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Neural Plasticity and Repair
National Center of Competence in Research

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

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COVER STORY

The Art of Neocortex

Thirty thousand years ago one of our distant ancestors crept inside a cave in south-eastern France carrying a flaming torch and some paint. Deep inside the cave she found a smooth vertical wall, placed her right hand against the rock and blew paint over it to leave an outline (Fig. 1). These stenciled hands are amongst the earliest painted images in Europe and they heralded a creative stream of 'art' objects, including realistic carvings and paintings, jewelry and even musical instruments, such as bone flutes. When we now look around us, the art and tools we have created are ubiquitous and uncountable, yet the extraordinary thing is, our brain is in shape and size no different from that of our ancestors of 100'000 years ago: we still have the brain of a Paleolithic human.

How is it then that by the age of three, we have

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A detail from a typical painting by Auguste Renoir (1841–1919). How does the brain recognize the "Renoirness" of a Renoir? (see Cover Story Fig. 2)

Neocortex, the Master Mind

In this issue, Kevan Martin takes a look at the neocortex, arguably the most human part of the mammalian brain as the devastating consequences of disease demonstrate. Stroke and other forms of neurological disorder may not only severely disrupt functions we share with other species like the ability to move, to perceive or to remember, but may also impair functions exclusive to us humans such as language.

These days one can detect a tendency among laypersons to reduce the study of the neocortex to the application of non-invasive imaging techniques such as functional magnetic resonance imaging (fMRI). No doubt imaging human neocortex has decisively enriched our ability to draw inferences as to its functional architecture. Yet none of the modern imaging techniques is currently able to provide the resolution needed to understand how neocortical cells speak with each other, how this exchange develops from the beginning and how it may adapt to the changing needs of the subject.

This is why the study of suitable animal models of human neocortex, including nonhuman primates, allowing for fine-grained observation of the signatures of information processing as well as well-targeted pharmacological or genetic manipulations that are required to establish causality, has been indispensable. Some of the ramifications of neocortex research for neurological diseases, such as improved foundations for training programs, explored in Projects 5 and 8, may sound modest, but undoubtedly promise tangible benefits for patients in the immediate future. Others, like the hope of restoring lost functions by using neocortex to control artificial arms and hands, a long-term goal on the agenda of Project 5, are much more ambitious and may still have a hint of science fiction to them. In any case, independent of their time-scale and scope, these examples of translational physiology demonstrate the profound benefits patients and society at large will ultimately draw from the pursuit of human curiosity.

Peter Thier
Professor of Cognitive Neurology*

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already acquired competences that would be quite unknown to the adult Paleolithic man or woman? What really has changed in our brain since the Stone Age? In this short time we can effectively rule out any mutations in genes between Upper Paleolithic humans and ourselves so it seems that the major change is in the way we use our brains. Probably the principal component of this 'plasticity' is the neocortex and its connections, which form 85% of volume of the human brain. The principal aim of NCCR Project 5 on Cortical Plasticity is to discover how the networks of the adult neocortex reorganize functionally and structurally during the acquisition or improvement of skills. Remarkably, with just 5 subprojects, all the major lobes of the primate's neocortex are being explored. This breadth is highly unusual, but it provides us with a multilevel approach that combines structure and function, perceptual and motor learning, and cognitive processing in human and non-human primates.

It has been common amongst philosophers and psychologists to use the image of a Swiss Army knife to describe the functional organization of the neocortex. In this metaphor, the neocortex is viewed as a number of modules, each of which has a specialist task. Thus, the cortical modules are packed together in the same unit, like the components of the Swiss Army knife, but they are not designed to work in concert, as in a ma-

Fig. 1: This stencilled hand, from the Chauvet-Pont cave in southern France, was made by one of our ancestors during the Aurignacian era (30'000–32'000 years ago). The image was produced by blowing ochre over a right hand pressed against the cave wall.

Neocortex

Fig. 2: How does the brain recognize prototype faces? Subjects memorized prototypes of portraits by Renoir. Four days later, a memory retrieval session was conducted in the MR scanner. The familiar prototypes were mixed with new exemplars that were visually similar, ambiguous or different, and subjects had to indicate whether they had seen each picture before. The fMRI data analysis revealed activation in the lateral fusiform gyrus, a face-responsive region, where old prototypes evoked stronger activation than all new items regardless of their visual similarity. In contrast, in the intraparietal sulcus, modulation by visual similarity was found such that new items that were visually different evoked less activation than new items that resembled the prototypes. Adapted from Yago & Ishai, NeuroImage, 2006.

chine. Already the results of Project 5 suggest a different view - one in which the neocortical sheet is seen as a highly connected, dynamic network with many more cross-modal interactions than the modular hypothesis envisages. This new view develops from our quest to identify how the networks of cortical areas interact with each other for a given task. For example, what happens in neocortex when we learn 'prototypes' for classifying complex images, such as paintings (Fig. 2)?

The gestures we make are also learned. From an early age we learn about the properties of objects: we come to shape our hands appropriately as we reach to pick things up; we anticipate their weight, their temperature and their texture; we decide whether to use a precision or a power grip (see Fig. 3). These actions, which we perform with effortless ease as adults, require an enormously detailed interaction between a number of senses to arrive at a coherent perception of the object and very sophisticated motor planning and control. It is clear from the tools they made and the art objects they created that the people who made the earliest cave paintings had these hand-eye competences coupled to a vivid imagination of the animals they painted. One of the major goals of Project 5 is to understand how the neocortex learns these perceptual and motor skills.

Over a century ago, the great Spanish anatomist Ramon y Cajal speculated that 'Cerebral gymnastics are not capable of improving the organization of the brain by increasing the number of cells….but it can be admitted as very probable that mental exercise leads to a greater development of the dendritic apparatus and of the system of axonal collaterals in the most utilized cerebral regions.' His hypothesis is easily stated, but after a century of work we still are far from understanding even how the cortex reorganizes itself as it learns. Project 5 is an ambitious research program that will certainly require a great deal of mental exercise on the part of the scientists involved, but such exercise will take us another step toward understanding how we can best use this great gift we have inherited - a primate neocortex.

PROJECT 5

Cortical Plasticity

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Daniel Kiper	Institute of Neuroinformatics, University and ETH Zurich
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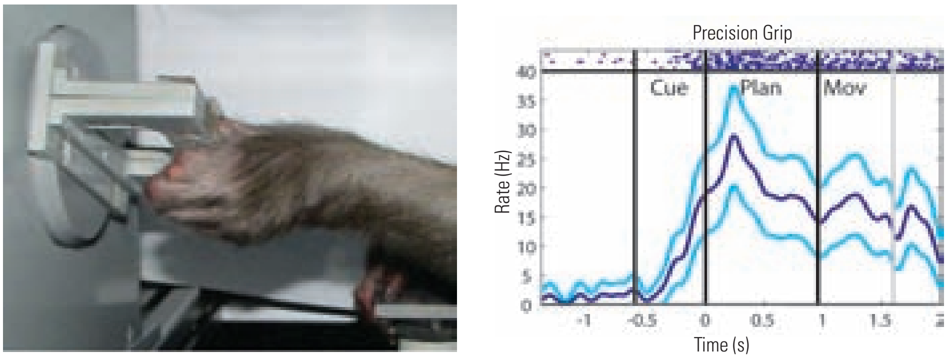

Fig. 3: Planning a hand movement. A macaque monkey has learned to grasp a handle-shaped object (left) with a precision or a power grip. Before the animal executes the movement, neurons in the parietal cortex (area AIP) fire vigorously already in the planning phase (right). The animal performs a delayed grasping task where the instruction (Cue) about which grip to make is separated in time from the planning (Plan) and movement execution (Mov). The panel on top shows the spike times during 9 task repetitions (rows of dots aligned above the planning period), and below, the average firing rate (dark-blue curve) and 95%-confidence interval (light-blue curves) of all trials. The example neuron was vigorously active for the planning and execution of a precision grip, but responded only moderately during the power grip task (not shown).

Kevan Martin
Leader of Project 5
Institute of Neuroinformatics,
University and ETH Zurich

Calendar of events

6th Day of Clinical Research
1–2 March 2007
University Hospital Zurich

Joint Meeting of the SSN - NCCR Neuro - MS Society
9–10 March 2007
Von Roll Areal, Berne

The NCCR Neuro Symposium 2007 will be organized as a Joint Meeting with the Swiss Society for Neuroscience (SSN) and the Swiss Society for Multiple Sclerosis (SSMS).
Further information and registration at: www.swissneuroscience.ch

BrainFair 2007
12–17 March 2007
University of Zurich

American Academy of Neurology 59th AAN Annual Meeting
28 April–5 May 2007
Boston MA, USA

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

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AWARDS

Sönke Boy, member of Project 7, was awarded the Best Poster Prize by the European Association of Urology at the EAU 2006 on 8 April 2006.

Volker Dietz, Co-Leader of Project 7, was awarded the prestigious Sobek Research Award for his achievements in understanding the locomotion control in health and disease, in particular in spasticity, on 10 November 2006.

Volker Dietz was awarded the distinguished Heiner Sell Lectureship in recognition of outstanding service and leadership by the American Spinal Injury Association in June 2006.

Rudolf Glockshuber, member of Project 2, received the Max-Bergmann Medal 2006 from the Max-Bergmann Kreis zur Förderung peptidchemischer Arbeiten for his contributions to the area of protein folding on 11 October 2006.

Mathias Heikenwälder, member of Project 6, received the Empiris Award for Research on Brain Diseases for his research on prions on 7 November 2006.

Christoph Hock, member of Project 2, received the Doron Prize 2006 in recognition for his outstanding achievements in Alzheimer research on 6 November 2006.

Alumit Ishai, member of Project 5, was awarded the Young Investigator Award in Cognitive Neuroscience 2006 given by the American Cognitive Neuroscience Society for her fMRI studies on the representation of objects and faces in the human brain.

Thierry Keller, member of Project 7 and 8, and **Klaus Schönenberger** received a Diploma CTI Medtech Award 2006 for the project smart electrodes: new transcutaneous electrical stimulation technology on 30 August 2006.

Lars Lünenburger, member of Project 7, and **Charles Remsberg** received the Diploma CTI Medtech Award 2006 for the project assessment tools for the robotic orthosis Lokomat: from automated to instrumented training on 30 August 2006.

Isabelle Mansuy, leader of Center 1 and member of Project 3, was elected as EMBO Member in 2006.

Matjaz Mihelj, member of Project 8, received the best poster award at the IEEE/RAS-EMBS International Conference on Biomedical Robotics and Biomechatronics on 22 February 2006.

Maurizio Molinari, member of Project 2, received the Friedrich Miescher Award 2006 given by the Friedrich Miescher Institute in Basel and the Swiss Societies for Experimental Biology on 24 February 2006.

Tobias Nef, member of Project 8, won the Student Prize of the German, Austrian and Swiss Society for Biomedical Technology for his article ARMin - results of the first pilot survey on 9 September 2006.

Tobias Nef won the Presentation Award for Young Scientists at the AUTOMED Workshop held on 24 March 2006.

Tobias Nef and **Robert Riener** were awarded a Swiss Technology Award for the arm rehabilitation project **ARMin** on 27 January 2006.

Lukas Sommer, member of Project 1, won the GSK Neural Stem Cell FENS Research Award 2006 in recognition of his outstanding and innovative scientific work in neural stem cell research on 12 July 2006.

Joachim von Zitzewitz, member of Project 8, was awarded the Förderpreis for the Best Diploma Thesis on control strategies for robot-aided gait therapy by the Alumni Association at Graz University of Technology on 18 October 2006.

Björn Zörner, member of Project 7, won the Best Poster Award at the Combined Scientific Meeting ASIA / ISCOS on 28 June 2006.

PUBLICATION HIGHLIGHTS

Multiple Sclerosis

Interleukin 18-independent engagement of interleukin-18 receptor alpha is required for autoimmune inflammation.
Gutcher I, Urich E, Wolter K, Prinz M and Becher B. Nature Immunology, 7(9):946-53, 2006

A novel therapeutic strategy for the treatment of multiple sclerosis (MS) is proposed. This inflammatory demyelinating disease of the CNS involves loss of axonal integrity leading to progressive neurological deficit. Although the precise aetiology of the disease is unclear, it is widely held that an autoimmune attack against neuroantigen is the underlying cause. In the animal model of MS, the immune cells responsible for causing damage to the CNS are a subtype of T cells known as CD4+ T cells. However this pathogenic cell type must initially be instructed by antigen presenting cells (APCs) to perform the attack; thus our goal was to understand the communication between CD4+ T cells and such APCs during autoimmunity. We discovered that the expression of IL-18 receptors on APCs is absolutely vital for driving disease-inducing T cell yet independent of its known ligand, IL-18. By blocking this communication pathway, we were able to prevent CNS destruction without disturbing the normal defense mechanisms of the immune system.

Molecular Imaging

Basic Principles and Applications in Biomedical Research
Markus Rudin, Imperial College Press

Markus Rudin, leader of the Center for Animal Imaging, introduces in this book basic aspects of molecular imaging technology and probe design and presents numerous examples from current research. Molecular imaging is a rapidly emerging field that translates concepts developed for molecular biology and cellular imaging to in vivo imaging of animals including, ultimately, humans. Molecular imaging approaches will therefore become indispensable tools for biomedical research including drug discovery and development.