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Projects involving experiments on primates 2006 - Abstracts

Bloch Jocelyne

Cellular characterization and therapeutic impact of adult neural cell autotransplantation in non human primates

Nr. 3100A0-103924

01.06.2004 - 31.01.2008

In this preliminary study, we demonstrated the feasibility of an autotransplantation of adult brain cells in primates.

These findings are new and interesting because they support the principle that primate adult brain cells can easily be obtained, kept in culture, reimplanted in the donor, survive in vivo and can express neuronal marker such as MAP2.

Restoring function of the central nervous system is a challenging task, since adult brain and spinal cord have a limited ability for self-repair. The large fetal transplantation experience mainly acquired the last two decades in the context of Parkinson's and Huntington's diseases, has offered promising results, however, despite the great enthusiasm, ethical controversies, lack of fetal donors and possible immunological reactions remain a major problem. Therefore, autotransplantation of adult brain cells represents an potentially attractive restoration alternative.

First we had to produce adult brain cell primocultures. After optimisation of procedure for brain cell culture preparation, using medium with preselected fetal calf serum (pFCS), we succeeded in producing long-term primocultures of adult human brain cells from temporal lobe tissues obtained from epilepsy and trauma neurosurgical patients. We have described this specific procedure for adult brain cell primocultures in laboratory investigation, 2002, 82, p.809-812. In another previous paper in Cryobiology, 2004, 47, p.179-83, we have also described the possibility to cryopreserve adult brain tissue to obtain brain cells with the similar characteristics than primoculture adult brain cells. We successfully applied these procedures to monkey adult brain tissues to obtain adult brain cell cultures.

Cells were obtained from cortical biopsy in macaque monkeys and grown separately in vitro for one month. Cells were stereotaxically reimplanted in the donor. The first reimplantation site was located in an lesioned area of the left motor cortex. The second site was chosen in a normal parietal cortical area. Just prior to reimplantation, cells were stained with fluorescent viable dyes. The animals were sacrificed at one month and at three months after reimplantation. Autotransplanted labeled cells were shown to survive in vivo at one month in both, the lesioned and the intact sites. At three months the reimplanted cells survived in the lesioned site but not in the intact area. Moreover, migration was observed in distal areas surrounding the lesioned area. Furthermore, at one month, most of the implanted cells still express nestin, a neural stem cell marker. At three months many reimplanted cells express MAP2, a neuronal marker. These re-

sults have just been accepted for publication in Experimental Neurology 196: 195-198 (2005). No one else has performed this kind of work to our knowledge.
After the feasibility study, the next steps are the evaluation of long-term impact of autotransplantation in brain repair. Currently, two studies are carrying out in the lesioned motor cortex model in monkeys.
In the first study, a group of monkeys are trained for manual dexterity tasks before motor cortex lesion. Their scores are collected before and after brain cell autotransplantation for a few months. Results will then be compared to those obtained in a group of lesioned motor cortex monkeys that were not treated.
These attractive results and our current experiments open new perspectives in the field of brain repair in the central nervous system through the autologous brain cell transplantation. However, a lot of work remain to be done, to consider this approach for clinical application in humans. (18.05.2006)

Fehr Ernst

The Foundations of Human prosociality: Social preferences in marmosets, chimpanzees, and humans

105312-114107

01.12.2006 - 30.11.2009

Humans exhibit a wide array of prosocial and cooperative behaviors. Economic experiments have shown that people consistently pay absolute costs to enforce equitable income distributions. Similarly, people have also shown a willingness under the right conditions to contribute to projects that increase the economic productivity of the social group, even though they face incentives to free-ride. Human prosociality, in fact, is so notable that it has become one of the central theoretical puzzles in the study of human evolution. Specifically, are humans more prosocial than other animals? And if so, how much more prosocial are they? Moreover, what conditions would have supported the evolution of a species with such distinctive cooperative tendencies?
These questions are currently difficult to answer because researchers have not produced data allowing direct comparisons between human prosocial behavior and that of other animals. Economic experiments typically used in the study of human cooperation have recently been adapted for non-human primates. For example, a simple representative experiment might present a trained chimpanzee with a choice like the following: one banana for me and one banana for another chimpanzee, or one banana for me and two for the other. If the chimpanzees consistently choose an even split, the result would imply that chimps do not like having less than their peers. If, however, they choose the uneven option, it would imply that they prefer helping their peers when no cost is involved. Lastly, if chimps tend to choose both options with roughly the same frequency, it suggests that they principally care about their own well-being and are indifferent to that of their peers.
Our work expands on this research. First, we also consider the common marmoset, which like chimpanzees and humans, are highly social, but less cognitively sophisticated, allowing the differentiation of behavioral effects related to cognitive sophistication and to social living. In addition, we examine several experimental conditions in all three species showing how circumstance affects cooperation. Research has shown that prosociality is rarely unconditional in humans, but depends on context, and could prove to be equally so in non-human primates; our task in part is to determine if this is so. Specifically, we examine the effects of communication, relatedness between players, and relative position in the social hierarchy. We also plan to implement experiments that allow players to sanction uncooperative individuals. We implement similar procedures in all species in order to maximize our ability to compare social behaviors among the three primate groups. (22.09.2006)

Hess Bernhard J.M.

Neuronal organization of otolith-ocular reflexes

3100A0-100802

01.04.2004 - 30.09.2007

Eye movements are amongst the most precisely controlled and at the same time very elementary organized movement forms in man and animal. They are of primary importance for vision. A large part of everyday brain activity is concerned in some way or another with eye movements. Moreover, in man and in animals with frontally placed eyes, the brain very precisely coordinates the movement of the two eyes, a precondition for the intriguing capacity of spatial vision and stereoperception.

One of the big challenges of the brain in controlling eye movements for the sake of vision is to stabilize the gaze lines during passive and active movements of the head. This task is by no means trivial because even small disturbances of head position, for example by the all time present heart beats, can make reading of a newspaper impossible, as observable after acute loss of the sensory inputs from the balance organs in the inner ear.

One oft the main objectives of our project is to investigate how the sensory signals from the balance organs in the inner ear interact with the mechanisms underlying a stable and robust perception of the visual world (that is independent of active or passive self-motion) and with associated gaze orienting movements. Along these lines a series of experiments focus on the stabilization mechanisms that are at work during the execution of simple behavioral tasks while head and body orientation relative to earth vertical passively change. While performing a particular, visually demanding task, for example fixation of a stationary or moving object relative to a complex visual background, the subjects are sitting inside an artificial visual environment that can be tilted and moved in various ways relative to earth vertical. By means of such experimental manipulations we aim at dissociating orienting responses, which normally include movements of the eyes, head and torso or body, from associated mechanisms that underlie the generation of a stable and robust perception of the visual surround. The obtained information about the interaction and central processing of multisensory motion cues, including those from the balance organs in the inner ear, in a given experimental configuration allows us to formulate testable hypotheses that can be followed up by invasive physiological techniques (single unit recordings, reversible focal inactivation of brain areas etc) exploring the function of brain areas that are known to be involved in balance control and stabilizing visual perception.

A detailed knowledge of the neural mechanisms involved in the generation of orienting responses is of great clinically interest. Our experiments in particular aim at showing how gravity-dependent transformations of gaze-control signals are implemented at various levels in the brain. For this, we try to better characterize the pathways and mechanisms in the brainstem/cerebellum that are involved in orienting behavior. The results will lead to a better understanding of the pathology of ocular control mechanisms and their interactions with vision. It is, for example, still not well understood how patients with lower brain-stem infarctions may show deviations in the perception of earth vertical or even experience attacks of up-side-down inversions of vision (room tilt illusions) although the traditional visual pathways are not affected.

Animal models in general will continue to be an indispensable tool for studying brain functions at both the behavioral, cellular network and single nerve cell level. Such models provide important guidelines in the search for a better understanding and development of new diagnostic tools and treatments of human orientation disorders (see Disorders of the Vestibular System, edited by Robert Baloh & Michael Halmagyi, Oxford University Press, 1996; Th. Brandt: Vertigo - Its multisensory Syndroms, Springer, 1999). To answer the questions addressed in our project it is advantageous to work with non-human primates because of the many similarities in the behavioral as well as neural organization of eye/head movements and the visual system. (17.05.2006)

Kiper Daniel C.

Perceptual learning in primate visual cortex

51NF40-111381 (NCCR Neuro)

01.06.05 – 31.05.09

The goal of this project is to understand the neural mechanisms that support perceptual learning. Perceptual learning is defined as an performance amelioration in a perceptual task that is induced by training.

In particular, we aim to understand what are the cortical events that lead to learning in a visual acuity task. This project is part of a larger effort to reveal the mechanisms underlying neural plasticity in the central nervous system. Understanding how neural systems learn and become more efficient after training is necessary to develop efficient strategies for the treatment of central nervous system diseases.

We train Rhesus macaques to perform a visual acuity task, known as Vernier acuity. In this task, the monkey has to indicate whether a short, vertical line segment is positioned to the left or right of an abutting, longer segment positioned at a fixed location on a computer screen. This task is known to yield considerable perceptual learning in humans, but its physiological basis is currently unknown. We will record the activity of individual neurons in the early cortical stages of visual processing to determine where learning occurs, and what kind of neuronal events are responsible for the improved performance. We apply standard operant methods to train monkeys to perform in this task, and use standard methodology to record extracellularly the activity of single cortical neurons in awake, behaving monkeys.

Martin Kevan

Cortical circuits underlying plasticity

51NF40-111381 (NCCR Neuro)

01.06.05 – 31.05.09

This subproject seeks to explore the question, what is the structure of the cortical networks that are involved in some important aspects of plasticity in the primate cortex? The project focusses on the dopaminergic innervation of the premotor and prefrontal cortical areas that are known to be involved in cognitive functions such as attention and action. The goal is to provide both techniques and insights that will provide the means to link different levels of plasticity in monkey and man.

Pryce Christopher

Long-term neurobehavioural disruption of emotion by early-life stress in the marmoset monkey: environment-gene interactions in the development of emotional phenotype

310000-110010

01.12.2005 - 28.02.2006

Das Ziel des Projekts ist ein besseres Verständnis des Zusammenhanges zwischen Störung der frühkindlichen Bindung zur Mutter und der Anfälligkeit für depressive Erkrankungen im späteren Leben.

Rouiller Eric M.

Recovery of motor control after cortical lesion and polysensory-motor integration in the primate

310000-110005

01.10.2005 - 30.09.2008

Stroke is the third most frequent cause of death in industrialized countries and is the most frequent one causing permanent acquired intellectual and physical impairment in adult human

subjects. In particular, stroke is the leading cause of motor disability in adult human subjects. Despite recent progress, motor functional recovery remains largely incomplete after stroke.
In the preliminary steps of this study, we found that monkeys treated with an antibody neutralizing Nogo-A, a neurite growth inhibitor, recovered substantially better manual dexterity following unilateral lesion of the opposite primary motor cortex, as compared to monkeys subjected to the same lesion, but not treated with anti-Nogo-A.
These findings are new and of interest because it is the first evidence in adult primates that such anti-Nogo-A treatment may enhance functional recovery of motor control after a lesion of the cerebral cortex located in the primary motor area. The present study thus represents an additional step towards the development of a treatment based on the neutralization of Nogo-A. Indeed, since the pioneering work of Dr. Martin Schwab and his collaborators demonstrating that Nogo-A, produced by oligodendrocytes, prevents regeneration of sectioned nerve fibers in the central nervous system of adult rats, a therapeutical strategy based on the neutralization of Nogo-A was found to be efficient in adult rats subjected to a lesion of the spinal cord (see Schwab, 2004, for review). In contrast to control lesioned rats, anti-Nogo-A treated rats exhibited a regeneration of transected corticospinal axons, correlated with a better recovery of motor function. In recent work, our team provided evidence that the anti-Nogo-A treatment also leads to enhancement of motor recovery in adult monkeys subjected to a lesion of the cervical cord. The present study thus extends these data from spinal cord lesion to cortical lesion, also in adult monkeys. Moreover, our findings also extend to the primates previous observations in the rat that anti-Nogo-A treatment enhanced motor recovery following cortical lesion (Papadopoulos et al., 2002; Emerick et al., 2003; Emerick and Kartje, 2004). The preliminary evidence that anti-Nogo-A strategy is also valid for cortical lesions is of great clinical relevance if one considers that such trauma are far more numerous than spinal lesions.
The present pilot study is conducted on adult monkeys (macaca fascicularis; 3-4 years old), trained in three behavioral tests consisting of reach and prehension tasks, to quantify their manual dexterity for each hand. Once they reach a stable performance (plateau), the hand representation in the primary motor cortex (M1) is precisely located in each hemisphere. To do so, chronic intracorticical microstimulation (ICMS) is applied daily during 3-4 months to map the left and right M1. Sites in M1 are thus identified where electrical stimulation produced movements of the fingers of the opposite hand, thus corresponding to the so-called “hand area”. The digit representation (hand area) of the left M1 is then lesioned by injecting the same volume of ibotenic acid (an excitotoxic drug). A subgroup of monkeys is treated with antibodies neutralizing Nogo-A during 2 weeks, whereas the other subgroup of monkeys is not treated. Following the lesion, the monkeys show a severe paralysis of the contralateral hand, which is reflected by low behavioral scores in the manual dexterity tests, whereas there is no impairment of the ipsilesional hand. The recovery of precision grip is generally nearly complete for the treated monkeys after couple of weeks post-lesion, but remained incomplete for the untreated monkeys, reaching a level of 65% below pre-lesion score.
To investigate if changes took place in the lesioned territory, ICMS sessions are repeated after the plateau of behavioral scores was reached. It is also proposed to assess the post-lesional plastic re-organization of the motor cortex using an optical imaging method (Laser Speckle Imaging). To test whether the re-organized territory in the treated monkey play a role in the functional recovery, it is reversibly inactivated pharmacologically by injecting the GABA agonist muscimol.
The present, preliminary data indicate that treatment with anti-Nogo leads to better and faster recovery after cortical lesion, extending to the primate previous results obtained in the rat. However, further experiments are needed to confirm this preliminary result on a larger number of monkeys. (12.05.2006)

Rouiller Eric M.

Polysensory-motor integration in the primate

310000-110005-2

01.10.2005 – 30.09.2008

How the brain processes sensory information is fairly well established for several modalities taken individually, such as vision, hearing, olfaction, taste, touch, etc. Indeed, the mechanisms of transduction in the sensory organs are well known as well as the progressive transformation of information along the respective pathways reaching finally the primary cortical areas, such V1 (for vision), A1 (for hearing) or S1 (touch) for instance. In these cortical areas, we know fairly well how the sensory information is represented and how individual neurons respond to the corr sponding unimodal stimuli. However, a major challenge of modern neuroscience is to assess how the multiple senses are integrated giving rise to a poly-sensory perception of the external world. For instance, how and where vision and hearing are combined remains largely unknown, in pa ticular at which level does multisensory integration begin: only in high order associative cortical areas or already at early stages, such as at the level of primary cortical areas or even earlier in the thalamus? We have collected preliminary evidence that poly-sensory integration may take place very early. Indeed, adult macaque monkeys trained to respond in a reaction time paradigm to sensory stimuli by reaching a target with one arm when a flash (light) or a tone are presented exhibited an early interaction between the two senses. Reaction times to tones presented alone were shorter than reaction times to flash presented alone, in line with well established data. However, the original observation is that simultaneous presentation of tone and flash led to shorter reaction time than tones presented alone. In other words, the combination of the two modalities generated a synergy between the two sensory channels, supporting the notion of early integration between vision and hearing, most likely before the information reached each of the primary cortical areas. To test this hypothesis of early poly-sensory integration, as suggested by the above behavioral (psychophysical) data, two lines of experiments are conducted: i) Neur anatomical tracers are injected in various auditory and visual areas in order to study their connectivity with the thalamus and determine whether some thalamic nuclei may be poly-sensory by projecting to both auditory and visual cortical areas; ii) Electrophysiologically, in the same mo keys subjected to the psychophysical tests mentioned above, neuronal activity is chronically recorded when the monkeys are performing the reaction time task. Recordings are derived from various auditory and visual cortical areas and, even more important, from the thalamus, in order to search evidence for early poly-sensory integration. Poly-sensory integration represents a fairly sophisticated cognitive ability, most exquisitely developed in primates, especially in human subjects. Along this line, numerous studies aim at studying poly-sensory integration in human subjects using non-invasive psychophysical, electrophysiological (EEG) and/or brain imaging techniques. However, neither investigation aimed at assessing the behavior of single neurons nor anatomical studies to establish the connectivity underlying poly-sensory integration can be conducted in human subjects. These approaches can be conducted only in animal models. However, only monkeys have an organization of the sensory pathways close enough to human subjects allowing comparison of behavioral, anatomical and electrophysiological data with human data (behavioral, EEG, brain imaging). A more elaborate knowledge of the structures and mechanisms involved in poly-sensory information in primates will allow better interpretation and maybe treatment of poly-sensory deficits observed in human subjects following brain injury or as a consequence of neurodegenerative/cognitive diseases.

Scherberger Hansjörg

Hand grasping signals in the premotor and parietal cortex

3100A0-108323

01.04.2005 - 31.03.2008

The use of the human hand plays a central role in our motor behavior and what defines us of being human. Many brain areas are involved in the generation of hand movements, but two regions in the premotor and parietal cortex play a particular important role for the initial, or high-level, planning of hand movements. The generation of these first hand movement intentions involves the transformation of visual information into a motor plan that can be further processed and executed.

In paralyzed patients, e.g., patients with severe spinal cord injury or stroke, the execution of such movements is disrupted, but the planning capacity for hand movements in the brain is still preserved. While neural commands can no longer reach the hand muscles, it may be possible to artificially read out and interpret these brain signals and deliver them to either the natural or a prosthetic hand - if one would understand how hand planning signals are generated and represented in the brain.

This project investigates how intentions to move the hand are generated and represented in the brain of macaque monkeys. Animals are trained to perform a delayed hand grasping task, in which an object can be grasped with two different grasping behaviors (precision grip or power grip) and in 5 different hand orientations. Animals are rewarded for each successful execution of the task with small amount of juice. Once the animal has learned the task, neural activity is recorded from two brain areas, the anterior intraparietal area (AIP) and the area F5, which both generate early hand grasping instructions. By correlating the neural responses with each other and with the animal's behavior, it is determined how high-order grasping plans are encoded in AIP and F5 and how these areas interact.

For these experiments, the use of macaque monkeys (rhesus monkeys) is essential for several reasons. First, only primates share with humans the dominant role of the visual system, the hand dexterity, and the way objects are grasped. Other species don't have this hand dexterity. Second, since the ultimate goal of understanding the hand movement system is to develop a neural prosthesis for human patients, studying the neural control of hand grasping in non-human primates is a necessary and appropriate fist step prior to human applications. We expect that results from this study will bring us several steps closer to understanding how hand movements are generated in the primate brain. (3.5.2006)

Scherberger Hansjörg

Decoding of premotor and parietal hand grasping signals for the control of a neural prosthesis

51NF40-111381 (NCCR Neuro)

01.06.05 – 31.05.09

This project investigates the question if hand grasping signals of two high-order brain areas (in the premotor and parietal cortex) can be used for the real-time control of a robotic hand. Macaque monkeys are trained to grasp an object (handle) with various hand grips, while neural activity is recorded from these brain areas. Using computer programs that interpret the recorded activity continuously when the animal is planning a hand movement, we attempt to decode the animal's movement intentions and use them to control a virtual or robotic hand, which the animal can see and move - instead of its own hand - to fulfill the task. Results of these experiments could bring us several steps closer to the development of a neural hand grasping prostheses that can be used to restore hand function in patients that suffer from stroke or spinal cord injuries.

Van Schaik Carolus Philippus

Variation in size and complexity of cultural repertoires in chimpanzees: an experimental approach

3100A0-111915

01.05.2006 - 30.04.2009

There is increasing evidence that great apes have huge repertoires of cultural variants, defined as socially transmitted innovations.

Nonetheless, human culture shows extensive differences to great-ape cultures. One major difference is the presence of cumulative culture in humans, the fact that many of the skills routinely acquired during development are beyond the cognitive range of normal individual development. In contrast, the skills of wild great apes tend to be within the cognitive reach of individuals, i.e. the skills are not more complex than a reasonably intelligent individual great ape could be expected to invent in its own lifetime. This difference must have evolved during hominin evolution. It seems fair to assume that the ancestral hominin started out with the general great-ape form of culture. Therefore, our only chance to help understanding the possible evolutionary changes is to investigate great ape cultures.

Observations and experiments in the field have only limited control over variables like previous knowledge and exposure history. Studies in the laboratory, on the other hand, differ in too many respects from the natural situation. We will conduct experiments in captivity, providing a controlled situation, but attempting to maximize the socioecological validity of laboratory experiments by examining the processes of innovation and social transmission in social groups living in an enriched environment without the direct involvement of humans, offering them tasks that closely resemble natural foraging tasks, and to provide them with enough time.

We will examine four main issues in four groups of captive chimpanzees: (i) the effect of the social structure and individual abilities on the lik elihood that a naïve individual socially learns a new skill; (ii) the adoption rules followed by these individuals; (iii) the effects of social structure and individual abilities on the origin and spread of innovations; and (iv) the degree to which there is a tension between innovation and social learning.

At first, data on dominance relationships and social bonds will be collected in continuous behavioural observations of the groups. Additional food sharing experiments will reveal the grade of tolerance among the group members. To study observational learning mechanisms the groups will be presented with several foraging tasks that allow for two distinct solutions ('two-action method'). Each task will be tested in three groups:

(a) in one group an individual group member will be trained to become expert in solution A, (b) in the second group one individual will become expert in solution B, and (c) in the third group no expert will be trained (control). The expert will be trained outside the group. By examining the distribution of the two solution variants among the individuals in the groups in relation to the kind of expert they were exposed to, we can study the adoption rules used by naïve individuals and the role of social structure.

Furthermore, we will examine innovation and exploration and their relation to social learning abilities. Both issues will be tested both in the groups and in individual settings. For testing exploration we will conduct experiments with novel objects as plush toys, novel foods etc., while for testing innovation we will use several food puzzles.

Additionally, we will collect information on individual innovation tendencies by conducting supplementary experiments on innovation under subtle environmental change in the group setting.

This investigation will contribute to clarifying the nature of the differences between humans and great apes in their cultural abilities, thus allowing us to identify the biological substrates and/or socioecological conditions that have served to keep the great apes at a modest level of culture while releasing at least some representatives of the hominin lineage. In particular, this project

will inform attempts to model cultural evolution by clarifying the degree to which innovation and social learning are competing activities and the conditions in which innovations spread as well as the pathways of spread and the conformity among the new experts.

Wannier Thierry M. J.

Does a BDNF treatment protect corticospinal and rubrospinal neurons from the secondary damages in spinalized monkey and add to the functional recovery obtained with an anti-Nogo treatment?

3100A0-104061

01.08.04 – 31.07.07

Patients suffering from a spinal cord injury and who are now sitting in a roll chair know it only too well: their spinal cord does not repair spontaneously and medicine is presently poorly armed to help! One reason accounting for this situation in the adult central nervous system is the presence in the whole brain and spinal cord of growth inhibitory substances, such as that scientists call "Nogo" and which hinders the growth of the lines interconnecting distant nervous cells, the axons. Without these lines, which have been damaged by the injury, the spinal cord remains divided into two parts which are not communicating. Thus, the signals from the brain do not travel further from the lesion and cannot act on the severed portion of the spinal cord. Thereby the repertoire of movements that one can generate becomes limited. Various laboratories are working to find out if an injured spinal cord can be repaired if the inhibitory action of Nogo is neutralized. Among them, the laboratory of Prof. M. Schwab in Zürich has investigated this question in the rat with a technique which consists of neutralizing Nogo by "covering" it with another substance, in this case, with an antibody specifically attaching to Nogo. Used on isolated nervous cells, this technique promotes the growth of axons. Used in rats subjected to a spinal cord lesion, a limited but consistent growth of axons has been observed. In this case, not only is the growth sufficient to build a bridge over the lesion, but some functional improvements have also been found. This is therefore one among other techniques which may ultimately find its way to clinic and help patients to recover better from a spinal cord injury.

If the results from the rat experiments are encouraging, their direct translation to human is hazardous. For instance, this technique promotes the growth of axons but does not ensure that in human the growing axons will not build aberrant circuits with an overall deleterious effect. Therefore, if safe clinical trials are the final goal, supporting data should first be obtained by repairing spinal cords of non-human primates (monkeys), in a species which shares much of the organisation and complexity of the human spinal cord. The aim of our study is to investigate this question using macaque monkeys as a model.

A group of adult macaque monkeys (macaca fascicularis) is first trained to perform a battery of motor tasks, testing essentially the manual dexterity. When the animals master the tasks, they are anaesthetized and a portion of their spinal cord is cut on one side. The lesion is set so as to interrupt a bundle of axons (the dorsolateral funiculus) which is prominent in primates and humans, and whose section is known to permanently disable the generation of precise fine finger movements. A subgroup of lesioned animals are treated with an antibody directed against Nogo, whereas the other subgroup of lesioned animals, called control animals hereafter, receive a control antibody which does not interfere with Nogo.

The day after the surgery, the animals show a loss of motor ability for the hand affected by the lesion. Weeks later, they recover most of their capacity to walk, climb or jump, and little distinguish these animals from intact animals. However, if their manual dexterity is thoroughly tested using quantitative analysis, a clear difference emerged. A simple but powerful test consists in presenting a board with wells filled with small food pellets to the animals. The wells are elongated and orientated either horizontally or vertically. The monkey has to retrieve the pellets, a task

which depends upon the ability to perform small precise finger movements. From the time required to get the pellets, from the capacity to get them out of both vertical and horizontal holes, and from the way the fingers are used, a picture of the recovery level can be obtained. In general, the control animals are able to retrieve food pellets out of the vertical holes, but retrieval from the horizontal slots remains difficult. The movements are considerably slowed down, and the position of the fingers is also abnormal: the thumb is not moved actively, but remains flexed in the palm and is only used as a passive substrate on which the forefinger clinched the pellet. This is indicative of a strategy of substitution rather than of a real recovery of normal finger movements. In contrast, the anti-Nogo treated animals recover faster and to substantially better levels. They are able to grasp pellets out of both vertical and horizontal wells, and though somewhat slower than normal. Also the way to use the fingers appear closer to normal: the thumb is moved in opposition to the forefinger and the pellet held between their tips. Also in two other motor tasks requiring motor dexterity, the level of recovery is considerably higher for the anti-Nogo treated animals. However, when testing the motor capacity of the hind limb, both animals show similar limited levels of recovery.

In parallel to the enhancement of motor recovery by anti-Nogo treatment, anatomical investigations on the same monkeys allowed to demonstrate that anti-Nogo treatment promotes a reconstruction of the lesioned corticospinal track caudal to the lesion, possibly representing the anatomical support for the enhanced functional rehabilitation.

These are encouraging results, suggesting for the first time that, by blocking the action of Nogo, one can help the spinal cord of primates to re-establish some severed connections and thereby to recover in part from an injury. In this respect, our observations are in agreement with those previously obtained in rats. Another important observation derived from these experiments is that the anti-Nogo treated monkeys do not exhibit signs of pain, epilepsy or unusual behaviour, indicating that the treatment does not produce undesired marked secondary effects. In summary, these data in monkeys pave the way towards safer pilot clinical tests in human subjects, although this model in monkeys remains crucial in order to address the fundamental issue of the mechanisms involved in the re-growth of transected axons favoured by the anti-Nogo treatment.

19. April 2007