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# Progress in Developing Transgenic Monkey Model for Huntington's Disease

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## Abstract

Huntington's disease (HD) is a complex neurodegenerative disorder that has no cure. Although treatments can often be given to relieve symptoms, the neuropathology associated with HD cannot be stopped or reversed. HD is characterized by degeneration of the striatum and associated pathways that leads to impairment in motor and cognitive functions as well as psychiatric disturbances. Although cell and rodent models for HD exist, longitudinal study in a transgenic HD nonhuman primate (NHP; i.e. rhesus macaque; HD monkeys) shows high similarity in its progression with human patients. Progressive brain atrophy and changes in white matter integrity examined by magnetic resonance imaging (MRI) are coherent with the decline in cognitive behaviors related to corticostriatal functions and neuropathology. HD monkeys also express higher anxiety and irritability/aggression similar to human HD patients that other model systems have not yet replicated. While a comparative model approach is critical for advancing our understanding of HD pathogenesis, HD monkeys could provide a unique platform for preclinical studies and long-term assessment of translatable outcome measures. This review summarizes the progress in the development of the transgenic HD monkey model and the opportunities for advancing HD preclinical research.

### Keywords

Transgenic animal model; nonhuman primates; Huntington's disease; comparative animal models

## Introduction

Neurodegenerative disorders such as Parkinson's disease (PD) and Huntington's disease (HD) that severely impair basal ganglia functions are complex disorders that lead to motor and/or psychological impairments. Different models from cell culture to rodents to nonhuman primates (NHPs) have been developed to investigate disease mechanisms and

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develop cures for PD and HD. The key for clinical translation to assess effective diagnostics and the therapeutic efficacy of novel treatments has relied on the development of animal models with measurable clinical and pathological features consistent with those seen in human patients. In that regard, this review will highlight the progress made towards the development of a transgenic HD monkey model. Data from these animals will be compared with those gathered from various rodent HD models. The advantages and challenges in developing such an animal model will be discussed.

## Brief Overview of Basal Ganglia

The basal ganglia play a key role in motor and non-motor functions affected in various brain disorders including PD and HD. The basal ganglia consist of the dorsal striatum that comprises the caudate nucleus and putamen, and the ventral striatum that comprises the nucleus accumbens and olfactory tubercle. In general, the caudate nucleus can be subdivided into the head, body and tail (Yeterian and Van Hoesen 1978). Although the caudate nucleus and putamen are separated by the internal capsule and often referred to collectively as the dorsal striatum in primates, they are functionally distinct with the putamen involved in sensorimotor processing while the caudate nucleus is involved in cognitive functions (Hewitt 1961; Smith et al. 2014). Basal ganglia nuclei also include the pallidum that is comprised of the internal and external segments of the globus pallidus (GP) in primates, which is referred to as GPi and GPe, respectively. The subthalamic nucleus (STN) is another important structure in the basal ganglia. Moreover, the substantia nigra is comprised of two sub-nuclei. The substantia nigra pars compacta (SNc) contains dopaminergic neurons and the substantia nigra reticulata (SNr) contains GABAergic projection neurons.

The striatum receives input from nearly all of the cerebral cortex. In the dorsal striatum, major cortical inputs originate from associative and sensorimotor cortices (Selemon and Goldman-Rakic 1985), while the ventral striatum receives its main cortical input from limbic cortices. Although relatively homogenous in cell density, acetylcholinesterase staining (and other neurochemical markers) reveal a patchwork pattern to the striatum (Graybiel and Ragsdale 1978), referred to as striosomes and matrix compartments. Dysregulation of this compartmentation may be involved in the development of repetitive motor behaviors (Canales and Graybiel 2000).

Striatal neurons can be categorized as projection neurons and interneurons. The main projection neurons are medium spiny neurons (MSNs). These GABAergic neurons are found in both the striosomes and matrix, accounting for over 90-95% of the total neuron population in the rat striatum (Fujiyama et al. 2011; Kawaguchi et al. 1989; Oorschot 1996; Penny et al. 1988). MSNs of the striosomes receive input from the corticolimbic cortex and amygdala, and project to the SNc (Fujiyama et al. 2011; Graybiel and Ragsdale 1978; Kawaguchi et al. 1989; Kincaid and Wilson 1996). Matrix MSNs mainly receive input from the sensorimotor cortex and nigrostriatal pathway and project to the GP and SNr (Fujiyama et al. 2011; Graybiel and Ragsdale 1978; Kawaguchi et al. 1989; Kincaid and Wilson 1996).

The direct and indirect pathway model has been widely used for the understanding of basal ganglia functions (DeLong 1990). The direct pathway is comprised of neurons that

preferentially express D1 dopamine receptors, substance P and dynorphin, and project directly to the GPi and SNr via monosynaptic connections that link the striatum and basal ganglia output nuclei. Selective activation of this pathway is thought to facilitate locomotion, likely through disinhibition of thalamocortical neurons from their tonic GABAergic control by the basal ganglia output nuclei (Freeze et al. 2013; Roseberry et al., 2016). On the other hand, the indirect pathway is comprised of neurons that preferentially express D2 dopamine receptors and enkephalin and project to the GPe and the STN via polysynaptic pathways that link the striatum and GPi/SNr. The indirect pathway is considered as the NO-GO pathway because its selective activation decreases locomotion, most likely through increased basal ganglia inhibitory tone over thalamocortical neurons that reduces cortical outflow (Freeze et al. 2013; Lim et al. 2014; Roseberry et al., 2016, Sato and Parent 1998). The distinct functions of the two pathways allow bidirectional modulation of the basal ganglia network. Normal basal ganglia function relies on balanced activity between these two pathways (Lim et al. 2014).

The functions of the direct and indirect pathways are mediated through the GABAergic MSNs, the principal output cells whose activities are regulated by striatal interneurons (Hu et al. 2014; Lim et al. 2014). There are four main types of striatal interneurons based on their neurochemical content which include (1) choline acetyltransferase (ChAT), (2) parvalbumin (PV), (3) calretinin (CR) and (4) neuronal nitric oxide synthase (NOS), β-nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d), somatostatin (SS) and neuropeptide Y (NPY) (Figueredo-Cardenas et al. 1996; Hu et al. 2014; Lanciego et al. 2012; Maurice et al. 2015; Petryszyn et al. 2014; Petryszyn et al. 2017; Smith et al. 2014; Wu and Parent 2000). Morphological heterogeneity among striatal interneurons are well described in rats, monkeys and humans (Petryszyn et al. 2014). Striatal interneurons constitute approximately 20%-25% of all striatal neurons in primates, but only 2–3 % in rodents (Graveland and DiFiglia 1985; Graveland et al. 1985; Tepper and Bolam 2004). Cholinergic (or ChAT) interneurons in the striatum are large and aspiny (Lim et al. 2014). Cholinergic interneurons are categorized as tonically active neurons (TANs) and play a key role in dopamine-dependent striatal plasticity, reward-related learning and motivated behaviors (Aosaki et al. 1994; Apicella 2007; Wang et al. 2006). Parvalbumin (PV) interneurons are also named GAGAergic fast-spiking parvalbumin-positive interneurons that are involved in feedback and feedforward inhibition of projection neurons activity (Hu et al. 2014; Lee et al. 2017). Recent study demonstrated that suppression or over-activation of PV interneurons activity can regulate MSN firing (Lee et al., 2017), which provides evidence for their key regulatory role in striatal microcircuits to enhance early stage learning (Lee et al. 2017; Xu et al. 2016). Calretinin (CR) interneurons are the most abundant striatal interneurons in nonhuman primates and humans (Petryszyn et al. 2014; Wu and Parent 2000). The rodent striatum comprises primarily medium-sized CR interneurons, while the monkey and human striatum contain both large and medium-sized CR interneurons that create an elaborated network (Petryszyn et al. 2017). Moreover, large-sized $CR^+/ChAT^+$ striatal interneurons are only found in monkeys and humans, but not in rodents, which further suggests their crucial role in striatal functions in primates (Petryszyn et al. 2017). The fourth population of striatal interneurons co-express NADPH-d/SS/NPY/NOS and are categorized as “persistent and low-threshold spike” neurons (Kawaguchi et al. 1995; Smith et al. 2014). However,

variations in the quantity and combination of these chemicals were observed, suggesting unique functional roles, perhaps even related to neurodegeneration and excitotoxicity (Figueredo-Cardenas et al. 1996). Overall, the basal ganglia regulate activity of multiple brain regions in order to control motion function, motor learning, executive functions, and emotions (Lanciego et al. 2012). Additional details about the function and anatomy of the basal ganglia can be found in other reviews part of this Special Issue.

## HD Symptoms

HD patients display a variety of symptoms that can be classified as motor, cognitive or psychiatric in nature. Although motor symptoms of the disease are often the most notable and the reason for the initial name “Huntington’s chorea,” a multidimensional approach assessing all three impacted areas may be more appropriate for diagnosis (Biglan et al. 2013; Rub et al. 2016). One of the earliest motor symptoms of HD is impairment of eye saccades (Rub et al. 2016; Tabrizi et al. 2012). Many juvenile-onset patients also experience rigidity and seizure (Cloud et al. 2012; Geevasinga et al. 2006; Nance and Myers 2001; van Dijk et al. 1986). Patients quickly deteriorate in motor ability (Roos 2010; Ross et al. 2014; Tabrizi et al. 2012; Tabrizi et al. 2013), most notably in bradykinesia and chorea (Biglan et al. 2013).

Other early symptoms include cognitive deficits such as speech delay in juvenile-onset HD (Solomon et al. 2007; Yoon et al. 2006). In fact, mild cognitive deficits may be noticed before formal diagnosis (Lawrence et al. 1998; Tabrizi et al. 2012; Vaccarino et al. 2011). In a study in which subjects were asymptomatic but genetically confirmed for the HD mutation, there were already signs of cognitive decline (Lawrence et al. 1998). These “preclinical” subjects showed deficits in attention set shifting with significantly more errors than non-carriers on a visual discrimination test involving an extradimensional shift. Cognitive symptoms progress as disease severity increases. In early stages of symptomatic HD, patients started showing “subcortical” dementia, with errors in executive function like planning and decision-making which is different from Alzheimer’s disease (Lawrence et al. 1996). These early-stage HD patients were also significantly worse at pattern and spatial recognition, exhibited shortened spatial span, used a less efficient search strategy during spatial working memory tasks, had slower thinking times and continued to show difficulty with attention set shifting. At advanced stages, patients experienced more widespread dementia that included temporal lobe and hippocampal cognition (Lange et al. 1995). Most patients have difficulty with memory recall (Zizak et al. 2005), specifically immediate memory recall (Ho et al. 2003). Primary deficits include decreased processing speed, decreased attention, difficulty with initiation, poor executive function independent of medication, motor impairment or altered psychological state (Bates et al. 2015; Beglinger et al. 2010; Duff et al. 2010; Ho et al. 2003; Paulsen et al. 2013; Peavy et al. 2010; Ross et al. 2014; Tabrizi et al. 2013). These studies suggest cognitive decline begins pre-symptomatically and progressively worsens along with the disease course in HD patients (Beglinger et al. 2010; Duff et al. 2010; Stout et al. 2011).

Psychiatric symptoms include aggression, affective disorders, irritability, obsession-like symptoms, behavioral disorders and personality disorders (Berrios et al. 2001). Perhaps the

first psychiatric symptoms include apathy (Tabrizi et al. 2013) and difficulty recognizing emotion (Tabrizi et al. 2012). Depression is common and suicide is increased in HD patients compared to the general population (Di Maio et al. 1993). Some have suggested that the presence of psychiatric symptoms, such as affective disorders like depression, may be genetically linked to the family tree (Folstein et al. 1983). In fact, this study showed that in certain families, depression rates were as high as 41% and began as many as 20 years before HD onset. Suicide is a major concern in HD, even being noted as a feature of the illness in Huntington's original description (Huntington 1872). There is not only an increase in suicide rates among HD patients, but also in patients who are suspected of having HD, but have not yet been diagnosed (Di Maio et al. 1993; Schoenfeld et al. 1984). This suggests that psychiatric symptoms may actually peak during early stages of the illness and not related to the diagnosis itself.

Many of these symptoms result from damage to the pathways connecting to and from the striatum or secondary brain regions affected by HD. Oftentimes rodent models are limited from replicating the HD phenotype seen in patients (Chan et al. 2015; Howland and Munoz-Sanjuan 2014; Morton and Howland 2013; Pouladi et al. 2013). No effective treatment has been developed based on successful outcomes in rodent models of HD which is largely due to inherent differences between the two species, but new rodent models are being developed with better representation of human conditions including neuropathology and molecular mechanisms (Alexandrov et al. 2016; Ament et al. 2017; Howland and Munoz-Sanjuan 2014; Pouladi et al. 2013). There is no doubt that rodent models will continue to be a relevant model for elucidating HD pathogenesis and assessing new therapies (Crook and Housman 2011); however, it is also clear that a large preclinical animal model is needed that could better capture a broader, if not full, spectrum of progressively evolving clinical symptoms in human HD patients (Chan et al. 2015; Howland and Munoz-Sanjuan 2014; Morton and Howland 2013; Pouladi et al. 2013).

## Huntington Disease Overview-Genetics and Pathology

HD is a genetic disorder caused by an unstable CAG expansion at the N-terminus of the Huntingtin (*HTT*) gene (MacDonald et al. 1993; Snell et al. 1993). HD is characterized by neuronal aggregates and cell loss initially at the striatum (Alzheimer 1911; Jelgersma 1908) and cerebral cortex, which subsequently extend to other brain regions (Sapp et al. 1997). With CAG repeats above 40, individuals are at risk for developing HD (Gil and Rego 2008; Langbehn et al. 2010; Li and Li 2006; Ross et al. 2014). The CAG expansion in the precoding region for *HTT* causes misfolding of the HTT protein and the formation of HTT aggregates (Bates et al. 2015; Crook and Housman 2013; DiFiglia et al. 1997; Gupta et al. 2012; Sieradzan et al. 1999). These changes result in oligomerization and aggregation of HTT in neurons throughout the brain, disrupting cellular functions including transcriptional dysregulation of BDNF and impairment of proteostasis that have led to the loss or alteration of neural functions such as synaptic dysfunction, mitochondrial toxicity and impairing axonal transport, thus resulting in the elevation of glutamate, reduction of BDNF and neuronal death (Bates et al. 2015; Crook and Housman 2013; Sieradzan et al. 1999).

HD aggressively targets the GABAergic MSNs of the striatum (Crook and Housman 2013; Davies and Ramsden 2001; Gil and Rego 2008; Li and Li 2006; Ross et al. 2014), affecting both the direct and indirect pathway with earlier pathology in the indirect pathway neurons (Deng et al. 2004; Vonsattel and DiFiglia 1998). Mouse models for HD suggest that aggregates in the MSNs precede symptom onset (Laforet et al. 2001). The first areas of the striatum compromised include the caudal putamen, the tail of the caudate nucleus and the dorsomedial head of the caudate nucleus (Rub et al. 2016; Rub et al. 2015; Tabrizi et al. 2012; Vonsattel et al. 1985). During early stages of the disease, nuclear inclusions and cell loss increase and spread through the rest of the striatum that lead to degeneration of the GPe, SNr and SNc (Deng et al. 2004; Rub et al. 2016; Rub et al. 2015). Although there is significant loss of projection neurons such as MSNs, the interneurons are often spared in HD (Petryszyn et al. 2017). For example, the sparing of the CR interneurons has been suggested for their neuroprotection role in maintaining intracellular calcium homeostatsis via calcium binding property of calretinin (Petryszyn et al. 2017). Direct interaction between CR and mutant HTT (mHTT) has been demonstrated *in vitro* while over expression of CR can ameliorate mHTT induced cytotoxicity (Dong et al. 2012). In the cerebral cortex, isocortical layers III, V and VI show the most severe cell loss (Rub et al. 2015). As the disease progresses, secondary structures such as the motor and limbic pathways of the thalamus, cerebellum, oculomotor nuclei of the brainstem, pontine nucleus, inferior olive, reticulo-tegmental pons, raphe nucleus, superior olive and vestibular nuclei are also implicated (Rub et al. 2015). It has been theorized that HD is a multisystem degenerative disease in which all affected structures are connected to well-known targets, but spread far beyond the striatum and its cortical circuits (Lange and Aulich 1986; Rub et al. 2013; Vonsattel 2008). An fMRI study suggested that impairment is due not simply to atrophy of these structures, but to decreased connectivity (Dumas et al. 2013). Even presymptomatic HD patients showed signs of decreased connectivity of the left frontal, right parietal and bilateral visual cortices (Dumas et al. 2013). A recent report on changes in white matter of HD monkey further support the widespread progressive temporal-spatial microstructural changes of fiber bundles connecting cortical areas to the striatum as disease progress (Meng et al. 2017). Clearly the neural pathology of HD is a complex multisystem disorder and not limited to the striatum and cerebral cortex.

## HD animal models

### Mouse HD models

Many transgenic mouse models have been developed and used extensively in HD research trying to replicate human HD conditions to find a cure for HD. These include transgenic mice expressing the N-terminal of the HTT gene(Davies et al. 1997; Schilling et al. 1999), transgenic mice expressing full-length HTT (Slow et al. 2005) and CAG repeats knock-in mice (Ament et al. 2017; Holter et al. 2013; Kumar et al. 2016; Wheeler et al. 2000). Among the wealth of HD mouse models, R6/2 and N171-82Q are two of the most commonly used models in HD research. Both models were developed about 20 years ago and were very well characterized (Mangiarini et al. 1996; Schilling et al. 1999). The R6/2 mouse carries exon 1 with 115-156 CAG repeats and 262 base pairs of intron 1 under control of the human *HTT* promoter (Mangiarini et al. 1996). R6/2 mice show signs of motor deficit between five to six

weeks, failure to gain weight at seven weeks, neurodegeneration at 10 weeks, and death between 12-14 weeks (Stack et al. 2005; Turmaine et al. 2000; Wade et al. 2008). N171-82Q mice carry a 171 amino acid fragment of human HTT with 82 CAG repeats under control of the mouse prion promoter (Schilling et al. 1999). N171-82Q mice fail to gain weight at eight to10 weeks, show motor deficit at 12 weeks, develop neurodegeneration at 16-20 weeks and die at 24-30 weeks (Li et al. 2003; Saydoff et al. 2006).

### Monkey HD model

In addition to rodent models, the recent development of HD monkeys has led to a new interest in transgenic nonhuman primate modeling of human diseases (Jennings et al. 2016; Niu et al. 2015; Niu et al. 2014; Yang et al. 2008). Longitudinal assessment continues throughout the lifespan of HD monkeys and is ongoing. A current effort is underway to establish a self-sustainable colony and the production of HD monkeys for HD research community with emphasis in preclinical research. One key distinction between rhesus macaque and humans is the *HTT* gene in rhesus macaques carries only 10-11 CAG repeats while threshold for CAG repeats in human HD is ~35 (Bates et al. 2015; Putkhao et al. 2013). To date, data from eight HD monkeys have been reported, and five of them were part of a longitudinal study since they were one week old (Berrios et al. 2001; Chan et al. 2015; Chan et al. 2014; Kocerha et al. 2013; Meng et al. 2017; Yang et al. 2008). rHD1-5 carried exon 1 of the human *HTT* gene regulated by human polyubiquitin-C promoter, which expressed N-terminal 67 amino acids. rHD1 carried a single copy of the transgene with 29 CAG repeats and rHD2 had two copies of the transgene with 83 CAG repeats (Chan et al. 2014; Yang et al. 2008). rHD3 expressed 84 CAG repeats with two copies, rHD4 expressed 27 CAG repeats with two copies and rHD5 expressed 88 CAG repeats with two copies (Yang et al. 2008). rHD3-5 were euthanized soon after birth due to severe motor impairment. rHD6, 7 and 8 carried exons 1-10 of the human *HTT* gene coding N-terminal 508 amino acids with 67-72 CAG repeats under control of the human *HTT* promoter (Chan et al. 2015; Kocerha et al. 2013; Meng et al. 2017; Raper et al. 2016).

## Comparative neuropathological hallmarks of HD Patients to HD Mice and NHPs

As mentioned, neuropathology in HD patients begins in the striatum and cerebral cortex (Alzheimer 1911; Jelgersma 1908; Rub et al. 2016; Sapp et al. 1997). It then follows the circuitry of the striatum to affect widespread regions of the brain in later stages of the disease (Rub et al. 2015; Vonsattel et al. 1985). Both R6/2 and N171-82Q express high levels of the mutant HTT in the brain. Immunohistochemistry revealed nuclear aggregates of mutant HTT in the striatum of both mouse models. Striatal atrophy is found in the R6/2 model with up to 25% neuronal loss (Stack et al. 2005). Cortical and striatal atrophy is also found in the N171-82 Q model (Aggarwal et al. 2012). Ultimately, atrophy of the thalamus, hippocampus and piriform cortex occurred in the R6/2 model (Aggarwal et al. 2012). The N171-82Q mice also showed significant atrophy of the neocortex, hippocampus, piriform cortex and amygdala by the end of the disease at five to six months of age (Aggarwal et al. 2012). Furthermore, changes in neural activity of the GPe and decreased connectivity of the

MSNs of the indirect pathway in R6/2 mice were also observed (Akopian et al. 2016; Cepeda et al. 2013).

Similar to HD rodent models, post-mortem brain tissues of infant HD monkeys (rHD4 and 5) revealed high levels of mutant HTT aggregate in the striatum, cerebral cortex, hippocampus and cerebellum (Fig 1a). Widespread nuclear inclusions and axonal aggregates of mutant HTT were also observed throughout the striatum and cerebral cortex (Fig 1b–f). Axons appeared dystrophic and fractured, indicating distress and degeneration (Wang et al. 2008). Recent studies on two adult HD monkeys (rHD1 and rHD7) at five years of age reveal the accumulation of mHTT aggregate, intranuclear inclusions and extensive neuronal loss in the striatum, but with a distinct pattern correlated with genotypes and expression levels of the *mHTT* transgene (Chan et al. 2015). rHD1 had significant loss of striatal mass while rHD7 retained comparable volume with control monkeys even with a significant decrease in neural cells, suggesting ongoing neurodegeneration in rHD7 (Chan et al. 2015). Together with progressive decline in cognitive and motor impairment in these animals, neuropathology supports the dysfunction in the fronto-striatal pathways and abnormal striatal outflow (Chan et al. 2015). Although neuropathological studies on HD monkeys are limited due to the number of available animals and resources, further in-depth neuropathological study on HD monkeys and comparison with rodents and humans will provide insightful mechanisms on HD pathogenesis.

Using MRI, brain volume changes were observed in a small cohort of HD and wild-type control monkeys with respect to age. The rate of the change in brain volume was influenced by mutant *HTT* transgenes. rHD1 had the highest mutant HTT expression and heavily aggregated mutant HTT protein and exhibited a significantly faster reduction rate in striatal volume and enlargement of lateral ventricles compared to the controls (Fig 2a, b) and HD monkeys (rHD6-8s) with lower mutant HTT expression (Chan et al. 2015). These results suggest progressive striatal atrophy, similar to that seen in HD patients. *In vivo* proton magnetic resonance spectroscopy (MRS) for N-acetylaspartate (NAA) was used to assess neuronal survival (Chan et al. 2015). MRS data showed decreased NAA in the caudate nucleus and putamen of HD monkeys compared to the controls, suggesting the loss of striatal neurons (Fig 2c). Stereological counting of cells in the caudate nucleus and putamen of post-mortem brain sections indicated a decrease, not just in striatal volume, but in the number of neurons in both the caudate nucleus and putamen (Fig 2d, e). Interestingly, rHD1 and rHD7 carried two distinct mutant *HTT* transgenes in which rHD1 developed at a more rapid rate of striatal atrophy and cell loss. Although MRI did not reveal significant striatal atrophy in rHD7 compared to the controls, MRS and post-mortem neuropathology indicated significant reduction in neurons that further suggest a slower progression rate occurred in rHD7 compared to rHD1, while the loss of striatal neurons preceded the loss of striatal volume (Chan et al. 2015). These results indicate progressive death of striatal neurons, not simply shrinkage or glial cell loss as disease progress in HD monkeys (Chan et al. 2015). Recent study on white matter integrity of HD monkeys by longitudinal diffuse tensor imaging (DTI) reveals progressive changes in whole brain white matter as disease progress from infancy to adulthood (Meng et al. 2017). Thus the combination of noninvasive structural MRI and MRS is important to reveal HD status of the affected areas because compensatory response to neuronal cell loss might occur to maintain physical mass of the

areas at early stages of the disease. Together with DTI, noninvasive MR imaging can be used as a powerful diagnostic tool for clinical assessment.

While neuropathological assessment of HD monkeys is ongoing and very limited data is available for comprehensive comparison with rodent models and human patients, encouraging data including evidence of axonal aggregates, cell distress and neurodegeneration revealed in HD monkey brain suggest the resemblance between HD monkeys and humans patients. Even though neuropathology of HD monkeys may be similar to that seen in HD patients, in-depth analyses with additional HD monkeys in the future is critical to fuhrther confirm and support our findings, thus to better assess the potential of the HD monkey model in HD translational research.

## Cognitive behavioral assessment in HD rodents and monkeys

Perhaps the most notable symptoms for HD are motor deficits, with the hallmark feature being a dance-like movement called chorea (Huntington 1872). Many patients also experience rigidity and bradykinesia (Biglan et al. 2013). Although not as obvious, oculomotor impairment is often one of the first symptoms to present (Tabrizi et al. 2012; Rub et al. 2015).

Several tests have been developed to evaluate motor deficits in mice. These tests include swimming, walking across a narrow beam and walking or running on a spinning rod. However, some mouse models such as the short-stop and C6R models never show motor deficit (Wang et al. 2008). R6/2 mice begin to display motor symptoms as early as five to six weeks and N171-82Q mice start showing deficits after 12 weeks (Pouladi et al. 2013; Wang et al. 2008). In the swimming tank test where mice swim to a platform to escape the water, R6/2 mice displayed abnormal front and hind limb kicking (Carter et al. 1999). This abnormal swimming stroke caused them to take longer to reach the platform than control mice. As animals age, R6/2 mice also showed decreased speed in beam walking, with some even falling off the beam during late stages of sickness (Carter et al. 1999). N171-82Q mice also showed decreased speed crossing the beam (Southwell et al. 2009). On the spinning rotarod test, both R6/2 and N171-82Q mice progressively worsened on maintaining balance on the spinning rotarod (Carter et al. 1999). However, N171-82Q mice did not exhibit difficulty until five months of age (Southwell et al. 2009). With age, R6/2 mice began to show gait abnormalities, most notably with reduced stride length and increased front/hind paw overlap (Carter et al. 1999), while N171-82Q mice showed abnormal gait characterized by hyperkinesia and rigidity (Preisig et al. 2016).

Compared to HD rodents, HD monkeys with severe impairment presented with dystonia, chorea, difficulty swallowing and difficulty breathing as early as at birth (Yang et al. 2008). In order to evaluate motor impairment over time, a rating scale, Huntington’s Disease Primate Motor Rating Scale (HDPMRS), similar to that used in patients was developed. Using a scale of 0-4, the test assesses ability, bradykinesia, rigidity, dystonia and chorea in various regions of the body. HD monkeys had an elevated score on the assessment compared to age-matched controls at two years of age (Chan et al. 2014). Lower limb dystonia was the most noticeable deficit. Motor impairment interfered with cognitive testing around 16

months of age and was measured by the object discrimination reversal (ODR) and detour reaching/barrier task. In this study, monkeys had to reach around a barrier to retrieve a reward such as M&M candy. The HD NHPs had significantly more motor-related problems with reward retrieval on both easy and difficult tasks (Fig 3) (Chan et al. 2015; Chan et al. 2014). These findings aligned with neuropathology of rHD1 and rHD6, 7 & 8 which suggest fronto-striatal dysfunction as discussed previously. rHD1 also presented with tonic-clonic seizures around 22 months of age. Seizure is commonly developed in a juvenile form HD patient rather than an adult form (Cloud et al. 2012; Geevasinga et al. 2006; van Dijk et al. 1986). Overall, motor impairment gradually increased with age in HD monkeys (Chan et al. 2015; Chan et al. 2014).

In addition to motor symptoms, HD patients also experience cognitive difficulties. Oftentimes, patients are already showing signs of cognitive impairment at the onset of motor symptoms (Duff et al. 2010; Paulsen et al. 2013; Peavy et al. 2010; Stout et al. 2012; Vonsattel and DiFiglia 1998). Speech and language delay, psychiatric and cognitive difficulties were observed in juvenile HD (Ribai et al. 2007; Yoon et al. 2006). Cognitive deficit in HD is very different from dementia in Alzheimer's disease. Impairment in HD is most notable with attention shifting and executive function (Lawrence et al. 1996), with more global deficits in late stages of the disease (Lange et al. 1995).

In the spatial learning task called the Morris water maze, R6/2 mice acquired the task as easily as control mice (Lione et al. 1999). However, they failed to continue to improve on subsequent trials like control mice did starting at nine weeks of age (Fink et al. 2013). This difference was not due to motor impairment, as swimming speed was no different between the two groups until day 16 of testing when R6/2 mice began to swim more slowly (Lione et al. 1999). These findings indicate that the mice were not impaired at learning pre-symptomatically, but showed cognitive decline after onset of motor symptoms. Additionally, a two-choice tank swim test was used to test visual and reversal discrimination. Once HD mice became symptomatic, their ability to acquire this task severely decreased (Lione et al. 1999; Menalled and Brunner 2014; Oakeshott et al. 2013). The HD mice also failed to learn reversal discrimination at older ages using light as a visual stimulus. R6/2 mice were significantly worse than control mice at alternation tests in a T maze (Lione et al. 1999). These results show cognitive decline in R6/2 HD mice can be assessed.

Due to the much longer lifespan of monkeys, age-appropriate behavioral tests can be designed throughout life. Both control monkeys and rHD1 showed normal acquisition of cognitive tasks early in life (Chan et al. 2014). This finding showed normal cognitive development, which is consistent with that of HD patients. However, with age, rHD1 showed deterioration of cognitive skills. At eight months, there was a delay on a pattern discrimination test (Fig 4a). By nine months, rHD1 consistently failed to reach criterion for a discrimination task when all age-matched control NHPs were successful (Fig 4b) (Chan et al. 2014). These tests evaluate function of the striatocortical loop, meaning that the neuropathology seen in these monkeys was producing a cognitive deficit similar to that of humans. In an object discrimination task meant to test prefrontal cortical function, this same HD monkey was making almost twice the mistakes of control monkeys at 16 months. This difference was notable for barrier and perseveration reaches in both moderate and difficult

version of the test (Fig 4c, d). rHD1 also showed impairment on a recognition memory task testing the function of the medial temporal lobe and hippocampus. Impairment was seen as early as four months and persisted through the 16-month testing (Fig 4e, f). In addition to rHD1, three additional HD monkeys (rHD6-8s) with expectation of slower disease progression also participated in similar cognitive testing (Chan et al. 2015). At eight months, they performed more barrier reaches and perseveration errors than age-matched control monkeys (Fig 5a, b). Interestingly, at 36 months, they showed increased latency on a visuomotor lifesaver task in which they had to remove candy lifesavers off a metal rod that could not be ascribed to motor deficits (Fig 5c, d). All monkeys acquired tasks normally, which indicate normal cognitive development. Based on the aforementioned reports, HD monkeys displayed cognitive deficit with increasing age (Chan et al. 2015).

HD monkeys displayed progressive cognitive deficits similar to those of HD patients that exhibit damage to subcortical processing as well as executive functions of the prefrontal cortex. It is important to note that an ongoing effort is to characterize the HD monkey model from infancy and throughout their lifespan in order to lay out the disease development timeline with milestone clinical events. Although this is an ongoing study, recent reports suggest the promise and potential of the HD monkey model in facilitating the finding of HD cures. Nonetheless, future study in a larger cohort of HD monkeys will help in compiling necessary data before cognitive therapies could be effectively tested using only the NHP model.

Psychiatric disturbance is one of the clinical areas that most HD patients also experience (Killoran and Biglan 2012; Raper et al. 2016; Ross 2004; Thompson et al. 2012). Psychiatric impairment may not be linked to other markers of disease course or symptoms, but rather they seem to develop independently (Zappacosta et al. 1996). Symptoms include aggression, irritability, affective disorders, behavioral disorders and personality disorders (Berrios et al. 2001; Bouwens et al. 2015; Dale and van Duijn 2015; Paulsen et al. 2005; Van den Stock et al. 2015). Depression is common (Paulsen et al. 2005), and suicide is increased in HD patients compared to the general population (Di Maio et al. 1993).

Studying the psychiatric status of mice is a challenging task with limitations that might be difficult to overcome. Open field-testing is one of the most common methods to study emotions such as fear. Depression in mice can be studied by using a forced swim test in which “depressed” mice float instead of swimming or trying to climb out. R6/2 mice show increased tendency of floating shortly after symptoms emerge when compared to control mice on a forced swim test, suggesting possible depression (Ciamei et al. 2015). Monitoring home cage behavior such as grooming, fighting and time spent in groups are also commonly used for evaluating mouse psychiatric conditions. However, quantitative measurement of psychiatric behavioral changes such as emotion and mood swing remains challenging and difficult in rodents due to limitation in quantitative tools for measuring progression of a broad spectrum of psychiatric symptoms observed in HD patients.

Assessment of psychiatric changes in NHPs is feasible and well established (Raper et al. 2016). Acute stressor has been successfully used to measure emotional and hormonal responses in nonhuman primates including HD monkeys (Kalin and Shelton 1998; Raper et

al. 2016; Raper et al. 2013). HD monkeys were evaluated at five years of age, which is the equivalent to a young adult human. At this age, HD monkeys showed increased coo vocalizations (Fig 6a). Baby monkeys usually use this call to try to re-connect with their family. Using a coo vocalization at this age and in this way suggests increased anxiety (Hauser 1991; Pfefferle et al. 2014; Rowell and Hinde 1962). They also showed less freezing compared to age-matched control monkeys (Fig 6b), but increased hostility (Fig 6c). These two findings combined suggest that, although HD monkeys may exhibit decreased fear, they also have increased anger and aggression (Raper et al. 2016). In fact, one of the HD monkeys, rHD1, had to be stopped from visuospatial cognitive testing due to self-injurious behavior developed during testing (Chan et al. 2015). Study on emotional dysfunctions in adult HD monkeys strongly suggested the development of increased anxiety and irritability/aggression and are parallel with hyperactivity in innate immune response (Raper et al. 2016). Similar observation has also been reported in human HD patients (Bjorkqvist et al. 2008; Bouwens et al. 2015; Dale and van Duijn 2015; Forrest et al. 2010; Paulsen et al. 2005; Shannon and Fraint 2015; Van den Stock et al. 2015; Vassos et al. 2007; Wild and Tabrizi 2014). Due to the high homology in socio-emotional behavior between humans and NHPs (Watson and Platt 2012; Yue et al. 2014), findings in HD monkeys further suggest their potential in replicating progressive psychiatric disturbance in HD patients which is important in understanding HD pathogenesis and developing early diagnostic tools as well as novel cures for HD. One of the ongoing efforts is to develop a cohort of second generation HD monkeys and establish a small social group, thus progressive decline in psychiatric functions and change in social behavior can be closely monitored and possible biological markers can be identified to reveal disease progression and translation readiness.

Anxiety, aggression, irritability and self-injurious behavior have all been identified in HD patients and in HD monkeys (Dale and van Duijn 2015; Raper et al. 2016; Van den Stock et al. 2015; Vassos et al. 2007). The HD monkey model provides a unique opportunity and platform for understanding how HD impacts psychiatric behaviors. To date, no effective treatments have been developed using the currently used HD mouse models (Wild and Tabrizi 2014). With further characterization, HD monkeys can be a potential preclinical large animal model to study all three aspects of the disease; motor, cognitive and psychiatric. Thus novel therapeutics, or combinations of therapies, can be evaluated by assessing all symptoms simultaneously.

## Discussion

Over the past several decades, NHPs have provided models for various diseases, many of which have resulted in successful therapies and vaccines. For example, deep brain stimulation, a commonly used and highly successful treatment for Parkinson’s disease, was first tested in a NHP model for the disease (Benazzouz et al. 1993) and later corroborated in patients (Limousin et al. 1995). Nonetheless, practicality and ethical boundaries should be cautiously assessed prior to considering the NHP model.

Although HD monkeys may hold great promise, there are limitations in NHP research. Unlike rodents, rhesus macaque has a long pubertal age and gestation time; thus, the breeding of HD monkeys is a relatively challenging, slow and expensive process.

Neurodegenerative disease such as HD is a progressive inherited disorder that evolves throughout the lifespan of affected individuals. There is increasing evidence that suggests that motor deficits are preceded by cognitive behavioral dysfunctions and the development of early dysfunctional biomarkers has been the key interest in multiple longitudinal human studies and the development of therapeutic targets. While the development of HD in human patients is a relatively long process dictated by the size of CAG repeats, the benefit of a large animal model such as HD monkeys that is capable of capturing key clinical features with similar disease progression determined by using similar clinical assessment tools for humans may facilitate clinical translation (Howland and Munoz-Sanjuan 2014; Menalled and Brunner 2014; Morton and Howland 2013; Pouladi et al. 2013). Thus the longer developmental course in HD monkeys may allow key clinical development of HD that may not be possible to capture in short lived rodents. The recently established Transgenic Huntington's Disease Monkey Resource (THDMR) sponsored by the NIH has a specific mission to produce and promote the preclinical applications of the HD monkey model (Chan et al. 2015; Meng et al. 2017; Moran et al. 2015; Raper et al. 2016). Besides the production of HD monkeys, a biological material bank was also established with samples including serum, plasma and cerebrospinal fluid (CSF) that were collected throughout the lifespan of HD monkeys from prodromal to symptomatic stages are available for the HD research community.

Increased interest in cell models for HD may be appropriate for studying the response of isolated neurons in terms of cell death, aggregates, or dystrophia (An et al. 2012; Carter et al. 2014; Kunkanjanawan et al. 2016). However, isolated cells cannot address the complex circuitry of the human brain or, obviously, the symptoms of the disease. Mouse models for the disease may be used to address the neuropathology and motor symptoms, but assessment of cognitive and psychiatric symptoms remains challenging and their translational value has yet to be determined. There is no perfect model of human diseases, as HD rodent and NHP models are equally important for the understanding of HD pathogenesis and the cures for HD. Translational value of rodents has drawn concerns after failure in clinical translation while the increasing interest in developing large preclinical animal models further suggest the potential of the HD monkeys (Menalled and Brunner 2014; Philips et al. 2014; Zeidler et al. 2015). In fact, our HD monkey is the first transgenic NHP model of human disease and is the prototype model of the species. Continued effort in longitudinal assessment and the development of social group study will greatly benefit our understanding on how cognitive behavioral dysregulation has evolved in HD. HD monkeys provide a unique opportunity to investigate some of the most important clinical aspects in HD that are largely unanswered. HD monkeys also allow the testing of therapeutics against the neuropathological, motor, cognitive and psychiatric changes associated with the disease and can be assessed simultaneously using similar human clinical tools. Therefore, one should consider it unethical not to consider the potential of HD monkeys in advancing preclinical research and facilitating clinical translation of novel therapeutics and treatments for HD patients.

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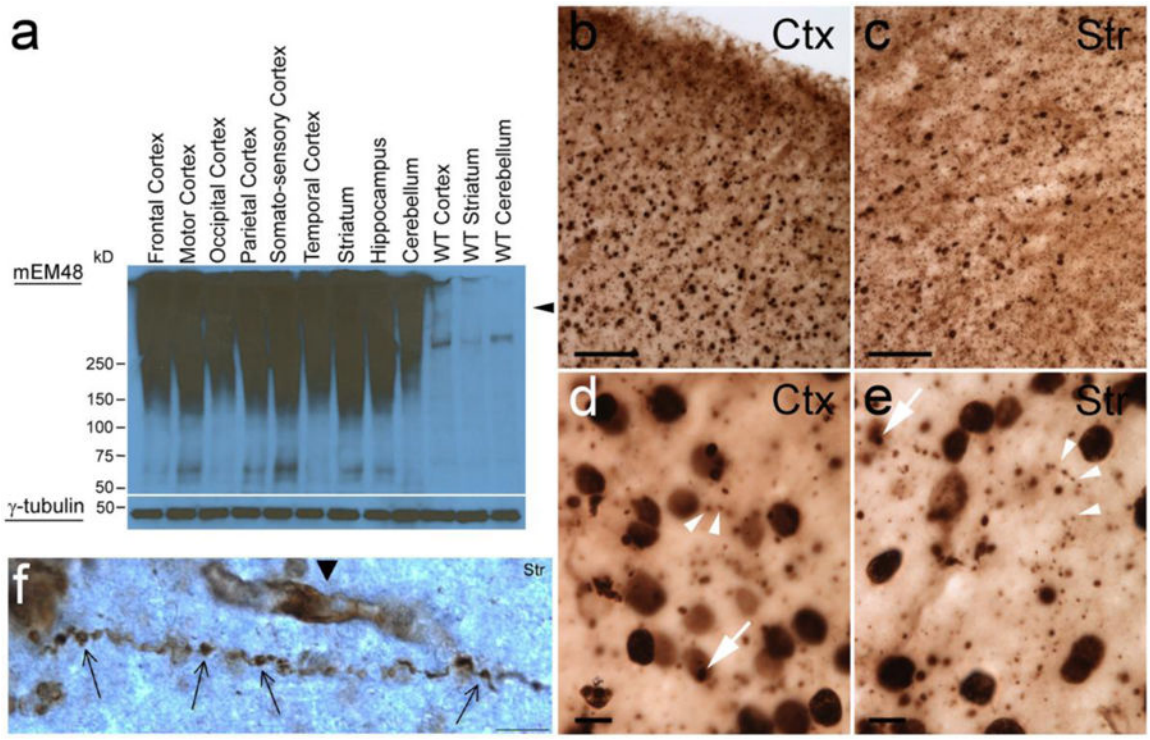


**Fig 1. Neuropathological changes in NHP model for HD**

(a) Immunoblot for mEM48 shows high molecular mass oligomeric HTT (arrow head) and soluble HTT using γ-Tubulin as a control. (b–e) HTT inclusions in the cerebral cortex and striatum as shown by immunohistochemistry for mEM48. (b–c) Scale bars = 100mm (d–e) Scale bars = 10mm. (f) HTT aggregates causing disruption of the axon in a cortical neuron, scale bar = 5 μm (Yang et al. 2008; Wang et al 2008).

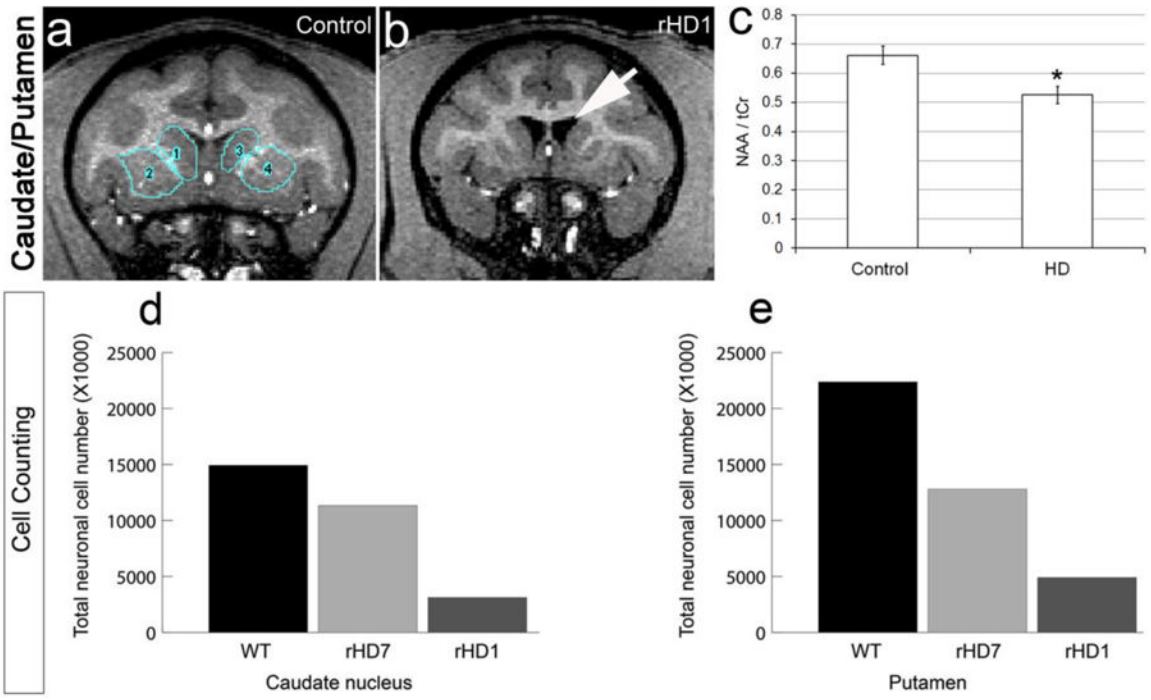


**Fig 2. Decrease in striatal volume and cell number in HD NHPs**

(a–b) Increase in lateral ventricles and decrease in striatal volume of HD transgenic NHP compared to control NHP shown by MRI. (c) Decrease in striatal NAA at 48 months of HD NHP compared to control NHP assessed by proton MRS. (d) Decrease in Nissl-positive cells by stereological counting in the caudate nucleus and (e) putamen of HD NHPs compared to control. rHD1 carried exon 1 of the human *HTT* gene regulated by human polyubiquitin-C promoter, which expressed N-terminal 67 amino acids with 29 polyQ repeats. rHD7 carried exons 1-10 of the human *HTT* gene coding N-terminal 508 amino acids with approximately 67-72Q under the control of the human *HTT* promoter. (Chan et al. 2015).

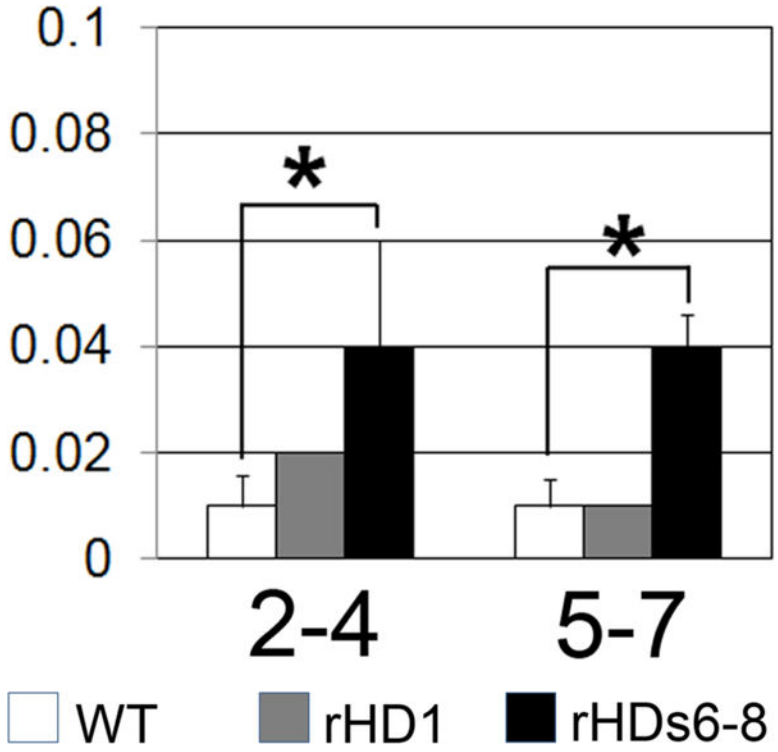


**Fig 3. Motor difficulty in HD NHPs**

HD NHPs show increased motor problems on an object retrieval detour task at 16 months. rHD1 showed no impairment, but rHDs6-8 showed significant ($p<0.05$) impairment. rHD1 carried exon 1 of the human *HTT* gene regulated by human polyubiquitin-C promoter, which expressed N-terminal 67 amino acids with 29 polyQ repeats. rHD6, 7, and 8 (rHDs6-8), on the other hand, carried exons 1-10 of the human *HTT* gene coding N-terminal 508 amino acids with approximately 67-72Q under the control of the human *HTT* promoter. rHD1 carried exon 1 of the human *HTT* gene regulated by human polyubiquitin-C promoter, which expressed N-terminal 67 amino acids with 29 polyQ repeats. (Chan et al. 2015).

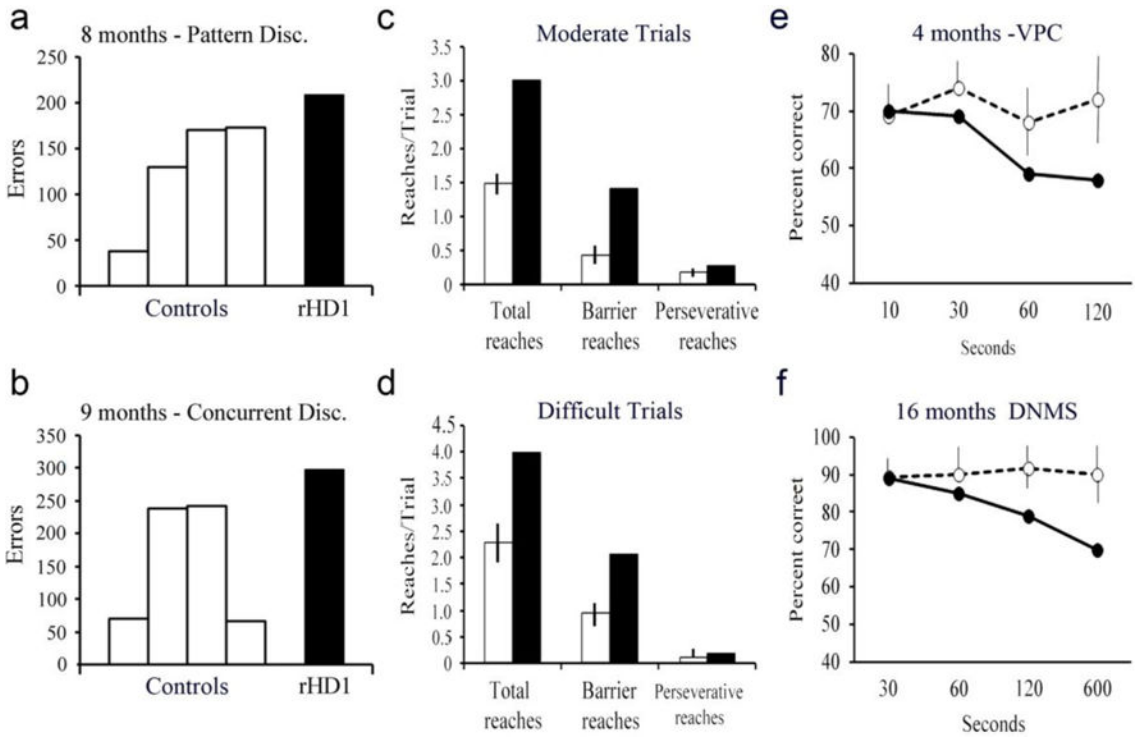


**Fig 4. Cognitive impairment in HD NHPs**

(a) HD NHPs show a slight increase in the number of errors made before reaching criteria on a pattern discrimination task at 8 months. (b) There is also a slight increase in errors at a concurrent discrimination task at 9 months. At 16 months, HD NHPs made almost twice as many barrier and preservative reaches as control NHPs on moderate (c) and difficult (d) trials. (e) Memory recognition test visual paired comparison at 4 months, scores are percent correct when looking at novel objects at a delay of 10, 30, 60, or 120 seconds. (f) Memory recognition test delayed non-matching to sample at 16 months, scores are percent correct at 30, 60, 120, and 600 seconds. rHD1 carried exon 1 of the human *HTT* gene regulated by human polyubiquitin-C promoter, which expressed N-terminal 67 amino acids with 29 polyQ repeats. rHD7 carried exons 1-10 of the human *HTT* gene coding N-terminal 508 amino acids with approximately 67-72Q under the control of the human *HTT* promoter. (Chan et al. 2014).

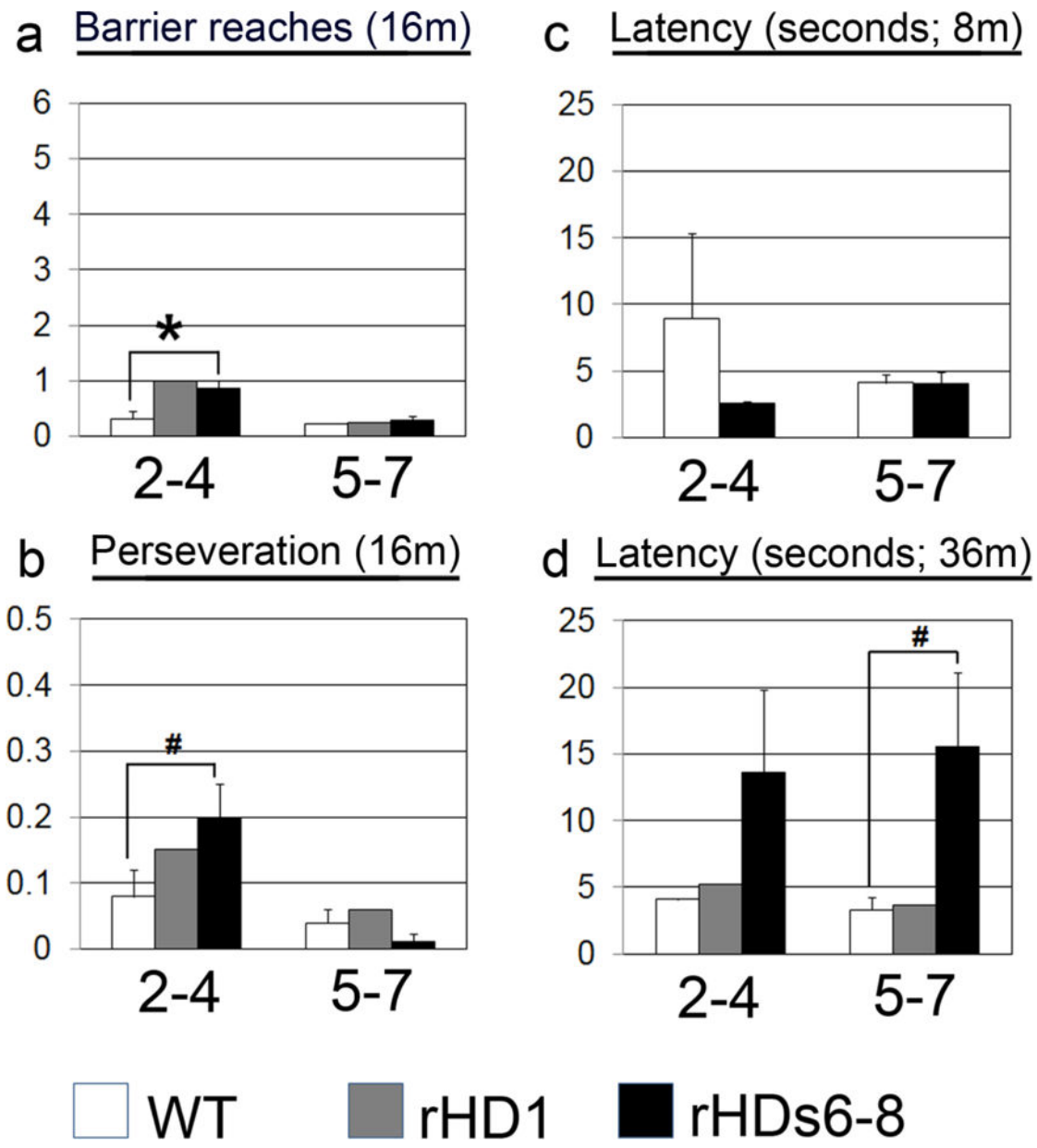


**Fig 5. Cognitive impairment in HD NHPs**

(a) At 16 months, HD NHPs showed more barrier reaches than control NHPs on an object retrieval detour task. (b) At 16 months, HD NHPs also showed an increase in the number of preservative reaches on the same task. (c-d) HD NHPs increased in latency on a visuomotor task at 36 months (d), but not at 8 months (c) compared to control NHPs. rHD1 carried exon 1 of the human *HTT* gene regulated by human polyubiquitin-C promoter, which expressed N-terminal 67 amino acids with 29 polyQ repeats. rHD7 carried exons 1-10 of the human *HTT* gene coding N-terminal 508 amino acids with approximately 67-72Q under the control of the human *HTT* promoter. (Chan et al. 2015).

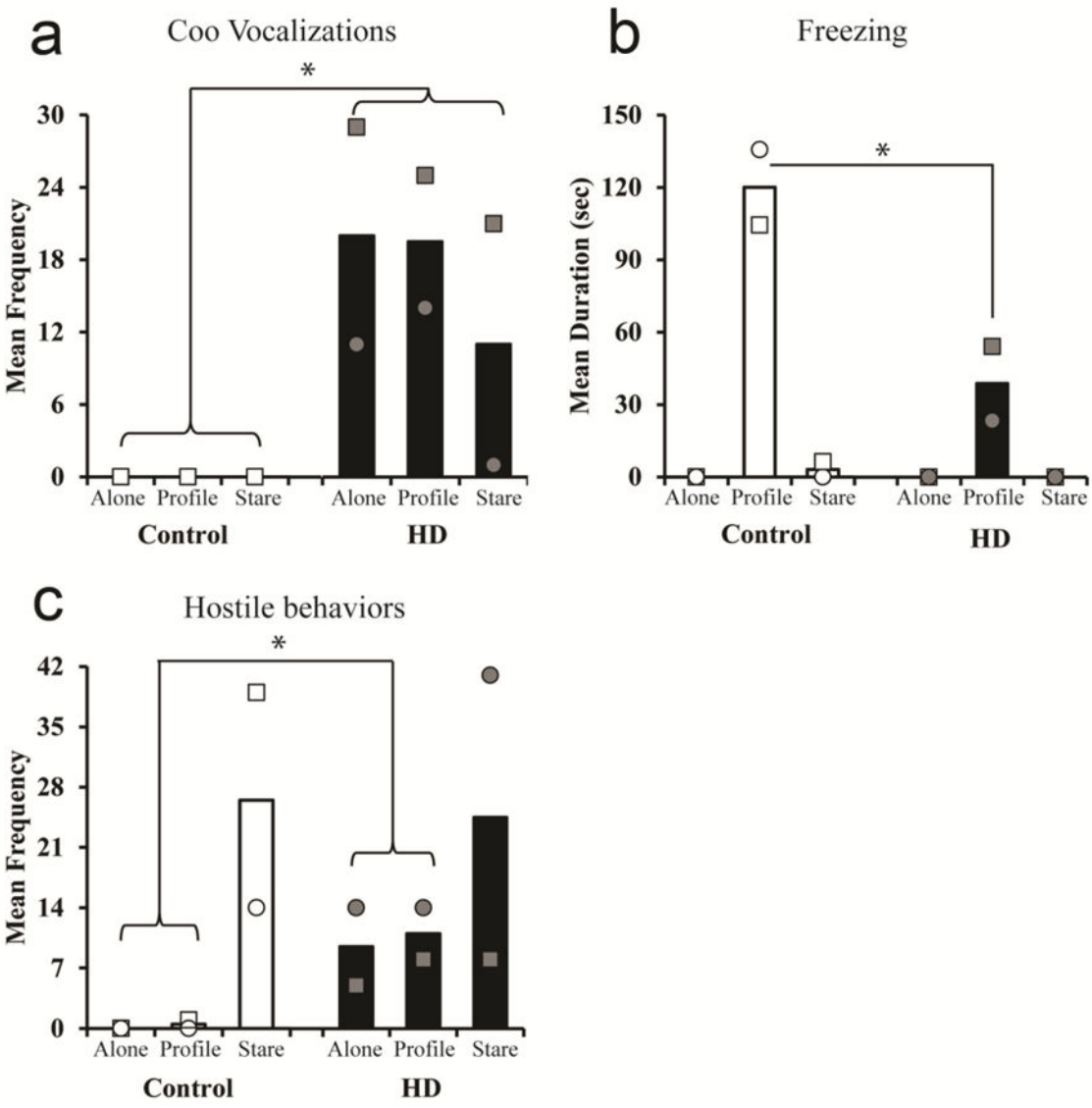


**Fig 6. Psychological symptoms in HD NHPs**

(a) Mature HD NHPs showed an increase in coo vocalizations when alone or introduced to an intruders profile or stare compared to control NHPs. (b) HD NHPs exhibited decreased freezing compared to control NHPs when presented with an intruder profile. (c) Overall, HD NHPs increased in hostile behavior compared to control NHPs when alone or introduced to an intruder's profile (Raper et al. 2016).