Sophisticated Life Science Research Instrumentation

Инновационные методы и инструменты для поведенческих in-vivo исследований

Международная конференция «Реальный путь от научных разработок до лекарственных средств» Москва, Россия

1-2 ноября, 2018

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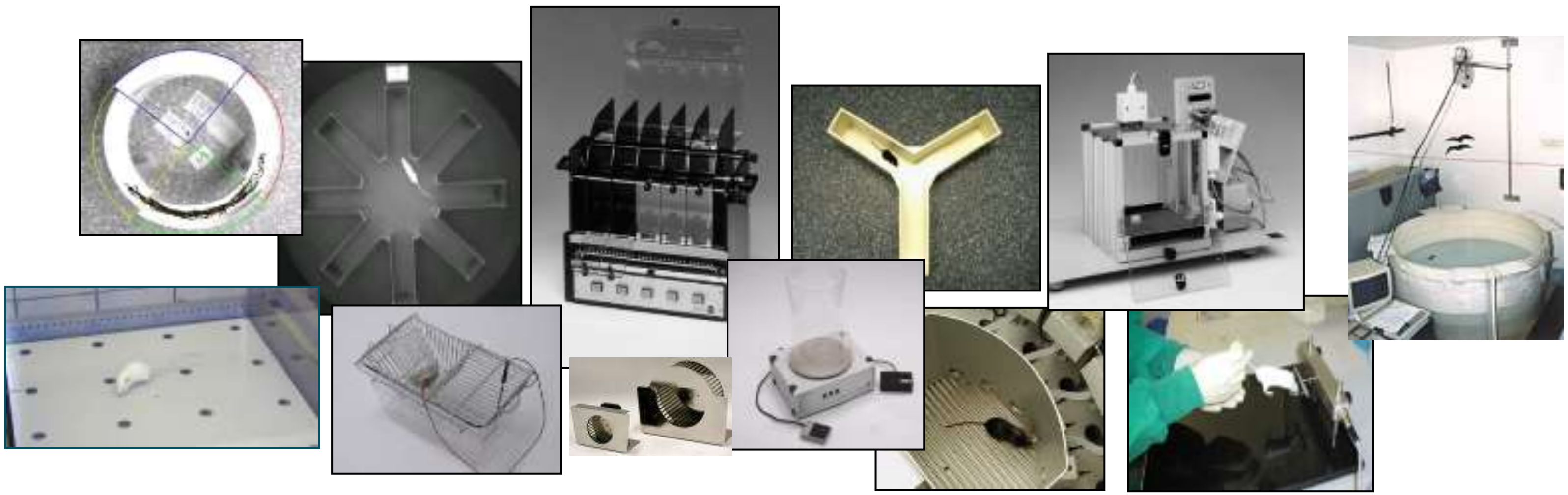
Золотые стандарты изучения поведения



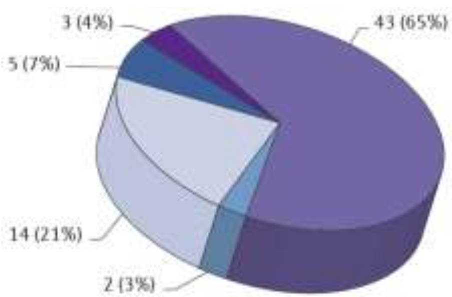
Недостаток: Отдельно стоящие системы требуют множество ресурсов

(Оборудование, помещение, животные, время, персонал)

Факторы воздействующие на поведение грызунов

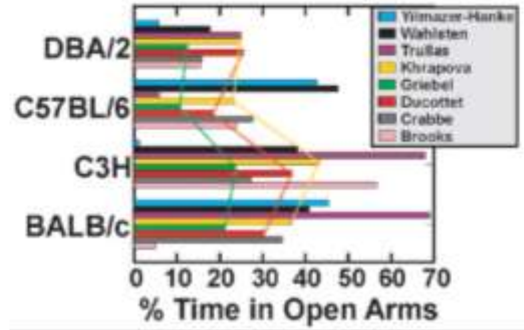
Доверять или нет: насколько мы можем полагаться на публикумые данные на рынке медикаментов?

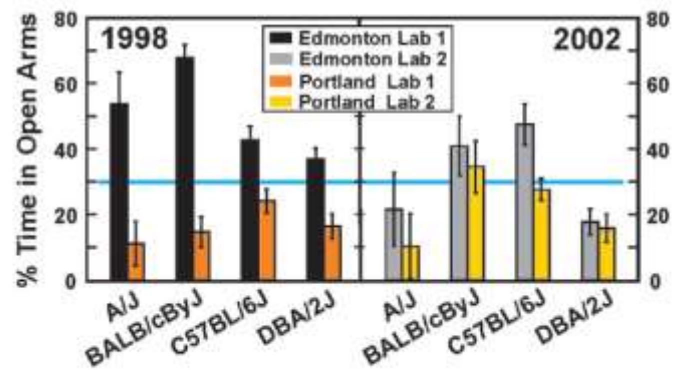
NATURE REVIEWS | DRUG DISCOVERY



Analysis of the reproducibility of published data in 67 in-house projects.

- Inconsistencies
- Not applicable
- Literature data are in line with in-house data
- Main data set was reproducible
- Some results were reproducible





Что мы предлагаем

Использовать следующие методы:

- Минимизировать взаимодействие человека с животными
- Существенно сократить время исследования
- Долгосрочное тестирование с возможностью социального взаимодействия
- Автоматизировать получение данных

TSE Systems - Решения

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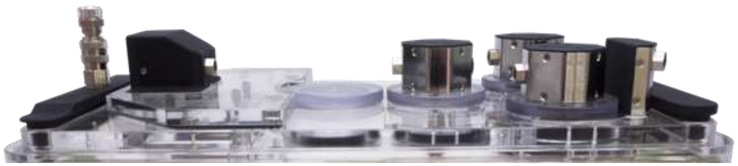
PhenoMaster – Модульная Система

Контроль потребления пищи,

жидкости, иземенения массы тела



Оперантная стенка

Непрямая калориметрия

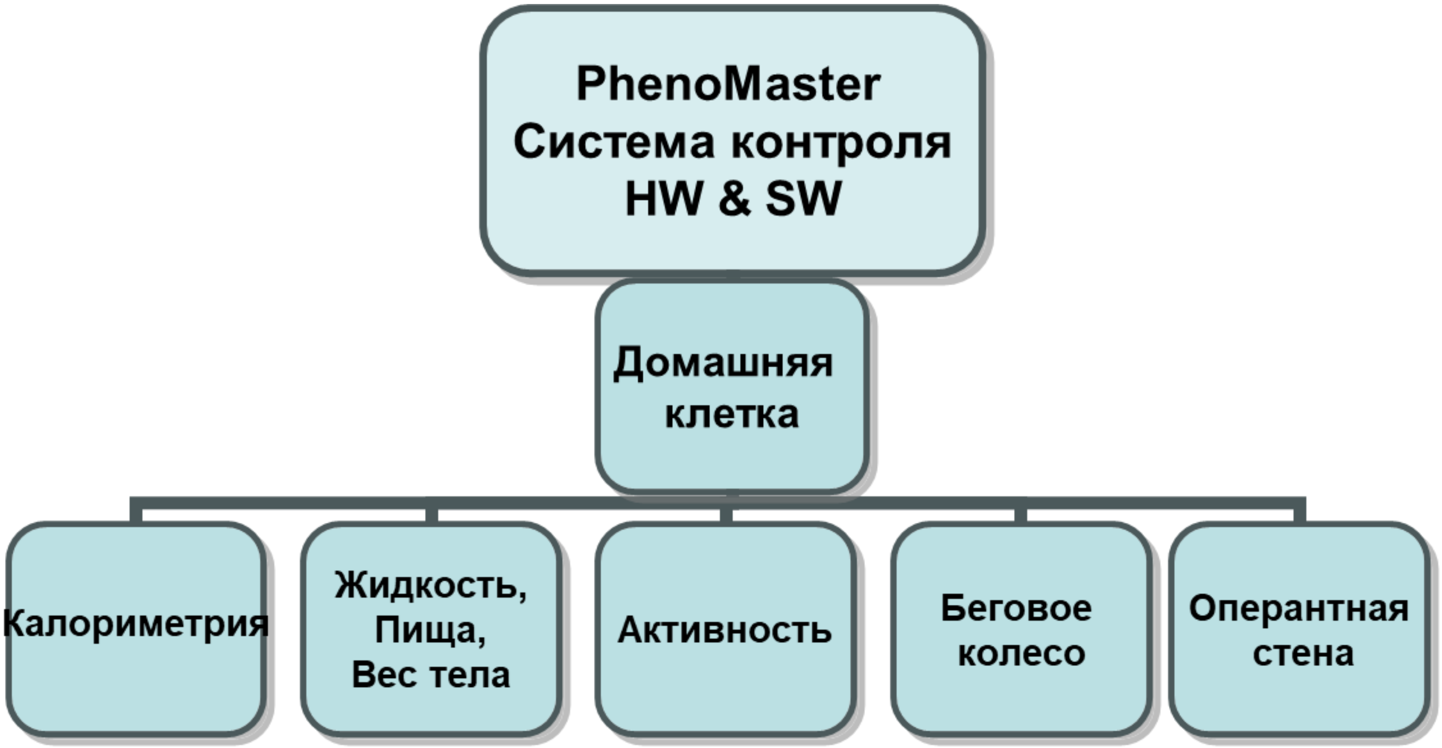
Климатический шкаф

ИК-рамки измерения активности

Беговое колесо

Концепция PhenoMaster

Техническое и программное обеспечение



PhenoMaster -технология Swivel

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

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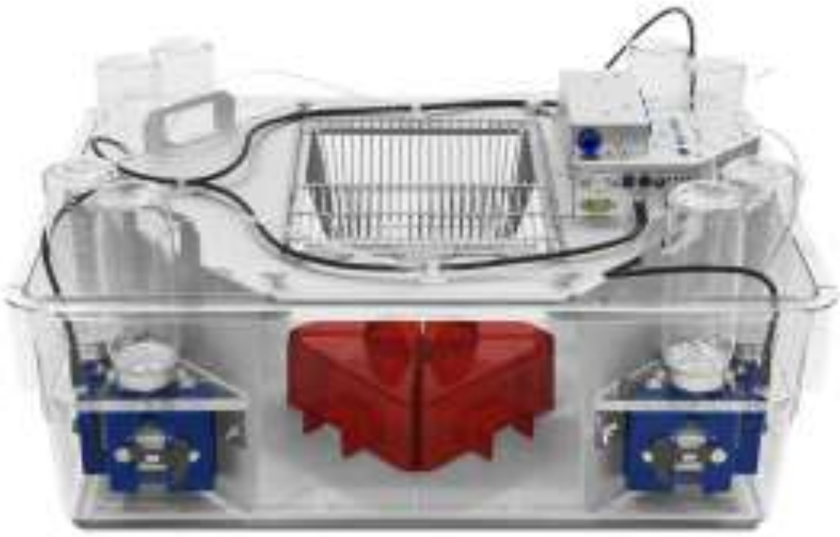
IntelliCage

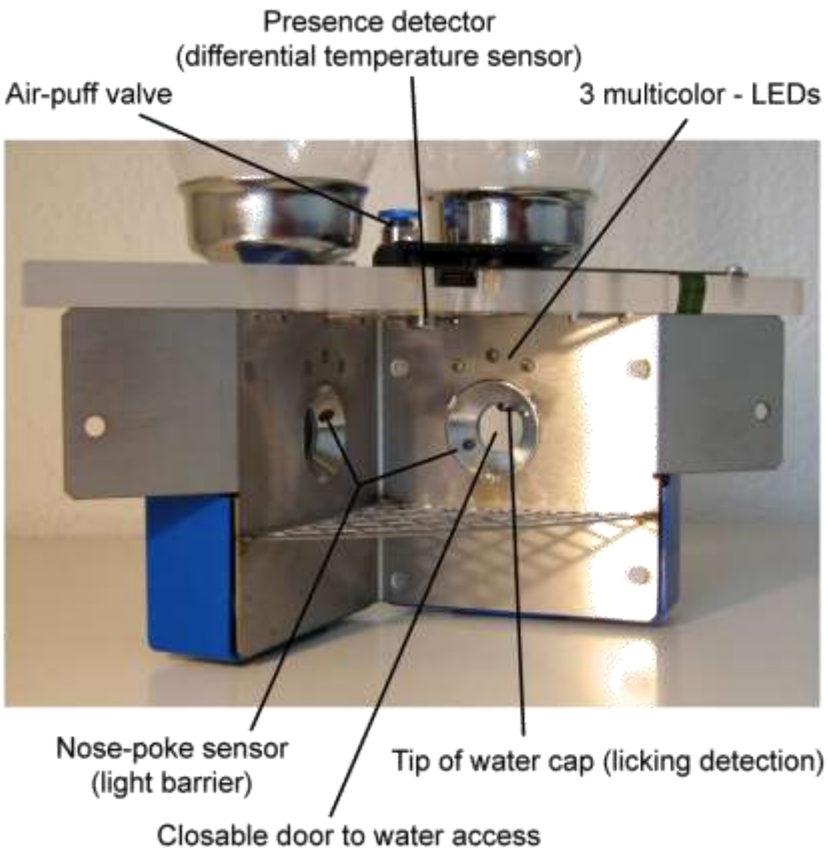
Исследование поведения в полностью автоматизированной групповой домашней клетке



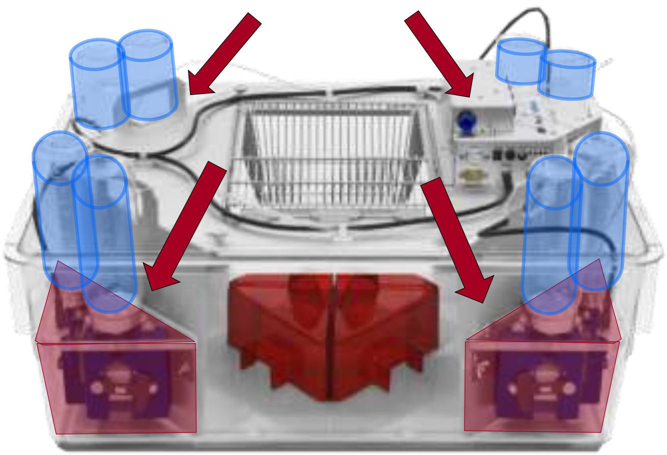
IntelliCage - 4 условно-оперантных угла

Sophisticated Life Science Research Instrumentation

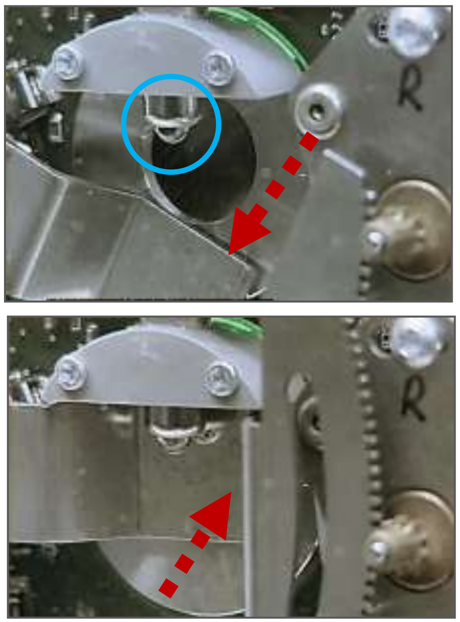
NewBehavior



IntelliCage для мышей



- Установка для автоматического поведенческого скрининга и оценки когнитивных функций
- Просторный центральный отсек с сеткой для еды и укрытием
- 4 угла для программирования задач
- Технология RFID-транспондера; вводятся подкожно
- RFID антенны идентифицируют посещение животными углов системы

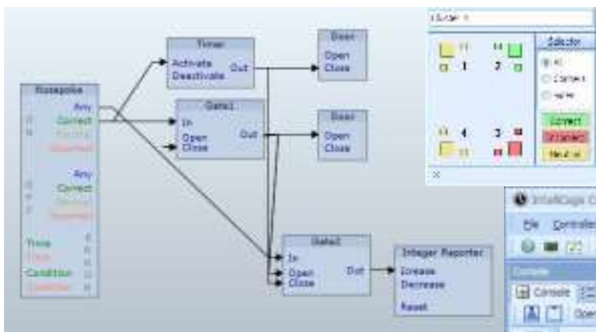


Моторизирован ная дверь

Световые стимулы

Воздушные стимулы

Программное обеспечние



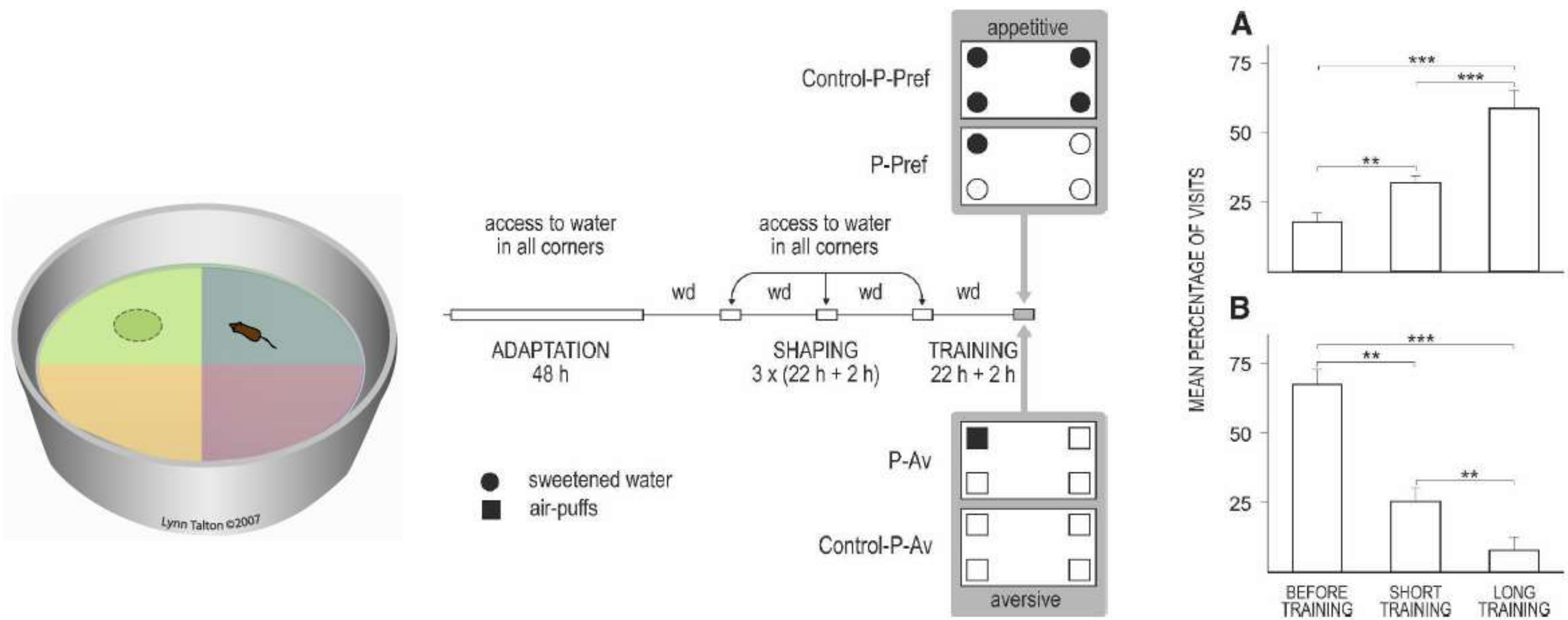
Дизайнер

Контроллер

Аналайзер

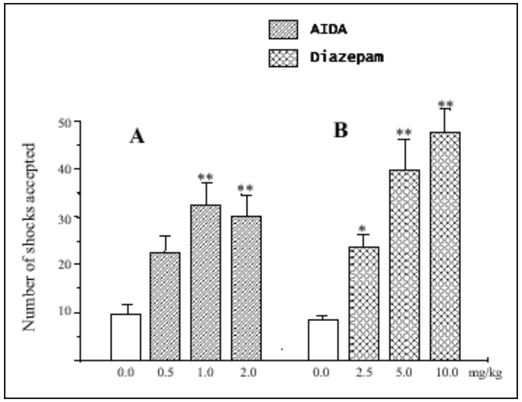
Перенос классических поведенческих парадигм в автоматизированную систему

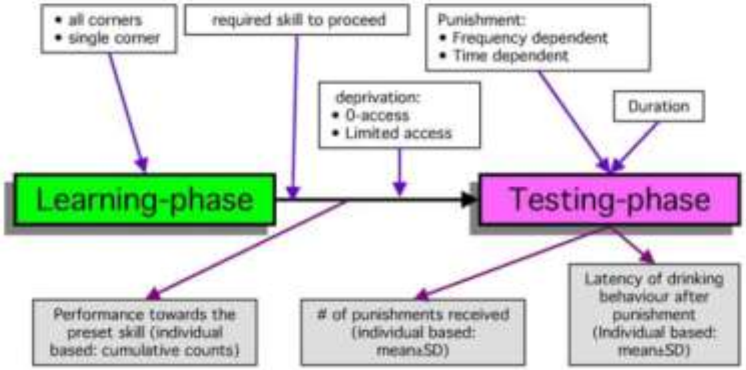
Пространственное обучение и память



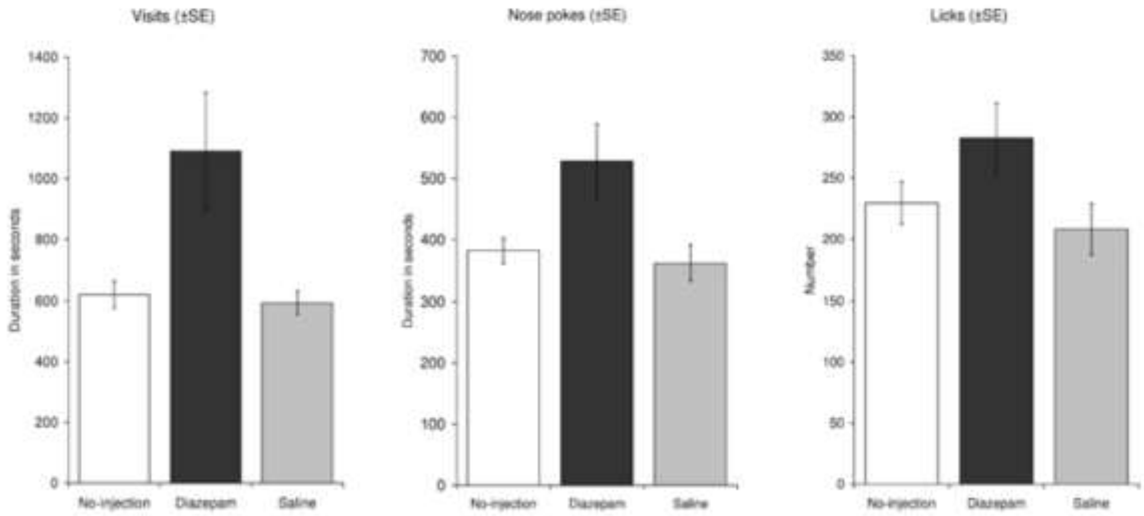
Knapska et al., 2006

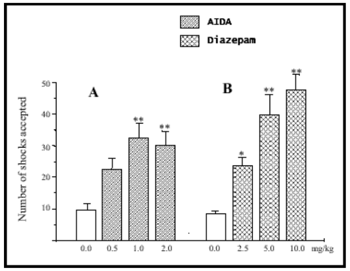
Тестирование воздействия препаратов на страх и тревожность





Изучение эффектов анксиолитического препарата в IntelliCage





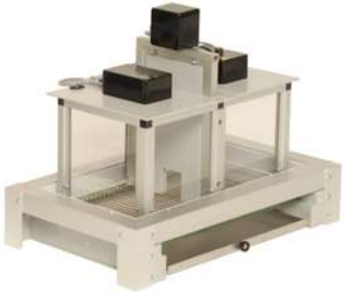
Валидированные поведенческие парадигмы могут быть реализованы в системе IntelliCage с одновременным решением проблем стандартизации

Safi et al., 2006

Модульная платформа Multi Conditioning

Тест Реакция страха

Активное избегание



Пасивное избегание

Предпочтение места

И многое другое...

Multi Conditioning – парадигмы

Реакция страха
Активное избегание
Пасивное избегание
Латентное торможение
Выученная беспомощность
Предпочтение места
Светло-темная камера
Паническое расстройство
Локомоторная активность
Открытое поле

Разработка лекарственных препаратов

- Скрининг лекарств (желаемые эффекты, побочные эффекты)
- Фармакологические и токсикологические исследования

MCS – преимущества

- **Исключение влияния** человеческого фактора на чистоту эксперимента
- Тестирование **при любом освещении**, в том числе и в полной темноте
- **Экономия места**, требуется только один базовый модуль
- **Гибкость**, применима к множеству моделей
- **Выгодная цена**, для реализации нескольких парадигм

Телеметрия Stellar – инновация- технология - преимущества

Экспериментальные данные для неограниченного количества животных считываются с помощью одной антенны !

Антенна может быть размещена на стене, потолке или установлена в отдельном помещении (виварий, лаборатория, вольер)
Диапазон действия 5 м (15ft.)

Плата с памятью „on board“, размером 1 Гб – свобода передвижения без зависимости от расположения антенны

Антенна имеет только одно подключение USB к компьютеру или ноутбуку

Спасибо за внимание!

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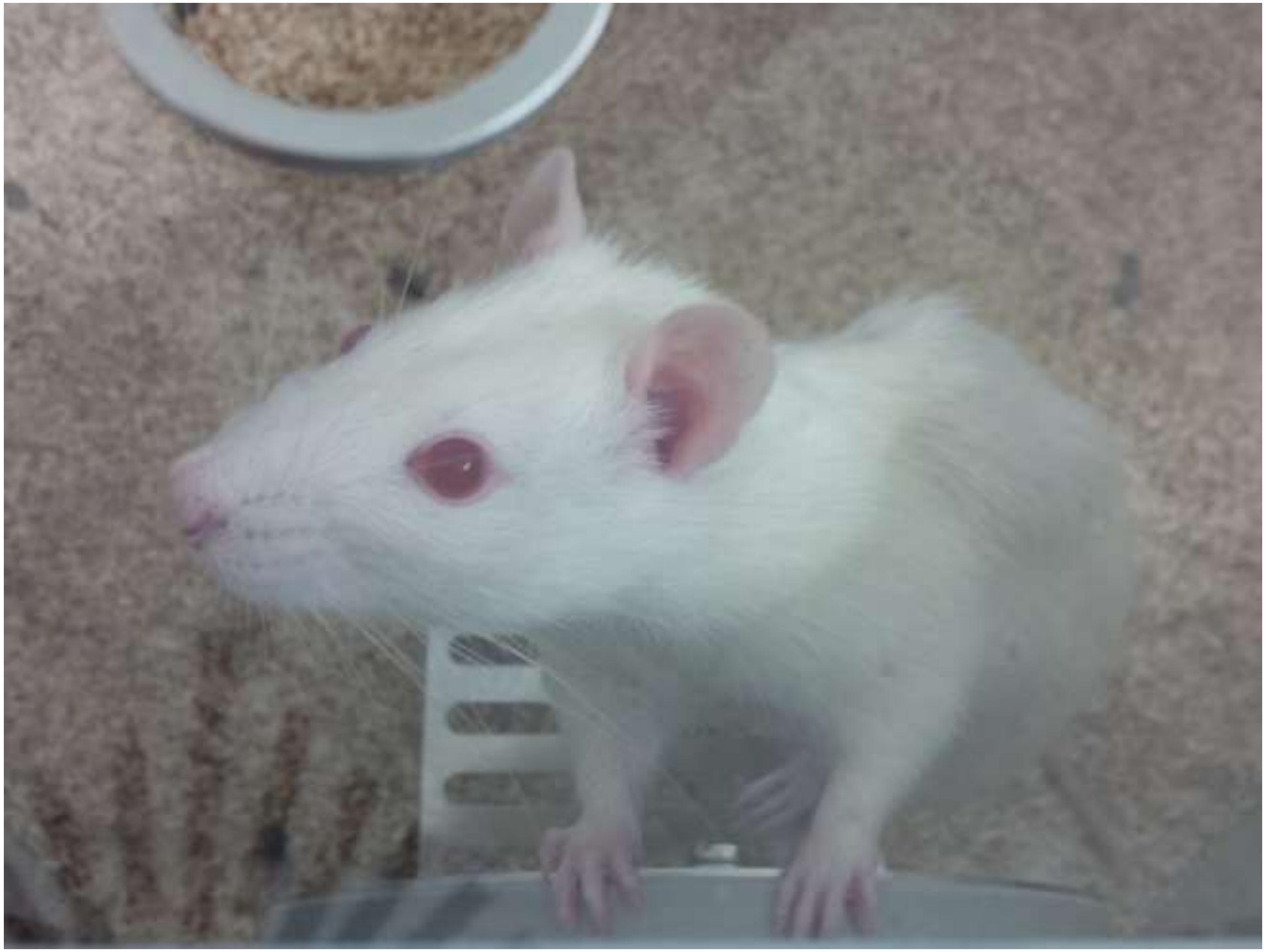

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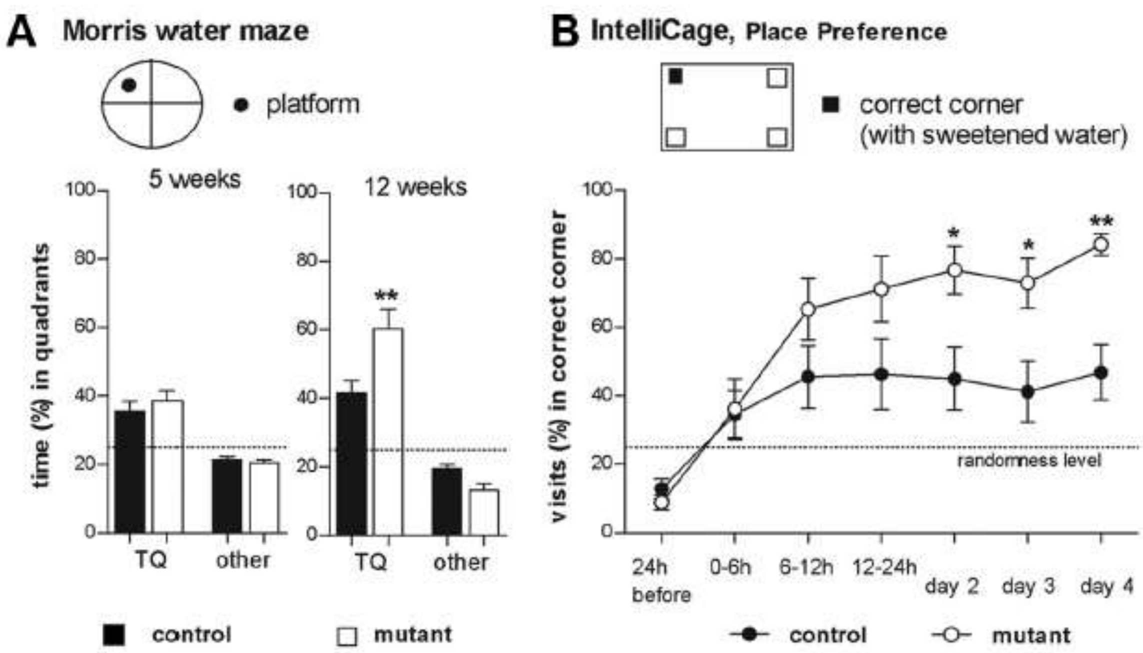
Transfer of validated behavioral paradigms into automated setup

Spatial learning and memory



Konopka et al., 2010

Behav Genet
DOI 10.1007/s10519-017-9853-3

ORIGINAL RESEARCH

Rsk2 Knockout Affects Emotional Behavior in the IntelliCage

Matthias Fischer[1] · Victoria Cabello[1] · Sandy Popp[2] · Sven Krackow[3] ·
Leif Hommers[1] · Jürgen Deckert[1] · Klaus-Peter Lesch[2,4,5] ·
Angelika G. Schmitt-Böhrer[1]

Behavioral tests in the IntelliCage

About 10–16 mice per IntelliCage (approximately equal numbers of KO and WT mice) were subjected to behavioral tests. Prior to each conditioning test, subjects were given an adaptation period of 6 days with all doors open and free access to the drinking bottles. Standard lab rodent food was provided ad lib throughout experiments. In addition, 2 days were given for the animals to adapt to nosepoking for door opening, i.e., doors were closed and opened for 7 s per visit only after the subject poked at a door (exception: 5 s for motor impulsivity).

Several experiments (all place learning schemes, anxiety test) were conducted using two drinking sessions during dark phase (21–23 and 3–5 h for place learning, 23–3 h for anxiety test) in order to increase learning motivation. Conditioning schemes were applied during drinking sessions only, IntelliCage doors stayed shut outside those sessions. In these cases, animals were given 2 days of adaptation to the schedule, i.e. doors opened at nosepoke for 7 s during drinking sessions, but kept close otherwise, before conditioning schemes were applied.

Activity and exploratory behavior

During the 6 days of free adaptation, the following behavioral measures were extracted for characterisation of spontaneous activity of each subject: NPvisits = Visits with Nosepoke without Licks/h; Lvisits = visits with licks/h; Svisits = visits without licks and nosepokes/h; NPVdur = median duration of visits w/np w/out lick; Nosepokes = mean number of nosepokes during visits w/np w/out licks; NPduration = median duration of such np during a visit; Licks = median number of licks per visit; Lduration = median duration of licking during a visit; Lcontact = median bottle cap contact time during a visit; Nocturnal = relative night activity [(visits during night − visits during day)/(total no. of visits)]; Repetitive = log(sum of observed returns to same corner/sum of expected such switches); Regularity = sqrt(sum of squared non-diag transition matrix residuals/sum of non-diag transition matrix observed values). We used the beginning of this 6 days adaptation period after placing the mice into the IntelliCage to investigate exploratory activity of a new environment by measuring time till first visit/nosepoke/lick, number of visits till first nosepoke/lick or time and number of visits before visiting, nosepoking or drinking in all four corners. Means are taken for frequencies with few levels when medians could strongly mislead in small samples and mask differences in large ones. Medians for durations and licks cut out outliers, like corner sleepover or spurious hits of sensors during exiting.

Place learning

After free adaptation, nosepoke adaptation, and drinking session adaptation, a series of place learning experiments was carried out consecutively, with several experimental groups. In all cases, visits with nosepokes represented a trial that could either be correct or not (25% success by chance).

Place preference

Nosepokes opened the door only in one of the four corners for each subject for 6 sessions (3 days). Rewarded corner was randomly assigned to each subject and balanced between genotypes. After that, rewarded corner was swapped to the opposite corner (reversal) for another 6 sessions.

Place75

Consecutive to Place learning reversal, rewarded corner was set to the next corner in clockwise direction and reward given with a probability of 75%, for another 6 sessions.

Place change

For 6 sessions the rewarded corner was swapped randomly (excluding the prior rewarded corner), at every session.

Chaining

For 8 sessions, the rewarded corner was switched after each visit with nosepoke to the next corner in clockwise direction. Hence, subjects had to circle around the IntelliCage to get water during the drinking sessions. After that, direction of rewarded corner switch was reversed to counterclockwise (reversal) for another 16 sessions.

Patrolling

Same as chaining except that the rewarded corner switched to the next corner after each *correct* visit with nosepoke, i.e. only after a visit with nosepoke that led to door opening. Hence, in contrast to chaining, the position of the rewarding corner was not switched until it was successfully entered. After 12 such sessions (6 days), direction of rewarded corner switch was changed from clockwise to counterclockwise (reversal) for 16 sessions.

Motor impulsivity

During training phase (first 3 days) the door initially poked at with the first nosepoke of a visit opened 0.5, 1.5 or 2.5 s after the initial nosepoke. The length of the delay varied randomly. After the delay 3 green LEDs were switched on on the side of the first nosepoke and the door opened at this side for 5 s. During the training phase (first 3 days) a nosepoke before the LEDs were switched on (premature nosepoke) had no effect.

In the following test phase (5 days) premature second nosepokes (before LED on) terminated the trial, i.e., the animals would have to leave the corner and visit again to start a new trial. Hence, animals had to learn, that after an initial nosepoke they had to wait with the second one till LED was switched on, not knowing if it would take 0.5, 1.5 or 2.5 s.

Impulsivity level was therefore measured by the proportion of correct responses (i.e., visits without premature nosepokes).

Cognitive impulsivity

In each corner one bottle was filled with water and one with 2% sucrose. A nosepoke at one door prevented opening of the other door during a visit. During 4 days mice were allowed to develop a preference for sucrose.

After that, the delay discounting condition scheme allowed drinking after nosepoking at the water bottle side without delay, as before, but at the sucrose side mice had to wait for some period of time till a nosepoke could open the door. The delay increased from 0.5 s every day by 0.5 s, up to 8 s delay. An earlier breakdown of preference for sucrose side would be taken as evidence of higher cognitive impulsivity in a group.

Chaining, patrolling and impulsivity were determined with similar designs as applied in Kobayashi et al. (2013).

Anxiety

In each corner one bottle was filled with water and one with 2% sucrose. WT and KO mice were assigned randomly and balanced within strains to two groups, respectively. One group had access only to the water bottles, the other group only to the sucrose bottles.

After general adaptation to the IntelliCage with water in all bottles and 3 days adaptation to the described sucrose and water side situation, eight days of airpuff-application followed. From 23 h till 3 h a nosepoke in one or the four corners initiated an airpuff for 1 s and with about 1 bar ("anxiety" phase). The anxiety corner was assigned randomly and balanced within strains to each mouse. During the intervening time periods no airpuffs were delivered ("inter" phase).

As an indicator of state anxiety, we measured the time it took a subject, after reception of the first airpuff, to nosepoke again in the airpuff delivering corner.

Cognitive Flexibility

frontiers in
BEHAVIORAL NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 29 April 2014
doi: 10.3389/fnbeh.2014.00140

A novel automated behavioral test battery assessing cognitive rigidity in two genetic mouse models of autism

*Alicja Puścian[1], Szymon Łęski[1], Tomasz Górkiewicz[1], Ksenia Meyza[1], Hans-Peter Lipp[2,3] and Ewelina Knapska[1]**

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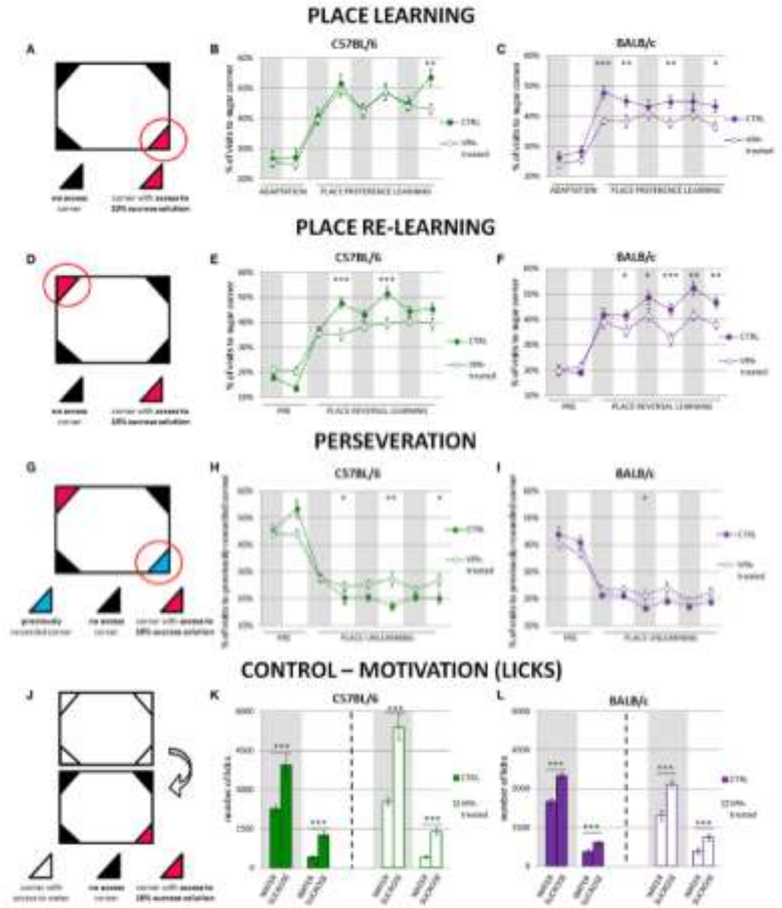
[3] Department of Physiology, School of Laboratory Medicine, KwaZulu-Natal University, Durban, South Africa

	Adaptation phases		Training phases	
	Simple adaptation	Nosepoke adaptation	Place preference learning	Place reversal learning
Days	1–5	6–7	8–10	11–13
Liquid in bottles	Tap water	Tap water	10% sucrose	10% sucrose
Learning chambers with liquid access	All 4	All 4	One per animal	One per animal (opposite to the one accessible during the previous phase)
IntelliCage overview				



Effort choice behavior

Addiction Biology

PRECLINICAL STUDY doi:10.1111/j.1369-1600.2011.00194.x

Characterization of an alcohol addiction-prone phenotype in mice

Kasia Radwanska & Leszek Kaczmarek

Laboratory of Molecular Neurobiology, Nencki Institute, Poland

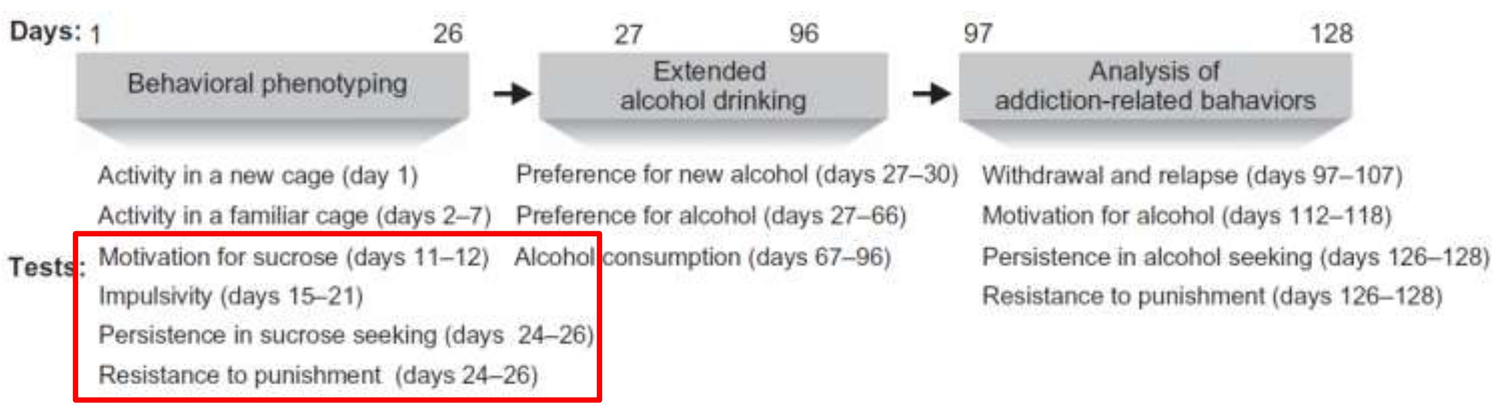


Figure 1 Experimental timeline