# IntelliCage for Rat & Mouse

Cognitive & Behavioral
Screening of Individual
**Animals Living in Social Groups**

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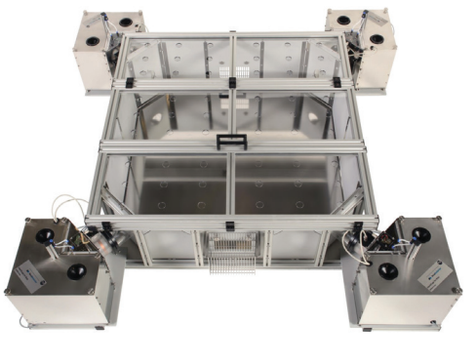
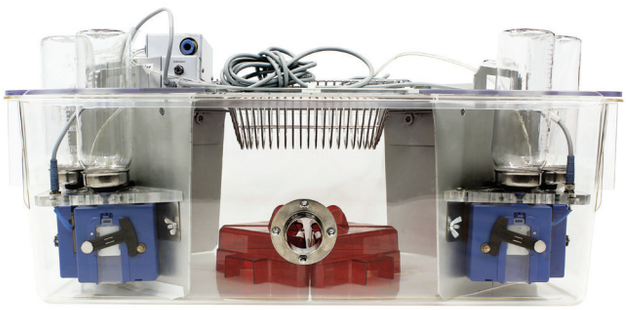
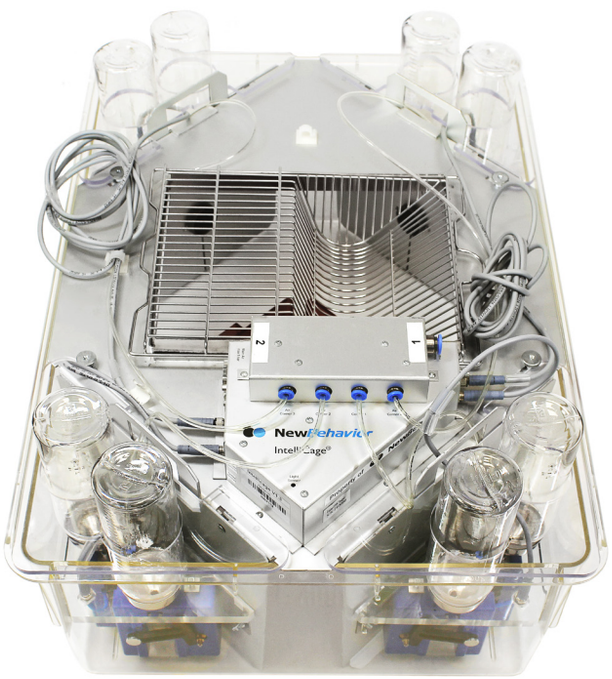
## IntelliCage for Rats



## IntelliCage for Mice



**The IntelliCage is the only system on the market which combines group-housed automated high-throughput screening in one home cage setup. Simple to complex behavioral and conditioning tasks can be designed for cohorts of eight rats or 16 mice through RFID-tagged transponders, allowing individually tailored protocols and recognition. The IntelliCage is comprised of four operant conditioning corners, equipped with sensors for continuous 24-hour recording of behavioral events for real-time access to recorded data anytime during ongoing experiments. IntelliCage offers exceptional high standardization, reproducibility, and minimal workload, a frequent requirement in biomedical, behavioral, neurobiological, pharmacological, and genetic research.**



## IntelliCage: **Unique features**

- Screening of Individuals in a Social Context
- Efficient, up to eight rats or 16 mice per respective rat or mice IntelliCage
- Maximal Standardization & Reproducibility
- High Validity (Minimal Human Intervention)
- Fully Automated Task Performance
- Broad Variety of Accessible Data
- Flexible Design of Paradigms

# IntelliCage: **Applications**

**Being able to capture behavioral changes within the organism is an important part of biomedical research. The IntelliCage provides a broad variety of accessible data for the following areas:**

## Behavioral Phenotyping

Automated high-throughput behavioral phenotyping in a social group. With highly standardized phenotyping procedures, the IntelliCage covers multiple behavioral and cognitive domains and allows the comparison of multiple animal models of any disease or single/ multiple gene knockouts.

## True longitudinal studies

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

## Mechanistic studies

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

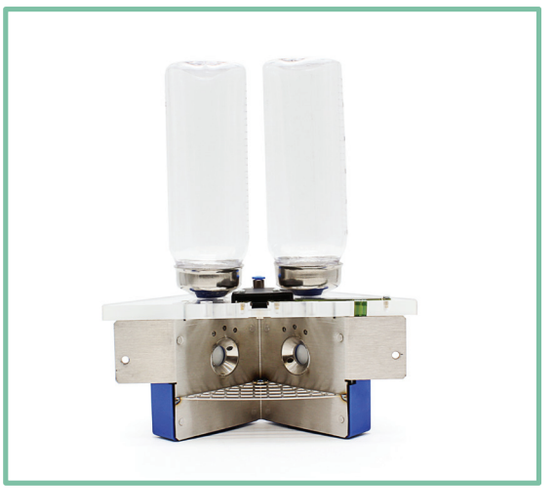
## Pharmacological studies

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 comparisons of data of different sexes, age groups, or genetic backgrounds.

## Wireless telemetry studies

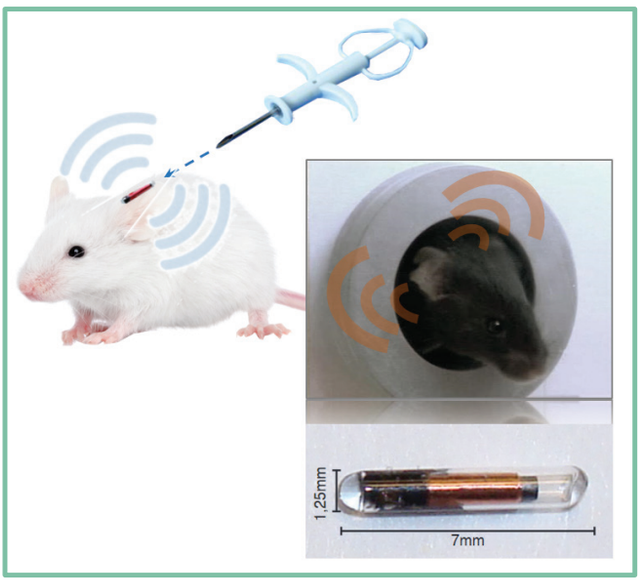
The ability to combine the automated behavioral phenotyping of the IntelliCage with our wireless telemetry system Stellar for simultaneous EEG, ECG, Blood Pressure, and Activity measurements.

# IntelliCage: **Technical details**



## Operant Corner:

The IntelliCage contains four identical operant conditioning corners, each corner can accommodate one mouse at a time and is equipped with two nose poke holes left and right that give access to water bottles. 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.

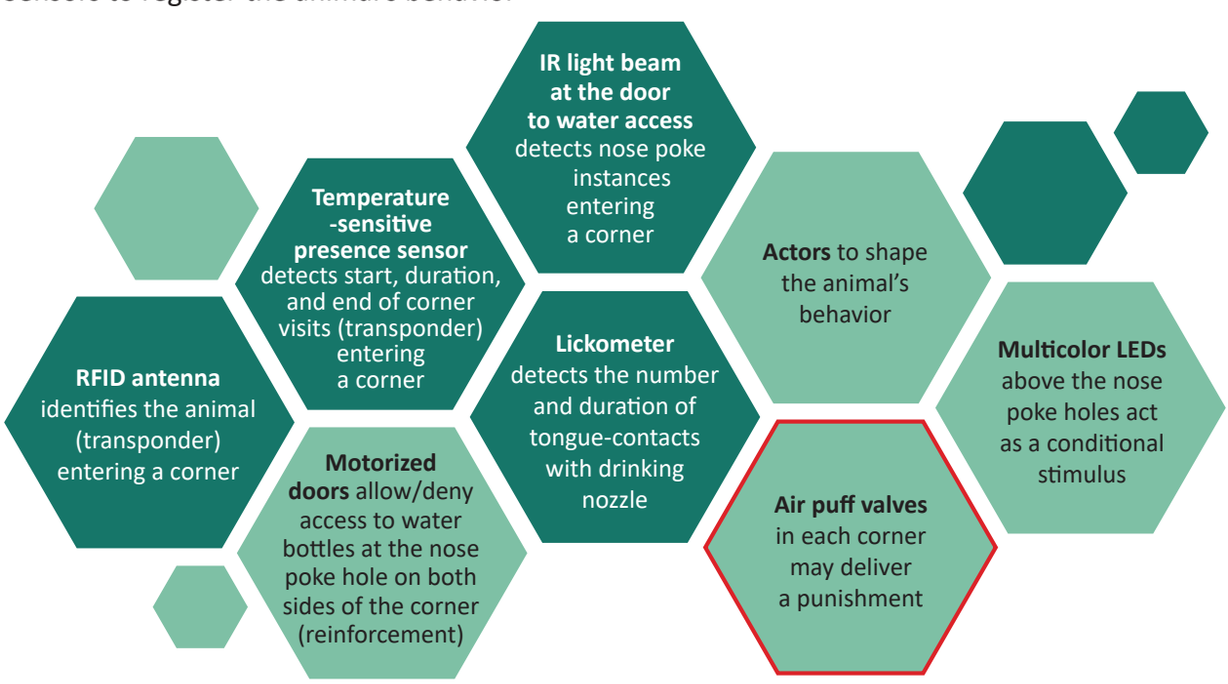



## RFID Transponder:

Rice corn-shaped RFID-transponders are subcutaneously injected within minutes, which allow individual recognition of an animal within one IntelliCage. To increase high-throughput, testing up to four IntelliCages can be connected to a single computer (testing of up to 64 animals at the same time).

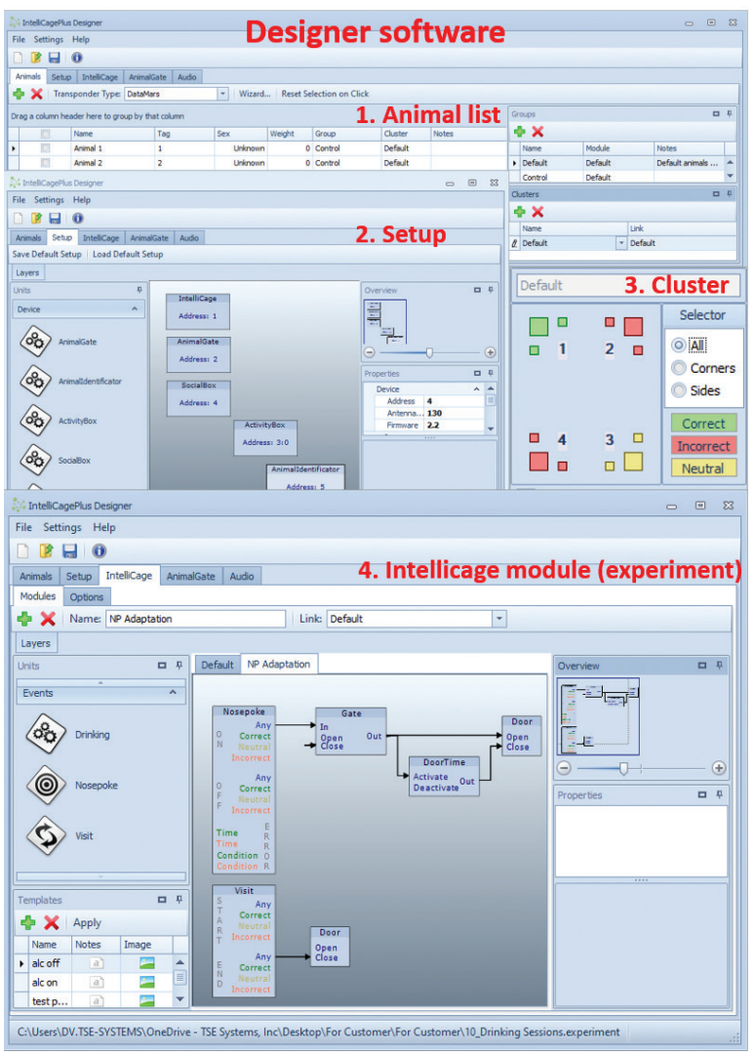
## Sensors & Actors:

Sensors to register the animal's behavior



## 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.




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 in an experiment and switched according to the accomplishment of behavioral challenge/task (switches between clusters/modules that can be driven by individual behavior)

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.

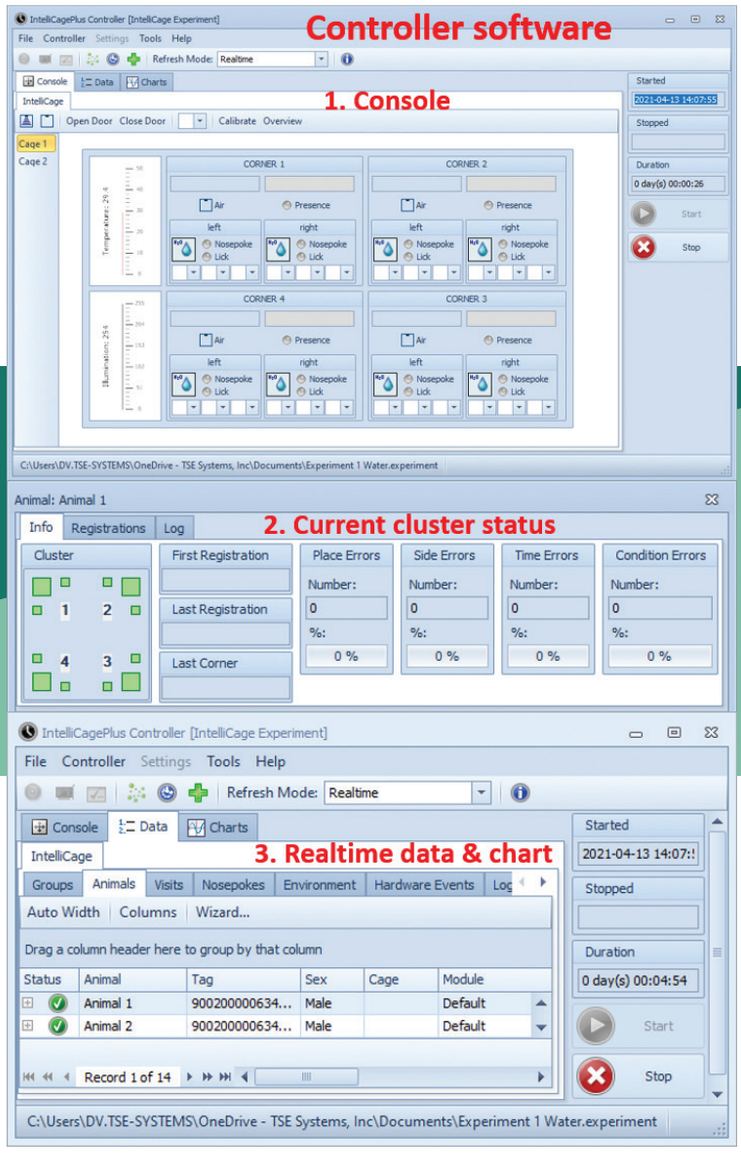
1 Specification of hardware setup

2 Generation of the 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

Controller:

## Run & visualize experiments




**01** Experimental files from the Designer are loaded and executed by the Controller software

**02** It extracts and stores all behavioral events (visits, nose pokes, licks), as well as environmental data (lighting, temperature) from the incoming stream of Sensor data.

**03** Events and corresponding actions can be monitored and visualized on-screen during ongoing experiments in an overview console view.

**04** All data are retrievable from various tables showing the correct or incorrect presence of individuals in conditioning corners, location and correctness of nose poke, incidences/extent of drinking behavior, and the occurrence of negative reinforcement (air-puffs).

**05** 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.

**06** The Controller can be programmed to send alerts if individual animals show no visits or licks during specified periods.

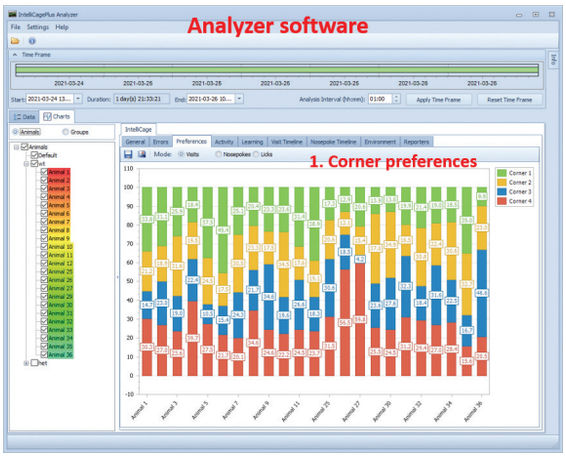
**07** After experiments, raw data from standard tab-delimited text files are saved into a zip-folder-archive which can be loaded into the Analyzer.

Analyzer:

## Filter, graph & export data

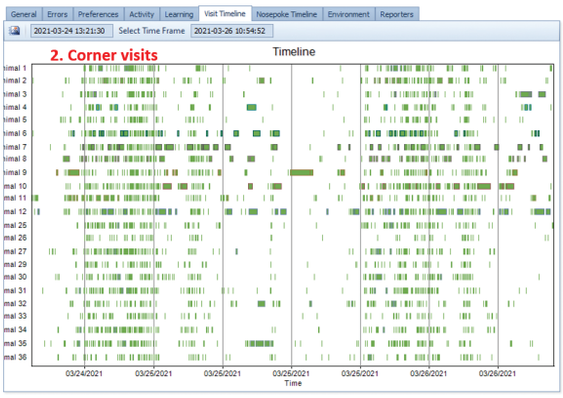
**1**

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 nose pokes of control animals during dark phase”).



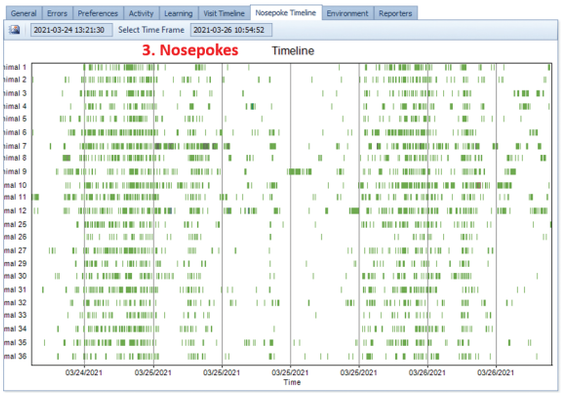

**2**

Filtering efficiently facilitates data evaluation while the original data remain accessible at any time.



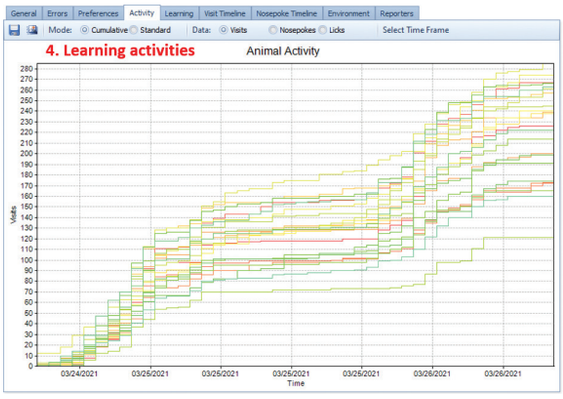

**3**

All applied filters can be stored to re-apply them for analyses of further experiments.




**4**

All graphs and figures can be saved as different image files.

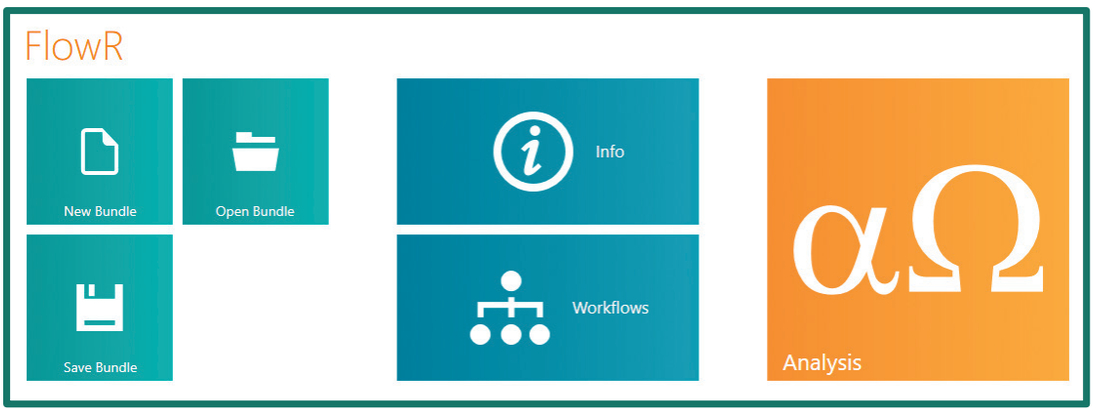


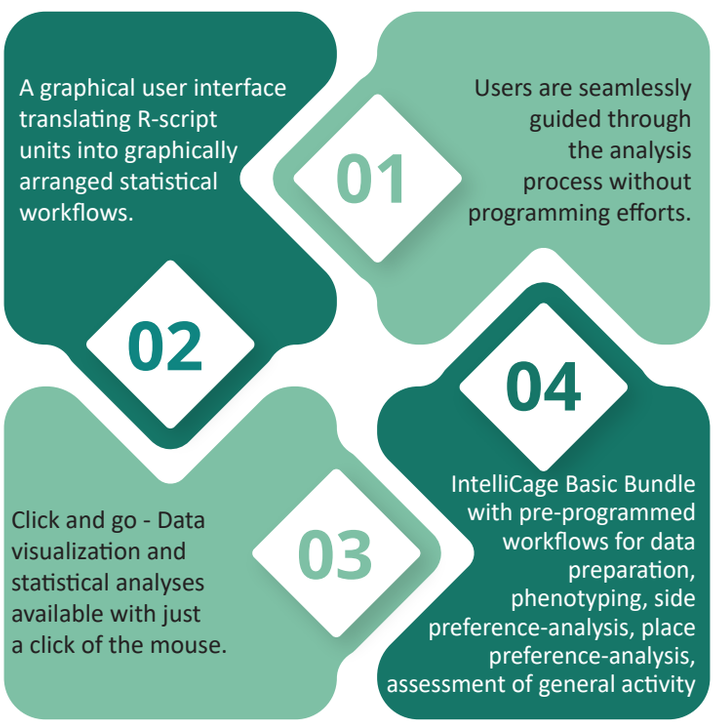

**5**

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”).

FlowR-Software by XBehavior:

## Statistical analysis & visualization optimized for IntelliCage data




## IntelliCage allows the transfer of multiple established behavioral paradigms into an automated setup.

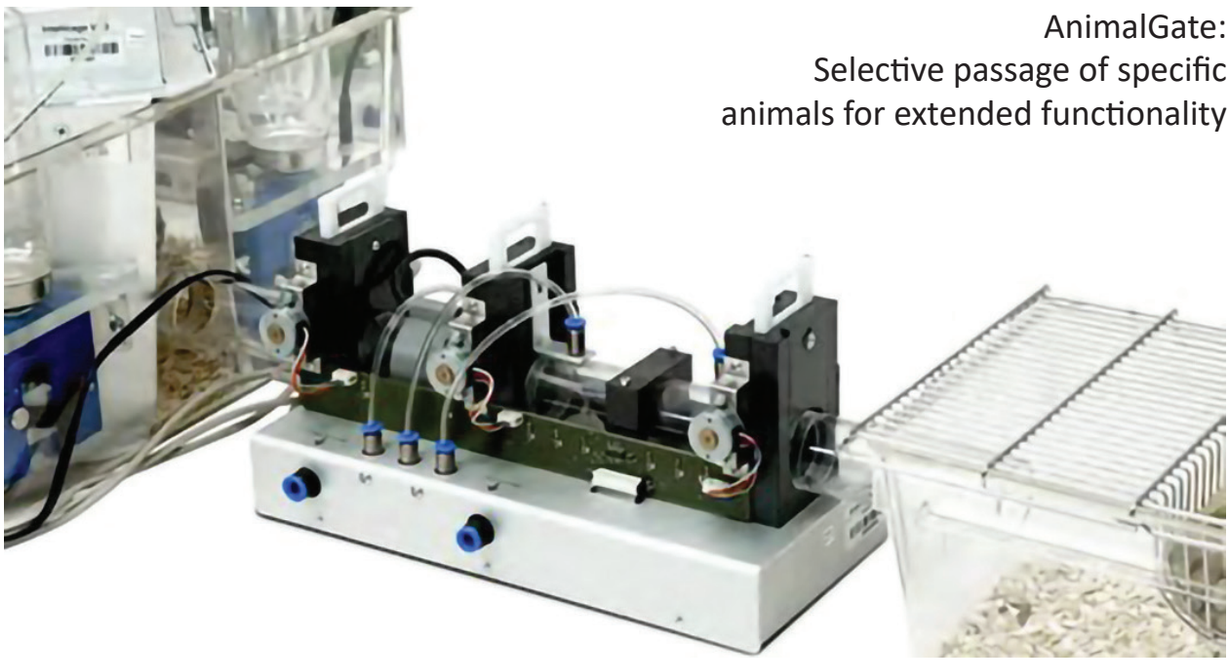
- Morris Water-Maze
- Radial Arm-/Y-/T-Maze
- Open-Field
- Sucrose-Preference
- Social-Defeat
- Competition- and Hierarchy-Tasks
- Vogels' Conflict-Test
- Novel-Object-Preference-Tests
- Operant-Conditioning (Fixed-/Progressive-Ratio, equivalent to SkinnerBox)
- Many other procedures for assessing general processes of learning & memory, executive function, behavioral flexibility, cognitive rigidity, effort choice behavior, 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, Alzheimer's Disease, Parkinson's Disease, Dementia, Epilepsy, Anxiety Disorders, Depression, Anhedonia, Neophobia, Pain, Obesity, Stress Disorders, Cognitive Disorders, Aberrant social behavior (non-exhaustive).

| 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* | A reward corner is changed to reverse prior spatial preference. |
| 6. Alternation | A reward side is alternated. |
| 7. Serial Reversal | A reward corner is changed serially according to the animal's performance. |
| 8. Patrolling | Reward corner shifts (anti-)clockwise after a correct response (visit, nose poke, or drink) – similar to spatial learning in an 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 & nighttimes. |
| 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) | Reward corners are indicated by the 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 | Probe trial tests for acquired aversion to unconditioned reinforce. |
| F. Operant Conditioning | |
| 20. Conditioned Stimulus (LED Scheme) | The conditioned stimulus (lights on/off) indicates reward side(water bottle access). |
| 21. Fixed Ratio* | A fixed number of responses is required to access a reward.The 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 ofLow Responding (DRL)* | Progressive response inhibition by reinforcing long time intervals betweenresponse (nose poke) incidents. |

## Add-Ons: **Expand the IntelliCage to a multi-arena system**



AnimalGate:
Selective passage of specific animals for extended functionality

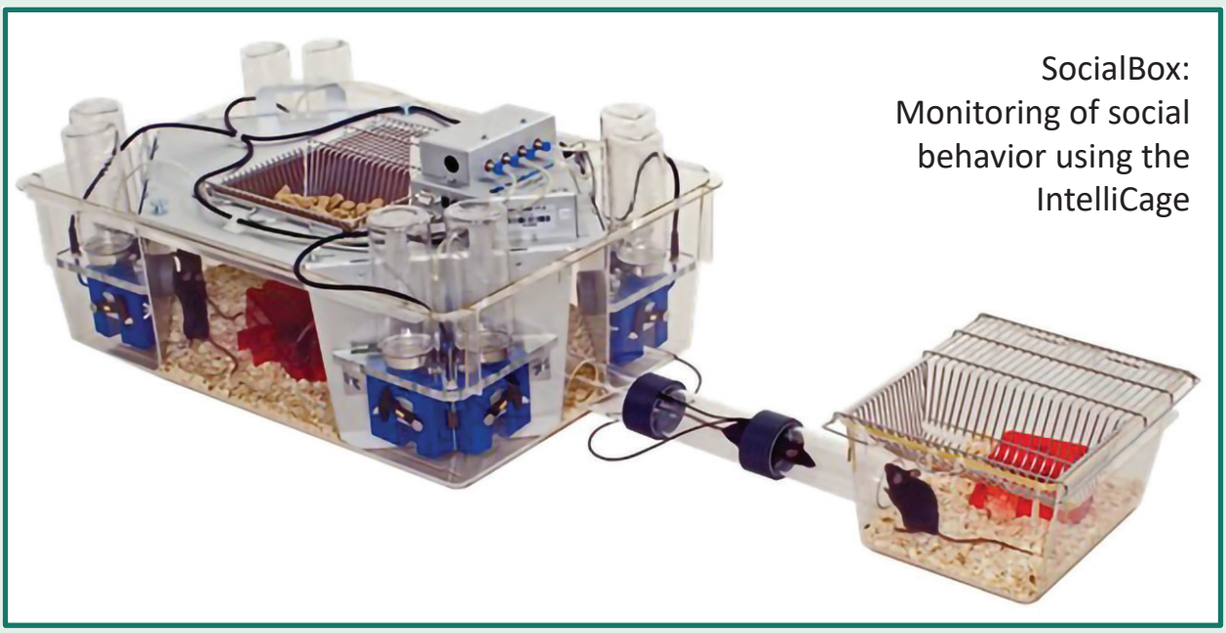
Senses the direction of movement & allows/denies passage to satellite cage

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

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 five compartments of a multi-arena system.

**Running wheel:**
Monitoring of motor activity using the IntelliCage

Up to four running wheels can be added to one IntelliCage

Monitoring of individual mice motor movement on running wheel directly from Intellicage controller

## Selected Publications


- Sun L et al. (2021) Antidepressant treatment is associated with epigenetic alterations of Homer1 promoter in a mouse model of chronic depression. J Affect Disord. 2021; 279: 501–509.
- Kiryk A et al. (2020) IntelliCage as a tool for measuring mouse behavior – 20 years perspective. Behav Brain Res. 2020; 388:112620.
- Mehr A et al. (2020 Lack of APP and APLP2 in GABAergic Forebrain Neurons Impairs Synaptic Plasticity and Cognition. Cereb Cortex. 2020; 30: 4044–4063.
- van Dijk RM et al. (2019) Consistent within-group covariance of septal and temporal hippocampal neurogenesis with behavioral phenotypes for exploration and memory retention across wild and laboratory small rodents. Behav Brain Res. 2019; 372: 112034.
- Hardt S et al. (2019) Distal infraorbital nerve injury: A model for persistent facial pain in mice. Pain. 2019; 160: 1431–1447.
- 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. 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


## Watch this Video:

https://www.jove.com/video/58009/automated-long-term-behavioral-assay-for-cognitive-functions-multiple

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