Non-Human Primate Models in Neuroscience Research

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Summary
Neuroscience is progressively increasing its comprehension of the normal functioning of the central and peripheral nervous system. Such understanding is essential to challenge important neurodegenerative disorders and clinical conditions such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, etc. The aim of neuroscience research is to improve understanding of normal and pathological functions and to develop therapeutic strategies and tools. Fundamental neuroscience utilizes a variety of techniques which include: electrophysiology, imaging, and computational modelling and entails interactions with clinical studies. Non-human primates are the closest species to humans in terms of biological, physiological, immunological and neurological characteristics; their closeness has been, and is still, an important reason for using them in biomedical studies. These animals have a vertebrate brain that is most like that of humans in terms of neural circuitry and this, together with similarities with human physiological and behavioural characteristics, makes them more valuable and accurate models of neurological and psychiatric diseases than other animals. This article provides an overview of the contribution of non-human primate models in fundamental neuroscience research and in generating clinically relevant findings and therapeutic developments.

Introduction
Non-human primates are the animals most closely related to human beings from which they have relatively recently separated from the common branch of the evolutionary tree. Sharing most of the genetic background, they own many distinctive similarities with humans in terms of physiology, anatomy, development, social complexity and cognitive capabilities. Although rodent species have a general organisation of the nervous system which is comparable in many respects to that of humans, non-human primates are still essential and irreplaceable in several areas of fundamental and translational neuroscience research.
Due to their similarities to human beings, they are supposed to have a high degree of sentience and capability to feel pain so, in recent years, a wide public concern about the use of non-human primates in experiments has highlighted the need to guarantee their psychological well-being. In addition, many regulations dictate that studies on non-human primates are only justified when the potential benefit of the research, balanced against the pain imposed on the animal, is substantial and no realistic alternatives exist. For these reasons, non-human primates are currently used in limited numbers in biomedical research; nevertheless, they have an important role in basic and translational neuroscience research (*Capitanio et al., 2008*).
Non-human primates have a central nervous system and a neural circuit organisation that most resemble those of humans. The brain size of a rhesus macaque is approximately 15 times smaller than that of a human being that is 750 larger than that of a rat. The brain of rodents has a smooth appearance with few fissures (sulci) of the thin outer layer of its cortical mantle, while that of a macaque has a sulcal pattern that, although less convoluted, is similar to that of humans (*Chiavaras et al., 2000*). Anatomical and

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connection findings (*Fellerman et al., 1991; Young, 1993*) from a large number of publications in the literature show that the macaque brain is the closest approximation to the human brain in conventional anatomical tracing and connectivity experiments (*Parvizi et al., 2006*). In addition, the brain of non-human primates resembles that of humans showing a considerable expansion and sub-divisions of the neocortex (*Lewis et al., 2000*), similar patterns of neural activities in interconnection networks, an enlarged prefrontal cortex, large forward-facing eyes and complex visual behaviour with specialised areas devoted to different aspects of vision such as colour (*Gegenfurtner, 2003; Conway et al., 2006*) and motion (*Newsome et al., 1986*); also the mechanisms of focal visual attention are comparable in macaques and humans (*Joonyeol et al., 2007; Treue, 2001; Shipp, 2004*).

Techniques in neuroscience research

Neuroscientists use a variety of techniques to investigate the structure and function of the nervous system. Classical electrophysiology techniques involve placing electrodes into a neuron or in continuity with the extracellular space. Single-cell recording is used to observe changes in voltage or current in a cell while an animal is performing a specific task and aims at assessing the relationship between the activity of that particular neuron and the behavioural performance. Parallel recording of neuronal activity from multiple individual neurons simultaneously (*Averbeck et al., 2003; Csicsvari et al., 2003*) in the brain is also a tool for the understanding of neuronal representation and storage of information. Computing and mathematical modelling of the nervous system are recent neurotechnologies that can help to understand the innumerable complexities of the brain functioning (*Maass et al., 2002; Chan et al., 2006*).

In recent years, there has been a gradual increase in the application of non-invasive imaging techniques used to either directly or indirectly explore the structure and function of the brain. These relatively new techniques comprise: Computed Axial Tomography (CAT), Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), functional Magnetic Resonance Imaging (fMRI), Diffuse Optical Tomography (DOT, Magnetoencephalography (MEG) and Event Related Optical Signal (EROS). These non-invasive techniques are able to acquire whole brain images non invasively allowing a greater amount of information on brain structure to be obtained. Functional neuroimaging techniques measure an aspect of brain function with the aim of understanding the relationship between activity in certain brain areas and specific mental functions. They are primarily used as a research tool in cognitive neuroscience and cognitive psychology/neuropsychology.

Functional magnetic resonance imaging (fMRI) is the most widely non-invasive brain imaging method used in human studies and the introduction of this technique in non-human primates has allowed comparative analyses of brain activation. Over the last years, functional neuroimaging has risen in prominence relative to the lesion studies (*Fellows et al., 2005*). Traditionally, lesion studies have had their greatest results on the understanding of the functional architecture of cognition since they enable one to associate a cognitive function to a brain area and to establish a causal relation between structure and behaviour. These techniques imply the induction of a finely localised lesion in a small region of brain tissue (*Harrington et al., 2001*); lesions are produced by passing electrical current through an electrode or with chemically specific toxins that destroy neurons. A lesion can also be made surgically by cutting a tract of fibres or by suction removal of part of the brain. A reversible lesion can be made by cooling (then rewarming) part of the brain or by injecting drugs. Lesions are performed using stereotaxic techniques under full recovery anaesthesia. The observation of functional impairment induced by the lesion indicates that the affected area is essential for the compromised function.

Alternatives to some lesioning studies might be provided by the continuous developments in imaging techniques such as Transcranial Magnetic Brain

Stimulation that allows the non invasive activation of cortical motor neurons and elicits responses in a wide range of muscles (*Rösler, 2001; Ishiguchi et al., 1997*).

None of the techniques currently used for correlating cognitive processes with brain areas are suited by themselves of identifying the information processing in the brain area. Each technique should be complemented by the results of others to obtain additional information about the phenomenon under investigation. For example, several research programs now combine brain lesion techniques and single cell recording with MRI imaging and clinical observations.

Non-human primate models in fundamental research

Basic neuroscience aims at providing explanations of cellular biology, neuron structure and function; neuroanatomy, neurophysiology, neuropharmacology and experimental therapeutics for neurological diseases are also areas of interest for fundamental research. Non-human primates, sharing numerous cognitive and physiological characteristics with humans, provide a bridge between rodent and human data and constitute invaluable models to further understanding of fundamental brain functions.

An important field of neuroscience research is the study of vision, investigating how visual information is perceived, learned and used to guide behaviour. These visually-based processes rely on activation patterns in neural circuits distributed in distinct regions of the primate brain. Therefore, to fully understand the neural mechanisms of vision, it is essential to study networks of neurons. Only recently it has become possible to investigate the properties of networks of neurons in non-human primates due to the advent of new research techniques like chronic multi-electrode recordings in multiple brain areas in awake, behaving animals. These experiments are performed in combination with behavioural, fMRI and computational approaches and will help to understand the principles of neural coding (*Tolias et al., 2005*). A recent study recording macaque primary visual cortex (V1) in animals experiencing prolonged exposure to chromatic modulation has allowed a better comprehension of the mechanisms involved in the elaboration of chromatic tuning (*Tailby et al., 2008*). Investigations on colour vision are mainly performed on macaque monkeys, whose trichromatic visual system is highly similar to the human (*Jacobs, 1993*). The perception of colour is a central component of primate vision. Colour facilitates object perception and recognition and plays an important role in visual memory. Despite the long history of colour vision studies, much has still to be learned about the physiological basis of colour perception (*Gegenfurtner, 2003*). Early evidence for the existence of a unique colour center in the visual cortex came from single-unit recordings of macaque monkey area V4 (*Zeki, 1983*).

Human and non-human primates show a wide repertoire of motor behaviours. Researchers are interested to understand the neural processes that underlie this flexibility and the mechanisms in the spinal cord and cerebral cortex that produce skilful movements of the arm and hand. The intended target of a movement must be transformed into a spatial and temporal pattern of muscle activity, a "motor pattern", to execute an appropriate behaviour; cortical and spinal pathways accomplish this transformation by integrating a number of specific signals (*Seki et al., 2003*). In various lower mammals, there is no direct projection from motor cortex to the motor neurons within the spinal cord; many of the projections derive from both sensory and motor cortex and synapse upon dorsal horn neurons which in turn project to the motor neurons within the ventral horn.

In primates, the area devoted to the motor cortex is highly specialized and separated from the sensory cortex and direct synapses from corticospinal neurons can be found on primary motor neurons within the ventral horn. The activity of individual neurons, pairs of neurons, and localized groups of neurons can be recorded in macaque monkeys while performing different motor behaviours; this enables one to elucidate the organization and function of the cortical and spinal circuitry that controls movement.

Establishing the underlying neural organization will improve our knowledge of physiological and environmental factors that contribute to disorders affecting sensory, oculomotor and motor function. Studies in non-human primates will continue to be needed for understanding special features of the human motor system, including feed-forward control of skilled hand movements. These movements are often particularly vulnerable to neurological disease, including stroke, cerebral palsy, movement disorders, spinal injury, and motor neuron disease (*Lemon et al., 2005*).

Investigations on complex cognitive behaviours entail the use of non-human primates since only they can be trained and tested in complex tasks, useful to explain cognitive functions. Several researches focus on the cognitive abilities of non-human primates, involving learning and memory. For instance, the hippocampus is important for the acquisition of spatial representations of the environment and consequently in contextual memory. It has been suggested that the neural substrates underlying spatial cognition might be essential for remembering specific life episodes (*Lavenex et al., 2006*). In monkeys, bilateral lesions of frontal cortical areas cause deficits on a large number of different memory tasks. Conditional learning, object recognition memory, reversal learning, visual discrimination learning, memory for multiple spatial locations, and the delayed response task have all been reported to be impaired by bilateral lesions to prefrontal cortical area (*Browning et al., 2007*).

Non-human primate models in clinical research

Non-human primate models offer a unique contribution in the translation of fundamental research findings into clinical applications and in the development of new treatments for neurological diseases (*Capitanio et al., 2008*). In this article, I will describe three examples of neuroscience research with prominent clinical relevance: Parkinson's disease, stroke and Alzheimer's disease.

Parkinson's disease

This common neurodegenerative disorder is characterized by the accumulation of fibrous protein deposits in neuronal cytoplasm (Lewy bodies) and nerve fibres (Lewy neurites) in the brain; these deposits may interfere with normal neuronal function. Selective death of the neurons that normally secrete the neurotransmitter dopamine results in a movement disorder that is characterized by muscle rigidity and resting tremor. The neurons that are affected are found in the substantia nigra and the locus coeruleus. Parkinson's disease (PD) has not been described in non-human primates; nonetheless, monkeys show age-related dysfunction of the nigrostriatal system, associated with motor impairments, that model the role of ageing in the development of the neurodegenerative disease and serve to investigate the relations between age, nigrostriatal activity and motor function. For this reason, aged non-human primates present a unique opportunity to study neuroprotective strategies (*Emborg et al., 1998*). The neurotoxins 6-OHDA and MPTP are widely used agents for modelling PD and for testing of neuroprotective strategies. Dopamine neurodegeneration induced by MPTP is currently the best available primate model of Parkinson's disease (*Beal, 2001; Dawson et al., 2002*). In adult monkeys, MPTP administration induces profound loss of dopamine neurons in the substantia nigra and motor impairments similar to those seen in idiopathic PD (*Emborg-Knott et al., 1998*).

Recently, a non-human model of PD has been described in adult marmosets (*Kirik et al., 2003*): a recombinant adeno-associated virus vector was utilized to express alpha-synuclein in the substantia nigra of adult animals; the alpha-synuclein protein was expressed in 90-95% of all nigral dopamine neurons that developed severe neuronal pathology and the treated monkeys showed motor impairment. This model offers new opportunities for the study of pathogenetic mechanisms and exploration of new therapeutic targets of particular relevance to human PD. Although in addition to MPTP several parkinsonian agents have been tested in animals; the

intracarotid MPTP model in the monkey presents the advantage of producing replicable lesions and a predictable pattern of neurodegeneration that provides the opportunity for identifying neuroprotective strategies and testing anti-parkinsonian drugs (*Jenner, 2003a*).

Non-human primates given MPTP respond to anti-parkinsonian drugs and have the same motor complications associated with their long-term use, making these animals ideal models to assess pathophysiology of dyskinesias (*Jenner, 2003b*). The MPTP model in non-human primates have been essential in the development and understanding of the mechanism of action of Deep Brain Stimulation (DBS) (*Meissner et al., 2005*). This is a well-established therapeutic approach for the treatment of late-stage PD consisting of high frequency stimulation (HFS) of the subthalamic nucleus. Behavioural studies and functional imaging have recently revealed that monkey (*Macaca fascicularis*) embryonic stem cell lines, conditioned to develop a dopaminergic phenotype, after transplantation into the putamen of MPTP-monkeys, function as dopaminergic neurons and attenuate MPTP-induced neurological symptoms with significant improvements in motility and posture recovery (*Takagi et al., 2005*).

Stroke

A stroke is caused by a sudden blockage or rupture of a blood vessel in the brain. The area that is deprived of oxygen-rich blood dies and this can result in severe brain damage or death and, of those who survive, the disability may consist of weakness or paralysis of one side of the body, loss or impairment of speech, disturbed vision and confusion. Understanding the mechanisms of injury and neuroprotection in these diseases is critical and can only be obtained by the appropriate animal model. Models of focal cerebral ischemia developed in non-human primates provide clinically relevant platforms for investigating pathophysiological alterations associated with ischemic brain injury, microvascular responses, treatment responses and clinically relevant outcomes that may be appropriate for ischemic stroke patients (*Fukuda et al., 2003*).

Models of focal cerebral ischemia in the primate have used single arterial occlusion or occlusion of multiple supply arteries to achieve a region of ischemic injury (*del Zoppo et al. 1986*). The relative reproducibility of stroke-related findings and the similar variability in injury volume make the non-human primate a clinically relevant model with direct applicability to human focal cerebrovascular ischemia. An intravascular stroke model designed for magnetic resonance imaging was developed in *Macaca fascicularis* to characterize serial stroke lesion evolution. This model produced a range of stroke lesion sizes which closely mimics human stroke evolution (*D'Arceuil et al., 2006*). A non-human primate model of stroke using the common marmoset (*Callithrix jacchus*) was also developed; the animals were assessed performing a variety of tasks to which they became highly proficient and then the monkeys were retested 3 and 10 wk after surgery (blockage of the middle cerebral artery on one side of the brain). Effects of neuroprotective drugs were then assessed again performing the pre-surgery tasks to evaluate the protective effects on brain function (*Marshall et al., 2003*).

Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease of senile life. The pathological hallmark of the disease is the production and accumulation of β amyloid (Aβ) peptide that affect a variety of neural circuits in multiple regions of the brain. Many of the vulnerable neurons develop neurofibrillary tangles (NFT), filamentous intracellular aggregation of abnormally phosphorylated tau protein in neuronal cell bodies and proximal dendrites and neuritis. Clinically, AD is characterized by progressive impairments in memory, cognition, language, and behaviour. Although non-human primates do not spontaneously develop AD, their highly developed cerebral cortex and cognitive abilities allow for assessment of structures and functions affected by AD. In addition, aged monkeys show behavioural and cellular abnormalities, some of which

are similar to AD-affected people (*Peters et al., 1996*). Studies on AD-type brain alterations have been performed with non-human primate models as they develop behavioural and brain abnormalities similar to those in humans (*Price et al, 1994*). It is well documented that aged non-human primates spontaneously develop dystrophic neurites, Aβ deposits and senile plaques within the cerebral cortex (*Hof et al., 2002; Nakamura et al., 1998; Bertoni-Freddari et al., 2006*).

Researchers at the Yerkes National Primate Research Center have recently discovered the first conclusive evidence of Alzheimer's-like NFT in an aged chimpanzee. The occurrence of both tau and Aβ pathology indicates that the cellular and molecular mechanisms for generating neurofibrillary tangles and β amyloidosis are present in aged chimpanzees. In addition, these results lead us to reconsider the assumption that humans are the only primates to manifest Alzheimer-like tauopathy with age. (*Rosen et al., 2008*). Non-human primates are also valuable models to assess the efficacy and safety of therapeutic agents and to identify new treatment strategies for the disease. Many investigations are aimed at either reducing the production of Aβ or enhancing its clearance**.** Immunisation with fulllength Aβ against Aβ deposits has been performed in aged Caribbean vervets resulting in reduced cerebral Aβ levels and gliosis; proposed mechanisms of Aβ clearance by immunotherapy include disruption of Aβ aggregates, Aβ phagocytosis by microglia, neutralization of Aβ oligomers at the synapse, and increased efflux of Aβ from brain to blood (*Lemere et al., 2006*). Nerve growth factor (NGF) has been widely evaluated as a treatment for AD. It has been shown that chronic infusion of (NGF) intracerebroventricularly in *Macaca fascicularis* can prevent degenerative changes in basal forebrain cholinergic neurons (*Tuszynski et al., 1990*). As an alternative to conventional drug delivery, genetic transfer approaches have received recent consideration as potential treatment modalities for neurodegenerative disorders. Research on the monkey model of AD which has proven the effectiveness of NGF in preventing cell death in ageing brains has led to the first human clinical trial of gene therapy for AD (*Tuszynski et al., 2005*). However, the gene therapy approach requires the use of risky surgical procedures to implant modified cells in the patients' brain parenchyma. The development of a less invasive delivery method for NGF, therefore, may significantly improve the prospects of NGF clinical uses.

Conclusions

The biological similarities and close genetic affinity with humans mean that non-human primates constitute indispensable models in neuroscience either in fundamental research, to improve understanding of structures and functions of the nervous system, and in translational research, to develop methods of prevention and treatment of diseases. Examples of such diseases are Parkinson's disease and Alzheimer's disease, which are the most frequent progressive neurodegenerative disorders in humans. Nonetheless, for their high level of sentience and capability to feel pain and distress, non-human primates should only be used when other alternative methods or species with lower development of the nervous system are not available to meet the scientific objectives. In Europe, most countries already have an ethical evaluation process in place for scientific procedures on animals and special consideration to non-human primates is given so that their use is avoided or minimised as far as possible. The number used in Europe in 2005 was about 10,000 and approximately 18 % was for studies on human nervous and mental diseases (*Commission of the European Communities, 2007*). Standards for the accommodation and care of non-human primates are high and maintenance guidelines have recently been updated within EU countries (*Commission Recommendation, 2007*). At the current state of knowledge and for the foreseeable future, these animals are likely to continue to be used as the only models for addressing important scientific and medical needs. The optimization of non-human primate keeping and breeding considering welfare and ethical guidelines, the development and standardisation of procedures and methods for

their use, advances in technology and the cooperation and share of information between institutions will allow the efficient use of these valuable animals.

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