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► **To cite this version:**

Erwan Bézard. Models of hyperkinetic disorders in primates. Journal of Neuroscience Methods, 2020, 332, pp.108551. 10.1016/j.jneumeth.2019.108551 . hal-02490894

HAL Id: hal-02490894

<https://hal.science/hal-02490894>

Submitted on 21 Dec 2021

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Erwan Bezard^{1,2#}

¹ Univ. de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France;

² CNRS, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France.

#: To whom correspondence should be addressed: Institute of Neurodegenerative Diseases, Université de Bordeaux, CNRS UMR 5293, Centre Broca Nouvelle-Aquitaine, 146 rue Léo Saignat, 33076 Bordeaux cedex, France. E-mail: erwan.bezard@u-bordeaux.fr

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Erwan Bezard^{1,2#}

¹ Univ. de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France;

² CNRS, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France.

#: To whom correspondence should be addressed: Institute of Neurodegenerative Diseases, Université de Bordeaux, CNRS UMR 5293, Centre Broca Nouvelle-Aquitaine, 146 rue Léo Saignat, 33076 Bordeaux cedex, France. E-mail: erwan.bezard@u-bordeaux.fr

1. Abstract

Hyperkinetic movement disorders include tremors, dystonia, chorea, tics, myoclonus, stereotypies, restless legs syndrome, and various other disorders with abnormal involuntary movements. Although several disorders could be included in such a broad spectrum, a limited number of conditions are modeled in non-human primates. These disabling conditions include notably L-dopa-induced dyskinesia in Parkinson's disease, tardive dyskinesia, essential tremor and Huntington's disease. Non-human primate models of these conditions exist. This short opinionated review surveys the current state of use of these models as well as the future developments.

2. Introduction

Hyperkinetic movement disorders include tremors, dystonia, chorea, tics, myoclonus, stereotypies, restless legs syndrome, and various other disorders with abnormal involuntary movements. Although a number of disorders could be included in such a broad spectrum, a limited number of conditions are modeled in non-human primates (NHPs). These conditions include notably L-dopa-induced dyskinesia (LID) in Parkinson's disease (PD), tardive dyskinesia (TD), essential tremor (ET) and Huntington's disease (HD). NHP models of these conditions exist. They were or are currently in use in a limited number of laboratories throughout the world. Although the translational value of NHP in neurological research is widely acknowledged, the field is everywhere submitted to non-scientific concerns and hence pressure towards diminishing their use, thereby actually limiting the number of teams achieving top-notch science in these species. Moving away from such valuable models would however ultimately jeopardize our capability to develop effective treatments for the neurological conditions of concern, would we be left with the sole rodent models whose brain physiology and anatomy are in nature different from the one of primate lineage to which human beings belong. This short opinionated review surveys the current state of use of these models as well as the future developments.

3. Primate models of L-DOPA induced dyskinesia in Parkinson disease

Searching for therapeutic solutions has fuelled the search for valid translational experimental NHP models of the L-dopa-induced side effects in animals. Modeling LID in NHPs became possible because of the development of the now gold-standard model of parkinsonism obtained by exposure to the toxin MPTP. MPTP is a neurotoxin that induces a form of

parkinsonism in humans which is indistinguishable from idiopathic PD (Langston et al., 1983). Primates exposed to MPTP show most of the motor problems typically encountered with L-dopa therapy, including wearing-off and peak-dose dyskinesia (but not on-off fluctuations) (Clarke et al., 1987; Crossman, 1987; Crossman et al., 1987; Langston and Ballard, 1984). They are moreover sensitive to the main risk factors for LID, such as the loss of nigrostriatal DA projections (Guigoni et al., 2005), the dosage of L-dopa (Huot et al., 2012, 2013; Porras et al., 2014) and an increased incidence of dyskinesia with chronic L-dopa treatment (Bezard et al., 2001; Iderberg et al., 2012).

Four species have been regularly used, namely the macaque monkeys (*Macaca mulatta* and *Macaca fascicularis*), the common marmoset (*Callithrix jacchus*) and the squirrel (*Saimiri sciureus*) monkeys. The vast majority of pathophysiological studies have however been conducted in the macaque monkeys, the species on which this review focuses. A thorough review of the pros and cons of the different species is reviewed by Bastide et al. (Bastide et al., 2015). The cynomolgus (*Macaca fascicularis*) and rhesus (*Macaca mulatta*) macaques display the human-like symptoms of PD and LID and are currently the species of choice to study LID (Bezard et al., 2001; Iderberg et al., 2012; Johnston et al., 2010; Johnston et al., 2013; Koprach et al., 2013; Langston et al., 2000; Morin et al., 2013; Porras et al., 2012). Dyskinetic MPTP-intoxicated macaques exhibit various combinations of choreic-athetoid (i.e. characterized by constant writhing and jerking motions), dystonic and even ballistic movements (i.e. large-amplitude flinging, flailing movements), although less frequently for those latter (Ahmed et al., 2010; Bezard et al., 2001; Bezard et al., 2003; Iderberg et al., 2012; Johnston et al., 2010; Johnston et al., 2013; Koprach et al., 2011; Koprach et al., 2013; Langston et al., 2000; Morin et al., 2013; Porras et al., 2012). Both the repertoire and severity of dyskinesia are not distinguishable from LID occurring in PD patients (Bezard et al., 2003; Fox et al., 2012).

Once MPTP-induced parkinsonism is stable, macaques are then treated with daily administration of L-dopa (L-dopa/carbidopa, ratio 4:1) for 4-5 months at an individually tailored dose designed to produce a full reversal of the parkinsonian condition, i.e. in a clinically relevant approach. Over this period, animals develop consistent and reproducible dyskinesia (Iderberg et al., 2012). Moreover, even if the L-dopa treatment is stopped for months, only one L-dopa administration will be sufficient to induce the same AIMs scores as observed before (Ahmed et al., 2010; Bezard et al., 2003; Bezard et al., 2004; Fasano et al., 2010; Gold et al., 2007; Iderberg et al., 2012; Porras et al., 2012; Rylander et al., 2010), i.e. a profile of response observed in humans as well who do not benefit from drug holidays.

Although L-dopa doses are individually tailored, the benefit of the L-dopa therapy is invariable and consistent for each MPTP macaque, which mimics the treatment adaptation to parkinsonian patients performed in the clinic and underlies how this model is relevant before undergoing clinical trials.

Even if the similarity to human symptoms makes the MPTP macaque relevant on a clinical level for LID, this model is expensive, sizable (weighing up to 7-10kg) and need specialized infrastructures with highly qualified personnel to handle the animals (Iderberg et al., 2012; Morin et al., 2013).

4. Primate model of tardive dyskinesia

Tardive dyskinesia (TD) is a disabling motor complication encompassing all persistent, abnormal, involuntary hyperkinetic movements occurring in the setting of chronic therapy with dopamine receptor-blocking agents, such as antipsychotic drugs (Blanchet, 2003). Although of relatively high prevalence with old anti-psychotics, developing NHP models of this debilitating complication has remained challenging over the years (Blanchet et al., 2012), notably characterized by the instability of the displayed symptoms often present with together with acute dystonic reactions (Gunne and Barany, 1976, 1979). These issues explain the existing gap in knowledge between the TD and LID pathophysiologies.

At odds with LID, TD are mostly modeled in new world NHP species such as squirrels (*Saimiri sciureus*), capuchins (*Cebus apella*) and marmosets (*Callithrix jacchus*) while macaques were originally used (Blanchet et al., 2012). The current knowledge of basal ganglia physiology and pathophysiology derives mainly from knowledge accumulated in macaque species (Camus et al., 2015; Porras et al., 2012). NHP models of any condition generated in a non-macaque species are thus limited in their biological scope as molecular and physiological anatomies are then unknown.

Phenotypically, a pre-cautious long-term (typically over a year) exposure to intramuscular depot of haloperidol elicits abnormal movements are similar to those found in humans and typically stereotyped, without concomitant acute dystonic reaction or interference with food intake and well-being. The list of manifestation is as long as in humans, complicating the rating, including orofacial dyskinetic movements (e.g. forehead contractions, chewing movements, tongue protrusions, and lip retraction), neck rotation, intermittent back extension, and flexion/extension movements of the toes (Blanchet et al., 2012). Those manifestations may last for several months following drug withdrawal as in human TD, although irreversible TD are often reported in patients (at odds with the NHP models).

5. Primate model of essential tremor

Although ET is the most common movement disorder, its pathophysiology remains elusive despite early attempts to decipher its pathophysiology. The field has however clearly not yet benefited from the progress in physiology and in molecular neuroscience as it should have and so are as well the NHP models of ET. A classical NHP model (rodent as well) of ET is the harmaline- induced model, promoting the concept that the action tremor induced by harmaline treatment through enhancing the coupling between the inferior olivary neurons is actually ET. Although far-fetched because of little evidence that harmaline-related alkaloids might be present in plasma of ET patients, it is a phenotypic model of ET in a wide variety of animals, including mice, rats, cats and NHPs (Battista et al., 1970) suggesting an evolutionarily conserved olivocerebellar circuit for tremor generation. Interestingly the frequency of ET in macaque monkeys (EB unpublished observations) corresponds to ET patients (4-12 Hz) (Bhatia et al., 2018) but, like in other species, present some differences in term of pharmacological response (Pan et al., 2018). A recent thorough review of animal models of ET noted a very limited number of peer-reviewed contributions that used NHP in ET research (Pan et al., 2018).

6. Primate model of Huntington disease

Contrary to the three other conditions presented in this short review, HD, a rare monogenic autosomal dominant inherited fatal disease, is subject to an intense, although mainly technological, research in NHP because of the apparent simplicity of its cause (Aron Badin, 2018). Phenotypic models have been first developed while pathocopies are now being proposed thanks to the progress of genetic engineering for which HD has become a school case (Yang et al., 2008). Neurotoxins, i.e. excitotoxic agents (quinolinate, kainate, ibotenate and malonate) or the mitochondrial toxin 3-nitropropionate (3NP), have been used to replicate some features of HD in rodents, but also in NHPs (Brouillet et al., 2005; Burns et al., 1995; Ferrante et al., 1993; Hantraye et al., 1990; Roitberg et al., 2002). The local overexpression of the huntingtin protein using viral vectors is another approach to replicate this monogenic disease that has seen a NHP version with the lentiviral-mediated overexpression of the pathologic (80Q) exon 1 of the human huntingtin protein in the putamen of adult macaques that induces motor abnormalities (spontaneous chorea, limb and orofacial dyskinesia, leg dystonia) similar to those observed in HD patients (Palfi et al., 2007). Most models, however, suffer from the limited number of investigations and each model is only partially characterized. To address that issue, Lavis et al. in an unprecedented effort, characterized an

excitotoxic (intra-striatal quinolinic acid) lesion model of striatal dysfunction using cognitive and motor behavior assessment as well as functional imaging and post-mortem anatomical analyses (Lavissee et al., 2019). They convincingly showed that this NHP model presents specific behavioral (learning, execution and retention of cognitive tests) and metabolic functional deficits that were not mimicked by any available large animal model of striatal dysfunction (Lavissee et al., 2019). In addition, such deficits correlated to a significant cell loss in the striatum and its main input and output structures (Lavissee et al., 2019).

As good as is this phenotypic model, it does not, however, bear the progressive accumulation and aggregation of huntingtin, limiting its relevance to symptomatic treatments of HD and not for the validation of putative disease-modifying approaches. As soon as 2008, the first transgenic NHP model of a neurological condition targeted HD (Yang et al., 2008). The hope generated by this first breakthrough was however dampened by the complexity and the enormous workload required for generating a few transgenic animals, a burden justified by the interesting motor disorders displayed by the offspring. A two-year longitudinal study of a transgenic HD macaque revealed a progressive reduction in striatal volume (Chan et al., 2014) further confirmed by post-mortem histopathological analysis (Chan et al., 2015). The observed motor impairment worsened over time (Snyder and Chan, 2018). In parallel, several other neurodegenerative and neurological diseases are being modelled, more or less successfully. The development of the next generation of tools paves the way, however, to future success that it uses systemic administration of viral vectors (Chansel-Debordeaux et al., 2017; Dehay et al., 2012; Foust et al., 2010) or next transgenesis methodologies (Kang et al., 2015; Liu et al., 2014; Liu et al., 2016; Niu et al., 2014).

7. Considerations for the use of primate in translational research

This author strongly supports the need of NHPs in Neuroscience on the ground that it is indispensable to the translation of knowledge to the human brain (Roelfsema and Treue, 2014), despite the obvious challenges faced by basic and applied scientific researchers, such as expense and technical expertise. While this may be reflected in the relative number of monkeys used for research compared to other species like rodents (0.1% vs. 80%, respectively) (Roelfsema and Treue, 2014), NHPs remain critical for the accumulation of biomedical knowledge given that they are the closest resemblance to humans in aspects of anatomy, physiology, immunology, social behaviors, and cognitive function (Roelfsema and Treue, 2014). The anatomy, physiology and pharmacology of the brain are sufficiently different between primates and non-primates to make uncertain the extrapolation to primates

(including man) of data obtained in non-primates such as rodents. For instance, while the neuronal density decreases uniformly with the increase of cortex neurons in most mammalian species, the primate brain shares the unique characteristic of keeping a stable neuronal density with an increased number of neurons (Herculano-Houzel et al., 2014; Wallis, 2011). Using functional magnetic resonance imaging and cluster analysis, evidence has been provided for several topologically and functionally correspondent human and monkey networks in sensory-motor and attention regions, especially for the human ventral attention network (Mantini et al., 2013). The brain size (Wallis, 2011), the biophysical properties of the cerebro-spinal fluid, the intercellular structure delimiting the extracellular space are as well very different that extrapolation to humans requires NHPs. Only NHPs appear to be capable of the physical expression of certain forms of movement disorder (e.g. chorea) (Crossman, 1987; Porras et al., 2012) or of cognitive disorders (frontal syndrome, dementia as they are the only one exhibit a real frontal cortex) (Camus et al., 2015; Wallis, 2011) in a way that makes it possible to recognize their human counterpart. Among other differences, it is worth noting that several neuronal populations have a different physiology between rodents and primates. Notable, a key difference between rodent and NHP dopaminergic neurons is the lack of neuromelanin in rodents (Barden and Levine, 1983; Carballo-Carbajal et al., 2019). Only NHPs exhibit the accumulation of neuromelanin in the substantia nigra dopamine neurons (thus its name “nigra”) (Marsden, 1961). It has been suggested that the presence of this neuromelanin plays a pivotal role in buffering toxic insults or in modulating the vulnerability of dopamine neurons in PD (Hirsch et al., 1988; Vila et al., 2019). The microenvironment of neurons is different in primates versus non-primate species. Primate brain is heavily enriched in non-neuronal cells (i.e. glial cells) that are at least three times more numerous in monkey brain compared to rodent brain (Charron et al., 2014; Herculano-Houzel, 2009). Since their role in organizing the extracellular space as well as in pathologies such as psychosis, Alzheimer and Parkinson’s disease and is documented, one shall use a species exhibiting a ratio of glial cells / neuronal cells comparable to the Human when tackling such issues. Experimental neurology has demonstrated that it is possible to produce an outstanding model of human neurological disorders using NHPs. A comprehensive system of measures of cognitive and motor performances has been specifically developed for NHPs, that are homologous to those used in man for clinical trial purposes.

When using models, whatever the species, researchers are facing a catch-22 situation (*i.e.* unsolvable as it involves mutually conflicting or dependent conditions). Controversies regarding animal models might come from the distinct definitions of validities used by

researchers. But it is also likely that a good animal model requires more than the expected validity criteria. The “homological validity” (involving the species and strain choices regarding the aim of the model) or the “remission validity” (*i.e.* the reversal of the pathological state by treatments should involve the same mechanisms in animals and Humans) are obvious although hard to achieve. More and more often, the issue of sample sizes is raised since it is often too small to be soundly analyzed (Button et al., 2013). Sample sizes are twice as important as they guarantee the relevance of the results’ statistical significance. Underpowered studies might lead to false-negative or false-positive results (Button et al., 2013). However, this should be balanced with the ethical legislation, such as the 3R rule (*i.e.* replacement of animal models when possible, refinement of experimental conditions and reduction of sample sizes). Therefore, and contrary to a general assumption, it is neither ethical nor statistically valid to use a low number of NHPs while a properly weighted study, although involving more NHPs, is perfectly scientifically valid and hence ethical because the data can be trusted.

8. Concluding remarks

NHP models of hyperkinetic movement disorders have been developed for L-dopa-induced dyskinesia in Parkinson’s disease, tardive dyskinesia, essential tremor and Huntington’s disease. Heuristic, predictive and hence translational phenocopic NHP models exist for the symptomatic management of L-dopa-induced dyskinesia in Parkinson’s disease and Huntington’s disease. Validating pathocopies of these hyperkinetic disorders is now required for hoping to develop disease-modifying strategies.

9. Acknowledgments

This review was supported by INSERM, CNRS and University of Bordeaux. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. This review did not intend to be exhaustive and only reflect the opinion of the author.

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