SPCCR

The importance of non-human primate research in neuroscience

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In the general context of the benefits of animal experimentation to human health, the specific contribution of the model of non-human primates (monkeys) is well recognised (see e.g. Weatherall report 2006: https://royalsociety.org/topics-policy/publications/2006/weatherall-report/). For several decades, this animal model has played a major role in the development of numerous vaccines (e.g. yellow fever, measles, hepatitis B, poliomyelitis, etc) and treatments (e.g. renal dialysis, immunosuppressive treatment for organ transplantation, chemotherapy and many others). In the field of neuroscience, the non-human primate model also played a role in the acquisition of crucial knowledge as well as in the transfer to clinical applications (Capitanio and Emborg, 2008).

Several non-human primate centres and laboratories worldwide have contributed to these efforts. As far as Switzerland is concerned, the academic environment has been host for several decades now to two non-human primate infrastructures, namely at the Universities of Fribourg and Zürich (also involving ETH Zürich). In 2013, these two non-human primate sites joined their efforts in order to create a Swiss Primate Competence Center for Research (SPCCR), whose aims are presented in detail on the SPCCR website www.unifr.ch/spccr/ . In brief, this project, financially supported by the Swiss Confederation, aims to coordinate scientific activities across the two sites (Fribourg and Zürich), exchange competences and knowledge, implement common scientific and ethical high standards and ensure optimal training of young scientists for this specific animal model.

On the site of the University of Fribourg, as of 1975, a long tradition has been established in the field of studying motor control in monkeys or, to be more specific, the neural mechanisms underlying the precise and sophisticated control of voluntary movements, with emphasis on the hand. As far as manual dexterity is concerned (the capacity to perform independent and well organised movements with the individual fingers, for instance playing a music instrument), the hand of the macaque monkey (our experimental model) has morphological properties close to those of humans, even closer than humanoid monkeys (Almecija et al., 2015). Furthermore, the manual dexterity performance of macaque monkeys has been shown to be behaviourally speaking highly comparable to that of humans, with an index of 6 on a scale from 1 to 7, the latter value corresponding to the human manual dexterity performance (Courtine et al., 2007).

In contrast, rodents have a manual dexterity index of 3 on the same scale. This difference in manual dexterity performance is related to a very different anatomical organisation of the motor system between rodents and primates (Figure 1). First, the population of corticospinal neurons responsible for the transfer of motor commands from the brain (motor cortex) to the spinal motoneurons includes more than 100,000 neurons in the rat, compared to 400,000 in the macaque and more than a million in humans. Second, the corticospinal axons travel in the spinal cord at different locations. Third, and most importantly, the connection between corticospinal neurons and motoneurons is indirect in rodents (via interneurons), whereas in primates

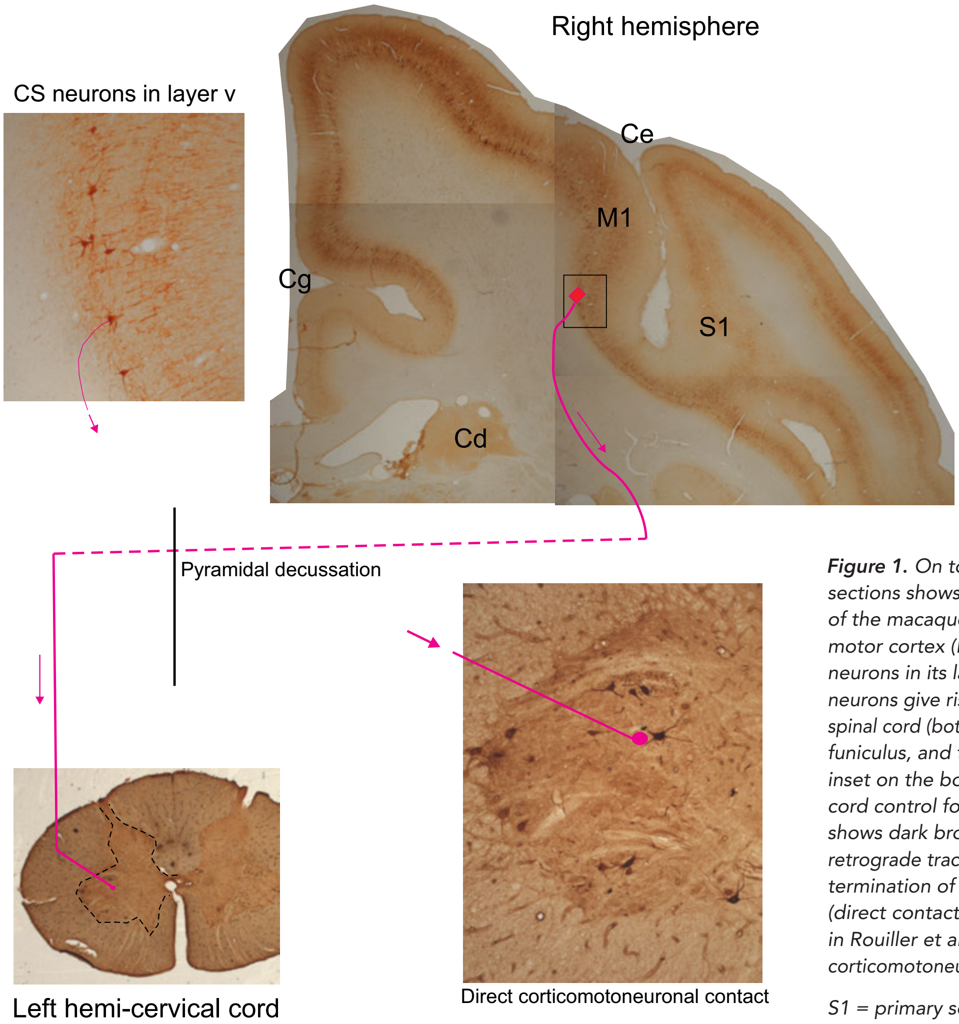

***Figure 1.** On top right, a montage of SMI-32 stained sections shows the upper part of the right hemisphere of the macaque brain, with the location of the primary motor cortex (M1), containing large corticospinal neurons in its layer V (see inset on the top left). The CS neurons give rise to axons projecting to the contralateral spinal cord (bottom left inset), travelling in the dorsolateral funiculus, and terminating on cervical motoneurons (see inset on the bottom right). Motoneurons in the cervical cord control forelimb muscles. The bottom right inset shows dark brown motoneurons labelled as a result of a retrograde tracer (CB) injected in hand muscles. Note the termination of the CS axons in red in close apposition (direct contact) with a motoneuron (as demonstrated in Rouiller et al., 1996), corresponding to the corticomotoneuronal (CM) system, a specialty of primates.*

S1 = primary somatosensory cortex; Cd = caudate nucleus; Ce = central sulcus; Cg = cingulate sulcus.

there are direct contacts, corresponding to the corticomotoneuronal (CM) system (Figure 1). Being a specialty of primates, the CM system is believed to be the anatomical support of sophisticated manual dexterity, which is a prerogative of primates (Lemon, 2008).

Based on these phylogenetical considerations, the macaque monkey has been selected in our laboratory as a pertinent model to study various aspects of manual dexterity, including issues related to pathology, namely the consequences of a lesion either at the level of the spinal cord or at the level of the motor cortex (e.g. Liu and Rouiller, 1999; Freund et al., 2006, 2009; Kaeser et al., 2011; Hoogewoud et al., 2013; Wyss et al., 2013). Some of these studies involved the goal of testing various therapeutic approaches in order to enhance (spontaneous) mechanisms of plasticity underlying functional recovery. Evidence for the benefit of such treatments can be seen in relation to spinal cord injury (www.unifr.ch/neuro/rouiller/research/recoveryvideo.html) or to motor cortex lesion (www.unifr.ch/neuro/rouiller/ACCI/videos.htm).

In order to conduct such translational studies, macaque monkeys are hosted in the SPCCR site at the University of Fribourg, under conditions strictly regulated by the Swiss veterinary authorities, delivering the requested authorisations to host monkeys and perform the experimental protocols, which are evaluated by an independent ethical committee. The housing conditions of the monkeys at the SPCCR in Fribourg are shown on a video sequence available on the web site of the SPCCR (www.unifr.ch/spccr/about/housing). First monkeys are housed in a room of 45 m^3, in which a group of 2-5 individuals interact among each other. As social animals, this permanent inter-individual interaction is crucial in order to guarantee a normal behaviour

Temporal course of the overall protocol in a representative monkey, before and after unilateral M1 lesion (hand area at day 0)

Modified Brinkman Board Task

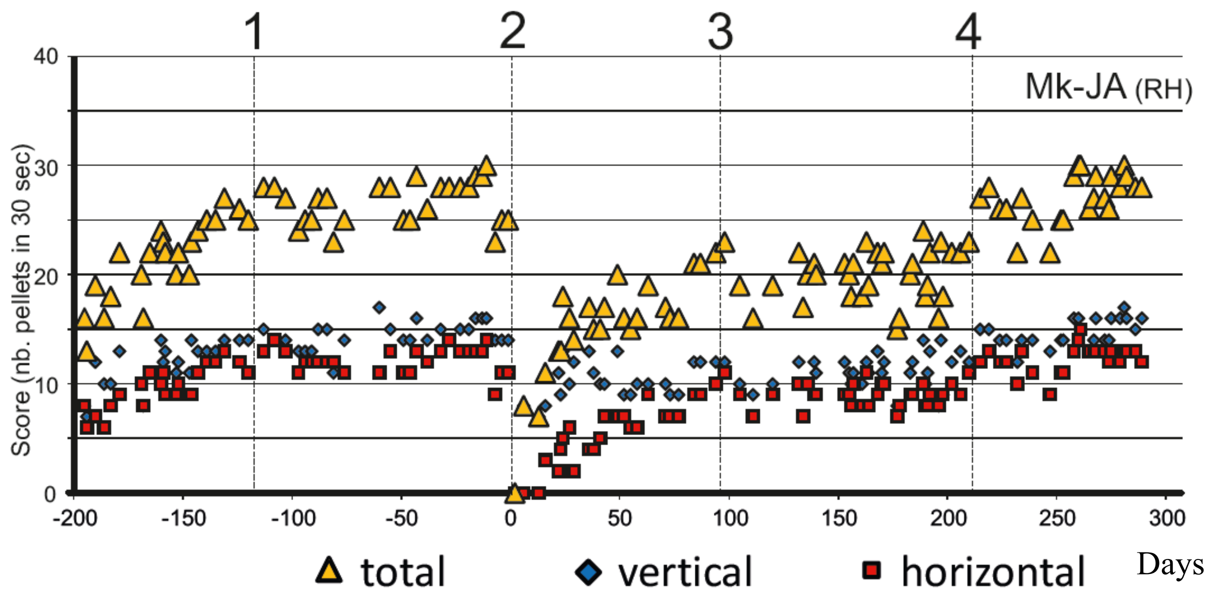

Figure 2. Graph illustrating a typical quantitative assessment of the motor performance of manual dexterity derived from the modified Brinkman board task. The monkey (Mk-JA) performed the task with its right dominant hand (see Chatagny et al., 2013), consisting in retrieving food pellets from a board comprising 50 slots. The score (number of pellets successfully retrieved from the slots) is indicated in ordinate as a function of the daily session (abscissa), separately for the vertical slots (n=25; blue diamonds) and for the horizontal slots (n=25; red squares). The total score (yellow triangles) is the sum of the vertical score and the horizontal score. The first time window (left to the vertical dashed line No 1) corresponds to the initial learning phase of the task. The next time window (left to the vertical dashed line No 2) corresponds to a stabilization of the performance at a plateau (pre-lesion), before the lesion of M1 hand area which took place at day 0. The following time window (in between the vertical dashed lines No 2 and No 3) represents the post-lesion phase of (incomplete) functional recovery leading to a first post-lesion plateau phase. The latter is represented by the time window between the vertical dashed lines No 3 and No 4. Finally, on the right of the vertical dashed line No 4, there was a second phase of functional recovery, in relation to a cell therapy treatment, representing an additional enhancement of functional recovery.

of the monkeys, favoured also by enrichment of the environment (trees, branches, toys, etc). Second, and this is not part of the legal requirement, the monkeys have access to an outdoor space providing an additional zone where they can interact under external climatic conditions.

The same video sequence emphasises also the procedures used to prepare the animals for transport to the experimental laboratories. Based on extensive training using positive reinforcement (food), the monkeys are patiently trained to go by themselves into a primate chair, without direct manipulations from the experimenter on the animals. This procedure presents the advantage to reduce stress for the monkeys and, for the experimenter, to minimise the risks (e.g. bites, scratches). Such habituation procedure lasts usually about 3 months, a worthwhile investment of time to optimise experimental conditions.

Following this initial training and when the monkey is in the primate chair, the animal is transported to the laboratory where different behavioural tasks are performed (http://www.unifr.ch/neuro/rouiller/research/motorcontcadre.php), in order to quantify various attributes of manual dexterity (see Schmidlin et al., 2011). As illustrated for one of the motor tasks – the modified Brinkman board task (Figure 2) – a score reflecting motor performance is established daily, corresponding to the number of food pellets retrieved with one hand using the precision grip from a board comprising 50 slots, 25 vertically oriented and 25 horizontally. Such quantitative behavioural data represent the basis to assess the extent and time course of the lesion consequences and monitor the spontaneous capacity of the nervous system to initiate plastic reorganisation, underlying (incomplete) functional recovery. The next step, using the same model, is to test whether a specific treatment may enhance functional recovery, as compared to the control case in absence of treatment. Two treatments were tested: the neutralisation of Nogo-A, a molecule which prevents severed axons from regenerating in the adult CNS, and the implantation of autologous adult progenitor cells. For both treatments tested, there is preliminary evidence in favour of an enhancement of functional recovery: anti-Nogo-A treatment for spinal (Freund et al., 2006, 2009) and motor cortex lesion (Wyss et al., 2013), whereas the cell therapy treatment was tested for motor cortex lesion (Kaeser et al., 2011).

As compared to large European non-human primate centres (hosting several hundreds or thousands of animals, including breeding colonies), the entire SPCCR is a very small infrastructure, limited to a few dozen animals, without a breeding colony. The monkeys are therefore imported from officially authorised breeders, following a strict procedure (quarantine, health status, etc). On the SPCCR site in Fribourg, five rooms of 45 m^3 allow a theoretical maximal capacity of 25 monkeys, providing that groups of five animals (upper legal limit) can be formed in each room. The transition, more than 15 years ago, from detention in individual cages to group housing in rooms of 15 m^3 (first until 2010) and then of 45 m^3 (since 2010) represented a major improvement for the wellbeing of the monkeys. Nevertheless, group housing, especially with 2-5 male monkeys, is not without risk due to the hierarchical organisation of the group. When the hierarchy is challenged, violent interactions may take place, resulting in severe injuries. The difficulty here is to prevent and tentatively control such unwanted events. As illustrated in the video on detention (see above), we are presently testing the feasibility of forming a group of one male and 2-4 females, the latter being subjected to long-lasting contraceptive treatment with subcutaneous implants. The preliminary observations are very promising in the sense of more peaceful groups of monkeys.

With a maximal capacity of 25 monkeys in the SPPCR facility of Fribourg, the experimental protocols are based on a limited number of animals, especially if one considers that an individual monkey remains in the protocol for several years (between 2 to 5 years usually). Indeed, research projects involving lesion of the brain or the spinal cord involve a long period of pre-lesion assessment, followed by an equally long post-lesion observation time window. As a consequence, the data are usually based on a relatively low number of subjects (typically 4 to 8 animals, over several years). One may argue that such low number of monkeys represents a limitation for the interpretation of the data. Nevertheless, in contrast to clinical study, the strength of the present macaque model is that it allows a close comparison within the same individual between the pre-lesion and the post-lesion periods. More precisely, it is possible to establish a percentage of functional recovery post-lesion, as compared to the (normal) pre-lesion performance. This approach based on an emphasis on intra-individual comparison allows us to reduce the impact of inter-individual variability, which represents a major obstacle in clinical studies comparing two cohorts of patients. In other words, it is our policy to emphasise parsimonious use of monkeys, based on a highly profound investigation of each individual, in order to respect the 3Rs principle (replacement, reduction and refinement) which encourages reducing the number of animals enrolled in research.

Further technical improvements, such as imaging (MRI, PET) or optimisation of implants (Lanz et al., 2013), were introduced to be in line with the 3Rs principle of refinement. Imaging guarantees more precise targeting of specific areas of the brain or spinal cord when a lesion is experimentally performed or to conduct electrophysiological investigations.

In conclusion, the macaque monkey represents a pertinent non-human primate model to investigate the mechanisms involved in motor control and its functional recovery following lesion of the central nervous system (brain or spinal cord). The experimental protocols are long-lasting and restricted to a small number of animals. Nevertheless, data derived from behavioural and electrophysiological experiments in the motor cortex of macaque monkeys conducted over decades led to recent and outstanding developments such as brain-machine interfaces (e.g. Jackson, 2012).

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Research and innovation – Investing in the future

State Secretariat for Education, Research and Innovation (SERI) highlights to Adjacent Government how research and innovation is gaining momentum in Switzerland, as it remains one of the most innovative countries in the world...

Research and innovation have gained increasing importance in light of social and environmental challenges. With its highly knowledge-based economy, Switzerland spends heavily on education, research and innovation and gives priority to international networking. The private sector and public sector are equally committed – and both actively contribute – to ensuring that Switzerland remains one of the most innovative and competitive countries in the world.

The Swiss higher education landscape is comprised of a diverse and comprehensive range of high-quality cantonal universities, federal institutes of technology, universities of applied sciences and universities of teacher education. Swiss higher education institutions have demonstrated internationally recognised performance and have made significant contributions to the economic, cultural and social development of our country. The quality of the Swiss higher education sector is reflected, among other things, in international university ranking lists. Swiss universities hold strong to very strong positions in these international ranking lists. Foreign nationals account for around a quarter of all students, and over 40% of researchers enrolled at Swiss higher education institutions.

Mutually supportive dynamics between the public and private sector

The traditional distribution of private and public sector roles has meant that fundamental research has mainly been the preserve of federal institutes of technology and cantonal universities. In contrast, applied research as well as the development of research findings into marketable innovations have mainly been driven by the private sector and the universities of applied sciences.

Public expenditure for research is mainly the result of personal initiatives on the part of researchers. Research funding is awarded on a competitive basis, according to qualitative assessment criteria. The Confederation is responsible for providing research funding through 2 federal agencies: the Swiss National Science Foundation (SNSF) and the Commission for Innovation and Technology (CTI). The Confederation also provides funding to the institutions and research institutes within the ETH Domain as well as to 30 non-university research infrastructures. For their part, the Cantons are responsible for managing and co-funding cantonal universities and universities of applied sciences.

Considerable weight is given to expenditure on education and research: just under 6% of Swiss GDP is devoted to education each year, around 3% more is spent on research and development activities. It is mainly private companies that invest the most in R&D, each year spending around CHF 13 billion (2012). This corresponds to about one-third of their total expenditure.

Creating ideal general conditions for research and innovation

The Swiss Confederation does not pursue an innovation policy per se – industrial policy is not an option. Nevertheless, the state does have a central role to play: it must create favourable conditions for private sector innovators as well as for researchers. These include a good-quality education system, which can provide highly trained workers for all phases of the innovation chain.

In addition to its higher education sector, Switzerland has a good-functioning system of vocational and professional education and training (VPET), which receives strong support from the private sector. Education and training is centred on the competences that are actually in demand as well as on occupations and professions for which there are existing job vacancies. This direct correlation with the labour market is the main reason why Switzerland has one of the lowest youth unemployment rates in Europe.

Other general conditions include fundamental and applied research; advisory and networking support for small- and medium-sized enterprises; reliable protection of intellectual property; removal of administrative hurdles; and finally, access to international knowledge and technology transfer. It is precisely this final point – international knowledge and technology transfer between higher education institutions and economic partners in different countries – that is of paramount importance.

Excellent research achieved thanks to international cooperation in research

International research cooperation is very important for Switzerland. First of all, it enables our country to play a part in numerous international research organisations such as CERN, the European Space Agency ESA, the Europe-wide network for cross-border cooperation in market-driven industrial research and development EUREKA, and COST the initiative for European cooperation in science and technology, as well as in multi-year research programmes such as the EU's research framework programmes.

In addition to this foreign scientific policy focussed almost exclusively on continental Europe, the federal government has recently set a new initiative for bilateral cooperation with priority partner countries outside Europe. The federal government has 3 main instruments to implement its bilateral foreign scientific policy:

- A network of Swiss science and technology counsellors, who are stationed in strategically important regions around the world;
- Swissnex, Swiss houses for scientific and technological exchange abroad, that help raise the level of awareness of Switzerland as a location for expertise and know-how;
- Specific programmes to promote research cooperation with selected priority countries.

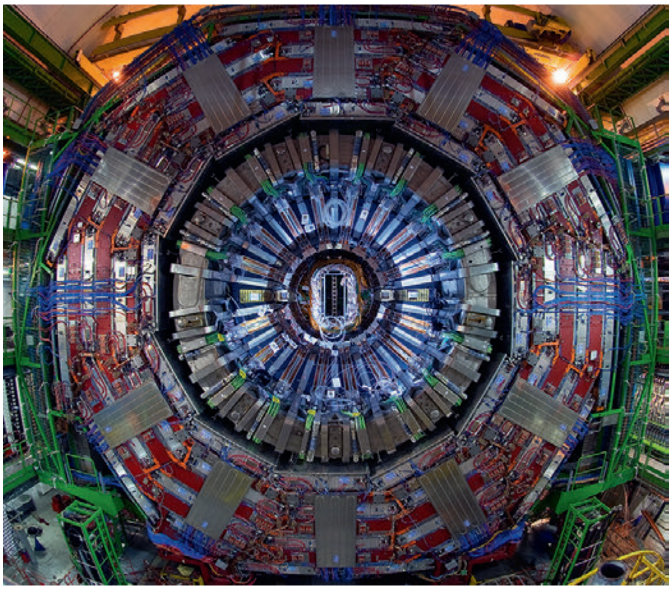

Image: © CERN

Based in Geneva, CERN, the European Organisation for Nuclear Research, is the largest particle physics research facility in the world. With help from giant particle accelerators such as the Large Hadron Collider (LHC) – the biggest of its kind in the world. CERN researchers are able to study the basic constituents of matter and how elementary particles interact

Key figures for Switzerland

Surface area: 41,300 km^2

Population: 8 million inhabitants

National languages: German, French, Italian and Romansh

GDP: USD 440 billion (2013)

Per capita GDP: USD 54,130 (2013)

Annual GDP growth: 2% (2013)

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