Primate **matters**

Professors Eric Rouiller and **Gregor Rainer** give an overview of a new facility in Switzerland which aims to ensure research using non-human primates is both ethical and transparent

To begin, could you introduce the Swiss Non-Human Primate Competence Centre for Research (SPCCR)?

The mission of the SPCCR is to promote research activities with non-human primates (NHPs) in Switzerland. The Centre was established this year for an initial funding period of four years to consolidate and integrate biomedical research with NHPs at the two SPCCR partner institutions, the universities of Zürich and Fribourg. This is an important signal, underlining that NHP research is considered an important part of biomedical research in Switzerland for the foreseeable future.

SPCCR is committed to open communication with the media and public. We support the principles of the Basel declaration, which emphasise the importance of ethical use of animals in research, and also transparency in research.

Why are primates used for some research rather than, say, rodents?

While rodents and primates have a mammalian brain in common, many details of the organisation of their underlying nervous systems are different. This is especially true of the neocortex, where even the primary sensory processing areas of mouse and monkey have some marked differences in organisation, and where the prefrontal cortex in primates, including humans, is greatly expanded relative to rodents. Primates have far more complex behaviours because their cognitive functions are much more elaborate than in rodents (for example, sophisticated motor control, attention and memory).

Can you describe some of specific theoretical and practical skills that experts bring to this area of biomedical research?

NHP research often involves behavioural training of monkeys on particular tasks of interest; involving, for example, tests of manual dexterity or short-term memory. This means that the researcher has to have a deep knowledge of learning theory. The behavioural work is very practical and intensive, and requires a close relationship between researchers and individual monkeys that participate in the experiment, such that the monkey comes to trust the experimenter. A detailed knowledge of animal behaviour and the application of learning theory is thus of considerable importance in this relationship.

Practically, experimenters need to get to know the traits of the monkeys they work with in order to adapt and optimise training procedures for that individual. Another important area is anaesthesia and surgical procedures, which are very similar to those used in human surgery. This necessitates considerable theoretical and practical training of researchers involved and is a major task of the new Centre.

A variety of research is conducted at the Centre. Which areas are currently being explored?

SPCCR currently focuses on basic biomedical research that aims to advance our understanding about the structure and function of neural circuits in primates.

Professor Eric M Rouiller conducts research on the mechanisms involved in functional recovery from lesions of the cerebral cortex, as well as the basic principles underlying multisensory and sensorimotor integrations.

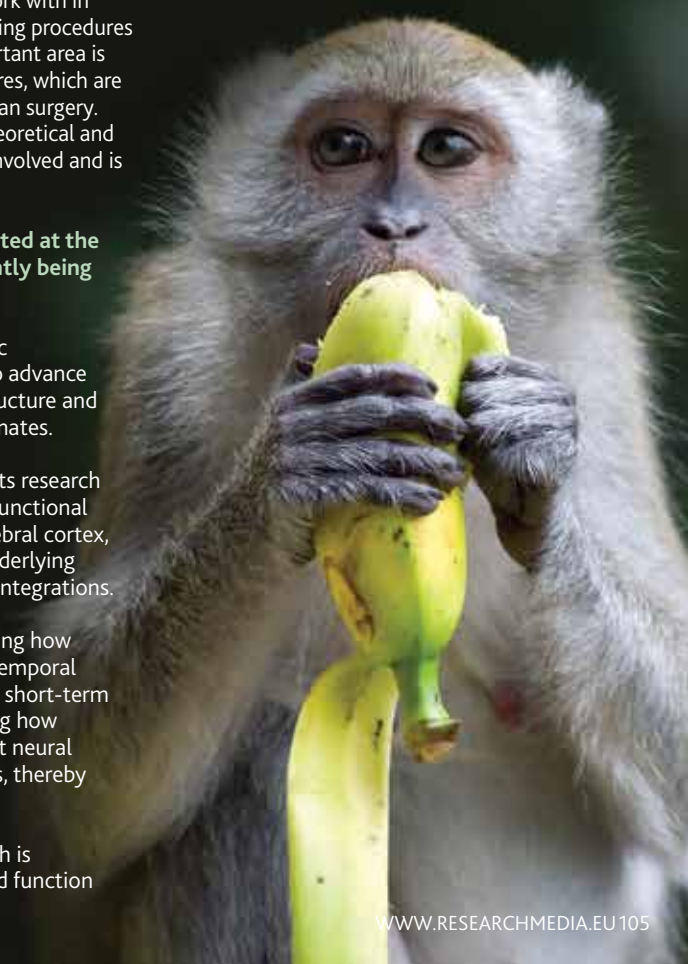
Professor Gregor Rainer is studying how brain circuits in the frontal and temporal lobe cooperate to support visual short-term memory and planning, examining how deep brain stimulation can affect neural cooperation within these circuits, thereby impacting cognitive functions.

Professor Kevan Martin's research is concerned with the structure and function of cortical circuits in different areas of the primate brain in order to answer the question, are there common principles of structure and function that underlie seemingly very different regions of the cortex, such as visual, motor and prefrontal cortex? An answer to this question has very significant implications for our understanding of the function of the multiple cortical areas of the large brain that we humans possess. Detailed computational models of the cortical circuits and simulations of the action of important neuromodulator systems, like dopamine, provide the specific predictions that direct experimental work.

Are you keen to collaborate with certain organisations in future years?

We are particularly interested in extending our collaborations in two directions. We aim to contribute to translational projects that link specific advances in basic scientific knowledge with benefits for patients, and we wish to strengthen our ties with the medical equipment industry to further develop and refine biomedical devices that can be used for the treatment of brain disorders, based on our current technical development work in cooperation with Professor Marco Mazza.

We believe that close collaboration with short feedback turnaround times between the medical device industry and basic research on pertinent animal models can lead to rapid progress in medical device development for human patients.



Promoting **best practice** with primates

The **Swiss Non-Human Primate Competence Centre for Research** will consolidate resources and procedures to maximise the efficiency and utility of experiments and protect the welfare of the animals used

THE PRACTICE OF medical research using animal subjects is contentious and the relevance of such research is frequently called into question, since the biology of many animal subjects is very different from that of humans. The primary exception to this is investigations using non-human primates (NHPs), whose genetic makeup and biological functions are very similar. However, the use of NHPs in research poses unique ethical questions; because of their psychological similarity to humans, it seems likely that constraint, restraint and medical procedures will evoke distress in NHPs.

In 2006, a report detailing the findings of a working group chaired by Sir David Weatherall found that the use of NHPs is mandatory to further understanding in fields such as neuroscience, infectious diseases, reproductive biology, pharmacology, genetics and ageing. Some recommendations were for efficient use of NHPs to limit the number of animals used; that best practice should be employed to safeguard animal welfare; and that other approaches, like cellular and molecular biology or computer modelling and systems biology, should be exhausted before NHP research is considered.

The Basel Declaration of 2011 on research in the life sciences sector signed by 1,440 researchers states that, while animal testing is essential for medical progress in the 21st Century, the signatories will make every effort to follow the 3R principle of replacement, reduction and refinement of the usage of any animals in their field.

The 3R principle and the Weatherall report are the guiding forces for the approach taken towards NHPs use in the newly created Swiss Non-Human Primate Competence Centre for Research (SPCCR) based primarily at the University of Fribourg, as well as the University of Zürich. These sites have worked independently with NHPs for the last 50-60 years. SPCCR has now been established under the leadership of Professor Eric M Rouiller from the University of Fribourg to unify and maximise experiments with NHPs in Switzerland.

HUB OF SWISS INVESTIGATION

Prior to the formation of SPCCR, each canton in Switzerland had different animal licensing regulations, which led to divergent protocols, policies and operating procedures across the country. SPCCR will rectify this, putting in place common standards and guidelines for all aspects of working with NHPs: animal welfare and nutrition, breeding, behavioural training, surgery, pathology, ethics, public relations, legal requirements and safety. The Centre will foster exchange of information and knowledge, and offer expertise and training to any Swiss institution requiring access to NHPs for a defined research purpose.

The main area of interest at the Centre is the workings of the brain. Most of the NHPs involved are macaque monkeys bred elsewhere for research, as SPCCR does not have a breeding facility. The Centre operates in line with recent guidelines for animal care, housing NHPs in groups of two to five in 45 m^3 spaces.

RECENT RESEARCH RESULTS FROM THE CENTRE

Roullier's most recent investigations centred upon injuries to the adult mammalian central nervous system which lead to persistent motor and sensory deficits. By neutralising the neurite growth inhibitor Nogo A, the hypothesis was that some of these functions could recover quicker and more fully by promoting regenerative axonal sprouting. To prove this, Roullier and his fellow investigators created manual dexterity tests on primates subjected to spinal cord lesion. 13 adult monkeys were studied; seven received an anti-Nogo-A antibody whereas a control antibody was infused into the other monkeys. After lesion the hand was severely impaired in all monkeys, but this was followed by progressive functional recovery. As hypothesised, anti-Nogo-A antibody-treated monkeys recovered faster and significantly better than control antibody-treated monkeys.

Professor Kevan Martin of the University of Zürich and ETH Zürich is also a committee member of SPCCR. He investigates the prefrontal cortical area of the frontal eye field (FEF) in primates, which is important in eye movement, working memory, decision making and mechanisms of attention. Recent work has tested the prediction that FEF preferentially excites inhibitory neurons in target areas during attentional modulation. Using two adult female cynomolgus monkeys and one adult female rhesus monkey, Martin has managed to add to our so far incomplete understanding of the wiring that makes up the inter- and intra-areal circuits forming the 'pathways of attention'.

Third and final committee member Professor Gregor Rainer of the University of Fribourg investigates the mechanisms behind short-term memory, which requires communication between multiple brain regions that collectively mediate the encoding and maintenance of sensory information. Giving monkeys a visual short-term memory task, Rainer and his team studied neural interactions between visual

The Centre will foster exchanges of information and knowledge, and will offer expertise and training to any Swiss institution requiring access to non-human primates for a defined research purpose

area V4 and the lateral prefrontal cortex. This uncovered a mechanism that coordinates action potential communication between V4 and the prefrontal cortex, which may contribute to the maintenance of visual short-term memories.

REDUCTION AND REFINEMENT

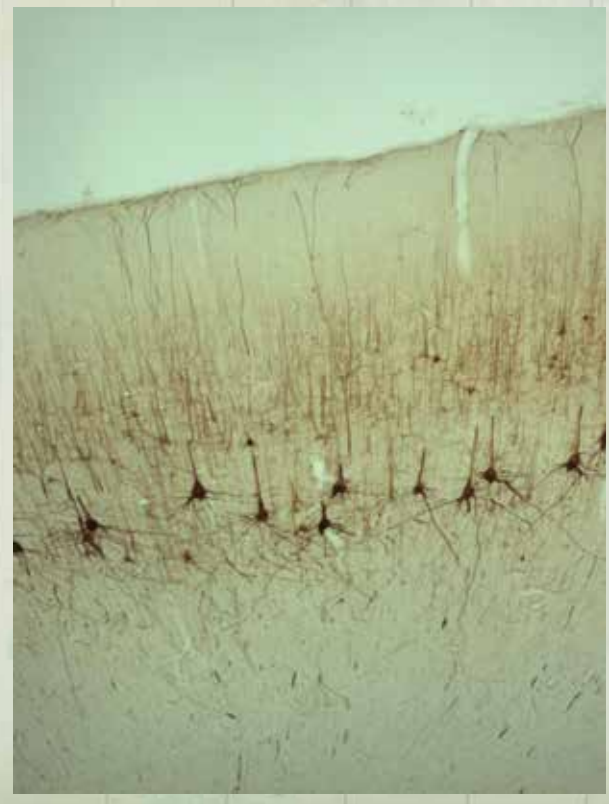
The Centre is currently analysing and elaborating standards between Fribourg and Zürich universities to establish a common set. This task should be completed by the end of June this year, with implementation taking place over the next six months. SPCCR will then coordinate techniques and protocols across research programmes to improve standard operating methods and procedures.

A key offering is a structured training programme for researchers and animal care personnel, tailored to specific skills related to working with NHPs. The first two- to three-day course, in collaboration with pharmaceutical companies that host NHP research, such as Roche and Novartis, will be staged this year. In 2014, the Centre will call for further collaborations with other institutions for projects and make selections in conjunction with additional expert inputs.

The Centre already has a number of collaborative projects in progress and is open to future endeavours with further partner institutions. SPCCR will create a central bank of NHP organs and tissues, and offer blood samples for genetic and other analyses. In terms of reducing the number of NHPs used – in those cases where a neuroscience project, for example, requires analysis of the nervous system and an NHP has to be sacrificed – the NHP's other organs, such as the heart, liver and kidneys, will be made available for other scientists' use or for teaching purposes. With regard to managing expectations and concerns, the Centre will also provide training to researchers in explaining what they do and the purpose of such investigations to the public.

Current collaborations involve the universities of Zürich, Fribourg, Lausanne and Geneva in various projects with live animals and post-mortem material, which include testing a strategy for improving recovery from spinal cord injury and cerebral cortex lesions; device development, such as robotic prosthetics; cell therapy for Parkinson's disease and electroencephalogram recordings; a therapy based on auto-transplantation of adult progenitor cells after lesion of the cerebral cortex; and involvement with a project observing the behaviours of captive NHPs. "In the human brain, scientists have one of the greatest challenges, not only to understand how it works, but also how it constructs itself and how we learn to be part of society," enthuses Rainer. "Meticulous work with primates is the critical bridge from studies with animals like mice to a new comprehension of the human brain."

PYRAMIDAL NEURONS IN THE MACAQUE CORTEX



Although initial funding for SPCCR will end in 2017, the plan is to continue as scientific projects with NHPs tend to last between five and 10 years. The possibility of contributions from other institutions with ongoing projects will then be explored.

INTELLIGENCE

SWISS PRIMATE COMPETENCE WCENTRE FOR RESEARCH (SPCCR)

OBJECTIVES

- To extend collaborations between Swiss biomedical research institutions and the Swiss Non-Human Primate Competence Center for Research (SPCCR)
- To create a central bank of organ tissue derived from NHPs (macaque monkeys) for post-mortem histological analysis

KEY COLLABORATORS

Committee members: **Professor Gregor Rainer**; **Professor Eric M Rouiller**; **Professor Kevan Martin**

Associate members: **Professor Pierre Lavenex**, University of Fribourg, Switzerland • **Professor Carel Van Schaik**, University of Zürich, Switzerland

Present external collaborations: **Professor Martin Schwab**, University of Zürich and ETH Zürich, Switzerland • **Professor Karl-Heinz Krause**; **Professor Christoph Michel**, University of Geneva, Switzerland • **Dr Jocelyne Bloch**; **Dr Jean-Francois Brunet**, University of Lausanne, Switzerland

FUNDING

Conference of Swiss Universities (CUS) • State Secretary for Education and Research (SER)

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PROFESSOR ERIC M ROUILLER earned his PhD in Auditory Neurophysiology from the University of Lausanne. He became Associate Professor in 1996 and since 2003 Full Professor in Neurophysiology at the University of Fribourg, with research focusing on motor control of NHPs.

PROFESSOR GREGOR RAINER received his PhD in Systems Neuroscience from Massachusetts Institute of Technology. Currently, he is Associate Professor at the University of Fribourg looking into visual neurophysiology and behaviour.

PROFESSOR KEVAN A C MARTIN obtained a DPhil from Oxford University. He is Double Professor of System Neurophysiology and Director of the Institute of Neuroinformatics at the University of Zürich and ETH Zurich.

SPCCR