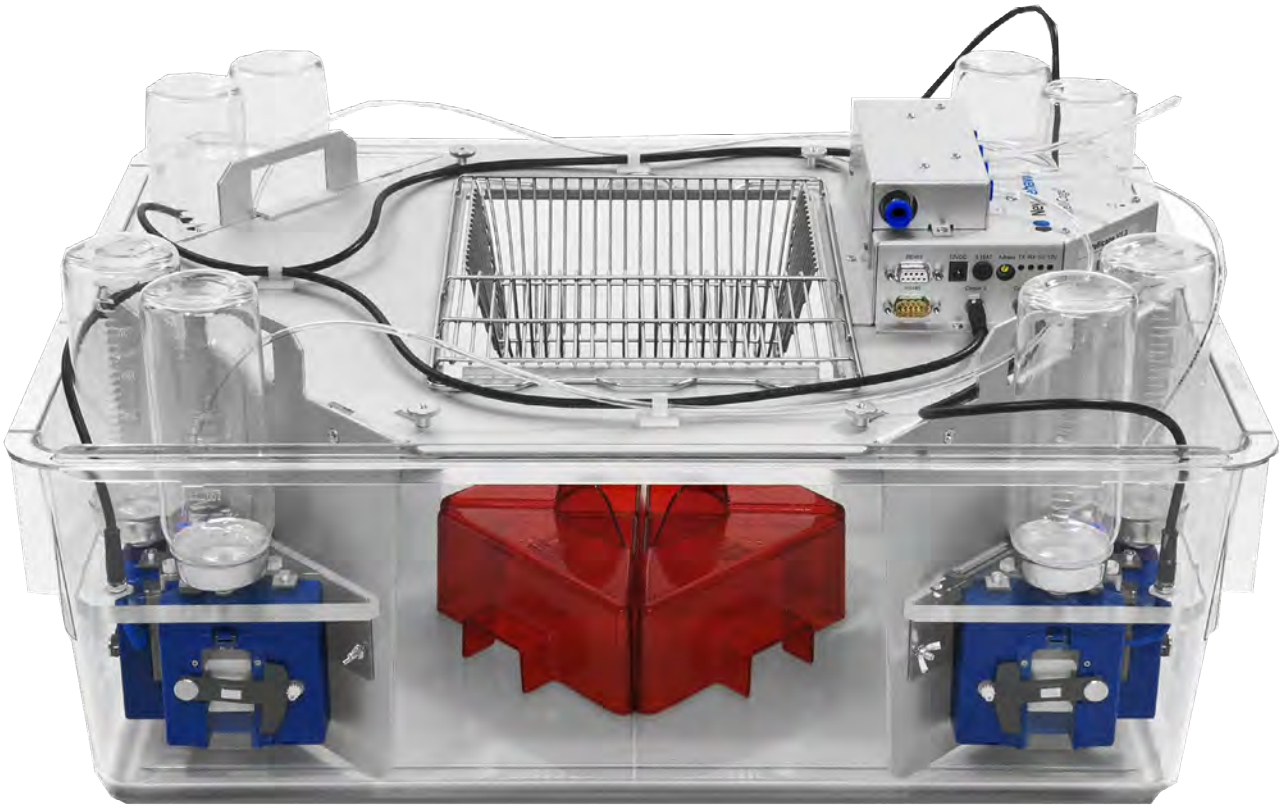
Sophisticated Life Science Research Instrumentation

IntelliCage

Cognitive & Behavioral Screening of Individual Mice Living in Social Groups



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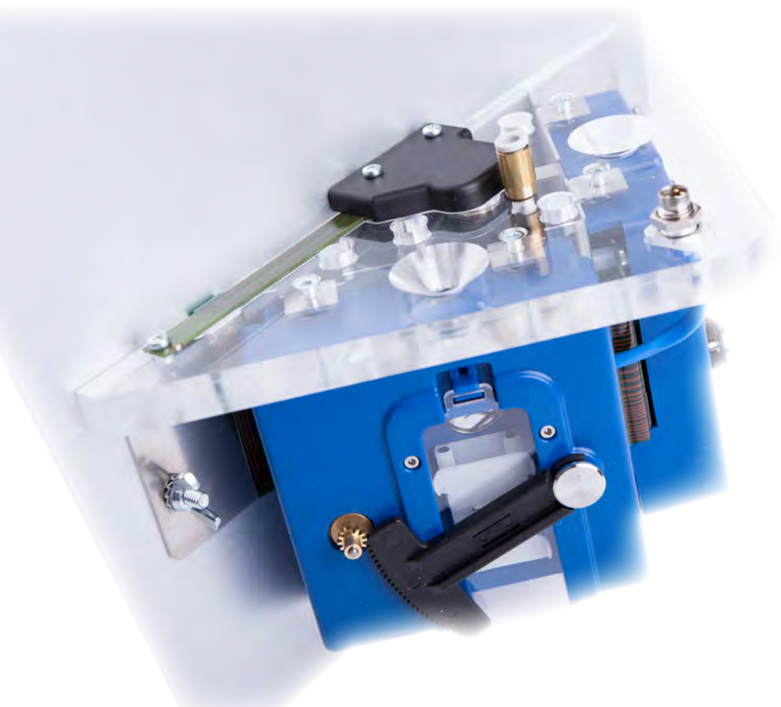
IntelliCage

Flexible cognitive testing in social groups

SMART DESIGN for long-term investigation of laboratory mice. Cohorts of 16 transponder tagged mice are group housed and perform a variety of programmable behavioral and cognitive tasks in their home cage. Simple and complex conditioning experiments can be graphically designed and automatically run for each individual animal in the IntelliCage.

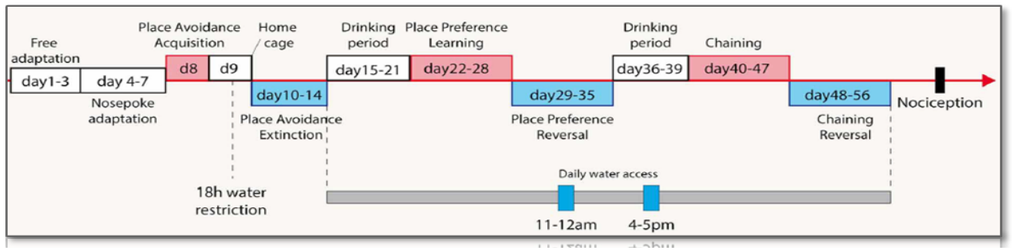
Such a behavioral screening is frequently required in biomedical and basic behavioral, neurobiological, pharmacological and genetic research and can be done by the IntelliCage with exceptionally high standardization, efficiency and minimal work load.



Unique features

- Screening of Individuals in a Social Context
- Efficient: Up to 16 Animals per Cage
- Maximal Standardization & Reproducibility
- High Validity (Minimal Human Intervention)
- Fully Automated Task Performance
- Broad Variety of Accessible Data
- Flexible Design of Paradigms

Applications



Behavioral changes are sensitive readouts for any alterations within the organism. Careful phenotypical characterization is therefore an important part of biomedical research. The following fields profit enormously from IntelliCage Technology:

Automated high-throughput behavioral phenotyping

in a social group. With highly standardized phenotyping procedures, the IntelliCage covers multiple behavioral and cognitive domains and allows to study and compare multiple animal models of any disease or single/multiple gene knockouts

True longitudinal studies

where animals either stay in the IntelliCage for a prolonged period or re-visit the system several times during their life-span. Both approaches allow the detection of age-dependent signs or disease symptoms (e.g. Huntington's disease, Alzheimer's disease, animal models of aging)

Mechanistic studies

e.g. brain lesion studies for testing the involvement of specific structures in different behavioral domains, leading to a better general understanding behavior and underlying brain functions.

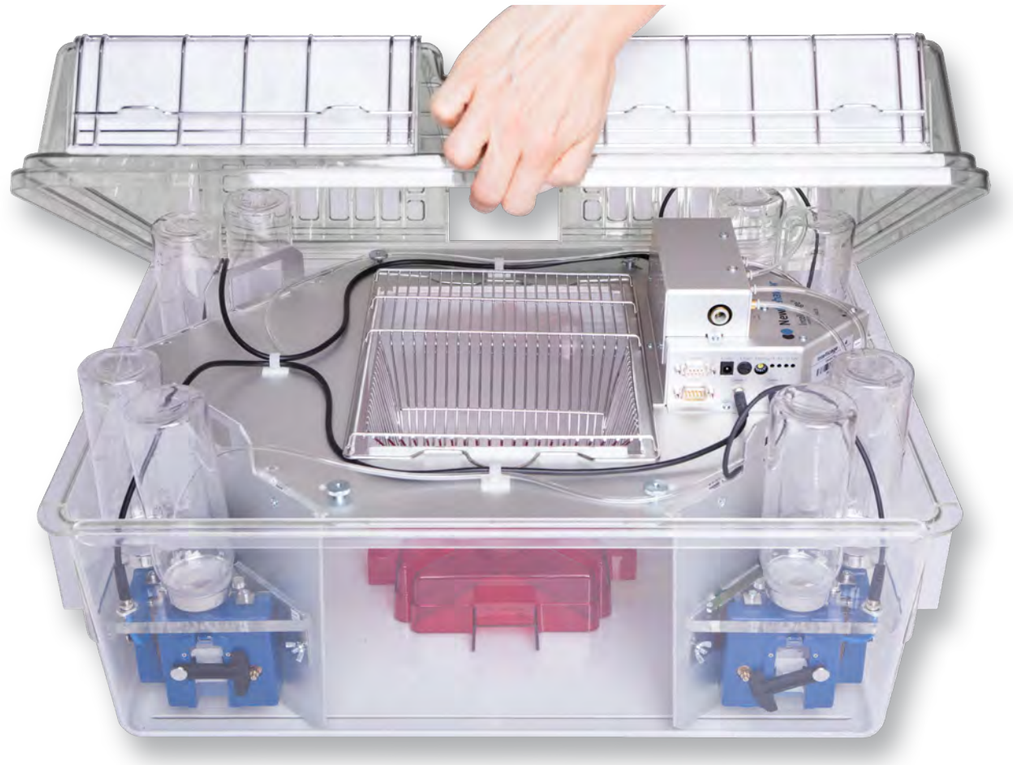
Pharmacological studies

drugs can be administered orally in the drinking water or via osmotic mini-pumps while the animals are undergoing behavioral or cognitive testing. Highly standardized conditions and protocols allow to compare data of different sexes, age groups or genetic backrounds.

Wireless telemetry studies

combine the automated behavioral phenotyping of the IntelliCage with our wireless telemetry system Stellar for simultaneous EEG, ECG, Blood Pressure and Activity measurements

STELLAR TELEMETRY



IntelliCage allows transfer of multiple established behavioural paradigms into an automated setup:

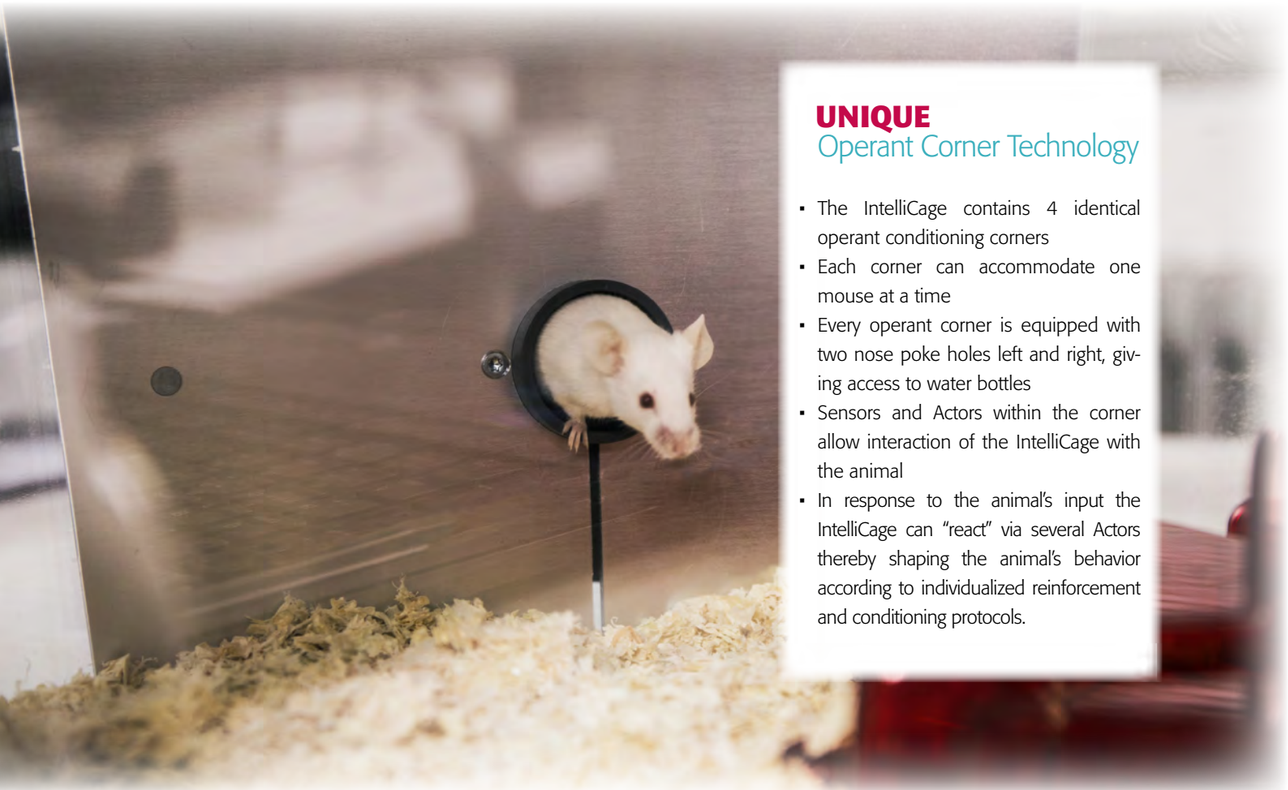
- Morris' Water-Maze
- Radial Arm-/Y-/T-Maze
- Open-Field
- Sucrose-Preference
- Social-Defeat
- Competition- and Hierarchy-Tasks
- Vogels' Conflict-Test
- Novel-Object-Preference-Tests
- Operant-Conditioning (Fixed-/Progressive-Ratio, equivalent to SkinnerBox)
- …and many other procedures for assessing general processes of learning & memory, executive function, behavioural flexibility, cognitive rigidity, effort choice behaviour, circadian activity, acute/chronic stress- or drug-treatment effects.

The enormous flexibility enables you to set up individual test-batteries for behavioral and cognitive assessment of animal models on:

Autism, Alzheimers' Disease, Parkinsons' Disease, Dementia, Epilepsia, Anxiety Disorders, Depression, Anhedonia, Neophobia, Pain, Obesity, Stress Disorders, Cognitive Disorders, aberrant social behaviour (non-exhaustive).

RFID Transponder Technology

- Ricecorn-shaped RFID-transponders are subcutaneously injected within minutes
- RFID-transponders allow individual recognition
- Up to 16 mice can be housed within one single IntelliCage
- For high-throughput testing up to 4 IntelliCages can be connected to a single computer (testing of up to 64 animals at the same time)



UNIQUE
Operant Corner Technology

- The IntelliCage contains 4 identical operant conditioning corners
- Each corner can accommodate one mouse at a time
- Every operant corner is equipped with two nose poke holes left and right, giving access to water bottles
- Sensors and Actors within the corner allow interaction of the IntelliCage with the animal
- In response to the animal's input the IntelliCage can "react" via several Actors thereby shaping the animal's behavior according to individualized reinforcement and conditioning protocols.

Sensors & Actors

combine to create customized conditioning protocols

SENSORS
register behavior

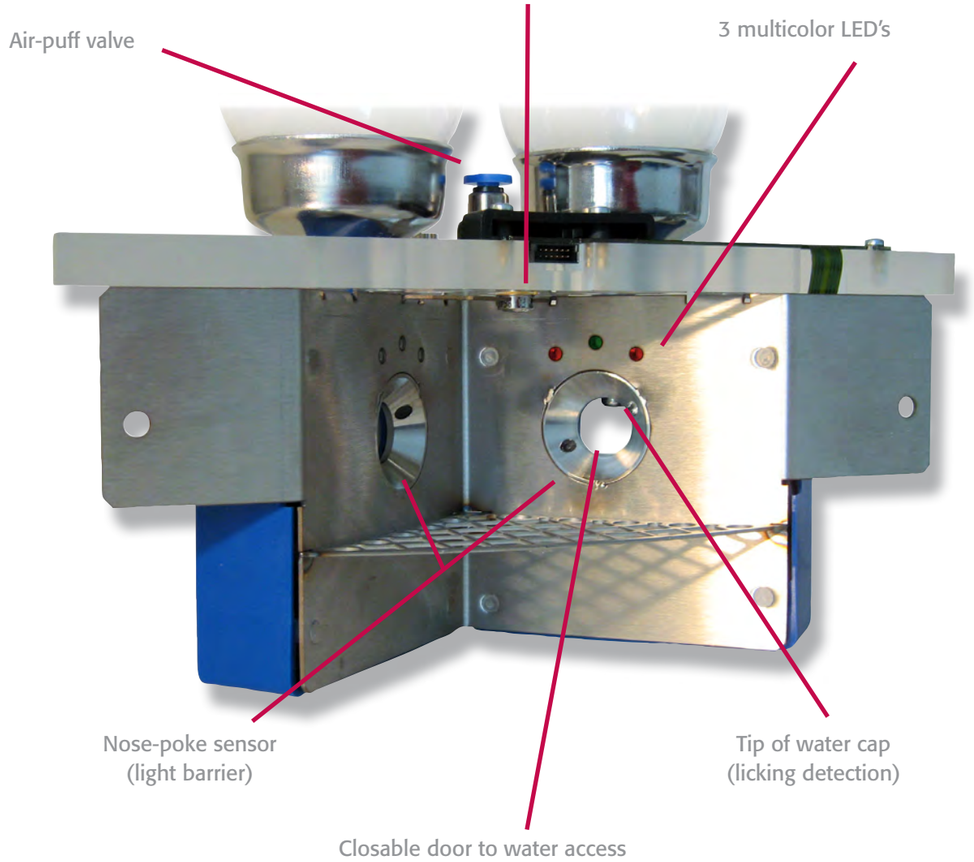
ACTORS
shape behavior

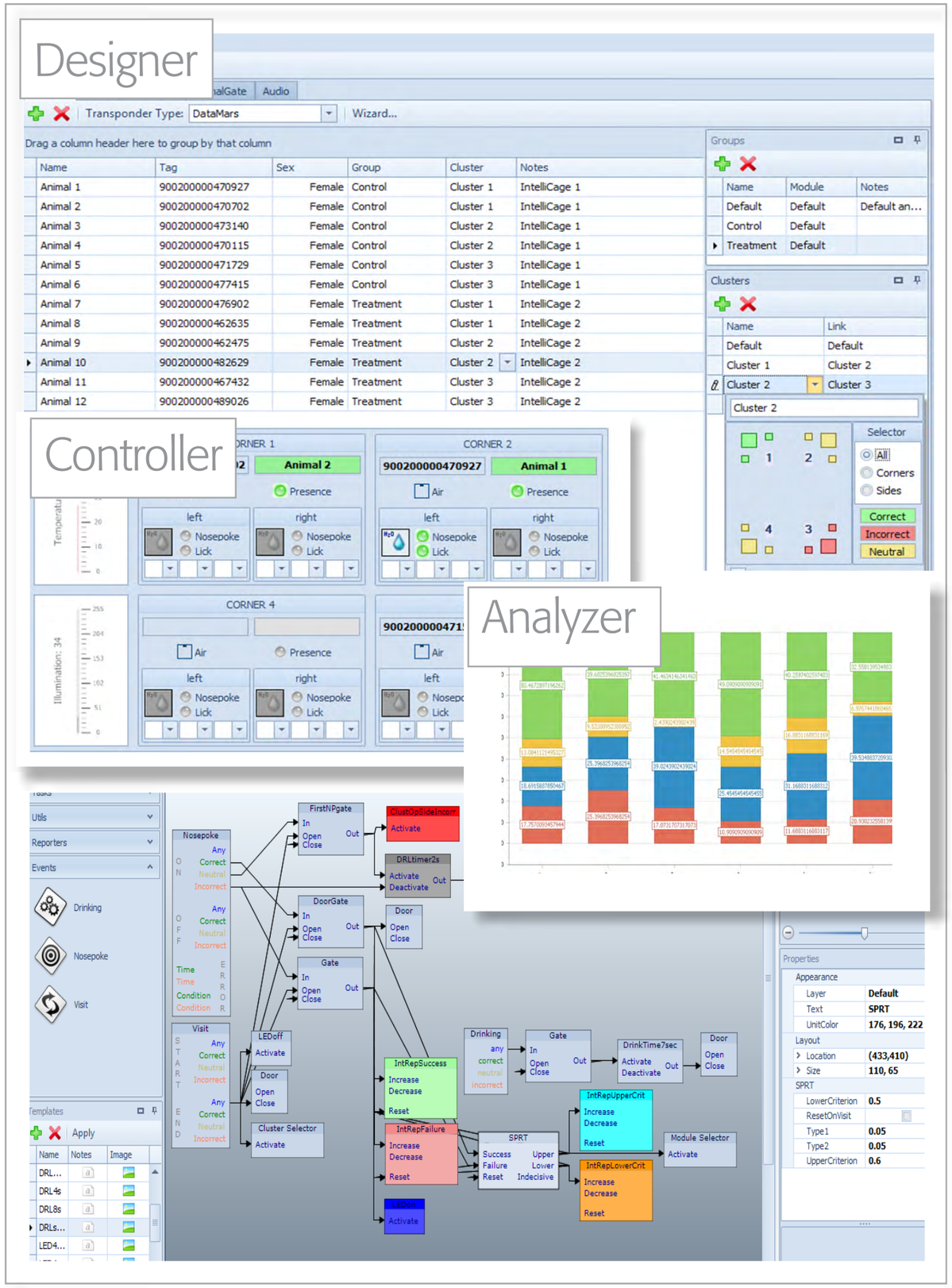
Sensors register the animal's behavior

- RFID antenna - identifies the animal (transponder) entering a corner
- Temperature-sensitive presence sensor - detects start, duration and end of corner visits
- IR light beam at the door to water water access - detects nose poke instances
- Lickometer - detects the number and duration of tongue-contacts with drinking nozzel

Actors shape the animal's behavior

- Motorized doors allow / deny access to water bottles at the nose poke hole on both sides of the corner (reinforcement)
- Air puff valves in each corner may deliver a punishment
- Multicolor leds above the nose poke holes act as conditional stimulus





IntelliCage Software

IntelliCage is run by a unique and user-friendly software package consisting of three separate parts: **Designer** (allows programming of individual experimental designs), **Controller** (executes/monitors pre-programmed experimental designs and records data), and **Analyzer** (for efficient data-exploration, extraction and export of recorded data, creating customized data-charts). The software modules work as independent entities. Designer and Analyzer can be installed and run on any computer you will need to comfortably program and analyze your experiments.

Intuitive
Flexible
Customized
Logical

Designer

Configure experiments in 3 basic steps:

1. Specification of hardware setup
2. Generation of animal list containing individual specifics such as ID, transponder number, sex, group and assigned cluster
3. Programming customized designs containing one or multiple experimental phases

- Clusters define the status of individual corners and doors for each animal assigned to this cluster.
- Corners and doors can be independently defined as correct, incorrect or neutral for multiple clusters.
- Behavioral events (Visits, Nosepokes, Drinking) are connected to different actions (Rewards, LED, Air-puffs) using logical units.
- The experiments can be flexibly designed, almost comparable to programmed codes, with the user-friendliness of a graphical user interface.
- Several modules can be created and imply switches between clusters / modules that can be driven by individual behavior.
- Moreover, automated switches between clusters / modules can be executed at fixed day-times by creating customized day patterns.
- After programming, the complete experiment is stored in an Experimental file to be loaded into the Controller Software.

Controller

Run & visualize experiments

- Experimental files from the Designer are loaded and executed by the Controller software
- It extracts and stores all behavioral events (visits, nosepokes, licks), as well as environmental data (lighting, temperature), from the incoming stream of Sensor data.
- Events and corresponding actions can be monitored and visualized on screen during ongoing experiments in an overview console view.
- All data are retrievable from various tables showing correct or incorrect presence of individuals in conditioning corners, location and correctness of nosepokes, incidences/extent of drinking behavior and the occurrence of negative reinforcement (air-puffs).
- The data are accessible any time during the experiment and behavioral parameters for individual animals are further visualized in different graphs, allowing online-monitoring of all events and their temporal evolution.
- The Controller can be programmed to send alerts if individual animals show no visits or licks during specified periods.
- After experiments, raw data from standard tab-delimited text files are saved into a zip-folder-archive which can be loaded into the Analyzer.

Analyzer

Filter, graph & export data

- Archive-files from the Controller are loaded into the Analyzer, which uses Boolean operators to filter data for different time-windows or conditions of particular interest (e.g. “all correct nosepokes of control animals during dark phase”).
- Filtering efficiently facilitates data evaluation while the original data remain accessible any time.
- All applied filters can be stored to re-apply them for analyses of further experiments.
- All graphs and figures can be saved as different image files.
- Raw data tables, filtered data, as well as data underlying graphs and figures can be exported as tab-delimited text-files for more sophisticated analyses in other programs such as standard graphical and statistical packages, e.g. FlowR (see “add ons”).

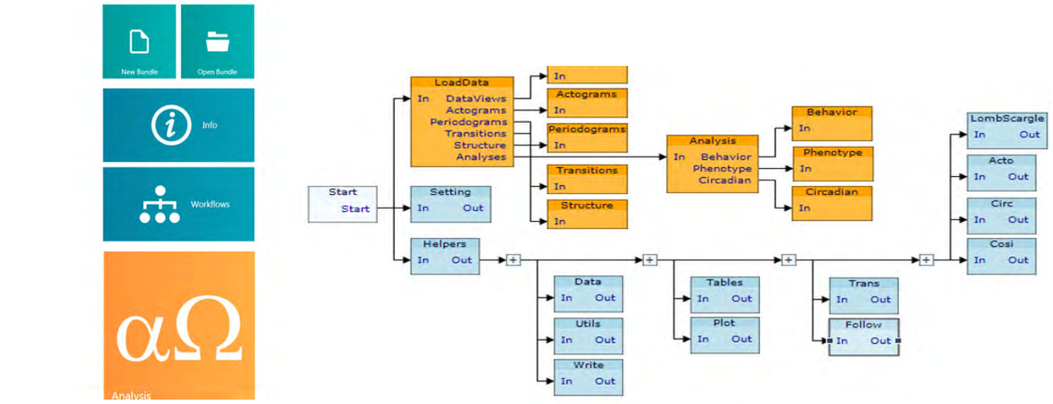
IntelliCage – Behavioral Paradigms

A. Spontaneous Behavior	
1. Free Adaptation*	Animals are adapted to the use of corners to access water.
2. Nosepoke Adaptation*	Nosepoking is required to access water bottles – equivalent to Fixed-Ratio-1 schedules.
B. Spatial and Temporal	
3. Place Learning*	Access to water is restricted to defined corners in space.
4. Avoidance Learning	Visits to defined corners in space are punished with air-puffs – equivalent to Vogel Test.
5. Reversal Learning*	Rewarded corner is changed to reverse prior spatial preference.
6. Alternation	Rewarded side is alternated.
7. Serial Reversal	Rewarded corner is changed serially according to animal's performance.
8. Patrolling	Rewarded corner shifts (anti-)clockwise after correct response (visit, nosepoke, or drink) – similar to spatial learning in 8-arm radial maze.
9. Coverage	Rewards reinforce regular corner switching (random sequence patrolling).
10. Drinking Sessions / Temporal Learning*	Access to water bottles is restricted to certain day & night times.
C. Social and Others	
11. Competition / Hierarchy Analysis	All individuals have water access restricted to certain corners and day & night times.
12. Differential Synchronization	Single individuals are assigned to different day & night patterns of water access to test for social cohesion.
D. Discrimination Learning and Preferences	
13. Light Discrimination (LED Scheme)	Rewarded corners are indicated by light regime.
14. Taste Aversion	Consumption pattern reveals taste aversion.
15. Compound Cue	Water bottles are inoculated with different drugs.
E. Memory	
16. Impulsivity & Delay Discounting	Animals can have immediate access to a plain reward (water) or wait for a pre-defined delay period to get access to a more salient reward (sucrose solution).
17. Attentional Shift	Side and number of LEDs indicating reward are randomly shifted for each visit.
18. Neophobia	Olfactory/gustatory cues in corners/bottles are switched to induce novelty.
19. Conditioned Aversion	A probe trial tests for acquired aversion to unconditioned reinforce.
F. Operant Conditioning	
20. Conditioned Stimulus (LED Scheme)	The conditioned stimulus (lights on/off) indicates rewarded side (water bottle access).
21. Fixed Ratio*	A fixed number of responses is required to access a reward. Ratio depends on reward salience (determined by place).
22. Progressive Ratio*	The requirement to access a reward increases on a trial-by-trial basis.
23. Impulsivity & Diff. Reinforcement of Low Responding (DRL)*	Progressive response inhibition by reinforcing long time intervals between response (nosepoke) incidents.

* Paradigms will be delivered with the tutorial for IntelliCage Designer Program

XBehavior

FlowR



FlowR-Software by XBehavior

Statistical analysis & visualization optimized for IntelliCage data

- Graphical user interface translating R-script units into graphically arranged statistical workflows.
- Users are seamlessly guided through the analysis process without programming efforts.
- Data visualization and statistical analyses (incl. xxxANOVA,xxx) comes at a mouse click.
- Incl. IntelliCage Basic Bundle with pre-programmed workflows for data preparation, phenotyping, side preference-analysis, place preference-analysis, assessment of general activity

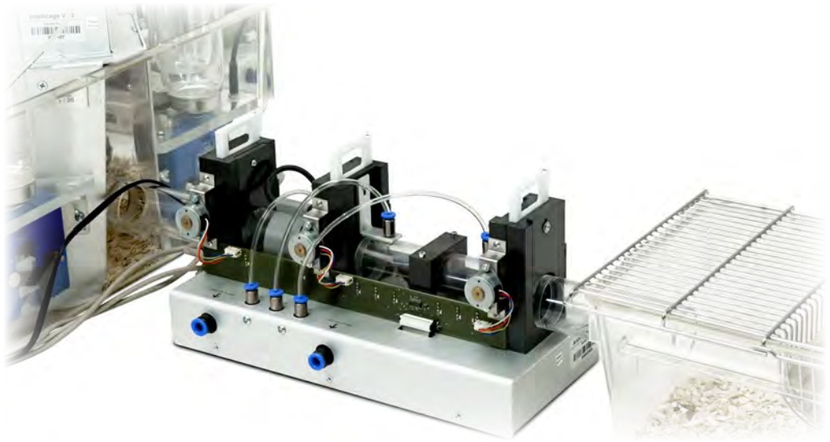
Add-Ons

Expand the IntelliCage to a multi-arena system

AnimalGate

Selective passage of specific animals for extended functionality

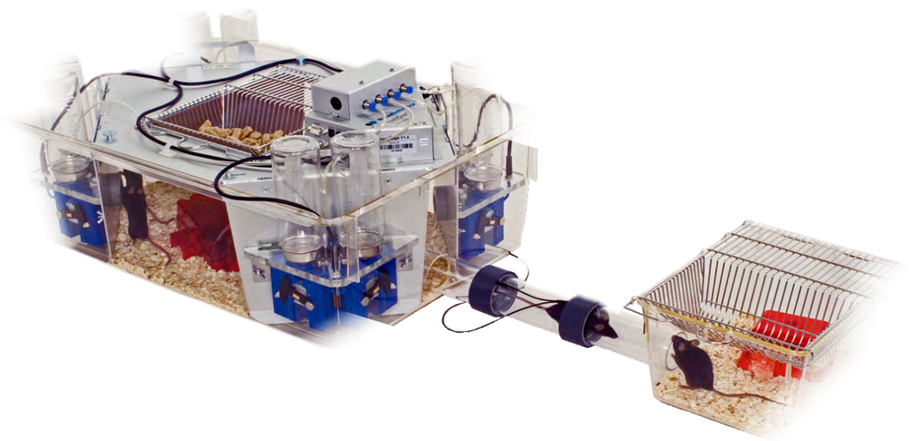
- Senses the direction of movement & allows/denies passage to satellite cage
- Allows black- or whitelisting of individuals
- Measures body weight of passing mice
- Extends the IntelliCage to measure food/liquid consumption
- Allows additional application of different treatments to individuals without handling

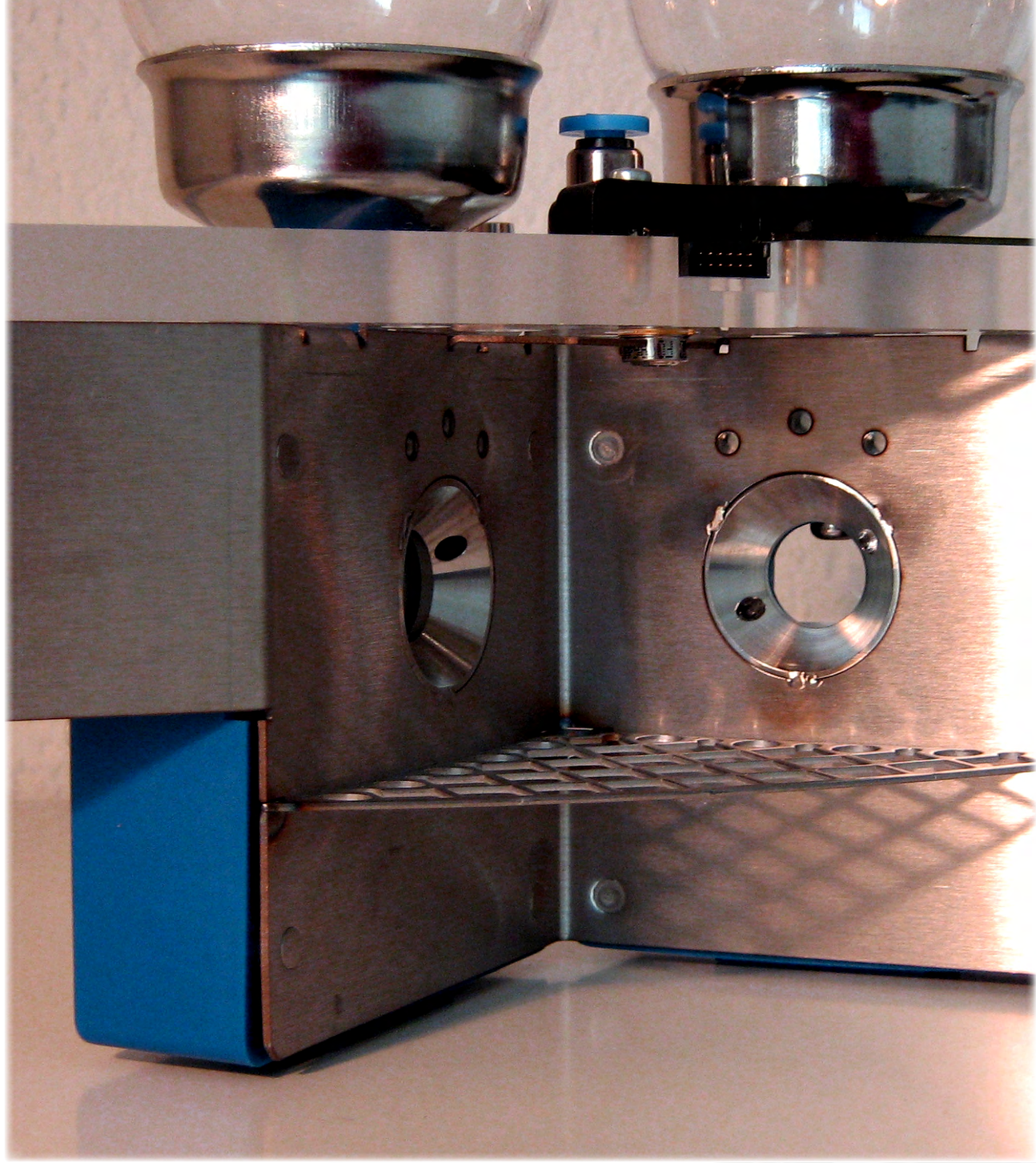


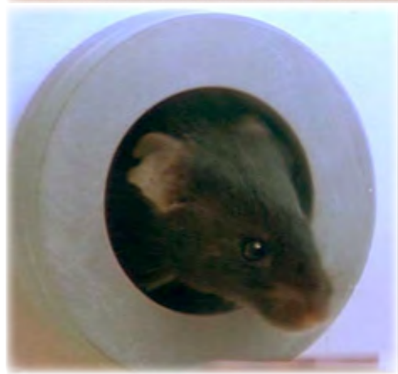
SocialBox

Monitoring of social behavior using the IntelliCage transponder-based RFID – technology

- Used for different tasks including social interactions between animals
- Monitoring of individual spatial preference/avoidance patterns by creating different environments in the boxes (e.g. differential lighting, temperature, color or padding, by olfactoric/acoustic devices or novel objects
- Up to four SocialBoxes can be added to one IntelliCage creating 5 compartments of a multi-arena system.







Selected Publications

- **Dere E et al. (2018)** Cognitive, emotional and social phenotyping of mice in an observer-independent setting.
  Neurobiol Learn Mem; 150:136-150

- **Voikar V et al. (2017)** Automated dissection of permanent effects of hippocampal or prefrontal lesions on performance at spatial, working memory and circadian timing tasks of C57BL/6 mice in IntelliCage.
  Behav Brain Res; pii: S0166-4328(17)30962-2.[Epub ahead of print]

- **Stefaniuk M et al. (2017)** Matrix Metalloproteinase-9 and Synaptic Plasticity in the Central Amygdala in Control of Alcohol-Seeking Behavior.
  Biol Psychiatry; 81(11):907-917.

- **Jastrzebska K et al. (2016)** Loss of NMDA receptors in dopamine neurons leads to the development of affective disorder-like symptoms in mice.
  Sci Rep. 2016 Nov 17;6:37171.

- **Masuda A et al. (2016)** Cognitive deficits in single App knock-in mouse models.
  Neurobiol Learn Mem; 2016 Nov;135:73-82

- **Heidari M et al. (2016)** Brain iron accumulation affects myelin-related molecular systems implicated in a rare neuro-genetic disease family with neuropsychiatric.
  Mol Psychiatry 2016; 1-9

- **Benner S et al. (2015)** Environmental insults in early life and submissiveness later in life in mouse models.
  Front Neurosci 2015; 9:91

- **Vannoni E et al. (2014)** Spontaneous behavior in the social homecage discriminates strains, lesions and mutations in mice.
  Neurosci Methods 2014; 234:26-37

- **Smutek M et al. (2014)** A model of alcohol drinking under an intermittent access schedule using group-housed mice.
  PLoS One; 9(5):e96787

- **Too LK et al. (2014)** The pro-inflammatory cytokine interferon-gamma is an important driver of neuropathology and behavioural sequelae in experimental pneumococcal meningitis.
  Brain Behav Immun 2014; 40:252-68

- **Puscian A et al. (2014)** A novel automated behavioral test battery assessing cognitive rigidity in two genetic mouse models of autism.
  Front Behav Neurosci; 8(140):1-11

- **Knapska E et al. (2013)** Reward learning requires activity of matrix metalloproteinase-9 in the central amygdala.
  J Neuroscience; 33(36):14591-14600

- **Branchi I et al. (2013)** Antidepressant treatment outcome depends on the quality of the living environment: a pre-clinical investigation in mice.
  PlosOne; 8(4): e62226

- **Parkitna JR et al. (2013)** Novelty-seeking behaviors and the escalation of alcohol drinking after abstinence in mice are controlled by metabotropic glutamate receptor 5 on neurons expressing dopamine D1 receptors.
  Biological Psychiatry; 73(3): 263-70

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