ILAR Journal, 2017, Vol. 58, No. 2, 190–201

doi: 10.1093/ilar/ilx021
Article

Nonhuman Primate Models of Neurodegenerative Disorders

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Abstract

Alzheimer's (AD), Huntington's (HD), and Parkinson's (PD) disease are age-related neurodegenerative disorders characterized by progressive neuronal cell death. Although each disease has particular pathologies and symptoms, accumulated evidence points to similar mechanisms of neurodegeneration, including inflammation, oxidative stress, and protein aggregation. A significant body of research is ongoing to understand how these pathways affect each other and what ultimately triggers the onset of the disease. Experiments in nonhuman primates (NHPs) account for only 5% of all research in animals. Yet the impact of NHP studies for clinical translation is much greater, especially for neurodegenerative disorders, as NHPs have a complex cognitive and motor functions and highly developed neuroanatomy. New NHP models are emerging to better understand pathology and improve the platform in which to test novel therapies. The goal of this report is to review NHP models of AD, HD, and PD in the context of the current understanding of these diseases and their contribution to the development of novel therapies.

Key words: alpha synuclein; Alzheimer's disease; beta amyloid; huntingtin; Huntington's disease; nonhuman primates; Parkinson's disease

Introduction

Neurodegenerative disorders are a group of age-related diseases characterized by progressive neuronal cell death. Alzheimer's (AD), Huntington's (HD), and Parkinson's (PD) disease are examples of these disorders. Although each one of them has particular pathologies and symptoms, accumulated evidence points to similar mechanisms of neurodegeneration, including inflammation, oxidative stress, and protein aggregation (Granholm et al. 2008). In that regard, reports in all three disorders suggest that the accumulated misfolded proteins may have prion-like behavior. A significant body of research is ongoing to understand how these pathways affect each other and what ultimately triggers the onset of the disease to prevent, stop, or slow down disease progression. Mapping of the human genome was accomplished in 2003; improved genetic methods have accelerated the identification of an array of mutations linked to these disorders. New animal models are being developed to better understand pathology and improve the platform in which to test novel therapies.

Animal models of neurodegenerative disorders have been developed in multiple species in vertebrates and invertebrates aiming to understand different aspects of these diseases and identify new therapies (AD: Ji et al. 2016; Onos et al. 2016; HD: Brooks and Dunnett 2015; Howland and Munoz-Sanjuan 2014; Krench and Littleton 2017; PD: Chesselet and Richter 2011; McDowell and Chesselet 2012; Tenreiro et al. 2017). Experiments in nonhuman primates (NHPs) account for a small percentage of all research in animals. Yet the impact of NHP studies for clinical translation is much greater, especially for neurological disorders,

as NHPs have a highly developed cerebral cortex and cognitive function, complex motor skills, and neuroanatomy. The mapping of the rhesus (*Macaca mulatta*) and common marmosets' (*Callithrix jacchus*) genomes was accomplished in 2007 and 2014, respectively; they are used as a resource to identify similarities and divergences between species as well as to improve NHP models of disease. The goal of this report is to review NHP models of AD, HD, and PD in the context of the current understanding of these diseases and their contribution to the development of novel therapies.

AD

AD is the most common age-related neurodegenerative disorder and form of dementia. It is estimated that one in nine persons over 65 years old has AD and that over 5 million Americans are affected by AD. Five percent of all AD cases are inherited and are diagnosed between the age of 30 and 60 years old (early onset) (Younger/Early Onset Alzheimer's & Dementia 2017. Available online).

AD patients present cognitive or intellectual symptoms (e.g., amnesia, aphasia, apraxia, and agnosia) as well as psychiatric ones (e.g., personality changes, depression, hallucinations, and delusions). In 2011 Alzheimer's Association and the National Institute on Aging issue an updated criteria and guidelines for diagnosing AD and emphasized the urgency of defining preclinical AD stage. AD is usually diagnosed when patients are already in the middle stages of the disease and activities of daily living and sleep become difficult. During the more advanced, severe stages, AD patients may not be able to communicate, recognize him/herself and family members, may lose bladder and/or bowel control, and require help with all activities. Current AD treatments are symptomatic. For psychiatric symptoms, antipsychotic or antianxiety medications may be prescribed. For cognitive loss, enhancing cholinergic transmission by inhibition of the enzyme acetylcholinesterase is a usual treatment. N-methyl-D-aspartate receptor antagonists, which work by regulating the activity of glutamate, are used for improving memory and learning (Melnikova 2007).

Pathologically, AD is characterized by progressive neuronal loss in the hippocampus, entorhinal cortex, and basal forebrain cholinergic system combined with the presence of ß-amyloid plaques and tau-positive neurofibrillary tangles. Neuroinflammation is observed in areas of neurodegeneration. As AD progresses, it greatly compromises the cerebral cortex and eventually induces global brain deterioration (Braak et al. 1993; Schliebs 2005). The loss of cholinergic neurons is thought to be a leading factor in the decline of cognitive function; loss of serotoninergic and catecholaminergic neurotransmission are proposed as contributing factors (Palmer et al. 1987a; 1987b).

The cause of AD is not clear. For most AD cases, a combination of genetic, environmental, and lifestyle factors, which varies between individuals, has been proposed. In that regard, having the apolipoprotein E ε4 gene on chromosome 19 increases risk for AD and is also associated with an earlier age of disease onset. Early onset has been linked to gene mutations on chromosomes 21, 14, or 1. Interestingly, each of these mutations affects the breakdown of abnormal amyloid precursor protein, generating amyloid plaques (Lane-Donovan and Herz 2017; Serretti et al. 2007). It has also been proposed that AD may share similarities with prion diseases based on evidence that ß-amyloid can be "seeded," yet further confirmation is needed (Kovacs 2016).

Modeling AD in NHPs

NHPs' cognitive abilities and brain complexity are well documented and have contributed to the understanding of the neuroanatomical basis of AD. This knowledge combined with the identification of AD risk factors has facilitated the development of NHP models of AD. Aging or targeted lesioning of rich cholinergic brain areas are typical methods to mimic AD in monkeys. New NHP models based on ß-amyloid and tau pathology are emerging.

Aged monkeys, like aged humans, develop behavioral and cellular abnormalities over time and some of them resemble AD (Albert 2002). Age-related deficits in memory and attention, deposits of amyloid plaques, and atrophy and/or loss of cholinergic and monoaminergic neurons are well documented in NHPs (Peters et al. 1996; Price et al. 1991). Upregulation of Aβ42 in the brain and bodily fluids is found in aged rhesus macaques (Zhao et al. 2017). Aged marmoset monkeys also present Aβ40 in vascular deposits, while Aβ42 is mostly found in plaques associated with swollen neurites but not abnormally phosphorylated tau (Geula et al. 2002). Although aging is not AD, aged models are excellent platforms to understand aging as a risk factor for AD, and, with certain limitations, as models of early AD.

The loss of cholinergic basal forebrain neurons and associated cognitive deficits can be mimicked in NHPs by stereotaxic injections of the cytotoxin ibotenic acid into the basal forebrain or by transection of the fornix (Kordower and Fiandaca 1990; Voytko et al. 1994). Lesions limited to the hippocampal region mainly impair monkeys' performance in tasks of recognition memory (Zola et al. 2000) and learning two-choice discriminations. In comparison, the caudate nucleus is necessary for learning more difficult, gradually acquired discrimination tasks (Teng et al. 2000).

New models based on the intracerebral delivery of ß-amyloid plaques and neurofibrillary tangles are currently being pursued. It should be noted that evaluation of ß-amyloid transmission to NHPs was reported in 1993 (Baker et al. 1993). Three marmoset monkeys were intracerebrally injected with brain tissue from an AD patient. Analysis of the monkey brains 6–7 years later showed moderate numbers of amyloid plaques, dystrophic neurites, and cerebral amyloid angiopathy, but no neurofibrillary tangles. These pathologies were not found in age-matched controls ($n = 6$) or animals injected with normal brain tissues ($n = 12$). A few plaques were found in the brains of two of four marmosets that received brain tissue from three elderly patients with age-related pathology, of which two may have had possible prion disease. Results of a follow-up study in which marmoset monkeys were injected with AD brain homogenates, synthetic Aβ-peptides, or CSF found approximately 3.5 years later that β-amyloid seemed to be partially responsible for initiating or accelerating the process of cerebral amyloidosis (Ridley et al. 2006). In that regard, marmoset monkeys that were co-injected with β-amyloid fibrils and lipopolysaccharide to elicit inflammation presented plaques 5 months post surgery, suggesting that the inflammation accelerated β-amyloid deposition (Philippens et al. 2017).

Contributions of NHP Research to the Improvement of AD Treatments

Candidate AD therapeutic approaches can be grouped into neurorestorative and neuroprotective. Neurorestorative approaches using fetal tissue or stem cells to replace cholinergic neurons lost to the disease have been proposed (Sugaya 2003). Yet, the

focus of the AD field has shifted towards the development of neuroprotective strategies due to the progressively widespread neurodegeneration and the complexity of the behaviors affected by AD.

Lifestyle modification has been proposed to decrease AD risk. Healthy diet and exercise are typical medical suggestions, in part because obesity is associated with type II diabetes, which in turn increases the risk of AD (Grizzanti et al. 2016). NHP studies in calorie restriction (CR) support this concept. Rhesus macaques following a CR diet have significantly better glucose regulation than age-matched controls, greater preservation of gray matter in frontal and parietal cortices, and better learning of a motor task (Kastman et al. 2012). Postmortem brain analysis of CR monkeys compared to age-matched controls showed that CR modulates inflammation and offset the burden of oxidatively damaged proteins (Sridharan et al. 2014; Willette et al. 2013). The consequences of a sedentary life are not limited to weight gain but also decreased cognitive ability. Studies in middle-age rhesus macaques trained to run daily in a treadmill for a period of 5 months have shown that improved fitness increases both the rate of learning and blood flow to the cerebral cortex, at least during the period of regular exercise (Rhyu et al. 2010).

In the last decade, a number of NHP preclinical and clinical trials evaluating neuroprotective strategies have been performed with differing levels of positive behavioral effects (Akwa et al. 2005). Although several trophic factors are available today, nerve growth factor (NGF) remains the favorite for AD treatment. Several lines of research have confirmed NGF support of cholinergic neurons and more recently have linked it to decreased amyloid burden (Triaca et al. 2016). NGF cannot cross the blood brain barrier; thus, it requires chronic intracerebral targeted delivery, as intracerebroventricular administration induces adverse side effects (Winkler et al. 1997). Studies in rodents and NHP models of AD have shown that NGF delivery by direct protein or *ex vivo gene* therapy can protect cholinergic neurons from degeneration and sustain cholinergic function (Tuszynski et al. 1990). The safety, toxicity, and efficacy of autologous fibroblasts genetically modified to deliver NGF (Tuszynski et al. 1996) have been tested in NHPs before clinical trials. A phase I study has shown safety and some improvements (Tuszynski et al. 2005). Postmortem analysis of patients that received the therapy a decade earlier showed a positive response to NGF (Tuszynski et al. 2015). As an alternative to personalized cell preparation, adeno-associated viral vectors (AAV) (Mandel et al. 1999) and lentiviral vectors (Blesch et al. 2005) encoding for NGF have been tested in NHPs, with results similar to *ex vivo* treatments. The results of a phase I clinical trial, using bilateral stereotactic administration of AAV-NGF to the nucleus basalis of Meynert, demonstrated the feasibility of the approach (Rafii et al. 2014). AAV-NGF was well tolerated and able to produce long-term, biologically active NGF expression (Tuszynski et al. 2015). Based on these data, a multicenter, double-blind, sham surgery-controlled trial is currently ongoing (clinicaltrials.gov).

Several other therapies are currently being tested for AD treatment; of particular interest to the field are the ones targeting β-amyloid, such as vaccines, antibodies, and inhibitors or modulators of γ- and β-secretase and vaccines against tau protein. The role of NHP research in these studies has been mainly to assess tolerability and safety, and provide some evidence of efficacy in aged monkeys. Clinical trials using Aβ antibodies (solanezumab, gantenerumab, crenezumab) have not yet proven successful as disease-modifying therapies. New clinical trials targeting populations at risk of developing AD, compared to more advanced cases, may have a better chance to succeed (clinical trials.org) (Godyn et al. 2016; Marciani 2016).

HD

HD is an autosomal-dominant, progressive neurodegenerative disorder. It is estimated that 5 to 10 per 100,000 individuals have HD, with variations between populations (Harper 1992; Rawlins 2010); more than 30,000 Americans are affected by HD.

HD onset is usually observed in patients 30 to 50 years old; juvenal HD refers to cases with disease onset before 20 years of age (Lee et al. 2012). Patients with HD display dystonia and involuntary choreiform movements of the arms, legs, head, face, and upper body. They also develop dementia, with frontal-type cognitive impairments, and psychiatric manifestations, including alterations in mood, like depression, anxiety, anger and irritability, and obsessive-compulsive behaviors (Leroi and Michalon 1998; Mendez 1994; Rosenstein 1998). Although HD onset is defined by the development of the movement disorder, mutation carriers may present a combination of subtle clinical and neuroimaging parameters for several years before diagnoses. Treatments are mainly symptomatic, with limited efficacy, and can have severe side effects. The movement disorder can be treated with tetrabenazyne or antipsychotic drugs; the latter are also beneficial for severe anger or threatening behavior. Cognitive deficits are difficult to manage and are not responsive to cholinesterase inhibitors (Ha and Fung 2012).

Pathologically, HD is characterized by progressive loss of gamma aminobutyric acid (GABA) producing neurons in the striatum. Severe neuronal loss also occurs in deep layers of the cerebral cortex; neuroinflammatory markers are increased in areas of neurodegeneration. As HD progresses, neuronal loss and atrophy are observed in the globus pallidus, thalamus, subthalamic nucleus, substantia nigra, and cerebellum (Huntington 2003).

In 1993 the gene responsible for HD was identified in chromosome 4 (1993); a diagnostic test is currently available. The HD mutation consists of an expansion of a cysteine-adenosine-guanine (CAG) repeat encoding a polyglutamine tract in the N-terminus of the protein huntingtin. In normal conditions, huntingtin is found in the cytoplasm; it seems to have a role in normal cellular interactions, including transport vesicles, synaptic vesicles, microtubules, and mitochondria. N-terminal fragments of mutant huntingtin accumulate and form inclusions in the cell nucleus in the brains of patients with HD. Interestingly, huntingtin inclusions are rarely found in striatal neurons (compared to the cortex) and when present are observed in interneurons, which are typically spared in HD neurodegeneration (Saudou and Humbert 2016).

Modeling HD in NHPs

Modeling HD in NHPs has evolved over time. Neurotoxin models can be induced by direct stereotaxic injections into the striatum of an **N**-methyl-**d**-aspartate receptor agonist such as kainic, ibotenic, or quinolinic acid. These excitotoxins are reported to induce preferential loss of striatal GABAergic neurons, although some studies have found widespread neuronal loss in the lesion area (Beal et al. 1986; Burns et al. 1995; Coyle and Schwarcz 1976; Coyle et al. 1978; Davies and Roberts 1987; Ellison et al. 1987; Isacson et al. 1990; Schwarcz et al. 1983; Storey et al. 1994). In these models, systemic administration of

apomorphine is administered to elicit dyskinesias; quinolinic acid has been shown to induce frontal cognitive deficits. An alternative modeling method uses chronic systemic administration of the mitochondrial complex II inhibitor 3-nitropropionic acid (3-NP) (Brouillet et al. 1995; Palfi et al. 1996, 2000). In baboon monkeys (*Papio papio*), 3-NP intoxication induces spontaneous and apomorphine-induced dyskinesia and a frontal-type cognitive decline (Palfi et al. 1996); in capuchin monkeys (*Cebus apella*), it also induces progressive dystonia (Palfi et al. 2000; Roitberg et al. 2002). The behavioral changes are associated with bilateral neuronal cell loss in the striatum, with a dorsoventral gradient, and relative sparing of the reduced nicotinamide-adenine dinucleotide phosphate positive interneurons and cholinergic neurons (Brouillet et al. 1995; Palfi et al. 1996; Roitberg et al. 2002).

With the identification of the mutated huntingtin gene emerged the possibility of generating genetic HD animal models. Due to the complexity of producing transgenic HD monkeys, investigators evaluated the effect of injecting lentiviral vectors encoding for the first 171 amino acids of the Huntingtin protein with 19 (wild-type: Htt171-19Q/19Q) or 82 (mutated: Htt171-82Q) polyglutamine repeats into the dorsolateral sensorimotor putamen of macaques (Palfi et al. 2007). In a first phase, cynomolgus macaques (*Macaca fascicularis*) were studied for 9 weeks. Apomorphine administration induced progressive chorea, dystonia, and ipsilateral turning behavior to the Htt171-19Q/82Q animals (n-4), while the Htt171-19Q/19Q ($n = 2$) or an additional buffer control ($n = 1$) showed no abnormal behavior. Postmortem, the Htt171-82Q subjects presented neuritic and nuclear huntingtin aggregates, astrocytosis, and neuronal loss. Then the investigators injected Htt171-82Q bilaterally into the dorsolateral putamen of three monkeys. Fifteen weeks after surgery, the animals progressively developed spontaneous dyskinesia of the legs, arms, and trunk and, in one case, tics that persisted for 30 weeks.

In 2008, the first transgenic monkey model of HD was reported (Yang et al. 2008). Mature rhesus oocytes were injected into the perivitelline space with high titer lentiviruses expressing exon 1 of the human *HTT* gene with 84 CAG repeats (*HTT*-84Q) and lentiviruses expressing the green fluorescent protein (*GFP*) gene, under the control of the human polyubiquitin-C promoter. Five live newborns were delivered at full term. All monkeys carried the transgenic mutant *HTT* and *GFP* genes, although the repeat length varied between subjects and ranged between 27 to 88 repeats. One animal survived for 1 month and two survived for less than a day. Based on preliminary observations, the severity, frequency, and onset of the involuntary movements seemed to depend on the length of the CAG repeats and the number of integration sites. The early death of the animals carrying a higher copy number of transgenes expressing a small amino-terminal HTT fragment suggests that the N-terminal mutant HTT fragments are pathogenic. Postmortem analysis of these three monkeys showed HTT aggregates or inclusions in the striatum and cortex, mostly located in the nuclei and neuropil; no clear signs of neurodegeneration were observed. Reports on the longitudinal evaluation of additional transgenic subjects identified progressive cognitive and motor impairment associated with a reduction in striatal volume observed with neuroimaging. Postmortem neuropathological analyses confirmed striatal neuronal loss (Chan et al. 2014, 2015). Germ line of the mutant huntingtin was confirmed in both embryonic stem cells generated from three male HD monkey founders and in second-generation offspring produced via artificial insemination (Moran et al. 2015).

Contributions of NHP Research to the Improvement of HD Treatments

Cell replacement strategies to alleviate GABAergic neuronal loss have been proposed using either fetal tissue sources or stem cell lines. In 3-NP-intoxicated monkeys, fetal striatal allografts induced recovery in a frontal-type cognitive task 2 to 5 months after surgery as well as reduced the occurrence of dystonia (Palfi et al. 1998). The clinical translation was first reported as favorable (Freeman et al. 2000), as the pathological brain evaluation of a patient that died 18 months after transplantation (due to cardiovascular disease) demonstrated survival of grafted cells, which presented typical morphology of the developing striatum and no huntingtin aggregates or neuritic dystrophies. Yet a follow-up report of the postmortem analysis of HD patients that received bilateral striatal fetal grafts 10 years earlier showed that the grafted neurons underwent HD-like neuronal degeneration (Cicchetti et al. 2009), including the presence of mutant huntingtin aggregates (Cicchetti et al. 2014).

Due to the aggressive and progressive nature of HD, effective neuroprotective strategies are urgently needed. The oral drug riluzole interferes with glutamate activity, and it has been shown to be neuroprotective in 3-NP-intoxicated monkeys (Palfi et al. 1997). In HD patients, riluzole preserved brain glucose metabolism and increased production of neurotrophins (Cicchetti et al. 2009). Gene therapy for the delivery of ciliary neurotrophic factor has also been tested in monkeys treated with 3-NP with positive effects (Mittoux et al. 2000). A new generation of gene therapy strategies aiming to deliver short hairpin RNA (shRNA) to silence the expression of mutated huntingtin is currently being investigated in NHPs (Dufour et al. 2014; McBride and Clark 2016; McBride et al. 2008, 2011; Monteys et al. 2017).

PD

PD is the second-most common age-related neurodegenerative disorder after AD, affecting 1% of the population over 65 years old. PD is diagnosed by the presence of typical motor symptoms, including tremor, rigidity, bradykinesia (slowness of movement), and postural instability. Over time, PD progression may severely affect walking, talking, or completing simple tasks. PD patients also present nonmotor symptoms such as depression, orthostatic hypotension, fatigue, urinary problems or constipation, and sleep disruptions (Titova et al. 2016). Most importantly, the onset of nonmotor symptoms may precede motor dysfunction for many years, and their identification is proposed for diagnosis of prordromal PD. In that regard, in 2015 the International Parkinson and Movement Disorder Society presented a report with guidelines for refined PD diagnosis and produced criteria for prodromal PD (Berg et al. 2015).

Dopamine (DA) replacement (usually combined with carbidopa) is the mainstay therapy for PD motor symptoms. Dopamine agonists and anticholinergics can be used alone or in combination with levodopa. Monomine oxidase B inhibitors, such as rasagiline and selegiline, are many times preferred for early PD or as a complement to DA replacement. PD nonmotor symptoms are not alleviated by DA replacement therapy; their identification is critical to provide symptomatic relief and/or include lifestyle modifications as part of the treatment plan. Disruption of the basal ganglia neural circuitry by targeted ablations or, more recently, deep brain stimulation, are possible surgical options. Compared to AD and HD, advancements in PD

treatments have greatly improved patients' quality of life. Yet as PD progresses, drug efficacy declines and side effects, such as dyskinesias, increase.

The pathologic hallmarks of the disease are the loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of intracytoplasmic inclusions called Lewy bodies (LBs) and Lewy neurites (LNs), which are found in neurons of the central (CNS) and peripheral (PNS) nervous system (Braak et al. 1995; Del Tredici and Braak 2016). LBs and LNs are composed of over 70 different proteins (Wakabayashi et al. 2007); α-synuclein (α-syn) is their main component. PD motor symptoms are related to the loss of dopamine in the striatum, the main area of projection of nigral dopaminergic neurons. PD nonmotor symptoms are associated with neuropathology in other areas of the CNS and PNS (e.g., cardiac dysautonomia symptoms are related to sympathetic ganglia neurodegeneration).

The cause of PD is still unknown. Identified risk factors include aging, exposure to environmental toxins, and genetics. In 1997, the first gene mutation linked to PD was identified: a single point mutation of alanine to threonine in the 53rd (A53T) amino acid residue in the α-syn protein sequence of patients with familial early-onset PD (Polymeropoulos et al. 1997). Following this discovery, additional mutations in the α-syn gene (SNCA) have been identified in familial PD cases, such as A30P, G51D, and triplication (Kruger et al. 1998; Lesage et al. 2013; Singleton et al. 2003). Several other gene mutations including in LRRK2, PINK1, and DJ-1 in addition to SNCA, have been linked to PD (Puschmann 2013). Five percent of all PD cases are estimated to be familial; it should be noted that the LRRK2 mutation G2019S has been observed in sporadic cases, and its incidence varies between populations (e.g., 40% of PD cases in the African Arab population) (Lesage et al. 2006).

Although the etiology of PD is unclear, inflammation, mitochondrial dysfunction, oxidative stress, and protein aggregation have been identified as mechanisms contributing to PD neurodegeneration (Blesa et al. 2015; Hirsch et al. 2012; Mullin and Schapira 2015). The identification of α-syn as a component of LBs and LNs has led to hypotheses on PD neurodegeneration centered on potential α-syn toxicity and its potential spread from the PNS to and through the CNS in a prion-like fashion (Braak et al. 2004; Chu and Kordower 2015). An alternative and maybe complementary theory is that α-syn simultaneously damages CNS and PNS neurons, but differing regional plasticity affects which dysfunction and symptoms appear first (Engelender and Isacson 2016).

Modeling PD in NHPs

NHP models of PD are based on identified risk factors including aging, neurotoxins, and genetics. Progress in the understanding of the mechanisms of PD pathology and the complexity of PD is shaping the methods of model development as well as the evaluation of the animals.

Aged NHPs have proven to be useful platforms to understand the role of aging in PD. Like humans, monkeys develop age-related dysfunction of the nigrostriatal system and motor impairments, such as slight tremor, stooped posture, and gait and balance disturbances (Emborg et al. 1998). Changes in α-syn expression, including translocation into the neuronal bodies, have been observed with age (Chu and Kordower 2007).

Neurotoxin NHP models of PD are induced by the administration of 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP). 6-OHDA is a catecholaminergic neurotoxin (Senoh et al. 1959a, 1959b) with a molecular structure similar to dopamine, which facilitates its specific uptake by catecholamine transporters. Once inside neurons, 6-OHDA impairs mitochondrial function through direct interaction with complex I; it also rapidly undergoes autoxidation, generating reactive oxygen species and eliciting inflammation, which further promotes neurodegeneration. 6-OHDA does not cross the blood-brain barrier; thus, to exert CNS toxic effects, it must be injected directly into the brain, usually unilaterally into the nigrostriatal system (Rodriguez-Pallares et al. 2007). Systemic administration of 6-OHDA induces catecholaminergic neurodegeneration in the PNS and can be used to replicate cardiac dysautonomia (Joers et al. 2012, 2014).

MPTP is a highly lipophilic mitochondrial complex I inhibitor that easily crosses the blood-brain barrier. The enzyme MAO-B, which is found in astrocytes in the brain and in multiple peripheral organs, is responsible for converting MPTP into its toxic metabolite 1-methyl-4-phenylpyridinium. Similar to 6-OHDA, 1-methyl-4-phenylpyridinium is preferentially uptaken by the dopamine transporter system; it induces neurodegeneration by impairing mitochondrial function (Dauer and Przedborski 2003; Mizuno et al. 1987; Nicklas et al. 1985; Rappold and Tieu 2010). Nigral α-syn expression has been found to increase after MPTP dosing and, in some cases, it may accumulate (Halliday et al. 2009; Kowall et al. 2000; McCormack et al. 2008).

MPTP administration to monkeys can be done sc, im, iv, or via the carotid artery, using different dosing regimens (Emborg 2007). Similar to PD patients, monkeys exposed to MPTP present tremor, bradykinesia, hypokinesia, rigidity, and disturbance in fine motor skills as well as posture, balance, and gait abnormalities (Burns et al. 1983; Langston et al. 1984). Systemic dosing of MPTP induces a bilateral PD motor syndrome, while intracarotid artery injection induces hemiparkinsonism. MPTP can affect other neuronal groups beyond dopaminergic nigral neurons, which contribute to the onset of motor and nonmotor symptoms, including prefrontal cognitive deficits (Schneider 1990). Cardiac catecholaminergic loss, mimicking postganglionic autonomic dysfunction typical of PD, has been described, although the effects seem to be temporary (Goldstein et al. 2003). Catecholaminergic neurons in the locus coeruleus and pedunculopontine nucleus are also affected (Herrero et al. 1993a, 1993b; Masilamoni et al. 2011, 2017; Pifl et al. 1991). Similar to PD, MPTP can induce neuronal loss in caudal intralaminar thalamic nuclei, which may precede the development of motor symptoms in PD and may account for some of the cognitive deficits in attentional set-shifting (Villalba et al. 2014). Cholinergic neuronal loss in the peduculopontine nucleus of aged MPTP-treated monkeys was reported to contribute to abnormal gait and posture (Karachi et al. 2010).

Typical anti-parkinsonian medications are effective against MPTP-induced PD motor symptoms, and prolonged daily use of L-DOPA therapy induces dyskinesias, as observed in humans.

Intracerebral injection of viral vectors encoding for mutated α-syn or administration of LB extracts have been tested for modeling genetic-like PD in NHPs (Vermilyea and Emborg 2015). Nigral overexpression of human α-syn wild type and A53T using AAV vectors induced PD-like motor symptoms, significant nigral dopaminergic cell loss, and α-syn aggregates in common marmoset monkeys (Eslamboli et al. 2007; Kirik et al. 2003). AAV and lentiviral vectors encoding for A53T α-syn were tested in cynomolgus (Koprich et al. 2016) and rhesus macaques (Yang et al. 2015), inducing nigral cell loss and α-syn accumulation and aggregation; behavioral changes were not reported. AAV-induced overexpression of Parkin and A53T α-syn decreased striatal dopaminergic markers and α-syn

accumulation and phosphorylation in cynomolgus, motor symptoms were not observed. Intracerebral inoculation of α-syn fibrils has not yet been used in monkeys, although several reports in rodents are available (e.g., Luk et al. 2012; Paumier et al. 2015). Cadaveric LB extracts have been injected into the striatum or nigra of cynomolgus macaques with or without previous MPTP challenge (Recasens et al. 2014), inducing some decreases in striatal and nigral dopaminergic markers and increases in α-syn expression, yet PD motor symptoms were not detected.

The first report of transgenic PD rhesus macaques used lentiviral vectors encoding for human A53T SNCA that were injected into fertilized oocytes (Niu et al. 2015). Compared to a stillborn control, an A53T animal had elevated levels of α-syn expression in the nigra, but no change in the S129 phosphorylation of α-syn a marker of possible pathology. Brain MRIs of 1.5- ($n = 2$) and 2.5- ($n = 2$) year-old A53T NHPs did not show evidence of neurodegeneration in the MRI, although the animals exhibited some difficulty in fine motor skill tests. Lastly, a 2.5-year-old A53T monkey presented cognitive deficits and an increase in the amount of time spent walking in circles compared to an age-matched control, which the investigators interpreted as increased anxiety.

Contributions of NHP Research to PD

NHP PD models have been essential for the development of efficacious therapeutic strategies (Capitanio and Emborg 2008). They provide a platform to identify the neuronal circuitry affected by the disease, generate rational surgical approaches, like deep brain stimulation, and evaluate the efficacy and safety of novel DA replacement therapies. Their role continues to be critical to ensure the safety and efficacy of inovative compounds aiming to decrease the adverse effects associated with long-term use.

As an alternative to dopamine replacement by drugs, nigral fetal grafts were tested in monkeys and translated to human trials with controversial clinical results (Fitzpatrick et al. 2009). In addition to lack of efficacy, some patients developed graft-induced dyskinesias. These uncontrolled abnormal movements were not related to L-DOPA medication and did not decrease when L-DOPA dosing was reduced or stopped. Another potential complication was the postmortem finding of LB-like pathology in the cells grafted a decade earlier (Kordower et al. 2008; Li et al. 2008). Although the impact of the aggregates on the functionality of the grafts is unknown, most important was the fact that PD could be transferred to the grafted cells. Several other cell sources have been tested in monkeys, including retinal pigmented and carotid ganglion cells, which have been proposed as an alternative source for cell replacement. Although many of these novel cells have been translated into the clinic and positive results were found in early phase trials, phase II studies have not demonstrated efficacy. More recently, stem cell lines conditioned or not to develop a dopaminergic phenotype have been developed, and reports of transplants in monkeys using these cells have been published (Vermilyea and Emborg 2017).

Gene therapy has been proposed as an alternative method to induce functional restoration by delivering enzymes responsible for dopamine production (to increase dopamine availability) or GABA synthesis (to affect neurotransmitter balance in the basal ganglia neural network). Based on rodent and monkey preclinical data (Hadaczek et al. 2010), a phase I open label clinical trial using AAV2 encoding for aminoacid decarboxylase (AADC), the enzyme necessary for the decarboxylation of L-DOPA into dopamine, was performed. AAV2-AADC was infused into the putamen; the results of the trial met criteria for safety (Christine et al. 2009). Currently, a new AAV2-AADC phase I trial is ongoing, in which the viral vector suspension is infused into the putamen using MRI-guided convection and the target population is PD patients with fluctuating responses to L-DOPA (clinicaltrials.gov).

The first PD gene therapy trial proposed to use intracerebral injections of AAV2 encoding for glutamic acid decarboxylase (GAD, the rate-limiting enzyme for the synthesis of GABA) into the subthalamic nucleus to inhibit overactive glutamatergic neurons. As rodent and NHP data (Emborg et al. 2007) suggested feasibility, a phase I clinical trial was performed that confirmed the safety of the approach (Kaplitt et al. 2007) and suggested efficacy (Feigin et al. 2007). A follow-up, double-blind, sham-surgery-controlled randomized phase II trial in which AAV2-GAD was bilaterally delivered into the subthalamic nucleus of patients with advanced PD demonstrated efficacy (LeWitt et al. 2011).

Due to the progressive nature of PD, neuroprotective strategies are urgently needed. Several compounds that can be administered systemically such as MAOB inhibitors, dopaminergic agonists, immunophilines, gangliosides, and nicotinic agonists have being evaluated, but none has shown clear clinical efficacy (Stocchi 2015). Glial derived neurotrophic factor (GDNF) is a potent dopaminotrophic factor that requires targeted delivery to be effective without inducing side effects (Lapchak et al. 1997). Intracerebral infusions have presented controversial results; the method of delivery and protein distribution have been identified as issues that need to be addressed (Sherer et al. 2006). Gene therapy is envisioned as a more efficient way to chronically deliver trophic factors (e.g., Kordower et al. 2000). AAV2 encoding for GDNF has been shown to be effective in PD monkeys (Kells et al. 2010). A phase 1, open-label, dose escalation, safety and tolerability study of AAV2-GDNF for patients with advanced PD is currently ongoing. AAV2 encoding for neurturin (a trophic factor related to GDNF) has shown a similar preclinical success than GDNF (Herzog et al. 2008), suggesting that it could be used as an alternative treatment. AAV2-neurturin clinical trials, first targeting the putamen and then the putamen and nigra, showed encouraging results in phase I but failed in phase II studies (Kordower 2016).

New therapies aiming to address synucleinopathy are now proposed, including silencing the α-syn gene or increasing α-syn clearance (Wong and Krainc 2017). Interestingly, in vervet monkeys (*Chlorocebus aetiops*), nigral injection of AAV-shRNA to knockdown α-syn induced a region-specific decrease in TH-positive nigral cell number and striatal innervation compared to animals that received scrambled shRNA; no behavioral changes were reported (Collier et al. 2016). Administration of kinase inhibitors are currently in the process of being evaluated (clinical trials.org). Without regards of the therapy, patients' PD stage at the time of the trial will be an issue for neuroprotective success. By the time of diagnoses, PD patients have already lost 50% of nigral dopaminergic neurons, suggesting that the chances for inducing neuroprotection are limited. A recent example is the result of the evaluation of the peroxisome proliferator receptor gamma agonist termed pioglitazone, which in PD animal models including NHPs showed positive effects (Swanson et al. 2011), and although its clinical translation showed some effects, it failed to achieve significance (Investigators 2015).

Conclusions

The contribution of NHP research to the AD, HD, and PD fields has yielded a number of advancements toward the understanding of

neural networks affected by each disorder, and basically provided a canvas (and still does) to assess the safety and feasibility of novel therapies. It is clear that much work is still needed, especially toward the development of neuroprotective strategies. In that regard, the identification of biomarkers of early disease onset will play a critical role for successful clinical translation. In the case of HD, mutation carriers can be targeted, yet the age of disease onset is not easily predictable. For AD and PD, the identification of vulnerable populations will be more difficult, as in most cases disease onset depends on a combination of factors. Can NHP studies help untangle the clues?

Whether β-amyloid, huntingtin, and α-syn have the potential to act as prions is still debatable (Collinge 2016; Stopschinski and Diamond 2017), yet they seem to have a role in neurodegeneration, similar to inflammation and oxidative stress (Gasiorowski et al. 2017; Kannarkat et al. 2013; Manoharan et al. 2016; Silajdzic et al. 2013). A new generation of NHP models is emerging. Although most of these models need validation and characterization, they represent an opportunity to assess the efficacy of novel therapies, which cannot be tested in toxin models. Furthermore, transgenic models will facilitate the search of biomarkers of disease onset and progression, as the animals can be studied from birth. New genomic editing technologies (e.g., Gaj et al. 2016) that allow for creating point mutations, instead of overexpression of a mutated protein, hold promise for the creation of true-to-life models.

Common marmosets have emerged as an alternate NHP resource (Cyranoski 2014) as they present certain advantages for the generation of genetic models compared to more traditional NHP species, like rhesus macaques. Marmosets regularly give birth to twins or triplets compared to rhesus singletons, and they have a shorter lifespan (~16 vs. ~35 years), which facilitates the study of age-related disorders (Abbott et al. 2003; Schultz-Darken et al. 2016). Yet, when planning a research project, investigators should also consider the species brain volume, behavior, and genetic makeup, among other things, and how these issues relate to the hypothesis to be analyzed. For example, a mutation in the α-syn gene that leads to the replacement of the amino acid alanine by threonine at the 53rd residue (A53T) has been linked to early-onset familial PD. In normal conditions marmosets and most other vertebrates, with the exception of humans, apes, and macaques (Hamilton 2004), naturally have a threonine at the 53rd residue of the α-syn sequence. Thus, studies on the impact of α-syn pathology will benefit from using rhesus as a model organism.

As mentioned in the introduction, NHP studies represent a small but important percentage of the overall research enterprise. Clinical trials solely based on rodent studies have been shown to have lower rates of translational success compared to the ones following a stepwise approach that included NHP investigations (Zeiss 2017; Zeiss et al. 2017). NHP's role is most relevant for longitudinal studies, evaluating first-in-class and invasive therapies, beyond exploratory studies but to assess specific questions of efficacy and safety (Zeiss 2017). This approach requires a thorough understanding of the disease as well as the model to be used. Although NHP models of neurodegenerative disorders continue to be improved, they are not perfect, and many need to be validated. Neurodegenerative disorders are complex and their presentation varies between individuals; therefore, one model will not necessarily provide all needed answers. The best a scientist can do is to match the NHP model and the experimental design to the scientific question at hand and apply rigorous and unbiased scientific methods for data collection and analysis. Ultimately, all results, positive and negative, should be shared to maximize the usefulness of the study and to contribute to finding a cure for neurodegenerative disorders.

Acknowledgments

This research was supported by NIH grants R24OD019803, P51OD011106, UL1TR000427 (ICTR UW-Madison, Clinical and Translational Science Award), and the UW-Madison Office of the Vice Chancellor for Research and Graduate Education.

References

1993. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 72(6):971–983.

Abbott DH, Barnett DK, Colman RJ, Yamamoto ME, Schultz-Darken NJ. 2003. Aspects of common marmoset basic biology and life history important for biomedical research. Comp Med 53(4):339–350.

Akwa Y, Allain H, Bentue-Ferrer D, Berr C, Bordet R, Geerts H, Nieoullon A, Onteniente B, Vercelletto M. 2005. Neuroprotection and neurodegenerative diseases: From biology to clinical practice. Alzheimer Dis Assoc Disord 19(4):226–239.

Albert MS. 2002. Memory decline: The boundary between aging and age-related disease. Ann Neurol 51(3):282–284.

Baker HF, Ridley RM, Duchen LW, Crow TJ, Bruton CJ. 1993. Evidence for the experimental transmission of cerebral beta-amyloidosis to primates. Int J Exp Pathol 74(5):441–454.

Beal MF, Kowall NW, Ellison DW, Mazurek MF, Swartz KJ, Martin JB. 1986. Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. Nature 321 (6066):168–171.

Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, Gasser T, Goetz CG, Halliday G, Joseph L, Lang AE, Liepelt-Scarfone I, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. 2015. MDS research criteria for prodromal Parkinson's disease. Mov Disord 30(12):1600–1611.

Blesa J, Trigo-Damas I, Quiroga-Varela A, Jackson-Lewis VR. 2015. Oxidative stress and Parkinson's disease. Front Neuroanat 9:91.

Blesch A, Conner J, Pfeifer A, Gasmi M, Ramirez A, Britton W, Alfa R, Verma I, Tuszynski MH. 2005. Regulated lentiviral NGF gene transfer controls rescue of medial septal cholinergic neurons. Mol Ther 11(6):916–925.

Braak H, Braak E, Bohl J. 1993. Staging of Alzheimer-related cortical destruction. Eur Neurol 33(6):403–408.

Braak H, Braak E, Yilmazer D, Schultz C, de Vos RA, Jansen EN. 1995. Nigral and extranigral pathology in Parkinson's disease. J Neural Transm Suppl 46:15–31.

Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. 2004. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 318(1):121–134.

Brooks SP, Dunnett SB. 2015. Mouse models of Huntington's disease. Curr Top Behav Neurosci 22:101–133.

Brouillet E, Hantraye P, Ferrante RJ, Dolan R, Leroy-Willig A, Kowall NW, Beal MF. 1995. Chronic mitochondrial energy impairment produces selective striatal degeneration and abnormal choreiform movements in primates. Proc Natl Acad Sci USA 92(15):7105–7109.

Burns LH, Pakzaban P, Deacon TW, Brownell AL, Tatter SB, Jenkins BG, Isacson O. 1995. Selective putaminal excitotoxic

lesions in non-human primates model the movement disorder of Huntington disease. Neuroscience 64(4):1007–1017.

Burns RS, Chiueh CC, Markey SP, Ebert MH, Jacobowitz DM, Kopin IJ. 1983. A primate model of parkinsonism: Selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci USA 80(14):4546–4550.

Capitanio JP, Emborg ME. 2008. Contributions of non-human primates to neuroscience research. Lancet 371(9618):1126–1135.

Chan AW, Jiang J, Chen Y, Li C, Prucha MS, Hu Y, Chi T, Moran S, Rahim T, Li S, Li X, Zola SM, Testa CM, Mao H, Villalba R, Smith Y, Zhang X, Bachevalier J. 2015. Progressive cognitive deficit, motor impairment and striatal pathology in a transgenic Huntington disease monkey model from infancy to adulthood. PLoS One 10(5):e0122335.

Chan AW, Xu Y, Jiang J, Rahim T, Zhao D, Kocerha J, Chi T, Moran S, Engelhardt H, Larkin K Neumann A, Cheng H, Li C, Nelson K, Banta H, Zola SM, Villinger F, Yang J, Testa CM, Mao H, Zhang X, Bachevalier J. 2014. A two years longitudinal study of a transgenic Huntington disease monkey. BMC Neurosci 15:36.

Chesselet MF, Richter F. 2011. Modelling of Parkinson's disease in mice. Lancet Neurol 10(12):1108–1118.

Christine CW, Starr PA, Larson PS, Eberling JL, Jagust WJ, Hawkins RA, VanBrocklin HF, Wright JF, Bankiewicz KS, Aminoff MJ. 2009. Safety and tolerability of putaminal AADC gene therapy for Parkinson disease. Neurology 73(20): 1662–1669.

Chu Y, Kordower JH. 2007. Age-associated increases of alpha-synuclein in monkeys and humans are associated with nigrostriatal dopamine depletion: Is this the target for Parkinson's disease? Neurobiol Dis 25(1):134–149.

Chu Y, Kordower JH. 2015. The prion hypothesis of Parkinson's disease. Curr Neurol Neurosci Rep 15(5):28.

Cicchetti F, Lacroix S, Cisbani G, Vallieres N, Saint-Pierre M, St-Amour I, Tolouei R, Skepper JN, Hauser RA, Mantovani D, Barker RA, Freeman TB. 2014. Mutant huntingtin is present in neuronal grafts in Huntington disease patients. Ann Neurol 76(1):31–42.

Cicchetti F, Saporta S, Hauser RA, Parent M, Saint-Pierre M, Sanberg PR, Li XJ, Parker JR, Chu Y, Mufson EJ, Kordower JH, Freeman TB. 2009. Neural transplants in patients with Huntington's disease undergo disease-like neuronal degeneration. Proc Natl Acad Sci USA 106(30):12483–12488.

Collier TJ, Redmond DE Jr, Steece-Collier K, Lipton JW, Manfredsson FP. 2016. Is alpha-synuclein loss-of-function a contributor to Parkinsonian pathology? Evidence from non-human primates. Front Neurosci 10:12.

Collinge J. 2016. Mammalian prions and their wider relevance in neurodegenerative diseases. Nature 539(7628):217–226.

Coyle JT, Molliver ME, Kuhar MJ. 1978. In situ injection of kainic acid: A new method for selectively lesioning neural cell bodies while sparing axons of passage. J Comp Neurol 180(2): 301–323.

Coyle JT, Schwarcz R. 1976. Lesion of striatal neurones with kainic acid provides a model for Huntington's chorea. Nature 263(5574):244–246.

Cyranoski D. 2014. Marmosets are stars of Japan's ambitious brain project. Nature 514(7521):151–152.

Dauer W, Przedborski S. 2003. Parkinson's disease: Mechanisms and models. Neuron 39(6):889–909.

Davies SW, Roberts PJ. 1987. No evidence for preservation of somatostatin-containing neurons after intrastriatal injections of quinolinic acid. Nature 327(6120):326–329.

Del Tredici K, Braak H. 2016. Review: Sporadic Parkinson's disease: Development and distribution of alpha-synuclein pathology. Neuropathol Appl Neurobiol 42(1):33–50.

Dufour BD, Smith CA, Clark RL, Walker TR, McBride JL. 2014. Intrajugular vein delivery of AAV9-RNAi prevents neuropathological changes and weight loss in Huntington's disease mice. Mol Ther 22(4):797–810.

Ellison DW, Beal MF, Mazurek MF, Malloy JR, Bird ED, Martin JB. 1987. Amino acid neurotransmitter abnormalities in Huntington's disease and the quinolinic acid animal model of Huntington's disease. Brain 110(Pt 6):1657–1673.

Emborg ME. 2007. Nonhuman primate models of Parkinson's disease. ILAR J 48(4):339–355.

Emborg ME, Carbon M, Holden JE, During MJ, Ma Y, Tang C, Moirano J, Fitzsimons H, Roitberg BZ, Tuccar E, Roberts A, Kaplitt MG, Eidelberg D. 2007. Subthalamic glutamic acid decarboxylase gene therapy: changes in motor function and cortical metabolism. J Cereb Blood Flow Metab 27(3):501–509.

Emborg ME, Ma SY, Mufson EJ, Levey AI, Taylor MD, Brown WD, Holden JE, Kordower JH. 1998. Age-related declines in nigral neuronal function correlate with motor impairments in rhesus monkeys. J Comp Neurol 401(2):253–265.

Engelender S, Isacson O. 2016. The threshold theory for Parkinson's disease. Trends Neurosci 40(1):4–14.

Eslamboli A, Romero-Ramos M, Burger C, Bjorklund T, Muzyczka N, Mandel RJ, Baker H, Ridley RM, Kirik D. 2007. Long-term consequences of human alpha-synuclein overexpression in the primate ventral midbrain. Brain 130(Pt 3):799–815.

Feigin A, Kaplitt MG, Tang C, Lin T, Mattis P, Dhawan V, During MJ, Eidelberg D. 2007. Modulation of metabolic brain networks after subthalamic gene therapy for Parkinson's disease. Proc Natl Acad Sci USA 104(49):19559–19564.

Fitzpatrick KM, Raschke J, Emborg ME. 2009. Cell-based therapies for Parkinson's disease: Past, present, and future. Antioxid Redox Signal 11(9):2189–2208.

Freeman TB, Cicchetti F, Hauser RA, Deacon TW, Li XJ, Hersch SM, Nauert GM, Sanberg PR, Kordower JH, Saporta S, Isacson O. 2000. Transplanted fetal striatum in Huntington's disease: Phenotypic development and lack of pathology. Proc Natl Acad Sci USA 97(25):13877–13882.

Gaj T, Sirk SJ, Shui SL, Liu J. 2016. Genome-editing technologies: Principles and applications. Cold Spring Harb Perspect Biol 8(12).

Gasiorowski K, Brokos B, Echeverria V, Barreto GE, Leszek J. 2017. RAGE-TLR crosstalk sustains chronic inflammation in neurodegeneration. Mol Neurobiol [Epub ahead of print].

Geula C, Nagykery N, Wu C-K. 2002. Amyloid-β deposits in the cerebral cortex of the aged common marmoset (Callithrix jacchus): Incidence and chemical composition. Acta Neuropathol 103(1):48–58.

Godyn J, Jonczyk J, Panek D, Malawska B. 2016. Therapeutic strategies for Alzheimer's disease in clinical trials. Pharmacol Rep 68(1):127–138.

Goldstein DS, Li ST, Holmes C, Bankiewicz K. 2003. Sympathetic innervation in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of Parkinson's disease. J Pharmacol Exp Ther 306(3):855–860.

Granholm AC, Boger H, Emborg ME. 2008. Mood, memory and movement: An age-related neurodegenerative complex? Curr Aging Sci 1(2):133–139.

Grizzanti J, Lee HG, Camins A, Pallas M, Casadesus G. 2016. The therapeutic potential of metabolic hormones in the treatment of age-related cognitive decline and Alzheimer's disease. Nutr Res 36(12):1305–1315.

Ha AD, Fung VS. 2012. Huntington's disease. Curr Opin Neurol 25(4):491–498.

Hadaczek P, Eberling JL, Pivirotto P, Bringas J, Forsayeth J, Bankiewicz KS. 2010. Eight years of clinical improvement in MPTP-lesioned primates after gene therapy with AAV2-hAADC. Mol Ther 18(8):1458–1461.

Halliday G, Herrero MT, Murphy K, McCann H, Ros-Bernal F, Barcia C, Mori H, Blesa FJ, Obeso JA. 2009. No Lewy pathology in monkeys with over 10 years of severe MPTP Parkinsonism. Mov Disord 24(10):1519–1523.

Hamilton BA. 2004. alpha-Synuclein A53T substitution associated with Parkinson disease also marks the divergence of Old World and New World primates. Genomics 83(4): 739–742.

Harper PS. 1992. The epidemiology of Huntington's disease. Hum Genet 89(4):365–376.

Herrero MT, Hirsch EC, Javoy-Agid F, Obeso JA, Agid Y. 1993a. Differential vulnerability to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine of dopaminergic and cholinergic neurons in the monkey mesopontine tegmentum. Brain Res 624(1–2): 281–285.

Herrero MT, Hirsch EC, Kastner A, Ruberg M, Luquin MR, Laguna J, Javoy-Agid F, Obeso JA, Agid Y. 1993b. Does neuromelanin contribute to the vulnerability of catecholaminergic neurons in monkeys intoxicated with MPTP? Neuroscience 56(2):499–511.

Herzog CD, Dass B, Gasmi M, Bakay R, Stansell JE, Tuszynski M, Bankiewicz K, Chen EY, Chu Y, Bishop K, Kordower JH, Bartus RT. 2008. Transgene expression, bioactivity, and safety of CERE-120 (AAV2-neurturin) following delivery to the monkey striatum. Mol Ther 16(10):1737–1744.

Hirsch EC, Vyas S, Hunot S. 2012. Neuroinflammation in Parkinson's disease. Parkinsonism Relat Disord 18(Suppl 1): S210–S212.

Howland DS, Munoz-Sanjuan I. 2014. Mind the gap: Models in multiple species needed for therapeutic development in Huntington's disease. Mov Disord 29(11):1397–1403.

Huntington G. 2003. On chorea. George Huntington, M.D. J Neuropsychiatry Clin Neurosci 15(1):109–112.

Investigators NETiPDF-Z. 2015. Pioglitazone in early Parkinson's disease: A phase 2, multicentre, double-blind, randomised trial. Lancet Neurol 14(8):795–803.

Isacson O, Hantraye P, Maziere M, Sofroniew MV, Riche D. 1990. Apomorphine-induced dyskinesias after excitotoxic caudate-putamen lesions and the effects of neural transplantation in non-human primates. Prog Brain Res 82:523–533.

Ji L, Zhao X, Lu W, Zhang Q, Hua Z. 2016. Intracellular abeta and its pathological role in Alzheimer's disease: lessons from cellular to animal models. Curr Alzheimer Res 13(6):621–630.

Joers V, Dilley K, Rahman S, Jones C, Shultz J, Simmons H, Emborg ME. 2014. Cardiac sympathetic denervation in 6-OHDA-treated nonhuman primates. PLoS One 9(8):e104850.

Joers V, Seneczko K, Goecks NC, Kamp TJ, Hacker TA, Brunner KG, Engle JW, Barnhart TE, Nickles RJ, Holden JE, Emborg ME. 2012. Nonuniform cardiac denervation observed by 11C-meta-hydroxyephedrine PET in 6-OHDA-treated monkeys. PLoS One 7(4):e35371.

Kannarkat GT, Boss JM, Tansey MG. 2013. The role of innate and adaptive immunity in Parkinson's disease. J Parkinsons Dis 3(4):493–514.

Kaplitt MG, Feigin A, Tang C, Fitzsimons HL, Mattis P, Lawlor PA, Bland RJ, Young D, Strybing K, Eidelberg D, During MJ. 2007. Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: An open label, phase I trial. Lancet 369(9579):2097–2105.

Karachi C, Grabli D, Bernard FA, Tande D, Wattiez N, Belaid H, Bardinet E, Prigent A, Nothacker HP, Hunot S, Hartmann A, Lehéricy S, Hirsch EC, François C. 2010. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J Clin Invest 120(8):2745–2754.

Kastman EK, Willette AA, Coe CL, Bendlin BB, Kosmatka KJ, McLaren DG, Xu G, Canu E, Field AS, Alexander AL, Voytko ML, Beasley TM, Colman RJ, Weindruch RH, Johnson SC. 2012. A calorie-restricted diet decreases brain iron accumulation and preserves motor performance in old rhesus monkeys. J Neurosci 32(34):11897–11904.

Kells AP, Eberling J, Su X, Pivirotto P, Bringas J, Hadaczek P, Narrow WC, Bowers WJ, Federoff HJ, Forsayeth J, Bankiewicz KS. 2010. Regeneration of the MPTP-lesioned dopaminergic system after convection-enhanced delivery of AAV2-GDNF. J Neurosci 30(28):9567–9577.

Kirik D, Annett LE, Burger C, Muzyczka N, Mandel RJ, Bjorklund A. 2003. Nigrostriatal alpha-synucleinopathy induced by viral vector-mediated overexpression of human alpha-synuclein: A new primate model of Parkinson's disease. Proc Natl Acad Sci USA 100(5):2884–2889.

Koprich JB, Johnston TH, Reyes G, Omana V, Brotchie JM. 2016. Towards a non-human primate model of alpha-synucleinopathy for development of therapeutics for Parkinson's disease: Optimization of AAV1/2 delivery parameters to drive sustained expression of alpha synuclein and dopaminergic degeneration in macaque. PLoS One 11(11):e0167235.

Kordower JH. 2016. AAV2-neurturin for Parkinson's disease: What lessons have we learned? Methods Mol Biol 1382: 485–490.

Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW. 2008. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat Med 14(5):504–506.

Kordower JH, Emborg ME, Bloch J, Ma SY, Chu Y, Leventhal L, McBride J, Chen EY, Palfi S, Roitberg BZ, Brown WD, Holden JE, Pyzalski R, Taylor MD, Carvey P, Ling Z, Trono D, Hantraye P, Déglon N, Aebischer P. 2000. Neurodegeneration prevented by lentiviral vector delivery of GDNF in primate models of Parkinson's disease. Science 290(5492):767–773.

Kordower JH, Fiandaca MS. 1990. Response of the monkey cholinergic septohippocampal system to fornix transection: A histochemical and cytochemical analysis. J Comp Neurol 298(4):443–457.

Kovacs GG. 2016. Can Creutzfeldt-Jakob disease unravel the mysteries of Alzheimer? Prion 10(5):369–376.

Kowall NW, Hantraye P, Brouillet E, Beal MF, McKee AC, Ferrante RJ. 2000. MPTP induces alpha-synuclein aggregation in the substantia nigra of baboons. Neuroreport 11(1):211–213.

Krench M, Littleton JT. 2017. Neurotoxicity pathways in drosophila models of the polyglutamine disorders. Curr Top Dev Biol 121:201–223.

Kruger R, Kuhn W, Muller T, Woitalla D, Graeber M, Kosel S, Przuntek H, Epplen JT, Schols L, Riess O. 1998. Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nature Genet 18(2):106–108.

Lane-Donovan C, Herz J. 2017. The ApoE receptors Vldlr and Apoer2 in central nervous system function and disease. J Lipid Res 58(6):1036–1043.

Langston JW, Forno LS, Rebert CS, Irwin I. 1984. Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-

1,2,5,6-tetrahydropyrine (MPTP) in the squirrel monkey. Brain Res 292(2):390–394.

Lapchak PA, Gash DM, Collins F, Hilt D, Miller PJ, Araujo DM. 1997. Pharmacological activities of glial cell line-derived neurotrophic factor (GDNF): Preclinical development and application to the treatment of Parkinson's disease. Exp Neurol 145(2 Pt 1):309–321.

Lee JM, Ramos EM, Lee JH, Gillis T, Mysore JS, Hayden MR, Warby SC, Morrison P, Nance M, Ross CA, Margolis RL, Squitieri F, Orobello S, Di Donato S, Gomez-Tortosa E, Ayuso C, Suchowersky O, Trent RJ, McCusker E, Novelletto A, Frontali M, Jones R, Ashizawa T, Frank S, Saint-Hilaire MH, Hersch SM, Rosas HD, Lucente D, Harrison MB, Zanko A, Abramson RK, Marder K, Sequeiros J, Paulsen JSPREDICT-HD study of the Huntington Study Group (HSG), Landwehrmeyer GB; REGISTRY study of the European Huntington's Disease Network, Myers RH; HD-MAPS Study Group, MacDonald ME, Gusella JF; COHORT study of the HSG. 2012. CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. Neurology 78(10):690–695.

Leroi I, Michalon M. 1998. Treatment of the psychiatric manifestations of Huntington's disease: A review of the literature. Can J Psychiatry 43(9):933–940.

Lesage S, Durr A, Tazir M, Lohmann E, Leutenegger AL, Janin S, Pollak P, Brice A. 2006. LRRK2 G2019S as a cause of Parkinson's disease in North African Arabs. N Engl J Med 354(4):422–423.

Lesage S, Anheim M, Letournel F, Bousset L, Honoré A, Rozas N, Pieri L, Madiona K, Dürr A, Melki R, Verny C, Brice A; French Parkinson's Disease Genetics Study Group. 2013. G51D α-synuclein mutation causes a novel parkinsonian-pyramidal syndrome. Ann Neurol 73(4):459–471.

LeWitt PA, Rezai AR, Leehey MA, Ojemann SG, Flaherty AW, Eskandar EN, Kostyk SK, Thomas K, Sarkar A, Siddiqui MS, Tatter SB, Schwalb JM, Poston KL, Henderson JM, Kurlan RM, Richard IH, Van Meter L, Sapan CV, During MJ, Kaplitt MG, Feigin A. 2011. AAV2-GAD gene therapy for advanced Parkinson's disease: A double-blind, sham-surgery controlled, randomised trial. Lancet Neurol 10(4):309–319.

Li JY, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ, Lashley T, Quinn NP, Rehncrona S, Bjorklund A, Widner H, Revesz T, Lindvall O, Brundin P. 2008. Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. Nat Med 14(5):501–503.

Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, Lee VM. 2012. Pathological alpha-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science 338(6109):949–953.

Mandel RJ, Gage FH, Clevenger DG, Spratt SK, Snyder RO, Leff SE. 1999. Nerve growth factor expressed in the medial septum following in vivo gene delivery using a recombinant adeno-associated viral vector protects cholinergic neurons from fimbria-fornix lesion-induced degeneration. Exp Neurol 155(1):59–64.

Manoharan S, Guillemin GJ, Abiramasundari RS, Essa MM, Akbar M, Akbar MD. 2016. The role of reactive oxygen species in the pathogenesis of Alzheimer's disease, Parkinson's disease, and Huntington's disease: A mini review. Oxid Med Cell Longev 2016:8590578.

Marciani DJ. 2016. A retrospective analysis of the Alzheimer's disease vaccine progress—The critical need for new development strategies. J Neurochem 137(5):687–700.

Masilamoni GJ, Bogenpohl JW, Alagille D, Delevich K, Tamagnan G, Votaw JR, Wichmann T, Smith Y. 2011. Metabotropic glutamate receptor 5 antagonist protects dopaminergic and noradrenergic neurons from degeneration in MPTP-treated monkeys. Brain 134(Pt 7):2057–2073.

Masilamoni GJ, Groover O, Smith Y. 2017. Reduced noradrenergic innervation of ventral midbrain dopaminergic cell groups and the subthalamic nucleus in MPTP-treated parkinsonian monkeys. Neurobiol Dis 100:9–18.

McBride JL, Boudreau RL, Harper SQ, Staber PD, Monteys AM, Martins I, Gilmore BL, Burstein H, Peluso RW, Polisky B, Carter BJ, Davidson BL. 2008. Artificial miRNAs mitigate shRNA-mediated toxicity in the brain: Implications for the therapeutic development of RNAi. Proc Natl Acad Sci USA 105(15):5868–5873.

McBride JL, Clark RL. 2016. Stereotaxic surgical targeting of the nonhuman primate caudate and putamen: Gene therapy for Huntington's disease. Methods Mol Biol 1382:409–428.

McBride JL, Pitzer MR, Boudreau RL, Dufour B, Hobbs T, Ojeda SR, Davidson BL. 2011. Preclinical safety of RNAi-mediated HTT suppression in the rhesus macaque as a potential therapy for Huntington's disease. Mol Ther 19(12):2152–2162.

McCormack AL, Mak SK, Shenasa M, Langston WJ, Forno LS, Di Monte DA. 2008. Pathologic modifications of alpha-synuclein in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated squirrel monkeys. J Neuropathol Exp Neurol 67(8):793–802.

McDowell K, Chesselet MF. 2012. Animal models of the non-motor features of Parkinson's disease. Neurobiol Dis 46(3): 597–606.

Melnikova I. 2007. Therapies for Alzheimer's disease. Nat Rev Drug Discov 6(5):341–342.

Mendez MF. 1994. Huntington's disease: Update and review of neuropsychiatric aspects. Int J Psychiatry Med 24(3):189–208.

Mittoux V, Joseph JM, Conde F, Palfi S, Dautry C, Poyot T, Bloch J, Deglon N, Ouary S, Nimchinsky EA, Brouillet E, Hof PR, Peschanski M, Aebischer P, Hantraye P. 2000. Restoration of cognitive and motor functions by ciliary neurotrophic factor in a primate model of Huntington's disease. Hum Gene Ther 11(8):1177–1187.

Mizuno Y, Sone N, Saitoh T. 1987. Effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and 1-methyl-4-phenylpyridinium ion on activities of the enzymes in the electron transport system in mouse brain. J Neurochem 48(6):1787–1793.

Monteys AM, Ebanks SA, Keiser MS, Davidson BL. 2017. CRISPR/Cas9 editing of the mutant Huntingtin allele in vitro and in vivo. Mol Ther 25(1):12–23.

Moran S, Chi T, Prucha MS, Ahn KS, Connor-Stroud F, Jean S, Gould K, Chan AW. 2015. Germline transmission in transgenic Huntington's disease monkeys. Theriogenology 84(2): 277–285.

Mullin S, Schapira AH. 2015. Pathogenic mechanisms of neurodegeneration in Parkinson disease. Neurol Clin 33(1):1–17.

Nicklas WJ, Vyas I, Heikkila RE. 1985. Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4-phenyl-pyridine, a metabolite of the neurotoxin, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. Life Sci 36(26):2503–2508.

Niu Y, Guo X, Chen Y, Wang CE, Gao J, Yang W, Kang Y, Si W, Wang H, Yang SH, Li S, Ji W, Li XJ. 2015. Early Parkinson's disease symptoms in alpha-synuclein transgenic monkeys. Hum Mol Genet 24(8):2308–2317.

Onos KD, Sukoff Rizzo SJ, Howell GR, Sasner M. 2016. Toward more predictive genetic mouse models of Alzheimer's disease. Brain Res Bull 122:1–11.

Palfi S, Brouillet E, Jarraya B, Bloch J, Jan C, Shin M, Conde F, Li XJ, Aebischer P, Hantraye P, Déglon N. 2007. Expression of

mutated huntingtin fragment in the putamen is sufficient to produce abnormal movement in non-human primates. Mol Ther 15(8):1444–1451.

Palfi S, Conde F, Riche D, Brouillet E, Dautry C, Mittoux V, Chibois A, Peschanski M, Hantraye P. 1998. Fetal striatal allografts reverse cognitive deficits in a primate model of Huntington disease. Nat Med 4(8):963–966.

Palfi S, Ferrante RJ, Brouillet E, Beal MF, Dolan R, Guyot MC, Peschanski M, Hantraye P. 1996. Chronic 3-nitropropionic acid treatment in baboons replicates the cognitive and motor deficits of Huntington's disease. J Neurosci 16(9):3019–3025.

Palfi S, Leventhal L, Goetz CG, Hantraye T, Roitberg BZ, Sramek J, Emborg M, Kordower JH. 2000. Delayed onset of progressive dystonia following subacute 3-nitropropionic acid treatment in Cebus apella monkeys. Mov Disord 15(3):524–530.

Palfi S, Riche D, Brouillet E, Guyot MC, Mary V, Wahl F, Peschanski M, Stutzmann JM, Hantraye P. 1997. Riluzole reduces incidence of abnormal movements but not striatal cell death in a primate model of progressive striatal degeneration. Exp Neurol 146(1):135–141.

Palmer AM, Francis PT, Bowen DM, Benton JS, Neary D, Mann DM, Snowden JS. 1987a. Catecholaminergic neurones assessed ante-mortem in Alzheimer's disease. Brain Res 414 (2):365–375.

Palmer AM, Wilcock GK, Esiri MM, Francis PT, Bowen DM. 1987b. Monoaminergic innervation of the frontal and temporal lobes in Alzheimer's disease. Brain Res 401(2):231–238.

Paumier KL, Luk KC, Manfredsson FP, Kanaan NM, Lipton JW, Collier TJ, Steece-Collier K, Kemp CJ, Celano S, Schulz E, Sandoval IM, Fleming S, Dirr E, Polinski NK, Trojanowski JQ, Lee VM, Sortwell CE. 2015. Intrastriatal injection of preformed mouse alpha-synuclein fibrils into rats triggers alpha-synuclein pathology and bilateral nigrostriatal degeneration. Neurobiol Dis 82:185–199.

Peters A, Rosene DL, Moss MB, Kemper TL, Abraham CR, Tigges J, Albert MS. 1996. Neurobiological bases of age-related cognitive decline in the rhesus monkey. J Neuropathol Exp Neurol 55(8):861–874.

Philippens IH, Ormel PR, Baarends G, Johansson M, Remarque EJ, Doverskog M. 2017. Acceleration of amyloidosis by inflammation in the amyloid-beta marmoset monkey model of Alzheimer's disease. J Alzheimers Dis 55(1):101–113.

Pifl C, Schingnitz G, Hornykiewicz O. 1991. Effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on the regional distribution of brain monoamines in the rhesus monkey. Neuroscience 44 (3):591–605.

Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL. 1997. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276(5321):2045–2047.

Price DL, Martin LJ, Sisodia SS, Wagster MV, Koo EH, Walker LC, Koliatsos VE, Cork LC. 1991. Aged non-human primates: An animal model of age-associated neurodegenerative disease. Brain Pathol 1(4):287–296.

Puschmann A. 2013. Monogenic Parkinson's disease and parkinsonism: Clinical phenotypes and frequencies of known mutations. Parkinsonism Relat Disord 19(4):407–415.

Rafii MS, Baumann TL, Bakay RA, Ostrove JM, Siffert J, Fleisher AS, Herzog CD, Barba D, Pay M, Salmon DP, Chu Y, Kordower JH, Bishop K, Keator D, Potkin S, Bartus RT. 2014. A phase1 study of stereotactic gene delivery of AAV2-NGF for Alzheimer's disease. Alzheimers Dement 10(5):571–581.

Rappold PM, Tieu K. 2010. Astrocytes and therapeutics for Parkinson's disease. Neurotherapeutics 7(4):413–423.

Rawlins M. 2010. Huntington's disease out of the closet? Lancet 376(9750):1372–1373.

Recasens A, Dehay B, Bove J, Carballo-Carbajal I, Dovero S, Perez-Villalba A, Fernagut PO, Blesa J, Parent A, Perier C, Fariñas I, Obeso JA, Bezard E, Vila M. 2014. Lewy body extracts from Parkinson disease brains trigger alpha-synuclein pathology and neurodegeneration in mice and monkeys. Ann Neurol 75(3):351–362.

Rhyu IJ, Bytheway JA, Kohler SJ, Lange H, Lee KJ, Boklewski J, McCormick K, Williams NI, Stanton GB, Greenough WT, Cameron JL. 2010. Effects of aerobic exercise training on cognitive function and cortical vascularity in monkeys. Neuroscience 167(4):1239–1248.

Ridley RM, Baker HF, Windle CP, Cummings RM. 2006. Very long term studies of the seeding of beta-amyloidosis in primates. J Neural Transm (Vienna) 113(9):1243–1251.

Rodriguez-Pallares J, Parga JA, Munoz A, Rey P, Guerra MJ, Labandeira-Garcia JL. 2007. Mechanism of 6-hydroxydopamine neurotoxicity: the role of NADPH oxidase and microglial activation in 6-hydroxydopamine-induced degeneration of dopaminergic neurons. J Neurochem 103(1):145–156.

Roitberg BZ, Emborg ME, Sramek JG, Palfi S, Kordower JH. 2002. Behavioral and morphological comparison of two nonhuman primate models of Huntington's disease. Neurosurgery 50(1):137–145; discussion 145–6.

Rosenstein LD. 1998. Differential diagnosis of the major progressive dementias and depression in middle and late adulthood: A summary of the literature of the early 1990s. Neuropsychol Rev 8(3):109–167.

Saudou F, Humbert S. 2016. The biology of huntingtin. Neuron 89(5):910–926.

Schliebs R. 2005. Basal forebrain cholinergic dysfunction in Alzheimer's disease–Interrelationship with beta-amyloid, inflammation and neurotrophin signaling. Neurochem Res 30(6–7):895–908.

Schneider JS. 1990. Chronic exposure to low doses of MPTP. II. Neurochemical and pathological consequences in cognitively-impaired, motor asymptomatic monkeys. Brain Res 534(1–2):25–36.

Schultz-Darken N, Braun KM, Emborg ME. 2016. Neurobehavioral development of common marmoset monkeys. Dev Psychobiol 58(2):141–158.

Schwarcz R, Whetsell WO Jr, Mangano RM. 1983. Quinolinic acid: An endogenous metabolite that produces axon-sparing lesions in rat brain. Science 219(4582):316–318.

Senoh S, Creveling CR, Udenfriend S, Witkop B. 1959a. Chemical, enzymatic and metabolic studies on the mechanism of oxidation of dopamine1. J Am Chem Soc 81(23): 6236–6240.

Senoh S, Witkop B, Creveling CR, Udenfriend S. 1959b. 2,4,5-trihydroxyphenethylamine, a new metabolite of 3,4-dihydroxyphenethylamine. J Am Chem Soc 81(7):1768–1769.

Serretti A, Olgiati P, De Ronchi D. 2007. Genetics of Alzheimer's disease. A rapidly evolving field. J Alzheimers Dis 12(1): 73–92.

Sherer TB, Fiske BK, Svendsen CN, Lang AE, Langston JW. 2006. Crossroads in GDNF therapy for Parkinson's disease. Mov Disord 21(2):136–141.

Silajdzic E, Rezeli M, Vegvari A, Lahiri N, Andre R, Magnusson-Lind A, Nambron R, Kalliolia E, Marko-Varga G, Warner TT, Laurell T, Tabrizi SJ, Björkqvist M. 2013. A critical evaluation of inflammatory markers in Huntington's Disease plasma. J Huntingtons Dis 2(1):125–134.

Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K. 2003. Alpha-Synuclein locus triplication causes Parkinson's disease. Science 302(5646):841.

Sridharan A, Bendlin BB, Gallagher CL, Oh JM, Willette AA, Alexander AL, Kemnitz JW, Colman RJ, Weindruch RH, Johnson SC. 2014. Effect of age and calorie restriction on corpus callosal integrity in rhesus macaques: A fiber tractography study. Neurosci Lett 569:38–42.

Stocchi F. 2015. Neuroprotection in Parkinson's disease: A difficult challenge. Lancet Neurol 14(8):780–781.

Stopschinski BE, Diamond MI. 2017. The prion model for progression and diversity of neurodegenerative diseases. Lancet Neurol 16(4):323–332.

Storey E, Cipolloni PB, Ferrante RJ, Kowall NW, Beal MF. 1994. Movement disorder following excitotoxin lesions in primates. Neuroreport 5(10):1259–1261.

Sugaya K. 2003. Neuroreplacement therapy and stem cell biology under disease conditions. Cell Mol Life Sci 60(9): 1891–1902.

Swanson CR, Joers V, Bondarenko V, Brunner K, Simmons HA, Ziegler TE, Kemnitz JW, Johnson JA, Emborg ME. 2011. The PPAR-gamma agonist pioglitazone modulates inflammation and induces neuroprotection in parkinsonian monkeys. J Neuroinflammation 8:91.

Teng E, Stefanacci L, Squire LR, Zola SM. 2000. Contrasting effects on discrimination learning after hippocampal lesions and conjoint hippocampal–caudate lesions in monkeys. J Neurosci 20(10):3853–3863.

Tenreiro S, Franssens V, Winderickx J, Outeiro TF. 2017. Yeast models of Parkinson's disease-associated molecular pathologies. Curr Opin Genet Dev 44:74–83.

Titova N, Padmakumar C, Lewis SJ, Chaudhuri KR. 2016. Parkinson's: A syndrome rather than a disease? J Neural Transm (Vienna).

Triaca V, Sposato V, Bolasco G, Ciotti MT, Pelicci P, Bruni AC, Cupidi C, Maletta R, Feligioni M, Nistico R, Canu N, Calissano P. 2016. NGF controls APP cleavage by downregulating APP phosphorylation at Thr668: Relevance for Alzheimer's disease. Aging Cell 15(4):661–672.

Tuszynski MH, Roberts J, Senut MC, U HS, Gage FH. 1996. Gene therapy in the adult primate brain: Intraparenchymal grafts of cells genetically modified to produce nerve growth factor prevent cholinergic neuronal degeneration. Gene Ther 3(4): 305–314.

Tuszynski MH, Thal L, Pay M, Salmon DP, U HS, Bakay R, Patel P, Blesch A, Vahlsing HL, Ho G, Tong G, Potkin SG, Fallon J, Hansen L, Mufson EJ, Kordower JH, Gall C, Conner J. 2005. A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nat Med 11(5):551–555.

Tuszynski MH, U HS, Amaral DG, Gage FH. 1990. Nerve growth factor infusion in the primate brain reduces lesion-induced cholinergic neuronal degeneration. J Neurosci 10(11): 3604–3614.

Tuszynski MH, Yang JH, Barba D, U HS, Bakay RA, Pay MM, Masliah E, Conner JM, Kobalka P, Roy S, Nagahara AH. 2015. Nerve growth factor gene therapy: Activation of neuronal responses in Alzheimer disease. JAMA Neurol 72(10):1139–1147.

Vermilyea SC, Emborg ME. 2015. alpha-Synuclein and nonhuman primate models of Parkinson's disease. J Neurosci Methods 255:38–51.

Vermilyea SC, Emborg ME 2017. The role of nonhuman primate models in the development of cell-based therapies for Parkinson's disease. J Neural Transm (Vienna).

Villalba RM, Wichmann T, Smith Y. 2014. Neuronal loss in the caudal intralaminar thalamic nuclei in a primate model of Parkinson's disease. Brain Struct Funct 219(1):381–394.

Voytko ML, Olton DS, Richardson RT, Gorman LK, Tobin JR, Price DL. 1994. Basal forebrain lesions in monkeys disrupt attention but not learning and memory. J Neurosci 14(1):167–186.

Wakabayashi K, Tanji K, Mori F, Takahashi H. 2007. The Lewy body in Parkinson's disease: Molecules implicated in the formation and degradation of alpha-synuclein aggregates. Neuropathology 27(5):494–506.

Willette AA, Coe CL, Birdsill AC, Bendlin BB, Colman RJ, Alexander AL, Allison DB, Weindruch RH, Johnson SC. 2013. Interleukin-8 and interleukin-10, brain volume and microstructure, and the influence of calorie restriction in old rhesus macaques. Age (Dordr) 35(6):2215–2227.

Winkler J, Ramirez GA, Kuhn HG, Peterson DA, Day-Lollini PA, Stewart GR, Tuszynski MH, Gage FH, Thal LJ. 1997. Reversible Schwann cell hyperplasia and sprouting of sensory and sympathetic neurites after intraventricular administration of nerve growth factor. Ann Neurol 41(1):82–93.

Wong YC, Krainc D. 2017. [alpha]-synuclein toxicity in neurodegeneration: Mechanism and therapeutic strategies. Nat Med 23(2):1–13.

Yang SH, Cheng PH, Banta H, Piotrowska-Nitsche K, Yang JJ, Cheng EC, Snyder B, Larkin K, Liu J, Orkin J, Fang ZH, Smith Y, Bachevalier J, Zola SM, Li SH, Li XJ, Chan AW. 2008. Towards a transgenic model of Huntington's disease in a non-human primate. Nature 453(7197):921–924.

Yang W, Wang G, Wang CE, Guo X, Yin P, Gao J, Tu Z, Wang Z, Wu J, Hu X, Li S, Li XJ. 2015. Mutant alpha-synuclein causes age-dependent neuropathology in monkey brain. J Neurosci 35(21):8345–8358.

Younger/Early Onset Alzheimer's & Dementia. 2017. Available online (http://www.alz.org/alzheimers_disease_early_onset.asp), accessed on June, 2017.

Zeiss CJ. 2017. From reproducibility to translation in neurodegenerative disease. ILAR J:1–9.

Zeiss CJ, Allore HG, Beck AP. 2017. Established patterns of animal study design undermine translation of disease-modifying therapies for Parkinson's disease. PLoS One 12(2): e0171790.

Zhao Q, Lu J, Yao Z, Wang S, Zhu L, Wang J, Chen B. 2017. Upregulation of Abeta42 in the brain and bodily fluids of rhesus monkeys with aging. J Mol Neurosci 61(1):79–87.

Zola SM, Squire LR, Teng E, Stefanacci L, Buffalo EA, Clark RE. 2000. Impaired recognition memory in monkeys after damage limited to the hippocampal region. J Neurosci 20(1):451–463.