FP6 - 037965

INTELLIMAZE

High-throughput, fully automated and cost-effective behavioural phenotyping of normal, clinical and genetic mouse models

SME/STREP HEALTHSCI

PUBLISHABLE FINAL ACTIVITY REPORT

Period covered: from 01/11/2006 to 31/10/2009

Date of preparation: 31/10/2009

Start date of project: 01/11/2006

Duration: 36 months

Project coordinator name: Hans-Peter Lipp
Project coordinator organisation name: NewBehavior AG

SECTION 1

PROJECT EXECUTION

1.1. Description of project objectives

This SME project allied three SME's and four academic partners **for developing and validating a compact, economic and fully automated modular platform, INTELLIMAZE,** that will permit both high-throughput and detailed behavioural characterisation of current and future mouse models in biomedicine. The technical development was done by two SMEs (NewBehavior, and Frank Buschmann International) and one academic partner (Anokhin Institute of Normal Physiology of the Russian Medical Academy of Science). The **commercial objective** was to obtain a significant market share of the developing market of automated test systems, and to tailor such systems for small biotech SME's in need of behavioural characterisation. The joint **scientific objectives** of the academic partners were **validation** of this novel technology and inter-laboratory **standardisation**. According to their expertise, they had also to implement the novel technology specifically for:

- in-depth behavioural **profiling of brain lesions** in mice, focussing on hippocampus, striatum and prefrontal cortex
- development of novel behavioural paradigms for **mouse models of anxiety and depression**
- monitoring the progress of brain malfunction in **mouse models of Alzheimer's disease**

The final goal was **a fully automated behavioural test system for mice inside a home cage, and outside in traditional test arenas, working without supervision**, and outputting data in familiar format and ready for statistics. Moreover, **cross-laboratory standardisation** was achieved with minimal efforts, **and animal welfare guaranteed**. In order to achieve better market penetration, NewBehavior has concluded a **distribution agreement with another SME** (TSE Systems Germany), thus realising one of the objectives of the STRE/SME FP6 programme.

1.2. Contractors involved

NewBehavior AG	Prof. Hans-Peter Lipp	Zurich	Switzerland
Frank Buschmann International GmbH	Dr. Frank Buschmann	Essen	Germany
Istituto Superiore di Sanità	Prof. Enrico Alleva	Rome	Italy
Neurotec Karolinksa Institute	Prof. Abdul Mohammed	Stockholm	Sweden
University of Zürich	Prof. David Wolfer	Zurich	Switzerland
Anokhin Institute Russian Academy of Medical Science	Prof. Kostya Anokhin	Moscow	Russian Federation
Evotec Neurosciences GmbH	Dr. Antje Willuweit	Hamburg	Germany

Co-ordinator contact details

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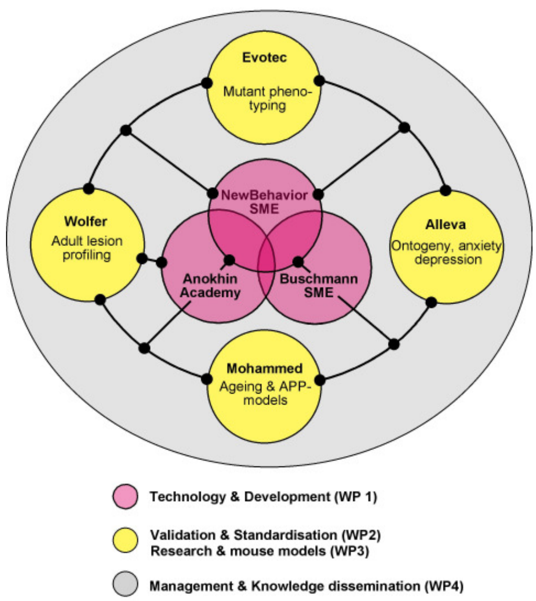
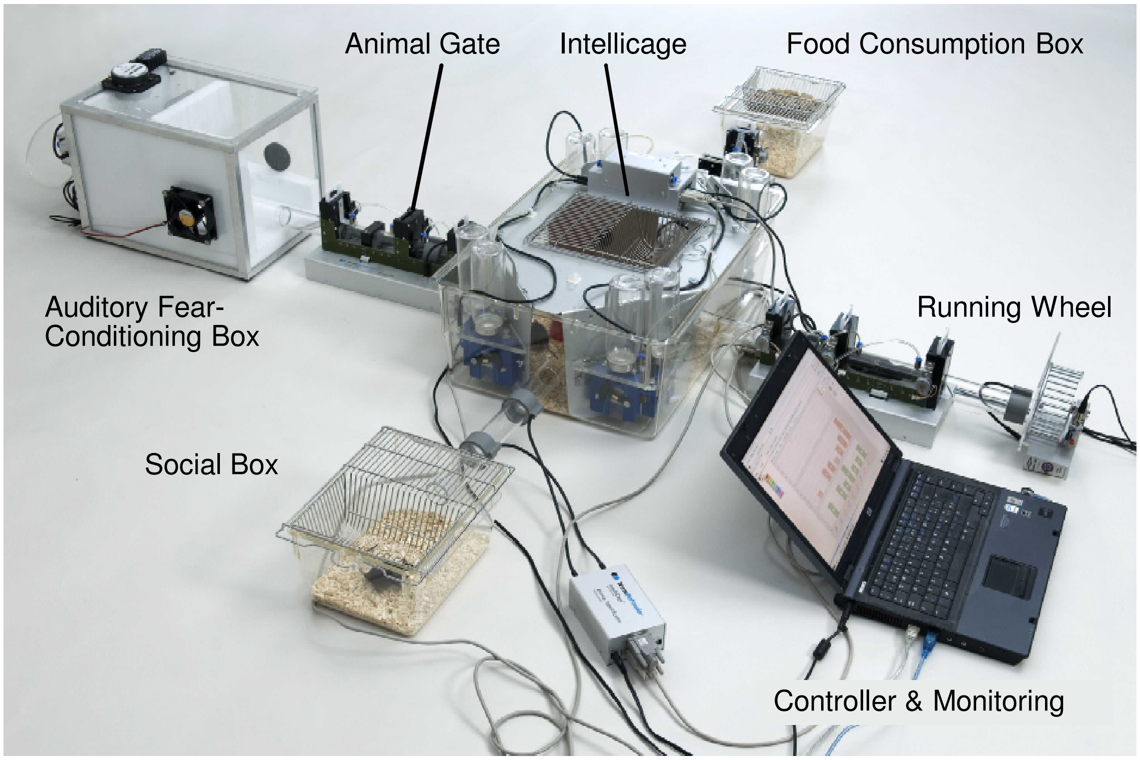
1.3. Organisation of the project

The project included three partners responsible for technical progress in terms of hard- and software development, and four partners from scientific institutions evaluating prototype systems and providing feedback for technical refinement.

This SME/STREP project was coordinated by an SME itself. Therefore, the project objectives were primarily commercial: developing as fast as possible a set of novel mouse test apparatus that can be commercialized in a minimal time, and to obtain scientific evidence that would help in sales of systems.

INTELLIMAZE: organisation of work packages





Typical configuration of an IntelliMaze system with some add-ons developed during the project period

1.4. Main achievements

1.4.1. Realisation of the IntelliMaze set-up (NewBehavior Zurich, FBI Science Essen, Anokhin Institute of Normal Physiology Moscow)

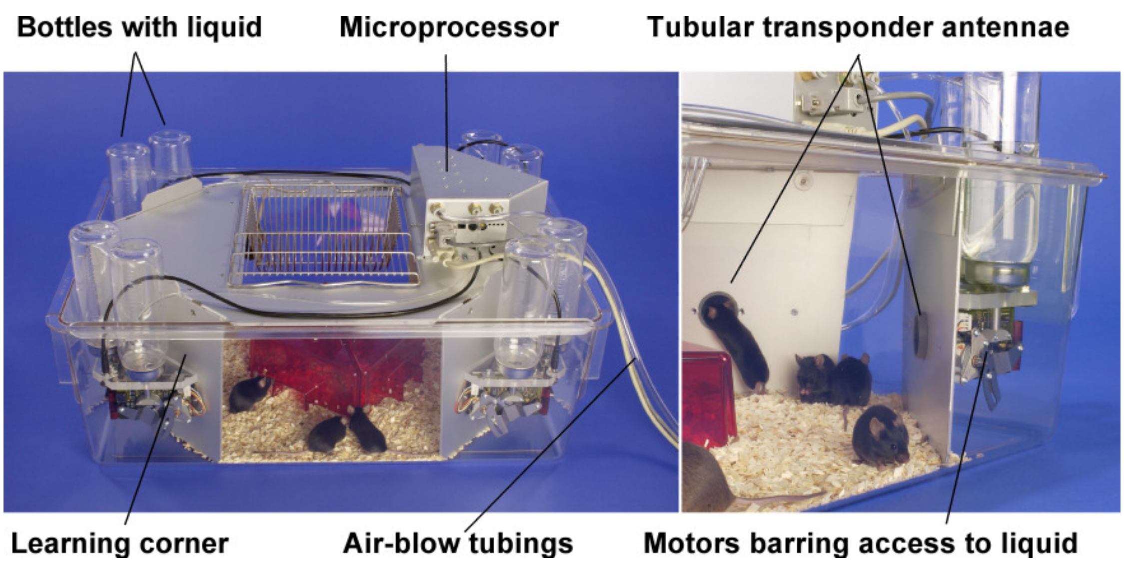
The picture above summarizes the hardware achievements of the project. One **IntelliCage**, a central home cage equipped with 4 learning corners houses 12-16 mice (mostly females) equipped with implanted RFID microchips that permit individual recognition when entering a learning corner. Their spontaneous activity patterns, spatial behaviour as well as performance in a variety of spatial and non-spatial learning tasks is controlled and monitored by a laptop or industrial PC, depending on location of the system.

In the **IntelliMaze set-up**, the mice have the opportunity to visit outside locations through tubes. Tubes can be equipped with RFID sensors that just record passages of mice (e.g.) to a **Social Box.** Access to external devices can be controlled by **Animal Gates** that may allow or deny access for individual mice at given time periods, depending on the controller program. Animal gates can be equipped with an **integrated balance permitting to record body weight** during passing, for example to an external feeder site as shown here. The set-up here includes an **Auditory Fear Conditioning Box**, as acoustic stimuli cannot be presented within an IntelliCage. Finally, the set-up includes a

Running Wheel permitting to evaluate the effects of physical activity on cognitive performance within the IntelliCage or its add-ons.

One should note that this set-up testing simultaneously mice around the clock corresponds roughly to **three conventional behavioural laboratory rooms equipped with multiple standard test boxes**. It also allows conducting about **90% of conventionally used memory and learning tests**, yet without human supervision. Lastly, it provides **statistical outputs and graphs** for a variety of behavioural parameters and learning scores.

1.4.2. Further development of IntelliCage® (NewBehavior)



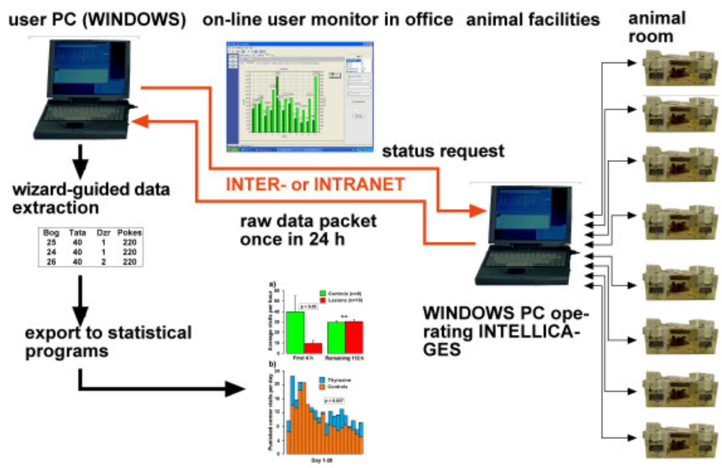
IntelliCage set-up with mice. Right picture: learning corner.

The IntelliMaze project also advanced the development of the central unit. An IntelliCage houses 12-16 female mice tagged with transponders. Usually, the cage contains controls and treated animals raised together after weaning, a design facilitating statistical analysis. Male mice can be tested also, albeit in lower numbers from 4-8. Each IntelliCage contains **four complete operant conditioning units** with dual reward delivery located in the corners of the cage. A central computer can operate up to 8 IntelliCage with a total of 32 learning corners, running **the same or different test programs**, even for individual mice. In order to obtain liquid, animals must enter these chambers through tubular antennae identifying individuals. They can obtain access to the liquid dispenser bottles by performing nose-pokes (an universal behaviour in rodents) that open barring gates. Reinforcement can be plain water, sucrose or other liquids such as alcohol, liquid nutrition, drugs etc. Depending on tasks, the system can also punish wrong choices by delivering air-blows.

IntelliCage monitors animals **continuously over days and weeks**, recording visits, nose-pokes and liquid consumption by means of an integrated lickometer. **Software modules** monitor spontaneous behaviours such as circadian activity and place preferences. Other modules control and measure cognitive behaviours such spatial patrolling, conditioned place preference or avoidance, visual and gustatory discrimination learning, and several forms of operant conditioning. Data are collected and sent to other computers for analysis using data base extraction procedures corresponding to the control programs.

Usually, IntelliCages **are placed in the animal facility with a controlling computer**, which itself connects to the experimenters desktop computer via Intranet (or even Internet). Spontaneous activity and progress of learning activity can be displaced on the remote monitor, **permitting supervision without entering the animal rooms**.

Possible set-up of the IntelliCage system with a controller (laptop or industrial PC) controlling and monitoring the learning behaviour of 96-108 mice simultaneously over days and weeks.



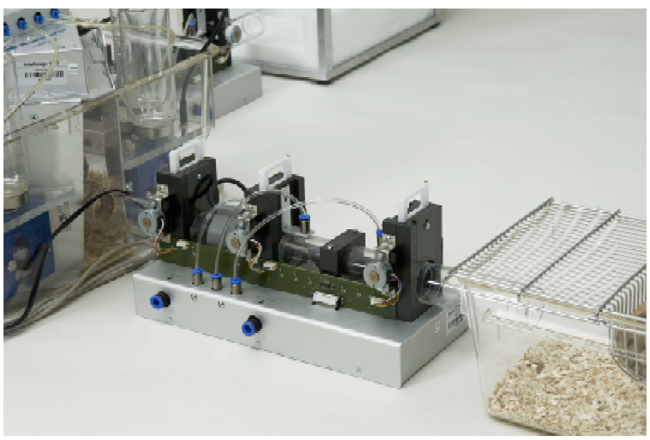
The unique feature of the system is **the incorporated know-how for mouse behavioural testing**. **Behavioural control modules** for basic conditioning such as place preference and operant conditioning suitable for mice **are already pre-programmed**, and different schedules can even be applied to selected individual mice in the cage if necessary. The **results are stored in text files** including all events recorded by sensors (RFID antennae, movement detectors and photo beams), output actions of the system (opening gates, delivery of air puffs), and activities of the individual mice (visiting test corners, making nose-pokes, licking at dispensers). **The resulting data file is protected** and cannot modified in any way after completion, a feature facilitating implementing **good laboratory practice (GLP)**.

The most demanding task is to extract from this information behavioural measures relevant for interpretation by the user. In theory, this could be left to a power-user experienced in data mining and interpretation of animal behaviour. These are relatively rare, however. Therefore, programming of test schedules and data extraction requires in-depth knowledge of the test methods used in various field of behavioural neuroscience and pharmacology, and must also take into account mouse biology and behavioural peculiarities of this species. During the IntelliMaze project, significant progress in this respect was achieved in scheduling and data presentation, enabling the **development of user-tailored application modules** that can be purchased by inexperienced users such as small biotech companies.

1.4.3. Development of a transponder-based mouse distribution system (NewBehavior)

The heart-piece of the Intellimaze concept requires a transponder-operated mouse distribution system that permits to guide mice from a home-cage to a variety of test arenas. This task has been completed, surpassing the specifications set out in the initial application. In brief, mice wishing to leave their home cage approach an identification chamber where they are identified by means of an implanted microchip. Depending upon access privileges, the supervising computer system may then grant access or deny it. If accepted, the mouse can continue through a tube containing an integrated balance assessing and storing body weight electronically, and proceed to the entrance of a test chamber. Once entered, the mouse remains confined to the test chamber until it is allowed to return to the home cage. Direction of movement (leaving or returning) is measured by an ingenuous system of serial photocells. While the system was ready at the mid-term of the project, it required about 12 months efforts in tuning the software to the many peculiarities of mouse behaviour. The final solution takes into account the varying responses of individual mice when facing novel technical devices, which range from fear to curiosity. Therefore, users have now software options to familiarize and habituate the mice to the system

This device was ready for marketing in the second half of 2008, has been presented at various scientific exhibitions (see PUDK), and specimens have been sold.



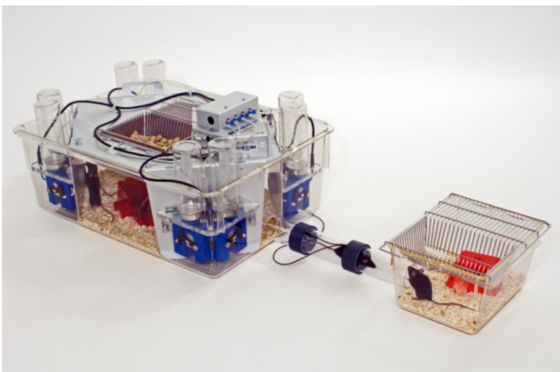
Mouse distributor system (AnimalGate) providing individually controllable transit to micro chipped mice, measuring body weight and direction of movement. To the right, normal mouse cage with a food hopper. Thus, body weight of every mouse in the IntelliCage mice can be monitored continuously.

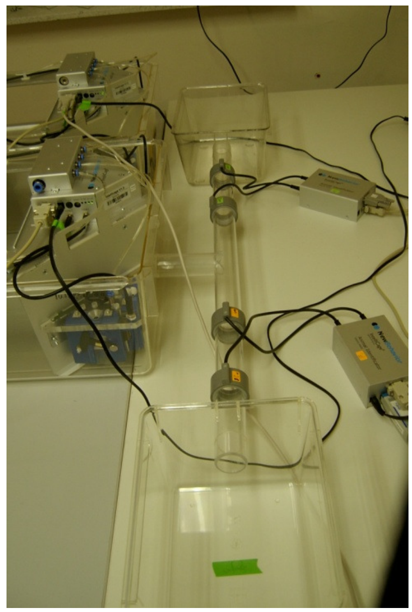
1.4.4. Development of a IntelliCage add-ons – hardware and software

The kernel configuration of the modular Intellimaze System included popular add-ons to the established IntelliCage system:

1.4.4.1. Social box and Novelty detection (NewBehavior)

A passage system to small outdoor cages, a so-called **"Social Box"** records automatically which mice follow or chase each other, quantifying the degree of social interactions. Another application is the detection of novelty (objects, smell, other animals) when two boxes are attached to an IntelliCage. In this case, similar items are placed in both boxes until visiting activity of the mice has decreased. The one of the objects is changed, provoking the curiosity of the mice, which start visiting the novel object more frequently. Similar yet not automated paradigms are used for testing mouse models of autism, schizophrenia and other forms of memory deficits. Commercialisation started April 2008.





Social box system permitting passive assessment of social following or avoidance of individually recognized microchipped mice. The right picture shows a double arrangement allowing for novelty detection by comparing the number of visits to objects or other mice in the two boxes.

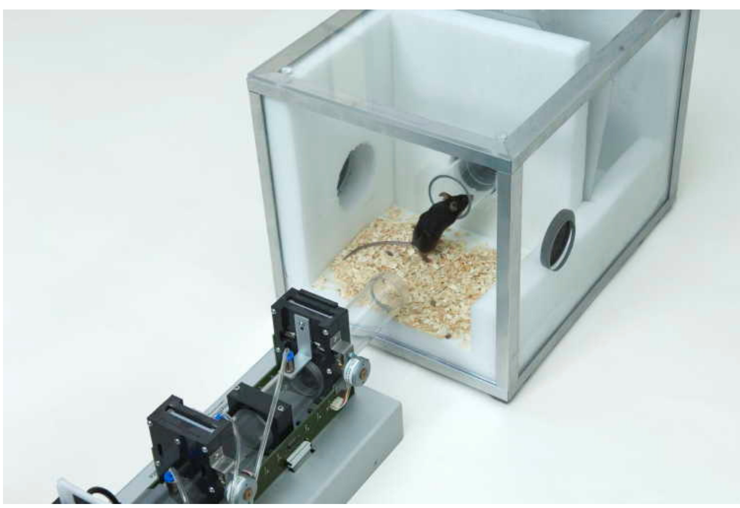
1.4.4.2. External running wheels (NewBehavior)

A further add-on developed was a **running wheel measuring activity of individual mice**.

Mouse in running wheel. In this configuration, access to the running wheel can be controlled by means of an AnimalGate. An identificator antenna at the entry of the running wheel permits attaching the device to a home cage without access control.

1.4.4.3. Auditory fear conditioning box (NewBehavior)

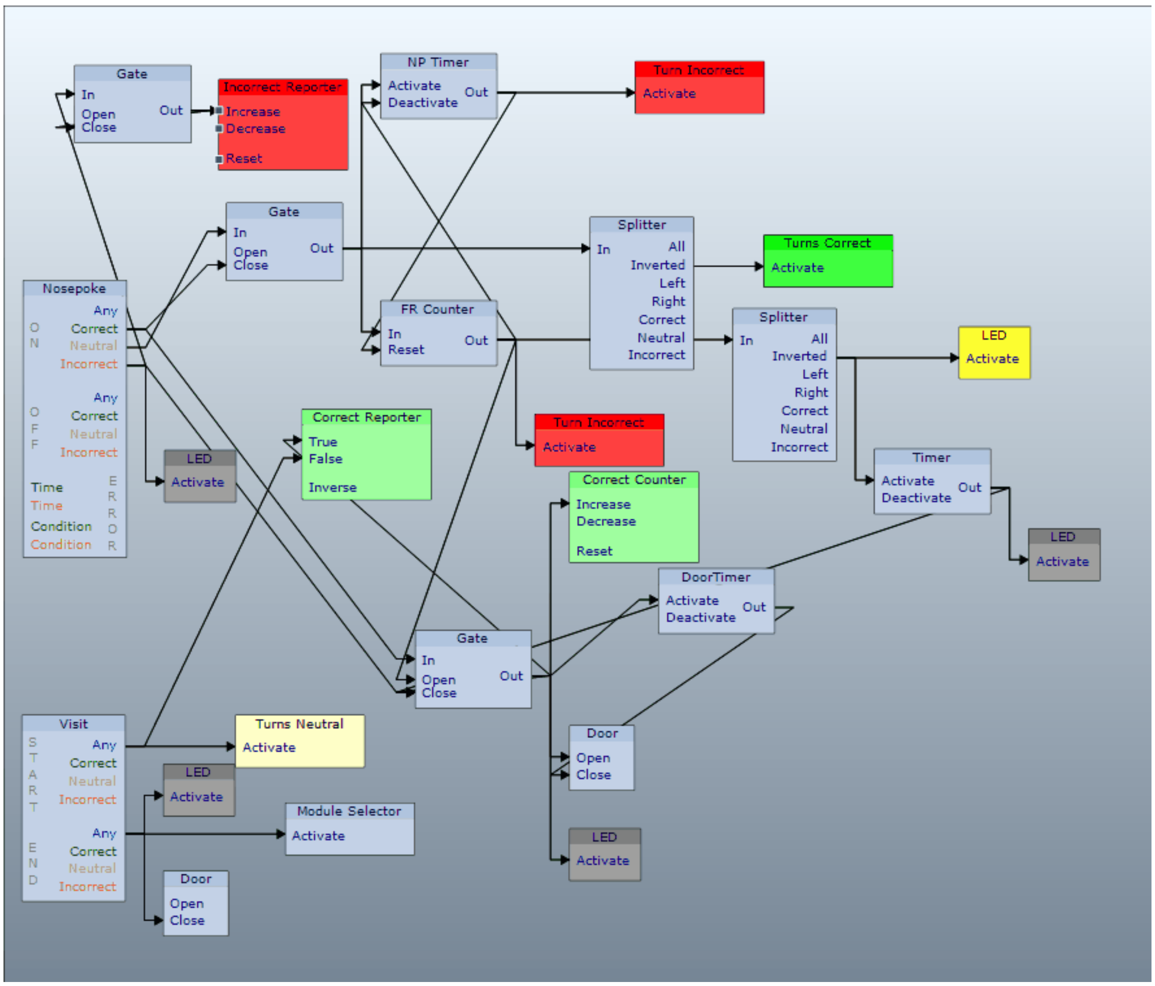
An auditory fear conditioning box was developed in cooperation with another FP6 project, Noveltune. This allows to assess **auditory discrimination abilities and auditory memory** for punishment-related sounds. Such conditioning cannot be applied within the confinements of the IntelliCage home cage.



External auditory fear conditioning permitting to train mice for auditory discrimination of novel sounds and memory for punishment related sounds. The box contains an IntelliCage corner familiar to the mice. The salient sounds are associated with air puffs, and the system measures whether the mouse interrupts ongoing drinking behaviour or leaves the corner upon perceiving a threatening sound.

1.4.4.4. Development of a graphic programming tool for behavioural test modules

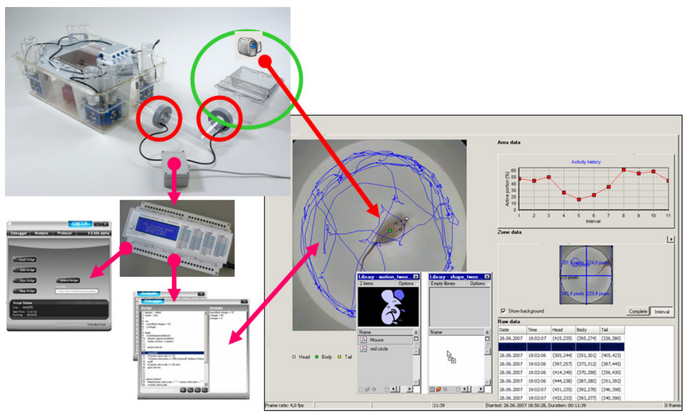
Apart from corrections of bugs in the programs controlling and monitoring the activity of the automated systems, the main work in adapting both IntelliCage and IntelliMaze to the needs of the users was the development of a powerful graphic programming tool called DESIGNER that allowed the user to program both simple and complex behavioural measures and training schedules. This approach provided the necessary flexibility for rapid adaptation to specific needs and so-called program modules assessing specific behavioural impairments after lesions, neurodegeneration and in transgenic mice. Such modules can be developed by experienced users, while novices or users without behavioural knowledge may purchase them, or buy specified modules.



Example of a complex design: fixed ratio learning in a defined IntelliCage corner, during which the mice must make an increasing number of nosepokes in order to obtain a liquid reward, combined with activation of LEDs. Once programmed and stored, the schedule only requires the transponder code of the mice to be tested. Screenshot from DESIGNER program.

1.4.4.5. “Huddle box” (FBI Science)

A remarkable development by FBI Science International is the **“Huddle-Box“,** in which a camera system analyses the movements of multiple mice entering the social box, and identifies those clustering together. This add-on aims at analyzing mouse models of autism and depression, in which the social cohesion or lack thereof is important. We expect commercial distribution to begin 2010.



A video system supervises a social box or arena and tracks the individual mice. Thus, it can recognize which mice start huddling together, and recognizes lone individual sleeping alone. To be marketed by FBI Science.

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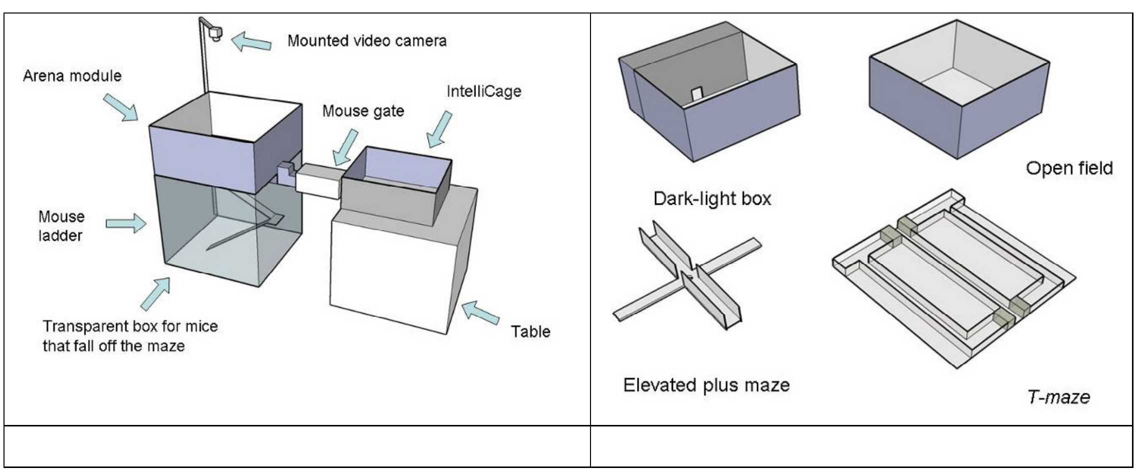
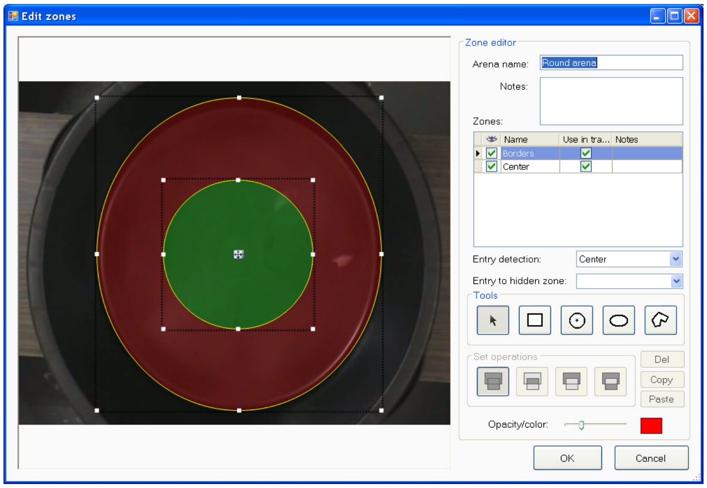
1.4.4.6. Video-supervised external arenas (Anokhin Intitut of Normal Physiology Moscow)

An Intellicage system is too compact to assess movements of mice outside of identification antenna. Therefore, the Russian partner developed apparatus and software that can be connected, through an Animal Gate, to an IntelliCage. Integrated software permits that mice can enter these arenas, one after the other. Once in test arena, the video-tracking of the mice is left to a dedicated software, planned to be licensed to manufacturers offering such single test systems, since the type of apparatus attached is not specific to Intellicage software.



Arena types supported by the Video tracking system

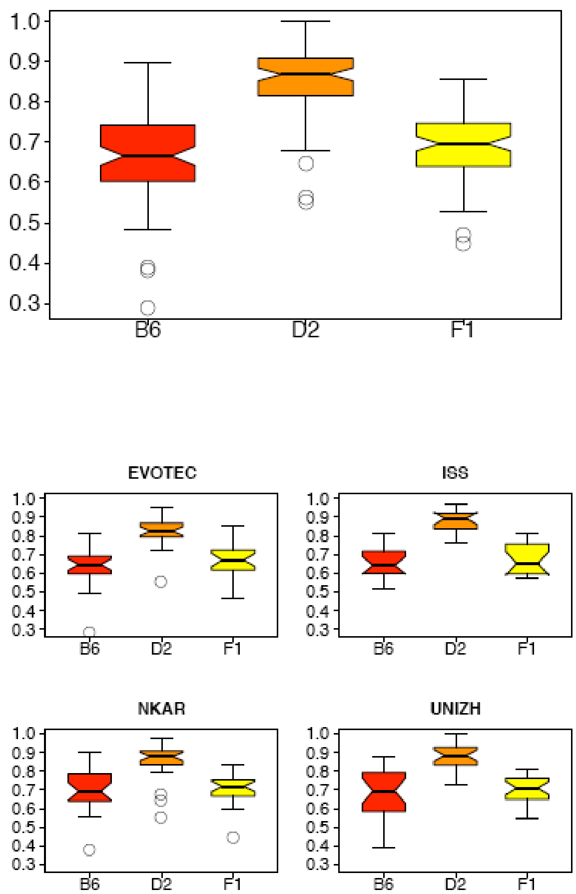


Software: Zone definition set-up

1.5. Standardization and comparisons across Europe

1.5.1. Trans-European comparative study using automated IntelliCage systems (Istituto Superiore di Sanita Rome, University of Zurich, Evotec Hamburg, Karolinska Institute Stockholm)

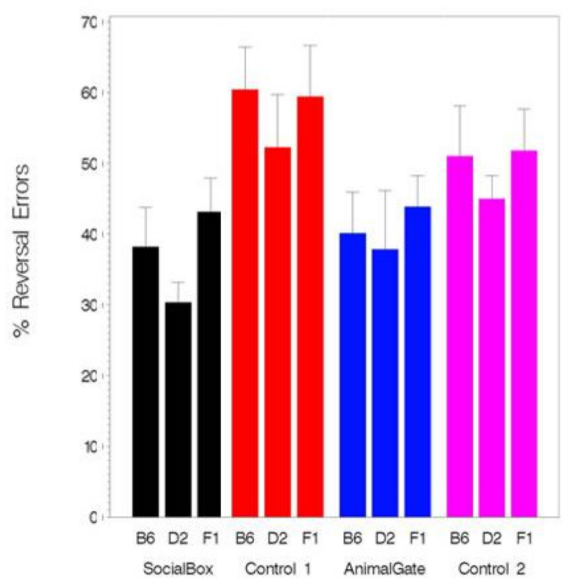
Changes in spontaneous activity and locomotion characterise many neurodegenerative and genetic mouse models, but comparability across laboratories has yielded conflicting results. Our project tested behavioural differences between commonly used laboratory strains of mice (C57BL/6, DBA/2 and their F1 hybrids) in 4 laboratories (Evotec Hamburg, Neurotec Stockholm, University of Zurich, and Istituto Superiore di Sanita). The results show overall excellent comparability of strain differences in measures of spontaneous activity in a complex environment. This is an important proof of concept, because it shows that equivalent genetic differences in genetically dependent behaviour can be demonstrated in different laboratories. It is of particular relevance for studies in mice with neurodegenerative diseases for which cross-comparisons has proven to be difficult. Now, a test module that has shown differences for a given mouse model in one laboratory can be tested in other models elsewhere for similarities or differences, simply by using an IntelliCage and the appropriate module. The data are submitted for publication.



Example of genetic differences in corner visiting activities, expressed as proportion of nocturnal to overall activity during day and night time. The mouse strain DBA/2 shows a strong focusing on nocturnal activity as compared to the two other strains. Upper diagram: pooled data from 4 laboratories (4 x 72 female mice tested in 3 cohorts). Lower diagrams: data sets from the 4 different laboratories. Each laboratory used two IntelliCages housing a cohort of 12 female mice of different genotypes. Note the almost identical data sets obtained by the fully automated recording systems.

1.5.2. Trans-European comparative study using automated IntelliMaze components (Istituto Superiore di Sanità Rome, University of Zurich, Evotec Hamburg Karolinska Institute Stockholm)

This second comparative study was conducted after shipping animal gates, social boxes and cohorts of mice with identical birth weeks to the four partner laboratories. Strains used were again DBA/2, C57BL/6 and their F1 hybrids. The data have been analysed, and presented in poster form at the Society for Neuroscience Meeting in October 2009, and will be submitted to publication in 2010. The main findings were that, again, the strain differences across the four test laboratories persisted. **An unexpected yet highly interesting observation was that access to external devices reduced the error rates of mice when performing learning tasks in the central IntelliCage**. This implies that enriched environment presented by visiting external arenas appears to improve learning behaviour in the habitual home cage situation. Further studies focussing on this phenomenon are under way in the partner laboratories having IntelliCages.



Reduced error rates of mouse strains during reversal learning in Intellicages with and without access to external devices. Bars are standard deviations. Data are pooled from four laboratory using Intellicages (EVOTEC, NKAR, UNIZH, ISS).

1.6. Development of software modules and procedures for assessing effects of neuro-degenration, brain lesions, and anxiety and depression

In close interaction with the scientific staff of NewBehavior, the partner laboratories at Karolinska, Evotec, University of Zurich and Istituto Superiore di Sanita have developed and refined behavioural tests and data analysis procedures covering a broad spectrum of tests used in behavioural neuroscience.

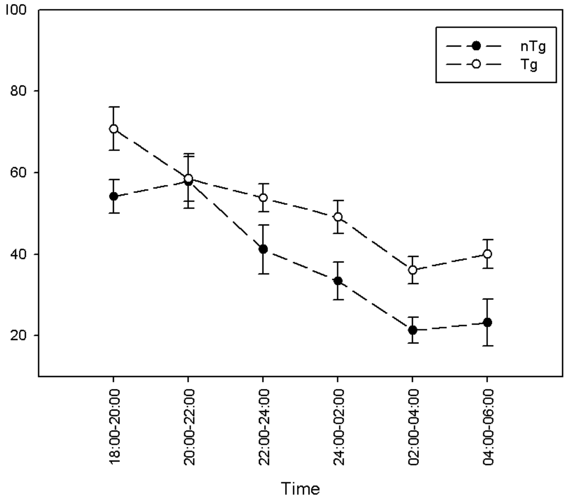
1.6.1. Analysing phenotypes of Alzheimer mouse models (Evotec Hamburg and Neurotec Karolinska)

Using a battery of conventional behavioural tests, IntelliCages and IntelliMaze set-ups, thee two labs have aimed to discover discrete early signs in their transgenic Alzheimer models occurring before or with the early onset of plaque formation.

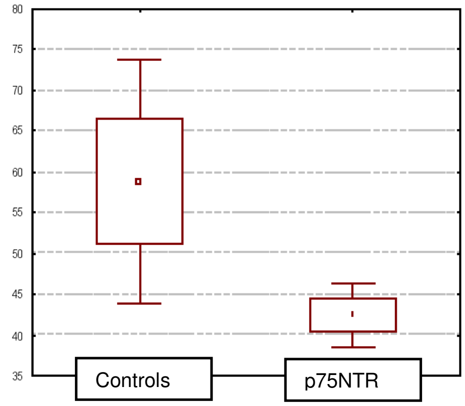
Their main combined finding was that there is **no unique phenotype of Alzheimer mouse models** as testing in the standardised environment of IntelliCages revealed model-specific phenotypes. **This will facilitate the analysis of drug effects on neurodegenerative diseases in different laboratories**, because possible idiosyncratic test procedures of a laboratory will no longer represent a confounding factor.

The **Neurotec Karolinska** used the IntelliCage system also **for screening a novel Alzheimer model, namely p75NTR transgenic mice** overexpressing the human neurotrophin receptor p75 (p75NTR). This receptor plays an important role in the survival of cholinergic neurons in the basal forebrain, which are specifically affected by Alzheimer's disease. The behaviour of these mice being unknown, they were subjected to a test series in IntelliCages with the aim of discovering behavioural peculiarities warranting further in-depth analysis. Like other Alzheimer models, these transgenic p75NTR mice showed higher activity in the cage, but unlike other models, they committed less errors when they had to learn a particular corner location for obtaining water, the control mice making more visits to unrewarded corners (a behaviour usually associated with higher activity). This example illustrates the power of automated test systems in screening procedures, since IntelliCage measured multiple behaviours difficult to assess in single sessions in conventional tests. **Further experiments using either refined IntelliCage protocols or standard behavioural tests can now be employed to dissect this behavioural phenotype**, the question being whether the observation reflects a true superiority of the transgenic mice, or else a loss in systematic patrolling the other corners in the cage.

Increased activity of p75NTR transgenics



Reduced error rates of p75NTR transgenics

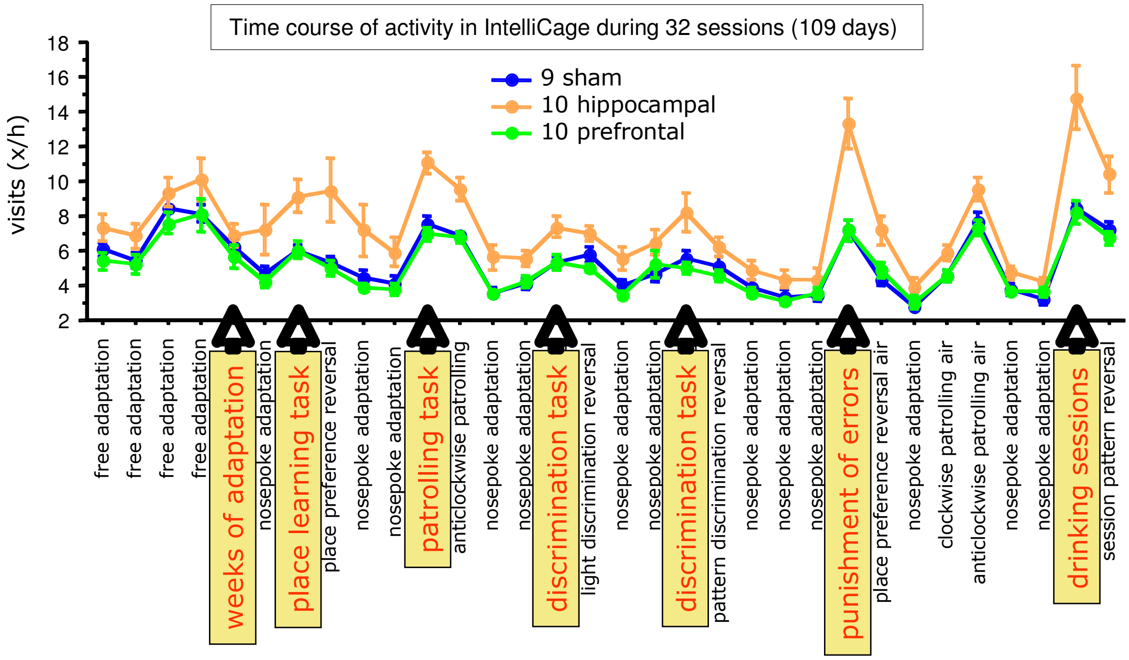


1.6.2. Automated profiling of brain lesions in C57BL/6 mice

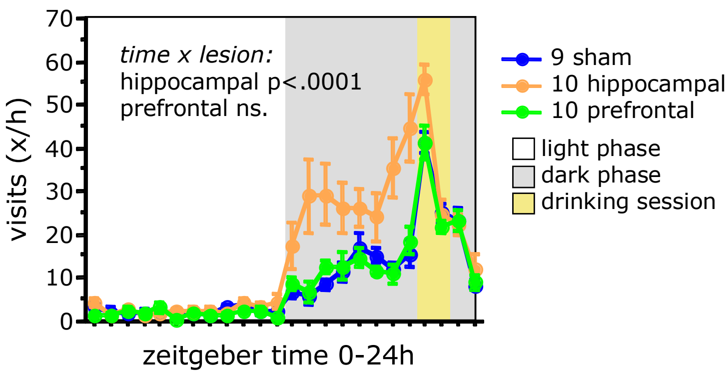
The Wolfer laboratory at the University of Zurich has completed a long series of studies in mice with bilateral removal of the **hippocampus**, **prefrontal cortex** or **striatum**, both in conventional tests and in Intellicage and IntelliMaze set-ups.

For this purpose, they developed a set of test **modules mimicking classic single tests** such as the **Morris water maze** and **spontaneous alternation.** For example, individual mice can be trained to avoid a corner in IntelliCage after having received air puffs when visiting this location during 24 h. Afterwards, the mice are taken out, and re-introduced into the IntelliCage after 24 h. Normal mice develop a good **spatial memory** for the “dangerous” corner and avoid it. This is much less the case in mice with hippocampal lesions, thus confirming the data in the Morris water maze. On the other hand, hippocampal mice are able to develop spatial corner preferences as long as they are not punished, indicating that spatial memory deficits observed after hippocampal lesions may depend on motivational states.

A remarkable finding not obtainable with conventional behavioural tests was that **mice with hippocampal lesions are hyperreactive after any change in the experimental set-up**, and habituate slowly to such changes.

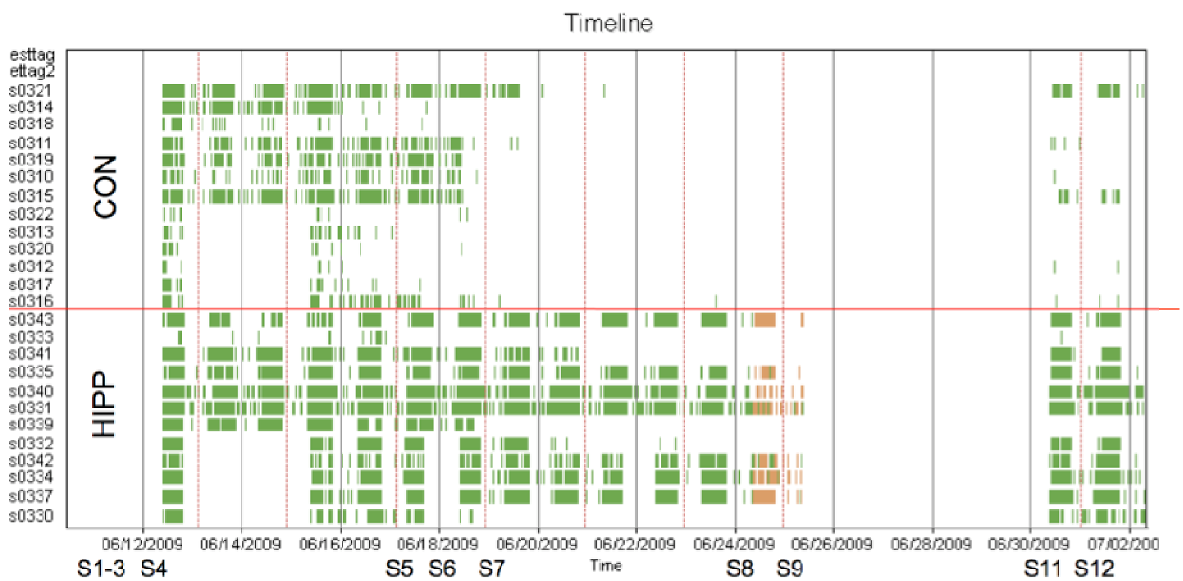


Another finding that would be extremely difficult to verify in single conventional test seesions is an **impaired sense of time in mice with hippocampal lesions**.



Circadian activity profile with drinking sessions (3d). Mice could obtain water only during a limited time. Note that controls and mice with prefrontal lesions were timing their corner visits precisely, in contrast to mice with hippocampal lesions that increased corner visits a long time before the drinking session started.

While the figures above have been compiled from extracted data sets, **the behaviour of hippocampally lesioned mice can also been visualized easily on the system monitor**. One of the many studies shows the effects of hippocampal lesions on visiting external boxes connected to an IntelliCage where the mice could obtain a sweetened solution. It is evident that the visit frequency is much enhanced in bilaterally lesioned animals, and that they even continue to visit the boxes after removal of bottles with sweetened liquid.



Individual activity patterns of mice with sham and hippocampal lesions indicated by passing the AnimalGates to boxes with sweetened water. **S** denotes various phases; S11 and 12 phases without further delivery of saccharine (11) or any liquid at all (12). Note the persisting hyperactivity of the hippocampal mice. The graph was directly copied from the ANALYZER program visualizing and quantifying various parameters. Similar graphs are displayed on-line during the experimental sessions.

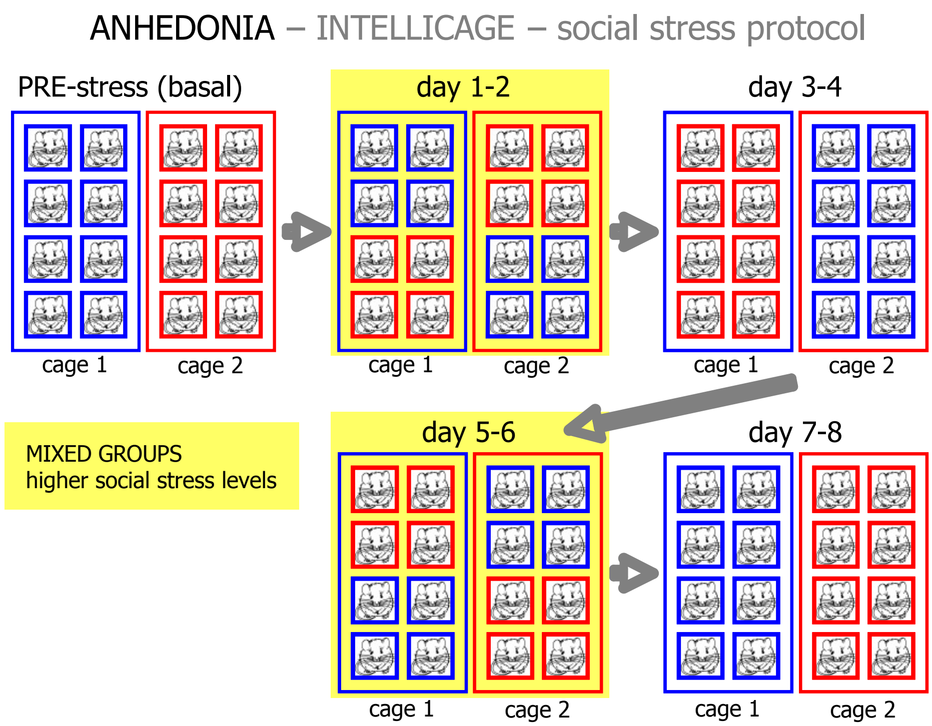
1.6.3. Novel paradigms for research in depression and anxiety (Istituto Superiore di Sanità, Rome)

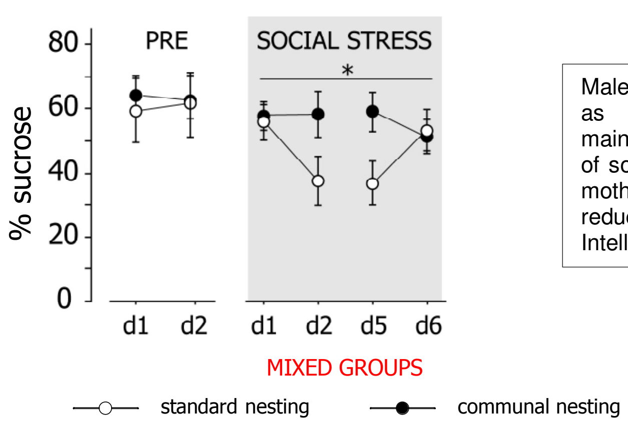
The group at ISS (Alleva, Cirulli and Branchi) has developed automated assays aimed at assessing signs of depression in social groups of males housed in IntelliCage. **Using sucrose preference as an indicator of anhedonia**, they have developed an intriguing and elegant procedure varying social stress, and could demonstrate significant effects of differential treatments during early postnatal life, in particular effects of communal versus individual nursing. These developments are significant because **traditional stress research in mice is based on a multitude of different stressors that are difficult to replicat**e. For example, mice are exposed to rats walking on the cage, have to stay in wet saw-dust, and are not allowed to sleep, undergo shaking of the home cage, to name a few. The approach presented below is based on the perhaps ethologically most relevant stress in mice, at least in males, namely temporary agonistic interactions.

They kept male mice that had grown up together, each cohort separately in an Intellicage. A classic indicator of perceived stress is anhedonia, expressed as reduced consumption of sweet solutions.

Thus, sucrose preference was tested in the habitual session. Thereafter, the male cohorts in the Intellicages were mixed. This entailed social conflicts and agonistic interactions, resulting in decreased sucrose preference. Re-establishing the former groups restored the sucrose preference. **The degree of social stress could be increased by attaching a social box presenting an (inaccessible) female**. This usually increased the activity of the dominant male and exacerbated the stress of the lower ranked companions.

Ingenuous protocol for inducing variations of social stress in groups of male mice housed in groups of 8 per Intellicage. They undergo periods in which they are mixed, and periods in which they are kept in the original established group. Mixing of groups increases levels of social stress. Branchi et al., privileged communication. Branchi et al. 2010, Psychoneuroendocrinology*,* in press.





Male mice that experienced communal nesting as pups (nursing by different mothers) maintained sucrose preference during episodes of social stress, while mice kept with individual mothers showed anhedonia as indicated by reduced sucrose consumption versus water in Intellicage.

1.7. CONCLUSIONS

- Technically, this project has fulfilled all expectations: the mouse testing community in industry and academia has now a tool that permits fully automated mouse testing, even with a minimum of behavioural knowledge. **IntelliCages themselves represent an extremely efficient high-throughput tool for testing large numbers of mice in a minimum of time.** Their unmatched advantage is a standardization of the environment and testing procedures. The most economical way of use is **screening for long-lasting or slowly changing behavioural alterations** induced by genetic engineering, toxicants, neurological and any form of somatic diseases, as well as developmental, social and environmental manipulations. The IntelliMaze add-ons provide the ability to expand the IntelliCage system, enabling it – using the same software – to conduct **behavioural tests requiring larger arenas**, **to measure food consumption**, and **to quantify social behaviour**. In the form presented here, the combined systems could replace about 90% of behavioural tests that are traditionally employed.
- Commercially, the availability of a system with pre-programmed mouse-adapted modules for specific needs and questions makes the system suitable not only for **specialized phenotyping laboratories** but even for **small biotech companies lacking behavioural expertise** wishing to screen the effects of novel drug compounds.
- The cross-European comparisons between different user laboratories have shown a **high comparability of genetically dependent behaviour of mice**. Notably, the inherent variability due to **social interactions does not mask the strain differences**. In technical terms, the minor variations induced by social interactions prevent one of the disadvantages of total standardization, namely unpredictable effects of subtle idiosyncrasies in the testing environment. Therefore, the systems provide a high level of equivalence in test results. **Comparing the many mouse models of neurodegenerative diseases is thus greatly facilitated by using IntelliCage and IntelliMaze systems**.
- Scientifically, the project has resulted in a **large data set referencing the effects of brain lesions to standard tests for impaired hippocampal, prefrontal and striatal functions**. Therefore, it is possible to classify behavioural phenotypes of many mouse models as discovered by IntelliCage and IntelliMaze according to the potential involvement of these structures. In addition, the project has generated **novel approaches to study depression** in mice, and to **quantify deficits in social behaviour** characteristic for autism and schizophrenia in humans.
- From the viewpoint of animal welfare, both IntelliCage and IntelliMaze contribute significantly to the 3R principle: replace, reduce, refine. **The systems anticipate the legislative trend towards more stringent regulations in the field of animal testing systems**. They offer not only **minimal handling** by experimenters, but also a **social and enriched environment** yet permitting to conduct almost any type of behavioural experiments.

SECTION 2

DISSEMINATION AND USE

2.1. Upcoming scientific publications

Psychoneuroendocrinology, in press

Shaping brain development: mouse communal nesting blunts adult neuroendocrine and behavioural response to social stress and modifies chronic antidepressant outcome

Igor Branchi, Ivana D'Andrea, Francesca Cirulli, Hans-Peter Lipp and Enrico Alleva

Neuroscience and Biobehavioral Reviews, in press.

Early life influences on emotional reactivity: evidence that social enrichment has greater effects than handling on anxiety-like behaviours, neuroendocrine responses to stress and BDNF levels

Francesca Cirulli, Alessandra Berry, Luca Tommaso Bonsignore, Francesca Capone, Ivana D'Andrea, Igor Branchi and Enrico Alleva

In revision Genes Brain Behavior

Consistent behavioral phenotype differences between inbred mouse strains in the IntelliCage

Sven Krackow, Elisabetta Vannoni, Alina Codita3, Abdul H. Mohammed, Francesca Cirulli, Igor Branchi, Enrico Alleva, Anja Reichelt, Antje Willuweit, Vootele Voikar, Giovanni Colacicco, David P. Wolfer, J.U. Frank Buschmann, Kamran Safi, Hans-Peter Lipp

2.2. Commercial products

NewBehavior/TSE are already marketing jointly **IntelliCage hardware and new software modules.** Likewise, main Intellimaze components such as **AnimalGate**, **Running wheels**, **Feeding Monitors** and **Social Box** are already on the market. Thus, contacts to Industry for marketing and exploitation are not necessary for this project.

Taken together, the FP6 support for SMEs in form of the targeted STREP/SME calls proved to be a success story.