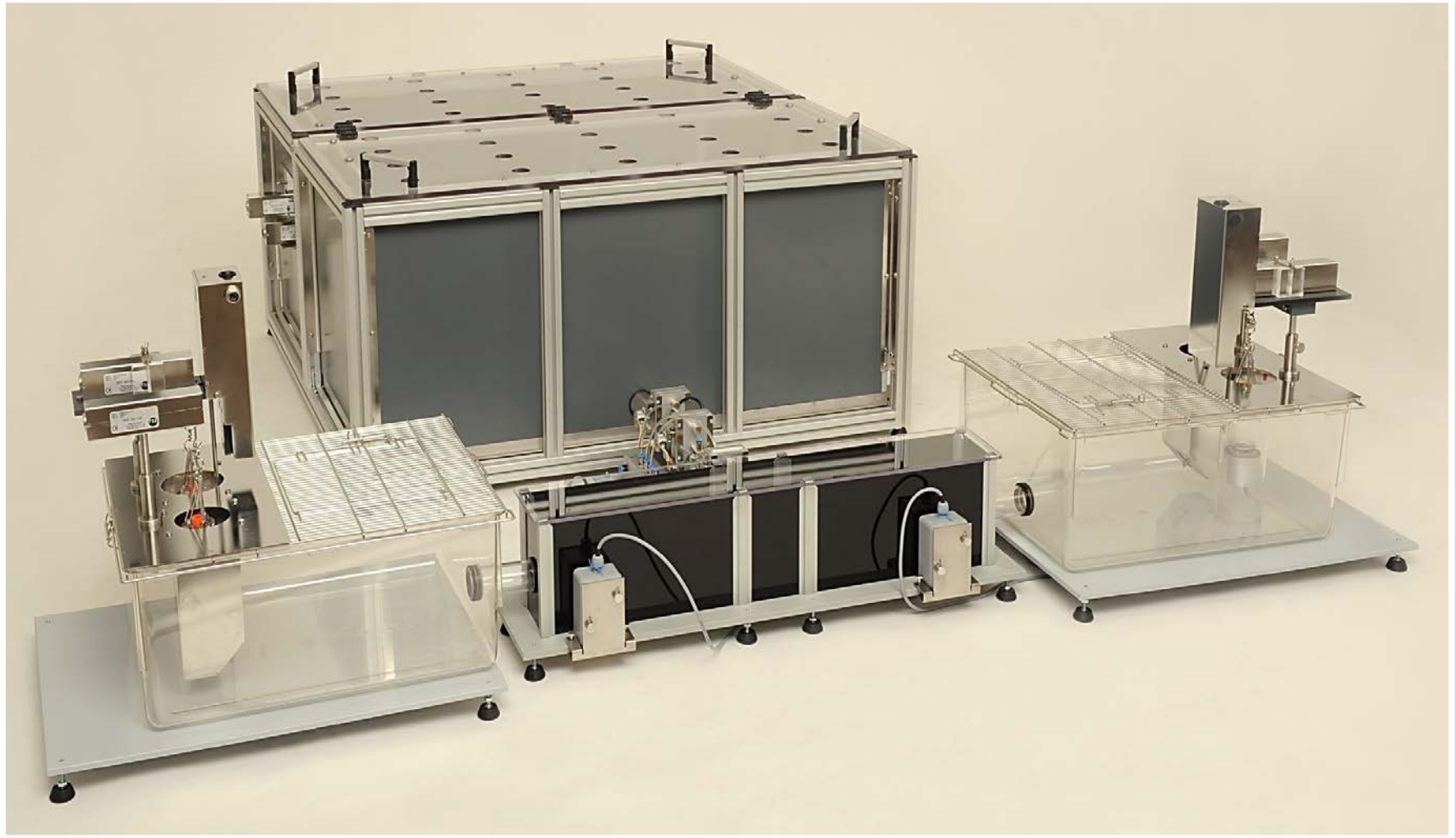
- CenterCage
- AnimalGate
- T-Maze
- 2 PhenoCages





PhenoWorld “Addiction” 5 Mice

Sophisticated Life Science Research Instrumentation



PhenoWorld

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PhenoWorld System for 48 Mice (Paris)

TSE Project 2014

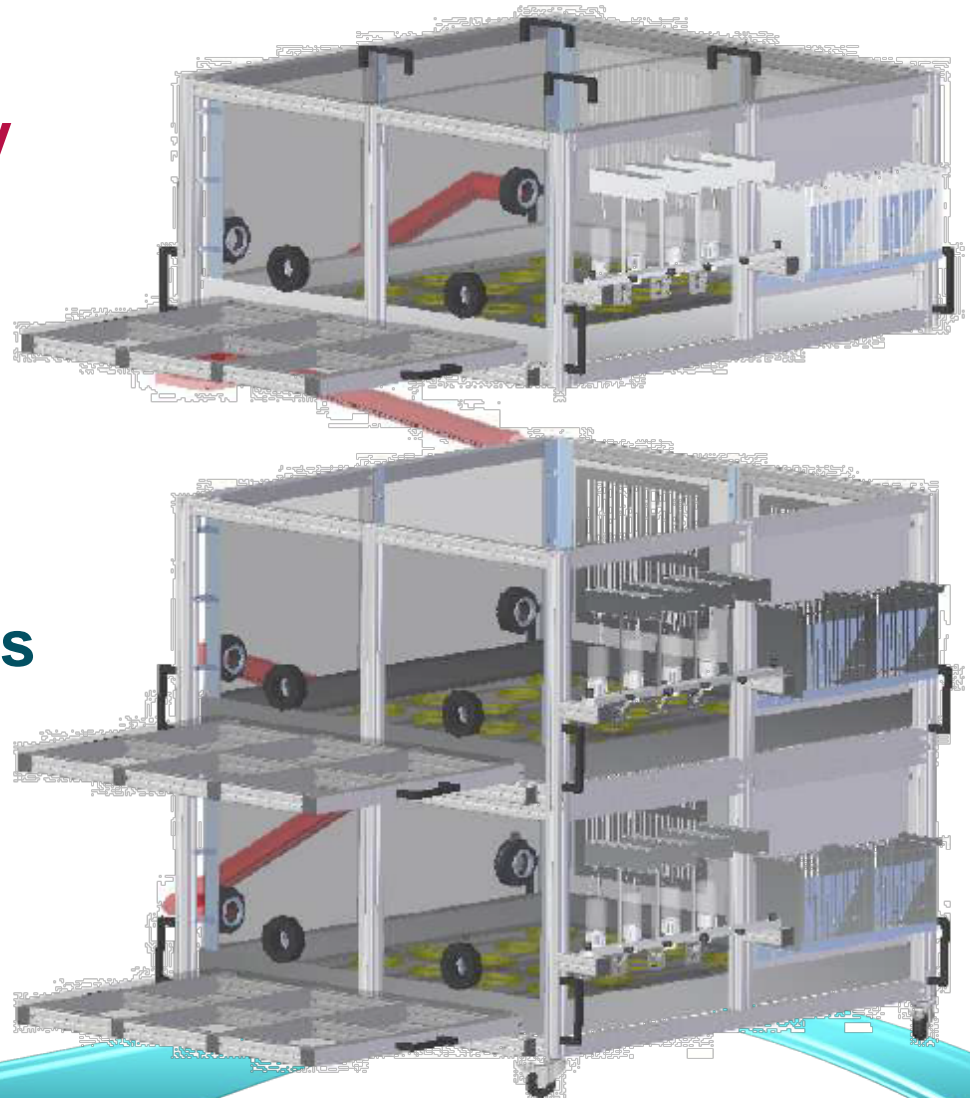
PhenoTower: Super-Enriched Environment

Sophisticated Life Science Research Instrumentation



SocioMot – Group Activity

- Modular design
- Functional flexibility
- Several floors high
- Attachments at balconies

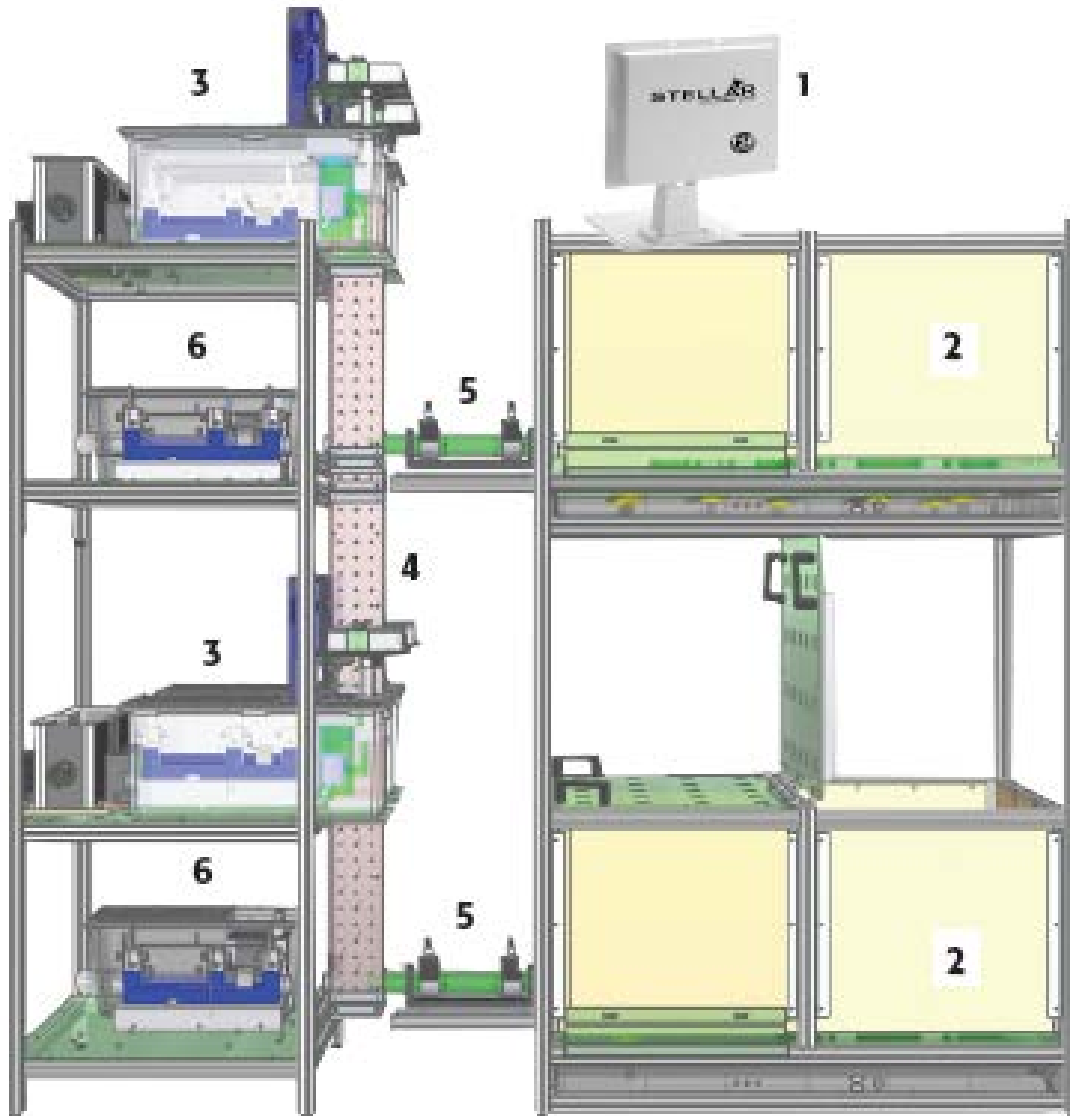


PhenoWorld

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PhenoTower “Addiction” Mice

Sophisticated Life Science Research Instrumentation

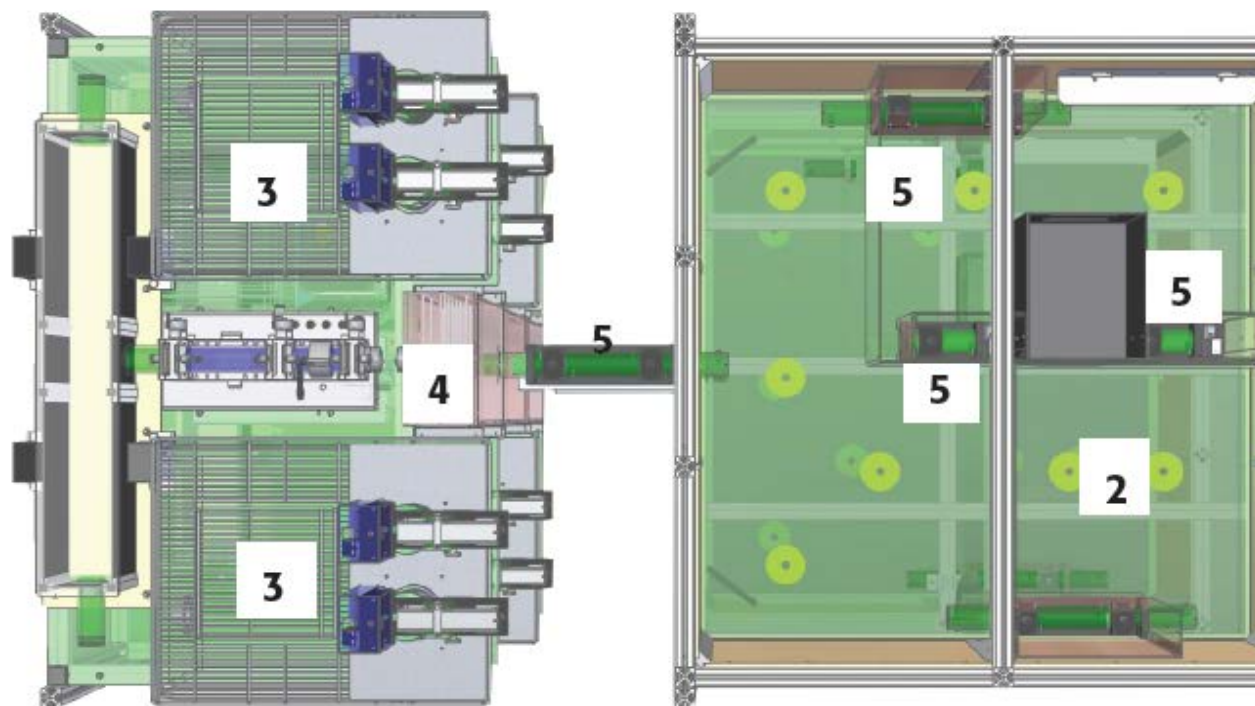


- 1 Stellar Telemetry**
- 2 Social Main Arenas**
- 3 Choice Arenas**
- 4 Stairway**
- 5 AnimalGate/SocialTubes**
- 6 Operant Conditioning Arenas**

PhenoWorld

PhenoTower “Addiction” Mice

Sophisticated Life Science Research Instrumentation

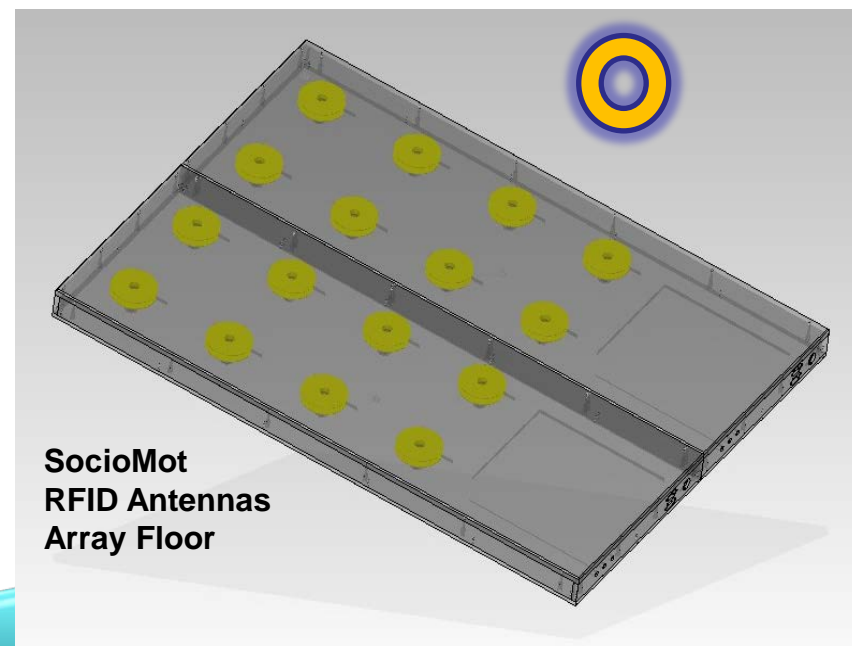


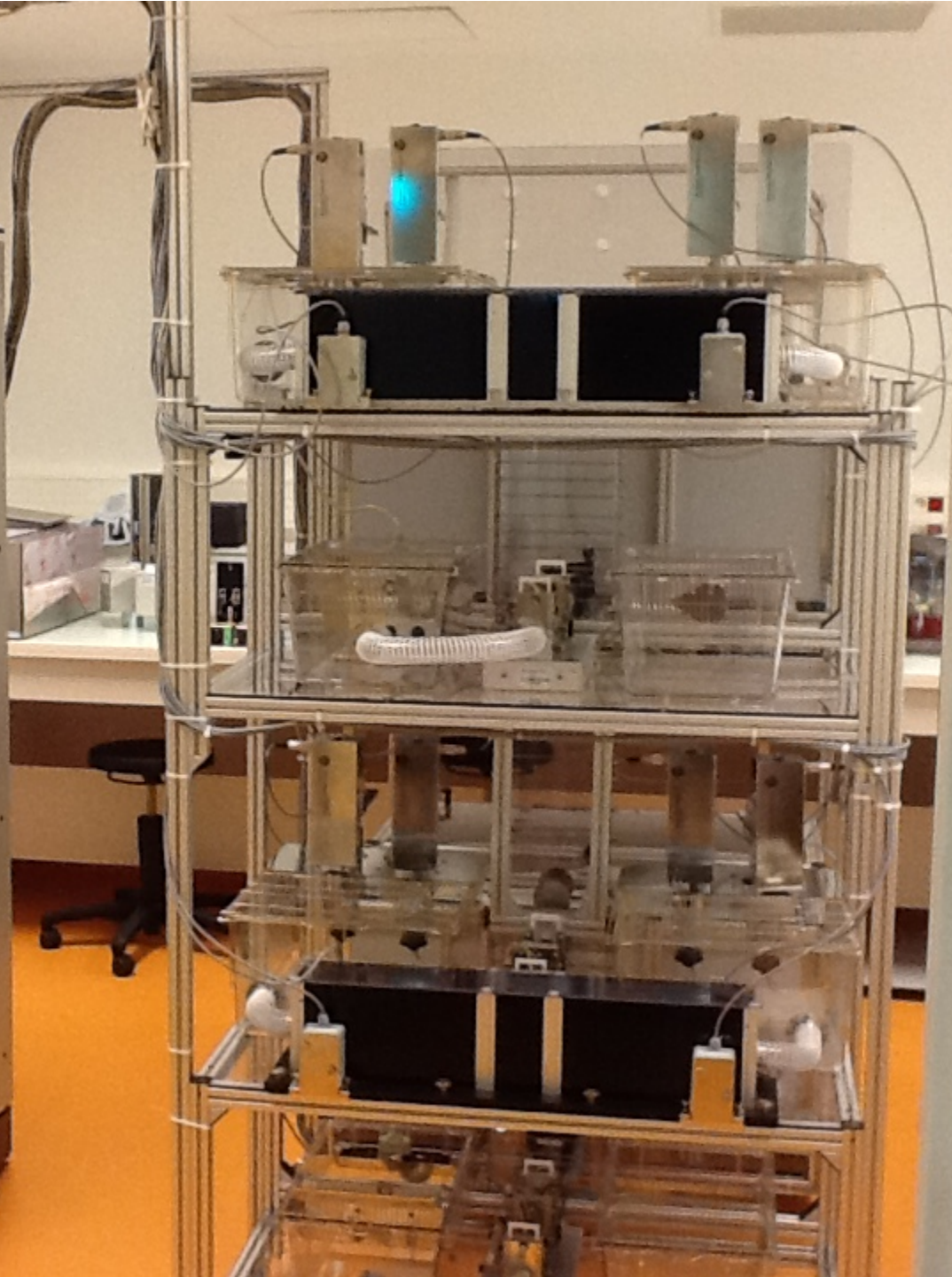
- 1 Stellar Telemetry**
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- 5 AnimalGate/Tubes**
- 6 Operant Conditioning Arenas**

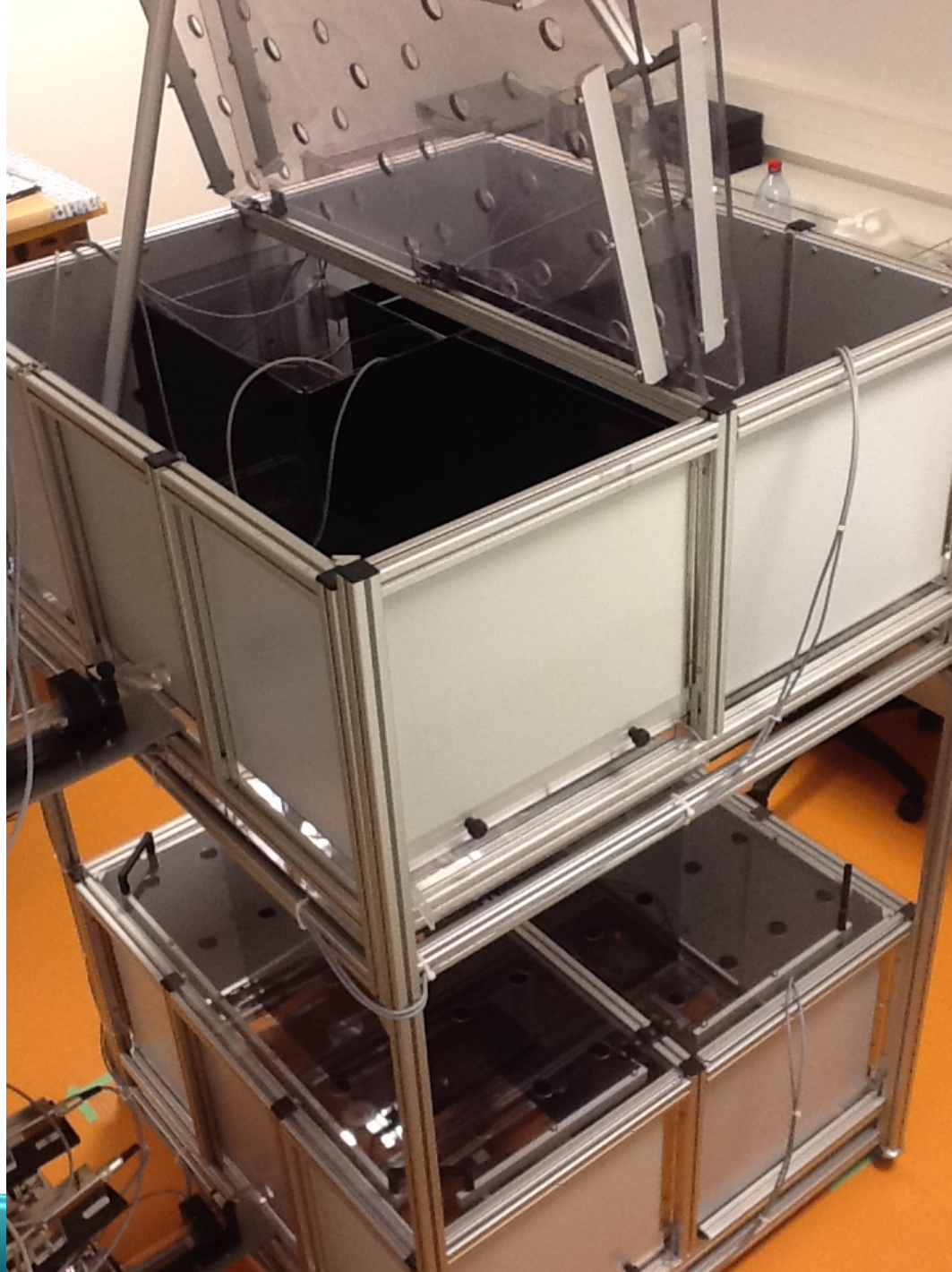
PhenoTower: Super-Enriched Environment

SocioMot – Group Activity

- Transponder antennas floors for Activity Monitoring in 3D
- Modular design
- Plates with 8 antennas
- Any floor sizes for many mice simultaneously







mentation



Sophisticated Life Science Research Instrumentation



PhenoWorld

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Stellar Telemetry

**The Freedom to move anywhere, anytime and anyhow
singly or in a social group**

> still collecting physiological data

Stellar Telemetry – Measurement Parameters



- **Measurement Parameters:**
Blood Pressure, Heart Rate, ECG, EMG, EEG, EOG, Body Core Temperature, Activity
- No receiver platforms under cage
- **Group housing of many animals**
- No fluid filled catheters for BP
- **Can be used in combination with any Phenotyping, Metabolic, Behavioral & Inhalation systems** on today's market

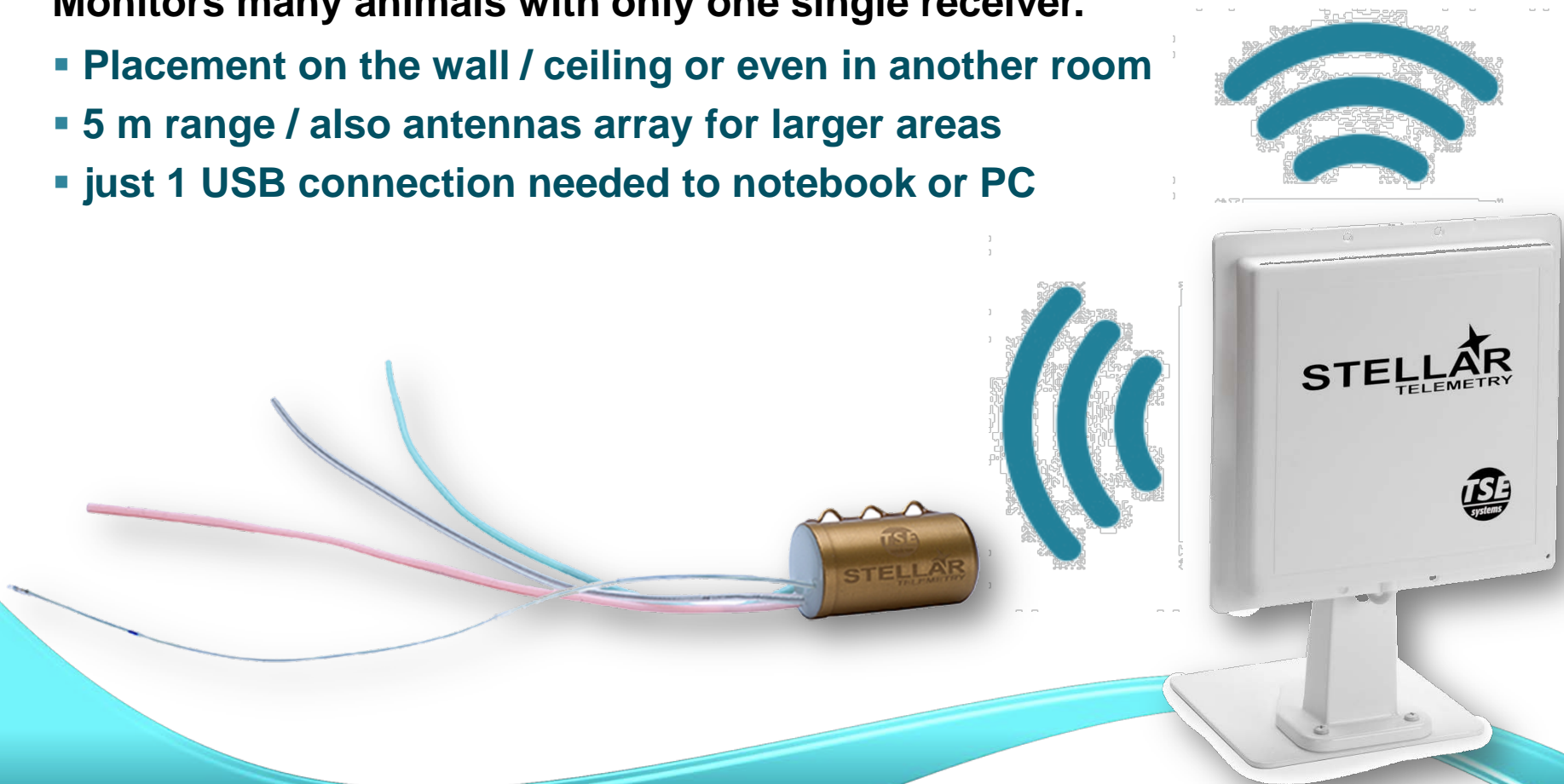
Stellar Telemetry – Unique Features & Benefits

- Monitoring of many animals – **ONE telemetry receiver only**
- **Group-housing of animals & Social interactions** - no interference
- Telemetry transmitter **AND data logger** within one implant
- **Long-range recording (5 m)** – time programmed read-out
- **Catheter tipped pressure transducer for BP (HR)**
- **Biopotentials (ECG / EMG / EEG / EOG)**
- **Temperatures (Body Core Temp. / Two differential Temperatures)**
- Cost effective, **Power saving for implant**

Stellar Telemetry – Receiver

Monitors many animals with only one single receiver.

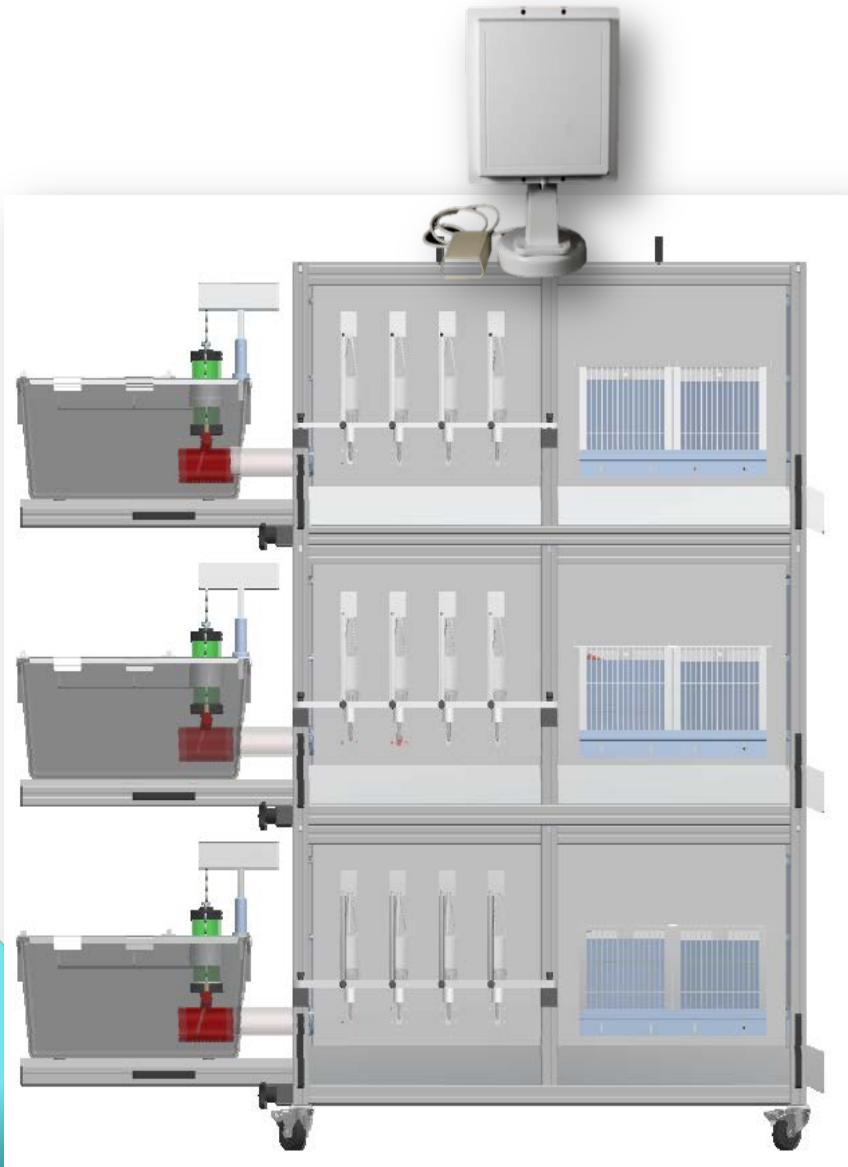
- Placement on the wall / ceiling or even in another room
- 5 m range / also antennas array for larger areas
- just 1 USB connection needed to notebook or PC



Stellar Telemetry

Stellar Telemetry – Receiver Placement





Super-enriched environment for multiple animals

- **One Antenna** – maximum freedom for Physiological recordings
- Activity Measurement **SocioMot** (Transponders)
- **Food & Liquid** Intake / Control
- Cognitive tasks
- Etc. etc. ...

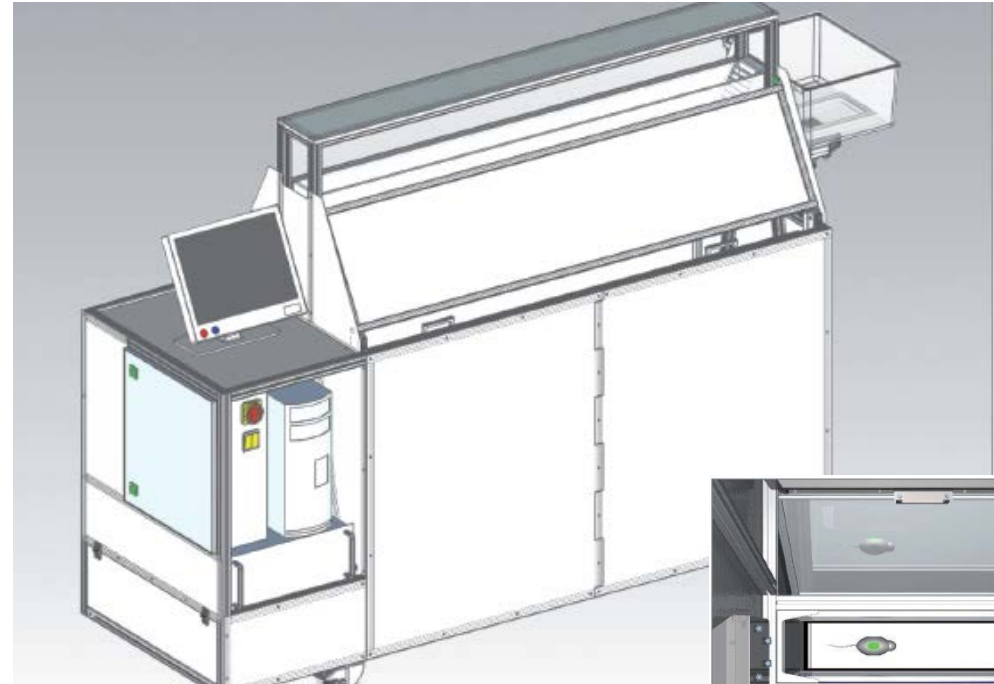
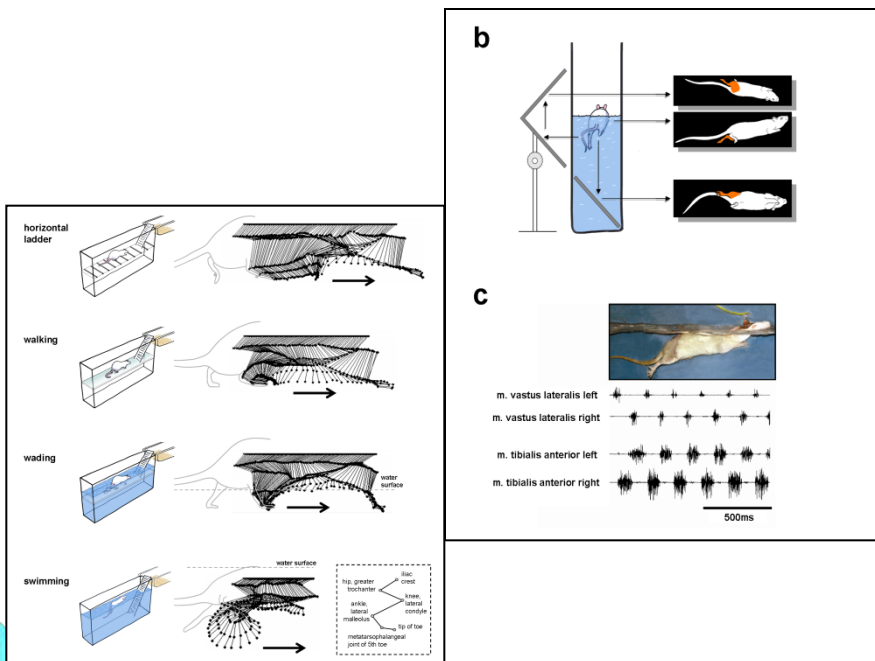
MotoRater

A novel standardized modular system for evaluation of locomotor functions in rodents

Sophisticated Life Science Research Instrumentation



High-speed video tracking of ladder running, walking, wading and swimming



Zörner et al. (2010)
Nature Methods

Create your own PhenoWorld !

PhenoTower > PhenoTown ?

**Thank you
for your attention**