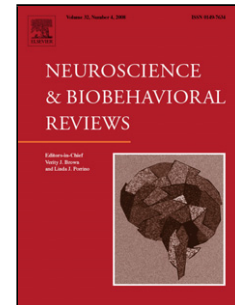


## Accepted Manuscript

Title: The hidden side of Parkinson's disease: studying pain, anxiety and depression in animal models

Authors: Fanny Faivre, Anil Joshi, Erwan Bezard, Michel Barrot



PII: S0149-7634(18)30505-0  
DOI: <https://doi.org/10.1016/j.neubiorev.2018.10.004>  
Reference: NBR 3238

To appear in:

Received date: 5-7-2018  
Revised date: 14-9-2018  
Accepted date: 12-10-2018

Please cite this article as: Faivre F, Joshi A, Bezard E, Barrot M, The hidden side of Parkinson's disease: studying pain, anxiety and depression in animal models, *Neuroscience and Biobehavioral Reviews* (2018), <https://doi.org/10.1016/j.neubiorev.2018.10.004>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**The hidden side of Parkinson's disease:****studying pain, anxiety and depression in animal models**

Fanny Faivre <sup>a</sup>, Anil Joshi <sup>a</sup>, Erwan Bezard <sup>b,c</sup>, Michel Barrot <sup>a,\*</sup>

<sup>a</sup>Centre National de la Recherche Scientifique, Université de Strasbourg, Institut des Neurosciences Cellulaires et Intégratives, F-67000 Strasbourg, France

<sup>b</sup>Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France;

<sup>c</sup>Centre National de la Recherche Scientifique, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France

\*Corresponding author at: Institut des Neurosciences Cellulaires et Intégratives, 5 rue Blaise Pascal, F-67000 Strasbourg, France

*E-mail address:* mbarrot@inci-cnrs.unistra.fr

**Highlights**

- Non-motor symptoms are present in Parkinson's disease
- Parkinson's disease patients have a high prevalence of pain, anxiety and depression
- There is a variety of preclinical models of Parkinson's disease
- Preclinical models can recapitulate non-motor symptoms of Parkinson's disease

**ABSTRACT**

Parkinson's disease is a neurodegenerative disease leading to the loss of midbrain dopamine neurons. It is well known and characterized by motor symptoms that are secondary to the loss of dopamine innervation, but it is also accompanied by a range of various non-motor symptoms, including pain and psychiatric disorders such as anxiety and depression. These non-motor symptoms usually appear at early stages of the disease, sometimes even before the first motor symptoms, and have a dramatic impact on the quality of life of the patients. We review here the present state-of-the-art concerning pain, anxiety and depression-like parameters in animal models of Parkinson's disease.

*Keywords:* Parkinson's disease; non-motor symptoms; pain; anxiety; depression

Parkinson's disease is a neurodegenerative disorder classically known for the loss of dopamine neurons in the midbrain, and most often accompanied by the presence of cytoplasmic inclusions of  $\alpha$ -synuclein proteins called Lewy bodies. However, although the disease is primarily related to the loss of the nigrostriatal pathway, several other brain areas are also degenerating (often to a lesser extent), including the locus coeruleus, the dorsal raphe nucleus, the nucleus basalis of Meynert, the pedunculopontine nucleus, with a cortical thinning occurring at later stage (Ehringer and Hornykiewicz, 1960; Halliday et al., 1990; Jellinger, 1991; Zarow et al., 2003). Synuclein pathology is not restricted either to the nigrostriatal pathway but displays extensive spread in the nervous system. Indeed, observations of post-mortem human brains (Braak et al., 2002, 2003, 2004) showed early Lewy bodies inclusions in the IX (glossopharyngeal) and X (vagal) nerves and in the olfactory bulbs, later spreading beyond these structures to include the lower raphe nuclei, the magnocellular portion of the reticular formation and the locus coeruleus, to then affect the substantia nigra pars compacta, and finally gradually invade the entire neocortex.

Clinically, Parkinson's disease is classically defined by a triad of motor symptoms: bradykinesia (*i.e.* a slowdown to initiate voluntary movements), muscle rigidity and resting tremors. Beside these classical symptoms, different non-motor symptoms can be present and sometimes even appear a long time before the first motor symptoms (Bezard and Fernagut, 2014; Blanchet and Brefel-Courbon, 2017; Pont-Sunyer et al., 2015), which may lead to a misdiagnosis or delayed diagnosis (O'Sullivan et al., 2008) and has a negative impact on the quality of life of the patients (Nègre-Pagès et al., 2008; Rieu et al., 2016). Three major phases have thus been proposed to describe the development of Parkinson's disease (Stern et al., 2012). The phase 1, the "preclinical Parkinson's disease", corresponds to the beginning of the  $\alpha$ -synuclein accumulation in the central and/or the peripheral autonomic nervous system, in the absence of detectable clinical signs. The second phase, referred to either as "pre-motor" or "prodromal" phase, can exceed ten years before the clinical diagnosis of the disease and is usually associated to the apparition of non-motor symptoms due in part to extranigral alterations. It should also be noticed that early subtle motor symptoms can often be present in this prodromal phase of the disease (Mahlknecht et al., 2015). During this phase, Parkinson's disease patient can display higher anxiety as early as 16 years before the diagnosis of the disease; and depression becomes significantly prevalent among Parkinson's disease patients in the last 2-3 years preceding the diagnostic (Darweesh et al., 2017). The phase 3 is the "motor Parkinson's disease", which is the one that is clinically visible and more easily diagnosed.

The non-motor symptoms include notably (but not exclusively) sleep disorders, gastrointestinal and autonomic symptoms (nausea, constipation), sensory symptoms (olfactory disturbance), pain and neuropsychiatric symptoms (depression, anxiety) (Barone et al., 2009; Chaudhuri et al., 2006; O'Sullivan et al., 2008; Park and Stacy, 2009; Pont-Sunyer et al., 2015). The anxiety, depression and pain symptoms display significantly greater severity than in the

general population (Rana et al., 2016), and an increased frequency of the non-motor symptoms is associated with Parkinson's disease duration and severity (Barone et al., 2009).

Understanding the pathophysiological mechanisms underlying non-motor symptoms in Parkinson's disease is important, but requires relevant pre-clinical models. Alterations concerning olfaction, sleep and the gastrointestinal tract are clinically well known (Reichmann, 2017) and addressed in models of the disease (Titova et al., 2017). On the other hand, pain, anxiety and depression still remain understudied. In this review, we provide an overview of the present state-of-the-art in the field by rapidly presenting pain and mood non-motor symptoms in Parkinson's disease patients, by evoking the different pre-clinical models used in research and by detailing the literature on measures of nociception, anxiety-like and depression-like symptoms in rodent and non-human primate models of Parkinson's disease.

## **1. The non-motor symptoms in Parkinson's disease patients**

This section provides a rapid overview of some clinical data concerning pain, anxiety and depression in Parkinson's disease. For more details concerning these clinical aspects, please refer to the following references (Blanchet and Brefel-Courbon, 2017; Chaudhuri et al., 2006; Schapira et al., 2017).

### *1.1. Pain in Parkinson's disease (Figure 1)*

Parkinson's disease patients exhibit sensory symptoms such as numbness, coldness, burning or pain (Koller, 1984). Pain is one of the often neglected non-motor symptoms for which there is no truly effective treatment (Wasner and Deuschl, 2012), even though it was already noted in the original description of the disorder by James Parkinson. Nevertheless, it is the non-motor symptoms which is the most frequent in Parkinson's disease patients (O'Sullivan et al., 2008),

with a prevalence between 30% and 83% of the patients depending on the considered epidemiological study (Allen et al., 2016; Beiske et al., 2009; Nègre-Pagès et al., 2008; Wasner and Deuschl, 2012).

Clinical data showed that both pain thresholds and tolerance to pain are significantly lower in Parkinson's disease patients compared to the control population (Blanchet and Brefel-Courbon, 2017; Zambito Marsala et al., 2011), and that these patients can suffer from a variety of different pain (Beiske et al., 2009; Lee et al., 2006). Because of the variety of pain expressed by Parkinson's disease patients, a classification was proposed to identify different types by using criteria such as "topography, duration, frequency, aggravating factors, temporal and topographical relationship to Parkinson's disease, influence of motor complications, influence of antiparkinson medication, and patient's opinion about the relationship between pain and Parkinson's disease" (Wasner and Deuschl, 2012). Such classification led to separate pain directly/partly related to Parkinson's disease itself, indirectly related to it (*i.e.* aggravated by Parkinson's disease) and unrelated to the disease itself (Figure 1) (Blanchet and Brefel-Courbon, 2017; Nègre-Pagès et al., 2008; Wasner and Deuschl, 2012).

Pain in Parkinson's disease can be a nociceptive pain, defined by the International Association for the Study of Pain as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors" (<https://www.iasp-pain.org/>). Those include for example pain that is associated with the motor disturbances and partly due to muscle rigidity. Indeed, rigidity, akinesia, postural abnormality or dystonia can lead to musculoskeletal nociceptive pain and back pain (Wasner and Deuschl, 2012). Patients can also display neuropathic pain, *i.e.* "pain caused by a lesion or disease of the somatosensory nervous system", which may be of peripheral origin, such as radicular pain, or of central one (Blanchet and Brefel-Courbon, 2017; Wasner and Deuschl, 2012). Miscellaneous pain, which cannot be classified in the above two categories, can also be observed. Those include for example

akathisia (*i.e.* restless legs syndrome) and pain associated with depression, which is the one that appears mostly during the prodromal phase (Schapira et al., 2017; Wasner and Deuschl, 2012) (Fig. 1). The patients with pain more directly related to Parkinson's disease itself are often younger at non-motor and motor disease onsets and show higher parkinsonism severity than those without pain or with pain unrelated to the disease (Nègre-Pagès et al., 2008; Zambito Marsala et al., 2011). The gender has also an influence, with women more frequently reporting pain symptoms (Beiske et al., 2009; Zambito Marsala et al., 2011). The loss of dopamine in the basal ganglia may partly explain the changes in pain thresholds; however, the absence of a total recuperation of these symptoms with dopaminergic medication suggests also a role of non-dopaminergic mechanisms in the appearance or maintenance of pain symptoms (Brefel-Courbon et al., 2005; Schapira et al., 2017).

### *1.2. Anxiety and depression in Parkinson's disease*

There is a notable comorbidity of mood disorders with Parkinson's disease (Dissanayaka et al., 2010). Moreover, the risk to be diagnosed with Parkinson's disease is significantly increased in patients that have already been diagnosed with affective disorders (Nilsson et al., 2001), which reflect the fact that these psychiatric pathologies are part of the early non-motor symptoms appearing during the prodromal phase of the disease (Jacob et al., 2010). Mood disorders can indeed appear 5 to 20 years before the motor symptoms (Shiba et al., 2000).

According to the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> edition (American Psychiatric Association, 2013), "anxiety disorders include disorders that share features of excessive fear and anxiety and related behavioral disturbances". 34 to 65% of Parkinson's disease patients experience anxiety, including panic disorders, generalized anxiety disorder or social phobia (Barone et al., 2009; Chaudhuri et al., 2006; Dissanayaka et al., 2010;

Park and Stacy, 2009; Schapira et al., 2017; Szatmari et al., 2017). The risk to develop these disorders has been observed to be much higher (ninefold) in “younger” patients (<62 years old) than in older subjects (Dissanayaka et al., 2010). The pathophysiological basis for these symptoms is however not clearly identified yet. Beside alterations in dopaminergic system, including a correlation between striatal dopamine transporter availability and anxiety (Erro et al., 2012; Moriyama et al., 2011; Weintraub et al., 2005), a structural change in amygdala size has also been proposed to contribute to this symptom (Vriend et al., 2016). Moreover, a loss of noradrenaline neurons in the locus coeruleus (Bertrand et al., 1997; Delaville et al., 2011; German et al., 1992; Hughes et al., 1992) and of serotonin cells in the dorsal raphe (Kish, 2003) has been described in patients, which could also contribute to the presence of anxiety and depression (Marsh, 2013; Remy et al., 2005; Schapira et al., 2017).

Depressive disorders are common psychiatric disorders characterized by the presence of a sad, empty or irritable mood, accompanied by somatic and cognitive changes that impact everyday life function. According to the World Health Organization, they affect 300 million people worldwide (<http://www.who.int/>). Approximately 40% of the patients with Parkinson’s disease display depressive disorders (Burn, 2002; Chaudhuri et al., 2006; Cummings, 1992; Jacob et al., 2010). Anhedonia and apathy are frequent symptoms that can occur during the prodromal phase (Ishihara and Brayne, 2006; Pont-Sunyer et al., 2015), which leads to the fact that, at time of Parkinson’s disease diagnosis, the proportion of patients who already consulted for depression is more than twice higher than in the control population (Leentjens et al., 2003). Classical antidepressant drugs as well as deep brain stimulation and L-DOPA therapy can be useful to improve these symptoms (Czernecki et al., 2002; Schapira et al., 2017). Even if the detailed mechanism underlying depression is unknown, different hypotheses have been proposed. Indeed, alterations in the monoaminergic systems (Chaudhuri et al., 2006; Reichmann, 2017; Schapira et al., 2017), as well as in structural and metabolic

alterations in brain regions known for their implication in affective disorders, such as the hippocampus and the amygdala (Huang et al., 2013; Surdhar et al., 2012; van Mierlo et al., 2015), may likely contribute to the depressive symptoms in Parkinson's disease.

## **2. Animal models to study Parkinson's disease**

This section mostly focuses on animal models (rodents and monkeys) of Parkinson's disease for which data related to pain, anxiety or depression like behaviors are available. For a more exhaustive view of existing models, readers can consult following reviews (Bastías-Candia et al., 2018; Bové and Perier, 2012; Creed and Goldberg, 2018; Francardo, 2018; Grandi et al., 2018; Koprach et al., 2017; Volta and Melrose, 2017).

### *2.1. Toxin-induced Parkinson's disease models*

The more widely used models of Parkinson's disease are based on 6-hydroxydopamine (6-OHDA), a drug that selectively acts on catecholamine containing terminals and cells bodies (Ungerstedt, 1968). Due to its homology with dopamine and noradrenaline, 6-OHDA is caught by plasma membrane dopamine and noradrenaline transporters to enter into cells. It accumulates into the cytosol, producing reactive oxygen species that are toxic to the cell and quinones that inactivate biological macromolecules important to neuronal integrity (Bové and Perier, 2012; Dauer and Przedborski, 2003; Sachs and Jonsson, 1975). 6-OHDA does not easily cross the brain-blood barrier, it is thus injected directly into the structure of interest, either in the area of dopamine cell bodies (substantia nigra *pars compacta*), in the dopamine passing fibers (medial forebrain bundle) or at terminal level (striatal complex) (Blum et al., 2001; Gubellini and Kachidian, 2015; McDowell and Chesselet, 2012). This 6-OHDA administration induces a degeneration of dopamine neurons, leading to motor impairments that partially mimic

the motor-symptoms of Parkinson's disease (Bové and Perier, 2012; Ungerstedt, 1968). The injection can be unilateral, producing a hemiparkinsonism model with asymmetric circling behaviors that can be used to test treatments for motor symptoms (Bové and Perier, 2012; Dauer and Przedborski, 2003; Hefti et al., 1980; Ungerstedt and Arbuthnott, 1970). The bilateral injection in the mesencephalic region of dopamine cell bodies can however induce a notable mortality of the animals, due to adverse effects such as aphagia, adipsia and seizures (Bezard and Przedborski, 2011; Bové and Perier, 2012; Ungerstedt, 1971), which limits in part this direct targeting of cell bodies. As 6-OHDA is toxic for all catecholamine neurons, a pretreatment with a blocker of noradrenaline re-uptake and/or catabolism (monoamine oxidase B inhibitor) may be used to protect noradrenaline neurons and have a more specific dopamine lesion. However, it has also been proposed that administration of 6-OHDA without such neuroprotection may lead to a richer phenotype that better mimics Parkinson's disease (Bezard et al., 2013).

The use of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to mimic the disease was discovered in the 1980's, after the observation that an accidental production of MPTP during the manufacture of a synthetic opioid drug could lead to symptoms similar to those observed in Parkinson's disease in users of this drug (Blum et al., 2001; Davis et al., 1979; Langston et al., 1983). In animal research, MPTP is mainly used in non-human primates and in mice, even though rodents are less sensitive to its toxicity (Schober, 2004), especially rats in which dopamine neurons are resistant to systemic delivery of MPTP (Betarbet et al., 2002; Bové and Perier, 2012; Boyce et al., 1984; Chiueh et al., 1984b; Sahgal et al., 1984). However, local intracerebral delivery of the active metabolite MPP<sup>+</sup> can induce dopamine neuron loss in rats and in guinea-pigs (Chiueh et al., 1984a). The effects of MPTP depend on various parameters, such as the administration mode, species and age (Blum et al., 2001). Due to its facility to cross the brain-blood barrier, MPTP is classically administered through systemic injection

(Bankiewicz et al., 2001). After such injection, MPTP enters the brain and is metabolized in 1-methyl-4-phenyl-2,3-dihydropyridinium ion (MPP<sup>+</sup>). The MPP<sup>+</sup> binding site is located in the electron leak site, within the complex I of the electron transport chain of the mitochondria (Betarbet et al., 2002). MPP<sup>+</sup> inhibits the complex I of the mitochondrial electron transport chain, leading to significant ATP depletion, production of reactive oxygen species and cell loss, particularly in the nigrostriatal pathway which is the brain region the most sensitive to the compound, but not the only one (Betarbet et al., 2002; Chan et al., 1991; Dauer and Przedborski, 2003; Engeln et al., 2015; Fabre et al., 1999).

The above two toxins are the most used to model Parkinson's disease, but other drugs can be found in the literature. Rotenone is a compound used as pesticide which easily crosses the brain-blood barrier, entering neuron mitochondria through the same mechanism as MPP<sup>+</sup> and inhibiting mitochondrial complex I (Dauer and Przedborski, 2003; Heinz et al., 2017; Li et al., 2003). It produces  $\alpha$ -synuclein accumulation and causes a degeneration of the nigrostriatal dopaminergic pathway following oxidative stress (Betarbet et al., 2000, 2002). In rodents, rotenone can be administrated by systemic injections or by stereotaxic delivery directly into the brain. However, its use is strongly limited by the high mortality that follows its administration at high doses (Antkiewicz-Michaluk et al., 2003). Based on epidemiological toxicology, the herbicide paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride), the fungicide maneb (Mn-ethylene-1,2-bisdithiocarbamate) and the cycad flour (from *cycas micronesica*) are also used to model Parkinson's disease. Paraquat is in fact a structural analog of MPP<sup>+</sup>, the active metabolite of MPTP (Betarbet et al., 2002; Bové and Perier, 2012). Its systemic injections induce  $\alpha$ -synuclein accumulation and causes degeneration of dopamine neurons of the substantia nigra *pars compacta* (Dauer and Przedborski, 2003; Manning-Bog et al., 2002; McCormack et al., 2002; McDowell and Chesselet, 2012). Maneb easily crosses the brain-blood barrier neuron and causes damage in the substantia nigra *pars compacta* and the striatum, leading to locomotor

and coordination impairments. Combined exposure to maneb potentiates the effect of paraquat (Bastías-Candia et al., 2015; Thiruchelvam et al., 2003). Finally, mice fed with cycad flour exhibit  $\alpha$ -synuclein accumulation in multiple brain regions and dopamine neuron loss in the substantia nigra *pars compacta*, which induces cognitive deficits and Parkinson's disease-like symptoms (McDowell and Chesselet, 2012; Wilson et al., 2002).

Moreover, it has been shown that an intranigral, intra-striatal or intra-pallidal injection of lipopolysaccharides induces an inflammation process associated with the activation of microglia. This inflammation favors a degeneration of the dopamine neurons of the nigrostriatal pathway and lead to locomotor impairments similar to the ones seen in other models of Parkinson's disease (Castaño et al., 1998; Liu and Bing, 2011; Zhang et al., 2005).

Lastly, injections of Lewy body extracts from post mortem Parkinson's disease patients in the substantia nigra *pars compacta* or the striatum in mice or monkey induce a progressive nigrostriatal degeneration. In mice, this degeneration is accompanied by an astrogliosis in the substantia nigra and impaired motor coordination and balance in the pole test (Recasens et al., 2014).

## 2.2. Genetic models of Parkinson's disease

While Parkinson's disease is often sporadic, familial forms have also been described which are due to autosomal dominant or recessive genetic mutations (Singleton et al., 2013), and corresponding animal models have been developed.

In 1997, a family form of Parkinson's disease caused by a mutation of the  $\alpha$ -synuclein gene (*SNCA* gene) was discovered (Polymeropoulos et al., 1997). This mutation consists of a single base pair change from a guanine to an adenosine at position 209, leading to an alanine to threonine substitution in the protein at position 53 (p.A53T) (Polymeropoulos et al., 1997).

Other point mutations of the *SNCA* gene were also linked to familial forms of Parkinson's disease, such as the p.A30P mutation (Krüger et al., 1998) corresponding to an alanine to proline substitution in the position 30 of the protein and the p.E46K mutation (Zarranz et al., 2004) corresponding to a glutamic acid to lysine substitution in position 46. All of these mutations lead to an autosomal dominant form of the disease (Hernandez et al., 2016). Beside these point mutations, whole locus duplication or triplication of the *SNCA* gene has also been reported as a cause of family forms of the disease (Ibáñez et al., 2004; Singleton et al., 2003), the number of *SNCA* copies correlating with the early-onset and severity of the disease, suggesting a dose dependent effect (Ibáñez et al., 2004). The discovery of these different familial forms was the starting point for the development of transgenic models for the study of Parkinson's disease.

To explore the function of the  $\alpha$ -synuclein protein and its implication in the disease, several lines of transgenic mice expressing either the wild-type or a mutated (p.A53T or p.A30P) human  $\alpha$ -synuclein were produced (for review, see Fernagut and Chesselet, 2004). The first transgenic mouse overexpressing human  $\alpha$ -synuclein used the wild-type form of the protein under the control of the platelet-derived growth factor  $\beta$  promoter (Fernagut and Chesselet, 2004; Masliah et al., 2000), leading to  $\alpha$ -synuclein accumulation in synapses from the neocortex, the hippocampus, the substantia nigra and the olfactory regions (Masliah et al., 2000). However, the use of other promoters and/or forms of  $\alpha$ -synuclein can lead to different patterns and levels of  $\alpha$ -synuclein expression and of behavioral phenotypes (Fernagut and Chesselet, 2004). For example,  $\alpha$ -synuclein expression driven by the Thy-1 promoter has been used to produce various transgenic lines that differ in terms of presence (Kahle et al., 2000; Rockenstein et al., 2002) or absence (Rabl et al., 2017) of  $\alpha$ -synuclein accumulation in the striatum or in the presence (Fleming et al., 2004; Rabl et al., 2017) or absence (Kahle et al., 2000) of motor impairment. This variability is not only related to the chosen protein form (wild-type or mutated) but may also be related to the transgene insertion site (Chesselet, 2008).

An expression of the wild-type (Lim et al., 2010; Nuber et al., 2008) or the p.A30P mutated (Marxreiter et al., 2013) human  $\alpha$ -synuclein driven by the calmodulin-dependent protein kinase II $\alpha$  promoter induces a degeneration of neurons in the dentate gyrus, the olfactory bulb and in some midbrain and forebrain regions (Lim et al., 2010; Marxreiter et al., 2013; Nuber et al., 2008). This  $\alpha$ -synuclein accumulation leads to cognitive and progressive motor impairments (Nuber et al., 2008). Interestingly, if the construct was repressed until weaning, no neuronal loss was observed in the hippocampal region, indicating that the dentate gyrus neurons are more vulnerable during development than after maturation (Lim et al., 2010). Transgenic mice expressing either wild-type or A53T mutated  $\alpha$ -synuclein under the mouse prion protein promoter display age-dependent intracytoplasmic neuronal  $\alpha$ -synuclein inclusions (Giasson et al., 2002) and motor impairments that lead to paralysis and death a few days after the first motor symptoms due to motoneuron loss (Giasson et al., 2002; Giraldo et al., 2018). In this model, intracerebral injections of preformed  $\alpha$ -synuclein fibrils in young asymptomatic mice accelerate the formation of intracellular inclusions and the development of neurological symptoms (Luk et al., 2012).

To more specifically target  $\alpha$ -synuclein expression to dopamine neurons (which is a useful model of dopamine cell loss but does not reflect the more widespread expression observed in both central and peripheral nervous system in patients), lines of transgenic mice with a truncated wild-type (Tofaris et al., 2006) or mutated (p.A53T) (Wakamatsu et al., 2008)  $\alpha$ -synuclein expression under the control of the tyrosine hydroxylase promoter were developed. These mice display pathological  $\alpha$ -synuclein-positive inclusions in the substantia nigra and in the olfactory bulb, and a decrease in striatal dopamine levels associated with a progressive reduction of the spontaneous activity (Tofaris et al., 2006; Wakamatsu et al., 2008).

In addition to the classical transgenic models exposed above, the use of adeno-associated viral vectors to overexpress  $\alpha$ -synuclein has also been developed. This overexpression in the

midbrain induces a nigrostriatal degeneration and the formation of insoluble  $\alpha$ -synuclein aggregates in mice, rats and non-human primates (Bourdenx et al., 2015; Ip et al., 2017; Ulusoy et al., 2010). This method reproduces many characteristics of the pathology and provides an interesting model in both rodents and primates (Ulusoy et al., 2010).

Mutations in the *PARK8* gene coding for the leucine-rich repeat kinase 2 (LRRK2) protein have also been described to be associated with familial autosomal-dominant and sporadic forms of Parkinson's disease (Funayama et al., 2002; Healy et al., 2008; Paisán-Ruiz et al., 2013). Mutations of this protein mostly target the GTPase and kinase domains of the protein (Dawson et al., 2010; Gubellini and Kachidian, 2015) and cause late-onset forms of the disease (Dawson et al., 2010; Healy et al., 2008). Transgenic mice with bacterial artificial chromosome (BAC) expressing LRRK2 R1441C/G (*i.e.* mutation in the GTPase domain) have been used to model Parkinson's disease, showing age-dependent and progressive motor symptoms but no nigrostriatal degeneration (Li et al., 2009). The development of LRRK2 knock-in mice also failed to produce the classical brain alterations of the disease, such as dopamine cell degeneration or  $\alpha$ -synuclein accumulation (Bezard et al., 2013; Dawson et al., 2010; Volta and Melrose, 2017). More conclusively, a rat LRRK2 model has been developed, using adenoviral-mediated expression of LRRK2 G2019S mutation (*i.e.* mutation in the kinase) to induce a progressive degeneration of nigral dopamine neurons (Dusonchet et al., 2011).

Mutations in the *PRKN* gene (or *PARK2*), which encodes for parkin, an E3 ubiquitin ligase, were identified as a genetic cause of autosomal-recessive and early-onset Parkinson's disease, as well as of some forms of sporadic cases (Gubellini and Kachidian, 2015; Dawson et al., 2010). These parkin mutations lead to a loss-of-function and are responsible for a loss of substantia nigra *pars compacta* dopamine neurons without formation of Lewy bodies (Dauer and Przedborski, 2003). However, mouse models produced by partial or full deletion of the parkin gene exhibit few or no dopamine loss (Itier et al., 2003; Perez and Palmiter, 2005; Von Coelln

et al., 2004) and only limited behavioral deficits (Perez and Palmiter, 2005). On the other hand, the overexpression of the mutant human *parkin* using a BAC transgenic mouse model leads to a late-onset and progressive degeneration of dopamine neurons, associated with progressive motor deficits (Dawson et al., 2010; Gubellini and Kachidian, 2015; Lu et al., 2009).

Mutations in the *PINK-1* (PTEN-induced putative kinase 1) gene can cause autosomal recessive forms of the disease (Dawson et al., 2010; Gubellini and Kachidian, 2015; Valente et al., 2004). *PINK-1* interacts with *parkin* to induce *parkin*-mediated autophagy of damaged mitochondria and thus protect cells from mitochondrial dysfunctions (Gubellini and Kachidian, 2015; Lazarou et al., 2013; Narendra et al., 2008). However, similar to *parkin* null mice, *PINK-1* knock-out mice do not display notable neurodegeneration of substantia nigra dopamine neurons, and show few or no Lewy body-like inclusions (Gispert et al., 2009; Kitada et al., 2007).

A missense mutation in the *DJ-1* gene (*PARK7*) is responsible for an autosomal recessive and early-onset form of Parkinson's disease (Bonifati et al., 2003a, 2003b; Dawson et al., 2010; Lim and Ng, 2009). *DJ-1* knock out mice have been developed, but failed to show nigrostriatal dopaminergic loss. However, a reduced striatal dopamine release and a decreased locomotor activity has been observed, making this model interesting as model of early stages of the disease (Chandran et al., 2008; Chen et al., 2005; Dawson et al., 2010; Goldberg et al., 2005; Lim and Ng, 2009; Yamaguchi and Shen, 2007).

Beside the above genetic models that are based on human gene mutations associated with the disease, other transgenic models have also been designed targeting the dopamine system. One of these models is based on the mutation or the deletion of the homeobox transcription factor *Pitx3* which is known to be selective to dopamine neurons, thus inducing a dopaminergic loss in the nigrostriatal pathway. The *Pitx3*-null mice exhibit different markers of the disease, including a decline in substantia nigra *pars compacta* cell number, a reduction in striatal

dopamine release, and motor symptoms such as motor coordination impairment, body tremors and decreased locomotion (Filali and Lalonde, 2016; Le et al., 2015). The *Pitx3*<sup>416insG</sup> mutant mice, relying on a spontaneous mutation (an inserted G in position 416 of the *Pitx3* gene in the chromosome 19), induces microphthalmia or anophthalmia and a loss of dopamine neurons in the substantia nigra, which induces motor impairment and increased nociceptive response (Rosemann et al., 2010). Another interesting mouse model, MitoPark, has been obtained by selectively removing the mitochondrial transcription factor A (Tfam) from dopamine midbrain neurons. These transgenic mice model an adult-onset of the disease, with a progressive loss of dopamine cell bodies and terminals, associated with tremors, limb rigidity and a progressive decline of locomotion and rearing (Ekstrand et al., 2007; Galter et al., 2010).

### **3. Non-motor symptoms in animal models of Parkinson's disease**

#### *3.1. Nociception and pain in rodent Parkinson's disease models (Figure 2)*

According to the definition from the International Association for the Study of Pain, pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. This sensory/emotional duality is a critical element. It distinguishes pain from nociception, which encompasses “the neural process of encoding noxious stimuli” and do not necessarily imply the presence of pain. However, distinguishing pain from nociception remains challenging in animal-based research, and tests that are referred to as “pain tests” are usually based on reflex responses that may reflect nociceptive responses (Barrot, 2012). Moreover, because of the implication of reflex motor responses in most of the tests used to study nociception in rodents and the potential slow-down

of motor reflexes in Parkinson's disease, it can also be challenging to correctly assess and interpret some nociceptive responses in rodent models of this disease.

Data reported below show that the nociceptive hypersensitivity observed in patients with Parkinson's disease (response to evoked pain) can be reproduced in some of the animal models. However, the presence of spontaneous pain, which may for example result from rigidity, akinesia, postural abnormality or dystonia, has not been studied yet in these models. While challenging, such question could now also be addressed in rodents. Indeed, procedures were developed in the past decade to test the aversive state induced by ongoing pain in rats and mice (Barthas et al., 2015; Johansen et al., 2001; King et al., 2009; Qu et al., 2011; Sellmeijer et al., 2018)

### 3.1.1. *Electrical sensitivity*

The threshold responses to electrical shocks can be used to assess pain sensitivity. In such test, electrical stimuli of increasing intensities are delivered through a grid floor and the threshold intensity eliciting the first response (*i.e.* flinch, vocalization, jumping or running) is measured (Barrot, 2012). Rats with a unilateral 6-OHDA lesion of the dopamine neurons show an hypersensitivity either in the ipsilateral (Chen et al., 2013) or the contralateral body side of the lesion (Carey, 1986) (Table 1).

### 3.1.2 *Mechanical sensitivity*

Although different tests are available to assess the response to mechanical stimuli in rodents (Barrot, 2012), particularly in rats (von Frey filaments, Randall-Selitto's paw pressure test...), most of the data from Parkinson's disease rodent models found in the literature are based on the von Frey filaments test. Mechanical nociceptive thresholds are usually lower in animal models of Parkinson's disease, regardless of the rodent species (mice or rat) or of the chosen model (6-OHDA, MPTP, *Pitx3*) (Cao et al., 2016; Charles et al., 2018; Chudler and Lu, 2008; Gee et al., 2015; Gómez-Paz et al., 2017; Nascimento et al., 2018; Park et al., 2015; Rosemann

et al., 2010; Saadé et al., 1997; Takeda et al., 2005, 2014; Wang et al., 2017; Zengin-Toktas et al., 2013). While this mechanical hypersensitivity now appears as well established, there are some discrepancies among published reports using a unilateral lesion (Charles et al., 2018; Chudler and Lu, 2008; Gee et al., 2015; Gómez-Paz et al., 2017; Nascimento et al., 2018; Saadé et al., 1997; Takeda et al., 2005, 2014), with results that may differ regarding the time-course and/or the laterality of the hypersensitivity. Changes in mechanical sensitivity have been correlated with decreased tyrosine hydroxylase expression in the substantia nigra *pars compacta* (Zengin-Toktas et al., 2013) and can be compensated by a neural transplantation of fetal ventral mesencephalon tissue in lesioned animals (Takeda et al., 2014) (Table 1).

Painful rigidity of the face, chin or jaw and trigeminal neuralgia-like pain can be present in the prodromal phase of Parkinson's disease (Waseem and Gwinn-Hardy, 2001). This trigeminal sensitivity can be tested in rodents with different approaches, using procedures assessing static or dynamic mechanical sensitivity. To test static (pressure) mechanical allodynia of the face, von Frey filaments can be applied to the vibrissae region. The bilateral lesion of the substantia nigra *pars compacta* leads to an increased nociceptive sensitivity of the two side of the face (Dieb et al., 2016), while a unilateral lesion in the caudate/putamen does not affect this response (Chudler and Lu, 2008). To test the dynamic mechanical allodynia, gentle air puff is applied on the animal face. Bilateral lesioned animals display a dynamic mechanical allodynia of the face, which is inversely correlated with the number of tyrosine hydroxylase positive cells (Dieb et al., 2014) (Table 1).

### 3.1.3 Thermal sensitivity

The tail flick test measures the withdrawal latency following tail exposure to a heat stimulus, by using an infrared heat beam or a warm-controlled water bath (Barrot, 2012; Le Bars et al., 2001). The response in this test is a nociceptive spinal reflex that is, however, influenced by descending controls from the brain. Mice with intraperitoneal injections of MPTP have reduced

tail flick latency (Park et al., 2015; Rosland et al., 1992), whereas *Pitx3*<sup>416insG</sup> mutant mice showed no significant difference (Rosemann et al., 2010). On the other hand, the literature concerning the thermal sensitivity in 6-OHDA models of Parkinson's disease is controversial, with opposite results that can be reported: increased latency (Grossmann et al., 1973; Tassorelli et al., 2007), no difference (Gee et al., 2015; Morgan and Franklin, 1990; Ogata et al., 2015) or decreased latency (Dolatshahi et al., 2015; Gómez-Paz et al., 2017; Haddadi et al., 2018; Nascimento et al., 2018; Saadé et al., 1997). A possible explanation for these discrepancies could be the co-presence of thermal hypersensitivity and of reflex slow-down. Depending on the location and the extent of the lesion, and on the test procedure and temperature settings, one or the other aspect may be predominant, which highlights the potential difficulty to interpret tail-flick results in these models. (Table 1).

The hot plate test measures the response to nociceptive heat by placing the animal on a plate at fixed and controlled temperature, often set in the 52 to 55°C range with a 0.1°C precision. The latency before the apparition of a withdrawal behavior, such as paw licking, paw withdrawal or eventually jumping, is measured (Barrot, 2012; Le Bars et al., 2001). Usually, whatever the model (MPTP or 6-OHDA) and the species (mouse or rat) that is used, the articles report an increased pain sensitivity (Chen et al., 2013; Dolatshahi et al., 2015; Gee et al., 2015; Lin et al., 1981; Nascimento et al., 2018; Park et al., 2015; Rosland et al., 1992; Saadé et al., 1997). In the paw immersion test, consisting in placing the animal's paw in a water bath at a fixed and controlled temperature, rats with 6-OHDA lesion in the ventral tegmental area and the substantia nigra displayed a decreased withdrawal latency, *i.e.* a hypersensitivity, concerning the paw contralateral to the lesion (Saadé et al., 1997) (Table 1).

In the radiant heat paw-withdrawal test, often referred to as the Hargreaves's method (Hargreaves et al., 1988), a controlled heat beam system is directed toward the plantar surface of the animal's hind paws in order to measure the withdrawal latency (Barrot, 2012). In this

test, *Pitx3*<sup>416insG</sup> mutant mice (Rosemann et al., 2010), rats at 3 weeks following 6-OHDA lesion of the caudate/putamen nuclei (Chudler and Lu, 2008) rats with 6-OHDA lesion of the right medial forebrain bundle (Charles et al., 2018), rats at 4 and 5 weeks following 6-OHDA bilateral lesion of the striatum (Cao et al., 2016) and rats with bilateral lesion of the substantia nigra *pars compacta* at 2 and 4 weeks post-surgery (Wang et al., 2017), displayed hyperalgesia as illustrated by decreased paw withdrawal latencies (Table 1).

Cold sensitivity is more rarely tested but can be assessed by for example applying a drop of acetone on the animal's paw. Rat with a unilateral lesion of the substantia nigra *pars compacta*, but not control animals, exhibit nocifensive responses such as paw withdrawal, licking, shaking or rubbing (Gómez-Paz et al., 2017), showing the presence of a cold allodynia.

#### 3.1.4 Response to nociceptive chemical exposure

The intradermal injection of a formalin solution models short-term inflammatory pain. It results in paw withdrawal, licking, biting or shaking. In rodents, these responses are classically divided in 2 phases: an initial phase during the first 5 or 10 minutes after the injection, related to the stimulation of nociceptors; and a second phase, lasting between 20 to 40 min, corresponding to both inflammatory mechanisms and central sensitization within the dorsal horn (Barrot, 2012; Le Bars et al., 2001). It has been shown that rats with 6-OHDA lesion, either in the cell bodies or terminals, displayed enhanced behavioral responses in the formalin test (Cao et al., 2016; Chudler and Lu, 2008; Gómez-Paz et al., 2017; Ogata et al., 2015; Tassorelli et al., 2007), thus reflecting hyperalgesia. This hyperalgesia was however detected in the second phase only (Chudler and Lu, 2008; Ogata et al., 2015) or in both phases (Cao et al., 2016; Gómez-Paz et al., 2017; Tassorelli et al., 2007), depending on the study. When formalin was delivered in the face (trigeminal pain) of rats with an unilateral striatal 6-OHDA lesion, grooming was significantly enhanced during the second (Chudler and Lu, 2008) or both phases of the test (Maegawa et al., 2015), reflecting an increased inflammatory pain response.

Changes in the formalin test following 6-OHDA lesion could also affect the sensitivity to pain relief, indeed midbrain 6-OHDA lesions suppressed D-amphetamine and morphine-induced analgesia in this test (Morgan and Franklin, 1990). On the other hand, in a transgenic LRRK2 model of Parkinson's disease, mutant mice did not show alteration of formalin test responses (Bichler et al., 2013), but this model displayed an overall limited range of symptoms. (Table 1)

In the writhing test, the irritant chemical are delivered intraperitoneally, which provokes abdominal contractions and twisting of dorso-abdominal muscles that can be quantified as an indicator of peritovisceral nociception (Le Bars et al., 2001). In *Pitx3*<sup>416insG</sup> mutant mice, visceral pain following intraperitoneal acetic acid delivery was significantly enhanced (Rosemann et al., 2010) (Table 1).

### *3.2. Blink reflex abnormalities in Parkinson's disease models (Figure 2)*

The blink reflex is related to the activity of the *orbicularis oculi* muscle and may be considered as a protective nociceptive response. The electrical stimulation of this muscle results in an electromyographic response composed of 2 different phases, the R1 and R2 components. The R1 component is the early component, which is only present on the stimulated side. The R2 component is present in both sides and appears later (Pearce, 2008). In Parkinson's disease, patients exhibit a hyperexcitability of the blink reflex, with shorter latency, increased amplitude and an increased habituation index (Esteban and Giménez-Roldán, 1975). In 6-OHDA lesioned rats, as in patients, a hyperexcitability of the blink reflex has also been observed, together with an impaired blink plasticity and a lower spontaneous blink rate (Basso et al., 1993; Kaminer et al., 2015) (Table 1).

### *3.3. Anxiety-like and depression-like behaviors in rodent Parkinson's disease models (Figure 3)*

Animal studies concerning anxiety and depression in Parkinson's disease mainly focused on dopaminergic mechanism, which unlikely reflects the complexity underlying the occurrence of these symptoms in patients. There is still indeed a paucity of studies addressing, beyond dopamine, the role of the other alterations of the nervous system, in particular for early stages of the disease.

### *3.3.1. Anxiety-like behavior in Parkinson's disease models*

Tests for anxiety-like behaviors in rodents, such as the elevated plus maze, the open field test and the hole-board test, are mostly based on exploratory behaviors in a novel environment. They more specifically rely on the natural tendency of rodents to explore novel environments and their innate avoidance of open, illuminated and/or elevated environment, and their behavioral response to anxiolytic drugs leading them to behave against their nature.

In the elevated plus maze, anxiety-like behavior is expressed by an increased time spend in the closed arms (or decreased time in the open arms) of the test (Pellow et al., 1985). This classical test has been used in various studies of experimental parkinsonism, but the motor disturbances present in some models may affect the response to this test, making important to have a control measure of locomotor activity (such as the number of crossing). Depending on the model, the species or the lesioned side, different findings were reported. In 6-OHDA models, most of the literature converge to report an increased anxiety-like profile in lesioned animals, corresponding to decreased time spent in the open arms of the test (Bonito-Oliva et al., 2014; Campos et al., 2013; Delaville et al., 2012; Faggiani et al., 2018; Hui et al., 2015; Jungnickel et al., 2011; Silva et al., 2016; Sun et al., 2015; Tadaiesky et al., 2008); but some articles reported no difference (Carvalho et al., 2013; Matheus et al., 2016) or even less anxiety-like behavior (Branchi et al., 2008). In these 6-OHDA models, the present number of studies does not allow to conclude whether the presence/absence of anxiety could be related to the

lesion side, to its unilateral/bilateral aspect or to the presence or no of a protection of noradrenergic fibers during the lesion procedure. However, a study showed that a co-lesion of either noradrenergic or serotonergic systems strongly potentiate anxiety-like behaviors after dopamine lesion (Delaville et al., 2012). Increased anxiety in the elevated plus maze has also been reported once in the paraquat (Campos et al., 2013) and lipopolysaccharide (Hritcu and Gorgan, 2014) models in rats, while the 2 studies in MPTP models reported either a lack (in mice) (Gorton et al., 2010) or a presence (in rats) (Ho et al., 2011) of increased anxiety. Results from neurotoxin-based models also mostly reported increased anxiety-like behaviors in other tests. This is the case for studies assessing social interactions (Branchi et al., 2008; Chiu et al., 2015; Eskow Jaunarajs et al., 2010; Matheus et al., 2016), for the marble burying test (Gorton et al., 2010), for two third of the literature concerning the open field test (Bonito-Oliva et al., 2014; Eskow Jaunarajs et al., 2010; Hui et al., 2015; Sun et al., 2015) and for one of the two publications using the hole-board test (Campos et al., 2013).

Conversely, genetic models mostly showed either a lack of change (Bichler et al., 2013; Campos et al., 2013; Caudal et al., 2015; Peña-Oliver et al., 2010) or a decrease (George et al., 2008; Oaks et al., 2013; Rothman et al., 2013; Yamakado et al., 2012) in anxiety-like behavior in the elevated plus maze test, thus differing from the above mentioned neurotoxin-based models (Table 2). While changes in behavior were observed in the presence of a predator odor (TMT) in a genetic model (Marxreiter et al., 2013; Nuber et al., 2008), a lack of increased anxiety-related responses has also been reported in the light-dark test (Peña-Oliver et al., 2010) and when looking at changes in body temperature under a stress condition (Caudal et al., 2015; Paumier et al., 2013). In the open-field test, genetic models were even mostly associated with an increased time spent in the center area (Oaks et al., 2013; Paumier et al., 2013; Rothman et al., 2013; Yamakado et al., 2012), which would normally reflect lower anxiety (Belzung, 1999) (Table 2). However, increased locomotor activity in the open-field, which may interfere with

anxiety-related data in this test, has for example been noted in Thy-1  $\alpha$ -synuclein mice (Lam et al., 2011). Studies may thus still be needed to understand whether these discrepancies between neurotoxin-based and genetic models reflect biological differences between models, in particular in their respective impact on aminergic and limbic systems, or reflect technical challenges in appropriately testing anxiety-like behaviors.

Lastly, only one article mentioned anxiety-like behaviors in a non-human primate model of Parkinson's disease (Niu et al., 2015). Authors analyzed potential ethological signs of anxiety (walking in circle, sucking on a finger or a toe, self-grasping) in 3 transgenic  $\alpha$ -synuclein rhesus monkeys and observed increased stereotypic behaviors in one of them (Niu et al., 2015) (Table 2). However, such "case report" does not allow concluding between pathological consequence and individual characteristics as explanation. More interestingly, some studies are now proposing measures of "spontaneous" abnormal or atypical behaviors in order to identify depressive-like behaviors in non-human primates (Camus et al., 2013a, 2013b, 2014). Using rhesus monkeys or cynomolgus macaques, it proposes to look at inactivity, feeding behaviors, social behaviors and body postures/orientations in these species. Applying this ethological approach to Parkinson's disease models still remains to be done.

### 3.3.2. *Depression-like behavior in Parkinson's disease models (Figure 4)*

The forced swim test consists of placing the animal in a water-filled cylinder with no possibility to escape. After an initial period of activity, *i.e.* swimming or attempts at climbing, the animal will stop to move and only make movements necessary to let its head above water. This immobility was qualified by Porsolt and colleagues as a characteristic of despair and resignation, and as a mean to screen antidepressant drugs because they reduce the duration of immobility in this test (Porsolt et al., 1977). Almost all studies with neurotoxin models of Parkinson's disease showed a decreased swimming time and/or increased immobility time (Berghauzen-Maciejewska et al., 2014; Bonito-Oliva et al., 2014; Branchi et al., 2008; Campos

et al., 2013; Casas et al., 2011; Chiu et al., 2015; Delaville et al., 2012; Hritcu and Gorgan, 2014; Ilkiw et al., 2018; Liu et al., 2015; Matheus et al., 2016; Santiago et al., 2014, 2010, Tadaiesky et al., 2010, 2008; Tuon et al., 2014). However, this effect is not always seen within the same time-frame, even in similar models (Berghauzen-Maciejewska et al., 2014; Matheus et al., 2016). Moreover, due to the potential presence of motor deficits, caution should likely be present when interpreting forced swim test data in models of Parkinson's disease. With the use of transgenic models, data are less consistent, with reports of increased immobility (Caudal et al., 2015; Taylor et al., 2009), of no difference (Bichler et al., 2013; Campos et al., 2013) or of decreased immobility (Nuber et al., 2011; Oaks et al., 2013). One hypothesis to explain these discrepancies would be that the deficits observed in genetic models could be progressive and age-dependent (Taylor et al., 2009) (Table 3).

Similar to the forced swim test, the tail suspension test is also based on an increased immobility response in a stress situation. In this test, used in mice only, the animal is suspended by its tail and the immobility time is measured. Acute antidepressant treatment given prior to the test is able to decrease this immobility (Duman, 2010). If some studies reported longer immobility time in mouse models of Parkinson's disease (Antunes et al., 2014; Bonito-Oliva et al., 2014; Taylor et al., 2009; Vucković et al., 2008), one third of the literature reported no difference with control animals (Bichler et al., 2013; Gorton et al., 2010). Again, this lack of phenotype has been proposed to be potentially related to the time-dependent development of the considered model (Taylor et al., 2009) (Table 3).

The sucrose preference test or sucrose consumption test is classically used as an indicator of anhedonia (lack of interest in rewarding stimuli), which is one of the symptoms that can be present in major depressive disorder. In pre-clinical models, the test usually consists in a two-bottle choice paradigm, with free access to a bottle with sucrose and one of water. A lack of preference (50% of preference) would be a sign of anhedonia, but the total amount of sucrose

intake can also be considered as a relevant parameter. Some studies reported no difference between animal models of Parkinson's disease and their controls (Branchi et al., 2008; Campos et al., 2013; Gorton et al., 2010; Vucković et al., 2008), but most of published data showed a significant reduction in either sucrose consumption and/or sucrose preference (Carvalho et al., 2013; Caudal et al., 2015; Chen et al., 2018; Delaville et al., 2012; Ilkiw et al., 2018; Kamińska et al., 2017; Krupina et al., 1995; Liu et al., 2015; Matheus et al., 2016; Santiago et al., 2010; Silva et al., 2016; Tadaiesky et al., 2008; Vecchia et al., 2018). As mentioned above, this difference can be time-dependent in the considered models (Caudal et al., 2015; Matheus et al., 2016; Santiago et al., 2010, 2014), and it has been suggested for both the forced swim test and the sucrose preference that adding a co-lesion of noradrenergic and serotonergic systems to the dopamine lesion favors depression-like behaviors (Delaville et al., 2012).

A recent trend for addressing depression-like phenotypes in rodents is to consider alterations of naturally occurring behaviors of animals, such as grooming or nesting. The splash test consists in a pulverization of a sugar solution on the coat of the animal and the measure of the grooming time. A reduction in this grooming time may relate to apathy in human, which is one of the symptoms of major depressive disorder. A 6-OHDA lesion of the dorsal striatum decreases grooming time at one week (but no more at 3 weeks) post-lesion (Matheus et al., 2016). In A53T mutant mice, a deficit in overall grooming behavior is also present, particularly at 2 and 6 months of age (Paumier et al., 2013). On the other hand, the nesting test consists in evaluating the quality of a nest made by the animal, with for example a score ranging from 0 to 4 or 5, 0 corresponding to an absence of nest and the highest score to a fully finished nest. This test is responsive to antidepressant drugs. A deficit and delay in cotton use for nest building has been observed in the Thy-1  $\alpha$ -synuclein mice (Fleming et al., 2004), which was proposed to be related to both deficits in fine motor skills and decreased motivation to build nest. In this test,

both the A53T mutant mice (Paumier et al., 2013) and the MitoPark model (Chen et al., 2018) also display a significant deficit in nest building (Table 3).

The learned helplessness paradigm consists in the exposure to an inescapable stress (*i.e.* footshocks), followed by an active avoidance test. Pre-exposed animals that display a reduced ability to escape from the shocks (Duman, 2010) are qualified as “helpless”. It is used as a model of either major depressive disorder or posttraumatic stress disorder, depending on the considered protocol. Both complete (98%) and partial (75% and 45%) 6-OHDA lesion increased the latency to escape shock presentation and the proportion of rats meeting “helpless” criteria (Winter et al., 2007) (Table 3). However, interpretation of those findings is not easy. Indeed, independently from shock pre-exposure, it has been reported 40 years ago that 6-OHDA injections into dopamine cell bodies or terminals induces a decrease in the number of avoidance responses in the active avoidance test (Delacour et al., 1977; Lin et al., 1978). While such deficit can be present even in the absence of significant alteration in locomotor activity (Delacour et al., 1977), it is unsure whether it is reflecting a deficit in learning the avoidance procedure or it is reflecting an actual “helpless” state.

#### **4. Conclusion**

Beyond dopamine cell loss and motor symptoms, Parkinson’s disease is a complex disease that leads to a variety of non-motor symptoms, including pain, anxiety and depression in a notable proportion of patients. For decades, experimental research on Parkinson’s disease has focused on the motor symptoms as well as on the dopamine system. Indeed, until recently, most data in animal models were limited to dopaminergic alterations, which could not explain Parkinson’s disease semiology, particularly in the early stage of the disease. A given symptom, however, may not necessarily arise from changes in a single given system. It can also be

hypothesized that alterations in different systems (including the dopamine one) may add-on to a symptom and cumulatively contribute to its severity.

While the search for disease-modifying strategies is intense, the acknowledgment of the non-motor symptoms' burden upon Parkinson's disease patient's quality of life has only recently come to experimental researchers' attention, as witnessed by the relatively sparse and recent literature (Figure 5). Nevertheless, the present literature suggests that existing models of Parkinson's disease allow modeling non-motor symptoms, thus making possible to address mechanistic aspects and/or take such symptoms into consideration for preclinical testing of new therapeutic approaches. Preclinical studies of non-motor symptoms will however still require more systematic characterization to establish their presence/absence and time-line in various models, in order to provide standardization with robust and reliable outputs for some of them. On the other hand, one might consider that individual variability in the presence/absence of these symptoms may be naturally present in experimental models as it is in patients, which may partly contribute to the heterogeneity in reporting these symptoms in experimental studies that are classically based on small cohorts. Progress would anyway require that these aspects of Parkinson's disease are more often tested and studied in rodent and non-human primate models.

## **5. Acknowledgments**

This work was supported by the Centre National de la Recherche Scientifique [contracts UPR3212 and UMR5293], the University of Strasbourg, the University of Bordeaux, the Agence Nationale de la Recherche [ANR-15-CE37-0005-02; Euridol ANR-17-EURE-0022], the Fondation pour la Recherche Médicale [FDT20170437322], the NeuroTime Erasmus Mondus Joint Doctorate and by a NARSAD distinguish investigator grant from the Brain and Behavior Research Foundation [24220].

**6. Conflict of interest statement**

The authors declare no conflict of interest.

ACCEPTED MANUSCRIPT

## 7. References

- Allen, N.E., Wong, C.M., Canning, C.G., Moloney, N., 2016. The Association Between Parkinson's Disease Motor Impairments and Pain. *Pain Med.* 17, 456–462. <https://doi.org/10.1111/pme.12898>
- Antkiewicz-Michaluk, L., Karolewicz, B., Romańska, I., Michaluk, J., Bojarski, A.J., Vetulani, J., 2003. 1-methyl-1,2,3,4-tetrahydroisoquinoline protects against rotenone-induced mortality and biochemical changes in rat brain. *Eur. J. Pharmacol.* 466, 263–269.
- Antunes, M.S., Goes, A.T.R., Boeira, S.P., Prigol, M., Jesse, C.R., 2014. Protective effect of hesperidin in a model of Parkinson's disease induced by 6-hydroxydopamine in aged mice. *Nutrition* 30, 1415–1422. <https://doi.org/10.1016/j.nut.2014.03.024>
- Bankiewicz, K.S., Sanchez-Pernaute, R., Oiwa, Y., Kohutnicka, M., Cummins, A., Eberling, J., 2001. Preclinical Models of Parkinson's Disease. *Curr. Protoc. Neurosci.* <https://doi.org/10.1002/0471142301.ns0904s09>
- Barone, P., Antonini, A., Colosimo, C., Marconi, R., Morgante, L., Avarello, T.P., Bottacchi, E., Cannas, A., Ceravolo, G., Ceravolo, R., Cicarelli, G., Gaglio, R.M., Giglia, R.M., Iemolo, F., Manfredi, M., Mecò, G., Nicoletti, A., Pederzoli, M., Petrone, A., Pisani, A., Pontieri, F.E., Quatrone, R., Ramat, S., Scala, R., Volpe, G., Zappulla, S., Bentivoglio, A.R., Stocchi, F., Trianni, G., Dotto, P.D., PRIAMO study group, 2009. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov. Disord.* 24, 1641–1649. <https://doi.org/10.1002/mds.22643>
- Barrot, M., 2012. Tests and models of nociception and pain in rodents. *Neuroscience* 211, 39–50. <https://doi.org/10.1016/j.neuroscience.2011.12.041>

- Barthas, F., Sellmeijer, J., Hugel, S., Waltisperger, E., Barrot, M., Yalcin, I., 2015. The anterior cingulate cortex is a critical hub for pain-induced depression. *Biol. Psychiatry* 77, 236–245. <https://doi.org/10.1016/j.biopsych.2014.08.004>
- Basso, M.A., Strecker, R.E., Evinger, C., 1993. Midbrain 6-hydroxydopamine lesions modulate blink reflex excitability. *Exp. Brain Res.* 94, 88–96.
- Bastías-Candia, S., Di Benedetto, M., D’Addario, C., Candeletti, S., Romualdi, P., 2015. Combined exposure to agriculture pesticides, paraquat and maneb, induces alterations in the N/OFQ-NOPr and PDYN/KOPr systems in rats: Relevance to sporadic Parkinson’s disease. *Environ. Toxicol.* 30, 656–663. <https://doi.org/10.1002/tox.21943>
- Bastías-Candia, S., Zolezzi, J.M., Inestrosa, N.C., 2018. Revisiting the Paraquat-Induced Sporadic Parkinson’s Disease-Like Model. *Mol. Neurobiol.* <https://doi.org/10.1007/s12035-018-1148-z>
- Beiske, A.G., Loge, J.H., Rønningen, A., Svensson, E., 2009. Pain in Parkinson’s disease: Prevalence and characteristics. *Pain* 141, 173–177. <https://doi.org/10.1016/j.pain.2008.12.004>
- Belzung, C., 1999. Chapter 4.11 Measuring rodent exploratory behavior, in: Crusio, W.E., Gerlai, R.T. (Eds.), *Techniques in the Behavioral and Neural Sciences, Handbook of Molecular-Genetic Techniques for Brain and Behavior Research*. Elsevier, pp. 738–749. [https://doi.org/10.1016/S0921-0709\(99\)80057-1](https://doi.org/10.1016/S0921-0709(99)80057-1)
- Berghauzen-Maciejewska, K., Kuter, K., Kolasiewicz, W., Głowacka, U., Dziubina, A., Ossowska, K., Wardas, J., 2014. Pramipexole but not imipramine or fluoxetine reverses the “depressive-like” behaviour in a rat model of preclinical stages of Parkinson’s disease. *Behav. Brain Res.* 271, 343–353. <https://doi.org/10.1016/j.bbr.2014.06.029>
- Bertrand, E., Lechowicz, W., Szpak, G.M., Dymecki, J., 1997. Qualitative and quantitative analysis of locus coeruleus neurons in Parkinson’s disease. *Folia Neuropathol.* 35, 80–86.

- Betarbet, R., Sherer, T.B., Greenamyre, J.T., 2002. Animal models of Parkinson's disease. *BioEssays* 24, 308–318. <https://doi.org/10.1002/bies.10067>
- Betarbet, R., Sherer, T.B., MacKenzie, G., Garcia-Osuna, M., Panov, A.V., Greenamyre, J.T., 2000. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat. Neurosci.* 3, 1301–1306. <https://doi.org/10.1038/81834>
- Bezard, E., Fernagut, P.-O., 2014. Premotor parkinsonism models. *Parkinsonism Relat. Disord.* 20 Suppl 1, S17-19. [https://doi.org/10.1016/S1353-8020\(13\)70007-5](https://doi.org/10.1016/S1353-8020(13)70007-5)
- Bezard, E., Przedborski, S., 2011. A tale on animal models of Parkinson's disease. *Mov. Disord.* 26, 993–1002. <https://doi.org/10.1002/mds.23696>
- Bezard, E., Yue, Z., Kirik, D., Spillantini, M.G., 2013. Animal models of Parkinson's disease: limits and relevance to neuroprotection studies. *Mov. Disord.* 28, 61–70. <https://doi.org/10.1002/mds.25108>
- Bichler, Z., Lim, H.C., Zeng, L., Tan, E.K., 2013. Non-motor and motor features in LRRK2 transgenic mice. *PloS One* 8, e70249. <https://doi.org/10.1371/journal.pone.0070249>
- Blanchet, P.J., Brefel-Courbon, C., 2017. Chronic pain and pain processing in Parkinson's disease. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* In press. <https://doi.org/10.1016/j.pnpbp.2017.10.010>
- Blum, D., Torch, S., Lambeng, N., Nissou, M., Benabid, A.L., Sadoul, R., Verna, J.M., 2001. Molecular pathways involved in the neurotoxicity of 6-OHDA, dopamine and MPTP: contribution to the apoptotic theory in Parkinson's disease. *Prog. Neurobiol.* 65, 135–172.
- Bonifati, V., Rizzu, P., Baren, M.J. van, Schaap, O., Breedveld, G.J., Krieger, E., Dekker, M.C.J., Squitieri, F., Ibanez, P., Joosse, M., Dongen, J.W. van, Vanacore, N., Swieten, J.C. van, Brice, A., Meco, G., Duijn, C.M. van, Oostra, B.A., Heutink, P., 2003a. Mutations in the DJ-1 Gene Associated with Autosomal Recessive Early-Onset Parkinsonism. *Science* 299, 256–259. <https://doi.org/10.1126/science.1077209>

- Bonifati, V., Rizzu, P., Squitieri, F., Krieger, E., Vanacore, N., van Swieten, J.C., Brice, A., van Duijn, C.M., Oostra, B., Meco, G., Heutink, P., 2003b. DJ-1( PARK7), a novel gene for autosomal recessive, early onset parkinsonism. *Neurol. Sci.* 24, 159–160. <https://doi.org/10.1007/s10072-003-0108-0>
- Bonito-Oliva, A., Masini, D., Fisone, G., 2014. A mouse model of non-motor symptoms in Parkinson's disease: focus on pharmacological interventions targeting affective dysfunctions. *Front. Behav. Neurosci.* 8, 290. <https://doi.org/10.3389/fnbeh.2014.00290>
- Bourdenx, M., Dovero, S., Engeln, M., Bido, S., Bastide, M.F., Dutheil, N., Vollenweider, I., Baud, L., Piron, C., Grouthier, V., Boraud, T., Porras, G., Li, Q., Baekelandt, V., Scheller, D., Michel, A., Fernagut, P.-O., Georges, F., Courtine, G., Bezard, E., Dehay, B., 2015. Lack of additive role of ageing in nigrostriatal neurodegeneration triggered by  $\alpha$ -synuclein overexpression. *Acta Neuropathol. Commun.* 3, 46. <https://doi.org/10.1186/s40478-015-0222-2>
- Bové, J., Perier, C., 2012. Neurotoxin-based models of Parkinson's disease. *Neuroscience* 211, 51–76. <https://doi.org/10.1016/j.neuroscience.2011.10.057>
- Boyce, S., Kelly, E., Reavill, C., Jenner, P., Marsden, C.D., 1984. Repeated administration of N-methyl-4-phenyl 1,2,5,6-tetrahydropyridine to rats is not toxic to striatal dopamine neurones. *Biochem. Pharmacol.* 33, 1747–1752.
- Braak, H., Del Tredici, K., Bratzke, H., Hamm-Clement, J., Sandmann-Keil, D., Rüb, U., 2002. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). *J. Neurol.* 249 Suppl 3, III/1-5.
- Braak, H., Del Tredici, K., Rüb, U., de Vos, R.A.I., Jansen Steur, E.N.H., Braak, E., 2003. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* 24, 197–211.
- Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., Del Tredici, K., 2004. Stages in the

- development of Parkinson's disease-related pathology. *Cell Tissue Res.* 318, 121–134.  
<https://doi.org/10.1007/s00441-004-0956-9>
- Branchi, I., D'Andrea, I., Armida, M., Cassano, T., Pèzzola, A., Potenza, R.L., Morgese, M.G., Popoli, P., Alleva, E., 2008. Nonmotor symptoms in Parkinson's disease: investigating early-phase onset of behavioral dysfunction in the 6-hydroxydopamine-lesioned rat model. *J. Neurosci. Res.* 86, 2050–2061. <https://doi.org/10.1002/jnr.21642>
- Brefel-Courbon, C., Payoux, P., Thalamas, C., Ory, F., Quelven, I., Chollet, F., Montastruc, J.L., Rascol, O., 2005. Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov. Disord.* 20, 1557–1563.  
<https://doi.org/10.1002/mds.20629>
- Burn, D.J., 2002. Beyond the iron mask: towards better recognition and treatment of depression associated with Parkinson's disease. *Mov. Disord.* 17, 445–454.  
<https://doi.org/10.1002/mds.10114>
- Campos, F.L., Carvalho, M.M., Cristovão, A.C., Je, G., Baltazar, G., Salgado, A.J., Kim, Y.-S., Sousa, N., 2013. Rodent models of Parkinson's disease: beyond the motor symptomatology. *Front. Behav. Neurosci.* 7, 175.  
<https://doi.org/10.3389/fnbeh.2013.00175>
- Camus, S.M.J., Blois-Heulin, C., Li, Q., Hausberger, M., Bezard, E., 2013a. Behavioural profiles in captive-bred cynomolgus macaques: towards monkey models of mental disorders? *PloS One* 8, e62141. <https://doi.org/10.1371/journal.pone.0062141>
- Camus, S.M.J., Rochais, C., Blois-Heulin, C., Li, Q., Hausberger, M., Bezard, E., 2014. Depressive-like behavioral profiles in captive-bred single- and socially-housed rhesus and cynomolgus macaques: a species comparison. *Front. Behav. Neurosci.* 8, 47.  
<https://doi.org/10.3389/fnbeh.2014.00047>

- Camus, S.M.J., Rochais, C., Blois-Heulin, C., Li, Q., Hausberger, M., Bezard, E., 2013b. Birth origin differentially affects depressive-like behaviours: are captive-born cynomolgus monkeys more vulnerable to depression than their wild-born counterparts? *PloS One* 8, e67711. <https://doi.org/10.1371/journal.pone.0067711>
- Cao, L.-F., Peng, X.-Y., Huang, Y., Wang, B., Zhou, F.-M., Cheng, R.-X., Chen, L.-H., Luo, W.-F., Liu, T., 2016. Restoring Spinal Noradrenergic Inhibitory Tone Attenuates Pain Hypersensitivity in a Rat Model of Parkinson's Disease. *Neural Plast.* 2016, 6383240. <https://doi.org/10.1155/2016/6383240>
- Carey, R.J., 1986. Acute ipsilateral hyperalgesia and chronic contralateral hypoalgesia after unilateral 6-hydroxydopamine lesions of the substantia nigra. *Exp. Neurol.* 91, 277–284.
- Carvalho, M.M., Campos, F.L., Coimbra, B., Pêgo, J.M., Rodrigues, C., Lima, R., Rodrigues, A.J., Sousa, N., Salgado, A.J., 2013. Behavioral characterization of the 6-hydroxydopamine model of Parkinson's disease and pharmacological rescuing of non-motor deficits. *Mol. Neurodegener.* 8, 14. <https://doi.org/10.1186/1750-1326-8-14>
- Casas, S., García, S., Cabrera, R., Nanfaro, F., Escudero, C., Yunes, R., 2011. Progesterone prevents depression-like behavior in a model of Parkinson's disease induced by 6-hydroxydopamine in male rats. *Pharmacol. Biochem. Behav.* 99, 614–618. <https://doi.org/10.1016/j.pbb.2011.06.012>
- Castaño, A., Herrera, A.J., Cano, J., Machado, A., 1998. Lipopolysaccharide intranigral injection induces inflammatory reaction and damage in nigrostriatal dopaminergic system. *J. Neurochem.* 70, 1584–1592.
- Caudal, D., Alvarsson, A., Björklund, A., Svenningsson, P., 2015. Depressive-like phenotype induced by AAV-mediated overexpression of human  $\alpha$ -synuclein in midbrain dopaminergic neurons. *Exp. Neurol.* 273, 243–252. <https://doi.org/10.1016/j.expneurol.2015.09.002>
- Chan, P., DeLanney, L.E., Irwin, I., Langston, J.W., Di Monte, D., 1991. Rapid ATP loss

- caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mouse brain. *J. Neurochem.* 57, 348–351.
- Chandran, J.S., Lin, X., Zapata, A., Höke, A., Shimoji, M., Moore, S.O., Galloway, M.P., Laird, F.M., Wong, P.C., Price, D.L., Bailey, K.R., Crawley, J.N., Shippenberg, T., Cai, H., 2008. Progressive behavioral deficits in DJ-1-deficient mice are associated with normal nigrostriatal function. *Neurobiol. Dis.* 29, 505–514. <https://doi.org/10.1016/j.nbd.2007.11.011>
- Charles, K.-A., Naudet, F., Bouali-Benazzouz, R., Landry, M., De Deurwaerdère, P., Fossat, P., Benazzouz, A., 2018. Alteration of nociceptive integration in the spinal cord of a rat model of Parkinson's disease. *Mov. Disord.* <https://doi.org/10.1002/mds.27377>
- Chaudhuri, K.R., Healy, D.G., Schapira, A.H.V., National Institute for Clinical Excellence, 2006. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol.* 5, 235–245. [https://doi.org/10.1016/S1474-4422\(06\)70373-8](https://doi.org/10.1016/S1474-4422(06)70373-8)
- Chen, C., Li, X., Ge, G., Liu, J., Bijou, K.C., Laing, S.D., Qian, Y., Ballard, C., He, Z., Masliah, E., Clark, R.A., O'Connor, J.C., Li, S., 2018. GDNF-expressing macrophages mitigate loss of dopamine neurons and improve Parkinsonian symptoms in MitoPark mice. *Sci. Rep.* 8, 5460. <https://doi.org/10.1038/s41598-018-23795-4>
- Chen, C.-C.V., Shih, Y.-Y.I., Chang, C., 2013. Dopaminergic imaging of nonmotor manifestations in a rat model of Parkinson's disease by fMRI. *Neurobiol. Dis.* 49, 99–106. <https://doi.org/10.1016/j.nbd.2012.07.020>
- Chen, L., Cagniard, B., Mathews, T., Jones, S., Koh, H.C., Ding, Y., Carvey, P.M., Ling, Z., Kang, U.J., Zhuang, X., 2005. Age-dependent motor deficits and dopaminergic dysfunction in DJ-1 null mice. *J. Biol. Chem.* 280, 21418–21426. <https://doi.org/10.1074/jbc.M413955200>
- Chesselet, M.-F., 2008. In vivo alpha-synuclein overexpression in rodents: a useful model of

- Parkinson's disease? *Exp. Neurol.* 209, 22–27.  
<https://doi.org/10.1016/j.expneurol.2007.08.006>
- Chiu, W.-H., Depboylu, C., Hermanns, G., Maurer, L., Windolph, A., Oertel, W.H., Ries, V., Höglinger, G.U., 2015. Long-term treatment with L-DOPA or pramipexole affects adult neurogenesis and corresponding non-motor behavior in a mouse model of Parkinson's disease. *Neuropharmacology* 95, 367–376.  
<https://doi.org/10.1016/j.neuropharm.2015.03.020>
- Chiueh, C.C., Markey, S.P., Burns, R.S., Johannessen, J.N., Jacobowitz, D.M., Kopin, I.J., 1984a. Neurochemical and behavioral effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in rat, guinea pig, and monkey. *Psychopharmacol. Bull.* 20, 548–553.
- Chiueh, C.C., Markey, S.P., Burns, R.S., Johannessen, J.N., Pert, A., Kopin, I.J., 1984b. Neurochemical and behavioral effects of systemic and intranigral administration of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the rat. *Eur. J. Pharmacol.* 100, 189–194.
- Chudler, E.H., Lu, Y., 2008. Nociceptive behavioral responses to chemical, thermal and mechanical stimulation after unilateral, intrastriatal administration of 6-hydroxydopamine. *Brain Res.* 1213, 41–47. <https://doi.org/10.1016/j.brainres.2008.03.053>
- Creed, R.B., Goldberg, M.S., 2018. New Developments in Genetic rat models of Parkinson's Disease. *Mov. Disord.* 33, 717–729. <https://doi.org/10.1002/mds.27296>
- Cummings, J.L., 1992. Depression and Parkinson's disease: a review. *Am. J. Psychiatry* 149, 443–454. <https://doi.org/10.1176/ajp.149.4.443>
- Czernecki, V., Pillon, B., Houeto, J.L., Pochon, J.B., Levy, R., Dubois, B., 2002. Motivation, reward, and Parkinson's disease: influence of dopatherapy. *Neuropsychologia* 40, 2257–2267. [https://doi.org/10.1016/S0028-3932\(02\)00108-2](https://doi.org/10.1016/S0028-3932(02)00108-2)
- Darweesh, S.K.L., Verlinden, V.J.A., Stricker, B.H., Hofman, A., Koudstaal, P.J., Ikram, M.A.,

2017. Trajectories of prediagnostic functioning in Parkinson's disease. *Brain J. Neurol.* 140, 429–441. <https://doi.org/10.1093/brain/aww291>
- Dauer, W., Przedborski, S., 2003. Parkinson's disease: mechanisms and models. *Neuron* 39, 889–909.
- Davis, G.C., Williams, A.C., Markey, S.P., Ebert, M.H., Caine, E.D., Reichert, C.M., Kopin, I.J., 1979. Chronic Parkinsonism secondary to intravenous injection of meperidine analogues. *Psychiatry Res.* 1, 249–254.
- Dawson, T.M., Ko, H.S., Dawson, V.L., 2010. Genetic animal models of Parkinson's disease. *Neuron* 66, 646–661. <https://doi.org/10.1016/j.neuron.2010.04.034>
- Delacour, J., Echavarria, M.T., Senault, B., Houcine, O., 1977. Specificity of avoidance deficits produced by 6-hydroxydopamine lesions of the nigrostriatal system of the rat. *J. Comp. Physiol. Psychol.* 91, 875–885.
- Delaville, C., Chetrit, J., Abdallah, K., Morin, S., Cardoit, L., De Deurwaerdère, P., Benazzouz, A., 2012. Emerging dysfunctions consequent to combined monoaminergic depletions in Parkinsonism. *Neurobiol. Dis.* 45, 763–773. <https://doi.org/10.1016/j.nbd.2011.10.023>
- Delaville, C., Deurwaerdère, P.D., Benazzouz, A., 2011. Noradrenaline and Parkinson's disease. *Front. Syst. Neurosci.* 5, 31. <https://doi.org/10.3389/fnsys.2011.00031>
- Dieb, W., Ouachikh, O., Durif, F., Hafidi, A., 2016. Nigrostriatal dopaminergic depletion produces orofacial static mechanical allodynia. *Eur. J. Pain* 20, 196–205. <https://doi.org/10.1002/ejp.707>
- Dieb, W., Ouachikh, O., Durif, F., Hafidi, A., 2014. Lesion of the dopaminergic nigrostriatal pathway induces trigeminal dynamic mechanical allodynia. *Brain Behav.* 4, 368–380. <https://doi.org/10.1002/brb3.214>
- Dissanayaka, N.N.W., Sellbach, A., Matheson, S., O'Sullivan, J.D., Silburn, P.A., Byrne, G.J., Marsh, R., Mellick, G.D., 2010. Anxiety disorders in Parkinson's disease: prevalence and

- risk factors. *Mov. Disord.* 25, 838–845. <https://doi.org/10.1002/mds.22833>
- Dolatshahi, M., Farbood, Y., Sarkaki, A., Mansouri, S.M.T., Khodadadi, A., 2015. Ellagic acid improves hyperalgesia and cognitive deficiency in 6-hydroxidopamine induced rat model of Parkinson's disease. *Iran. J. Basic Med. Sci.* 18, 38–46.
- Duman, C.H., 2010. Models of depression. *Vitam. Horm.* 82, 1–21. [https://doi.org/10.1016/S0083-6729\(10\)82001-1](https://doi.org/10.1016/S0083-6729(10)82001-1)
- Dusonchet, J., Kochubey, O., Stafa, K., Young, S.M., Zufferey, R., Moore, D.J., Schneider, B.L., Aebischer, P., 2011. A rat model of progressive nigral neurodegeneration induced by the Parkinson's disease-associated G2019S mutation in LRRK2. *J. Neurosci.* 31, 907–912. <https://doi.org/10.1523/JNEUROSCI.5092-10.2011>
- Ehringer, H., Hornykiewicz, O., 1960. Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. *Klin. Wochenschr.* 38, 1236–1239.
- Ekstrand, M.I., Terzioglu, M., Galter, D., Zhu, S., Hofstetter, C., Lindqvist, E., Thams, S., Bergstrand, A., Hansson, F.S., Trifunovic, A., Hoffer, B., Cullheim, S., Mohammed, A.H., Olson, L., Larsson, N.-G., 2007. Progressive parkinsonism in mice with respiratory-chain-deficient dopamine neurons. *Proc. Natl. Acad. Sci. U. S. A.* 104, 1325–1330. <https://doi.org/10.1073/pnas.0605208103>
- Engeln, M., De Deurwaerdère, P., Li, Q., Bezard, E., Fernagut, P.-O., 2015. Widespread Monoaminergic Dysregulation of Both Motor and Non-Motor Circuits in Parkinsonism and Dyskinesia. *Cereb. Cortex* 25, 2783–2792. <https://doi.org/10.1093/cercor/bhu076>
- Erro, R., Pappatà, S., Amboni, M., Vicidomini, C., Longo, K., Santangelo, G., Picillo, M., Vitale, C., Moccia, M., Giordano, F., Brunetti, A., Pellicchia, M.T., Salvatore, M., Barone, P., 2012. Anxiety is associated with striatal dopamine transporter availability in newly diagnosed untreated Parkinson's disease patients. *Parkinsonism Relat. Disord.* 18, 1034–

1038. <https://doi.org/10.1016/j.parkreldis.2012.05.022>
- Eskow Jaunarajs, K.L., Dupre, K.B., Ostock, C.Y., Button, T., Deak, T., Bishop, C., 2010. Behavioral and neurochemical effects of chronic L-DOPA treatment on nonmotor sequelae in the hemiparkinsonian rat. *Behav. Pharmacol.* 21, 627–637. <https://doi.org/10.1097/FBP.0b013e32833e7e80>
- Esteban, A., Giménez-Roldán, S., 1975. Blink reflex in Huntington's chorea and Parkinson's disease. *Acta Neurol. Scand.* 52, 145–157.
- Fabre, E., Monserrat, J., Herrero, A., Barja, G., Leret, M.L., 1999. Effect of MPTP on brain mitochondrial H<sub>2</sub>O<sub>2</sub> and ATP production and on dopamine and DOPAC in the striatum. *J. Physiol. Biochem.* 55, 325–331.
- Faggiani, E., Naudet, F., Janssen, M.L.F., Temel, Y., Benazzouz, A., 2018. Serotonergic neurons mediate the anxiolytic effect of l-DOPA: Neuronal correlates in the amygdala. *Neurobiol. Dis.* 110, 20–28. <https://doi.org/10.1016/j.nbd.2017.11.001>
- Fernagut, P.-O., Chesselet, M.-F., 2004. Alpha-synuclein and transgenic mouse models. *Neurobiol. Dis.* 17, 123–130. <https://doi.org/10.1016/j.nbd.2004.07.001>
- Filali, M., Lalonde, R., 2016. Neurobehavioral Anomalies in the Pitx3/ak Murine Model of Parkinson's Disease and MPTP. *Behav. Genet.* 46, 228–241. <https://doi.org/10.1007/s10519-015-9753-3>
- Fleming, S.M., Salcedo, J., Fernagut, P.-O., Rockenstein, E., Masliah, E., Levine, M.S., Chesselet, M.-F., 2004. Early and progressive sensorimotor anomalies in mice overexpressing wild-type human alpha-synuclein. *J. Neurosci.* 24, 9434–9440. <https://doi.org/10.1523/JNEUROSCI.3080-04.2004>
- Francardo, V., 2018. Modeling Parkinson's disease and treatment complications in rodents: Potentials and pitfalls of the current options. *Behav. Brain Res.* 352, 142–150. <https://doi.org/10.1016/j.bbr.2017.12.014>

- Funayama, M., Hasegawa, K., Kowa, H., Saito, M., Tsuji, S., Obata, F., 2002. A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2-q13.1. *Ann. Neurol.* 51, 296–301.
- Galter, D., Pernold, K., Yoshitake, T., Lindqvist, E., Hoffer, B., Kehr, J., Larsson, N.-G., Olson, L., 2010. MitoPark mice mirror the slow progression of key symptoms and L-DOPA response in Parkinson's disease. *Genes Brain Behav.* 9, 173–181. <https://doi.org/10.1111/j.1601-183X.2009.00542.x>
- Gee, L.E., Chen, N., Ramirez-Zamora, A., Shin, D.S., Pilitsis, J.G., 2015. The effects of subthalamic deep brain stimulation on mechanical and thermal thresholds in 6OHDA-lesioned rats. *Eur. J. Neurosci.* 42, 2061–2069. <https://doi.org/10.1111/ejn.12992>
- George, S., van den Buuse, M., San Mok, S., Masters, C.L., Li, Q.-X., Culvenor, J.G., 2008. Alpha-synuclein transgenic mice exhibit reduced anxiety-like behaviour. *Exp. Neurol.* 210, 788–792. <https://doi.org/10.1016/j.expneurol.2007.12.017>
- German, D.C., Manaye, K.F., White, C.L., Woodward, D.J., McIntire, D.D., Smith, W.K., Kalaria, R.N., Mann, D.M., 1992. Disease-specific patterns of locus coeruleus cell loss. *Ann. Neurol.* 32, 667–676. <https://doi.org/10.1002/ana.410320510>
- Giasson, B.I., Duda, J.E., Quinn, S.M., Zhang, B., Trojanowski, J.Q., Lee, V.M.-Y., 2002. Neuronal alpha-synucleinopathy with severe movement disorder in mice expressing A53T human alpha-synuclein. *Neuron* 34, 521–533.
- Giraldo, G., Brooks, M., Giasson, B.I., Janus, C., 2018. Locomotor differences in mice expressing wild-type human  $\alpha$ -synuclein. *Neurobiol. Aging* 65, 140–148. <https://doi.org/10.1016/j.neurobiolaging.2018.01.020>
- Gispert, S., Ricciardi, F., Kurz, A., Azizov, M., Hoepken, H.-H., Becker, D., Voos, W., Leuner, K., Müller, W.E., Kudin, A.P., Kunz, W.S., Zimmermann, A., Roeper, J., Wenzel, D., Jendrach, M., García-Arencibia, M., Fernández-Ruiz, J., Huber, L., Rohrer, H., Barrera, M.,

- Reichert, A.S., Rüb, U., Chen, A., Nussbaum, R.L., Auburger, G., 2009. Parkinson phenotype in aged PINK1-deficient mice is accompanied by progressive mitochondrial dysfunction in absence of neurodegeneration. *PloS One* 4, e5777. <https://doi.org/10.1371/journal.pone.0005777>
- Goldberg, M.S., Pisani, A., Haburcak, M., Vortherms, T.A., Kitada, T., Costa, C., Tong, Y., Martella, G., Tscherter, A., Martins, A., Bernardi, G., Roth, B.L., Pothos, E.N., Calabresi, P., Shen, J., 2005. Nigrostriatal dopaminergic deficits and hypokinesia caused by inactivation of the familial Parkinsonism-linked gene DJ-1. *Neuron* 45, 489–496. <https://doi.org/10.1016/j.neuron.2005.01.041>
- Gómez-Paz, A., Drucker-Colín, R., Milán-Aldaco, D., Palomero-Rivero, M., Ambriz-Tututi, M., 2017. Intrastriatal chromospheres' transplant reduces nociception in hemiparkinsonian rats. *Neuroscience*. <https://doi.org/10.1016/j.neuroscience.2017.08.052>
- Gorton, L.M., Vuckovic, M.G., Vertelkina, N., Petzinger, G.M., Jakowec, M.W., Wood, R.I., 2010. Exercise effects on motor and affective behavior and catecholamine neurochemistry in the MPTP-lesioned mouse. *Behav. Brain Res.* 213, 253–262. <https://doi.org/10.1016/j.bbr.2010.05.009>
- Grandi, L.C., Di Giovanni, G., Galati, S., 2018. Animal models of early-stage Parkinson's disease and acute dopamine deficiency to study compensatory neurodegenerative mechanisms. *J. Neurosci. Methods* 308, 205–218. <https://doi.org/10.1016/j.jneumeth.2018.08.012>
- Grossmann, W., Jurna, I., Nell, T., Theres, C., 1973. The dependence of the anti-nociceptive effect of morphine and other analgesic agents on spinal motor activity after central monoamine depletion. *Eur. J. Pharmacol.* 24, 67–77.
- Gubellini, P., Kachidian, P., 2015. Animal models of Parkinson's disease: An updated overview. *Rev. Neurol. (Paris)* 171, 750–761. <https://doi.org/10.1016/j.neurol.2015.07.011>

- Haddadi, H., Rajaei, Z., Alaei, H., Shahidani, S., 2018. Chronic treatment with carvacrol improves passive avoidance memory in a rat model of Parkinson's disease. *Arq. Neuropsiquiatr.* 76, 71–77. <https://doi.org/10.1590/0004-282X20170193>
- Halliday, G.M., Li, Y.W., Blumbergs, P.C., Joh, T.H., Cotton, R.G., Howe, P.R., Blessing, W.W., Geffen, L.B., 1990. Neuropathology of immunohistochemically identified brainstem neurons in Parkinson's disease. *Ann. Neurol.* 27, 373–385. <https://doi.org/10.1002/ana.410270405>
- Hargreaves, K., Dubner, R., Brown, F., Flores, C., Joris, J., 1988. A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. *Pain* 32, 77–88.
- Healy, D.G., Falchi, M., O'Sullivan, S.S., Bonifati, V., Durr, A., Bressman, S., Brice, A., Aasly, J., Zabetian, C.P., Goldwurm, S., Ferreira, J.J., Tolosa, E., Kay, D.M., Klein, C., Williams, D.R., Marras, C., Lang, A.E., Wszolek, Z.K., Berciano, J., Schapira, A.H.V., Lynch, T., Bhatia, K.P., Gasser, T., Lees, A.J., Wood, N.W., International LRRK2 Consortium, 2008. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. *Lancet Neurol.* 7, 583–590. [https://doi.org/10.1016/S1474-4422\(08\)70117-0](https://doi.org/10.1016/S1474-4422(08)70117-0)
- Hefti, F., Melamed, E., Sahakian, B.J., Wurtman, R.J., 1980. Circling behavior in rats with partial, unilateral nigro-striatal lesions: effect of amphetamine, apomorphine, and DOPA. *Pharmacol. Biochem. Behav.* 12, 185–188.
- Heinz, S., Freyberger, A., Lawrenz, B., Schladt, L., Schmuck, G., Ellinger-Ziegelbauer, H., 2017. Mechanistic Investigations of the Mitochondrial Complex I Inhibitor Rotenone in the Context of Pharmacological and Safety Evaluation. *Sci. Rep.* 7, 45465. <https://doi.org/10.1038/srep45465>
- Hernandez, D.G., Reed, X., Singleton, A.B., 2016. Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance. *J. Neurochem.* 139 Suppl 1, 59–74.

<https://doi.org/10.1111/jnc.13593>

- Ho, Y.-J., Ho, S.-C., Pawlak, C.R., Yeh, K.-Y., 2011. Effects of D-cycloserine on MPTP-induced behavioral and neurological changes: potential for treatment of Parkinson's disease dementia. *Behav. Brain Res.* 219, 280–290. <https://doi.org/10.1016/j.bbr.2011.01.028>
- Hritcu, L., Gorgan, L.D., 2014. Intranigral lipopolysaccharide induced anxiety and depression by altered BDNF mRNA expression in rat hippocampus. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 51, 126–132. <https://doi.org/10.1016/j.pnpbp.2014.01.016>
- Huang, C., Ravdin, L.D., Nirenberg, M.J., Piboolnurak, P., Severt, L., Maniscalco, J.S., Solnes, L., Dorfman, B.J., Henchcliffe, C., 2013. Neuroimaging markers of motor and nonmotor features of Parkinson's disease: an 18f fluorodeoxyglucose positron emission computed tomography study. *Dement. Geriatr. Cogn. Disord.* 35, 183–196. <https://doi.org/10.1159/000345987>
- Hughes, A.J., Daniel, S.E., Kilford, L., Lees, A.J., 1992. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J. Neurol. Neurosurg. Psychiatry* 55, 181–184.
- Hui, Y.P., Wang, T., Han, L.N., Li, L.B., Sun, Y.N., Liu, J., Qiao, H.F., Zhang, Q.J., 2015. Anxiolytic effects of prelimbic 5-HT(1A) receptor activation in the hemiparkinsonian rat. *Behav. Brain Res.* 277, 211–220. <https://doi.org/10.1016/j.bbr.2014.04.053>
- Ibáñez, P., Bonnet, A.-M., Débarges, B., Lohmann, E., Tison, F., Pollak, P., Agid, Y., Dürr, A., Brice, A., 2004. Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. *Lancet* 364, 1169–1171. [https://doi.org/10.1016/S0140-6736\(04\)17104-3](https://doi.org/10.1016/S0140-6736(04)17104-3)
- Ilkiw, J.L., Kmita, L.C., Targa, A.D.S., Nosedá, A.C.D., Rodrigues, L.S., Dorieux, F.W.C., Fagotti, J., Dos Santos, P., Lima, M.M.S., 2018. Dopaminergic Lesion in the Olfactory Bulb Restores Olfaction and Induces Depressive-Like Behaviors in a 6-OHDA Model of

- Parkinson's Disease. *Mol. Neurobiol.* <https://doi.org/10.1007/s12035-018-1134-5>
- Ip, C.W., Klaus, L.-C., Karikari, A.A., Visanji, N.P., Brothie, J.M., Lang, A.E., Volkman, J., Koprach, J.B., 2017. AAV1/2-induced overexpression of A53T- $\alpha$ -synuclein in the substantia nigra results in degeneration of the nigrostriatal system with Lewy-like pathology and motor impairment: a new mouse model for Parkinson's disease. *Acta Neuropathol. Commun.* 5, 11. <https://doi.org/10.1186/s40478-017-0416-x>
- Ishihara, L., Brayne, C., 2006. A systematic review of depression and mental illness preceding Parkinson's disease. *Acta Neurol. Scand.* 113, 211–220. <https://doi.org/10.1111/j.1600-0404.2006.00579.x>
- Itier, J.-M., Ibanez, P., Mena, M.A., Abbas, N., Cohen-Salmon, C., Bohme, G.A., Laville, M., Pratt, J., Corti, O., Pradier, L., Ret, G., Joubert, C., Periquet, M., Araujo, F., Negroni, J., Casarejos, M.J., Canals, S., Solano, R., Serrano, A., Gallego, E., Sanchez, M., Deneffe, P., Benavides, J., Tremp, G., Rooney, T.A., Brice, A., Garcia de Yebenes, J., 2003. Parkin gene inactivation alters behaviour and dopamine neurotransmission in the mouse. *Hum. Mol. Genet.* 12, 2277–2291. <https://doi.org/10.1093/hmg/ddg239>
- Jacob, E.L., Gatto, N.M., Thompson, A., Bordelon, Y., Ritz, B., 2010. Occurrence of depression and anxiety prior to Parkinson's disease. *Parkinsonism Relat. Disord.* 16, 576–581. <https://doi.org/10.1016/j.parkreldis.2010.06.014>
- Jellinger, K.A., 1991. Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. *Mol. Chem. Neuropathol.* 14, 153–197.
- Johansen, J.P., Fields, H.L., Manning, B.H., 2001. The affective component of pain in rodents: direct evidence for a contribution of the anterior cingulate cortex. *Proc. Natl. Acad. Sci. U. S. A.* 98, 8077–8082. <https://doi.org/10.1073/pnas.141218998>
- Jungnickel, J., Kalve, I., Reimers, L., Nobre, A., Wesemann, M., Ratzka, A., Halfer, N., Lindemann, C., Schwabe, K., Töllner, K., Gernert, M., Grothe, C., 2011. Topology of

- intrastratial dopaminergic grafts determines functional and emotional outcome in neurotoxin-lesioned rats. *Behav. Brain Res.* 216, 129–135.  
<https://doi.org/10.1016/j.bbr.2010.07.023>
- Kahle, P.J., Neumann, M., Ozmen, L., Muller, V., Jacobsen, H., Schindzielorz, A., Okochi, M., Leimer, U., van Der Putten, H., Probst, A., Kremmer, E., Kretschmar, H.A., Haass, C., 2000. Subcellular localization of wild-type and Parkinson's disease-associated mutant alpha-synuclein in human and transgenic mouse brain. *J. Neurosci.* 20, 6365–6373.
- Kaminer, J., Thakur, P., Evinger, C., 2015. Effects of subthalamic deep brain stimulation on blink abnormalities of 6-OHDA lesioned rats. *J. Neurophysiol.* 113, 3038–3046.  
<https://doi.org/10.1152/jn.01072.2014>
- Kamińska, K., Lenda, T., Konieczny, J., Czarnecka, A., Lorenc-Koci, E., 2017. Depressive-like neurochemical and behavioral markers of Parkinson's disease after 6-OHDA administered unilaterally to the rat medial forebrain bundle. *Pharmacol. Rep. PR* 69, 985–994.  
<https://doi.org/10.1016/j.pharep.2017.05.016>
- King, T., Vera-Portocarrero, L., Gutierrez, T., Vanderah, T.W., Dussor, G., Lai, J., Fields, H.L., Porreca, F., 2009. Unmasking the tonic-aversive state in neuropathic pain. *Nat. Neurosci.* 12, 1364–1366. <https://doi.org/10.1038/nn.2407>
- Kish, S.J., 2003. Biochemistry of Parkinson's disease: is a brain serotonergic deficiency a characteristic of idiopathic Parkinson's disease? *Adv. Neurol.* 91, 39–49.
- Kitada, T., Pisani, A., Porter, D.R., Yamaguchi, H., Tscherter, A., Martella, G., Bonsi, P., Zhang, C., Pothos, E.N., Shen, J., 2007. Impaired dopamine release and synaptic plasticity in the striatum of PINK1-deficient mice. *Proc. Natl. Acad. Sci. U. S. A.* 104, 11441–11446.  
<https://doi.org/10.1073/pnas.0702717104>
- Koller, W.C., 1984. Sensory symptoms in Parkinson's disease. *Neurology* 34, 957–959.
- Koprich, J.B., Kalia, L.V., Brotchie, J.M., 2017. Animal models of  $\alpha$ -synucleinopathy for

- Parkinson disease drug development. *Nat. Rev. Neurosci.* 18, 515–529.  
<https://doi.org/10.1038/nrn.2017.75>
- Krüger, R., Kuhn, W., Müller, T., Woitalla, D., Graeber, M., Kösel, S., Przuntek, H., Epplen, J.T., Schöls, L., Riess, O., 1998. Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. *Nat. Genet.* 18, 106–108. <https://doi.org/10.1038/ng0298-106>
- Krupina, N.A., Orlova, I.N., Kryzhanovskii, G.N., 1995. [The effect of parlodel on development of depressive syndrome in rats, caused by administering 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)]. *Biull. Eksp. Biol. Med.* 120, 66–70.
- Lam, H.A., Wu, N., Cely, I., Kelly, R.L., Hean, S., Richter, F., Magen, I., Cepeda, C., Ackerson, L.C., Walwyn, W., Masliah, E., Chesselet, M.-F., Levine, M.S., Maidment, N.T., 2011. Elevated tonic extracellular dopamine concentration and altered dopamine modulation of synaptic activity precede dopamine loss in the striatum of mice overexpressing human  $\alpha$ -synuclein. *J. Neurosci. Res.* 89, 1091–1102. <https://doi.org/10.1002/jnr.22611>
- Langston, J.W., Ballard, P., Tetrud, J.W., Irwin, I., 1983. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 219, 979–980.
- Lazarou, M., Narendra, D.P., Jin, S.M., Tekle, E., Banerjee, S., Youle, R.J., 2013. PINK1 drives Parkin self-association and HECT-like E3 activity upstream of mitochondrial binding. *J. Cell Biol.* 200, 163–172. <https://doi.org/10.1083/jcb.201210111>
- Le Bars, D., Gozariu, M., Cadden, S.W., 2001. Animal models of nociception. *Pharmacol. Rev.* 53, 597–652.
- Le, W., Zhang, L., Xie, W., Li, S., Dani, J.A., 2015. Pitx3 deficiency produces decreased dopamine signaling and induces motor deficits in Pitx3(-/-) mice. *Neurobiol. Aging* 36, 3314–3320. <https://doi.org/10.1016/j.neurobiolaging.2015.08.012>
- Lee, M.A., Walker, R.W., Hildreth, T.J., Prentice, W.M., 2006. A Survey of Pain in Idiopathic Parkinson's Disease. *J. Pain Symptom Manage.* 32, 462–469.

<https://doi.org/10.1016/j.jpainsymman.2006.05.020>

- Leentjens, A.F.G., Van den Akker, M., Metsemakers, J.F.M., Lousberg, R., Verhey, F.R.J., 2003. Higher incidence of depression preceding the onset of Parkinson's disease: a register study. *Mov. Disord.* 18, 414–418. <https://doi.org/10.1002/mds.10387>
- Li, N., Ragheb, K., Lawler, G., Sturgis, J., Rajwa, B., Melendez, J.A., Robinson, J.P., 2003. Mitochondrial complex I inhibitor rotenone induces apoptosis through enhancing mitochondrial reactive oxygen species production. *J. Biol. Chem.* 278, 8516–8525. <https://doi.org/10.1074/jbc.M210432200>
- Li, Y., Liu, W., Oo, T.F., Wang, L., Tang, Y., Jackson-Lewis, V., Zhou, C., Geghman, K., Bogdanov, M., Przedborski, S., Beal, M.F., Burke, R.E., Li, C., 2009. Mutant LRRK2(R1441G) BAC transgenic mice recapitulate cardinal features of Parkinson's disease. *Nat. Neurosci.* 12, 826–828. <https://doi.org/10.1038/nn.2349>
- Lim, K.-L., Ng, C.-H., 2009. Genetic models of Parkinson disease. *Biochim. Biophys. Acta* 1792, 604–615. <https://doi.org/10.1016/j.bbadis.2008.10.005>
- Lim, Y., Kehm, V.M., Li, C., Trojanowski, J.Q., Lee, V.M.-Y., 2010. Forebrain overexpression of alpha-synuclein leads to early postnatal hippocampal neuron loss and synaptic disruption. *Exp. Neurol.* 221, 86–97. <https://doi.org/10.1016/j.expneurol.2009.10.005>
- Lin, M.T., Chia, W.Y., Tsai, C.T., Yin, T.H., 1978. Effects of brain monoamine depletion on thermoregulation, active avoidance, and food and water intake in rats. *Experientia* 34, 756–757.
- Lin, M.T., Wu, J.J., Chandra, A., Tsay, B.L., 1981. Activation of striatal dopamine receptors induces pain inhibition in rats. *J. Neural Transm.* 51, 213–222.
- Liu, K.-C., Li, J.-Y., Tan, H.-H., Du, C.-X., Xie, W., Zhang, Y.-M., Ma, W.-L., Zhang, L., 2015. Serotonin<sub>6</sub> receptors in the dorsal hippocampus regulate depressive-like behaviors in unilateral 6-hydroxydopamine-lesioned Parkinson's rats. *Neuropharmacology* 95, 290–298.

- <https://doi.org/10.1016/j.neuropharm.2015.03.031>
- Liu, M., Bing, G., 2011. Lipopolysaccharide Animal Models for Parkinson's Disease. *Park. Dis.* <https://doi.org/10.4061/2011/327089>
- Luk, K.C., Kehm, V.M., Zhang, B., O'Brien, P., Trojanowski, J.Q., Lee, V.M.Y., 2012. Intracerebral inoculation of pathological  $\alpha$ -synuclein initiates a rapidly progressive neurodegenerative  $\alpha$ -synucleinopathy in mice. *J. Exp. Med.* 209, 975–986. <https://doi.org/10.1084/jem.20112457>
- Maegawa, H., Morimoto, Y., Kudo, C., Hanamoto, H., Boku, A., Sugimura, M., Kato, T., Yoshida, A., Niwa, H., 2015. Neural mechanism underlying hyperalgesic response to orofacial pain in Parkinson's disease model rats. *Neurosci. Res.* 96, 59–68. <https://doi.org/10.1016/j.neures.2015.01.006>
- Mahlknecht, P., Seppi, K., Poewe, W., 2015. The Concept of Prodromal Parkinson's Disease. *J. Park. Dis.* 5, 681–697. <https://doi.org/10.3233/JPD-150685>
- Manning-Bog, A.B., McCormack, A.L., Li, J., Uversky, V.N., Fink, A.L., Di Monte, D.A., 2002. The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein. *J. Biol. Chem.* 277, 1641–1644. <https://doi.org/10.1074/jbc.C100560200>
- Marsh, L., 2013. Depression and Parkinson's disease: current knowledge. *Curr. Neurol. Neurosci. Rep.* 13, 409. <https://doi.org/10.1007/s11910-013-0409-5>
- Marxreiter, F., Ettle, B., May, V.E.L., Esmer, H., Patrick, C., Kragh, C.L., Klucken, J., Winner, B., Riess, O., Winkler, J., Masliah, E., Nuber, S., 2013. Glial A30P alpha-synuclein pathology segregates neurogenesis from anxiety-related behavior in conditional transgenic mice. *Neurobiol. Dis.* 59, 38–51. <https://doi.org/10.1016/j.nbd.2013.07.004>
- Masliah, E., Rockenstein, E., Veinbergs, I., Mallory, M., Hashimoto, M., Takeda, A., Sagara, Y., Sisk, A., Mucke, L., 2000. Dopaminergic loss and inclusion body formation in alpha-

- synuclein mice: implications for neurodegenerative disorders. *Science* 287, 1265–1269.
- Matheus, F.C., Rial, D., Real, J.I., Lemos, C., Takahashi, R.N., Bertoglio, L.J., Cunha, R.A., Prediger, R.D., 2016. Temporal Dissociation of Striatum and Prefrontal Cortex Uncouples Anhedonia and Defense Behaviors Relevant to Depression in 6-OHDA-Lesioned Rats. *Mol. Neurobiol.* 53, 3891–3899. <https://doi.org/10.1007/s12035-015-9330-z>
- McCormack, A.L., Thiruchelvam, M., Manning-Bog, A.B., Thiffault, C., Langston, J.W., Cory-Slechta, D.A., Di Monte, D.A., 2002. Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. *Neurobiol. Dis.* 10, 119–127.
- McDowell, K., Chesselet, M.-F., 2012. Animal models of the non-motor features of Parkinson's disease. *Neurobiol. Dis.* 46, 597–606. <https://doi.org/10.1016/j.nbd.2011.12.040>
- Morgan, M.J., Franklin, K.B., 1990. 6-Hydroxydopamine lesions of the ventral tegmentum abolish D-amphetamine and morphine analgesia in the formalin test but not in the tail flick test. *Brain Res.* 519, 144–149.
- Moriyama, T.S., Felicio, A.C., Chagas, M.H.N., Tardelli, V.S., Ferraz, H.B., Tumas, V., Amaro-Junior, E., Andrade, L.A.F., Crippa, J.A., Bressan, R.A., 2011. Increased dopamine transporter density in Parkinson's disease patients with Social Anxiety Disorder. *J. Neurol. Sci.* 310, 53–57. <https://doi.org/10.1016/j.jns.2011.06.056>
- Narendra, D., Tanaka, A., Suen, D.-F., Youle, R.J., 2008. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J. Cell Biol.* 183, 795–803. <https://doi.org/10.1083/jcb.200809125>
- Nascimento, G.C., Bariotto-Dos-Santos, K., Leite-Panissi, C.R.A., Del-Bel, E.A., Bortolanza, M., 2018. Nociceptive Response to L-DOPA-Induced Dyskinesia in Hemiparkinsonian Rats. *Neurotox. Res.* <https://doi.org/10.1007/s12640-018-9896-0>
- Nègre-Pagès, L., Regragui, W., Bouhassira, D., Grandjean, H., Rascol, O., DoPaMiP Study

- Group, 2008. Chronic pain in Parkinson's disease: the cross-sectional French DoPaMiP survey. *Mov. Disord.* 23, 1361–1369. <https://doi.org/10.1002/mds.22142>
- Nilsson, F.M., Kessing, L.V., Bolwig, T.G., 2001. Increased risk of developing Parkinson's disease for patients with major affective disorder: a register study. *Acta Psychiatr. Scand.* 104, 380–386.
- Niu, Y., Guo, X., Chen, Y., Wang, C.-E., Gao, J., Yang, W., Kang, Y., Si, W., Wang, H., Yang, S.-H., Li, S., Ji, W., Li, X.-J., 2015. Early Parkinson's disease symptoms in  $\alpha$ -synuclein transgenic monkeys. *Hum. Mol. Genet.* 24, 2308–2317. <https://doi.org/10.1093/hmg/ddu748>
- Nuber, S., Petrasch-Parwez, E., Arias-Carrión, O., Koch, L., Kohl, Z., Schneider, J., Calaminus, C., Dermietzel, R., Samarina, A., Boy, J., Nguyen, H.P., Teismann, P., Velavan, T.P., Kahle, P.J., von Hörsten, S., Fendt, M., Krüger, R., Riess, O., 2011. Olfactory neuron-specific expression of A30P  $\alpha$ -synuclein exacerbates dopamine deficiency and hyperactivity in a novel conditional model of early Parkinson's disease stages. *Neurobiol. Dis.* 44, 192–204. <https://doi.org/10.1016/j.nbd.2011.06.017>
- Nuber, S., Petrasch-Parwez, E., Winner, B., Winkler, J., von Hörsten, S., Schmidt, T., Boy, J., Kuhn, M., Nguyen, H.P., Teismann, P., Schulz, J.B., Neumann, M., Pichler, B.J., Reischl, G., Holzmann, C., Schmitt, I., Bornemann, A., Kuhn, W., Zimmermann, F., Servadio, A., Riess, O., 2008. Neurodegeneration and motor dysfunction in a conditional model of Parkinson's disease. *J. Neurosci.* 28, 2471–2484. <https://doi.org/10.1523/JNEUROSCI.3040-07.2008>
- Oaks, A.W., Frankfurt, M., Finkelstein, D.I., Sidhu, A., 2013. Age-dependent effects of A53T alpha-synuclein on behavior and dopaminergic function. *PloS One* 8, e60378. <https://doi.org/10.1371/journal.pone.0060378>
- Ogata, M., Noda, K., Akita, H., Ishibashi, H., 2015. Characterization of nociceptive response

- to chemical, mechanical, and thermal stimuli in adolescent rats with neonatal dopamine depletion. *Neuroscience* 289, 43–55. <https://doi.org/10.1016/j.neuroscience.2015.01.002>
- O’Sullivan, S.S., Williams, D.R., Gallagher, D.A., Massey, L.A., Silveira-Moriyama, L., Lees, A.J., 2008. Nonmotor symptoms as presenting complaints in Parkinson’s disease: a clinicopathological study. *Mov. Disord.* 23, 101–106. <https://doi.org/10.1002/mds.21813>
- Paisán-Ruiz, C., Lewis, P.A., Singleton, A.B., 2013. LRRK2: cause, risk, and mechanism. *J. Park. Dis.* 3, 85–103. <https://doi.org/10.3233/JPD-130192>
- Park, A., Stacy, M., 2009. Non-motor symptoms in Parkinson’s disease. *J. Neurol.* 256 Suppl 3, 293–298. <https://doi.org/10.1007/s00415-009-5240-1>
- Park, J., Lim, C.-S., Seo, H., Park, C.-A., Zhuo, M., Kaang, B.-K., Lee, K., 2015. Pain perception in acute model mice of Parkinson’s disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Mol. Pain* 11, 28. <https://doi.org/10.1186/s12990-015-0026-1>
- Paumier, K.L., Sukoff Rizzo, S.J., Berger, Z., Chen, Y., Gonzales, C., Kaftan, E., Li, L., Lotarski, S., Monaghan, M., Shen, W., Stolyar, P., Vasilyev, D., Zaleska, M., D Hirst, W., Dunlop, J., 2013. Behavioral characterization of A53T mice reveals early and late stage deficits related to Parkinson’s disease. *PloS One* 8, e70274. <https://doi.org/10.1371/journal.pone.0070274>
- Pearce, J.M.S., 2008. Observations on the blink reflex. *Eur. Neurol.* 59, 221–223. <https://doi.org/10.1159/000114053>
- Pellow, S., Chopin, P., File, S.E., Briley, M., 1985. Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. *J. Neurosci. Methods* 14, 149–167.
- Peña-Oliver, Y., Buchman, V.L., Stephens, D.N., 2010. Lack of involvement of alpha-synuclein in unconditioned anxiety in mice. *Behav. Brain Res.* 209, 234–240. <https://doi.org/10.1016/j.bbr.2010.01.049>

- Perez, F.A., Palmiter, R.D., 2005. Parkin-deficient mice are not a robust model of parkinsonism. *Proc. Natl. Acad. Sci. U. S. A.* 102, 2174–2179. <https://doi.org/10.1073/pnas.0409598102>
- Polymeropoulos, M.H., Lavedan, C., Leroy, E., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E.S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Di Iorio, G., Golbe, L.I., Nussbaum, R.L., 1997. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 276, 2045–2047.
- Pont-Sunyer, C., Hotter, A., Gaig, C., Seppi, K., Compta, Y., Katzenschlager, R., Mas, N., Hofeneder, D., Brücke, T., Bayés, A., Wenzel, K., Infante, J., Zach, H., Pirker, W., Posada, I.J., Álvarez, R., Ispuerto, L., De Fàbregues, O., Callén, A., Palasí, A., Aguilar, M., Martí, M.J., Valdeoriola, F., Salamero, M., Poewe, W., Tolosa, E., 2015. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). *Mov. Disord.* 30, 229–237. <https://doi.org/10.1002/mds.26077>
- Porsolt, R.D., Le Pichon, M., Jalfre, M., 1977. Depression: a new animal model sensitive to antidepressant treatments. *Nature* 266, 730–732.
- Qu, C., King, T., Okun, A., Lai, J., Fields, H.L., Porreca, F., 2011. Lesion of the rostral anterior cingulate cortex eliminates the aversiveness of spontaneous neuropathic pain following partial or complete axotomy. *Pain* 152, 1641–1648. <https://doi.org/10.1016/j.pain.2011.03.002>
- Rabl, R., Breitschaedel, C., Flunkert, S., Duller, S., Amschl, D., Neddens, J., Niederkofler, V., Rockenstein, E., Masliah, E., Roemer, H., Hutter-Paier, B., 2017. Early start of progressive motor deficits in Line 61  $\alpha$ -synuclein transgenic mice. *BMC Neurosci.* 18, 22. <https://doi.org/10.1186/s12868-017-0341-8>
- Rana, A.Q., Qureshi, A.R.M., Rahman, L., Jesudasan, A., Hafez, K.K., Rana, M.A., 2016. Association of restless legs syndrome, pain, and mood disorders in Parkinson's disease. *Int.*

- J. Neurosci. 126, 116–120. <https://doi.org/10.3109/00207454.2014.994208>
- Recasens, A., Dehay, B., Bové, J., Carballo-Carbajal, I., Dovero, S., Pérez-Villalba, A., Fernagut, P.-O., Blesa, J., Parent, A., Perier, C., Fariñas, I., Obeso, J.A., Bezard, E., Vila, M., 2014. Lewy body extracts from Parkinson disease brains trigger  $\alpha$ -synuclein pathology and neurodegeneration in mice and monkeys. *Ann. Neurol.* 75, 351–362. <https://doi.org/10.1002/ana.24066>
- Reichmann, H., 2017. Premotor Diagnosis of Parkinson's Disease. *Neurosci. Bull.* 33, 526–534. <https://doi.org/10.1007/s12264-017-0159-5>
- Remy, P., Doder, M., Lees, A., Turjanski, N., Brooks, D., 2005. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain J. Neurol.* 128, 1314–1322. <https://doi.org/10.1093/brain/awh445>
- Rieu, I., Houeto, J.L., Pereira, B., De Chazeron, I., Bichon, A., Chéreau, I., Ulla, M., Brefel-Courbon, C., Ory-Magne, F., Dujardin, K., Tison, F., Krack, P., Durif, F., 2016. Impact of Mood and Behavioral Disorders on Quality of Life in Parkinson's disease. *J. Park. Dis.* 6, 267–277. <https://doi.org/10.3233/JPD-150747>
- Rockenstein, E., Mallory, M., Hashimoto, M., Song, D., Shults, C.W., Lang, I., Masliah, E., 2002. Differential neuropathological alterations in transgenic mice expressing alpha-synuclein from the platelet-derived growth factor and Thy-1 promoters. *J. Neurosci. Res.* 68, 568–578. <https://doi.org/10.1002/jnr.10231>
- Rosemann, M., Ivashkevich, A., Favor, J., Dalke, C., Hölter, S.M., Becker, L., Rácz, I., Bolle, I., Klempt, M., Rathkolb, B., Kalaydjiev, S., Adler, T., Aguilar, A., Hans, W., Horsch, M., Rozman, J., Calzada-Wack, J., Kunder, S., Naton, B., Gailus-Durner, V., Fuchs, H., Schulz, H., Beckers, J., Busch, D.H., Burbach, J.P.H., Smidt, M.P., Quintanilla-Martinez, L., Esposito, I., Klopstock, T., Klingenspor, M., Ollert, M., Wolf, E., Wurst, W., Zimmer, A., de Angelis, M.H., Atkinson, M., Heinzmann, U., Graw, J., 2010. Microphthalmia,

- parkinsonism, and enhanced nociception in Pitx3 ( 416insG ) mice. *Mamm. Genome* 21, 13–27. <https://doi.org/10.1007/s00335-009-9235-0>
- Rosland, J.H., Hunskar, S., Broch, O.J., Hole, K., 1992. Acute and long term effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in tests of nociception in mice. *Pharmacol. Toxicol.* 70, 31–37.
- Rothman, S.M., Griffioen, K.J., Vranis, N., Ladenheim, B., Cong, W., Cadet, J.-L., Haran, J., Martin, B., Mattson, M.P., 2013. Neuronal expression of familial Parkinson's disease A53T  $\alpha$ -synuclein causes early motor impairment, reduced anxiety and potential sleep disturbances in mice. *J. Park. Dis.* 3, 215–229. <https://doi.org/10.3233/JPD-120130>
- Saadé, N.E., Atweh, S.F., Bahuth, N.B., Jabbur, S.J., 1997. Augmentation of nociceptive reflexes and chronic deafferentation pain by chemical lesions of either dopaminergic terminals or midbrain dopaminergic neurons. *Brain Res.* 751, 1–12.
- Sachs, C., Jonsson, G., 1975. Mechanisms of action of 6-hydroxydopamine. *Biochem. Pharmacol.* 24, 1–8.
- Sahgal, A., Andrews, J.S., Biggins, J.A., Candy, J.M., Edwardson, J.A., Keith, A.B., Turner, J.D., Wright, C., 1984. N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) affects locomotor activity without producing a nigrostriatal lesion in the rat. *Neurosci. Lett.* 48, 179–184.
- Santiago, R.M., Barbiero, J., Lima, M.M.S., Dombrowski, P.A., Andreatini, R., Vital, M.A.B.F., 2010. Depressive-like behaviors alterations induced by intranigral MPTP, 6-OHDA, LPS and rotenone models of Parkinson's disease are predominantly associated with serotonin and dopamine. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 34, 1104–1114. <https://doi.org/10.1016/j.pnpbp.2010.06.004>
- Santiago, R.M., Barbiero, J., Gradowski, R.W., Bochen, S., Lima, M.M.S., Da Cunha, C., Andreatini, R., Vital, M.A.B.F., 2014. Induction of depressive-like behavior by intranigral

- 6-OHDA is directly correlated with deficits in striatal dopamine and hippocampal serotonin. *Behav. Brain Res.* 259, 70–77. <https://doi.org/10.1016/j.bbr.2013.10.035>
- Schapira, A.H.V., Chaudhuri, K.R., Jenner, P., 2017. Non-motor features of Parkinson disease. *Nat. Rev. Neurosci.* 18, 509. <https://doi.org/10.1038/nrn.2017.91>
- Schober, A., 2004. Classic toxin-induced animal models of Parkinson's disease: 6-OHDA and MPTP. *Cell Tissue Res.* 318, 215–224. <https://doi.org/10.1007/s00441-004-0938-y>
- Sellmeijer, J., Mathis, V., Hugel, S., Li, X.-H., Song, Q., Chen, Q.-Y., Barthas, F., Lutz, P.-E., Karatas, M., Luthi, A., Veinante, P., Aertsen, A., Barrot, M., Zhuo, M., Yalcin, I., 2018. Hyperactivity of Anterior Cingulate Cortex Areas 24a/24b Drives Chronic Pain-Induced Anxiodepressive-like Consequences. *J. Neurosci.* 38, 3102–3115. <https://doi.org/10.1523/JNEUROSCI.3195-17.2018>
- Shiba, M., Bower, J.H., Maraganore, D.M., McDonnell, S.K., Peterson, B.J., Ahlskog, J.E., Schaid, D.J., Rocca, W.A., 2000. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. *Mov. Disord.* 15, 669–677.
- Silva, T.P. da, Poli, A., Hara, D.B., Takahashi, R.N., 2016. Time course study of microglial and behavioral alterations induced by 6-hydroxydopamine in rats. *Neurosci. Lett.* 622, 83–87. <https://doi.org/10.1016/j.neulet.2016.04.049>
- Singleton, A.B., Farrer, M., Johnson, J., Singleton, A., Hague, S., Kachergus, J., Hulihan, M., Peuralinna, T., Dutra, A., Nussbaum, R., Lincoln, S., Crawley, A., Hanson, M., Maraganore, D., Adler, C., Cookson, M.R., Muentert, M., Baptista, M., Miller, D., Blancato, J., Hardy, J., Gwinn-Hardy, K., 2003. alpha-Synuclein locus triplication causes Parkinson's disease. *Science* 302, 841. <https://doi.org/10.1126/science.1090278>
- Singleton, A.B., Farrer, M.J., Bonifati, V., 2013. The genetics of Parkinson's disease: progress and therapeutic implications. *Mov. Disord.* 28, 14–23. <https://doi.org/10.1002/mds.25249>
- Stern, M.B., Lang, A., Poewe, W., 2012. Toward a redefinition of Parkinson's disease. *Mov.*

- Disord. 27, 54–60. <https://doi.org/10.1002/mds.24051>
- Sun, Y.-N., Wang, T., Wang, Y., Han, L.-N., Li, L.-B., Zhang, Y.-M., Liu, J., 2015. Activation of 5-HT<sub>1A</sub> receptors in the medial subdivision of the central nucleus of the amygdala produces anxiolytic effects in a rat model of Parkinson's disease. *Neuropharmacology* 95, 181–191. <https://doi.org/10.1016/j.neuropharm.2015.03.007>
- Surdhar, I., Gee, M., Bouchard, T., Coupland, N., Malykhin, N., Camicioli, R., 2012. Intact limbic-prefrontal connections and reduced amygdala volumes in Parkinson's disease with mild depressive symptoms. *Parkinsonism Relat. Disord.* 18, 809–813. <https://doi.org/10.1016/j.parkreldis.2012.03.008>
- Szatmari, S., Illigens, B.M.-W., Siepmann, T., Pinter, A., Takats, A., Bereczki, D., 2017. Neuropsychiatric symptoms in untreated Parkinson's disease. *Neuropsychiatr. Dis. Treat.* 13, 815–826. <https://doi.org/10.2147/NDT.S130997>
- Tadaiesky, M.T., Dombrowski, P.A., Da Cunha, C., Takahashi, R.N., 2010. Effects of SR141716A on Cognitive and Depression-Related Behavior in an Animal Model of Premotor Parkinson's Disease. *Park. Dis.* 2010, 238491. <https://doi.org/10.4061/2010/238491>
- Tadaiesky, M.T., Dombrowski, P.A., Figueiredo, C.P., Cargnin-Ferreira, E., Da Cunha, C., Takahashi, R.N., 2008. Emotional, cognitive and neurochemical alterations in a premotor stage model of Parkinson's disease. *Neuroscience* 156, 830–840. <https://doi.org/10.1016/j.neuroscience.2008.08.035>
- Takeda, R., Ikeda, T., Tsuda, F., Abe, H., Hashiguchi, H., Ishida, Y., Nishimori, T., 2005. Unilateral lesions of mesostriatal dopaminergic pathway alters the withdrawal response of the rat hindpaw to mechanical stimulation. *Neurosci. Res.* 52, 31–36. <https://doi.org/10.1016/j.neures.2005.01.005>
- Takeda, R., Ishida, Y., Ebihara, K., Abe, H., Matsuo, H., Ikeda, T., Koganemaru, G.,

- Kuramashi, A., Funahashi, H., Magata, Y., Kawai, K., Nishimori, T., 2014. Intrastriatal grafts of fetal ventral mesencephalon improve allodynia-like withdrawal response to mechanical stimulation in a rat model of Parkinson's disease. *Neurosci. Lett.* 573, 19–23. <https://doi.org/10.1016/j.neulet.2014.05.007>
- Tassorelli, C., Armentero, M.-T., Greco, R., Fancellu, R., Sandrini, G., Nappi, G., Blandini, F., 2007. Behavioral responses and Fos activation following painful stimuli in a rodent model of Parkinson's disease. *Brain Res.* 1176, 53–61. <https://doi.org/10.1016/j.brainres.2007.08.012>
- Taylor, T.N., Caudle, W.M., Shepherd, K.R., Noorian, A., Jackson, C.R., Iuvone, P.M., Weinshenker, D., Greene, J.G., Miller, G.W., 2009. Nonmotor symptoms of Parkinson's disease revealed in an animal model with reduced monoamine storage capacity. *J. Neurosci.* 29, 8103–8113. <https://doi.org/10.1523/JNEUROSCI.1495-09.2009>
- Thiruchelvam, M., McCormack, A., Richfield, E.K., Baggs, R.B., Tank, A.W., Di Monte, D.A., Cory-Slechta, D.A., 2003. Age-related irreversible progressive nigrostriatal dopaminergic neurotoxicity in the paraquat and maneb model of the Parkinson's disease phenotype. *Eur. J. Neurosci.* 18, 589–600.
- Titova, N., Schapira, A.H.V., Chaudhuri, K.R., Qamar, M.A., Katunina, E., Jenner, P., 2017. Nonmotor Symptoms in Experimental Models of Parkinson's Disease. *Int. Rev. Neurobiol.* 133, 63–89. <https://doi.org/10.1016/bs.irn.2017.05.018>
- Tofaris, G.K., Garcia Reitböck, P., Humby, T., Lambourne, S.L., O'Connell, M., Ghetti, B., Gossage, H., Emson, P.C., Wilkinson, L.S., Goedert, M., Spillantini, M.G., 2006. Pathological changes in dopaminergic nerve cells of the substantia nigra and olfactory bulb in mice transgenic for truncated human alpha-synuclein(1-120): implications for Lewy body disorders. *J. Neurosci.* 26, 3942–3950. <https://doi.org/10.1523/JNEUROSCI.4965-05.2006>
- Tuon, T., Valvassori, S.S., Dal Pont, G.C., Paganini, C.S., Pozzi, B.G., Luciano, T.F., Souza,

- P.S., Quevedo, J., Souza, C.T., Pinho, R.A., 2014. Physical training prevents depressive symptoms and a decrease in brain-derived neurotrophic factor in Parkinson's disease. *Brain Res. Bull.* 108, 106–112. <https://doi.org/10.1016/j.brainresbull.2014.09.006>
- Ulusoy, A., Decressac, M., Kirik, D., Björklund, A., 2010. Viral vector-mediated overexpression of  $\alpha$ -synuclein as a progressive model of Parkinson's disease. *Prog. Brain Res.* 184, 89–111. [https://doi.org/10.1016/S0079-6123\(10\)84005-1](https://doi.org/10.1016/S0079-6123(10)84005-1)
- Ungerstedt, U., 1971. Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta Physiol. Scand. Suppl.* 367, 95–122.
- Ungerstedt, U., 1968. 6-Hydroxy-dopamine induced degeneration of central monoamine neurons. *Eur. J. Pharmacol.* 5, 107–110.
- Ungerstedt, U., Arbuthnott, G.W., 1970. Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. *Brain Res.* 24, 485–493.
- Valente, E.M., Salvi, S., Ialongo, T., Marongiu, R., Elia, A.E., Caputo, V., Romito, L., Albanese, A., Dallapiccola, B., Bentivoglio, A.R., 2004. PINK1 mutations are associated with sporadic early-onset parkinsonism. *Ann. Neurol.* 56, 336–341. <https://doi.org/10.1002/ana.20256>
- van Mierlo, T.J., Chung, C., Foncke, E.M., Berendse, H.W., van den Heuvel, O.A., 2015. Depressive symptoms in Parkinson's disease are related to decreased hippocampus and amygdala volume. *Mov. Disord.* 30, 245–252. <https://doi.org/10.1002/mds.26112>
- Vecchia, D.D., Kanazawa, L.K.S., Wendler, E., de Almeida Soares Hocayen, P., Bruginski, E., Campos, F.R., Stern, C.A.J., Vital, M.A.B.F., Miyoshi, E., Wöhr, M., Schwarting, R.K.W., Andreatini, R., 2018. Effects of ketamine on vocal impairment, gait changes, and anhedonia induced by bilateral 6-OHDA infusion into the substantia nigra pars compacta in rats: Therapeutic implications for Parkinson's disease. *Behav. Brain Res.* 342, 1–10.

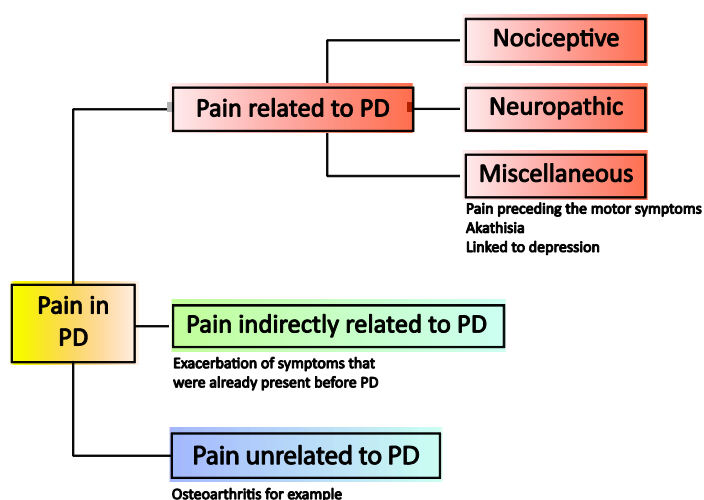
<https://doi.org/10.1016/j.bbr.2017.12.041>

- Volta, M., Melrose, H., 2017. LRRK2 mouse models: dissecting the behavior, striatal neurochemistry and neurophysiology of PD pathogenesis. *Biochem. Soc. Trans.* 45, 113–122. <https://doi.org/10.1042/BST20160238>
- Von Coelln, R., Thomas, B., Savitt, J.M., Lim, K.L., Sasaki, M., Hess, E.J., Dawson, V.L., Dawson, T.M., 2004. Loss of locus coeruleus neurons and reduced startle in parkin null mice. *Proc. Natl. Acad. Sci. U. S. A.* 101, 10744–10749. <https://doi.org/10.1073/pnas.0401297101>
- Vriend, C., Boedhoe, P.S.W., Rutten, S., Berendse, H.W., van der Werf, Y.D., van den Heuvel, O.A., 2016. A smaller amygdala is associated with anxiety in Parkinson's disease: a combined FreeSurfer-VBM study. *J. Neurol. Neurosurg. Psychiatry* 87, 493–500. <https://doi.org/10.1136/jnnp-2015-310383>
- Vucković, M.G., Wood, R.I., Holschneider, D.P., Abernathy, A., Togasaki, D.M., Smith, A., Petzinger, G.M., Jakowec, M.W., 2008. Memory, mood, dopamine, and serotonin in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. *Neurobiol. Dis.* 32, 319–327. <https://doi.org/10.1016/j.nbd.2008.07.015>
- Wakamatsu, M., Ishii, A., Iwata, S., Sakagami, J., Ukai, Y., Ono, M., Kanbe, D., Muramatsu, S., Kobayashi, K., Iwatsubo, T., Yoshimoto, M., 2008. Selective loss of nigral dopamine neurons induced by overexpression of truncated human alpha-synuclein in mice. *Neurobiol. Aging* 29, 574–585. <https://doi.org/10.1016/j.neurobiolaging.2006.11.017>
- Wang, C.-T., Mao, C.-J., Zhang, X.-Q., Zhang, C.-Y., Lv, D.-J., Yang, Y.-P., Xia, K.-L., Liu, J.-Y., Wang, F., Hu, L.-F., Xu, G.-Y., Liu, C.-F., 2017. Attenuation of hyperalgesia responses via the modulation of 5-hydroxytryptamine signalings in the rostral ventromedial medulla and spinal cord in a 6-hydroxydopamine-induced rat model of Parkinson's disease. *Mol. Pain* 13, 1744806917691525. <https://doi.org/10.1177/1744806917691525>

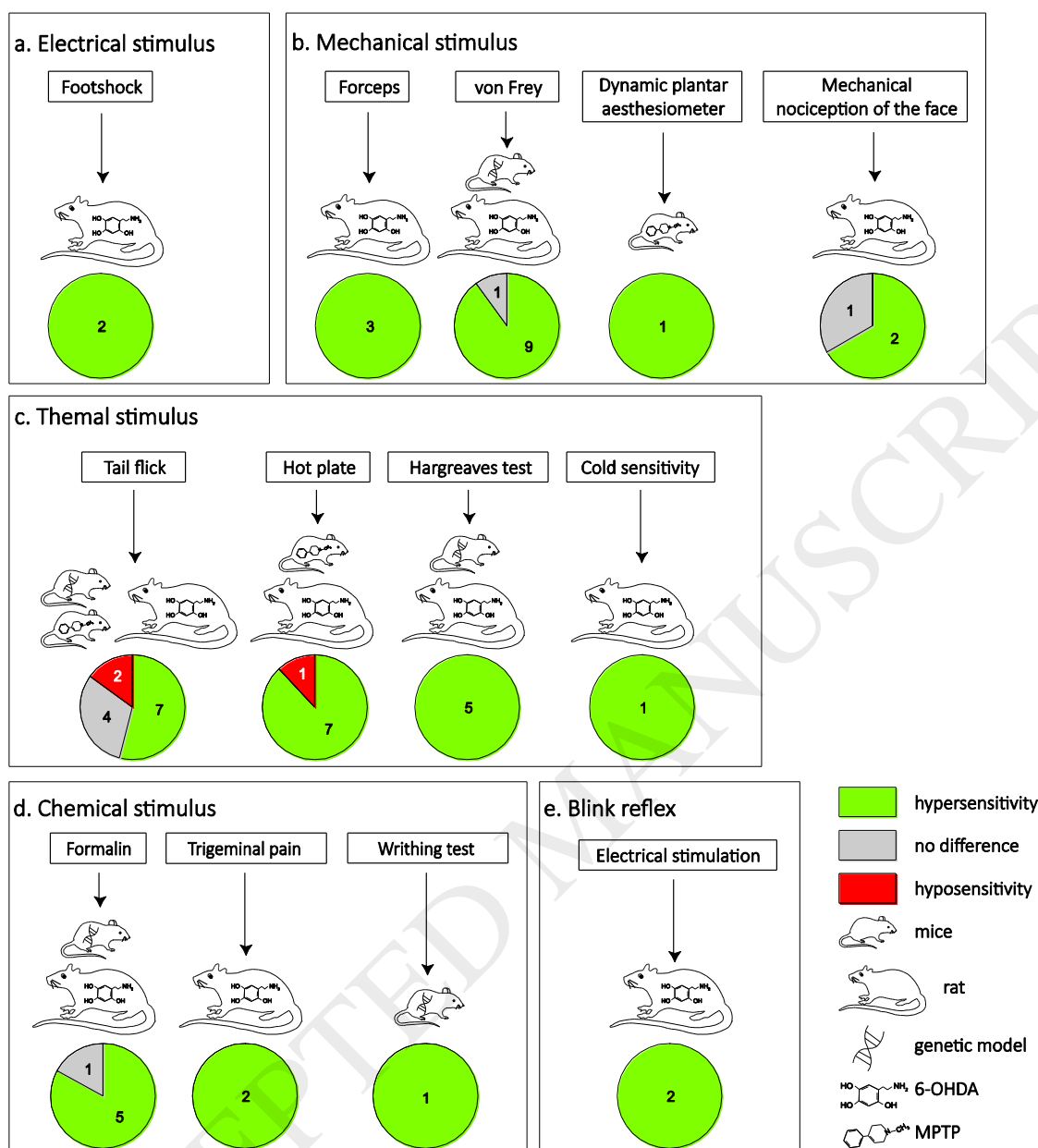
- Waseem, S., Gwinn-Hardy, K., 2001. Pain in Parkinson's disease. Common yet seldom recognized symptom is treatable. *Postgrad. Med.* 110, 33–34, 39–40, 46.
- Wasner, G., Deuschl, G., 2012. Pains in Parkinson disease--many syndromes under one umbrella. *Nat. Rev. Neurol.* 8, 284–294. <https://doi.org/10.1038/nrneurol.2012.54>
- Weintraub, D., Newberg, A.B., Cary, M.S., Siderowf, A.D., Moberg, P.J., Kleiner-Fisman, G., Duda, J.E., Stern, M.B., Mozley, D., Katz, I.R., 2005. Striatal dopamine transporter imaging correlates with anxiety and depression symptoms in Parkinson's disease. *J. Nucl. Med.* 46, 227–232.
- Wilson, J.M.B., Khabazian, I., Wong, M.C., Seyedalikhani, A., Bains, J.S., Pasqualotto, B.A., Williams, D.E., Andersen, R.J., Simpson, R.J., Smith, R., Craig, U.-K., Kurland, L.T., Shaw, C.A., 2002. Behavioral and neurological correlates of ALS-parkinsonism dementia complex in adult mice fed washed cycad flour. *Neuromolecular Med.* 1, 207–221. <https://doi.org/10.1385/NMM:1:3:207>
- Winter, C., von Rumohr, A., Mundt, A., Petrus, D., Klein, J., Lee, T., Morgenstern, R., Kupsch, A., Juckel, G., 2007. Lesions of dopaminergic neurons in the substantia nigra pars compacta and in the ventral tegmental area enhance depressive-like behavior in rats. *Behav. Brain Res.* 184, 133–141. <https://doi.org/10.1016/j.bbr.2007.07.002>
- Yamaguchi, H., Shen, J., 2007. Absence of dopaminergic neuronal degeneration and oxidative damage in aged DJ-1-deficient mice. *Mol. Neurodegener.* 2, 10. <https://doi.org/10.1186/1750-1326-2-10>
- Yamakado, H., Moriwaki, Y., Yamasaki, N., Miyakawa, T., Kurisu, J., Uemura, K., Inoue, H., Takahashi, M., Takahashi, R., 2012.  $\alpha$ -Synuclein BAC transgenic mice as a model for Parkinson's disease manifested decreased anxiety-like behavior and hyperlocomotion. *Neurosci. Res.* 73, 173–177. <https://doi.org/10.1016/j.neures.2012.03.010>
- Zambito Marsala, S., Tinazzi, M., Vitaliani, R., Recchia, S., Fabris, F., Marchini, C., Fiaschi,

- A., Moretto, G., Giometto, B., Macerollo, A., Defazio, G., 2011. Spontaneous pain, pain threshold, and pain tolerance in Parkinson's disease. *J. Neurol.* 258, 627–633. <https://doi.org/10.1007/s00415-010-5812-0>
- Zarow, C., Lyness, S.A., Mortimer, J.A., Chui, H.C., 2003. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. *Arch. Neurol.* 60, 337–341.
- Zarranz, J.J., Alegre, J., Gómez-Esteban, J.C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atarés, B., Llorens, V., Gomez Tortosa, E., del Ser, T., Muñoz, D.G., de Yebenes, J.G., 2004. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann. Neurol.* 55, 164–173. <https://doi.org/10.1002/ana.10795>
- Zengin-Toktas, Y., Ferrier, J., Durif, F., Llorca, P.-M., Authier, N., 2013. Bilateral lesions of the nigrostriatal pathways are associated with chronic mechanical pain hypersensitivity in rats. *Neurosci. Res.* 76, 261–264. <https://doi.org/10.1016/j.neures.2013.05.003>
- Zhang, J., Stanton, D.M., Nguyen, X.V., Liu, M., Zhang, Z., Gash, D., Bing, G., 2005. Intrapallidal lipopolysaccharide injection increases iron and ferritin levels in glia of the rat substantia nigra and induces locomotor deficits. *Neuroscience* 135, 829–838. <https://doi.org/10.1016/j.neuroscience.2005.06.049>

## Figure legends

**Figure 1****Fig. 1.** Classification of pain in Parkinson's disease (adapted from Wasner and Deuschl, 2012).

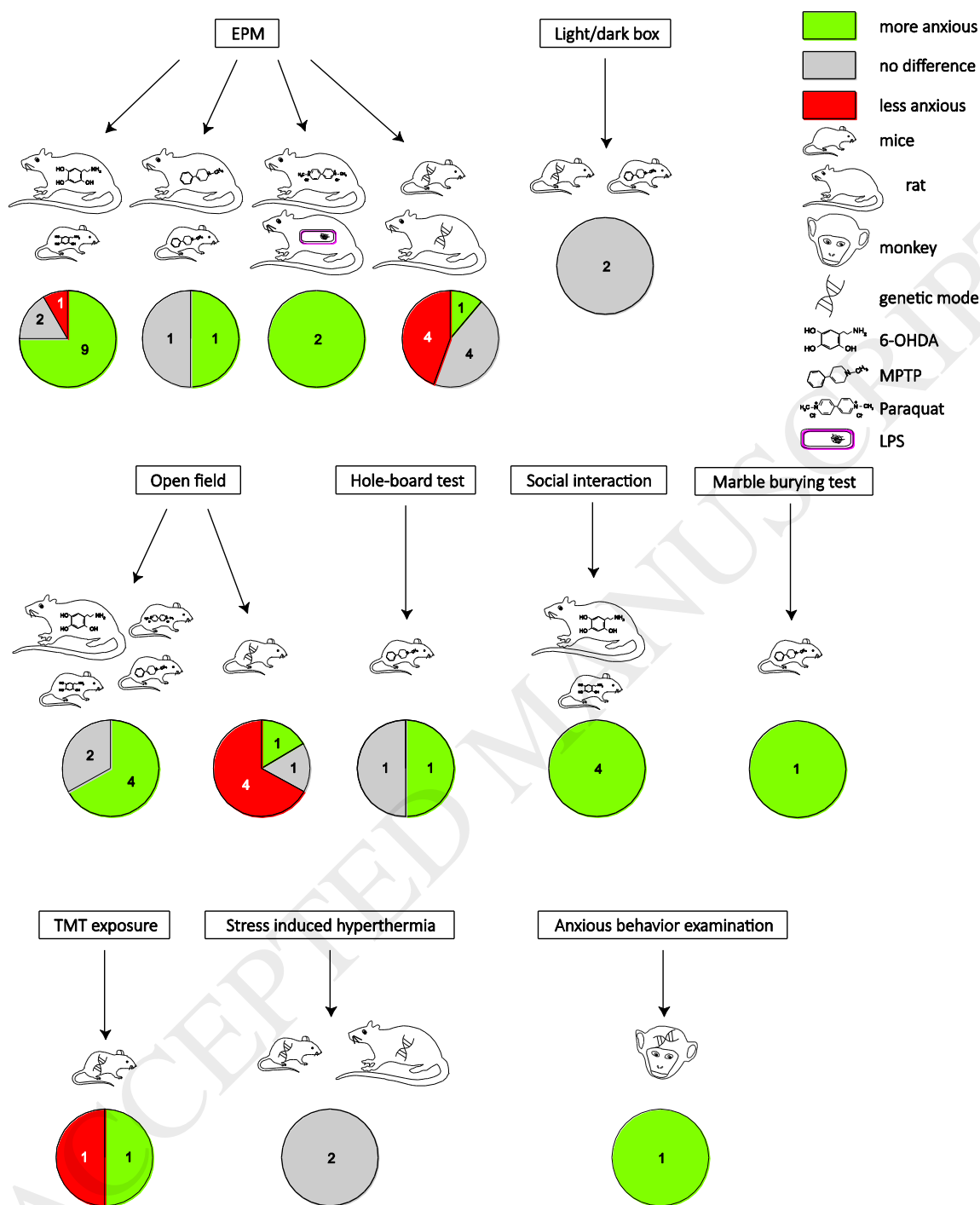
Pain directly or partly related to PD can be either nociceptive pain, neuropathic pain or miscellaneous pain. Other types of pain include pain indirectly related to PD, pain that can be aggravated by the disease, and pain unrelated to PD. PD, Parkinson's disease.

**Figure 2**

**Fig. 2.** Nociceptive responses in animal models of Parkinson's disease. Various nociceptive modalities have been tested in models of the disease. For a majority of these modalities and animal models, the existing literature converges to highlight a nociceptive hypersensitivity. The heat modality, and in particular the tail-flick test, shows the highest heterogeneity in reported findings, which might be related to potential slow-down of some withdrawal reflexes. "n" displayed in the figure correspond to the number of publications relative to the test (see Table

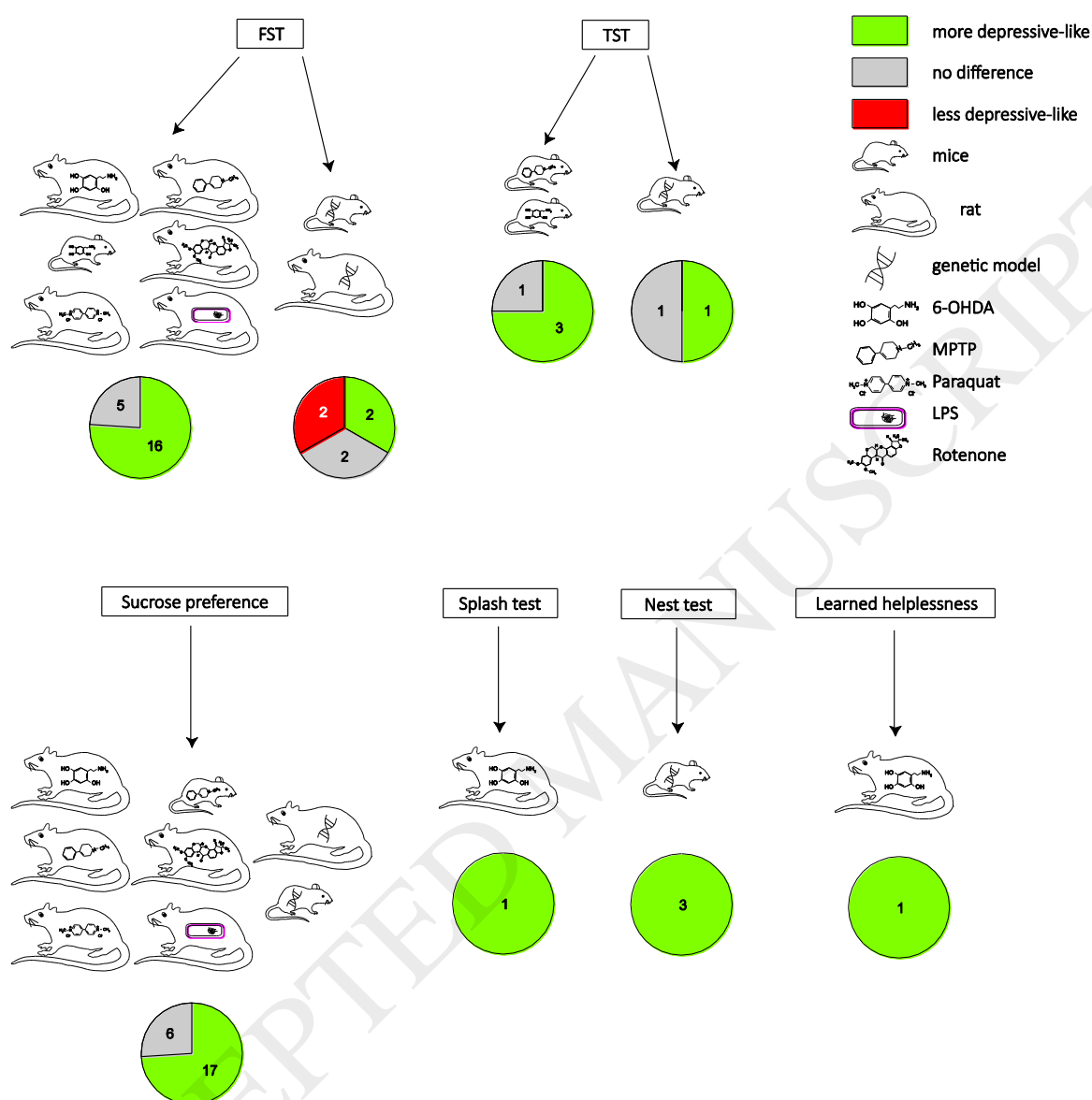
1 for more details and references). 6-OHDA, 6-hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

ACCEPTED MANUSCRIPT

**Figure 3**

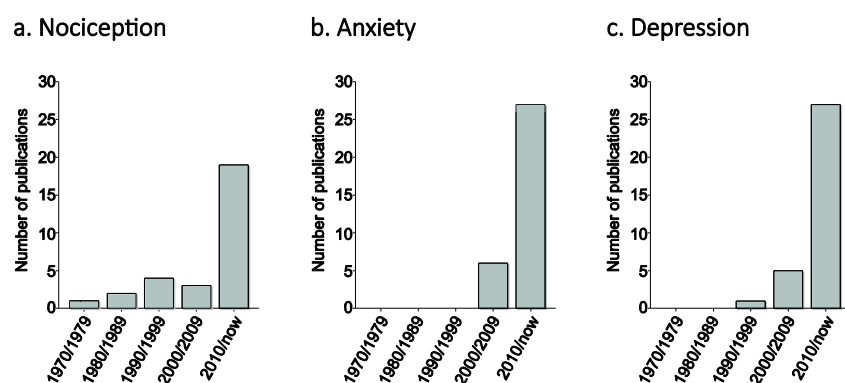
**Fig. 3.** Anxiety-like behaviors in animal models of Parkinson's disease. While in neurotoxin-based models of the disease most studies reported increased anxiety-like behaviors, literature is more controversial concerning genetic-based models of the disease. "n" displayed in the figure

correspond to the number of publications relative to the test (see Table 2 for more details and references). 6-OHDA, 6-hydroxydopamine; EPM, elevated plus maze; LPS, lipopolysaccharide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TMT, 2,3,5-trimethyl-3-thiazoline (*i.e.* fox odor).

**Figure 4**

**Fig. 4.** Depressive-like behaviors in animal models of Parkinson's disease. Studies mostly reported the presence of depressive-like behaviors in models of Parkinson's disease, even though FST data are more variable in genetic-based models. "n" displayed in the figure correspond to the number of publications relative to the test (see Table 3 for more details and references). 6-OHDA, 6-hydroxydopamine; FST, forced swim test; LPS, lipopolysaccharide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TST, tail suspension test.

ACCEPTED MANUSCRIPT

**Figure 5**

**Fig. 5.** Number of publications reporting data on pain, anxiety and depression related parameters in animal models of Parkinson's disease.

## Tables

Table 1. Nociception in Parkinson's disease models

Table 4 Nociception in Parkinson's disease models

Species	Model	Test	Results	Ref.
Rat	6-OHDA	Footshock	↗ contralat. jump thresholds and ↘ ipsilat. one ↘ nociceptive thresholds	(Carey, 1986) (Chen et al., 2013)
Rat	6-OHDA	Paw pressure	↘ latency for contralat. hindpaw ↘ latency at 1,2 and 12 weeks for ipsilat. hindpaw ↘ mechanical thresholds at 3 weeks	(Saadé et al., 1997) (Takeda et al., 2005) (Chudler and Lu, 2008)
Rat	6-OHDA	von Frey	↘ mechanical thresholds ↘ mechanical thresholds for ipsilat. hindpaw ↘ mechanical thresholds for both hindpaws ↘ mechanical thresholds after 4 weeks ↘ mechanical thresholds after 4 weeks ↘ mechanical thresholds for both hindpaws ↘ mechanical thresholds for both hindpaws ↘ mechanical thresholds for contralat. hindpaw No ≠	(Zengin-Toktas et al., 2013) (Takeda et al., 2014) (Gee et al., 2015) (Cao et al., 2016) (Wang et al., 2017) (Gómez-Paz et al., 2017) (Nascimento et al., 2018) (Charles et al., 2018) (Ogata et al., 2015)
Mice	<i>Pitx3<sup>416insG</sup></i>	von Frey	↘ mechanical thresholds	(Rosemann et al., 2010)
Mice	MPTP	Dynamic plantar aesthesiometer	↘ mechanical thresholds	(Park et al., 2015)
Rat	6-OHDA	von Frey (vibrissae) Air puff (face)	No ≠ ↗ pain score ↗ pain score	(Chudler and Lu, 2008) (Dieb et al., 2016) (Dieb et al., 2014)
Rat	6-OHDA	Tail flick	↘ latency  No ≠ ↗ latency	(Saadé et al., 1997) (Dolatshahi et al., 2015) (Gómez-Paz et al., 2017) (Haddadi et al., 2018) (Nascimento et al., 2018) (Morgan and Franklin, 1990) (Gee et al., 2015) (Ogata et al., 2015) (Grossmann et al., 1973) (Tassorelli et al., 2007)
Mice	MPTP	Tail flick	↘ latency	(Rosland et al., 1992) (Park et al., 2015)
Mice	<i>Pitx3<sup>416insG</sup></i>	Tail flick	No ≠	(Rosemann et al., 2010)
Rat	6-OHDA	Hot plate	↘ latency	(Lin et al., 1981) (Saadé et al., 1997) (Chen et al., 2013) (Dolatshahi et al., 2015) (Gee et al., 2015) (Nascimento et al., 2018)
Mice	MPTP	Hot plate	↗ latency ↘ latency	(Rosland et al., 1992) (Park et al., 2015)
Rat	6-OHDA	Hargreaves test	↘ latency on the contralat. side ↘ latency at 4 weeks ↘ latency at 2 and 4 weeks ↘ latency on the contralat. side	(Chudler and Lu, 2008) (Cao et al., 2016) (Wang et al., 2017) (Charles et al., 2018)
Mice	<i>Pitx3<sup>416insG</sup></i>	Hargreaves test	↘ latency in males and females	(Rosemann et al., 2010)
Rat	6-OHDA	Acetone	↗ behavioral responses	(Gómez-Paz et al., 2017)
Rat	6-OHDA	Formalin test	↘ effect of analgesics in the formalin test ↗ responses in the second phase ↗ responses in both phases ↗ responses (contralat.) in both phases ↗ responses (bilateral) in both phases	(Morgan and Franklin, 1990) (Ogata et al., 2015) (Cao et al., 2016) (Tassorelli et al., 2007) (Gómez-Paz et al., 2017)
Mice	LRRK2	Formalin test	No ≠ in both phases	(Bichler et al., 2013)
Rat	6-OHDA	Formalin test (orofacial)	↗ face grooming during the second phase ↗ face rubbing on the left lip in both phases	(Chudler and Lu, 2008) (Maegawa et al., 2015)

Mice	<i>Pitx3<sup>416insG</sup></i>	Writhing test	↗ number of responses	(Rosemann et al., 2010)
Rat	6-OHDA	Blink reflex	Hyperexcitability Hyperexcitability, impaired blink plasticity of the R2 but not the R1 component and lower spontaneous blink rate	(Basso et al., 1993) (Kaminer et al., 2015)

6-OHDA, 6-hydroxydopamine; contralat., contralateral; ipsilat., ipsilateral; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Note that “6-OHDA” gathers various models, either unilateral or bilateral, and with different lesion sites, with or without neuroprotection of non-dopamine systems.

Table 2. Anxiety-like behaviors in Parkinson's disease models

Table 5 Anxiety-like behaviors in Parkinson's disease models

Species	Model	Test	Results	Ref.
Rat	6-OHDA	EPM	<p>↗ entries/time spent in the open arms No ≠</p> <p>↘ entries/time spent in the open arms</p> <p>↘ entries/time spent in the open arms if depleting at least 2 of the monoamines</p>	(Branchi et al., 2008) (Carvalho et al., 2013) (Matheus et al., 2016) (Tadaiesky et al., 2008) (Jungnickel et al., 2011) (Campos et al., 2013) (Hui et al., 2015) (Sun et al., 2015) (Silva et al., 2016) (Faggiani et al., 2018) (Delaville et al., 2012)
Mice	6-OHDA	EPM	↘ time spent in the open arms	(Bonito-Oliva et al., 2014)
Rat	MPTP	EPM	↘ time spent in the open arms	(Ho et al., 2011)
Mice	MPTP	EPM	No ≠	(Gorton et al., 2010)
Rat	Paraquat	EPM	↘ time spent in the open arms	(Campos et al., 2013)
Rat	LPS	EPM	↘ entries/time spent in the open arms	(Hritcu and Gorgan, 2014)
Rat	α-syn	EPM	No ≠	(Campos et al., 2013) (Caudal et al., 2015)
Mice	A53T	EPM	↗ entries/time spent in the open arms	(George et al., 2008) (Oaks et al., 2013) (Rothman et al., 2013)
Mice	VMAT2	EPM	↘ time spent in open arms in young mice	(Taylor et al., 2009)
Mice	α-syn	EPM	No ≠ ↗ entries/time spent in open arms	(Peña-Oliver et al., 2010) (Yamakado et al., 2012)
Mice	LRRK2	EPM	No ≠	(Bichler et al., 2013)
Mice	MPTP α-syn	Light/Dark	No ≠	(Vucković et al., 2008) (Peña-Oliver et al., 2010)
Rat	6-OHDA	Open field	<p>↘ center entries and center vertical movements ↘ time spent in the center area</p>	(Eskow Jaunarajs et al., 2010) (Hui et al., 2015) (Sun et al., 2015)
Mice	6-OHDA	Open field	↘ time spent and distance covered in the center area	(Bonito-Oliva et al., 2014)
Mice	Paraquat	Open field	No ≠	(Litteljohn et al., 2008)
Mice	MPTP	Open field	No ≠	(Park et al., 2015)
Mice	α-syn	Open field	Tendency to a ↘ in entries and time spent in the center ↗ time spent in the central area	(Peña-Oliver et al., 2010) (Yamakado et al., 2012)
Mice	A53T	Open field	No ≠ ↗ time spent in the center area	(George et al., 2008) (Oaks et al., 2013) (Paumier et al., 2013) (Rothman et al., 2013)
Mice	MPTP	Hole-board test	No ≠ ↗ head dips	(Vucković et al., 2008) (Janakiraman et al., 2017)
Rat	6-OHDA	Social interactions	<p>↘ offensive behavior but ↗ propensity to interact ↘ frequency to approach counterpart ↘ social interaction</p>	(Branchi et al., 2008) (Eskow Jaunarajs et al., 2010) (Matheus et al., 2016)
Mice	6-OHDA	Social interactions	↘ time in contact	(Chiu et al., 2015)
Mice	MPTP	Marble burying	↗ buried marbles	(Gorton et al., 2010)
Mice	A30P	TMT exposure	<p>↘ time spent freezing ↘ time spent in the odor area</p>	(Nuber et al., 2011) (Marxreiter et al., 2013)
Rat	α-syn	Stress induced hyperthermia	No ≠	(Caudal et al., 2015)
Mice	A53T	Stress induced hyperthermia	No ≠	(Paumier et al., 2013)
Rhesus monkey	α-syn	Behavioral examination	↗ behavioral stereotypies	(Niu et al., 2015)

6-OHDA, 6-hydroxydopamine; α-syn, α-synuclein; EPM, elevated plus maze; LPS, lipopolysaccharide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TMT, 2,3,5-trimethyl-3-thiazoline. Note that “6-OHDA” gathers various models, either unilateral or bilateral, with different lesion sites, and with or without neuroprotection of non-dopamine systems.

Table 3. Depressive-like behaviors in Parkinson's disease models

Table 6 Depressive-like behaviors in Parkinson's disease models

Species		Model	Test	Results	Ref.
Rat		6-OHDA	FST	<p>↓ swimming time / ↑ immobility time</p> <p>↑ immobility time when the 3 monoamines are depleted</p> <p>No ≠</p>	<p>(Branchi et al., 2008) (Tadaiesky et al., 2008) (Santiago et al., 2010) (Tadaiesky et al., 2010) (Casas et al., 2011) (Berghauzen-Maciejewska et al., 2014) (Santiago et al., 2014) (Liu et al., 2015) (Matheus et al., 2016) (Ilkiw et al., 2018) (Delaville et al., 2012) (Eskow Jaunarajs et al., 2010) (Campos et al., 2013)</p>
Mice		6-OHDA	FST	↑ immobility time	(Bonito-Oliva et al., 2014) (Tuon et al., 2014) (Chiu et al., 2015)
Rat		Rotenone Paraquat MPTP LPS	FST	<p>No ≠</p> <p>↑ immobility time</p> <p>No ≠</p> <p>No ≠</p> <p>↑ immobility time</p>	<p>(Santiago et al., 2010) (Campos et al., 2013) (Santiago et al., 2010) (Santiago et al., 2010) (Hritcu and Gorgan, 2014)</p>
Rat		α-syn	FST	<p>No ≠</p> <p>↓ climbing</p>	(Campos et al., 2013) (Caudal et al., 2015)
Mice		VMAT2	FST	↑ immobility in old mice	(Taylor et al., 2009)
Mice		A30P	FST	↓ immobility time	(Nuber et al., 2011)
Mice		LRRK2	FST	No ≠	(Bichler et al., 2013)
Mice		A53T	FST	↓ immobility time	(Oaks et al., 2013)
Mice		6-OHDA	TST	↑ immobility time	(Antunes et al., 2014) (Bonito-Oliva et al., 2014)
Mice		MPTP	TST	<p>↑ immobility time</p> <p>No ≠</p>	<p>(Vucković et al., 2008) (Gorton et al., 2010)</p>
Mice		VMAT2	TST	↑ immobility time in old mice	(Taylor et al., 2009)
Mice		LRRK2	TST	No ≠	(Bichler et al., 2013)

Rat		6-OHDA	Sucrose pref.	<p>↘ preference/consumption</p> <p>↘ preference when the 3 monoamines are depleted No ≠</p>	<p>(Tadaiesky et al., 2008) (Santiago et al., 2010) (Carvalho et al., 2013) (Santiago et al., 2010) (Liu et al., 2015) (Matheus et al., 2016) (Silva et al., 2016) (Kamińska et al., 2017) (Vecchia et al., 2018) (Ilkiw et al., 2018) (Delaville et al., 2012) (Branchi et al., 2008) (Campos et al., 2013)</p>
Rat		Rotenone	Sucrose pref.	↘ preference	(Santiago et al., 2010)
Rat		LPS	Sucrose pref.	↘ preference	(Santiago et al., 2010)
Rat		Paraquat	Sucrose pref.	No ≠	(Campos et al., 2013)
Rat		MPTP	Sucrose pref.	↘ preference	(Krupina et al., 1995) (Santiago et al., 2010)
Mice		MPTP	Sucrose pref.	No ≠	(Vucković et al., 2008) (Gorton et al., 2010)
Rat		$\alpha$ -syn	Sucrose pref.	<p>↘ consumption</p> <p>No ≠</p>	(Caudal et al., 2015) (Campos et al., 2013)
Mice		MitoPark	Sucrose pref.	↘ preference	(Chen et al., 2018)
Rat		6-OHDA	Splash test	↘ grooming time	(Matheus et al., 2016)
Mice		$\alpha$ -syn	Nest test	Deficit and delay to build nest	(Fleming et al., 2004)
Mice		A53T	Nest test	↘ in nest building score	(Paumier et al., 2013)
Mice		MitoPark	Nest test	↘ in nest building score	(Chen et al., 2018)
Rat		6-OHDA	LH	↗ escape latency and ↗ % of helpless rats	(Winter et al., 2007)

6-OHDA, 6-hydroxydopamine;  $\alpha$ -syn,  $\alpha$ -synuclein; FST, forced swim test; LH, learned helplessness ; LPS, lipopolysaccharide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TST, tail suspension test. Note that “6-OHDA” gathers various models, either unilateral or bilateral, with different lesion sites, and with or without neuroprotection of non-dopamine systems.