Contributions of non-human primates to neuroscience research

John P Capitanio, Marina E Emborg

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California National Primate Research Center and Department of Psychology, University of California, Davis, CA, USA (Prof J P Capitanio PhD); **and Wisconsin National Primate Research Center and Department of Medical Physics, University of Wisconsin, Madison, WI, USA** (M E Emborg MD)

Correspondence to: Prof John P Capitanio, California National Primate Research Center and Department of Psychology, University of California, Davis, CA 95616, USA
jpcapitanio@ucdavis.edu

Non-human primates have a small but important role in basic and translational biomedical research, owing to similarities with human beings in physiology, cognitive capabilities, neuroanatomy, social complexity, reproduction, and development. Although non-human primates have contributed to many areas of biomedical research, we review here their unique contributions to work in neuroscience, and focus on four domains: Alzheimer's disease, neuroAIDS, Parkinson's disease, and stress. Our discussion includes, for example, the role of non-human primates in development of new treatments (eg, stem cells, gene transfer) before phase I clinical trials in patients; basic research on disease pathogenesis; and understanding neurobehavioural outcomes resulting from genotype–environment interactions.

Introduction

Neuroscience is an area in which research with non-human primates has played a major part in our understanding of basic neurobiology and the causes and potential treatments for human disorders. This animal model is especially valuable because of the many similarities between human and non-human primates that derive from their common ancestry, such as complex cognitive capabilities, great social complexity, details of reproductive biology, and intricacy of brain organisation. The importance of non-human primates to basic understanding of brain function was evident in the awarding of the 1981 Nobel Prize in Physiology or Medicine to Hubel and Wiesel for their studies on visual information processing.[1] Today, neuroscience research constitutes about 19% of published studies that use non-human primates as subjects.[2] Various areas are under active investigation. Here, we focus on four examples of basic and translational research in neuroscience with high clinical importance to highlight the breadth of research (neurodegenerative disorders, infectious disease, and psychosomatics) and to show the unique contributions of non-human primate models. The panel outlines reviews of other research areas.

Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disease and form of dementia. It affects 5% of the population older than 65 years, although earlier age of onset has been recorded. In the USA, more than 4 million people have this disorder.[10] Although the cause of the disorder remains unknown, evidence suggests that production and accumulation of β amyloid peptide is central to the pathogenesis of Alzheimer's disease.[11] Alternate hypotheses emphasise the role of tau-protein abnormalities, heavy metals, vascular factors, or viral infections.[12]

Alzheimer's disease usually starts with loss of short-term memory, followed by reduced executive function.[13] Classic symptoms include memory impairment, disorientation in time and space, deterioration of judgment, personality change, difficulty in learning, and loss of language and communication skills. Currently, the role of mild cognitive impairment in development of Alzheimer's disease is under debate.[14,15] This syndrome, typically recorded in elderly people, has been proposed as a risk state for Alzheimer's disease with different subtypes, some of which could be prodromal disorder.

Morphologically, Alzheimer's disease is characterised by progressive neurodegeneration, starting in layer II of the entorhinal cortex, followed by the hippocampus, the basal forebrain cholinergic system, cerebral cortex, and culminating in global brain deterioration.[16,17] Cell dysfunction and death in specific nuclear groups leads to deficits not only in the neurotransmitter acetylcholine but also in norepinephrine and serotonin.[18,19] Although the rate of Alzheimer's disease progression varies between cases, the disease eventually leaves its victims unable to care for themselves. Currently available therapies, most of which enhance cholinergic transmission by inhibition of the enzyme acetylcholinesterase, are restricted to treatment of symptoms.[20,21]

Non-human primate models of Alzheimer's disease

The highly developed cerebral cortex and cognitive abilities of non-human primates closely resemble those of human beings, and allow for assessment of structures and functions affected by Alzheimer's disease.[22] Use of monkeys in Alzheimer's disease research builds on a foundation of primate work that has investigated the role of various brain areas in memory, perception, and affect, dating back to the 1930s.[23–25] Non-human primates do not spontaneously develop Alzheimer's disease, yet aged

Search strategy and selection criteria

We searched for relevant articles in PubMed up to December, 2006, with keywords for up-to-date information in neuroAIDS, stress, Alzheimer's disease, and Parkinson's disease. Specific searches using "NeuroAIDS", "Stress", "Alzheimer's disease", or "Parkinson's disease" and "monkeys" or "primates" were undertaken. We did not limit our search by language. Owing to space limitations, references were chosen subjectively to review and illustrate every topic.

***Panel:* Additional examples of neuroscience research undertaken with non-human primates**

Ageing and cognitive decline[3]
Caloric restriction[4]
Cortical control of movement[5]
Focal cerebral ischaemia[6]
Neonatal brain injury[7]
Ovarian hormones and cognition[8]
Prenatal infection and CNS injury[9]

monkeys, similar to old people, show behavioural and cellular abnormalities, some of which resemble the disorder.[26–28] Functional declines are seen for selective attention, executive functions, and some components of declarative memory.[29] Neuronal numbers in the hippocampus and entorhinal cortex seem to be unaffected by ageing, although a substantial and extensive reduction in number and size of cholinergic basal forebrain neurons has been described,[30] as well as loss of monoaminergic neurons[26] and general changes in synaptic density and receptors.[31–34] Findings of early comparative studies established the presence and characteristics of tangles and senile plaques in the aged primate brain.[35–37] It is noteworthy that typical memory and attention deficits in aged monkeys seem to be unrelated to plaque burden.[38]

The loss of basal forebrain cholinergic neurons seen in Alzheimer's disease has been mimicked by stereotaxic injections of the cytotoxin ibotenic acid.[39] Systematic lesioning of the medial septum, nucleus of the diagonal band of Broca, and nucleus of Meynert indicated a role of basal forebrain cholinergic neurons restricted to attentional focusing, a deficit seen in Alzheimer's disease.[40] These lesions increased sensitivity to the cholinergic antagonist scopolamine in a non-matching-to-sample mnemonic task, showing that central cholinergic neurons were compromised. Transection of the fornix has also been used to examine the response of cholinergic septal/diagonal band neurons.[41] This method can induce a comprehensive loss of cholinergic fibres throughout the hippocampus, dentate gyrus, and entorhinal cortex ipsilateral to the lesion, which is associated with a reduction in cholinergic medial septal neurons. Reproducibility and stability of the lesion, however, depends on the surgeon's ability to undertake a specific and complete ablation. Although current methods to model Alzheimer's disease in monkeys have limitations (eg, lack of progression, partial behavioural impairments), they have provided a framework to understand the disorder and test new treatments.

Development of new treatments for Alzheimer's disease

Alzheimer's disease is still without an effective cure or preventive approach, and non-human primate research is playing an essential part in assessment of effectiveness and safety of first-in-class and invasive treatments for the disorder. Owing to the progressive nature of this disease, neuroprotective strategies are highly sought. Some proposed preventive treatments are antioxidants, anti-inflammatories, and antihypertensive compounds.[42] Immunisation against β amyloid deposits has become a major therapeutic strategy. In 2002, findings of a phase II clinical trial of immunisation with full-length β amyloid noted limited cognitive stabilisation and apparent plaque clearance in subsets of patients who generated antibody titres, yet the trial was halted because of the appearance of meningoencephalitis in about 6% of the participants. Although the exact cause of these adverse events is unknown, the immunogen—full-length β amyloid—might have been recognised as a self-antigen, leading to an autoimmune response in some individuals.[43] A follow-up study in aged Caribbean vervet monkeys[44] treated with a similar vaccine validated the immunisation paradigm in primates, showing reduction of cerebral β amyloid amounts and of gliosis. Currently, a passive immunisation trial with a recombinant humanised monoclonal antibody against β amyloid is underway in patients, and novel peptide immunogens are being developed.

Nerve growth factor (NGF), the first neurotrophic factor to be cloned, is at the top of the list of candidates to stop Alzheimer's disease progression.[45,46] Because NGF needs chronic targeted intracerebral release to be effective and safe,[47] gene transfer has emerged as an alternative delivery method. Non-human primate research was the platform to assess safety, toxic effects, and effectiveness of the invasive treatment before its transfer to the clinic.[48,49] A phase I dose-escalation clinical trial of primary autologous fibroblasts modified to produce NGF has been completed,[50] in which a mild but significant therapeutic benefit was recorded. A follow-up phase I/II clinical trial is now in progress, in which adeno-associated viral vectors encoding for NGF are introduced into cholinergic neurons of the basal forebrain in Alzheimer's disease patients. Although stem cells hold the promise of replacing neurons lost in Alzheimer's disease, their greater potential might be in pumping neuroprotective compounds in a so-called wild-type state or through genetic manipulation.[51,52]

NeuroAIDS

WHO estimates that more than 40 million people are infected with HIV worldwide.[53] This infection sometimes results in various neurological symptoms, collectively referred to as neuroAIDS. In the early years of the AIDS pandemic, the most obvious manifestation of neuroAIDS was HIV dementia, evident in late stages of AIDS, and manifesting with cognitive, motor, and behavioural symptoms. Since the advent of highly active antiretroviral therapy (HAART), the occurrence of dementia has declined in adults, affecting about 10% of those with AIDS, although this neurological disorder is seen in up

to 50% of HIV-infected children.[54] In addition to dementia, subtle changes—referred to as minor cognitive/motor disorder—have been estimated to affect as many as 30% of HIV-infected adults.[55,56] However, these figures best indicate the frequency in the developed world. In the developing world, prevalence is generally thought to be much higher, and diagnosis is complicated by—among other reasons—co-infections that are rarely seen in developed countries.[57]

Non-human primate models of neuroAIDS

Use of non-human primates in neuroAIDS research is based on the substantial similarity between the viruses that infect the hosts and the disease that they cause. Both simian and human immunodeficiency viruses are primate lentiviruses, are similar in both genomic organisation and genetic sequences,[58] target CD4+ T lymphocytes, monocytes, and macrophages and use the CCR5 chemokine receptor to gain entry to the target cells. Because simian immunodeficiency virus (SIV) does not cause disease in the species of African monkeys that are its natural hosts, Asian monkeys, particularly rhesus macaques, are the non-human primates most often used in AIDS research. Introduction of SIV into these animals leads to immunodeficiency that results in a clinical picture of wasting and opportunistic infections (eg, cytomegalovirus, pneumocystis) that is similar to what is seen in human AIDS. An important difference is that SIV disease arises in a much shorter timeframe—median survival in an archival cohort of 211 SIV-infected rhesus monkeys was 329 days,[59] compared with 8–12 years for HIV-infected individuals in the pre-HAART era.[60] Other animal-model systems, such as feline immunodeficiency virus in cats, exist and have been useful in understanding aspects of CNS disease.[61]

The pattern of SIV and HIV neuroAIDS is very similar,[62] and the SIV-macaque model has played a crucial part in understanding neuropathogenesis. Similar to HIV in human beings, SIV enters the CNS of monkeys soon after initial infection; however, the mechanism by which the virus crosses the blood–brain barrier and the predominant cell type that it infects was unclear originally. SIV research has shown convincingly that perivascular macrophages are largely implicated.[63] These cells have a higher rate of turnover than do parenchymal microglia, the other resident bone-marrow-derived immune cells of the CNS that can also be infected. Frequent replacement of perivascular macrophages by peripheral-blood monocytes supports the notion that lentiviruses enter the CNS via infected monocytes and macrophages.[63] This idea was also lent support by findings of previous SIV work, which noted a much higher prevalence of neurological signs and neuropathology in animals infected with a macrophage-tropic strain such as SIVmac251 compared with a lymphotropic strain such as SIVmac239.[64]

The ability to manipulate the virus itself continues to make the SIV-macaque model important for understanding neuropathogenesis. Findings of studies with recombinant and chimeric viruses have shown the role of *nef* and *env* genes in macrophage tropism and neurovirulence,[65] and have indicated that microglial cells might play a part—after infection in the CNS—with selection of neurovirulent strains of virus.[66] Development of neurovirulent strains for experimental use can be accomplished by serial passage of virus isolated from brains of animals with SIV encephalitis. Inoculation with these strains results in a high proportion of animals developing neurological complications. Examination of several clones derived from such animals, for example, indicates substantial similarity in the *env* and *nef* genes, suggesting convergent evolution in vivo for a brain-adapted genotype.[67] Finally, depleting SIV-infected monkeys of their CD8+ cells by administering antibodies to CD8 results in an accelerated disease course that includes CNS involvement. Moreover, findings of treatment studies of antiretroviral drugs that do not cross into the CNS have shown reductions in monocyte-associated virus and reversal of neuronal injury.[68] These data clearly suggest that reduction of peripheral viral load could be vitally important for prevention of neuroAIDS.

An important advantage of animal models is the ability to study events happening early in infection to understand pathogenesis and potentially to identify early correlates of later functional difficulties. Findings of studies with SIV-infected macaques have shown that increased expression of genes for proinflammatory cytokines such as interferon γ and tumour necrosis factor α—as well as increased expression of genes that are stimulated by interferons—can be detected in the CNS within the first 2 weeks post-inoculation,[69,70] that neuronal injury also takes place at this early stage,[71,72] and that indications of early CNS inflammation can be a marker for later development of SIV encephalitis.[73] Importantly, variations in metabolic changes indicating CNS inflammation and neuronal injury were correlated with plasma viral load and not time since infection, further suggesting the importance for the CNS of managing peripheral viral replication.[73,74]

The SIV-macaque model has also been useful in characterising cognitive and motor changes resulting from infection, including reduction in performance on tasks measuring spatial working memory, recognition memory, and motor function.[75] The pattern of deficits suggests involvement of brain dopamine, which is noted in regions subserving both memory and movement. In fact, changes in dopamine and serotonin metabolites in the cerebrospinal fluid have been reported in SIV-infected monkeys,[76] and a reduction in the dopamine content of the putamen early in SIV infection has been correlated with increased microglial activation.[77] Importantly, increasing dopamine availability pharmacologically produces deleterious neuropathological effects.[78] Because many drugs of abuse increase dopamine availability, this model can provide valuable information on mechanisms

relating to the severity of neuropathology seen in HIV-infected drug users.

In addition to the SIV-macaque model's value in testing antiretroviral drugs (eg, tenofovir),[79] data have shown that the neuroprotective antibiotic minocycline can reduce severity of encephalitis and suppress viral load in the brain.[80] This drug is now being tested in a phase II clinical trial.[81]

Parkinson's disease

Parkinson's disease is the second most frequent progressive neurodegenerative disorder, affecting 1% of the population older than 65 years.[82] The cause of sporadic Parkinson's disease remains unknown. Identified risk factors include genetics, old age, and exposure to environmental toxins.[83] Primary Parkinson's disease symptoms are tremor, rigidity, bradykinesia, and postural instability. Non-motor complications are also recorded, including urinary difficulties, constipation, skin disorders, sleep disruptions, depression, and other emotional changes.

The pathological hallmark of Parkinson's disease is loss of dopaminergic neurons in the substantia nigra pars compacta and presence of intracytoplasmic inclusions called Lewy bodies, formed mainly by α synuclein and ubiquitin.[84] Loss of dopamine in the striatum—the main area of projection of dopaminergic neurons in the substantia nigra—causes the parkinsonian motor syndrome.

Current treatments only focus on reducing parkinsonian symptoms.[85] The mainstay of therapy is levodopa, usually combined with carbidopa. Anticholinergic drugs and dopaminergic agonists are also used alone or in combination with levodopa. As symptoms worsen, effectiveness of treatments declines and drug-related side-effects such as dyskinesias increase, leaving many patients severely disabled.[86] Surgical options include disruption of the neural circuitry by targeted ablations or deep-brain stimulation.[87]

Non-human primate models of Parkinson's disease

The unique motor skills, working memory, and neuroanatomical complexity of non-human primates closely resemble those of human beings, providing a context to understand pathophysiology of Parkinson's disease. This disorder has not been described in monkeys, but similar to our species, monkeys present with age-related dysfunction of the nigrostriatal system that is associated with motor impairments such as tremor, stooped posture, and gait and balance disturbances,[88,89] making them ideal models to analyse the role of ageing in Parkinson's disease development and assess treatments in aged systems.[90,91]

Non-human primates are helping us to understand the genetic basis of Parkinson's disease. 5% of all cases of the disorder are familial and several genetic mutations have been identified, including in the α synuclein gene.[92] By injecting adeno-associated viral vectors encoding α synuclein into the substantia nigra of monkeys, investigators were able to induce mild symptoms of Parkinson's disease and a decrease of dopaminergic cells and terminals in the substantia nigra, linking α synuclein overexpression with nigral cell death.[93]

Neurotoxic models with 6-hydroxydopamine and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) are standard animal models of Parkinson's disease.[94] The MPTP model is currently the most widely used and the one that has had the most effect on research. MPTP is a mitochondrial complex I inhibitor that specifically causes dopaminergic neuronal loss in the substantia nigra.[94,95] It was first synthesised unknowingly by a clandestine home laboratory attempting to produce meperidine.[96,97] After the drug hit the streets, several drug users who had injected themselves with the contaminated substance developed a syndrome overnight that resembled advanced Parkinson's disease. The identification of MPTP as a human dopaminergic neurotoxin was only possible because it was tested in monkeys. Most rodent species are unaffected by MPTP, because the amount of monoamine oxidase B—the enzyme required to transform MPTP to its toxic metabolite MPP^+—is very low in the rodent brain compared with that found in primates.[98]

Monkeys exposed to MPTP present with a syndrome similar to Parkinson's disease.[99,100] Findings of electrophysiological studies in these animals[101] identified that nigral dopamine deficiency induces increased output from the globus pallidus pars interna and substantia nigra pars reticulata, and excessive inhibition of the brainstem and thalamocortical neurons, resulting in Parkinson's disease motor symptoms. Primates given MPTP, similar to patients with Parkinson's disease, 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.[86,102] Comparable with patients with Parkinson's disease, monkeys exposed to MPTP have non-motor signs, including frontal-striatal cognitive deficits,[103,104] autonomic disturbances,[105] and changes in sleep pattern.[106,107] Current monkey models of Parkinson's disease have some limitations (eg, lack of progression and of Lewy bodies),[95] yet they have been an invaluable resource to study the disease and develop treatments.

Development of new treatments for Parkinson's disease

MPTP studies in monkeys started a renaissance in Parkinson's disease research. Understanding of the neural circuit affected by the disorder led to targeted surgical ablation and deep-brain stimulation.[108,109] Symptomatic treatments such as dopamine agonists[110] were developed and, today, new generations of compounds are being investigated (eg, D3 dopamine agonists, A2a antagonists, and 5-HT1a antagonists).[86] Studies of dopaminergic cell replacement with mesencephalic fetal tissue in monkeys led to double-blind clinical trials in patients.[111–113] Inconsistent results created

the need for preclinical testing of factors affecting graft function, such as immunosuppression and dopamine-replacement treatments, because only primates can provide satisfactory answers to these questions. Retinal pigmented cells have been proposed as an alternative source for cell replacement. After their assessment in monkeys,[114] positive results have led to phase I and II clinical trials.[115] Stem cell lines conditioned to develop a dopaminergic phenotype have been developed and early reports of transplants in monkeys with these cells have been published.[116–121]

Non-human primates are playing an essential part in assessment of gene transfer as a method to restore function in Parkinson's disease. Based on rodent and monkey preclinical data,[122] a phase I/II clinical trial of adeno-associated viral vectors encoding for aminoacid decarboxylase—the enzyme necessary for decarboxylation of levodopa into dopamine—is currently underway.[123] As an alternative to functional restoration, injection of adeno-associated viral vectors encoding for glutamic acid decarboxylase (the rate-limiting enzyme for synthesis of γ aminobutyric acid) into the subthalamic nucleus has been proposed, to inhibit overactive glutamatergic neurons. Since findings of rodent studies[124] have confirmed this hypothesis, and work in non-human primates[125] has suggested feasibility, the first Parkinson's disease gene therapy trial was started in 2002.[126] The results of this phase I trial showed the treatment to be safe and well tolerated.[126]

Neuroprotection is currently an important goal of Parkinson's disease research and monkeys are valuable to assess novel candidate treatments.[127] Glial-derived neurotrophic factor has been identified as a potent dopaminotrophic substance.[128–131] Conflicting results were obtained from clinical trials of intrastriatal delivery of this factor by cannula and pump system,[132] and non-human primate research is helping to define factors implicated in the discrepancies and assess possible alternative treatments.[133,134] A gene therapy, phase I clinical trial of an adeno-associated viral vector expressing neurturin, a neurotrophic substance with structural and functional similarities to glial-derived neurotrophic factor, has been started.[135]

Stress

Stress is a psychological state that exists when demands exceed one's ability to cope, and it is a frequent disorder in the modern world. Researchers at the US National Institute for Occupational Safety and Health reported in 1999 that 29% of workers in the USA indicated that they feel "quite a bit or extremely stressed at work".[136] Stress is a risk factor for several health outcomes, and people reporting high stress have health-care expenditures that are 46% greater than those indicating low stress.[137]

A stressor can trigger two neural systems. First, the sympathetic–adrenomedullary system is activated almost immediately, which results in release of norepinephrine from sympathetic nerve terminals on target organs and release into blood of epinephrine and norepinephrine from the adrenal medulla. Second, in a slightly longer time frame, the hypothalamic–pituitary–adrenal (HPA) axis is activated, leading to release of corticotropin-releasing hormone from the hypothalamus into the portal blood supply, release of adrenocorticotropic hormone from the pituitary gland, and release of cortisol from the adrenal cortex.

Although stress can result in negative behavioural and physiological outcomes in the short term, effects can be substantially more severe when the disorder is chronic or when it arises during important periods of development. In both situations, stress can reorganise physiological systems with implications for health and disease. Primate models are especially valuable for studies: of prenatal effects (because rodents are born while still in an immature state, much brain and neuroendocrine development takes place postnatally, unlike in primates); in which social disruption or loss is the stressor (rodents do not generally show the same types of specific social bonds seen in primate species); and in which the later consequences of stressful experience are manifested in complex psychosocial outcomes, such as relationship formation, which rodents generally do not display.

Non-human primate models of stress

An important focus in primate stress research has been on understanding variation in responsiveness. As with human beings, individual non-human primates differ from each other in their biobehavioural characteristics, which can affect both behavioural and physiological responses to stressors. For example, adult male rhesus monkeys that have an excitable temperament show altered HPA function;[138] animals high in sociability (a characteristic indicating a tendency to affiliate) show raised IgG responses to immunisation after social separation;[139] and those with a fearful temperament have asymmetric patterns of frontal brain activity and increased concentrations of corticotropin-releasing hormone in the cerebrospinal fluid;[140] Research is focused on understanding the causes of these variations and their effects on health.

Prenatal stress

The prenatal period is sometimes overlooked in development, but interest in so-called fetal programming has focused attention on the role of prenatal events—including stimulation of the HPA axis—on later development and disease outcomes.[141,142] In primate research, the experimental stressor most frequently used has been an acoustic stimulus, with pregnant females being exposed to three 1 s bursts of 115 db sound at random intervals during a 10 min period.[143] Many results, however, have been mimicked by simple administration of adrenocorticotropic hormone for several days in mid gestation,[144] suggesting that activation of the HPA axis is mediating many effects of prenatal stress.

Outcomes of prenatal stress have been recorded in various systems and are remarkably persistent. When compared with offspring of undisturbed controls, prenatally stressed infants showed reduced birthweight, impaired neuromotor development, attentional and cognitive deficits, and disturbance behaviour under stressful conditions.[144] These behavioural effects are probably mediated by prenatal stress altering central neurochemistry, because evidence suggests that these animals have high concentrations of norepinephrine and dopamine metabolites in cerebrospinal fluid.[143] Structurally, prenatal stress results in a decline in both hippocampal volume and neurogenesis in the dentate gyrus, outcomes that might be related to rises in adrenocorticotropic hormone and cortisol that have been recorded in these animals.[145,146] Finally, prenatal stress has immunological and health implications. Such animals show impaired cellular immune function,[147] reduced proinflammatory cytokine production in vitro, greater leucocyte sensitivity to the effects of glucocorticoids,[148] and alterations in gut microflora.[149]

Postnatal experience

Findings of non-human primate research from several decades ago showed that adversity early in life was associated with various negative behavioural outcomes, such as heightened emotionality and increased risk of depression,[150] and these observations were instrumental in changing child-rearing practices.[151] The latest research has focused on neurobiological mechanisms mediating behavioural outcomes, neuroimmune results, and naturally occurring variation in biobehavioural functioning.

Studies of the effect of early adversity have used several model frameworks, the most frequent of which entails nursery rearing, in which infants are reared without adults but with one or more peers to provide some degree of social competence. Findings of such work have shown that early adversity is associated with altered brain neurochemistry, such as reduced serotonin turnover, as assessed by concentrations of the major serotonin metabolite 5-HIAA in cerebrospinal fluid,[152] and impaired impulse control.[153] Early adversity also leads to enhanced HPA responsiveness to social stress and increased alcohol consumption when tested as young adults,[154] and reductions in both affiliative behaviour and concentrations of oxytocin in cerebrospinal fluid.[155]

However, adversity does not affect all people in the same way. Research has identified candidate genes that predispose individuals to poor outcomes when adverse situations are encountered. Focus has been on the serotonin system and, in particular, variation in the promoter region of the serotonin transporter gene. Possession of one short allele (homozygosity for the short allele is rare) confers reduced transcriptional efficiency of the transporter gene, which produces a protein responsible for reuptake of serotonin from the synaptic cleft. Findings of several studies have indicated genotype effects for nursery-reared—but not for mother-reared—monkeys; specifically, nursery-reared heterozygotes (compared with long/long homozygotes) show lower orientation and attention scores in infancy,[156] reduced concentrations of 5-HIAA in cerebrospinal fluid,[157] higher levels of alcohol preference and consumption,[158] raised adrenocorticotropic hormone concentrations in response to a social stressor, and diminished basal cortisol concentrations.[159] These data have been extended to an infectious disease outcome in adult male rhesus monkeys that were inoculated with SIV: heterozygotes under stressful conditions were substantially more likely to show sustained aggression, which was associated with altered expression of immune response genes; gene expression, in turn, was related to higher SIV viral load.[160]

Conclusion

In neuroscience, non-human primates continue to have important roles in basic and translational research, owing to their behavioural and biological similarity to human beings. In the future, these animals are likely to continue to be the models of choice when whole-animal questions are being asked. Primate research is not undertaken lightly, and every effort is made by scientists and institutional review boards to ensure that the work is necessary, beneficial, and humane.

Because of the expense associated with breeding and rearing these animals, however, their numbers in research will always be small, as part of a continuum of neuroscience work that ranges from invertebrates to human beings. The US National Institutes of Health has produced a blueprint for neuroscience research, which aims to "develop research tools, create research resources shared by the entire neuroscience community, train a new generation of cross-disciplinary neuroscientists, and importantly, to develop a cooperative framework for the institutes and centers to plan and implement their neuroscience research efforts".[161] Non-human primate research is an important component of this blueprint; a cooperative orientation, advances in technology (eg, imaging), and a shared informatics infrastructure[162] will permit efficient use of these valuable animals.

Conflict of interest statement

We declare that we have no conflict of interest.

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