NO. 10 / AUGUST 2007

neuro TRANSMITTER

Neural Plasticity and Repair
National Center of Competence in Research

Newsletter of the Swiss National Center of Competence in Research in Neuroscience / NCCR Neuro

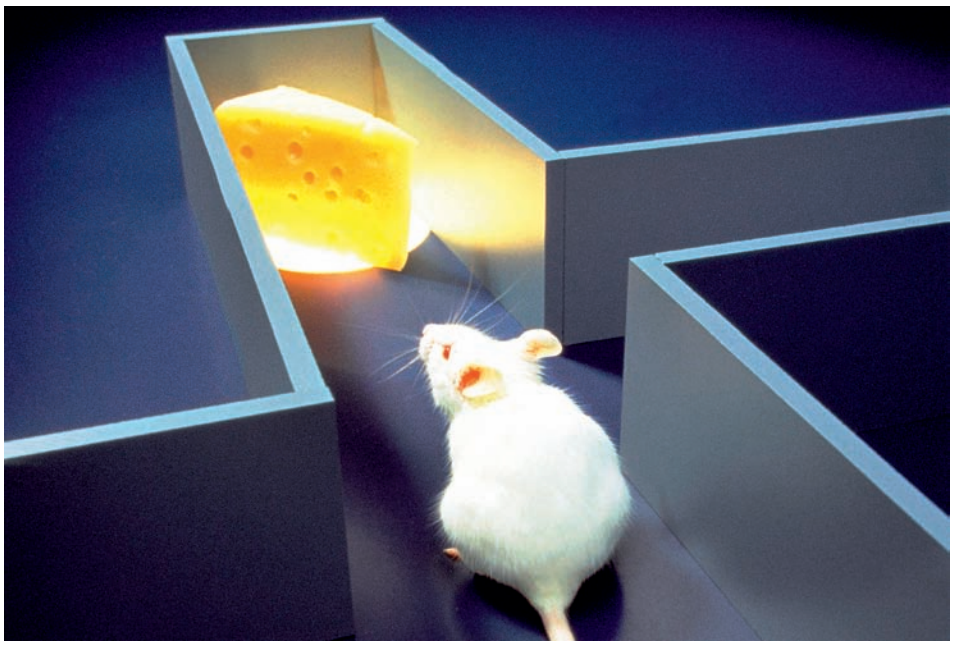
CONTENTS

COVER STORY

Of mice and men

In 1990, when electronic manuscript submission was still unknown, a thick parcel from a publishing house in my mailbox was an ominous sign. Indeed, a study on the behavior of mice lacking the corpus callosum had been sent back by the Journal of Neuroscience. The editor's comment was painfully short: „Whoever could be interested in the behavior of sick mice?" The "whoevers" have multiplied since. For 1998, PubMed lists 6 papers on the behavior of transgenic mice, while 719 papers were published in 2006. Given that only a fraction of the estimated 3000 mutant mouse models have been analyzed behaviorally, it is likely that this trend will continue. Three lines of behavioral brain research with mutant mice have emerged. One, known as phenotyping, aims at behavioral characterization of newly generated mouse lines. A second line deals with experimental documentation of predicted changes in brain mechanisms and behavior after elimination or modification of genes for intracellular signaling cascades, receptors and neurotransmitters. The third approach fo-

continued on next page



GETTY IMAGES, printed with permission

Schematic illustration of a maze with multiple arms which can be used to test the memory performance of mice in the search for food.

www.nccr-neuro.uzh.ch

FNSNF Swiss National Science Foundation

The National Centres of Competence in Research (NCCR) are a research instrument of the Swiss National Science Foundation.

uzh | eth | zürich

Research on animal behavior promotes human health

To effectively identify, prevent and treat diseases, it is essential to understand their causes and mechanisms, the way they affect the body, and how potential treatments can combat and cure them. Gaining such knowledge requires experimental research work, which effectively can be done only in animal models.

Research on diseases of the nervous system, in particular, requires elaborate and reliable animal models. These are essential, not only to study the basic functions of the nervous system, e.g., complex processes of vision, speech, and pain perception, or cognitive functions such as learning, memory and emotional processing, but also to explore the mechanisms that alter these functions in diseases. Rats and mice are unique research subjects because they are biologically similar to humans, are susceptible to many comparable diseases, and have a short lifespan, which allows them to be studied in old age, and for several generations. In addition, their environment and living conditions can be easily controlled and modified in the laboratory.

The advent of behavioral research in animals, pioneered by inspired experimentalists such as Ivan Pavlov (1849–1936) or the behaviorists John Watson (1878-1958) and Fred Skinner (1904-1990) over the last 100 years, has led to tremendous progress in understanding the functions and diseases of the nervous system. Nowadays, this field of neuroscience has evolved into a dynamic discipline that takes advantage of the most elaborate animal models, in particular those derived from genetic manipulation. Behavioral neuroscience will certainly continue to generate knowledge about the brain, contributing to further advances in human health.

Isabelle Mansuy
Professor of Molecular and Cognitive Neurosciences*

*Institute of Brain Research, University of Zurich, and
leader of the NCCR Neuro Center of Transgenesis Expertise

Of mice and

cuses on "clinical" mouse models, in which mutations or epigenetic processes known to result in human diseases have been produced experimentally. For example transgenic mice overexpressing beta-amyloid in the brain ("Alzheimer mice") permit study of the effects of therapeutic approaches (Fig. 2).
The need to deal with this surge of mouse data led to the creation of the Center for Advanced Behavioral Assessment of Rodents (Center 2) as part of the National Center of Competence in Research on Neural Plasticity and Repair (NCCR Neuro), whose four aims are:

- To provide services for other NCCR groups.
- To establish clinically relevant rodent models of brain malfunction or psychopathology.
- To develop novel test paradigms and technical methods for behavioral phenotyping.
- To transfer technology to industry and academia.

The main challenge is conceptual: how can we translate brain mechanisms, behavior and learning in mice to human brain, behavior and psychopathology? While mice and men share many features of the phylogenetically old parts of their brains (Fig. 3), remarkable differences exist, not only in size but also in intrinsic organi-

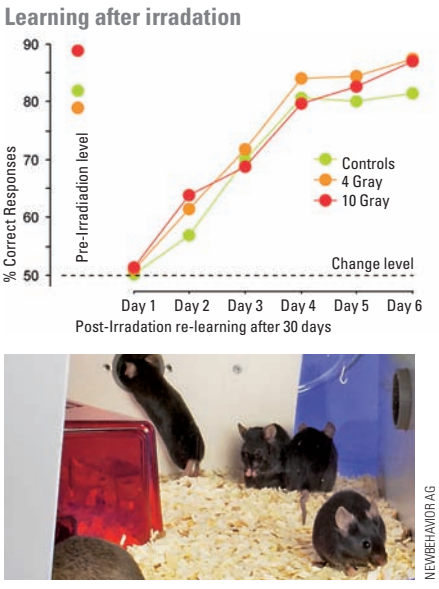


Fig. 1: Recovery of memory performance after irradiation-induced encephalopathy in mice. Irradiation of brain tumors, particularly in children, is known to entail long-lasting cognitive deficits. The irradiation-induced loss of neural precursor cells in mice did not impair learning performance, pointing to other causes of the cognitive deficit. (top graph). The behavioral tests were performed in an IntelliCage (bottom).

zation of the forebrain. Therefore, the contribution of behavioral neuroscience is to recognize species specific differences and to characterize carefully partial similarities with the human brain. This strategy is followed by the following groups of Center 2:

Joram Feldon's group uses an intriguing rodent model of schizophrenia, in which maternal infections result in behavioral impairments of their offspring. These animals are tested in a rodent task battery mimicking human psychological tests known to reveal schizophrenia-related deficits.

Florence Crestani's group focuses on the pathophysiology of panic disorders. A novel and ingenious apparatus is used to measure whether the escape behavior of a mouse is caused by panic or just by normal anxiety.

David Wolfer's laboratory compares the behavioral effects of lesions to mouse hippocampus, prefrontal cortex and striatum in a broad behavioral test battery in order to establish standardized benchmarks for judging a specific impairment of these structures in genetic and clinical mouse models.

Hans-Peter Lipp's group deals with the problem of high-throughput behavioral screening of the numerous present and future mouse models generated by molecular biology and mutagenesis programs. Behavioral testing is technically simple but tedious, requiring extensive manpower. Based on studies of the learning behavior of mice living together in outdoor environments, Center 2 developed IntelliCage, a home cage test system that automatically measures mouse behavior and learning (Fig. 1).

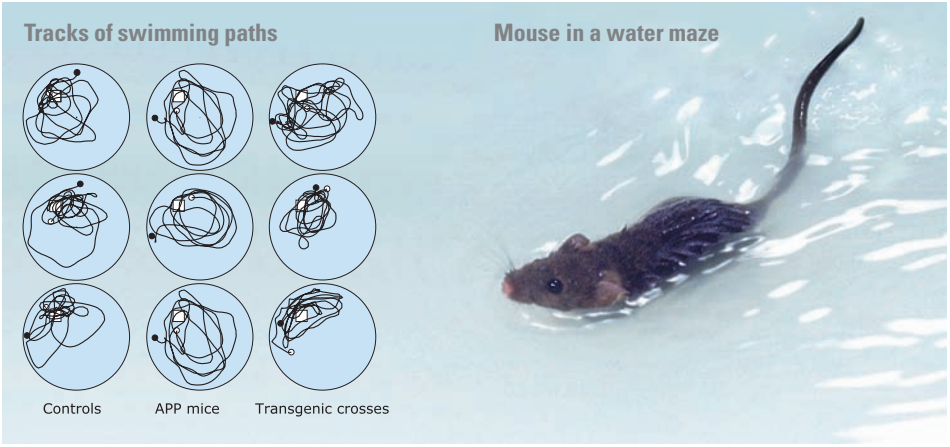


Fig. 2: Spatial memory of mice is tested in a water tank as they search for a submerged platform (right). The swimming path is recorded (left). In comparison to healthy controls (left column of tracks), an "Alzheimer mouse" (APP mice) lacks orientation to reach the platform (middle column). This deficit is reversed by a genetic manipulation affecting amyloid processing in the brain (right column).

The altered behavior of mice cannot always be attributed unequivocally to changes in a specific brain system. In such cases, concomitant changes in neuroanatomy and neurophysiology must be sought and documented, an approach called endophenotyping. For this purpose, Center 2 developed a "neurologger", an extremely small yet portable recording and logging system that monitors EEG and single neuron activity over hours or days. Neurologgers will be used by Hanns Ulrich Zeilhofer's group in studies of pain perception.

Last but not least, Center 2 is generating both academic and industrial synergies. In terms of citations, Center 2 maintains a leading position in the field of animal behavioral research. The spin-off company NewBehavior AG successfully markets IntelliCages and add-on products all over the world, and likewise hopes to do this with the recently licensed neurologger.

Hans-Peter Lipp
Leader of Center 2
Institute of Anatomy,
University of Zurich

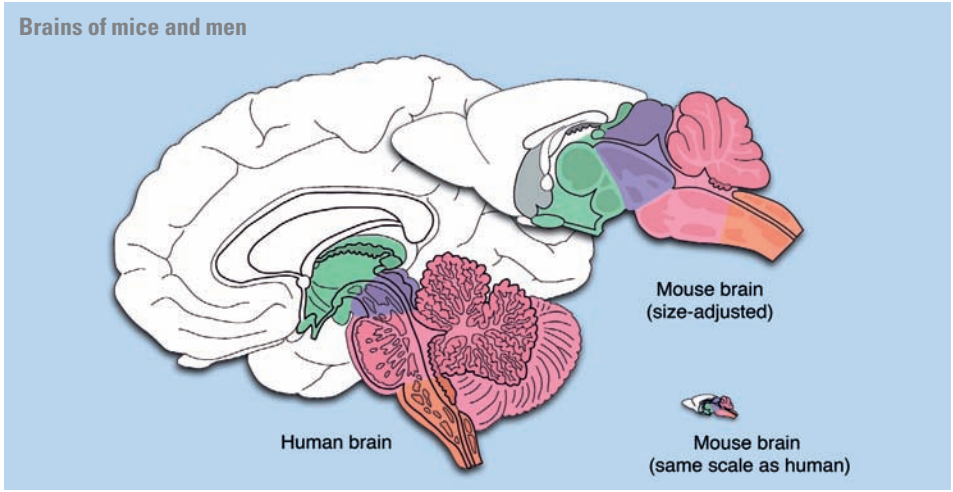


Fig. 3: The brain of man and mouse. The dominant role of the neocortex is much diminished in mice. Also, the connections between the hippocampus and the neocortex in humans differ somewhat from those in mice. These and other differences must be taken into account by behavioral neuroscience.

CENTER 2

Advanced Behavioral Assessment of Rodents

LEADER:

Hans-Peter Lipp	Institute of Anatomy, University of Zurich

MEMBERS:

Florence Crestani	Institute of Pharmacology and Toxicology, University of Zurich
Joram Feldon	Laboratory of Behavioral Neurobiology, ETH Zurich
David Wolfer	Institute of Anatomy, University of Zurich
Hanns Ulrich Zeilhofer	Institute of Pharmacology and Toxicology, University of Zurich and Institute of Pharmaceutical Sciences, ETH Zurich

Calendar of events

10th ZNZ Symposium
14 September 2007
University of Zurich – Irchel Campus

American Society for Neuroscience, Neuroscience 2007
3–7 November 2007
San Diego, USA

Life Science Zurich Meeting on "Prion Diseases"
22-23 November 2007
ETH Zurich

SSCN - The Swiss Stem Cell Network 4th Annual Meeting
14 December 2007
Zurich

NCCR Neuro Symposium
7–8 March 2008
Inselhotel Konstanz, Germany

BrainFair Zurich
8–16 March 2008
www.175jahre.uzh.ch

7th Day of Clinical Research
27–28 March 2008
University Hospital Zurich

XXIInd International Winter Meeting of the Swiss Society of Neuropathology
27–30 March 2008
St. Moritz

American Academy of Neurology 60th AAN Annual Meeting
12–19 April 2008
Chicago, USA

neuro TRANSMITTER

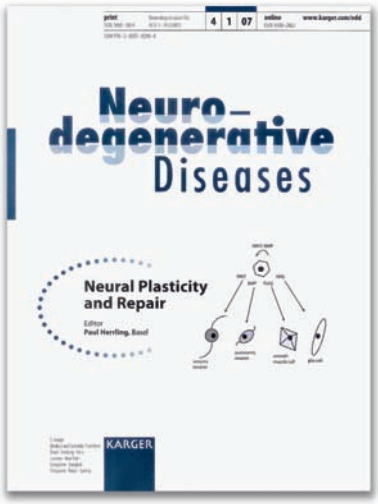
PUBLISHER Management Team NCCR Neuro: Martin E. Schwab, Roger M. Nitsch, Hanns Möhler and Wolfgang Knecht **EDITOR** Tamara Vranesic, Coordinator NCCR Neuro **DESIGN** Inform Agentur für visuelle Kommunikation AG, Zürich and Tamara Vranesic **PRINT** Druckerei Feldegg, Zürich **CONTACT** Tamara Vranesic, Winterthurerstrasse 190, 8057 Zürich, vranesic@neuroscience.uzh.ch

PUBLICATION HIGHLIGHTS

Neurodegenerative Diseases

Neural Plasticity and Repair
Editor: Paul Herrling, Basel

The April 2007 special issue of the journal Neurodegenerative Diseases summarizes the main research topics of the NCCR Neuro in one single publication. Sebastian Fuchs and Lukas Sommer elaborate on current knowledge regarding some of the factors that regulate neural crest stem cells. Verena Finder and Rudolf Glockshuber review the mechanisms of beta-amyloid assembly in vivo and in vitro in Alzheimer's disease. Detlev Boison focuses on the role of the endogenous adenosine system in regulating neuronal excitability to treat pharmacoresistant focal epilepsies. Daniel Kiper et al. investigate key aspects of cortical plasticity in primates and focus on perceptual learning and tasks involving perception and action. Ursula Malipiero et al. describe the functional role of endogenous transforming growth factor beta (TGF-beta) in bacterial meningitis, showing that TGF-beta suppresses host defense against bacterial infection. Anita Buchli et al. report on the joint approach of several research groups to develop a therapy applying anti-NOGO-A antibodies to the injured spinal cord. Finally, Eva Siekierka et al. present three new complementary technologies for acute-phase upper limb stroke rehabilitation and provide preliminary results from patient testing.



www.karger.com/ndd

PEOPLE

Gender equality in the NCCR Neuro

In a recent survey the NCCR community made valuable suggestions for the advancement of women

The NCCR Neuro is committed to creating equal conditions and opportunities for women and men within its research community. As in the past, the percentage of women in higher echelons is, even today, strikingly lower than that of men. This is an imbalance which is observed internationally in academia as well as in private enterprises, and similarly in the NCCR Neuro, where we find 40% female PhD students, 28% female senior researchers, 12% female professors and only 7% female project leaders.

A web-based questionnaire was designed to explore the opinion of women and men regarding this issue, to identify reasons for these circumstances and to define potential future actions for improvement. We addressed 516 researchers in total, spanning all communities of the NCCR Neuro and the Neuroscience Center Zurich (ZNZ) and received 116 responses.

A large majority of the respondents considered gender equality to be more (men) or less (women) established on the following issues: having access to PhD and continuing training programs (84%), having publishing opportunities (82%), receiving scientific and professional advice (81%), getting help with improving personal skills (76%) and salaries (67%). In contrast, the majority regarded the following points as favorable for men: combining career with private life and family (83%), having future prospects for a professorial position (59%) and receiving support to strive for higher positions (56%).

Many respondents explain the low percentage of women in higher positions with the difficulties women are confronted with in combining family and professional life. Others see the reason in the inhibition of aggression and dominance in females or in employers favoring men in top positions to avoid paying maternity leaves. It was also noted that even if there were perfectly equal opportunities, women would still make the personal choice of having a baby and then they might not be willing to sacrifice family life for a highly demanding career as a professor.

Currently, the NCCR management is evaluating specific actions based on the results of the questionnaire, such as improving child day care facilities and providing career mentoring. The report on the survey is available at www.nccr-neuro.uzh.ch/adm003.html.

The NCCR Neuro promotes gender equality in research.