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Review

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Rat models of major neurodegenerative disorders

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Abstract

No single animal model can recapitulate all the features of a particular human disease on its own. Historically, rats have been used to study neurobiology and underlying functional networks. Likewise, rat models have been created to study neurodegenerative mechanisms and therapeutic interventions. In the last decades, a shift towards the use of mice has been observed in many research fields, not least because of the comparatively easier genetic manipulation of mice. However, with the full sequence of the rat genome being available, advances in genetic manipulation of the rat, and advanced test regimens and biomarkers at hand, the rat presents itself once more as a valuable model organism for studying neurodegenerative disorders. This review provides an overview of currently available, well-characterized rat models of Alzheimer's disease, Parkinson's disease, and Huntington's disease, as well as their advantages for studying neurodegenerative disorders and evaluating therapeutic interventions.

Keywords: Genetic rat models, phenotypic rat models, Alzheimer's disease, Parkinson's disease, Huntington's disease

INTRODUCTION

Rattus norvegicus, the laboratory rat, was the first mammal to be domesticated and kept in captivity for research purposes[1,2]. Over time many inbred rat strains have been obtained to study various physiological aspects, disease mechanisms, and pharmacological questions. Both mice and rat models have been relied on

in basic and preclinical research. Their short generation times, relatively easy to establish housing conditions, and genetic similarities to humans have made them the largest group amongst animal models in research (EU commission, 2019 report). In general, rats are considered an ideal species for behavioral studies, and have been used far more than mice in behavioral research in the past, although the increasing use of transgenic mice in behavioral testing in recent years has inverted this trend[3]. Rats are easy to handle by experimenters and less aggressive towards conspecifics (i.e., members of the same species) than mice[4]. Rat behavior has been well characterized, and several behavioral tasks currently used in rodents may better fit the rat[5,6], as they were originally developed in rats[7,8]. In cognitive tests which are used to model cognitive deficits of human disorders, especially for tasks requiring swimming, such as the Morris water maze, rats display less floating and thigmotaxis[9] and perform better than mice[10,11], probably because they are adapted to the water environment and are natural swimmers. In a decision-making task, rats were shown to learn the task faster than mice[12]. Furthermore, compared to mice, rats display a more complex behavioral repertoire which is likely to result from the species' evolutionary history[13]. Increasing evidence in the last 15 years suggests that, similar to primates, rats present metacognition, that is, the awareness of one's own cognitive processes[14-16]. In the context of neurodegenerative disorders (NDs), this is relevant given that metacognitive impairment is a feature of Alzheimer's disease (AD) and other dementias[17].

Consequently, using rats to model cognitive symptoms could increase the robustness of cognitive assessments and enhance the accuracy of phenotypes. However, it is important to bear in mind that different rodent species differ in their behavioral traits[18,19] that could best mimic specific aspects of a human disorder, emphasizing the importance of using multiple model species, especially given the heterogeneity of deficits in several neurodegenerative disorders.

The rat's body size further offers advantages over mice and other small animal models, as surgical procedures can be performed more reliably and consistently. Repeated blood and cerebrospinal fluid (CSF) sampling of larger volumes is possible in rats, and neuroimaging and electrophysiological measurements are preferentially performed in rats. The rat remains the classical animal model in toxicological studies, as the eradication of toxins is more closely related between human and rat, than between human and mouse[20]. However, a close examination of the individual biological processes affected is necessary, as many differences exist between species[21]. Both mouse and rat genomes were published in the early 2000s[22,23] opening the way for genetic studies investigating rat genes that share similar traits in rats and humans[20]. With the advancement of genetic tools, mice have been favored over rats due to technical challenges in creating rat models carrying genetic mutations. By improving methods for harnessing rat embryonic stem cells and advances in genetic tools, like zinc finger nuclease and CRISPR/Cas systems, rat models have been created more successfully in the last two decades. However, with a certain time delay in comparison to respective mouse models[24].

For NDs, like AD, Parkinson's disease (PD), and Huntington's disease (HD), no natural mutation in the rat exists that would provide a rat strain to model the human disease. Therefore, rat lines have been created that mostly carry and overexpress the human disease gene, in order to elicit phenotypes that resemble pathology and behavioral alterations, reminiscent of what is observed in patients. However, the most prevalent NDs, AD and PD, are not monogenetic disorders, with a low proportion of familial cases and, therefore, inherently difficult to model.

AD is the most common neurodegenerative disorder. Patients suffer from progressive cognitive decline, affecting, for example, memory and orientation and with disease progression limiting activities of daily life. The decline in cognitive abilities and behavioral alterations are caused by preceding, exaggerated amyloid

beta (Aβ) peptide plaque formation and tau tangles. Progressive neuronal loss in the hippocampus and other brain regions further leads to reduced levels of neurotransmitters[25].

PD, like AD, is a highly prevalent neurodegenerative disorder that has a multifactorial etiology and is most often of idiopathic origin. Genetic and environmental factors contribute to the disorder that is primarily characterized by the lack of the neurotransmitter dopamine, leading to bradykinesia and other motor deficits in patients. Several PD-causing and PD-risk genes have been identified. Mutations in α-Synuclein (*SNCA*), Parkin (*PARK2*), PTEN-induced kinase 1 (*PINK1*), Protein deglycase DJ-1 (*DJ-1*), and Leucine-rich repeat kinase 2 (*LRRK2*) amongst others can cause the familial form of the disorder. On the cellular level, PD is characterized by mitochondrial dysfunction, altered protein degradation pathways, and increased neuroinflammation leading to synaptic dysfunction and neuronal loss in the substantia nigra pars compacta[26].

HD is a monogenetic ND caused by a CAG repeat expansion in exon 1 of the *huntingtin* gene (*HTT*), which translates to a poly-glutamine tract in the huntingtin protein (HTT)[27,28]. HD commonly manifests in adulthood, with CAG expansions in a range of 36 to 60 CAG repeats[29]. More than 60 CAG repeats are associated with juvenile HD, leading to symptom onset before the age of 20 years[30]. The neuropathological hallmarks of HD are extensive cell loss in the striatum and HTT aggregates localized in the neuropil, perikarya, and nucleus[31-33]. The clinical manifestations include motor deficits, cognitive impairment, and psychiatric disturbances[34].

This review provides an overview of rat models that have been generated to study the above-mentioned NDs, AD, PD, and HD. Neuropathological characteristics and behavioral phenotypes of well-characterized genetic models are summarized and stand in contrast to phenotypic/aspect-replicating rat models that are historically and currently more commonly used in biomedical research. We aim to highlight the advantages both types of rat models offer in terms of readouts and study design opportunities to improve translatability to human treatment.

GENETIC RAT MODELS TO STUDY AD, PD, AND HD

Neuropathological phenotypes

Neurodegenerative diseases represent a large group of neurological disorders with progressive loss of particular subsets of neurons. The most common NDs are Alzheimer's disease (AD) and Parkinson's disease (PD); and as a monogenic disease, Huntington's disease (HD), is well-studied. In addition to the progressive and selective neuronal cell loss, the second central characteristic of NDs is the presence of protein aggregates composed of misfolded proteins, specifically, the N-terminal fragment of mutant huntingtin in HD, Aβ peptide and hyperphosphorylated tau in AD, and α-synuclein (α-syn) in PD. The role of protein aggregates in NDs, whether neurotoxic or neuroprotective, is still a matter of debate since the distribution of protein aggregates does not reliably match the patterns of neuronal loss in different diseases[35]. Nevertheless, due to its commonality among NDs and its dependency on a specific molecular cascade (i.e., misfolding, oligomerization, and fibrillization), protein aggregate formation remains an important aspect of ND research. Thus, animal models that recapitulate the disease's characteristic protein aggregation pathologies can make great contributions to understanding the disease mechanisms and aid in the development of therapeutic strategies. For genetically modified animal models of NDs, the presence, as well as the regional and subcellular location of protein aggregates, depends on the genetic construct's promoter, protein expression levels, and genetic background of the animal. Mouse models have closely recapitulated the features of human NDs and provided essential insight into neuropathology. However, no single animal model can mimic all aspects of human diseases, not even all mouse models, collectively. Rats

and mice are closely related species, but still have genetic and physiological differences, such as the distinct expression pattern and localization of certain protein isoforms. These diversities lead to some variance between both species in resembling human pathological processes, making rat models a meaningful complement to mouse models. This section discusses the commonly used genetic rat models for AD, PD, and HD [Table 1], and describes to what extent they recapitulate the characteristic protein aggregate pathology.

Neuropathological phenotypes in genetic rat models of Alzheimer's disease: APP^{NL-G-F} knock-in, TgF344-AD and McGill-R-Thy1-APP transgenic rats

Amyloid plaques containing Aβ peptide and neurofibrillary tangles (NFTs) consisting of hyperphosphorylated microtubule-associated protein (tau) make up the typical protein aggregate forms in AD. While some studies suggested that tangles may precede plaques, it is commonly accepted that the amyloid plaques are formed first and trigger tau agglomeration (see review[49]). Nevertheless, both amyloid plaque and tau tangles are characteristic features of AD. The development of amyloid plaques appears to be dependent on the initial accumulation of Aβ, which is derived from amyloid beta precursor protein (APP) through sequential proteolytic cleavage by β and γ-secretase. Mutations in APP close to the main APP cleavage site and in the catalytic subunit of γ-secretase presenilin (*PSEN*) are major genetic causes of familial AD[50,51]. Ultimately, overexpression of APP with a combination of multiple mutations has been used to generate *APP* transgenic models[52-54], while double transgenic models expressing mutant *APP* and mutant *PSEN* represent *APP/PSEN* models (see review[36]).

Many transgenic *APP* mouse models recapitulate amyloid plaque formation and disease manifestation of AD and have thereby made essential contributions to understanding Aβ pathology in familial AD. In comparison, *APP* rat models often develop less accumulation of Aβ peptide and amyloid plaques. This cannot be simply explained by lower expression levels of transgenes in rats, or different transgene protein isoforms, or the applied promoters. One rat model, however, displays full amyloid pathology. Leon *et al.* developed an *APP* transgenic rat model expressing *hAPP751* under the control of the murine Thy1.2 promoter and containing the Swedish and Indiana mutations of APP (McGill-R-Thy1-APP rats)[55]. This rat model carries one copy of the transgene hemizygously and accordingly presents approximately double the amount of APP protein (i.e., both endogenous and transgenic) as wild-type rats. Homozygous rats show an early-onset and progressive accumulation of Aβ peptide starting at 1 week of age and develop extracellular Aβ deposition at 6 months of age. Particularly, at 20 months of age, McGill-R-Thy1-APP transgenic rats display dense-core plaques in most brain areas with predominant presence in the entorhinal and parietal cortices, and hippocampus, the typical brain structures that are vulnerable to AD[56-58]. In summary, despite the lower expression level of the transgene, McGill-R-Thy1-APP transgenic rats develop early-onset, progressive, characteristic amyloid plaque pathology making this model valuable for studying Aβ pathogenesis in a close to physiological condition.

In fact, the distribution and burden of amyloid plaques in AD patients do not correlate with neuronal loss, disease severity, or disease duration. In contrast, NFT formation strongly correlates with neuronal death and follows a typical progression from the frontal cortex and the CA1 area of hippocampus to the anterodorsal thalamus, and in later stages (IV), the CA4 region of hippocampus[59,60]. Instead, NFTs have only been found in AD mouse models carrying human mutant tau, mostly with P301L mutation[36]. P301L missense mutation in tau is the genetic cause of frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17); this mutation causes tau hyperphosphorylation and its subsequent aggregation into NFTs[61,62]. Different from FTDP-17, tau is not the only hyperphosphorylated neuronal protein in AD, and hyperphosphorylated tau is the result of a protein phosphorylation/dephosphorylation unbalance (see

Table 1. Genetic rat models of Alzheimer's, Parkinson's, and Huntington's disease

	FAD		FPD			HD	
Categories (Example)	Early onset AD (McGill-R-Thy1-APP rats, TgF344-AD)	Later onset AD (APOE epsilon 4 knock-in)	Autosomal recessive (PINK1 KO, DJ-1 KO)	Autosomal dominant (α-synuclein BAC, LRRK2 KO)		Juvenile-onset HD (BACHD)	Adult-onset HD (tgHD)
Molecular and biological basis	Mutation in APP, PSEN1, hyperphosphorylation of tau	rRsk factors, e.g., APOE variants	Mainly loss-of-function, e.g., PARKIN, PINK1 and DJ-1	Mainly gain-of function, e.g., SNCA, LRRK2		CAG expansion > 60	CAG expansion < 60
Strategy	• Expression/knock-in of a combination of multiple mutations in APP • Expression of mutations in APP + PSEN • Expression of mutations in MAPT	• Humanization of loci of AD relevant mutations	• Knock out of PARKIN, PINK1 or DJ-1	• Overexpression of wild-type or mutant SNCA	• Overexpression of wild-type or mutant LRRK2 • KO	• Overexpression of full-length mutant HTT	• Overexpression of the N-terminal fragment of mutant HTT
Pros	• Early and progressive recapitulation of neuropathological features • Tangle-like pathology • Spatial cognition deficits	• Physiological levels of protein expression	• Mitochondrial pathology can be studied • Cranial sensorimotor deficits can be studied (DJ-1 KO and PINK1 KO)	• LB pathology can be studied	• Effect of impaired dopamine homeostasis can be studied	• Early and progressive recapitulation of the HTT aggregation phenotype • Displays HD-like behavioral phenotypes	• Represents the major form of HD • Displays HD-like behavioral phenotypes
Cons	• Non-physiological condition • Represents a small portion of disease form (early onset AD accounts for < 5% of AD cases)	• Need to verify and characterize identified novel risk factors	• Most of them do not mimic the LB pathology of PD patients? • No motor behavior impairment in PARKIN KO		• No dopaminergic neurodegeneration	• Represent only juvenile HD • Long CAG repeats may change the HTT protein properties	• Mild and slow recapitulation of disease pathology
Literature	Reviewed in[36-39]	Reviewed in[40-42]	Reviewed in[43-47]			Reviewed in[48]	

AD: Alzheimer's disease; APOE: apolipoprotein E; APP: amyloid precursor protein; CAG: polyglutamine; DJ-1 (PARK7): Parkinson's disease protein 7; FAD: familial Alzheimer's disease; FPD: familial Parkinson's disease; HD: Huntington's disease; HTT: huntingtin; KO: Knockout; LB: Lewy body; LERRK2: leucine-rich repeat kinase 2; MAPT: microtubule-associated protein Tau; PINK1: PTEN-induced kinase 1; PSEN: presenilin; SNCA: synuclein alpha.

review[63]). This raises the debate of whether the P301L resulting tau aggregation can represent tau pathology in AD. Tau is a microtubule-associated protein stabilizing microtubules in the polymerized state[64,65]. Alternative splicing of tau in humans generates six isoforms containing microtubule-binding domain, including three (3R) or four (4R) microtubule-binding repeats[66]. It has been shown that rats express all six tau isoforms as humans, while mice only possess 3R tau isoforms[67].

The TgF344-AD rat is an AD transgenic model that carries transgenic constructs, expressing both the Swedish human mutant *APP* and the *PSEN1*(*PS1ΔE9*). These rats exhibit 2.6-fold human APP and 6.2-fold human presenilin-1 expression, respectively, compared to the endogenous rat homologs. Around 16 months of age, TgF344-AD rats develop amyloid plaques, some of which are thioflavin S-positive dense-core plaques. Strikingly, abundant insoluble tau structures have also been demonstrated in the cortex and hippocampus of aged transgenic animals, whose morphology recapitulates human NFTs. Frank and progressive neurodegeneration combined with neuroinflammation and cell apoptosis have been found in the same brain areas[68]. Similarly, tangle-like tau aggregates were also observed in a wild-type rat injection

model expressing mutant *APP* and *PSIN1*($PS1_{M146L}$) mediated by adeno-associated viruses[69].

Very recently, Pang and colleagues generated an *APP* KI rat model, App^{NL-G-F} rats, which carry three family *App* mutations G676R, F681Y, and R684H[70]. Both homo- and heterozygous rats manifested amyloid plaques rapidly at 1 and 4 months of age, respectively. Notably, the amyloid plaque manifestation in App^{NL-G-F} rats preceded faster in females compared to males[71]. Whether this sex difference in Aβ aggregation can be linked to the higher incidence rates of AD in women than in men requires further investigation. Interestingly, aggregated tau was found in 12-month-old homozygous App^{NL-G-F} rats and further manifested into NFTs at 22 months of age. Increased gliosis, apoptotic cell death and brain atrophy have been observed in App^{NL-G-F} rats at 12 months of age and older.

Taken together, several *APP* rat models have shown common AD neuropathological features in AD-affected brain areas, in particular NFT formation, a key pathogenic event in the disease process, which have not been recapitulated in *APP* mouse models. The lack of the 4R isoforms in mice may be the cause for the two rodents' differing abilities to model human tau pathology.

Neuropathological phenotypes in genetic rat models of Parkinson's disease: PINK1 KO, DJ-1 KO, and a-synuclein BAC rats

The characteristic neuropathological features of PD are intracellular α-synuclein positive inclusions known as Lewy bodies (LBs), and selective neuronal loss in the substantia nigra, which is strongly related to mitochondrial dysfunction (see review[72]). About 20 genes have been identified to cause familial PD, inherited in an autosomal dominant or recessive mode. In the following, we will focus on three PD genetic rat models, which made significant contributions to the PD field as compensations for mouse models: the α-synuclein transgenic rats, *PINK1 KO* rats, and *DJ-1*-KO rats.

α-synuclein BAC transgenic rat model

The major component of LBs is α-synuclein, which is encoded by the *SNCA* gene. This was the first gene revealed to have a causal link to PD development. To this date, six autosomal dominant *SNCA* point mutations (A53T, A30P, E46K, G51D, H50Q, and A53E) have been identified[73]. Moreover, duplication, triplication and quadruplication of the *SNCA* locus have been reported to be causal in genetically unrelated PD families[74-77]. A number of transgenic mice models bearing human mutant or wild-type *SNCA* have been generated. Many of these models exhibit proteinase K resistant, detergent-insoluble, and thioflavin S positive α-synuclein aggregates (see review[78]). Mouse models also show a neuronal loss in PD-relevant brain areas, that is, substantia nigra, neocortex, and hippocampus[79-83]. An α-synuclein BAC transgenic rat model using a bacterial artificial chromosome (BAC) construct consisting of full-length human wild-type *SNCA* locus with the upstream regulatory promoter sequences has been generated by the Riess lab[84]. These BAC transgenic rats showed key pathological features of PD, including progressive misfolding and accumulation of α-synuclein aggregates, striatal dopamine depletion, decreased TH-positive cell numbers, and characteristic dark dopamine neurons in the substantia nigra. These pathological features have been modeled comparably in α-synuclein transgenic mice. However, with larger body sizes, rats offer unique possibilities for surgical manipulations of the brain, serial sampling of cerebrospinal fluid and blood, and brain imaging.

Rat models for autosomal recessive mutations

Autosomal recessive forms of PD commonly present an early onset phenotype[85,86]. All three known autosomal recessive PD genes, *PARKIN*, *PINK1*, and *DJ-1*, are closely associated with mitochondrial dysfunction[87-89]. The PTEN-induced kinase 1 (PINK1) and Parkin are involved in the same pathway leading

to the degradation of damaged mitochondria. PINK1 acts as a sensor for depolarization of mitochondrial membrane potential[85,90-93], recruiting the E3 ubiquitin ligase Parkin which ubiquitinates substrates on the outer mitochondrial membrane, thus eliciting a vicious cycle resulting in mitophagy[94]. Protein deglycase DJ-1 is a stress-dependent chaperone localized in mitochondria, which plays an essential role in ATP production and complex I activity[95,96]. Interestingly, it has been observed that Lewy bodies can be absent in PD patients with either *PARKIN*, *PINK1*, or *DJ-1* mutation (see review[97]). In comparison, mitochondrial pathology and neuronal loss in animal models of autosomal recessive PD are expected as important pathological phenotypes. *PINK1* knockout (KO) rats show decreased complex I level and increased proton leak in the electron transport chain, indicating a mitochondrial respiration defect, as well as a reduced number of TH-positive neurons and proteinase K resistant α-synuclein aggregates[47,98]. By contrast, no evidence reflecting neurodegeneration was found in *PINK1* KO mice[99], not even in the triple knockout mice with deficiency of Parkin/PINK1/DJ-1, all known gene deficiencies related to autosomal recessive PD forms[100]. Similarly, *DJ-1* KO rats show significantly progressive neuronal loss with approximately 50% dopaminergic cell loss at 8 months of age in the substantia nigra, combined with altered mitochondrial respiration[101,102]. In contrast to rat models, no dopaminergic neuron loss-related event or mitochondrial dysfunction has been observed in all existing *DJ-1* KO mouse models, while one *DJ-1* KO mouse model only shows increased sensitivity to the neurotoxin MPTP[103-105]. Notably, *PARKIN* KO mice and rats also have been generated, while *PARKIN* KO mice exhibited increased striatal extracellular DA concentration, which is opposite as expected[106], *PARKIN* KO rats did not show any neuropathological differences compared to wild-type controls[101]. Whether these results can be explained by the genetic and biological differences between human and rodent remains unaddressed. Nevertheless, both *PINK1* and *DJ-1* monogenic KO rat models are valuable for investigating mitochondrial pathology in autosomal recessive PD, whereas the comparable mouse models lack disease-related neuropathological phenotypes.

Neuropathological phenotypes in genetic rat models of Huntington's disease: tgHD and BACHD rats

To date, two genetic rat models have been generated and well characterized for HD research. One carries the whole genomic sequence and regulatory elements of human *HTT* with 97 mixed CAG-CAA repeats in a bacterial artificial chromosome construct (BACHD rats), thereby bearing the mutation in its appropriate genomic context as in HD patients[107]. The interruption in CAG repeats avoids somatic instability of polyQ size and variation in repeat length within the animal colony. The other rat model carries N-terminal rat *Htt* cDNA fragments under the rat *Htt* promoter, with 51 CAG repeats (tgHD rats)[108]. In humans, the CAG length present in the tgHD construct would lead to an adult-onset of disease, whereas 97 CAGs, as in the BACHD rats, would result in the juvenile form of the disorder. Both BACHD and tgHD rat models have a wide expression pattern of transgene *HTT*/*Htt* throughout the brain that, to some extent, resembles the human condition. BACHD rats have a 4.5-fold higher expression level of transgenic *HTT* as the endogenous *Htt*, while tgHD rats show a strongly reduced transgene expression level compared to the endogene[107,108]. Both rat models show subtle evidence for neurodegeneration, including structural changes in white matter[109,110], reduced brain volume in BACHD rats[111], and age-dependent enlarged ventricles in tgHD rats.

Although neuronal loss in HD patients is most prominent in the striatum, mHTT aggregates have been more frequently detected in the cerebral cortex. Subcellular localization studies revealed a prevalent neuropil localization of mHTT aggregates, while smaller amounts of mHTT inclusion bodies were found in the nucleus[31-33]. One of these studies reported that in all 12 investigated HD brains, only 1%-4 % of striatal neurons had nuclear inclusion bodies, while a large number of mHTT aggregates were detected in the cortex with prominent subcellular localization in neuropil and perikarya. Although juvenile HD patients show an increased number of nuclear inclusion bodies compared to patients with adult-onset, neuropil aggregates were still predominantly distributed in the striatum and cortex[32]. Consistent with these

observations, BACHD rats exhibit more prominent mHTT aggregates in the cerebral cortex compared to subcortical areas, with aggregates distributed through all cortical layers, primarily in neurites. tgHD rats display a similar aggregate distribution pattern. Notably, tgHD rats display abundant mHTT aggregates in the dorsomedial part of the striatum and BACHD rats have been found to show a similar aggregate load in the lateral striatum. Interestingly, both HD rat models show a prevalent distribution of HTT aggregates in the limbic structures, with notable aggregate loads in the ventral striatum (nucleus accumbens), striatal terminal bed nucleus, and central nucleus amygdala[107,112,113]. In the BACHD rats, aggregates were also found in the hippocampus and hypothalamus. It is difficult to judge to what extent this relates to human disease, as the distribution of aggregates outside the striatum and cortex has barely been studied in HD patients.

In contrast to the aggregate pathology seen in patients and rat models, most mouse models display nuclear inclusion bodies rather than neuropil aggregates. Moreover, they display more abundant aggregates in the striatum compared to the cerebral cortex, regardless of the genetic construct or modification they are based on[114]. It is therefore clear that BACHD and tgHD rats provide a meaningful complement to HD mouse models for modeling and understanding the mHTT neuropathogenic mechanisms. mHTT aggregation is affected by several intrinsic factors, including polyQ-flanking sequences of mHTT, mHTT interaction partners, protein fragmentation, and post-translational modifications (see review[115]). Different subcellular localization of aggregates may initiate different cellular quality-control processes, resulting in different pathogenic processes. Working with a combination of mouse and rat models of HD, could therefore help tease apart what exactly causes one type of pathology over the other.

Behavioral phenotypes

Behavioral phenotypes in genetic rat models of Alzheimer's disease: APP^{NL-G-F} knock-in, TgF344-AD, and McGill-R-Thy1-APP transgenic rats

Memory impairment is an early symptom in AD patients, followed by language and mathematical deficits, decreased visuospatial orientation, and attention deficits[116,117]. One of the most common symptoms in subjects affected by AD is an impairment of spatial navigation which is the ability to define and retain trajectories between places[118]. Although attributing cognitive functions to specific brain areas does not embrace the complexity of brain networks regulating cognition, hippocampus and medial entorhinal cortex represent essential areas for spatial navigation[119] and are already affected in the early phases of AD[120]. Similar brain areas in humans and rodents appear to be involved in the regulation of specific types of memory, for example, spatial memory[9,121,122], which is important for modeling cognitive deficits in animal models.

Most of the behavioral results in AD genetic models come from the characterization of mouse models. On the other hand, the use of genetic rat models is increasing, and these models may be advantageous from a behavioral perspective, given that cognitive testing is central to AD research. In McGill-R-Thy1-APP transgenic rats, spatial learning and memory deficits already manifest by 3 months of age, prior to amyloid plaque deposition and are present in both homozygous and hemizygous rats which can sometimes differ in the degree of impairment. Spatial cognition deficits include reference and working memory impairment as detected in maze tasks for spatial learning, and problems with object location memory[55,123-125]. TgF344-AD transgenic rats show spatial cognition deficits as early as 4 months of age[126,127]. Similar to the McGill-R-Thy1-APP rats, they were shown to have a deficient performance in several paradigms for spatial cognition including tasks for reference and working memory[68,126,128,129] as well as reversal learning[68,130,131]. Moreover, TgF344-AD rats display a decreased accuracy in spatial trajectories[132]. In line with the results in the transgenic models of AD, five months old APP^{NL-G-F} knock-in rats were reported to display impaired spatial learning abilities[70]. Hence, defective spatial cognition is reproduced among different categories of AD genetic rat models.

A crucial factor in the process of translating behavioral readouts from animal models to humans is the similarity of the deficits measured in each species. Using similar assessments in animal models and patients is of great advantage, as this could ultimately increase the predictability of therapy effects. Accordingly, hippocampus-dependent navigation tasks, commonly used in rats, for example, the Morris water maze, were adapted for humans in the form of real and virtual versions, and revealed impairments in spatial memory and navigation abilities in AD subjects[133,134], consistent with results in transgenic rat models assessed in mazes for spatial learning[55,123,125,132]. Comparative water maze testing in healthy humans and wild-type rats showed a similar effect of scopolamine and donepezil normally used to model cognitive dysfunction and to treat cognitive deficits, respectively[135], indicating similar behavioral responses to pharmacological cholinergic modulation across species. The direct comparison of AD patients and genetic AD rat models would be more informative regarding the analogy between human and rat results in the context of AD.

Episodic memory, which allows to store and retrieve information about personal experiences along with the related spatial and temporal contexts, is dysfunctional in AD[136]. Recognition memory and associative learning, linked to episodic memory, are impaired as well[137-139]. McGill-R-Thy1-APP and TgF344-AD rats display deficits in some aspects of recognition memory and associative learning. In both rat models, deficits in novel object recognition have been reported, although results are overall mixed[123,124,140-143]. There are also signs of associative learning impairment in passive avoidance setups[142,144,145]. Additionally, fear conditioning analyses revealed that multiple memory recall components are impaired in homozygous and hemizygous McGill-R-Thy1-APP rats[124]. Moreover, testing on automated touch screen setups showed impaired associative learning in the McGill-R-Thy1-APP rat model and deficits in episodic-like memory in APP^{NL-G-F} knock-in rats[70,146]. Touchscreen methods like those applied in McGill-R-Thy1-APP rats are meaningful as analogous to platforms applied to assess cognition in AD patients[147].

A large portion of AD patients suffers from subtle neuropsychiatric symptoms, and the most common are apathy, depression, anxiety, and sleep disturbances[148]. Neuropsychiatric disorders, especially depression, have been associated with phenomena such as decreased hippocampal volume, inflammation, and alterations of the monoaminergic systems[149-152]. Mood alterations in rodent models of AD and other neurodegenerative disorders are most commonly assessed in terms of anxiety and depression-like behavior. Both phenotypes have been more extensively characterized in the TgF344-AD rat model relative to the McGill-R-Thy1-APP model. In TgF344-AD transgenic rats, anxiety-like behavior was detected at different ages in the elevated plus maze[128,145,153,154]. In McGill-R-Thy1-APP rats by the age of 5 months, there is evidence for anxiety-like behavior in the light-dark box[125]. Results obtained in the open field in both rat models are contradictory[123,125,143-145,154]. Regarding depression-related parameters, anhedonia-like behavior as well as behavioral despair were shown in TgF344-AD rats aged 10 months or older[131,145,154]. One of these studies assessed both males and females but did not report sex differences[131]. Nevertheless, given the evidence for sex differences in the prevalence of depression and apathy in AD[155], it would be worth examining sex differences more thoroughly in transgenic rat models. Also, the time course of depression-like phenotypes and cognitive impairment in TgF344-AD rats cannot be easily defined from the behavioral analyses in the model. Moreover, given that in AD, depression can predate cognitive symptoms[156], the assessment of depression-like behaviors in animal models from very early ages would be advisable. Apathy, the most frequent behavioral disturbance in AD[149], has not been assessed in detail in the genetic rat models reviewed here. Signs of apathy-related behavior could be inferred from the presence of anhedonia-like behavior and the reduced motivation to engage in goal-directed behaviors in some experiments in TgF344-AD; for example, rats display a decreased number of attempts in a maze test[128]. Similarly, in mouse models of AD, parameters of object and social exploration, as well as locomotor activity, have been used as

measures of apathy[157,158]. Alternative approaches, e.g., progressive ratio tasks[159], used in AD mice[160], may provide more compelling information on apathy-related motivational aspects.

Sleep disturbances are tightly linked to mood and behavioral disturbances. Sleep behavior characterization in 17-month-old TgF344-AD rats showed changes in sleep architecture, such as increased sleep fragmentation and alterations in sleep microstructure, consistent with the sleep alterations observed in the prodromal phase of AD[161]. Sleep analyses in McGill-R-Thy1-APP rats are lacking, although changes in circadian activity have been reported in this rat model by the age of 8-10 months[125]. In conclusion, both the McGill-R-Thy1-APP and TgF344-AD rat models reproduce the dysfunction in key memory aspects, typical of AD patients. Similar deficits are found in APP^{NL-G-F} knock-in rats, although only limited information is available on their phenotype so far, as this is a recent model. Neuropsychiatric changes have been examined in more detail in the TgF344-AD rats which manifest anxiety- and depression-like behaviors as well as sleep disruption. Apathy, a key symptom of AD, remains instead largely unexplored in these models.

Behavioral phenotypes in genetic rat models of Parkinson's disease: PINK1 KO, DJ-1 KO, and a-synuclein BAC rats

Typical motor symptoms in PD patients are bradykinesia, impaired fine motor skills, tremor, muscle rigidity, and deficits in gait, posture, and balance[162-164]. Homozygous *PINK1* KO and *DJ-1* KO rats display numerous abnormalities reminiscent of the human PD symptomatology. They have deficits in limb motor coordination and balance as well as rearing, gait and grip strength[46,101,165-168]. *DJ-1* KO rats additionally show postural instability[167], whereas *PINK1* KO rats display decreased locomotor activity[101,165]. Interestingly, female *PINK1* KO rats do not exhibit limb motor deficits like the ones observed in males of comparable age[169], indicating possible sex differences in the sensorimotor phenotype or in the age when the phenotype becomes manifest. Similar to the other models, the main features of motor impairments in α-synuclein BAC rats are decreased activity and rearing, impaired balance, and gait deficits, although most motor abnormalities in these rats start later compared to *PINK1* KO and *DJ-1 KO* rats[84,170,171]. Tremor, present in PD patients, was, to the best of our knowledge, not reported in the literature for any of these models. Fine paw skills for which specific assays are established in rodents[172,173] have been scarcely assessed, despite the impairments of fine motor skills and hand grasping in PD patients[162,164].

Olfactory dysfunction, dysphagia (i.e., difficulty swallowing), as well as hypokinetic dysarthria, a speech motor control disorder involving reduced voice loudness and altered articulation, are important components of PD symptomatology in a high percentage of patients[174,175]. These changes are not responsive to standard dopaminergic treatments[176], and knowledge of the underlying brain changes is rather limited.

Altered phonation in PD patients has been related to the rigidity of the phonatory posture of the larynx, and laryngeal muscle impairment has been associated with deficient motor control by the basal ganglia[174]. Moreover, an altered perception of speech volume in PD patients[177] has been suggested to result in poor control of speech production[174]. Studies in PD patients also showed deficits in the production and perception of speech-related emotions. The latter seems to be connected with cognitive impairment in the disease[177].

Vocalization in humans and ultrasonic vocalizations in rats share similar anatomical structures and neural pathways[178-182]. The periaqueductal gray, especially, plays an important role in the control of vocalization in mammals[183]. It receives motor and sensory inputs[183] as well as input from multiple limbic areas including cortex, amygdala, and hypothalamus[184-186] that could regulate social and motivational aspects of vocalization. The periaqueductal gray has also been linked to vocalization deficits in PD. This is consistent

with several results in animal models: (i) in mice overexpressing α-synuclein, vocalization deficits are paralleled by α-synuclein aggregates in the periaqueductal gray[187]; and (ii) in *PINK1* KO rats, gene expression analyses identified associations between the expression of specific gene modules in this brain region and female vocal behavior[188].

Both the *PINK1* KO and *DJ-1* KO rat models exhibit ultrasonic vocalization deficits[46,47]. *DJ-1* KO rats display an altered call profile and produce ultrasonic vocalization with decreased intensity, as reported between 2 and 8 months of age[46]. Similarly, male and female *PINK1* KO rats have a decreased ultrasonic vocalization average intensity at the same age[47,169], although opposite observations have been reported regarding ultrasonic vocalization intensity in male *PINK1* KO rats at a later age[189]. The vocalization intensity deficits in *PINK1* KO rats are stronger compared to *PINK1* KO mice[190]. The decreased ultrasonic vocalization intensity in genetic rat models resembles the decreased vocal intensity or loudness in PD subjects, which occurs in the early disease stages. Given that the vocalizations recorded in male and female rats are experimentally induced by exposure to a female and male, respectively, it remains unclear whether a possibly altered interest in the conspecific of different sex may have contributed to this phenotype in *PINK1* KO rats. This is important for two reasons: (i) decreased sexual interest and sexual dysfunction are reported in PD patients[191], and (ii) brain areas controlling vocalization in rats are also involved in sexual behavior[192,193]. Moreover, the connection of the periaqueductal gray, controlling rat vocalization, with limbic areas may involve emotional and cognitive aspects in control and in the impairment of vocalization, which would be interesting to assess in rat models of PD.

Characterization of vocalizations in *PINK1* KO male rats indicated progressively decreased peak frequency[189] and altered bandwidth[47] of frequency-modulated calls, in addition to deficits in call intensity. Although translating these changes from rats to patients seems not as straightforward as the vocalization intensity, the examined variables may be relevant indicators of vocalization dysfunction in rat models. Besides altered vocalization, similar to PD patients, both *PINK1* KO and *DJ-1* KO rats present early oromotor abnormalities[46,47,194]. Already at early ages, *DJ-1* KO rats have a decreased ability to regulate tongue force[46] and *PINK1* KO rats display an altered tongue function and biting deficits[47]. Videofluoroscopy, normally used to detect swallowing deficits in PD patients[195], showed that *PINK1* KO rats are dysphagic as assessed at the age of 4 months[194]. Hence, *PINK1* KO and *DJ-1* KO rats seem promising models regarding phenotypes of cranial sensorimotor dysfunction. However, the information on olfactory abilities in these rat models remains scarce. Sixteen-month-old DJ-1 rats were shown to have increased olfactory abilities, which is opposite to observations in patients[167]. On the contrary, analyses in the BAC α-synuclein rats detected smell discrimination impairment at 3 months, before the appearance of motor deficits[84], which would temporally mimic the manifestation of symptoms in human PD.

PD patients show non-motor symptoms, including psychiatric and cognitive symptoms, sleep disorders, and autonomic dysfunction[196-199]. Most PD patients experience disturbances such as apathy, anxiety, depression, and psychosis and several studies on PD have also reported disorders of impulsive control[197]. Even though some disturbances, for example, psychosis and impulsive control, may in part arise from or be enhanced by treatments, neuropsychiatric symptoms are already observed in the early phases of the disease[197,198,200]. Despite the obvious limitations in translating neuropsychiatric assessments between animal models and humans, genetic rodent models still offer the possibility to relate neuropsychiatric-like behaviors to relevant brain changes on multiple levels in treatment-free conditions, and to dissect their temporal dynamics. To date, neuropsychiatric-like phenotypes have not been characterized in depth in the genetic rat models described here, and the results obtained so far require further corroboration. Research on these PD genetic rat models hardly focused on apathy and impulsivity-related behaviors, although altered

motivation has been indirectly suggested in α-synuclein BAC rats, based on a faster decline in activity and a decreased exploration of the central zone of an automated cage apparatus over time, along with suppressed feeding[170]. Regarding depression, *DJ-1* KO rats show signs of behavioral despair by 6 months[167], and in *PINK1* KO female rats, there is evidence for anhedonia by the age of 8 months, whilst *PINK1* KO males were not assessed simultaneously[169]. In the α-synuclein BAC rats, both increased and decreased anxiety-like behaviors have been reported[84,201]. In the same rats, locomotor activity is enhanced in a novel environment by 3 months of age, and deficits in prepulse inhibition emerge as well at a more advanced age[201]. Both behavioral features have been associated with psychosis-like behavior in rodent models[202]. It is worth noting that the psychosis-like phenotype is stronger in α-synuclein BAC male rats relative to females, in agreement with evidence for sex differences in the PD symptomatology in patients[203]. This supports the assessment of sex differences in psychosis in the human population.

A significant percentage of PD patients suffer from a mild cognitive impairment which can convert into dementia with disease progression[196,199]. Cognitive deficits in early PD stages commonly impact several facets of executive functioning, visuospatial skills and memory and have been related to dysfunction in multiple neurotransmitter systems as well as common PD neuropathological alterations[199]. Analyses of some cognitive components have been performed in lesion rat models of PD, which present though some limitations in terms of cognitive phenotypes that can be reproduced[204,205]. On the contrary, cognition has rarely been investigated in PD genetic rat models. *PINK1* KO rats display normal recognition and spatial memory when tested at 3 months[206]. *DJ-1* KO rats were found to have altered short-term memory by 4.5 months, but unchanged goal-directed behavior[166,167]. Changes in short-term memory were also observed in *DJ-1* KO mice, but at a later age compared to *PINK1* KO rats[207]. Although it may not reflect the deficits in patients, the early rat phenotype is more consistent with the early appearance of cognitive deficits in human symptomatology, if the same temporal dynamics also apply to the familiar PD forms. In the α-synuclein BAC rats, knowledge of cognitive aspects is very limited.

In summary, all three PD rat models reflect, to a certain extent, the motor impairment in the disease. *DJ-1* KO and *PINK1* KO rats are ideal for reproducing cranial sensorimotor deficits and studying the underlying mechanisms. The α-synuclein BAC rats mimic the olfactory dysfunction and specific psychiatric features of the disease, but cognition remains scarcely examined in any of these models. Apathy, a frequent symptom in PD patients, has not been sufficiently investigated in genetic rat models of PD. Moreover, tremor, a main motor feature in the disease, does not appear to be reproduced in genetic rat models.

Behavioral phenotypes in genetic rat models of Huntington's disease: tgHD and BACHD rats

HD patients present motor impairment, cognitive deficits and psychiatric manifestations[208]. The tgHD and BACHD genetic rat models mimic many of these HD behavioral features. Compared to mouse fragment models, especially R6/2 mice, the phenotype in tgHD rats develops later and progresses at a slower pace[108,209]. Motor impairment starts earlier and has faster progression in BACHD rats compared to tgHD rats, with the first BACHD rat motor abnormalities starting at the age of 1 month[107] and the motor deficits in tgHD rats beginning at about 6 months[210]. In the tgHD rat model, phenotypes appear stronger in homozygous compared to hemizygous animals[210] and male rats were reported to be more sensitive to motor coordination impairment relative to females[211], while in the BACHD rat model, homozygous females seem to develop a stronger motor, emotional, and cognitive phenotype than males[212], although information on sex differences and homozygous animals in this model is still limited.

In general, the tgHD and BACHD rat models exhibit reduced motor coordination and balance[107,108,210,211,213,214], altered locomotor activity and rearing[107,211,213,215,216], decreased muscle endurance[215,217]

and gait abnormalities[107,213,218]. At late time points, tgHD rats are also affected by choreiform neck movements which are more frequent in homozygous individuals[219]. Prepulse inhibition of the startle response, a measure of sensorimotor gating, is decreased in HD patients[220]. In BACHD rats, there are mild sensorimotor gating deficits at the age of 9 months[213], whereas in tgHD rats, no sensorimotor deficits have been detected[216,221].

Emotional and behavioral symptoms in HD patients can precede motor symptoms by decades. A variety of psychiatric symptoms characterize the disease where apathy, depression, irritability, aggression, and anxiety are frequently reported[222]. Likewise, cognitive deficits in HD patients can be found several years before motor diagnosis[223] and are heterogeneous, embracing problems with executive function, visuomotor integration, psychomotor speed, and social cognition[224-227]. While the available tests in rodents can only partially assess the multidimensional nature of the neuropsychiatric disturbances in HD patients, emotional changes have been shown with different behavioral paradigms in HD rat genetic models. Both tgHD and BACHD rats show a low anxiety phenotype in different behavioral setups[107,108,210,211,214,228]. In tgHD rats, the emotional phenotype is already detectable at the age of 1 month, before motor deficits[210], whilst motor and emotional alterations in BACHD rats follow the opposite temporal pattern[107]. In BACHD rats, evidence for increased anxiety-like behavior was also found in specific paradigms[229], in line with human data. The contradictory anxiety phenotype remains mostly unexplained, although it could in part be dependent on age and on the different components of anxiety targeted by different typologies of behavioral tests which could in turn rely on distinct brain mechanisms. One study demonstrated that the disinhibition of the central nucleus of amygdala via $GABA_A$ receptor antagonist in BACHD rats increased avoidance and escape responses in an avoidance task as well as the social exploration in a social test[230], implicating an altered activity in the central nucleus of the amygdala as one of the mechanisms at the base of anxiety-related behavioral alterations. Further investigations of emotional phenotypes in tgHD rats revealed enhanced emotional learning in discriminative Pavlovian fear conditioning and hyperreactivity to aversive emotional events which were paralleled but not explained by shrinkage of the central nucleus of the amygdala[217].

Depression-like behavior reported in multiple studies in HD fragment and full-length mouse models[231-234] has not been studied in much detail in HD rat genetic models. An impaired hedonic reaction in response to sucrose in tgHD rats has been associated with anhedonia-like behavior[217] which was though not confirmed by later analyses[228]. BACHD rats show decreased sucrose preference at 3 months and this effect is maintained at later time points[235]. Along with hedonic deficits, BACHD rats present impaired reward-directed behavior by the age of 3 months[235], indicating a lack of motivation which could be representative of apathy, a core symptom of HD[223]. However, the BACHD rat shows notable obesity, and it is currently uncertain how that might interact with behavioral tests that are based on food rewards. Still, there do seem to be some indicators of the animals putting a lower hedonic value on small reward pellets[236,237].

A key cognitive impairment in HD is executive dysfunction. One of the main executive function deficits is impaired inhibitory control, which can be detected in specific behavioral tests in HD patients[238,239]. It was also shown in HD fragment and knock-in mouse models[240,241] and in transgenic rats[242-245]. Rat models, in general, may be advantageous over mouse models in the applied paradigms and have been largely used in preclinical research on impulsive control[246]. Impulsive-like behavior in tgHD rats was detected in both sexes at 15 months and with different strain backgrounds[243,245]. Deficits consistent with the inability to withhold inappropriate lever responses have been shown in BACHD rats already by the age of 3-4 months[242,244]. tgHD and BACHD rats further mimic several other facets of cognitive dysfunction in HD patients[223,247,248]. Deficits in both animal models were reported at different ages depending on the cognitive aspect considered. In both BACHD and tgHD rats, the first cognitive deficits were found early, at 3 and 4

months, respectively. In tgHD rats, cognitive deficits concern, among others, cognitive flexibility, attention, working memory, visuospatial and visual object memory, temporal perception and psychomotor performance[210,219,221,249-251]. BACHD rats show impaired reversal learning[111,214,252], deficits consistent with fronto-striatal dysfunction in different short-term memory tests[253], decreased performance in a decision-making task[254] and impaired associative memory[252].

Several aspects of social behavior and social cognition are abnormal in HD patients who face problems with emotion recognition and awareness as well as theory of mind and, to a certain extent, empathy, which have been associated with altered social skills and self-reported social distress[224,255-257]. Transgenic fragment and full-length HD mouse models display changes in various social behavior parameters[258-262]. Compared to mice, rats show lower group aggression[4] and are more interested in the interaction with male conspecifics[18]. Therefore, free social interaction experiments in males can be better performed in rats. Both male and female tgHD rats tend to interact more than wild-type rats with the same sex conspecific starting from 1 or 2 months of age, which was interpreted as a low anxiety-like phenotype[210,211]. An automated analysis of the BACHD rat behavior in a social interaction test between 2 and 8 months of age demonstrated alterations in multiple social interaction parameters[263]. Other analyses in the model further revealed changes in other areas of social cognition[229,263]. It is difficult to draw direct parallels between social behavior parameters measured in humans and rats as social behavior is highly species-specific. Nevertheless, given that brain correlates of social behavior are under several aspects comparable in humans and rodents[264], it is still reasonable to model main social behavior related functions in rats. Depending on age, in the BACHD rats, we find a more aggressive play behavior, decreased tendency to search for or interact with a conspecific and a decreased social preference[229,263], which in part indicates higher anxiety and may altogether be representative of a disrupted socio-cognitive function. It would then be important to relate social behavior alterations to changes in brain areas relevant to social behavior. In the BACHD rat model, in addition to the evidence for an involvement of the amygdala in the modulation of anxiety in a social context[230], a decreased BDNF gene expression was also reported in the ventral striatum[263]. While the striatum does not have a primary social function, it has been suggested to integrate social information into main striatal functions, like reward[265]. Future analyses could consider assessing the expression of markers relevant to social behavior, such as oxytocin and vasopressin[265,266], and focus on other brain areas affected in HD, like the hypothalamus, which shows changes in neuronal populations expressing these markers[267]. In HD patients, cerebrospinal fluid oxytocin levels were also found to be decreased and to correlate with social cognitive scores[268]. As part of social behavior, aggression is often reported in HD patients[255], but has not been assessed in transgenic rat models. While analyses of aggression could take advantage of well-established tests in rats, they may be sensitive to the model strain, which adds to the complexity of a phenotypic profile.

Altogether the BACHD and tgHD rat models reproduce many features of the HD triad of symptoms. Both models present motor and cognitive deficits, and some have been reproduced across studies. These rat models also display emotional alterations. The bidirectional anxiety phenotype in the BACHD rat model supports further assessments, especially in terms of underlying mechanisms. Furthermore, several phenotypes in the HD rat models and in the models of other neurodegenerative disorders have been assessed only once. Thus, their repeatability must still be determined. In addition, it remains largely unclear to what extent specific phenotypes in animal models and similar symptoms in humans share the same biological mechanisms, thereby representing the same kind of impairment.

PHENOTYPIC/ASPECT-REPLICATING MODELS TO STUDY AD, PD, AND HD

There is still a vast gap between preclinical studies to effective treatments for patients[269-271]. To date, translatability from animal models to humans in terms of treatment efficacy, adverse effects, and tolerability

has been found to often not correlate[272-274]. And likewise, a proportion of unknown size of therapeutics fails to enter the clinic, being not beneficial in animal models, though they might be effective in humans.

Despite the discouraging success rates in finding new therapies for NDs, rats have been essential for discerning many aspects of neurological functions. However, with the more readily genetic manipulation of mice and the discovery of many disease-causing genes for NDs, mice have outnumbered rats in studies evaluating behavioral aspects of neuroscientific questions in the last two decades[275]. Also, in studies describing therapeutic approaches in AD, PD, and HD, this trend towards using mice is reflected by the number of publications listed in PubMed [Figure 1].

Preclinical studies require a model to present a phenotype that is robust, fast developing, replicating key aspects of the human disease, and compatible with the form of treatment investigated. Some aspects of human disease are, however, only ever hardly modeled in animals. As one important example, cell loss is often not found in genetic models of neurodegeneration or only towards the end of the lifespan. Additionally, genetic rat models often display milder phenotypes than mouse models when based on the same construct, and these phenotypes often take relatively long to develop[276]. Therefore, we briefly describe in this section models with induced cell loss - though fairly artificial - which have helped to model neuronal demise and to evaluate therapies that can halt or even reverse this process. Commonly used models, with such induced neurodegenerative phenotypes, are summarized in Table 2. Their fast-appearing nature and cost-effectiveness, in comparison to generating new genetic rat lines, make them a resource to be relied upon frequently.

Phenotypic rat models of Alzheimer's disease

AD poses a challenge for finding appropriate models, because sporadic cases caused by mutations in AD-risk genes outnumber familial cases[285]. While rats are genetically closer to humans in terms of tau isoforms, rats seem to be more resistant to developing characteristic neuropathological features of AD when expressing human genes. They present fewer plaques and tau tangles are not present[67,276]. Injection of neurotoxins or overexpressing constructs of Aβ into the brain are commonly used to induce local cell death and to model the AD typical neuropathology. For this, the larger brain size of the rat offers advantages over mice, as stereotactic injections can be performed more consistently and with larger volumes. Additionally, these models have been mostly used in preclinical studies.

Rats with diminished cholinergic neuron populations or severed neuronal circuits show memory deficits and impaired learning[278], thereby resembling the cognitive symptoms observed in patients, but not the pathobiological origin of the disorder. Ibotenic and okadaic acid, amongst other cholinergic neuron harming compounds, or surgically lesioned rats, have been used to study neuroprotective or even regenerating therapies. Exemplary, with these phenotypic models, it was possible to demonstrate that neuronal stem cells or mesenchymal stem cells can replace or protect cholinergic neurons and improve spatial learning and memory[286-288]. Recapitulating early pathobiological events, Aβ-injected models have also been used to investigate the beneficial effects of stem cell transplantation[289-291]. It should be noted in this regard that the concentrations needed to induce the pathological phenotype by Aβ-injections exceed any physiological concentrations, and the stereotactic injections always produce unwanted tissue damage at the injection site. Genetic mouse models of AD have been used to elucidate the mechanisms underlying the observed amelioration in the genetic context of AD[292,293]. A meta-analysis of preclinical studies on stem cell therapy for AD found a large variation in the models used and origin of cells but concluded overall beneficial effects on memory and learning. Approximately 60% of the analyzed studies were performed on non-genetic rat models[294].

Table 2. Commonly used phenotypic models of NDs

	AD		AD/PD	PD	HD	
	Physical/chemical lesion of cholinergic centers	**Aβ injection**	**LPS**	**6-OHDA**	**QA**	**3-NP**
Aspect of disease reproduced	Degeneration of cholinergic neurons	Memory deficits behavioral alteration Neuroinflammation Aβ accumulation Local cell loss	Neuroinflammation cognitive deficits Aβ and tau accumulation Sickness behavior	Dopaminergic cell loss, lesions Sensitivity to apomorphine Neuroinflammation	Striatal lesions Behavioral alterations Excitotoxicity-induced cell loss	Striatal neurodegeneration of MSN Motor deterioration and behavior alterations impairs mitochondrial energy production
Acute or progressive?	Acute	Single injection (acute) Osmotic pump (progressive)	Acute, severity can be modulated by the amount of LPS challenges	Acute, compensatory mechanisms possible	Acute, chronic	Progressive over multiple injections
Pros	• Different protocols available • Easy to implement • Systemic injections are possible with some chemicals	• Rapid appearance of Aβ accumulation	• Aspects of neuroinflammation can be studied • Systemic injections	• Lesion intensity can be modulated • Dopaminergic neurons are targeted	• Similar to the pattern of cell loss in HD patients	• Systemic injections • Histological similarities to HD
Cons	• Many variables (age at lesioning, size/type of lesion, strain, *etc.*) • Limited to the lesioned brain area • No Aβ or tau pathology	• High concentration needed • Aging as a pathological factor neglected • Brain injury	• No AD/ PD-specific pathology	• Variability within animals • Compensatory effects in unilateral lesions	• Many variables (age at lesioning, size/type of lesion, strain, *etc.*)	• High inter-animal variability in lesioning • Many variables (age at lesioning, size/type of lesion, strain, *etc.*)
Literature	Reviewed in[277]	Reviewed in[277,278]	Reviewed in[279]	Reviewed in[280]	Reviewed in[281-283]	Reviewed in[284]

AD: Alzheimer's disease; PD: Parkinson's disease; HD: Huntington's disease; Aβ: amyloid beta (Aβ) peptide; LPS: lipopolysaccharide; 6-OHDA: hydroxydopamine; 3-NP: 3-nitropropionic acid; QA: quinolinic acid.

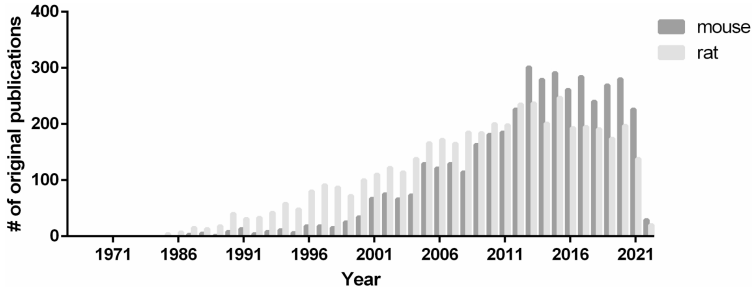

Figure 1. Studies referencing mice or rats in therapy approaches for Alzheimer's, Parkinson's and Huntington's disease. Results of PubMed search with terms "mice"/"mouse" and "rat"/"rats" in combination with above mentioned neurodegenerative disorders and "therapy". Review articles have been removed from the year in which they were published.

Aside from lesion models, what needs to be noted in AD and PD are lipopolysaccharide (LPS)-induced models, as chronic inflammation is associated with cognitive impairment in AD patients and the exacerbation of AD and PD pathology in models of the disease (reviewed in[295,296]). These models recapitulate the involvement of the immune system in the pathogenesis and show an increase in Aβ and phosphorylated tau and cognitive impairment[279,297,298].

Over the past decade, improvements in biomarker identification and quantification and improved preclinical study design have been implemented to increase translatability to human studies. Incorporating such study design, a genetic rat model has been used in a preclinical study with improved longitudinal assessment of biomarkers to improve translatability. Continuous CSF and plasma collection for measurement of Aβ and neurofilament light chain in combination with PET and MRI imaging have been used to evaluate an anti-amyloid therapy in McGill-R-Thy1-APP transgenic rats[299].

Phenotypic rat models of Parkinson's disease

Due to the multifactorial etiology of PD and most cases being of idiopathic origin, neurotoxin and lesion models are mostly relied on for preclinical Parkinson's research. The main neuropathological feature of the disease, the loss of dopaminergic neurons in the substantia nigra can be modeled through the injection of hydroxydopamine (6-OHDA) in most studies into the substantia nigra pars compacta or in the medial forebrain bundle[300]. Next to cell loss, lesioned rats show motoric deficits that are correlated to the degree of dopaminergic neuron loss, oxidative stress, and neuroinflammation[280,301]. Test paradigms have been developed to assess motor deficits, resembling akinesia, fine motor impairment, and showing rotational response to dopaminomimetic agents when extensive unilateral lesioning is produced[301]. While the lesions produced resemble cell loss in humans, unilateral lesions are mostly used in experimental settings, inducing cell loss in one hemisphere only. These lesions are mostly produced in rats, as mice are more prone to weight loss and post-lesion mortality which can be circumvented by modification of the injection sites and improved post-surgical surveillance[302-304].

Another neurotoxin model is the MPTP mouse model. In contrast to 6-OHDA, which does not cross the blood-brain barrier, MPTP can be administered systemically, but shows larger variation in neuronal loss in the substantia nigra and the motor phenotype is not fully equivalent to PD patients[305]. MPTP has been mainly used to mimic PD in mice in many different treatment studies, as rats are highly resistant to MPTP. One rat model of unilateral brain infusion with MPP+ has been developed, which shows progressive loss of dopaminergic neurons[306].

Phenotypic rat models of Huntington's disease

Only few preclinical studies have been performed in transgenic rat models of HD despite the monogenetic etiology of HD[111,307]. To a greater extent, neurotoxin models are used to model histopathological characteristics of the disease or mechanism of neuronal demise to test preventive therapies or therapies aiming at restoring functionality. The two most commonly used substances are quinolinic acid (QA) and 3-nitropropionic acid (3-NP). QA is an excitotoxin, binding to the N-methyl-d-aspartate (NMDA) receptor and more strongly affecting neurons within the hippocampus, striatum, and neocortex. It can induce different neuron and glia-damaging effects, also dependent on the dosage[308]. The lesions produced are structurally similar to HD characteristic lesions within the striatum and limited to the area around the injection site[283,309]. Impairment of paw use can be assessed in cylinder test, altered grooming behavior has been described, and learning and motoric abilities are altered in this model[310-312].

Systemic injection with 3-NP, an irreversible inhibitor of succinate dehydrogenase in the mitochondria, leads to striatal neuronal degeneration, as well. Rats are more sensitive to 3-NP than mice and develop lesions and behavioral alterations[284,313]. The lesions produced by 3-NP are more severe and cause a phenotype that includes learning impairment, reduced grip strength, and balance deficits that are more severe than in the QA model[310].

In current treatment approaches and clinical trials, HTT is lowered independently of the mutation or in an allele-selective manner[314]. Preclinical studies lowering HTT by micro-RNA (miRNA) have been performed in genetic mouse models of HD, an acute rat model of HD, a large animal model, and non-human primates[315-317]. Acute and local expression of HTT by lentiviral- or adenoviral vectors produces models that replicate typical neuropathological features HD, like aggregation and neuronal dysfunction[315,318,319]. This rat model can be used to evaluate the HTT lowering effects before a long preclinical trial is initiated, for example, by investigating behavioral readouts. Most allele selective therapies utilize heterozygous single nucleotide polymorphisms (SNPs) that are associated with the mutation-carrying allele. These therapeutic targets are only found in fractions of a population, and accordingly, they are also not necessarily present in the constructs that have been used to generate genetic models. Therefore, acute rat models can be used to test combinations and variations of SNP targeting molecules to advance personalized therapies.

CONCLUSION

Huge strides have been made towards generating genetic rat models in the past 20 years. These genetic models are an important asset for research on NDs to study physiological and pathophysiological mechanisms. Rats add to the functional understanding of disease by allowing electrophysiological measurements, harvesting of primary cell cultures and a wider range of surgical procedures. They offer the possibility to evaluate therapeutic effects more precisely due to their genetic similarities to humans, larger body size compared to mice, and the associated possibility of multiple sampling of biofluids over time. Many behavioral tests have been developed in rats, enabling a more robust assessment of behavioral phenotypes in rat models. Moreover, rats display a more complex behavioral repertoire than mice, allowing more sophisticated extrapolation to the human condition. Often efforts are being made to provide a complete characterization of the models, offering a good starting point to find an adequate fit for the biological question to be answered. Despite the long list of advantages rats offer, they are less represented in biomedical studies than mice. One reason for this is that genetic models have been generated with a delay due to the technically challenging manipulation of the rat genome. This, economic reasons, and the multifactorial etiology of many NDs have made phenotypic rat models commonly used models in preclinical research. Still today, they fill a gap when genetic models cannot reproduce certain aspects of disease, highlighting that in most cases only a combination of readouts, models, and model species can answer biomedical questions adequately. New rat models have been developed and characterized recently and can offer additional insight into disease mechanisms. Whether rats as models, combined with improved study design, can increase the translational value of biomedical research remains to be seen.

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Authors' contributions

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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