Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease

Matthieu F. Bastide[1,2]*, Wassilios G. Meissner[1,2,3]*, Barbara Picconi[4]*, Stefania Fasano[5]*, Pierre-Olivier Fernagut[1,2]*, Michael Feyder[6]*, Veronica Francardo[7]*, Cristina Alcacer[7]*, Yunmin Ding[8]*, Riccardo Brambilla[5], Gilberto Fisone[6], A. Jon Stoessl[9], Mathieu Bourdenx[1,2], Michel Engeln[1,2], Sylvia Navailles[1,2], Philippe De Deurwaerdère[1,2], Wai Kin D. Ko[1,2], Nicola Simola[10], Micaela Morelli[10], Laurent Groc[11,12], Maria-Cruz Rodriguez[13], Eugenia V. Gurevich[14], Maryka Quik[15], Michele Morari[16], Manuela Mellone[17], Fabrizio Gardoni[17], Elisabetta Tronci[18], Dominique Guehl[1,2], François Tison[1,2,3], Alan R. Crossman[19], Un Jung Kang[7], Kathy Steece-Collier[20], Susan Fox[21], Manolo Carta[18], M. Angela Cenci[7] and Erwan Bézard[1,2,19#]

MFB, WGM, BP, SF, POF, MF, VF, CA and YD should be considered as co-first authors.

[1]Univ. de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, 33000 Bordeaux, France, [2]CNRS, Institut des Maladies Neurodégénératives, UMR 5293, 33000 Bordeaux, France, [3]Department of Neurology, University Hospital Bordeaux, [4]Laboratory of Neurophysiology, Fondazione Santa Lucia, IRCCS, Rome, Italy, [5]Division of Neuroscience, Institute of Experimental Neurology, San Raffaele Scientific Institute, 20132 Milan, Italy, [6]Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden, [7]Basal Ganglia Pathophysiology unit, Department of Experimental Medical Science, Lund University, Lund, Sweden, [8]Department of Neurology, Columbia University, New York, USA, [9]Pacific Parkinson's Research Centre and National Parkinson Foundation Centre of Excellence, University of British Columbia, Vancouver, Canada, [10]Department of Biomedical Sciences, Section of Neuropsychopharmacology, Cagliari University, 09124, Cagliari, Italy, [11]Univ. de Bordeaux, Institut Interdisciplinaire de neurosciences, UMR 5297, 33000 Bordeaux, France, [12]CNRS, Institut Interdisciplinaire de neurosciences, UMR 5297, 33000 Bordeaux, [13]Department of Neurology, Hospital Universitario Donostia and Neuroscience Unit, Bio Donostia Research Institute, San Sebastian, Spain, [14]Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN 37232, USA, [15]Center for Health Sciences, SRI International, CA 94025, USA, [16]Department of Medical Sciences, Section of Pharmacology, University of Ferrara, Ferrara, Italy, [17]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, 20133 Milano, Italy, [18]Department of Biomedical Sciences, Physiology Section, Cagliari University, Cagliari, Italy, [19]Motac Neuroscience Ltd, Manchester, UK, [20]Michigan State University, College of Human Medicine, Department of Translational Science and Molecular Medicine & The Udall Center of Excellence in Parkinson's Disease Research, 333 Bostwick Ave noradrenaline, Grand Rapids, Michigan, 49503, [21]Morton & Gloria Shulman Movement Disorders Center, Toronto Western Hospital, Toronto, Ontario M4T 2S8, Canada.

#: To whom correspondence should be addressed: Erwan Bezard, Institut des Maladies Neurodégénératives, Université de Bordeaux, Bât 3B 1er étage, 146 rue Léo Saignat, 33076 Bordeaux cedex ; phone : +33 557 571 687 ; mail : erwan.bezard@u-bordeaux.fr.

Running head: Pathophysiology of L-dopa-induced dyskinesia

Number of characters in the title: 89 **Number of characters in the running head**: 41

Number of words in the abstract: 160 **Number of references:** 1139

Number of pages: 252 **Number of figures:** 5

Table of content

1. Abstract 4

2. Introduction 4

3. Spectrum of LID and other L-dopa-induced side effects 5

3.1. Clinical presentation 5
3.2. DA replacement therapy in PD 6
3.3. Genetics of LID 7
3.4. Current management of LID in PD patients 9
3.4.1. Amantadine 9
3.4.2. Deep brain stimulation (DBS) 10
3.5. Beyond LID: impulse control disorders and DA dysregulation syndrome 12
3.5.1. Impulse control disorders (ICDs) 12
3.5.1.1. Pathological gambling 12
3.5.1.2. Compulsive shopping 12
3.5.1.3. Hypersexuality 13
3.5.1.4. Compulsive eating 13
3.5.1.5. Punding 13
3.5.2. Dopamine dysregulation syndrome (DDS) 14
3.5.3. DA replacement therapy withdrawal syndrome 15
3.5.4. Dyskinesia and compulsive behaviours 16
3.6. Other adverse effects of L-dopa 16

4. Animal models of LID and other L-dopa-induced abnormal behaviours 17

4.1. Hyperlocomotion in the reserpine-treated rat model of PD 17
4.2. Behavioural sensitization in the 6-OHDA-lesioned rat 18
4.3. Abnormal involuntary movements in 6-OHDA-lesioned rodents 18
4.3.1. Rat model 18
4.3.2. Mouse model 20
4.4. Hyperlocomotion in the DA-deficient DA transporter knock-out mice 21
4.5. Genetic mouse models of bilateral dopamine deficit 21
4.6. Non-human primate models of LID 23
4.6.1. History 23
4.6.2. Macaque models 24
4.6.3. Marmoset model 26
4.6.4. Squirrel monkey model 27
4.6.5. Other species 28
4.7. Models of DDS/ICD 29
4.7.1. The role of the DAergic medication 30
4.7.2. The role of the DAergic lesion 31
4.7.3. The role of individual risk factors 33
4.8. Modelling other L-dopa-induced side-effects 35

5. Pathophysiology of peak of dose LID 35

5.1. Pharmacokinetics and pharmacodynamics 36
5.2. Imaging 37
5.2.1. Studies of the DA system 37
5.2.2. Studies of non-DAergic mechanisms 40
5.2.3. Potential future applications 41
5.3. Electrophysiology 42
5.3.1. *In vivo* extracellular recordings 42
5.3.1.1. *In vivo* single cell recordings 43
5.3.1.2. *In vivo* local field potentials 44
5.3.2. *Ex-Vivo* electrophysiology 46

5.4. Morphological changes related to LID **49**
5.4.1. Morphological re-sculpting of neurons and circuits in LID **49**
5.4.2. Striatal remodelling and graft-induced dyskinesia **54**
5.4.3. Non-neuronal factor involvement in dyskinesia **57**
5.5. Priming leads to LID **59**
5.6. Presynaptic component of LID pathophysiology **62**
5.6.1. Handling of L-dopa in the striatum **62**
5.6.2. Handling of L-dopa outside the striatum **67**
5.7. Impact of L-dopa on 5-HT transmission and relationship to LID **68**
5.8. Impact of L-dopa on amino acids: relationship to LID **70**
5.9. Postsynaptic changes in striatal medium spiny neurons **72**
5.9.1. LID is associated with an increased IEG expression **72**
5.9.2. Gene expression signature associated to LID **73**
5.9.3. Dopamine receptor signalling **76**
5.9.3.1. D_1 receptor canonical pathway 77
5.9.3.2. D_1 receptor non-canonical pathways 80
5.9.4. Other dopamine receptors **86**
5.9.4.1. D_2 receptor 86
5.9.4.2. D_3 receptor 88
5.9.4.3. D_4 receptor 90
5.9.5. Dysregulation of homologous DA receptor desensitization **90**
5.9.6. Dysregulation of lateral diffusion **101**
5.9.7. D_1 receptor stimulation impairs striatal proteasome activity **103**
5.9.8. Glutamate receptors **104**
5.9.8.1. NMDA receptors 105
5.9.8.2. AMPA receptors 106
5.9.8.3. Metabotropic glutamate receptors (mGluRs) 107
5.9.9. Adenosine receptors **108**
5.9.10. Acetylcholine (Ach) receptors **110**
5.9.11. Peptidergic transmission **113**
5.9.11.1. Classic opioid transmission 113
5.9.11.2. N/OFQ-NOP system 115
5.10. Postsynaptic changes in striatal interneurons **118**
5.11. Involvement of additional extrastriatal regions in LID pathophysiology **120**

6. Development of therapeutics 123
6.1. Continuous delivery of L-dopa 123
6.2. Serotonin 5-HT_{1A} agonists 125
6.3. NMDA antagonists 126
6.4. mGluR5 negative allosteric modulators 128
6.5. Antiepileptics 129
6.6. Antipsychotics 130
6.7. Other strategies 131

7. Concluding remarks 132

8. Acknowledgements 135

9. References 137

10. Figure legends 251

1. Abstract

Involuntary movements, or dyskinesia, represent a debilitating complication of levodopa (L-dopa) therapy for Parkinson's disease (PD). L-dopa-induced dyskinesia (LID) are ultimately experienced by the vast majority of patients. In addition, psychiatric conditions often manifested as compulsive behaviours, are emerging as a serious problem in the management of L-DOPA therapy. The present review attempts to provide an overview of our current understanding of dyskinesia and other L-DOPA-induced dysfunctions, a field that dramatically evolved in the past twenty years. In view of the extensive literature on LID, there appeared a critical need to re-frame the concepts, to highlight the most suitable models, to review the central nervous system (CNS) circuitry that may be involved, and to propose a pathophysiological framework was timely and necessary. An updated review to clarify our understanding of LID and other L-dopa-related side effects was therefore timely and necessary. This review should help in the development of novel therapeutic strategies aimed at preventing the generation of dyskinetic symptoms.

2. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting approximately 1% of the population over 65, the mean age at which the disease is first diagnosed. PD was first described by James Parkinson (Parkinson, 1817, 2002) and consists of a syndrome including bradykinesia/akinesia, rigidity, postural abnormalities and tremor. The principal pathological characteristic of PD is the progressive death of the pigmented neurons of the Substantia Nigra pars compacta (SNc) (Hassler, 1938). The discovery, in 1960, that degeneration of the dopamine (DA) supplying neurons of the SNc causes parkinsonism (Ehringer and Hornykiewicz, 1960) opened the way for the development of pharmacological therapies for PD that act to enhance synaptic DA transmission using the DA precursor L-$_{3,4}$-dihydroxypheylalanine (L-dopa) (Birkmayer and Hornykiewicz, 1961, 1962; Lees, 1994; Yahr *et al.*, 1968).

The initial enthusiasm surrounding the positive effects of L-dopa in PD soon gave way to the recognition that long-term L-dopa therapy is complicated by the development of adverse events related to fluctuations in motor response. Motor fluctuations include ON-OFF fluctuations, sudden and unpredictable changes in mobility, and the wearing-off phenomenon, a decrease in the duration of L-dopa action (Quinn, 1998). However, the most debilitating class of motor fluctuation is involuntary movements known as L-dopa-induced dyskinesia (LID). These abnormal involuntary movements (AIMs) have been noted from the first

introduction of L-dopa in the late 1960s (e.g. after 6 months of treatment over half of patients had developed dyskinesia) (Duvoisin, 1974). Long term experience has continued to report that the majority of L-dopa-treated patients experience dyskinesia, with up to 80% of patients having LID within 5 years of treatment (DeJong *et al.*, 1987; Lees and Stern, 1983; Lesser *et al.*, 1979; Marsden *et al.*, 1982; Rajput *et al.*, 1984). Eighty to ninety per cent of PD patients suffer from LID after 10 years of DA replacement therapy (Ahlskog and Muenter, 2001; Hauser *et al.*, 2007), a condition affecting their quality of life (Hechtner *et al.*, 2014). It should be noted that treatment-related dyskinesia are not solely a problem of L-dopa but DA receptor agonists are also capable of eliciting dyskinesia. Therefore, within this review, the term LID will be used to describe dopaminergic (DAergic) treatment–related dyskinesia generally. In the past 20 years, the understanding of the neural mechanisms underlying LID in PD has strongly advanced (Bezard *et al.*, 2001a; Cenci *et al.*, 1998; Fasano *et al.*, 2010; Fieblinger *et al.*, 2014b; Fisone and Bezard, 2011; Jenner, 2008; Picconi *et al.*, 2003). Dyskinesia has been associated with a sequence of events that include pulsatile stimulation of DA receptors, downstream changes in proteins and genes, abnormalities in non-DAergic transmitter systems all of which combine to produce alterations in the neuronal firing patterns that signal between the basal ganglia and the cortex.

In this review, we aim at focusing on the changes affecting both DAergic and non-DAergic transmission, and particularly focus on changes observed at the peak-dose of L-dopa plasma concentrations, that is when dyskinesia are more commonly expressed, so called - ON dyskinesia, as opposed to OFF dyskinesia where the pathophysiology relates to low levels of DA. We also review other L-dopa-induced side-effects and highlight their pathophysiology as well as possible links to pathophysiology of LID. This overview has the goal to advance our understanding of LID, which might contribute to the development of novel therapeutic strategies aimed at preventing dyskinetic symptoms.

3. Spectrum of LID and other L-dopa-induced side effects

3.1. Clinical presentation

LID can be classified into peak-dose dyskinesia (involuntary movements that coincide with the peak-action of levodopa and thus period of best anti-parkinsonian action), diphasic dyskinesia (involuntary movements that emerge just before the DA replacement therapy turns the patient ON and that reappear at the end of the therapeutic benefit) and OFF period

dystonia. The movement disorders most commonly associated with peak-dose LID are chorea, dystonia and ballism.

Chorea is characterized by involuntary, irregular, purposeless, non-rhythmic, abrupt and rapid movements that seem to flow from one part of body to the other. Choreic or larger amplitude choreo-athetotic movements are the most common forms of LID. They are most commonly associated with peak-dose dyskinesia. Chorea usually manifests first on the side of the body that is predominantly affected by PD. The severity of choreic movements varies from minor (involuntary movements may not be recognized by patients) to major (involuntary movements may significantly interfere with activities of daily living). Neck and limbs are most commonly affected.

Dystonia is the second most common form of LID. It is characterized by sustained contractions of agonist and antagonist muscles that may involve focal/segmental muscle groups. Dystonia as part of LID can be observed as peak-dose dyskinesia, diphasic dystonia or "OFF" dystonia. Diphasic dystonia usually presents as involuntary leg kicking movements. "OFF" period dystonia symptoms is most commonly seen as painful early morning dystonia of one foot or toes.

Ballism is characterized by very large amplitude unilateral or bilateral choreic movements of the proximal parts of the limbs. Ballistic movements are usually part of severe chore-athetosis rather than being isolated.

3.2. DA replacement therapy in PD

More than 50 years after its introduction (Cotzias *et al.*, 1967), L-dopa remains the most effective and best tolerated treatment for PD motor symptoms (Fox *et al.*, 2011; Goetz *et al.*, 2005). DA agonists have also proven their efficacy in large randomized trials as monotherapy in early PD and as adjunct therapy in advanced disease stages (Fox *et al.*, 2011; Goetz *et al.*, 2005). The main purpose of prescribing DA agonists to younger PD patients was to delay the onset of motor complications, such as wearing off and dyskinesia (Hubble, 2002). However, long term follow up of short term randomised controlled studies comparing early DA agonist vs. L-dopa administration shows that such delays are only short lived and once L-dopa is introduced, LID will occur regardless of early use of DA agonist or not (Hauser *et al.*, 2007; Katzenschlager *et al.*, 2008). Such view is counter-balanced by a recent meta-analysis suggesting that initial DA agonist treatment encompasses a lower risk for dyskinesia even

after the unavoidable introduction of L-dopa that increases the risk for dyskinesia in a dose-related manner (Chondrogiorgi *et al.*, 2014).

Other treatments are available adjunct to L-dopa to extend ON time, such as inhibitors of the DA degrading enzymes catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO). The efficacy of the COMT inhibitors tolcapone and entacapone have been extensively studied in PD patients with motor fluctuations (Adler *et al.*, 1998; Myllyla *et al.*, 2001; Olanow *et al.*, 2004; Poewe *et al.*, 2002; Rajput *et al.*, 1997; Shoulson *et al.*, 2002; Waters *et al.*, 1997). In clinical trials, new or worsening of dyskinesia was more frequently reported as side effect in patients receiving COMT inhibitors. However, dyskinesia generally subsided after L-dopa dose reduction and no differences were observed at study end between COMT inhibitors and placebo. Rasagiline, an inhibitor of monoamine oxidase (MAO)-B, is also used as monotherapy in early PD and add-on in more advanced disease stages (Parkinson Study, 2002; Parkinson Study Group, 2005). However, in clinic practice, both COMT and MAO-B inhibitors can worsen or induce dyskinesia.

3.3. Genetics of LID

The expanding field of genetics has also involved the search for factors that may result in greater susceptibility in developing LID. For instance, the autosomal recessive parkinsonism genes, PARK2 (*parkin*), PARK6 (*pink-1*) and PARK7 (*DJ-1*) are all associated with young-onset PD and often frequent appearance of dyskinesia suggesting the involvement of genetic factors related to parkinsonism (Dekker *et al.*, 2003). However genetic parkinsonism tends to affect individuals at a younger age, and age itself is known to be a risk factor for developing LID. However, observations suggest that subjects with *parkin*–related parkinsonism may have a delayed onset of dyskinesia, probably due to a lower daily L-dopa dose (Lohmann *et al.*, 2009). Patients with autosomal dominant *LRRK2* gene mutations (PARK8) had a higher rate of dyskinesia compared to genetically undefined patients in two studies (Lesage *et al.*, 2008; Nishioka *et al.*, 2010), while this difference was not observed in Israeli LRRK2 patients with parkinsonism and the cohort of the International LRRK2 Consortium (Healy *et al.*, 2008; Yahalom *et al.*, 2012). Noteworthy, the time to LID onset was longer in patients with mutations in LRRK2 than in patients with idiopathic PD in the cohort of the International LRRK2 Consortium but not in Israeli *LRRK2* patients. It remains therefore unclear if these genetic abnormalities have a direct effect on the risk of developing LID or if other mechanisms play a role.

Besides these genetic forms of PD, more classic loci of possible factors linked to dyskinesia have been investigated. Various studies have investigated genetic associations of DA and non-DA receptors implicated in basal ganglia function with LID, as well as DA transporters and enzymes involved in the metabolism of DA. Accordingly, polymorphisms of DA D_2 receptors (D_2R) but not of D_1 receptors (D_1R) seem to reduce the risk of developing LID (Oliveri *et al.*, 1999; Rieck *et al.*, 2012), a result not confirmed in more recent studies (Kaplan *et al.*, 2014). By contrast, the TaqIA polymorphism located in the gene encoding the D_2R was shown to increase the risk of developing motor fluctuations in PD patients (Wang *et al.*, 2001). This observation was not confirmed by others (Lee *et al.*, 2011; Rieck *et al.*, 2012). In a study investigating genetic susceptibility factors of diphasic and peak-dose LID, diphasic dyskinesia was associated with the DA D_3R p.S9G variant. Carrying the AA genotype was likely to shorten the onset of diphasic dyskinesia, while the presence of peak-dose LID was not associated with any of the genetic variants studied (Lee *et al.*, 2011). One recent study found that a polymorphism in the *SLC6A3* gene encoding for the DA transporter extends the time to LID onset (Kaplan *et al.*, 2014). Finally, a COMT Val158Met polymorphism is associated to an increased risk of developing dyskinesia (de Lau *et al.*, 2012).

Opioid receptors have also been implicated in the genetics of LID. In this view, carrying the G-allele of the A118G single nucleotide coding region polymorphism of the μ opioid receptor is associated with an increased risk of earlier onset of dyskinesia (Strong *et al.*, 2006).

The role of brain derived neurotrophic factor (BDNF) in LID has also been investigated. PD patients with the Val(66)Met allele of BDNF have a significantly higher risk of developing dyskinesia earlier in the course of their disease (Foltynie *et al.*, 2009). However, more recent studies did not observe an association between seven polymorphisms of the *BDNF* gene and LID onset (Cheshire *et al.*, 2014; Kaplan *et al.*, 2014).

Many of those studies are however in need of replications, thereby requiring that readers pay attention to their limits. While one polymorphism seems not enough to clearly enhance the risk for LID, the possibility that combined polymorphisms affecting more than 2 genes is a possible factor in determining an individual's lifetime L-dopa exposure warrants further investigation (Cheshire *et al.*, 2014). Taken together, the contribution of the genetic factors in the overall risk of developing LID needs further investigation or could be considered as of modest impact upon the propensity of patients to develop LID. New findings may however have implications for helping predict individual PD patients at risk of developing LID.

3.4. Current management of LID in PD patients

3.4.1. Amantadine

Currently the only evidence-based medicine review recommended add-on anti-dyskinetic agent is amantadine, a multi-target drug with antagonistic activity at the N-methyl-D-aspartate receptor (NMDA) receptor (Fox *et al.*, 2011). The efficacy of amantadine at reducing dyskinesia severity was first assessed during an acute intravenous L-dopa infusion in a small placebo-controlled cross-over study in 18 PD patients with motor fluctuations and peak-dose dyskinesia (Verhagen Metman *et al.*, 1998b). Amantadine reduced peak-dose dyskinesia severity without modifying PD motor symptoms. The level of dyskinesia reduction was related to plasma amantadine levels. The same patients were assessed 1 year later in a placebo-controlled follow-up paradigm while still receiving amantadine (Metman *et al.*, 1999). The magnitude of the anti-dyskinetic effect was similar suggesting a sustained effect of amantadine on peak-dose dyskinesia. Another randomized placebo-controlled study tested the effectiveness of amantadine in subsequent 18 consecutive PD patients with motor fluctuations and peak-dose dyskinesia (da Silva-Junior *et al.*, 2005). After three weeks of treatment, Unified Parkinson's Disease Rating Scale (UPDRS) scores were improved while CDRS scores were unchanged and not different from placebo. The effect of acute intravenous amantadine infusion was tested in 9 PD patients with motor fluctuations and peak-dose dyskinesia in a placebo-controlled cross-over study (Del Dotto *et al.*, 2001). Intravenous amantadine infusion reduced AIMs scores by 50% compared to placebo.

The observation of a benefit of amantadine treatment lasting for less than 8 months in a randomized, placebo-controlled study including 40 PD patients with motor fluctuations and peak-dose dyskinesia questioned the usefulness of this drug for treating dyskinesia in the long run (Thomas *et al.*, 2004). Withdrawal of the drug at study end induced a transient rebound with increase of LID in 11 patients.

The results of the trial by Thomas et al. (Thomas *et al.*, 2004) were challenged by two randomized placebo-controlled parallel-group studies that assessed the long-term anti-dyskinetic effect of amantadine in 32 and 57 PD patients, respectively (Ory-Magne *et al.*, 2014; Wolf *et al.*, 2010). In the first study, patients who received amantadine for LID for at least one year were switched in a double blind manner to amantadine or placebo. Dyskinesia scores worsened significantly in patients receiving placebo but not in those pursuing amantadine. In the second trial, patients were switched to either amantadine or placebo after at least six months of stable treatment with amantadine (Ory-Magne *et al.*, 2014). Similar to

the study by Wolf and colleagues (Wolf *et al.*, 2010), dyskinesia scores were significantly higher in the placebo group compared to patients pursuing amantadine. Moreover, dropouts for LID worsening and higher AIMs scores were observed in the discontinuing group.

Taken together, these results of both recent trials argue for long-term anti-dyskinetic effects of amantadine in PD patients with LID. The ongoing PREMANDYSK trial assesses the efficacy of amantadine in delaying the onset of LID in PD patients without motor complications (NCT01538329). Of note, the extended release formulation soon to be available (Pahwa *et al.*, 2015).

3.4.2. Deep brain stimulation (DBS)

Within the last two decades, deep brain stimulation (DBS) of the Subthalamic Nucleus (STN) and the internal part of the Globus Pallidus (GPi) have become routine surgical methods for treating well selected PD patients with severe motor fluctuations and LID (Deuschl *et al.*, 2006; Follett *et al.*, 2010; Krack *et al.*, 2003; Moro *et al.*, 2010; Volkmann, 2004; Weaver *et al.*, 2012).

DBS of the postero-ventral part of the GPi is particularly effective to treat LID. Accordingly, a reduction of 76% of LID severity was observed after surgery (Rodrigues *et al.*, 2007). Longer follow-up studies confirmed marked and sustained improvement of dyskinesia (75% in duration and 64-100% in severity) over 5-6 years of pallidal stimulation (Moro *et al.*, 2010; Volkmann, 2004). The efficacy of pallidal stimulation is independent of the type of LID and also includes respiratory dyskinesia (Oyama *et al.*, 2011). Although the underlying mechanisms remain unclear some evidences suggest that the reduction of LID could be related to the stimulation of inhibitory afferents coming from the striatum, the external part of the Globus Pallidus (GPe) or collaterals of GPi neurons to the posterior ventral pallidum (Boraud *et al.*, 1996; Wu *et al.*, 2001). Alternatively, GPi-DBS could reverse the abnormal pattern of neuronal activity that is induced by DA replacement treatment in the basal ganglia-cortex network (Guridi *et al.*, 2008; Wu *et al.*, 2001).

STN-DBS is the commonest target for advanced PD patients due to an excellent benefit on all PD symptoms and improvement in LID. Historically, lesioning of STN induced dyskinesia in normal subjects (Beurrier *et al.*, 1997) and so concerns arose as to the effects in PD subjects. During STN-DBS surgery, dyskinesia can occur due to a lesional effect of the implanted electrode but the occurrence of choreic or ballistic movements in the operating room is considered as an indication for the accurate placement of the stimulation leads within the

sensorimotor part of the STN. STN-DBS-induced involuntary movements are frequent during the first month following surgery (Zheng *et al.*, 2010). Rarely such movements persist and make additional GPi-DBS necessary (Reese *et al.*, 2011). In most cases, the duration and severity of LID decrease over time and patients experience a very good improvement in quality of life (Deuschl *et al.*, 2006; Follett *et al.*, 2010; Krack *et al.*, 2003; Simonin *et al.*, 2009). The shift from 130 Hz to 80 Hz may be helpful in patients with residual LID (Merola *et al.*, 2013). STN-DBS improves the entire spectrum of LID including peak-dose, biphasic and OFF period dyskinesia (Fraix *et al.*, 2010; Katayama *et al.*, 2006; Krack *et al.*, 1999). The mechanisms involved in the reduction of LID after STN-DBS remain unclear but the concomitant decrease in DA replacement therapy is frequently incriminated. Indeed, STN-DBS reduces LID by 46–85%, which is paralleled by a concomitant reduction of the equivalent daily L-dopa dose by 50% (Breit *et al.*, 2004; Guridi *et al.*, 2008). The delayed decrease in LID further suggests that the desensitization to LID requires several months of drug withdrawal (Russmann *et al.*, 2004). However, some authors have suggested direct effects of DBS on STN neurons and the structures in the vicinity of this nucleus. Accordingly, DBS dorsal to the STN (zona incerta, lenticulus fasciculari) seems to be able to directly suppress LID independently of changes in DAergic medication (Alterman *et al.*, 2004; Herzog *et al.*, 2003). DBS of this region may improve LID through a disruption of the pallido-thalamic connection or a modification of the activity pattern of STN neurons (Garcia *et al.*, 2003; Katayama *et al.*, 2006; Meissner *et al.*, 2005; Obeso *et al.*, 2000; Sankar and Lozano, 2011). Others have hypothesized that STN-DBS induces overall stabilization of the basal ganglia network and striatal synaptic function (Simonin *et al.*, 2009).

DBS of the thalamic centromedian and parafascicular complex (CM/PF) seems also effective in reducing LID severity in PD patients, but current evidence for the usefulness of this target remains weak (Caparros-Lefebvre *et al.*, 1999).

Taken together, DBS of GPi or STN are effective treatments of LID in PD patients suffering from motor fluctuations. To date, there is no study that has demonstrated a significant difference in efficacy against either LID or motor symptoms between both targets (Follett *et al.*, 2010; Lukins *et al.*, 2014; Odekerken *et al.*, 2013; Sako *et al.*, 2014). Thus, the choice of the target must be determined in a patient-by-patient fashion, with side effect profile such as cognitive and speech deficits taken into consideration.

3.5. Beyond LID: impulse control disorders and DA dysregulation syndrome

In addition to the wide array of non-motor symptoms occurring in PD, DA replacement therapy can induce non-motor side-effects. Among them, addiction-like disorders have been described with a growing interest since the early 2000's (Cilia *et al.*, 2014; Giovannoni *et al.*, 2000; Lawrence *et al.*, 2003; Weintraub and Nirenberg, 2013; Weintraub *et al.*, 2013; Weintraub and Potenza, 2006). They mainly encompass impulse control disorders (ICD), which can be seen as behavioural addictions and DA dysregulation syndrome (DDS), corresponding to compulsive medication use. While they mainly have a non-motor expression, their link with LID has been questioned (Voon *et al.*, 2009).

3.5.1. Impulse control disorders (ICDs)

ICDs are behavioural affections during which individuals fail to resist to internal or external stimuli, leading them to act inconsiderately. These impulsive behaviours generate anxiety and can result in dramatic alterations of the social or professional functioning (Pontone *et al.*, 2006). The clinical spectrum of ICD has been extensively described elsewhere (Voon *et al.*, 2009; Voon *et al.*, 2007a). Briefly, different types of ICD are reported.

3.5.1.1. Pathological gambling

Pathological gambling is the most common ICD and is found in 5 to 6% of PD patients (Avanzi *et al.*, 2006; Weintraub *et al.*, 2010). Parkinsonian gamblers are mainly interested in games providing immediate reward such as scratch cards, bets, casinos or internet gambling games (Voon *et al.*, 2009). Pathological gambling can have dramatic consequences on patient's life due to important monetary losses, with an average financial loss of US$10,000 (Voon *et al.*, 2006). Noteworthy, in the latest Diagnostic and Statistical Manual of Mental Disorders (i.e. the DSM V) (American-Psychiatric-Association, 2013), gambling disorders left the 'Impulse Control Disorders' category to be classified as 'Substance-related and addictive disorders', thus emphasising its 'Behavioural addiction' aspect (Weintraub *et al.*, 2015).

3.5.1.2. Compulsive shopping

Compulsive shopping is defined by continuous thoughts toward buying behaviour and results in high anxiety (Black, 2007). In PD, compulsive shopping is observed in 5.7% of patients (Weintraub *et al.*, 2010) but such troubles may be difficult to detect and necessitate the use of defined diagnostic criteria (McElroy *et al.*, 1994). The purchases are usually useless, very

expensive, time-consuming and anxiogenic and should be observed aside from any maniac episode. Compulsive shopping seems to be more commonly observed in women than in men (7.8% vs. 4.5% (Weintraub *et al.*, 2010)).

3.5.1.3. Hypersexuality

Hypersexuality has been defined by the presence of maladaptive preoccupation with sexual thoughts with the occurrence of intrusive paraphiliac ideations preventing the focusing on daily tasks. Orgasms are described as not satisfying and lead to the need of repeated sexual intercourses (Kaplan, 1994). Its prevalence is difficult to estimate but might reach 3.5% (Weintraub *et al.*, 2010) and diagnostic criteria have been proposed (Voon *et al.*, 2006). Hypersexuality appears to occur more frequently in men than in women (5.2% vs. 0.5% (Weintraub *et al.*, 2010)). Compulsive sexual behaviours are difficultly tolerated by PD patients and are often associated with depression (Klos *et al.*, 2005; Voon *et al.*, 2006). In addition to the discomfort felt by the patients, these behaviours can have disastrous consequences on the spouse or a third person (Muller *et al.*, 2013).

3.5.1.4. Compulsive eating

Compulsive eating refers to an irresistible need of food intake far beyond satiety (Nirenberg and Waters, 2006). Its occurrence in PD is estimated to 4.3% (Weintraub *et al.*, 2010). Unlike the majority of parkinsonian patients who are losing weight, an abnormal weight increase is usually a red flag (Nirenberg and Waters, 2006). Diagnostic criteria follow the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) items and include: the occurrence of binge eating along with a loss of control, rapid eating, feeling uncomfortably full, eating large amounts when not hungry, eating alone because of embarrassment of amounts, feeling disgusted or guilty after overeating, in the presence of visible distress. Such behaviours should be present during at least 2 days/week over 6 months in absence of compensatory behaviours, or during anorexia or bulimia nervosa (American-Psychiatric-Association, 2000).

3.5.1.5. Punding

Punding is not considered as an ICD *per se* but frequently follows the same classification because of its compulsive nature. Initially described in amphetamine and cocaine users (Rylander, 1972; Schiorring, 1981), punding can be defined as an intense fascination for repetitive tasks, which can be simple such as gathering, manipulating, sorting objects or more complex such as painting or gardening (Voon *et al.*, 2009). Other repetitive behaviours such as hobbyism and walkabout follow the same classification (Evans *et al.*, 2004; Giovannoni *et*

al., 2000). Punding is often misevaluated in PD because of the lack of precise diagnostic criteria, but studies reported a prevalence between 1.4 and 14% (Evans *et al.*, 2004; Miyasaki *et al.*, 2007). Punding is mainly observed with apomorphine and DA D_2R/D_3R agonists. Attempts are pursued to reduce punding in patients, such as repetitive transcranial magnetic stimulation that brings a transient beneficial effect, similar to that reported in PD patients with LID (Nardone *et al.*, 2014).

Finally, the spectrum of DA replacement therapy-induced ICD can be extended to various other behaviours such as excessive hoarding, kleptomania or reckless generosity (Bonfanti and Gatto, 2010; O'Sullivan *et al.*, 2010a; O'Sullivan *et al.*, 2010b).

Clinical studies reported the occurrence of ICD within 24 months following the beginning of the treatment and a cessation of the troubles when DA replacement therapy is tapered or stopped (Dodd *et al.*, 2005). They are preferentially observed with DA D_2R/D_3R agonists (Gallagher *et al.*, 2007), which might increase by 2 to 3.3 fold the risk of developing such troubles (Weintraub *et al.*, 2010). A cross-sectional study conducted in the United States and Canada identified the occurrence of at least one ICD in 13.6% of PD patients (Weintraub *et al.*, 2010). Interestingly, this study highlighted than an adjunctive L-dopa therapy increases the odds of an ICD by 50% compared to DA agonists alone. A younger age at disease onset, past experiences of illegal drug use or cigarette smoking might constitute risk factors (Bastiaens *et al.*, 2013; Weintraub *et al.*, 2010). A novelty seeking (Voon *et al.*, 2007b) or a sensation seeking (Djamshidian *et al.*, 2011a) personality have also been reported and are suspected to be important factors in the development of ICD.

3.5.2. Dopamine dysregulation syndrome (DDS)

DDS refers to a pathological overconsumption of the DAergic medication. Its occurrence is estimated between 3 and 4% of PD patients (Giovannoni *et al.*, 2000; Pezzella *et al.*, 2005), it is mainly found in patients with younger age at disease onset and it is associated with past legal or illegal drug use (Cilia *et al.*, 2014; Evans *et al.*, 2005; Giovannoni *et al.*, 2000; Lawrence *et al.*, 2003). In addition, most DDS cases are reported in patients taking fast-acting drugs such as subcutaneous apomorphine or L-dopa as opposed to long acting drugs (Giovannoni *et al.*, 2000). Despite appropriate treatment of motor symptoms, DDS patients feel under-medicated and start to increase their DA replacement therapy intake (Lawrence *et al.*, 2003). This is associated with a distorted perception of the motor status, and patients only feel ‘on’ when highly dyskinetic (Giovannoni *et al.*, 2000; Lawrence *et al.*, 2003). Moreover,

a sensation of pleasure, well-being and a psychostimulant effect are reported (Castrioto *et al.*, 2013; Tellez *et al.*, 2006). A core feature of DDS is an increased intake of DA replacement therapy, which will necessitate multiple providers (multiple physicians, internet purchases) or drug hoarding (Lawrence *et al.*, 2003; Tellez *et al.*, 2006). Thus, DDS has been associated to a 'hedonistic homeostatic dysregulation' (Giovannoni *et al.*, 2000) where the motivation to retrieve the pleasant feelings procured by the drug is driven by the unpleasant sensation of withdrawal (Koob and Le Moal, 1997; Solomon and Corbit, 1973). DDS is associated with the presence of LID and ICD (Catalan *et al.*, 2013; Giovannoni *et al.*, 2000).

The DDS diagnosis follows DSM-IV criteria for substance dependence (American-Psychiatric-Association, 2000) but its use has been discussed in the specific context of PD (Bearn *et al.*, 2004). Indeed, the excessive DA replacement therapy intake occurs in the context of a neurologic disease, which needs drug intake to relieve motor symptoms (Giovannoni *et al.*, 2000). Therefore, an alternative classification has been proposed. Mainly following the DSM-IV criteria, it considers the specificities of PD and proposes the diagnostic of a DDS when symptoms vary from a 'classical' parkinsonian syndrome (Giovannoni *et al.*, 2000).

3.5.3. DA replacement therapy withdrawal syndrome

In patients presenting DDS, tapering or stopping L-dopa or apomorphine may result in withdrawal signs including dysphoria, depression, irritability and anxiety (Giovannoni *et al.*, 2000; Lawrence *et al.*, 2003). These negative sensations are different from those classically occurring for end-of-dose fluctuations and have been considered as core features for the diagnosis of DDS. Withdrawal signs have also been observed in up to 19% of PD patients specifically treated with DA agonists (Rabinak and Nirenberg, 2010). They are similarly characterized by psychostimulant-like withdrawal symptoms such as anxiety, irritability, orthostatic hypotension and panic attack when the treatment is reduced and have been named DA agonist withdrawal syndrome (DAWS). Wearing-off symptoms refractory to L-dopa and psychiatric manifestation resistant to antidepressant or anxiolytic are specific features of DAWS. Interestingly, DAWS has exclusively been observed in patients presenting ICD (Pondal *et al.*, 2013; Rabinak and Nirenberg, 2010), suggesting a generalized dysfunction of reward systems (Nirenberg, 2013).

3.5.4. Dyskinesia and compulsive behaviours

The repetitive movements of LID and the compulsive behaviours of punding have been proposed to share common mechanisms (Voon *et al.*, 2009). An altered functioning of the basal ganglia network is associated with deficits in inhibiting competing behaviours (Mink, 1996). Clinical studies showed that PD patients with severe motor symptoms have deficits in on-line suppression of impulsive responses (Wylie *et al.*, 2010). Moreover, parkinsonian patients presenting punding behaviours exhibit more severe dyskinesia than other patients and punding severity correlates with LID severity (Silveira-Moriyama *et al.*, 2006). Finally, LID and compulsive DA replacement therapy use might share similar presynaptic mechanisms. Studies using [^{11}C]raclopride (a DA D_2R/D_3R ligand) binding revealed increased DA levels in the dorsal striatum after L-dopa intake in dyskinetic patients (de la Fuente-Fernandez *et al.*, 2004) whereas an increased DA release in the ventral striatum after L-dopa intake is observed in DDS patients (Evans *et al.*, 2006). Altogether, it appears that both LID and compulsive DA replacement therapy intake are two aspects resulting from abnormal DAergic stimulation. A better understanding of their common mechanisms will be crucial for their treatment.

3.6. Other adverse effects of L-dopa

In addition to the motor and neurobehavioral complications of DA replacement therapy, several other side effects have been reported. These include autonomic symptoms (nausea, orthostatic hypotension), excessive daytime sleepiness and psychiatric complications (hallucinations, delusions). However, some of these autonomic and psychiatric manifestations are also inherent to the disease and their link with L-dopa is thus not as straightforward as it is the case with LID and compulsive behaviours triggered by DA replacement therapy.

L-dopa (as well as DA receptor agonists) can induce nausea and vomiting, side-effects that were considered due to the stimulation of DA receptors of the area postrema (Duvoisin, 1972), which is devoid of blood-brain barrier. Hence, nausea and vomiting are significantly reduced since the use of peripheral aromatic L-amino acid decarboxylase (AADC) inhibitors which have allowed to dramatically decrease the daily dose of L-dopa (Lieberman *et al.*, 1975). In the same way, those side effects were commonly treated with domperidone, a peripheral DA receptor antagonist.

Orthostatic hypotension is a well-identified autonomic symptom of PD related to the involvement of the sympathetic nervous system early in the disease process (Fereshtehnejad and Lokk, 2014). Several lines of evidence indicate that L-dopa can have cardiovascular side-

effects, including worsening of orthostatic hypotension (Senard *et al.*, 1997), as well as a decrease in blood pressure and heart rate (Bouhaddi *et al.*, 2004).

Altered vigilance, including excessive daytime sleepiness and sudden-onset sleep attacks is frequent in PD patients. Several studies have demonstrated an association between L-dopa equivalent dosage and excessive daytime sleepiness (Brodsky *et al.*, 2003; Ghorayeb *et al.*, 2007; Ondo *et al.*, 2001). Intake of L-dopa has also been associated with increased risk of sleep attacks (Brodsky *et al.*, 2003) and L-dopa can also induce drowsiness in healthy subjects (Micallef-Roll *et al.*, 2001).

Hallucinations in PD have been historically described prior to the introduction of L-dopa (Fenelon *et al.*, 2006) and may affect up to 40% of PD patients (Fenelon *et al.*, 2000). Several studies have contributed to highlight a multifactorial origin of hallucinations in PD and have consistently identified several risk factors such as advanced age, duration of the disease and cognitive status (Biglan *et al.*, 2007; Fenelon *et al.*, 2000; Zhu *et al.*, 2013). Although some studies have found links between L-dopa dosage and the occurrence of hallucinations (Zhu *et al.*, 2013), others failed to report a significant association with L-dopa intake (Merims *et al.*, 2004; Williams and Lees, 2005). Even though DAergic treatments as a whole can be considered as one of many risk factors for hallucinations in PD, there is no definite evidence incriminating L-dopa rather than other anti-parkinsonian therapies.

4. Animal models of LID and other L-dopa-induced abnormal behaviours

Understanding the pathophysiology of LID as a basis for therapeutic solutions has fuelled the search for valid, translational experimental models of the L-dopa-induced side effects in animals.

4.1. Hyperlocomotion in the reserpine-treated rat model of PD

The reserpine model was the first animal model of PD. Carlsson and co-workers in 1957 showed for the first time that the central action of reserpine induced a sharp decrease in motor activity with resultant hypokinesia, akinesia and even catalepsy in several species (Carlsson *et al.*, 1957). Animals also presented other symptoms, which resemble those observed in human PD, the most frequent being rigidity of skeletal muscles, tremor and postural flexion. In the reserpine-treated rat model, administration of a high dose of L-dopa (150 mg/kg) produced a hyperkinetic state characterized by an increase in horizontal and vertical motor activity, which were later proposed to represent correlates of anti-parkinsonian and prodyskinetic activity,

respectively (Johnston *et al.*, 2005). Numerous studies have been conducted to investigate the potential of various agents to reduce LID-like hyperlocomotion. Some drugs that have retrospectively been found to reduce LID in parkinsonian primates and PD patients without compromising the anti-parkinsonian efficacy of L-dopa selectively and dose-dependently reduced vertical components of activity when co-administered with L-dopa in reserpine-treated rats (e.g. amantadine and idazoxan). Others, such as haloperidol (1 mg/kg), an agent blocking most effect of L-dopa, reduced both horizontal and vertical activity. The reserpine model, heavily used in the past, is no more included in the mainstream translational chain of models for validating either a putative therapeutic target or a therapeutic strategy for LID.

4.2. Behavioural sensitization in the 6-OHDA-lesioned rat

Behavioural sensitization to dopaminomimetic drugs (i.e. L-dopa, DA agonists or DA-releasing agents) was first described by Ungerstedt in a rodent model of PD (Ungerstedt, 1971b). The model consists of rats in which ascending DA nigrostriatal neurons are unilaterally destroyed by an intracerebral injection of 6-hydroxydopamine (6-OHDA), usually into the medial forebrain bundle (MFB). In this model, systemic administration of DAergic drugs results in turning (rotation) of the animal towards the side opposite to the lesion (contralateral turning) whereas DA-releasing agents (e.g. amphetamine) cause ipsilateral turning (Ungerstedt, 1971b). Such rotational behaviour is thought to result from the supersensitivity of DA receptors on the denervated side and requires an extensive denervation (>95%) to occur. The response is routinely used for confirming the extent of DA depletion prior to behavioural pharmacological studies (Schwarting and Huston, 1996a; Schwarting and Huston, 1996b).

4.3. Abnormal involuntary movements in 6-OHDA-lesioned rodents

4.3.1. Rat model

For decades, the Ungerstedt model (Ungerstedt, 1971b) has constituted the gold standard rodent model in PD until the behavioural repertoire of 6-OHDA-lesioned rodents has been more closely analysed, looking for parallels with human PD and LID (for review, see Cenci *et al.*, 2002).

In the late 1990's, Cenci and co-workers developed a scheme of rating AIMs in the L-dopa-treated, 6-OHDA-lesioned rat (Cenci *et al.*, 1998). They observed that rats were not simply

displaying a sensitized rotational behaviour but also a series of complex behaviours that resembled LID (Cenci *et al.*, 2002). In addition to the well-characterised contralateral circling behaviour, AIMs affected the forelimb contralateral to the lesion (limb dyskinesia), the trunk with twisting movements (axial dyskinesia) and the orofacial musculature (orofacial dyskinesia) (e.g. Cenci *et al.*, 1998; Lee *et al.*, 2000a; Lundblad *et al.*, 2002; Winkler *et al.*, 2002). These AIMs are quantified on the basis of their topographical distribution, amplitude and duration (e.g. Cenci *et al.*, 1998; Lee *et al.*, 2000a; Lundblad *et al.*, 2002; Winkler *et al.*, 2002), as is done in the clinic for rating human LID. The first rodent dyskinesia rating method was based on the proportion of observation time during which each AIM subtype was present, in a scale from 0 to 4 (Cenci *et al.*, 1998; Lundblad *et al.*, 2002). A variant of this method combined the time-based scores with descriptive categories regarding the severity of the movements (Lee *et al.*, 2000a). Further methodological refinements were afforded by combining the original time-based rating scale of Cenci et al. (Cenci *et al.*, 1998) with an additional scale that is based on the amplitude of the dyskinetic movements (Mela *et al.*, 2007; Rylander *et al.*, 2010a; Winkler *et al.*, 2002). A validation study has established that combining time- and amplitude-based scores affords greater sensitivity in detecting effects of anti-dyskinetic interventions in the rat (Breger *et al.*, 2013). AIMs appear with therapeutic doses of L-dopa, only when >80% of striatal DA terminals or nigral DA neurons are lost, and dyskinetic movements of maximal severity only occur when the extent of DA denervation exceeds 90% (Winkler *et al.*, 2002).

Importantly, the Cenci's group established that rotometry in L-dopa-treated 6-OHDA rat cannot discriminate between dyskinetic and anti-akinetic effects of anti-parkinsonian treatments (Lundblad *et al.*, 2002), a finding often replicated (Sgroi *et al.*, 2014). In other words, the rotational behaviour is not, in this model, a reliable analog of dyskinesia while AIMs are. L-dopa-induced AIMs share several features with human LID, such as: (i) their time course resembles peak-dose LID; (ii) they disrupt normal motor activities when they are severe (Lundblad *et al.*, 2002; Winkler *et al.*, 2002); (iii) their incidence and severity are conditional on the dose of L-dopa (Lindgren *et al.*, 2007; Picconi *et al.*, 2008; Putterman *et al.*, 2007); (iv) they are improved by drugs proven to be effective in dyskinetic patients, such as amantadine, and clozapine (Dekundy *et al.*, 2007; Lundblad *et al.*, 2002); (v) they are not induced to any significant extent by DA receptor agonists having low dyskinesiogenic potential in PD (Dekundy *et al.*, 2007; Lundblad *et al.*, 2002), unless rats are previously primed with L-dopa or apomorphine.

Because of the distinct anatomical features and less articulate behavioural repertoire of rodents, the AIMs seen in these species are not obviously translatable to the chorea and dystonia seen in patients (Cenci *et al.*, 1998; Henry *et al.*, 1999). However, Steece-Collier and collaborators have defined rating methods to distinguish between dystonic, stereotypic, and hyperkinetic components of rodent dyskinesia (Maries *et al.*, 2006; Steece-Collier *et al.*, 2003). These methods have been validated by other research groups (Breger *et al.*, 2013).

4.3.2. Mouse model

Since the systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice, although commonly used to produce degeneration of DA neurons, fails to produce consistent and stable symptoms of parkinsonism (Bezard *et al.*, 1998), the model is not in use for the study of LID. The 6-OHDA model has, therefore, been used from the mid 2000's in a few studies to produce stable, unilateral DA lesions in mice (Akerud *et al.*, 2001; Fredduzzi *et al.*, 2002). Cenci and co-workers have fully characterized this lesion procedure in mice sustaining injections of 6-OHDA either in the MFB or in the sensorimotor part of the striatum (Francardo *et al.*, 2011; Lundblad *et al.*, 2004). Both types of lesion produced a similar degree of forelimb akinesia on the contralateral side. The lowest dose of L-dopa that significantly relieved this akinetic deficit (i.e., 6 mg/kg) did not differ between MFB and intrastriatal lesions (Francardo *et al.*, 2011; Lundblad *et al.*, 2004). However, the L-dopa threshold dose for the induction of dyskinesia did differ between the two lesion types, requiring a daily dose of 6 mg/kg for MFB-lesioned mice in contrast to 18 mg/kg in the striatally-lesioned animals to develop abnormal movements affecting orofacial, trunk, and forelimb muscles on the side contralateral to the lesion (Lundblad *et al.*, 2004). Dose is currently much lower for inducing AIMs in the MFB-lesioned mice with doses as low as 1-3 mg/kg for a fixed 12.5 mg/kg of benserazide (Won *et al.*, 2014). Later studies showed that LID could be induced in striatally-lesioned mice even with lower doses of L-dopa (e.g. 10 mg/kg) (Santini *et al.*, 2012; Santini *et al.*, 2009b). However, with lower doses of L-dopa, some mice with intrastriatal 6-OHDA lesions will not display dyskinetic behaviors (Francardo *et al.*, 2011). In the mouse model, L-dopa-induced AIMs were not expressed by animals treated with ropinirole or KW-6002 at doses that improved forelimb akinesia, and were significantly reduced by the acute administration of compounds that have been shown to alleviate LID both in parkinsonian patients and in rat and monkey models of PD (e.g. amantadine, buspirone, riluzole) (Lundblad *et al.*, 2005).

The AIM mouse model, although laborious and behaviourally less articulate than its rat equivalent, offers the advantage of enabling molecular studies in genetically-modified mice. Consequently, a large number of ground-breaking papers relied upon this model (Ahmed *et al.*, 2010; Alcacer *et al.*, 2012; Cenci and Lundblad, 2007; Cerovic *et al.*, 2015; Crittenden *et al.*, 2009; Fasano *et al.*, 2010; Fieblinger *et al.*, 2014b; Francardo and Cenci, 2014; Francardo *et al.*, 2011; Marti *et al.*, 2012; Pavon *et al.*, 2006; Santini *et al.*, 2009a; Santini *et al.*, 2012; Santini *et al.*, 2009b; Santini *et al.*, 2010b; Santini *et al.*, 2007). It is, however, at the expense of intense animal care to control mortality rate. Indeed, at odds with the unilateral MFB rat model, unilateral lesion of the MFB in the mouse causes a rapid loss of body weight and body temperature. MFB-lesioned mice therefore need intense care in the 2-3 weeks post-surgery, including rehydration, a sugar-rich diet, and housing conditions affording a warmer atmosphere (Fasano *et al.*, 2010; Francardo *et al.*, 2011).

4.4. Hyperlocomotion in the DA-deficient DA transporter knock-out mice

Historically developed after the AIM models but conceptually closer to the reserpine model, the hyperlocomotive behaviour induced by L-dopa administered to DA transporter-knock out mice treated with a-methyl-p-tyrosine (DA deficient DAT-knock-out: DDD mice) is also used as a model of LID (Manago *et al.*, 2012; Sotnikova *et al.*, 2005). DA transporter knock-out mice display increased DA release and extracellular content (with only 5% of tyrosine hydroxylase (TH) expression) associated with hyperlocomotion (Giros *et al.*, 1996). After a-methyl-p-tyrosine treatment (250 mg/kg, i.p.), a potent irreversible inhibitor of TH, the mutant mice become akinetic due to DA deficiency (Costa *et al.*, 2006; Sotnikova *et al.*, 2005). As expected, L-dopa treatment reverses this phenotype and induces an increased activity proportionally to the dose of the drug (Manago *et al.*, 2012). The chronic hyperdopaminergia induced by the genetic deletion of DA transporter is likely responsible for the hypersensitization of these animals once DA depleted and stimulated by L-dopa. The DDD mouse model is now used as a screening tool before testing the strategy in the AIM rodent model.

4.5. Genetic mouse models of bilateral dopamine deficit

The aphakia mice selectively lose dopamine neurons in the midbrain, especially in the SNc early in development as a consequence of a naturally occurring deletion of the promoter region and the noncoding exon 1 of the *Pitx3* gene (Hwang *et al.*, 2003; Nunes *et al.*, 2003;

Smidt *et al.*, 2003; van den Munckhof *et al.*, 2003). Consistent with the loss of DA neurons in the SN, there is significant DA denervation in the dorsal striatum, which results in motor deficits that can be ameliorated by dopaminergic agents (Beeler *et al.*, 2010; Hwang *et al.*, 2005; van den Munckhof *et al.*, 2006). Aphakia mice also show AIMs that increase with repeated L-dopa exposure consistent with the characteristics of LID (Ding *et al.*, 2007; Li, 2013). Furthermore, pharmacological responses to amantadine and differential effects of D_1R versus D_2R agonists are also similar to those of other traditional LID models in rodents (section 4.3.1.) (Ding *et al.*, 2007; Li, 2013) and in PD patients. In addition, biochemical changes such as FosB and prodynorphin expression are similar to other rodent models of LID (Ding *et al.*, 2007; Li, 2013; Solis *et al.*, 2015). Although the underlying neurobiological changes associated with LID are similar in aphakia mice and unilateral PD models, as a bilateral lesion model, the dyskinetic behaviour in aphakia mice is quite different from that seen in unilateral PD rodents (Ding *et al.*, 2007; Li, 2013). There is no typical limb, axial and orolingual dyskinesia in aphakia mice treated with L-dopa. Rather, the animals adopt a vertical position next to the cage or testing chamber wall with their front paws sliding along the vertical surface, behaviour termed front-paw dyskinesia. With higher doses and/or longer L-dopa treatment, LID becomes more severe with additional involvement of one of the hind paws. In the most severe cases, dyskinetic aphakia mice can show four-paw dyskinesia with body weight supported by the tail. The dyskinetic behaviours typically seen in aphakia mice are also observed in other bilateral dopamine deficient models. For example, wild type mice treated with MPTP show similar behavioural response to a high dose of L-dopa (Nicholas, 2007), as do wild type mice with bilateral 6-OHDA-induced lesion in the dorsal striatum (Fu-Ming Zhou, unpublished). Of note, there is a need for replication in these neurotoxin-based models. Dopamine deficient (DD) mice with selective knock-out of TH in DA neurons show similar vertical movements upon repetitive L-dopa exposure (Chartoff *et al.*, 2001; Henschen *et al.*, 2013). These observations illustrate the common behavioural phenotype of LID in bilaterally DA-deficient models produced either by biochemical loss or by the degeneration of the nigrostriatal projection.

The aphakia mouse provides a unique model of PD in several ways: (i) DA depletion occurs predominantly in nigrostriatal system. (ii) Unlike the hemi-parkinsonian rodents, the denervation of striatal DA is bilateral. (iii) The loss of nigrostriatal system occurs very early in development, which may facilitate compensatory mechanisms that may underlie the generation of dyskinesia. Similar to aphakia mice, early-onset PD patients are more likely to develop LID than late-onset PD. (iv) Aphakia mouse represents a more consistent and less

heterogeneous model of nigrostriatal DA depletion which would facilitate molecular and biochemical analysis of mechanisms underlying LID and provide a test model for therapeutic approaches. However, the early loss of nigrostriatal projection may bring about other developmental changes, such as a deficit in midbrain GABAergic neuron migration (Vasudevan *et al.*, 2012). As with any animal models of human disease, the limitations of the model in recapitulating the specific aspects of human LID should be carefully considered, but aphakia mouse and other genetic models that produce bilateral nigrostriatal deficits present complementary models to traditional toxic lesion models.

4.6. Non-human primate models of LID

4.6.1. History

Modelling LID in non-human primates became possible because of the development of the now gold-standard model of parkinsonism obtained by exposure to the toxin MPTP. MPTP is a neurotoxin that induces a form of parkinsonism in humans which is indistinguishable from idiopathic PD (Langston *et al.*, 1983). Primates exposed to MPTP show all of the motor problems typically encountered with L-dopa therapy, including wearing-off and peak-dose dyskinesia (but not on–off fluctuations) (Langston and Ballard, 1984). MPTP-lesioned non-human primates chronically treated with L-dopa display all of the human symptoms of LID (Clarke *et al.*, 1987; Crossman, 1987; Crossman *et al.*, 1987). They are moreover sensitive to the main risk factors for LID, such as the loss of nigrostriatal DA projections (Guigoni *et al.*, 2005b), the dosage of L-dopa (Huot *et al.*, 2012b, 2013; Porras *et al.*, 2014) and an increase incidence of dyskinesia with chronic L-dopa treatment (Bezard *et al.*, 2001a; Iderberg *et al.*, 2012).

The significance of MPTP emerged from the discovery that a group of young drug addicts were found to display a clinical profile almost indistinguishable from PD after the self-administration of a synthetic heroin analogue contaminated by MPTP. The symptoms were so close to PD that, soon after, MPTP was administered to experimental animals, including non-human primates, in which it reproduced most of the clinical and pathological hallmarks of PD (Chiueh *et al.*, 1984; Crossman *et al.*, 1985; Doudet *et al.*, 1985; Langston *et al.*, 1984b). The discovery of MPTP as a cause of parkinsonism has led to the development of valuable experimental models of PD in non-human primates (Bédard *et al.*, 1992; Bezard *et al.*, 1998; Langston *et al.*, 2000). Intracarotid or systemic MPTP intoxication induces a degeneration of the DAergic neurons residing in the SNc, leading to a DA depletion in the caudate-putamen

similarly to PD (Bezard *et al.*, 2001c; Burns *et al.*, 1983; Engeln *et al.*, 2014b; Guigoni *et al.*, 2005c; Jan *et al.*, 2003; Jenner *et al.*, 1984; Leenders *et al.*, 1988). Lesions of the serotonergic and noradrenergic systems occur as in PD (Engeln *et al.*, 2014b; Mitchell *et al.*, 1985; Pifl *et al.*, 1991; Rylander *et al.*, 2010b). MPTP intoxication produces a parkinsonian syndrome in primates that is remarkably similar to PD (Benazzouz *et al.*, 1992; Bezard *et al.*, 1998; Clarke *et al.*, 1987; Crossman, 1987; Crossman *et al.*, 1987). The animals display bradykinesia, rigidity and postural abnormalities (e.g. Bédard *et al.*, 1992; Benazzouz *et al.*, 1992; Bezard and Przedborski, 2011; Langston *et al.*, 1984a; Langston *et al.*, 2000; Schultz *et al.*, 1985) and in some cases/species resting tremor (François *et al.*, 1998). Those symptoms respond positively to the medications available in the clinic (Cenci *et al.*, 2002; Fox and Brotchie, 2010). A number of DAergic (Iderberg *et al.*, 2012; Meissner *et al.*, 2011) or surgical (Aziz *et al.*, 1991; Benazzouz *et al.*, 1993; Jarraya *et al.*, 2009; Kordower *et al.*, 2006; Tass *et al.*, 2012) therapies have been investigated in MPTP-treated primates and subsequently successfully transferred into clinical practice. So far, effects observed in MPTP-treated primates have proven to be predictive of symptomatic efficacy in human, provided the magnitude of the effects in this model was large enough for overcoming the inherent disease and human variability. L-dopa treatment to such MPTP-lesioned primates causes dyskinetic motor manifestations that are remarkably similar to those displayed by patients; chorea and dystonia are easily distinguished and clearly equivalent to their human counterparts (for review, see Fox *et al.*, 2012; Langston *et al.*, 2000).

Four species have been regularly used, namely the macaque monkeys (*Macaca mulatta* and *Macaca fascicularis*), the common marmoset (*Callithrix jacchus*) and the squirrel (*Saimiri sciureus*) monkeys, while other species might appear in the literature such as baboon monkeys (*Papio anubis*) and African green monkeys (*Cercopithecus aethiops*). The vast majority of pathophysiological studies have however been conducted in the macaque monkeys.

4.6.2. Macaque models

The cynomolgus (*Macaca fascicularis*), rhesus (*Macaca mulatta*) and Japanese (*Macaca fuscata*) macaques display the human-like symptoms of PD and LID and are currently the species of choice to study LID (Bezard *et al.*, 2001a; Iderberg *et al.*, 2012; Johnston *et al.*, 2010a; Johnston *et al.*, 2013; Koprich *et al.*, 2013; Langston *et al.*, 2000; Morin *et al.*, 2013; Porras *et al.*, 2012b). Dyskinetic MPTP-intoxicated macaques exhibit various combinations of choreic-athetoid (i.e. characterized by constant writhing and jerking

motions), dystonic and even ballistic movements (i.e. large-amplitude flinging, flailing movements), although less frequently for those latter (Ahmed *et al.*, 2010; Bezard *et al.*, 2001a; Bezard *et al.*, 2003; Iderberg *et al.*, 2012; Johnston *et al.*, 2010a; Johnston *et al.*, 2013; Koprich *et al.*, 2011; Koprich *et al.*, 2013; Langston *et al.*, 2000; Morin *et al.*, 2013; Porras *et al.*, 2012b). Both the repertoire and severity of dyskinesia are not distinguishable from LID occurring in PD patients (Bezard *et al.*, 2003; Fox *et al.*, 2012).

Several rating scales exist to quantify LID in non-human primates and were reviewed and criticized, with a focus on macaques (Fox *et al.*, 2012). Fox and co-workers proposed a revised LID rating scale in monkeys as well as guidelines for their observation: the Non Human Primate Dyskinesia Rating Scale (NHPDysR), based on the Dyskinesia Disability Rating Scale (Fox *et al.*, 2012). For each AIMs, the monkeys are scored from a score of 0 to 4: 0 = no AIMs, 1 = mild LID: transient and intermittent AIMs present of less than 30% of the scoring time, 2 = moderate LID: monkeys display AIMs for more than 30% of the observation period and are still able to perform all motor tasks, 3 = marked LID: AIMs are present less than 70% of the scoring period and the monkeys are unable to eat with significant decrease in motor tasks, 4 = severe LID: AIMs are continuous and present for more than 70% of the observation period. LID interfere with the ability to do any motor task (Fox *et al.*, 2012). The anti-parkinsonian effect of L-dopa therapy is quantified using rating scales based on the UPDRS (Imbert *et al.*, 2000).

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

Even if the similarity to human symptoms makes the MPTP macaque relevant on a clinical level for LID, this model is expensive, sizable (weighing up to 7-10kg) and need specialized

infrastructures with highly qualified personnel to handle the animals (Iderberg *et al.*, 2012; Morin *et al.*, 2013). Moreover, neither the extent nor the pattern of nigrostriatal lesioning are sufficient to explain the occurrence of dyskinesia in the MPTP-treated macaque model of LID (Fernagut *et al.*, 2010; Guigoni *et al.*, 2005b). In addition, chronic administration of high dose L-dopa (80 mg/kg) for several months can provoke dyskinesia in normal macaque (Pearce *et al.*, 2001). Based upon these data, it is necessary to include in future investigations normal animals treated with L-dopa as control, in addition to another essential control group, L-dopa treated animals with nigral lesion that do not develop dyskinesia (Engeln *et al.*, 2014b; Fernagut *et al.*, 2010; Porras *et al.*, 2012a; Santini *et al.*, 2010a).

4.6.3. Marmoset model

Common marmosets (*Callithrix jacchus*) were used because of their small size and their convenience in housing and handling compared to macaques. They feature a cerebral conserved structural organization.

Parkinsonian marmoset models can be induced by either systemic MPTP intoxication (Jenner *et al.*, 1984) or by unilateral (Annett *et al.*, 1992) or bilateral (Mitchell and Carroll, 1997; Mitchell *et al.*, 1995) repeated intracerebral injections of 6-OHDA in the nigrostriatal bundle. Very few studies used the 6-OHDA-lesioned marmosets to analyse LID pathophysiology (Pirker *et al.*, 2001; Svenningsson *et al.*, 2002). Most studies relied upon the MPTP-treated marmoset that displays a parkinsonian state that reverses after administration of L-dopa and other DA agonists (Jenner *et al.*, 1984). Following L-dopa administration, MPTP-treated marmosets display dyskinetic-like abnormal involuntary behaviours including chorea-like (i.e. picking/flicking movements), dystonic-like (i.e. sustained posturing) and repetitive purposeless movements (Pearce *et al.*, 1995) as well as L-dopa-induced hyperlocomotion (Ando *et al.*, 2014). MPTP-intoxicated marmosets chronically treated with L-dopa are often restless and show consistent and continuous hyperkinetic behaviour at the L-dopa peak-time of action (Iderberg *et al.*, 2012; Morin *et al.*, 2013; Pearce *et al.*, 1995). Moreover, the marked hyperkinesia of dyskinetic marmoset highly complexities the distinct assessment of choreic-like and dystonic-like abnormal movements, which clearly differs from clinical observation of dyskinetic patients (Fox and Brotchie, 2010).

Kuoppamäki and co-workers reported on the relationship between L-dopa dose and the duration and severity of dyskinesia in MPTP-treated marmoset with marked nigral degeneration mimicking late stage of PD (Kuoppamaki *et al.*, 2007). With increasing doses of

L-dopa, locomotor activity increased and motor disability declined. The duration of dyskinesia following L-dopa administration dose-dependently increased and showed a linear correlation with total locomotor activity (Kuoppamaki *et al.*, 2007). In contrast, severity of dyskinesia showed a nonlinear correlation with total locomotor activity, low doses of L-dopa eliciting severe dyskinesia for short periods of time (Kuoppamaki *et al.*, 2007).

The use of the MPTP-treated marmoset model to study novel therapies for LID was facilitated by its property to respond with a strong motor activity to L-dopa therapy (Iderberg *et al.*, 2012), allowing to easily quantify the anti-parkinsonian state and the prototypical development of LID in response to a given test item (Hill *et al.*, 2003; Hill *et al.*, 2004a; Hill *et al.*, 2004b; Huot *et al.*, 2011, 2014; Johnston *et al.*, 2011; Kobylecki *et al.*, 2011; Maratos *et al.*, 2001; Nash *et al.*, 2004; Pearce *et al.*, 1998; Silverdale *et al.*, 2005). Such *de novo* protocol remains an asset of the model (Nash *et al.*, 2000) as the kinetics of LID appearance in this model is far less variable than in macaque (unless macaques are left without DAergic therapy for months before starting such *de novo* protocol). However, the difficulties in distinguishing choreic-like movements from dystonic-like ones during LID is not representative of the human LID pattern of expression and represent a drawback for this model to understand LID pathophysiology (Iderberg *et al.*, 2012; Morin *et al.*, 2013). Finally, while the marmoset model has been heavily used in the 1990's, the development of experimental research in macaques, making them relatively easily available, has led the field away from this species, as attested by the decreasing number of papers relying on this species in the past 5 years.

4.6.4. Squirrel monkey model

As for the common marmoset, squirrel monkeys (*Saimiri sciureus*) were employed for their convenience in handling and housing because of their small size. Squirrel monkeys intoxicated by MPTP develop parkinsonian-like syndromes as akinesia, rigidity and bradykinesia (Langston *et al.*, 1984a). MPTP-lesioned squirrel monkeys treated with L-dopa display dyskinetic-like movements including a choreic and dystonic component (Boyce *et al.*, 1990b; Di Monte *et al.*, 2000). However, chorea is always most prevalent at the L-dopa peak-time of effect while dystonia is barely noticeable (Boyce *et al.*, 1990b). The ability of squirrel monkeys to display dyskinesia allowed several investigations on LID pathophysiology using this model (Boyce *et al.*, 1990a; Boyce *et al.*, 1990b; Di Monte *et al.*, 2000; Hsu *et al.*, 2004; Neale *et al.*, 1984; Stephenson *et al.*, 2005) with a pronounced focus on the opioid (Chen *et*

al., 2005; Cox *et al.*, 2007; Quik *et al.*, 2002a) and nicotinic system (Quik *et al.*, 2003; Quik *et al.*, 2007; Quik *et al.*, 2013c; Quik *et al.*, 2002b; Quik *et al.*, 2005; Zhang *et al.*, 2013a). In addition, Togasaki and co-workers demonstrated that normal squirrel monkeys (i.e. unlesioned) treated twice daily with a therapeutically relevant dose of L-dopa (15mg/kg with carbidopa, *per os*) for 15 days can develop LID (Togasaki *et al.*, 2005; Togasaki *et al.*, 2001). These data are coherent with previous reports showing that L-dopa, at very high doses and after very long treatment, can induce dyskinesia in the absence of nigrostriatal damage in normal primates (Pearce, 1999; Pearce *et al.*, 2001; Sassin *et al.*, 1972). Normal squirrel monkeys however do develop LID after receiving clinically-relevant doses of L-dopa and over few days (Togasaki *et al.*, 2005; Togasaki *et al.*, 2001). Clinical findings might suggest it also does in non-parkinsonian patients (Goodwin *et al.*, 1970; Lieberman *et al.*, 1972) although such report has not been made since the 1970's and only in patients being responsive to L-dopa, for instance in TH deficient patients (Pons *et al.*, 2013) or in dopa-responsive dystonic patients in whom the nigrostriatal projections are also spared (Hwang *et al.*, 2001).

Even if this finding limits the translational value of the MPTP-intoxicated squirrel monkey in LID, it should be very interesting to understand the physiological and the molecular basis on how L-dopa can induce dyskinesia without any nigrostriatal denervation.

4.6.5. Other species

Other non-human primate species are used to investigate PD and LID pathophysiology such as the baboons (*Papio anubis*) or the African green monkeys (*Cercopithecus aethiops*).

African green monkeys can be qualified as mid-sized non-human primate weighing around 3 to 7 kg at adulthood requiring specific infrastructure, just like macaques. MPTP intoxication of African green monkeys is able to induce parkinsonian-like symptoms including akinesia, bradykinesia, rigidity and tremor (Elsworth *et al.*, 1987, 1990; Taylor *et al.*, 1994, 1997; Wichmann *et al.*, 1999). Therefore, since macaques seldom present tremor once lesioned, African green monkeys have been used to study parkinsonian tremor besides other aspects of PD pathophysiology (Bergman *et al.*, 1998; Boulet *et al.*, 2008; Guehl *et al.*, 2003; Mounayar *et al.*, 2007; Pessiglione *et al.*, 2003; Rosin *et al.*, 2011; Wichmann *et al.*, 1999). Only a few studies focused on LID pathophysiology (Heimer *et al.*, 2002; Heimer *et al.*, 2006) or risk for developing LID in response to transplantation of fetal DAergic neurons treatment (Redmond *et al.*, 2008).

Baboons are sizable non-human primates weighing up to 40 kg at adulthood and require particularly suitable infrastructure and highly qualified personnel to handle the animals. Only few research teams still work with them in the world. MPTP-intoxicated baboons develop PD symptoms such as hypokinesia, bradykinesia, postural impairments, rigidity and resting tremor (Hantraye *et al.*, 1993; Varastet *et al.*, 1994). They were used to mostly investigate PD pathophysiology and innovative surgical therapeutic approaches because of their brain size (Chen *et al.*, 2008; Drouot *et al.*, 2004; Ferrante *et al.*, 1999; Hantraye *et al.*, 1996; Kishima *et al.*, 2004; Todd *et al.*, 1996). Although not directly used for the pathophysiology of LID as chronic oral treatment in such animals is far too risky, they are physiologically capable of displaying AIMs. Baboons were indeed used to model Huntington's disease (Hantraye *et al.*, 1990; Isacson *et al.*, 1989; Palfi *et al.*, 1996). For instance, excitotoxic striatal lesions with 3-nitropropionic acid induces dyskinetic-like abnormal movements following apomorphine injection (Palfi *et al.*, 1997).

4.7. Models of DDS/ICD

Increased awareness about the dramatic consequences of DDS and ICD for PD patients (Giovannoni *et al.*, 2000; Lawrence *et al.*, 2003; Voon *et al.*, 2011b; Weintraub *et al.*, 2010), prompted to investigate their underlying mechanisms. Imaging studies (Evans *et al.*, 2006; Thobois *et al.*, 2010; van Eimeren *et al.*, 2010) as well as impulsivity evaluation (Djamshidian *et al.*, 2011a; van Eimeren *et al.*, 2009; Voon *et al.*, 2007b) have provided insights into some of the alterations underlying these troubles and regarding associated risk factors. However, these studies being mainly conducted in PD patients already under DAergic treatments and usually with documented DDS or ICD histories, it is virtually impossible to decipher the respective contributions of the degenerative process, DA replacement therapy, and individual vulnerability factors.

The progressive DAergic loss occurring in both nigrostriatal and mesolimbic pathways and the subsequent action of DA replacement therapy on these altered pathways have been proposed to disrupt the reward system (Ambermoon *et al.*, 2011; Giovannoni *et al.*, 2000; Lawrence *et al.*, 2003). Indeed, in many aspects DDS as well as ICD remind addiction to drug of abuse and behaviours associated with the abuse of psychostimulants. Multiple works thus proposed that, in addition to the data coming from experiments on basal ganglia dysfunction in PD, the addiction framework might help to understand and to study these non-motor side-effects (Ambermoon *et al.*, 2012; Ambermoon *et al.*, 2011; Bearn *et al.*, 2004; Giovannoni *et*

al., 2000; Lawrence *et al.*, 2003). The study of ICD and DDS might thus take advantage of works conducted in both the PD and the addiction fields. While there is a great diversity of experiments to test addiction theories in animals, there are currently no distinct DDS or ICD animal models as for LID. However, multiple aspects involved in the emergence of DDS or ICD can be reproduced in animal models and give information on their triggering factors that might not be directly assessed in patients.

4.7.1. The role of the DAergic medication

An action of DA replacement therapy on reward pathways has been proposed to disturb reward processing (Evans *et al.*, 2010). To measure the effectiveness of DA replacement therapy to act on these pathways, experiments conducted in rodents aimed to evaluate both reward processing disruption and reinforcing properties of DA replacement therapy. The D_2R/D_3R agonists have been mainly incriminated in ICD in humans (Gallagher *et al.*, 2007; Weintraub *et al.*, 2010). Using various operant conditioning paradigms, experiments on rats evaluated the impact of Pramipexole (PPX) on impulsive behaviours and revealed that naive rats dose-dependently do more impulsive choices under PPX, preferring smaller-sooner over larger-later rewards (Koffarnus *et al.*, 2011; Madden *et al.*, 2010). Such results are consistent with reports of parkinsonian patients doing more impulsive choices and being more sensitive to delay under DA agonists (Voon *et al.*, 2010). Other works evaluating the effect of PPX on risk taking in rats using operant tasks allowing the choice between a safe option providing a small reward and a more hazardous option offering a larger reward showed that under PPX, animals dose-dependently increase their choice toward the most risky option (Johnson *et al.*, 2011; Johnson *et al.*, 2012). These results are reminiscent of the described desensitization to punishment and increased risk taking of PD patients with pathological gambling under DA agonists (Djamshidian *et al.*, 2010; Voon *et al.*, 2011a; Voon *et al.*, 2007b). Finally, some studies evaluated the ability of D2/3 agonists to act on the reward pathway as hypothesized for ICD (Gschwandtner *et al.*, 2001; Schott *et al.*, 2007). In self-administration procedure, D2/3 agonists have been shown to dose-dependently maintain responding to stimuli previously paired with cocaine (substitution), but also to induce responding for stimuli associated with cocaine (Collins *et al.*, 2012; Collins and Woods, 2007). Later studies further revealed that naïve, as well as parkinsonian rats display conditioned place preference (Riddle *et al.*, 2012) or can self-administer PPX (Engeln *et al.*, 2012), demonstrating the rewarding properties of D_2R/D_3R agonists. Experiments evaluating the ability of DAergic treatments to

trigger ICD- or DDS-like features on naïve (e.g. non DA lesioned) animals might however bring incomplete insight on the nature of these troubles. Indeed, despite the fact that ICD are also reported in non DA-depleted individuals (Davie, 2007; Holman, 2009; Ondo and Lai, 2008), the neurodegenerative process occurring in PD has been questioned in the development of impairments in reward processing in both ICD and DDS (Lawrence *et al.*, 2003; Schott *et al.*, 2007).

4.7.2. The role of the DAergic lesion

The onset of ICD or DDS with the emergence of PD raised questions on the contribution of both nigrostriatal and mesolimbic DAergic degeneration in the emergence of these side-effects of DA replacement therapy (Lawrence *et al.*, 2003; Thobois *et al.*, 2010). While unilateral lesioning of mesencephalic DAergic systems is well-suited for the study of LID, owing to a marked DAergic asymmetry facilitating the quantification of abnormal motor behaviours, such models are not adapted for studying non-motor aspects of DA replacement therapy as drug-induced rotations will bias operant behaviours. Obtaining a viable bilateral lesion model is however uneasy (Dunnett and Lelos, 2010; Ungerstedt, 1971a) and might in part contribute to the relatively small number of work conducted so far in rodent models of PD. Using different bilateral lesioning strategies, several studies have investigated how the DAergic lesion may affect behavioural dimensions relevant to ICD and DDS. Lesion studies in rats first highlighted that a bilateral nigrostriatal lesion using 6-OHDA could reduce motivation in rats in various paradigms such as place preference, instrumental responding or food consumption test (Drui *et al.*, 2013; Faure *et al.*, 2005; Pioli *et al.*, 2008). Bilateral lesions of the nigrostriatal pathway obtained by injecting 6-OHDA in the dorsal striatum showed that the establishment of a conditioned place preference for PPX necessitated a greater dose in sham than in lesioned rats (Riddle *et al.*, 2012). Moreover, risk-taking evaluation showed that PPX increased intracranial self-stimulation-mediated probabilistic discounting in both sham and lesioned rats (Rokosik and Napier, 2012). Mixed bilateral nigrostriatal and mesolimbic lesions achieved with intracerebroventricular 6-OHDA infusion however resulted in similar reinforcing properties, comparable motivation and equally low drug-seeking for PPX between sham and lesioned rats using intravenous self-administration procedures (Engeln *et al.*, 2012). Conditioned place preference experiments in animals injected with small 6-OHDA doses in the MFB showed that high doses of bromocriptine (D_2R agonist) might have rewarding properties, but failed to report such results for supraliminal

(50-200 mg/kg) doses of L-dopa (Zengin-Toktas *et al.*, 2013). Recently, bilateral nigrostriatal lesions were obtained by using viral-mediated α-synuclein overexpression in the SNc (Engeln *et al.*, 2013). This latter model is promising as it reproduces many of the cellular and molecular features of PD, including early synaptic dysfunction as well as accumulation and aggregation of α-synuclein (Decressac *et al.*, 2012a; Decressac *et al.*, 2012b). In these animals, a moderate lesion of the SN was necessary and sufficient to reveal psychostimulant-like properties of L-dopa. Indeed, clinically relevant doses of L-dopa (12 mg/kg) elicited a conditioned place preference as well as a decreased interest for a non-drug reward exclusively in lesioned rats (Engeln *et al.*, 2013). These latter findings provided significant details on how L-dopa might act on altered DAergic pathway to result in reward dysfunction as observed in DDS.

In human, the role of the DAergic loss is difficult to evaluate, as it would require large prospective studies comparing patients before and after the diagnosis of PD. To date, only one study conducted in α-synuclein duplication carriers compared pre-symptomatic and symptomatic stages, showing reward impairments solely after the establishment of significant neurodegeneration (Szamosi *et al.*, 2013).

It is interesting to notice that in rodents, DA agonists may trigger addiction-like behaviour in both control and lesioned rats, while L-dopa is rewarding only in lesioned animals. Such observations are in agreement with clinical reports of low mood elevation effects of L-dopa in normal individuals (Liggins *et al.*, 2012). Thus, after evaluating the potential for DAergic treatments to act on the reward pathway of lesioned animals, studies are now evaluating their ability to affect impulsive behaviours.

Finally, clinical studies have suggested that individual risk factors could contribute to the emergence of both ICD and DDS (Djamshidian *et al.*, 2011b; Evans *et al.*, 2005; Voon *et al.*, 2007b). A family history of gambling, a higher alcohol consumption or previous use of legal or illegal drugs is associated with both increased DDS and ICD incidence (Evans *et al.*, 2005; Weintraub *et al.*, 2010). Similarly, personality traits such as sensation seeking, impulsiveness or risk taking might be triggering elements (Voon *et al.*, 2011b). These traits might be present before PD's motor symptoms and could also evolve with the progression of the disease process. While a study suggested that unmedicated *de novo* PD patients have no increased risk to develop ICD compared to the general population (Weintraub *et al.*, 2013), it is unknown if the ongoing degenerative process may affect impulsiveness in these patients. Experimental models will help to solve this question.

4.7.3. The role of individual risk factors

The most difficult aspect of ICD and DDS to investigate in human is the influence of the DAergic depletion on personality traits. Information on premorbid 'baseline' impulsive behaviours obtained retrospectively by interviewing patients or their family might be biased and misleading. Surprisingly, there is currently no animal study providing a longitudinal measurement of impulsive behaviours before and after DAergic depletion. A prelesional screening of impulsiveness might yet be crucial in the understanding of ICD pathophysiology. Behavioural tests such as delay discounting tasks, evaluation of impulsive choice and action, risk taking measures are available in rodents and could provide important information on the evolution of the personality trait over the course of the disease. Thus, prelesional vs. postlesional inhibitory control assessment would help to elucidate if and how the DAergic denervation may affect these individual traits. Moreover, the differential impact of DA replacement therapy on behavioural inhibition according to specific behavioural traits would help to assess individual responses to the treatment of PD. Future experiments in this direction will be mandatory as individual vulnerability appears to be a critical factor in the propensity to develop non-motor side effects of DA replacement therapy.

Rodent models of ICD and DDS offer the possibility to measure cellular and molecular changes occurring after lesion, drug exposure and behavioural tasks. Again, only few data are currently available regarding these factors. Experiments evaluating the reinforcing properties of DA D_2R/D_3R agonists in rats revealed that PPX induces striatal ΔFosB accumulation (Engeln *et al.*, 2012). Moreover, motivation for PPX was correlated with the density of ΔFosB-positive cells in different striatal compartments in sham and lesioned rats, suggesting the involvement of different cortico-subcortical loops in DA depleted animals. Interestingly, an increased ΔFosB expression was found in the dorsal striatum of lesioned rats, a region mainly described for its role in dyskinesia (Cenci *et al.*, 1999). In psychostimulant addiction, drug seeking (Yin *et al.*, 2005) and habit learning (Yin *et al.*, 2004) are known to involve dorsal regions of the striatum. ΔFosB accumulation is well known for its role in addiction (Nestler *et al.*, 2001), specifically in striatal subregions after various drug exposures (Lobo *et al.*, 2013). Altogether, these observations suggest that common mechanisms may operate in motor and non-motor side-effects of DA replacement therapy where specific molecular modifications underlie both motor and reward dysfunctions. Indeed, similarities between the repetitive movements of dyskinesia and the stereotyped behaviours of punding are observed.

It has been proposed that both dyskinesia and ICD or DDS might be part of the same continuum (Voon *et al.*, 2009). In rats, procedures used to induce stereotypies are comparable to those used to induce dyskinesia, and these two behaviours induce similar striatal molecular adaptations (Graybiel *et al.*, 2000). Moreover, according to the striosome/matrix organization of striatal functioning, while stereotypies induce molecular changes (including ΔFosB accumulation) in the matrix of the medial striatum, LID induce modifications in the matrix of the lateral striatum. In susceptible individuals, the activation of striosomes at the interface between the 'limbic' medial striatum and the 'motor' lateral striatum might underlie compulsive behaviours such as punding (Graybiel *et al.*, 2000). Studies conducted in DA-depleted rats further showed that an increase in the DAergic tone leads to a global involvement of the striatum and could jointly activate neuronal networks which were previously distinct (Saka *et al.*, 1999). It is thus possible that compulsive/addiction-like behaviours and dyskinesia may share similar neuronal circuits. Considering the limbic and motor interfaces of the striato-nigro-striatal spiralling pathways (Haber *et al.*, 2000), a molecular sensitization of the connectivity between the ventral and the dorsal striatum might operate both in motor and non-motor side-effects of DA replacement therapy. Studies investigating the possible common pathways of both LID and compulsive behaviours might provide new opportunities to approach broad basal ganglia modification linked with DA replacement therapy.

In summary, experimental modelling of DDS and ICD is still in its infancy and there is currently no validated animal model replicating the clinical features of these non-motor side effects of DA replacement therapy. However, works conducted in rodents already provided precious information on the respective and combined roles of the DA replacement therapy and the DAergic depletion in triggering ICD- and DDS-like features. Further studies are now required to understand the role and the evolution of personality traits over the course of the lesional process. Upcoming studies will also need to provide information regarding the cellular and molecular changes occurring in these troubles. It has to be noticed however that animal studies might carry some limitations. While LID may affect virtually all PD patients over chronic exposure, DDS occur in 1-4% and ICD are reported in 6 to 14% of PD patients (Giovannoni *et al.*, 2000; Weintraub *et al.*, 2010). Assuming that such prevalence would be reproduced in animals, large numbers of subjects will be required. Screenings of susceptible animals (Deroche-Gamonet *et al.*, 2004; Lenoir *et al.*, 2013) might however help to overcome these limitations. Dimensions of ICD and DDS, such as financial loss, are difficult to model

in rodents and could participate to experimental limitations. The use of primate models would be of great interest to study higher cognitive processes.

4.8. Modelling other L-dopa-induced side-effects

Autonomic and psychiatric side-effects of L-dopa have received very little attention in experimental models of PD. Even though several models recapitulate some of the cardiovascular features of PD, including depletion of norepinephrine and reduced meta-iodobenzylguanidine uptake (for review , see Fleming, 2011), the effects of L-dopa on cardiac function have not been examined in experimental models. There is however evidence in normal rats that L-dopa can affect the baroreflex and, interestingly, such effect may be related to a direct action of L-dopa in the nucleus of the solitary tract (Kubo *et al.*, 1992; Misu *et al.*, 1995; Yue *et al.*, 1994).

The effects of L-dopa on vigilance (excessive daytime sleepiness, sleep attacks) in experimental models of PD remain poorly understood. In MPTP-treated monkeys, L-dopa does not affect rest-activity rhythms (Vezoli *et al.*, 2011). On the other hand, a high-dose of L-dopa (50 mg/kg) increases wakefulness and decreases slow wave sleep and paradoxical sleep in MPTP-treated mice (Laloux *et al.*, 2008).

Few studies have investigated supposed "psychosis-like" behaviours in experimental models of PD and have assessed the effects of DA replacement therapy, including L-dopa (Johnston *et al.*, 2011; Visanji *et al.*, 2006a). Whether the observed behaviours (stereotypies, agitation/hyperactivity, repetitive grooming, staring or tracking an apparent non-stimulus) may represent adequate correlates of psychotic behaviours occurring in PD patients remain hypothetical. Indeed "psychosis-like" behaviours systematically occur in L-dopa-treated animals (Johnston *et al.*, 2011; Visanji *et al.*, 2006a), while such behaviours are only observed in a subset of PD patients. Given the multifactorial nature of psychosis in PD, including the occurrence of hallucinations and other psychotic behaviours unrelated to L-dopa treatment (Fenelon *et al.*, 2006), the relevance of experimental models to this aspect of PD remains difficult to ascertain.

5. Pathophysiology of peak of dose LID

In the present review, we aimed at focusing on changes observed at the peak-dose of L-dopa plasma concentrations. Indeed, in the literature, LID pathophysiology refers to various states.

In several papers, animals chronically exposed to L-dopa were considered as "dyskinetic" even when they were actually terminated OFF L-dopa (i.e. more than 3 hours after their last L-dopa injection). While the OFF state is very interesting and informative on the neuronal plasticity induced by chronic treatment, it cannot be considered as the ON LID state. Indeed, the ON LID state reflects the neuronal pathological events occurring at the peak effect produced by the treatment, at which LID are the most strongly expressed, and allows a correlation between the progressive motor response induced by L-dopa and the cellular alterations. We will therefore structure this part by clearly distinguishing: naïve animals (i.e. never exposed to dopamimetics), the ON state (i.e. peak of dose of L-dopa plasma concentrations, best anti-parkinsonian effect) with or without LID, and the OFF state (i.e. animals otherwise dyskinetic when challenged).

5.1. Pharmacokinetics and pharmacodynamics

Chronic L-dopa administration remains the best treatment for PD since its introduction in the 60's (Birkmayer and Hornykiewicz, 1961, 1962; Cotzias *et al.*, 1967; Lees, 1994; Yahr *et al.*, 1968). However, L-dopa therapy faces several challenges resulting from the complex interactions between the pharmacokinetics of L-dopa itself (LeWitt, 2014) and the progressive neuronal alterations induced by the neurodegeneration in PD. L-dopa displays particular peripheral characteristics (Contin and Martinelli, 2010; Contin *et al.*, 1993). First, it is highly metabolized into DA by peripheral AADC expressed in the gut allowing only 30% of L-dopa to reach the systemic circulation (Contin and Martinelli, 2010). This issue was overcome by concomitant administration of AADC peripheral inhibitors (AADCI) with L-dopa. Nowadays, two main AADCI are used: carbidopa at a L-dopa/carbidopa dose ratio of 4/1 or 10/1 and benserazide (L-dopa/benserazide ratio of 4/1) (Contin and Martinelli, 2010). The use of AADCI allowed to almost triple L-dopa oral bioavailability, strongly reducing the required L-dopa therapeutic dose (Contin and Martinelli, 2010; LeWitt, 2014). Interestingly, concomitant administration of L-dopa and AADCI induce a plasmatic peak in patients at 1.1 ± 0.2h (Okereke *et al.*, 2004) and in non-human primates, like macaques, at 1.6 ± 0.3h (Huot *et al.*, 2012b) associated with a brain Cmax which correlates with the peak of LID severity, around 60-90 minutes *post* oral administration (Huot *et al.*, 2012b) and 20 minutes *post* intravenous administration (Porras *et al.*, 2014) of L-dopa in macaques. Note that Huot et al. measured L-dopa in cerebrospinal fluid (Huot *et al.*, 2012b) while Porras et al. did access to extracellular levels in the striatum itself using microdialysis (Porras *et al.*, 2014). In addition, intravenous

(2.5 mg/kg) or oral (20 mg/kg) administrations give rise to comparable increase in extracellular striatal L-dopa levels (Porras *et al.*, 2014). Even though the oral doses of L-dopa administered to MPTP-lesioned macaques are higher than the doses frequently administered in idiopathic PD, the macaque plasma exposures are consistent with those achieved in clinical settings with acute challenges of 200 mg (Huot *et al.*, 2012b). The experimental data provide pharmacokinetic validation, to support the existing pharmacological validation, of the MPTP-lesioned macaque model of PD as a platform from which novel therapeutics, including those modulating L-dopa actions, might be developed.

L-dopa shares some similarities with neutral amino acids, notably in term of intestinal absorption and transport at the blood brain barrier (Nutt and Fellman, 1984). Indeed, L-dopa competes with the transport system of neutral amino acids during their absorption in the intestinal mucosa and at the blood brain barrier (Contin and Martinelli, 2010; Contin *et al.*, 1993). L-dopa transport from the plasma to the brain depends on the same system (Contin and Martinelli, 2010). The intake of high protein meals doubles the plasmatic concentration of neutral amino acids, which then interferes with the transport of L-dopa to the brain thereby decreasing its therapeutic efficacy (Nutt *et al.*, 1984). Consequently, L-dopa administration timing needs to be adapted to mealtime to optimize the therapeutic effect of L-dopa (Juncos *et al.*, 1987). Parkinsonism, however, does not seem to modulate the L-dopa cerebral bioavailability. The plasma and cerebrospinal fluid bioavailability of L-dopa was found comparable in healthy and MPTP-treated macaques (Thiollier *et al.*, 2015). Pharmacokinetics and pharmacodynamics experiments of drugs addressing PD might thus be performed in healthy animals unless the drugs are known to interact with the organic cation transporter (Thiollier *et al.*, 2015).

5.2. Imaging

5.2.1. Studies of the DA system

Neuroimaging studies have provided *in vivo* support for the role of pulsatile stimulation of DA receptors in the emergence of LID (Stoessl, 2014). DAergic function can be assessed using positron emission tomography (PET) with ligands that bind to the vesicular monoamine transporter type 2 (VMAT2), the plasmalemmal DAT (Au *et al.*, 2005; Brooks *et al.*, 2003) and postsynaptic DA D_1R and D_2R receptors. Additionally, the fluorinated analog of L-dopa, 6-[^{18}F]fluoro-L-dopa (6FD) can be used to assess uptake and decarboxylation of L-dopa to

DA, as well as storage of DA in synaptic vesicles and, when prolonged scans (4 hours, rather than the usual 90-120 minutes) are performed, DA turnover (Sossi *et al.*, 2001).

Dyskinesia tend to occur in more advanced PD. One might therefore anticipate a loose relationship between markers of presynaptic DAergic integrity and LID. With the possible exception of dyskinesia that emerge following fetal mesencephalic transplantation (see below), there is little evidence for this in the literature, apart from a report by Linazasoro and colleagues, who found an inverse relationship between 6FD uptake and dyskinesia (Linazasoro *et al.*, 2004) and a more recent study using [^{18}F]-FP-CIT PET showing that presynaptic dopaminergic denervation in PD plays a crucial role in the development of LID (Hong *et al.*, 2014). Fluctuations in motor function, which commonly occur together with dyskinesia, are associated with reduced 6FD uptake (de la Fuente-Fernandez *et al.*, 2000; Stoessl, 2014), but there is substantial overlap between patients with and without motor fluctuations, suggesting that other factors play an important role.

Traditional measures of presynaptic DAergic integrity give only a rough estimate of striatal DA nerve terminal density. As discussed elsewhere in this review, a critical factor in the emergence of motor complications is the pattern of DA receptor stimulation. Thus, assessment of the central pharmacokinetics of L-dopa action may provide greater insight. As previously described in this review, [^{11}C]raclopride labels D_2R andD_3R with relatively low affinity and its binding is subject to competition with endogenous DA (Breier *et al.*, 1997; Seeman *et al.*, 1989). Thus, interventions such as L-dopa therapy that result in increased synaptic DA concentrations will result in reduced [^{11}C]raclopride binding as assessed by PET (Tedroff *et al.*, 1996). De la Fuente-Fernandez et al. found a greater magnitude but less sustained decline in [^{11}C]raclopride binding in PD patients who had a stable response to L-dopa at the time of the PET study but who went on to develop motor fluctuations within 3 years compared to those subjects who had stable response to medication 3 years later (de la Fuente-Fernandez *et al.*, 2001). In a follow-up study, these authors found that the relative decrease in [^{11}C]raclopride binding 1 hour after oral L-dopa increases with disease duration and even after correction for this factor, is higher in subjects with LID compared to those with a stable response, while there is no difference between dyskinetic and non-dyskinetic subjects 4 hours after L-dopa (de la Fuente-Fernandez *et al.*, 2004). This is compatible with a more pulsatile pattern of L-dopa-induced DA release in subjects with motor complications (Stoessl, 2014). Similar findings have been reported by other groups. (Pavese *et al.*, 2006).

These findings are reminiscent of the sensitization of DA release that is associated with drug addiction as previously discussed in this review. In contrast to the motor complications, which

are associated with sensitized DA release in the putamen (i.e. motor striatum), PD patients with DDS have sensitized DA release restricted to the ventral striatum as assessed by change in [^{11}C]raclopride binding in response to L-dopa (Evans *et al.*, 2006). As is the case for ventral striatal release of DA induced by amphetamine in healthy control subjects (Leyton *et al.*, 2002), the change in [^{11}C]raclopride binding correlated with 'drug-wanting' rather than the subjective pleasure or 'liking' of drug.

Another way of looking at the kinetics of DA release and metabolism is to estimate DA turnover using prolonged scans with 6FD. While uptake measured over the standard 90-120 minute scan reflects uptake, decarboxylation to fluoroDA and trapping of fluoroDA in synaptic vesicles, prolonged scans also reflect the egress and subsequent metabolism of this trapped radioactivity. The model used to analyse the acquired radioactivity data thus shifts from one that assumes unidirectional transport of tracer (i.e. the radioactivity is trapped) to a reversible model. The effective distribution volume that is derived from this reversible tracer model correlates well with the inverse of the ratio of tracer loss to tracer uptake constants (Sossi *et al.*, 2001), which in turn correlates with classical neurochemical measures of DA turnover (Doudet *et al.*, 1998). DA turnover measured using this approach is increased early in PD (Sossi *et al.*, 2002) and further increases occur with disease progression (Sossi *et al.*, 2004). Furthermore, even when one accounts for disease severity, the magnitude of the abnormality in DA turnover is greater in PD patients with younger disease onset than the abnormality of 6FD uptake (Sossi *et al.*, 2006). This suggests that comparable degrees of denervation result in greater increases in DA turnover in younger individuals and is in keeping with the fact that such individuals are more prone to dyskinesia (Golbe, 1991; Grandas *et al.*, 1999; Quinn *et al.*, 1987) (Kumar *et al.*, 2005).

The determinants of DA turnover are not fully understood. However, it appears that in patients with PD, downregulation of the DAT results in increased turnover, again even after correcting for disease severity (Sossi *et al.*, 2007). One would therefore predict that downregulation of DAT beyond the degree expected based on disease severity (i.e. loss of DA nerve terminals) would be an independent predictor of the development of LID and this indeed appears to be the case (Troiano *et al.*, 2006). Thus, while downregulation of the DAT may serve a useful function in early disease in order to conserve levels of DA in the synapse (Calne and Zigmond, 1991; Lee *et al.*, 2000b), in the long run such a compensatory mechanism may prove deleterious. As discussed in the next section, increased DA turnover may result when exogenous L-dopa is converted to DA in surviving serotonergic neurons, which are unable to regulate the release and reuptake of DA.

Dyskinesia that occur following fetal mesencephalic transplantation may represent a special example, as they may occur either as an exaggerated form of LID or, in some patients, may occur off medication (Freed *et al.*, 2001; Olanow *et al.*, 2003). Ma and colleagues reported post-operative increases in 6FD uptake in the left posterodorsal putamen and left ventral striatum of patients who developed post-transplant dyskinesia (Ma *et al.*, 2002). In contrast, using a combination of 6FD and [^{11}C]raclopride, Piccini et al. found no evidence for increased graft-derived DA release in subjects with dyskinesia (Piccini *et al.*, 2005).

5.2.2. Studies of non-DAergic mechanisms

As reviewed elsewhere in this manuscript, there is extensive evidence from animal models of alterations downstream to striatal DA receptors following chronic DAergic stimulation, thought to contribute to LID. These include upregulation of immediate early genes and of several neuropeptides, including enkephalin and dynorphin. There is very limited evidence available in the imaging literature, largely reflecting the paucity of tools. Piccini and colleagues demonstrated reduced striatal binding of the opioid ligand [^{11}C]diprenorphine in PD patients with LID, presumably reflecting occupancy of striatal opioid receptors due to increased opioid levels (Piccini *et al.*, 1997). Whone and colleagues demonstrated in a preliminary study a reduction in thalamic NK1 neurokinin receptor binding in PD patients with LID (Whone *et al.*, 2002). Whether this represents a loss of NK1 receptors or increased receptor occupancy reflecting increased availability of endogenous substance P is unclear. Studies have demonstrated increased adenosine A_2 binding in PD patients with dyskinesias compared to those without (Mishina *et al.*, 2011). Using a marker of activated NMDA channels, Ahmed et al. (2011) demonstrated increased striatal responsiveness to L-dopa in PD patients with LID.

Studies of cerebral blood flow have been mainly used to infer changes in patterns of neuronal activity within the basal ganglia and its connections, although the two parameters may be independently regulated by certain pharmacological treatments. Hershey and colleagues used PET with [^{15}]H_2O to study the hemodynamic responses to L-dopa in PD patients with and without LID. They found increased cerebral blood flow following drug administration in the thalamus of dyskinetic patients, associated with reduced blood flow in primary motor cortex (Hershey *et al.*, 1998). As regional cerebral blood flow (rCBF) predominantly reflects synaptic activity, this finding is compatible with a sensitized response to L-dopa in the GPi and while it is not easily explained by standard “box and arrow” models of the basal ganglia

(Albin *et al.*, 1989; Calabresi *et al.*, 2014), it is very much in keeping with the reduction in LID that is consistently reported following pallidotomy (Fine *et al.*, 2000). Sanchez-Pernaute and colleagues have studied the hemodynamic response to a selective DA D3 receptor agonist using functional magnetic resonance imaging (fMRI) and found that the response was increased in rodent and non-human primates with LID (Sanchez-Pernaute *et al.*, 2007), in keeping with in vitro and behavioural evidence (Bezard *et al.*, 2003; Bordet *et al.*, 1997; van Kampen and Stoessl, 2003).

As to the regulation of cerebral blood flow in LID, an intriguing phenomenon has been discovered by Eidelberg and collaborators using a multimodal PET approach to image both blood flow and glucose metabolism in the same scanning session (Hirano *et al.*, 2008). While regional glucose metabolism and rCBF were well-matched in PD patients during the 'off' medication state, the administration of L-dopa greatly enhanced rCBF but not glucose metabolism in a brain network that includes putamen, pallidum, and midbrain-pons (Hirano *et al.*, 2008). In these regions, the dissociation between flow and metabolism was particularly striking in patients affected by LID (Hirano *et al.*, 2008). Because the cerebral metabolic rate for glucose is mainly dictated by synaptic activity, these findings suggest that L-dopa exerts hemodynamic effects that are independent of its modulation of neuronal metabolism. A similar phenomenon occurs in the rat model of LID, which features a large increase in rCBF 'ON' L-dopa in many parts of the basal ganglia, usually in the absence of large concomitant changes in glucose metabolism (Ohlin *et al.*, 2012). The flow-metabolism dissociation response is particularly intriguing because it points to a previously unappreciated effect of L-dopa on vessel-associated cells controlling the blood flow to the striatum and the midbrain (Choi *et al.*, 2006). The underlying mechanisms have not yet been resolved. On-going studies are addressing the hypothesis that an increased capillary density in the striatum and the midbrain (Faucheux *et al.*, 1999; Ohlin *et al.*, 2011) may drive more blood flow to these regions under conditions of high DAergic tone (note that DA can modulate cerebral blood flow by acting directly on brain arterioles and microvessel-associated cells, cf. (Choi *et al.*, 2006)).

5.2.3. Potential future applications

With the few exceptions noted above, most studies performed to date have focused either on DAergic mechanisms or on patterns of cerebral activation in response to medication. Within the DA system, study of the D_3R may be of particular interest, but investigation has been

hampered by the lack of selective positron-emitting tracers. Other neurotransmitters of interest with respect to their role in LID include serotonin (5-HT – 5-hydroxytryptamine), adenosine, excitatory amino acids, and GABA. There were however no relevant studies, in part reflecting the paucity of informative radioligands, until the studies of Politis et al. investigating the serotonergic mechanisms responsible for LID in PD patients (Politis *et al.*, 2014; Politis *et al.*, 2010; Smith *et al.*, 2015). These authors first demonstrated that dyskinesias in patients who had undergone fetal nigral transplants were associated with serotonergic hyperinnervation and that the dyskinesias responded to administration of a 5-HT_{1A} agonist, presumably reflecting activation of 5-HT somatodendritic autoreceptors (Politis *et al.*, 2010). Identical L-dopa doses induced markedly higher striatal synaptic DA concentrations in PD patients with LID compared with PD patients with stable responses to levodopa, confirming earlier studies. While patients with LID presented relative preservation of serotonergic terminals, oral administration of the 5-HT_{1A} receptor agonist buspirone prior to L-dopa reduced L-dopa-evoked striatal synaptic DA increases and attenuated LIDs (Politis *et al.*, 2014), supporting the model based on studies in animals (Carta *et al.*, 2007) that striatal serotonergic terminals contribute to LID pathophysiology via aberrant processing of exogenous L-dopa and release of DA as false neurotransmitter in the denervated striatum of PD patients with LID. In more recent work, Politis and colleagues have suggested that 5-HT innervation and aberrant DA release in the globus pallidus may play a role in LID (Smith *et al.*, 2015). While buspirone (Buspar) has a high affinity as a 5-HT_{1A} receptor partial agonist (IC_{50} = 35 nM), this drug also potently antagonizes D_2R at nanomolar concentrations (IC_{50} = 250 nm) (Taylor, 1988) (resulting in potentially anti-dyskinetic effect (Shin *et al.*, 2012a; Shin *et al.*, 2014)) and is metabolized to the potent $alpha_2$-adrenergic receptor antagonist, 1-(2-pyrimidinyl-piperazine) (Caccia *et al.*, 1986; Engberg, 1989; Gobert *et al.*, 1997).

5.3. Electrophysiology

5.3.1. *In vivo* extracellular recordings

Studies of neuronal activity of the basal ganglia in LID, both in animal models of parkinsonism and in PD patients, have been conducted using mainly two different approaches, single cell and local field potential recordings (**Figure 1**). In this review, human, non-human primate and rodent studies will be summarized.

5.3.1.1. *In vivo* single cell recordings

Single cell recording is obtained using microelectrodes and provides information about the frequency and the pattern of discharge of single neurons. The classical model of basal ganglia function considered that LID result from over-decreased neuronal firing rates in the GPi (Albin *et al.*, 1989; DeLong, 1990), the main output structure of the primate basal ganglia, leading to increased activity of thalamocortical motor circuits (**Figure 1**). Accordingly, micro-recording of the neuronal activity in MPTP-treated monkeys with DAergic-related dyskinesia showed a reduction of the firing frequency in the GPi in comparison with the OFF state (Boraud *et al.*, 2001; Filion *et al.*, 1991; Heimer *et al.*, 2006; Papa *et al.*, 1999) and with the ON state without dyskinesia (Boraud *et al.*, 2001; Heimer *et al.*, 2006; Papa *et al.*, 1999). There was also a change in the firing pattern concomitant with the onset of dyskinesia (Boraud *et al.*, 2001; Heimer *et al.*, 2006). A reduction in the fraction of oscillatory cells and in the oscillatory correlations among neurons was observed in the GPi during the ON state, which was higher when LID were present (Heimer *et al.*, 2006).

Although firing rate in GPe neurons was increased in the ON state respect to the OFF state (Boraud *et al.*, 2001; Heimer *et al.*, 2006), no differences either in the firing frequency or pattern of neuronal discharge were encountered between the dyskinetic and non-dyskinetic states (Boraud *et al.*, 2001). In contrast, Heimer et al, 2006 observed a reduction in the fraction of oscillatory cells only when LID were present (Heimer *et al.*, 2006). In addition, they observed that the ratio of the mean firing rate of the GPe/GPi increased during the LID recording respect to the ON state with optimal recovery of parkinsonism without dyskinesia (Heimer *et al.*, 2006).

Thus, single cell studies in the MPTP monkey indicated that LID would take place when frequency is excessively decreased in the GPi (i.e. lower than in the normal situation), and the firing pattern suffers a change in the oscillatory activity with a reduction in the fraction of oscillatory cells.

In human studies, dyskinesia induced intra-operatively by administration of apomorphine to patients with PD were associated with a reduction of the GPi firing rate respect to the OFF state (Lee *et al.*, 2007; Levy *et al.*, 2001; Merello *et al.*, 1999a), while differences between ON state with and without dyskinesia were not clearly observed (Lee *et al.*, 2007; Levy *et al.*, 2001). The firing pattern was also altered during ON state with dyskinesia respect to the OFF state with an increment in the burst-like (Levy *et al.*, 2001; Merello *et al.*, 1999a) or irregular (Lee *et al.*, 2007) discharges. In contrast, the mean firing rate of the neurons of the STN was not reduced during the ON state without dyskinesia respect to the OFF state while it was

significantly reduced when LID were present (Levy *et al.*, 2001). LID were also associated with an increment in the proportion of spikes in burst in the STN, which was not observed during the ON state without dyskinesia (Levy *et al.*, 2001). Of note, there was a high variability in the effect of apomorphine upon the firing rate of single STN and GPi neurons (Levy *et al.*, 2001). Regarding the GPe, just a few neurons have been studied, which had an increment in the firing rate by 50-90% (Lozano *et al.*, 2000).

Thus, in PD patients, LID are associated with reduced firing rate and change in the pattern of GPi neuronal discharges with respect to the parkinsonian state, while the major difference between the states ON with and without dyskinesia seems to be the firing pattern (**Figure 1**). In the STN, a reduction in the firing rate marked the presence of LID along with a more bursty or irregular firing pattern. Findings in the GPe are less consistent and further studies are needed to elucidate its role in LID.

5.3.1.2. *In vivo* local field potentials

The implantation of electrodes for DBS in the STN and GPi of patients with PD has allowed recording local field potentials (LFP) and recognizing specific patterns of activity according to the motor states. Thus, information about oscillatory activity of neuronal populations in the basal ganglia of PD patients with dyskinesia has become available more recently.

In the STN, peak-dose LID is associated with an increment in the power of the theta-alpha (4-10 Hz) band with a mean frequency at 8.38 Hz (Alonso-Frech *et al.*, 2006; Foffani *et al.*, 2005), a finding very much in line with recordings performed in substantia nigra pars reticulata (SNr) of dyskinetic 6-OHDA rats (Meissner *et al.*, 2006) and GPi of dyskinetic MPTP-treated macaques (Bezard, unpublished). The specificity of this relationship is confirmed by different facts. Firstly, the increment of the power in the theta-alpha band is only recorded when patients are exhibiting dyskinesia and not during the ON periods without such abnormal movements (Alonso-Frech *et al.*, 2006). Secondly, in patients with unilateral dyskinesia, this oscillatory activity was only recorded in the STN contralateral to the hemi-body where LID was present. In patients in whom LID starts in one hemi-body and then spreads to the other side, a gain of power of the theta-alpha activity is firstly recorded in the STN contralateral to the hemi-body where LID starts and then, time-locked with the beginning of LID, it starts in the other STN (Alonso-Frech *et al.*, 2006). In addition, patients who suffered diphasic dyskinesia, which are a subtype of LID that appear typically at the

onset and end of L-dopa anti-parkinsonian action, exhibit a similar theta-alpha activity (mean frequency 7.38 Hz) during this involuntary movement (Alegre *et al.*, 2012).

The theta-alpha activity associated with peak-dose dyskinesia was mainly recorded through the dorsal contacts of the electrode, which were located in the dorsal portion of the STN, therefore indicating that this oscillatory activity was generated in the motor region of the STN (Rodriguez-Oroz *et al.*, 2011).

In the GPi, a study conducted in 2 patients found a negative correlation between LFP power in the band comprised between 8 and 40 Hz and EMG recordings in the contralateral limb with LID (Silberstein *et al.*, 2005). In contrast to studies in the STN, this correlation was peaking in the 8-12 Hz in one case and the 21-30 Hz in the other case, but in both cases there was a strong negative correlation in the beta band. Beta oscillatory activity is typically observed in the parkinsonian state and correlates with rigidity and bradykinesia (Little *et al.*, 2012; Lopez-Azcarate *et al.*, 2010). The lowering of the power in this band during LID could be interpreted as an over-reduction of these motor signs during the abnormal excessive movements. For instance, a clinical observation is that rigidity is usually abolished in dyskinetic limbs. In addition, the suppression of the "antikinetic" activity of the beta band could also lead to the release of unwanted motor programs. On the other hand, the discrepancy between GPi and STN activity associated with LID could be due in part to methodological aspects (i.e GPi recording have been conducted in two patients, electromyogram recorded only in one muscle). On this regard, in one patient with unilateral LID induced by a lesion-like effect of the electrode implanted for DBS in the STN, enhanced STN-GPi coherence at low frequencies (10 Hz) was recorded in the nuclei contralateral to the dyskinetic hemi-body suggesting that an oscillatory activity in the theta-alpha band is probably present along the basal ganglia circuit during LID (Foffani *et al.*, 2005). Although there is no similar record in PD patients with LID, this might also be a feature of this state.

Recording the SNr has proven helpful as well for understanding pathological plasticity induced by L-dopa. Per-operatory recordings of the GPi and SNr in patients showed that patients with less severe dyskinesia underwent greater depotentiation following low frequency stimulation than patients with more severe dyskinesia (Prescott *et al.*, 2014). This demonstration of impaired depotentiation in basal ganglia output nuclei in PD patients with dyskinesia is an important validation of animal models of LID (see below the *ex vivo* section). Loss of the ability to depotentiate at the output nuclei may underlie, or contribute to the cellular basis of dyskinetic movements.

In summary, the classical model of the basal ganglia explained LID as the consequence of a striatal DAergic overstimulation that eventually causes an inhibition of the GPi. However, the fact that lesions of the GPi not only improved parkinsonism but abolished or greatly ameliorated LID proved this concept to be incorrect (Calabresi *et al.*, 2014). Interestingly, although in MPTP-lesioned monkeys studies the firing rate of the GPi was lower during the ON state with or without dyskinesia, this has not been demonstrated in PD patients as the neuronal firing rate was similar when patients were in ON state both with or without LID. In contrast, a more irregular and bursty pattern of discharge has been encountered in all single cells studies undertaken in primates and in humans. The importance of this finding has been somehow reinforced with the LFP recording given consistency to the notions that the pattern but not the frequency of discharge was the most relevant feature in the pathophysiology of LID. Current interpretation of the benefit of surgical interventions in the GPi (lesion and DBS) are more aligned with a disruption of a DAergic induced abnormal synchronization of neuronal activity along nuclei of the motor circuit (Hammond *et al.*, 2007). Recent contributions highlighted the role of cortico-striatal and striato-cortical connections, with the demonstration using functional imaging that dyskinetic PD patients display an immediate hypersensitivity of preSupplementary Motor Area (preSMA) and putamen to L-dopa, that would herald the failure of neural networks to suppress involuntary dyskinetic movements (Herz *et al.*, 2014, 2015). Such result resonates with experimental findings in AIM 6-OHDA rat model showing (i) that pronounced LFP oscillations in the primary motor cortex following L-dopa treatment are interrupted by the application of a DA antagonist onto the cortical surface leading to the dyskinetic symptoms disappearance (Halje *et al.*, 2012), (ii) that spine enlargement and the resultant hyperexcitability of intratelencephalic-type pyramidal neurons in the primary motor cortex (M1) (Ueno *et al.*, 2014) and (iii) that synaptic downscaling of cortico-striatal synapses across sleep episodes (Galati *et al.*, 2015) might contribute to the abnormal cortical neuronal plasticity in LID. The finding that abnormal cortical oscillations are a key pathophysiological mechanism calls for a revision of the prevailing hypothesis that links LID to an altered sensitivity to DA only in the striatum. In this context, the cortical exposure to L-dopa would drive the aberrant behaviour of the basal ganglia.

5.3.2. *Ex-Vivo* electrophysiology

The first paper addressing the electrophysiological plastic changes in neurons recorded from rats displaying dyskinetic movements dates back to 2003 (Picconi *et al.*, 2003). This paper

demonstrated for the first time that dyskinetic motor abnormalities are coupled to an absence of bidirectional synaptic plasticity in the striatal projecting neurons (Picconi *et al.*, 2003), opening the way to future studies on the possible synaptic mechanisms underlying LID (**Figure 2**).

The experimental model is the well characterized unilaterally 6-OHDA-lesioned rat (Schwarting and Huston, 1996a). Six weeks after the DA denervation, animals lose cortico-striatal plasticity, both long-term potentiation (LTP) and long-term depression (LTD) (Calabresi *et al.*, 1992; Centonze *et al.*, 1999b; Picconi *et al.*, 2003) (**Figure 2B**). Notably, the degree of DA denervation influences these two forms of plasticity in different ways, nearly full DA loss blocks the induction of both LTP and LTD, while partial DA depletion allows LTP induction but selectively alters its maintenance, leaving LTD induction and maintenance unaffected (Paille *et al.*, 2010) (**Figure 2B**).

Chronic L-dopa treatment (Cenci *et al.*, 1998; Picconi *et al.*, 2003) at a therapeutic dosage allows restoration of LTP in all the parkinsonian rats (**Figure 2C**) and distinguishes two different drug-induced behavioural responses. Animals that do not develop dyskinesia, e.g.: the "therapy responsive" rats, display the anti-parkinsonian effects of the drug and the physiological bidirectional synaptic plasticity (LTD, LTP and depotentiation). Conversely, dyskinetic rats show severe LID and normal LTP while they do not express either LTD or depotentiation induced by the low frequency stimulation (LFS) protocol (**Figure 2C**). Notably, the intrinsic properties of striatal medium spiny neurons (MSNs) recorded from dyskinetic and non-dyskinetic rats did not show differences (Picconi *et al.*, 2003). Such loss of bidirectional plasticity at cortico-striatal synapses may cause a pathological storage of non-essential motor information that would normally be erased, leading to the development and/or expression of abnormal motor patterns. Interestigly, this loss of bidirectional synaptic plasticity has also been found in PD patients in ON and OFF phases of L-dopa therapy. The loss of depotentiation of previously induced HFS-mediated LTP has been demonstrated in patients in ON medication during dyskinesia both in the substantia nigra (Prescott *et al.*, 2014) (**Figure 2D**) and in the cerebral motor cortex (Huang *et al.*, 2011d) (**Figure 2E**).

The biochemical studies indicated that the loss of depotentiation observed in dyskinetic animals is attributable to specific changes occurring along the D_1R signalling pathway leading to abnormally high levels of Thr34-phosphorylated dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) and consequent inhibition of protein phosphatase 1 activity (Picconi *et al.*, 2003; Santini *et al.*, 2010a; Santini *et al.*, 2007). This seminal work provided the first demonstration that combining electrophysiological, behavioural and

molecular analysis is possible to study the biological features of LID in rodent experimental models.

A further step forward was the electrophysiological characterization of depotentiation loss in chronically treated 6-OHDA-lesioned rats with two different regimen of L-dopa (Picconi *et al.*, 2004); a direct correlation between the daily dosage of L-dopa and the induction of dyskinetic movements was demonstrated. Moreover, this study established a critical pathophysiological link between the lack of synaptic depotentiation and LID expression. The phenotypic nature or anatomical identity of the striatofugal neurons was however unknown in these studies.

Starting from the observation that striatal cyclic guanosine monophosphate (cGMP) signalling is decreased in dyskinetic rats (Giorgi *et al.*, 2008), Picconi and colleagues explored the possibility that LTD, which strictly relies on the nitric oxide-dependent activation of protein kinase C (PKC), is also altered in dyskinetic rats. Chronic L-dopa-treated rats developing LID do not show this form of synaptic plasticity (Picconi *et al.*, 2011). Phosphodiesterase (PDE) inhibitors increase cGMP levels leading to the activation of PKG that represents a critical factor for LTD induction following high frequency stimulation (Calabresi *et al.*, 1999; Calabresi *et al.*, 2007; Centonze *et al.*, 1999a). Nitric oxide produced by NOs-positive striatal interneurons activates cGMP/PKG pathway that can be in turn modulated by PDE inhibitors, such as Zaprinast® and UK-343664 (Calabresi *et al.*, 2007; West and Tseng, 2011). Accordingly, a low dose of PDEs inhibitors applied *in vitro* rescues *ex vivo* the activity-dependent LTD in striatal slices obtained by dyskinetic rats. Moreover, intra striatal injection of these drugs in behaving dyskinetic rats rescues LTD, as measured in *ex vivo* slices, and reduces LID (Picconi *et al.*, 2011).

Usiello's group investigated the contribution of a basal hyperglutamatergic tone in the development of LID and the effect on DA-dependent bidirectional synaptic plasticity (Errico *et al.*, 2011).

Mutant Ddo$^{-/-}$ mice lacking the D-Aspartate Oxidase (Ddo) enzyme, display abnormally high levels of the excitatory free amino acids D-aspartate and NMDA (Errico *et al.*, 2008), and show an aberrant striatal synaptic plasticity. In the MSNs recorded from Ddo$^{-/-}$ mice, similar to what observed in dyskinetic animals, LFS protocol failed to depotentiate the high frequency stimulation-induced LTP (Errico *et al.*, 2011). When subjected to 6-OHDA lesions, Ddo$^{-/-}$ mice display increased sensitivity to L-dopa and earlier onset of LID (Errico *et al.*, 2011), further supporting the concept that increased glutamatergic release is a critical risk factor to develop LID.

An interesting study from Anthony Grace's group (Belujon *et al.*, 2010) provided evidence in support of a more complex pattern of plastic changes occurring in the striatal output neurons, by studying corticostriatal synaptic plasticity alterations in denervated rats chronically treated with L-dopa. In particular, the authors studied corticostriatal LTD using *in vivo* extracellular recordings from striatonigral pathway and striatopallidal pathway neurons in anesthetized rats (Belujon *et al.*, 2010). The authors confirm by the use of an *in vivo* experimental approach that LID might be due to an induction of aberrant plasticity, with their data suggesting that this alteration occurs in striatal indirect pathway neurons (i.e. projecting to GPe) combined with an inability to de-depress established plastic responses in direct pathway neurons (i.e. projecting to GPi/SNr).

Nash and co-workers further advanced our understanding of the pathological plasticity affecting the striatofugal pathways in LID (Thiele *et al.*, 2014). They applied spike-timing dependent plasticity protocols to cortico-striatal synapses in slices from 6-OHDA-lesioned mouse models of parkinsonism and LID, generated in BAC transgenic mice with eGFP targeting the direct or indirect output pathways, with and without L-dopa present. While naive mice showed bidirectional synaptic plasticity, i.e. LTP and LTD, in both striatal output pathways, both pathways exhibited unidirectional plasticity, irrespective of stimulation paradigm, in both parkinsonism and dyskinesia (Thiele *et al.*, 2014). In parkinsonian animals, the indirect pathway only exhibited LTP whereas the direct pathway only showed LTD. A symptomatic dose of L-dopa restored bidirectional plasticity on both pathways to levels comparable to naive animals. In the presence of L-dopa in dyskinetic animals, the indirect pathway exhibited only LTD whereas in the direct pathway, only LTP could be induced. Therefore, switching from bidirectional to unidirectional plasticity drives global changes in striatal pathway excitability, and underlies parkinsonism and dyskinesia, with opposite changes in nature of plasticity (Thiele *et al.*, 2014).

5.4. Morphological changes related to LID

5.4.1. Morphological re-sculpting of neurons and circuits in LID

As presented in this review, decades of research have revealed numerous pharmacological, neurochemical and neurophysiological abnormalities in the brain of dyskinetic patients and animal models of PD. An abundance of data clearly implicates enhanced glutamate signalling and persistent LTP in the absence of bidirectional plasticity as central to the behavioural sensitization phenomenon of LID. The basal ganglia, and in particular the striatum are

involved with procedural learning of goal-directed and routine/'habit' motor behaviours. Striatal motor learning is not only mediated by glutamatergic mechanisms but is uniquely sculpted by feedback from ascending nigral DA neurons that act to reinforce or inhibit action selection (e.g. Shen *et al.*, 2008). An accumulation of evidence suggests that LID represent a form of pathological experience-dependent learning secondary to aberrant synaptic plasticity (Fieblinger *et al.*, 2014a; Graybiel, 1995; Picconi *et al.*, 2003; Picconi *et al.*, 2005; Pisani, 2005). While experience-dependent alterations in behaviour are known to involve structural modifications of synaptic connectivity, only recently has the nature of structural and synaptic remodelling of MSNs in response to LID begun to be investigated. Emphasis has been put upon afferent inputs, as the striatofugal pathways appear not to be phenotypically modulated in dyskinetic vs. non-dyskinetic animals (Nadjar *et al.*, 2006).

A series of studies are providing novel insights into the morphological adaptations of striatal MSNs and re-wiring of basal ganglia circuits in the dyskinetic brain. It has been known for many years that there are profound effects of DA depletion on the architecture of the primary efferent neurons of the striatum, the MSNs, including retraction of dendrites and loss of dendritic spines (e.g. Day *et al.*, 2006; McNeill *et al.*, 1988; Soderstrom *et al.*, 2010). Anatomically, cortico-striatal glutamate afferents preferentially synapse onto the spines that stud MSNs, and thus with spine retraction in the parkinsonian striatum there is a loss of axospinous glutamatergic synapses (Day *et al.*, 2006; Ingham *et al.*, 1989; Ingham *et al.*, 1998; Zhang *et al.*, 2013b). There remains controversy on whether striatal DA depletion results in spine loss specifically in MSNs of the indirect pathway or occurs in MSNs of both striatofugal pathways (i.e.: indirect and direct) (Day *et al.*, 2006; Suarez *et al.*, 2014; Villalba *et al.*, 2009). However consensus is beginning to suggest a specific dynamic of spine re-modelling that occurs with dyskinesiogenic L-dopa treatment. Studies using transgenic mice with green fluorescent protein or tdTomato under the control of D_1R or D_2R regulatory elements have allowed selective visualization of the dynamic changes in the D_1R direct versus D_2R indirect pathway MSNs in dyskinetic parkinsonian subjects. Using such mice, Suarez and colleagues (2014) and Fieblinger and colleagues (2014a), both show that there is a decrease in spine density per μm of dendritic length in indirect pathway MSNs (iMSNs) with severe striatal DA depletion but that high dose L-dopa results in restoration of spine density in these neurons that is not different from that seen in the control striatum. In contrast and similar to what was reported previously (Day *et al.*, 2006), Fieblinger et al. (2014a) found that DA depletion did not affect spine density per μm of dendritic length (although there was a loss of total number of spines due to retraction of dendritic length) on direct pathway MSNs

(dMSNs) but interestingly they observed that dyskinetic high dose L-dopa resulted in significant reduction in spine density and further decline in total number of spines on the dMSNs. While Suarez and colleagues (2014) found that spine density in their mice decreased in both iMSNs and dMSNs with striatal DA depletion, similar to Fieblinger et al. (2014a), they too found that in the dyskinetic striatum, spine density in iMSNs was restored to control levels and significantly reduced in dMSNs. A similar spine remodelling paradigm has been observed in the 6-OHDA rat model of PD. Specifically, Nishijima et al. (2014) reported decreased spine density of iMSNs and no change in dMSNs in the DA depleted rat striatum, with LID development being uniquely associated with loss of spine density on dMSNs and apparent restoration of spine density in iMSNs.

With the re-establishment of dendritic spines it would be anticipated that there should be re-establishment of cortico-striatal input onto MSNs in the dyskinetic striatum. Using stereological immunoelectron microscopic and light microscopic 3-D neuron reconstruction in Golgi impregnated neurons, Zhang and colleagues (2013b) examined whether the two major glutamatergic striatal afferent pathways (i.e. the cortico-striatal and thalamo-striatal afferents) formed new or altered contacts onto dendrites or spines of striatal MSNs in parkinsonian rats treated with L-dopa that either developed dyskinesia or remained dyskinesia free. Using immunohistochemistry markers specific to cortico-striatal (VGlut1) or thalamo-striatal (VGlut2) terminals, this study provided the first structural evidence that cortico-striatal, but not thalamo-striatal remodelling was linked directly to dyskinesia *per se* (Zhang *et al.*, 2013b). While this study did not examine which population of MSN was involved with cortico-striatal remodelling, they found that the initial loss of cortico-striatal axospinous synaptic input following a nigrostriatal DA lesion was followed by a restoration of these corticostriatal synapses to control levels exclusively in dyskinetic rats. Based on the dendritic spine studies discussed above, it could be predicted that this restoration occurred on iMSNs. Indeed, in a thorough and elegant series of electrophysiological studies, Fieblinger and colleagues (2014a) concluded that of the many cell-specific plasticity responses that they observed, the only adaptation exclusively associated with LID was the restoration of iMSNs axospinous synapses. Despite what might appear as “physiological remodelling”, ultrastructural evidence has provided important insight that the synaptic restoration found in the striatum of dyskinetic subjects involved the re-establishment of atypical synaptic input patterns onto structurally modified MSNs. Specifically, Zhang et al. (2013b) found that the restoration in spine density involved a significant increase in the number of large mushroom spines and the occurrence of atypical multisynaptic cortico-striatal input onto individual

spines. Thus, in the dyskinetic striatum, an increase in spine head size appears to expand the active zone area through multiple inputs rather than through expansion of a single active zone. The larger active zone with new calcium-permeable glutamate receptors inserted into the post-synaptic membrane of mushroom spine with multisynaptic input could be theorized to be a structural correlate of the enhanced LTP associated with LID (Belujon *et al.*, 2010; Picconi *et al.*, 2003). While this body of evidence clearly implicates aberrant remodelling of iMSNs axospinous synapses in the phenomenon of LID, the additional pruning of dendritic spines and axospinous synapses of the dMSNs should not be discarded. The studies by Fieblinger et al. (2014a) indicate that the loss of spines on dMSN occurs with both low and high dose L-dopa, dissociating it from the induction of LID *per se* but these authors provided a detailed discussion of a more complex, perhaps timing dependent relationship of synaptic remodelling in this particular pathway.

While the striatum is undoubtedly of great importance in the manifestation of LID, the elucidation of a dramatic re-wiring, or 'mis-wiring' of cortico-striatal input highlights a new horizon of exploration that is needed for fully elucidating the neurobiology of LID. Specifically, clinical and preclinical data suggest that particular regions of the overlying cortex play an under-appreciated role for cortico-basal ganglia network remodelling in the dyskinetic brain (Finlay *et al.*, 2014; Halje *et al.*, 2012; Ostock *et al.*, 2011; Ueno *et al.*, 2014) and that there may be alterations in patterns of connectivity in the dyskinetic brain (Cerasa *et al.*, 2015; Finlay *et al.*, 2014). Briefly, human imaging studies using fMRI and PET have demonstrated that anatomical abnormalities in a variety of cortical regions are linked specifically to dyskinetic versus non-dyskinetic status in PD patients (for review see, Cerasa *et al.*, 2015; Finlay *et al.*, 2014). Further, in parkinsonian rats, infusion of either a 5-HT_{1A} agonist (Ostock *et al.*, 2011) or a DA antagonist (Halje *et al.*, 2012) into the M1 motor cortex were found to attenuate LID. The primary motor cortex (M1) normally projects to the dorsolateral striatum (e.g. Ramanathan *et al.*, 2002; Wall *et al.*, 2013) and is involved in motor learning (Hosp and Luft, 2013). Thus, two questions arise from these clinical and preclinical observations: (i) do physiologically relevant cortical regions (e.g.: M1 cortex) re-establish the abnormal synaptic input (Zhang *et al.*, 2013b) that leads to the pathological behavioural consequence of LID; or (ii) is afferent input to the striatum from atypical cortical regions (e.g. those that show significant increase in gray matter volume in LID patients (Cerasa *et al.*, 2011; Cerasa *et al.*, 2013)) the source of the aberrant circuit re-wiring seen in the dyskinetic striatum? Understanding the anatomical source of re-established cortico-striatal input and molecular signals that initiate the maladaptive structural plasticity could lead to a

novel therapeutic approach aimed at restoring physiological remodelling and lasting anti-dyskinetic therapy. While clinical evidence suggestive of neuroanatomical remodelling in dyskinetic PD patients is critical, current neuroimaging techniques lack resolution and exploratory studies in patients are unethical for elucidating answers to such questions. As such, relevant animal models continue to be valuable and necessary.

As research continues in preclinical models, knowing the right questions to ask will be paramount. One particularly cogent variable that has been suggested to be important, and which has largely remained unexamined in LID research is the timing of when the brain is examined in relationship to experimental manipulations (Fieblinger *et al.*, 2014a; Nadjar *et al.*, 2009). As reviewed by Nadjar and colleagues (2009), there is a void in our understanding of whether L-dopa priming is a feature inherent to the treatment or the disease/individual. The common view of priming for LID (for details see 5.5) is that repeated exposure of the DA depleted striatum to non-physiological DA during L-dopa treatment modifies and sensitizes the brain such that over time the chance of eliciting dyskinetic behaviour increases. Nadjar et al. (2009) posit the interesting proposition that "priming does not exist *per se* but is the direct and intrinsic consequence of the loss of DA innervation of the striatum, meaning that the first injection of DAergic drugs only exacerbates those mechanisms (sensitization) but do not induce them. In support of this concept, a significant portion of 6-OHDA lesioned rats and MPTP-lesioned marmosets and macaque monkeys develop LID during the first-ever administration of L-dopa (for review, see Nadjar *et al.*, 2009). In humans, the occurrence of LID has also been noted after just a few days of treatment in the case of MPTP-intoxicated individuals (Ballard *et al.*, 1985; Langston and Ballard, 1984) or while being challenged with L-dopa as part of PD diagnosis (see Nadjar *et al.*, 2009). Inarguably two key parameters for the induction of first drug exposure LID, regardless of the species, are the extent of DA depletion and time between intoxication and DA agonist drug administration. It is notable however that severe striatal DA depletion and non-physiological DA replacement alone are insufficient to induce LID, both in humans and rodents (e.g. Cotzias *et al.*, 1969; Konradi *et al.*, 2004; Zhang *et al.*, 2013b). The question remains, why do some individuals (rodent, non-human primate or human) not develop LID, or show remarkable resistance? Genomic and proteomic studies (e.g. (Konradi *et al.*, 2004); reviewed in (Heiman *et al.*, 2014; Nadjar *et al.*, 2009)) are revealing that there are robust and specific alterations of particular genes or proteins within the striatum of dyskinetic subjects, suggesting that expression of one or more specific molecular triggers may induce/permit the plastic changes underlying long-term adaptations of striatal circuits that result in LID. It is reasonable to suggest that structural

adaptations in the brain underlie the long-lasting behavioural consequences known to occur once LID are established in humans and experimental animals, and that these structural adaptations render palliative pharmacological approaches ineffective or suboptimal by administering drugs into a significantly altered target environment. However, it is unclear whether the cortico-striatal synapse plasticity and dynamic alterations of dendritic spines are a secondary event linked to the expression of dyskinesia, rather than a series of events that occur over time during a primary induction phase. It is further unclear the extent of brain structures involved in LID specific mis-wiring, whether they are responsible for the long-lasting behavioural consequences of LID, and if so, whether "depriming" is a possible therapeutic option.

5.4.2. Striatal remodelling and graft-induced dyskinesia

Given what is now known about the degree of functional and structural remodelling that occur in the parkinsonian dyskinetic brain (see 5.4.1), it is not surprising that clinical trials of embryonic DA neuron transplantation in PD patients resulted in an overall suboptimal therapeutic benefit and induction of additional aberrant behaviour. The idea of replacing DA neurons lost to PD by engrafting new ones has strong biological rationale and based on early preclinical studies appeared to offer great hope as an additional therapeutic option. While the overall lack of clinical efficacy was disappointing, the induction of graft-induced dyskinesia (GID) was an unacceptable side effect that resulted in a moratorium against clinical grafting trials. GID are another form of therapy-mediated dyskinesia linked specifically to the engraftment of embryonic DA neurons into the parkinsonian striatum rather than pharmacological drug administration. There have been many clinical and preclinical studies and reviews aimed at elucidating and discussing the underlying cause of GID. The tendency has been to promote single factors in the aetiology of this movement disorder. However, similar to LID, it is likely that a constellation of adaptations of neurons and circuits are linked to the expression of GID. While there is general consensus that LID and GID likely have distinct underlying pathology based on differential behavioural expression patterns and pharmacological responses (for review, see Breger and Lane, 2013; Garcia *et al.*, 2011; Steece-Collier *et al.*, 2012) a significant body of evidence suggests that similar to LID, DA, 5-HT and glutamate systems may all have some role in GID. It is not the intention of this review to consider the pros and cons of the various proposed mechanisms, but instead as an extension of the previous section we present here thoughts on whether the mis-wired striatum

into which DA neurons are grafted might: 1) contribute to the emergence of GID, and 2) benefit from these grafts.

From a very simplistic view, grafted neurons likely act as biological mini-pumps capable of providing tonic DA release in a way that could provide more effective symptomatic benefit than seen with pharmacological drug replacement. If this is the means by which grafted neurons are providing therapeutic benefit, it is reasonable that the graft should contain exclusively or primarily ventral mesencephalic DA neurons, and not for example, neighbouring mesencephalic 5-HT neurons that are also capable of synthesizing and releasing DA but in a non-regulated fashion (see section 6.2, e.g. Shin *et al.*, 2014; Shin *et al.*, 2012b).

A provocative and likely impact associated with grafting these biological mini-pumps is that DA neuron grafts may also be able to reverse the pathology linked to disease-mediated DA depletion and/or pharmacological DA replacement. Indeed, in both clinical (Freed *et al.*, 2001; Hagell *et al.*, 2002; Olanow *et al.*, 2003) and preclinical (Lane *et al.*, 2006; Lee *et al.*, 2000a; Maries *et al.*, 2006) grafting studies, a functional ventral mesencephalic graft can significantly reduce the severity of LID over time. Such findings could be taken to suggest that the reversal of LID behaviour is the consequence of homeostatic re-organization of the structural adaptations in the brain that underlie LID; however, this remains to be determined.

In contrast to ventral mesencephalic grafts reducing the severity of LID and other motor deficits, in some patients and in particular preclinical models, maturation of the graft results in an emergence of new graft-associated dyskinetic behaviours (i.e. GID). Given the direct link between synaptic changes and LID, it is reasonable to suggest that GID are also mediated by aberrant synaptic organization.

While critical assessment of numerous factors including the level of DA depletion, pre-transplant LID expression, and the ratio of 5-HT:DA neurons in the graft have all been associated with the occurrence of GID, a void remains in understanding precisely how and why these variable impact graft success. Clinically the degree of DA depletion outside the graft has been found to significantly correlate with GID (Piccini *et al.*, 2005). Striatal DA depletion and LID lead to significant loss of dendritic spines on MSNs, the dynamics of which are discussed above (5.4.1). Presumably related to the loss of these normal spinous contact sites on MSNs, it has long been known that grafted DA neurons form new synapses with dendrites (and the soma) more frequently than with spines (Freund *et al.*, 1985; Leranth *et al.*, 1998; Mahalik *et al.*, 1985; Triarhou *et al.*, 1990).

How significant is such an anatomical anomaly and is it possible that a DA neuron making a new synaptic contact onto the “wrong” part of the MSN (dendrite rather than spine) could

have such a dramatic impact on MSN activity and hence on behavioural output? While the perfect preclinical model of GID is lacking, the presence of a VM graft placed into the DA-depleted striatum of rats can induce the emergence of new graft-associated dyskinetic behaviours that have many qualities similar to GID in PD patients (Lane *et al.*, 2009; Lane *et al.*, 2006; Maries *et al.*, 2006; Steece-Collier *et al.*, 2009). Using the 6-OHDA lesioned rat and intrastriatal grafting of embryonic VM neurons, Soderstrom and colleagues (2008) used immuno-electronmicroscopy to examine whether abnormalities in synaptic profiles correlated with graft-derived aberrant behaviours. Similar to previous studies, they found that as the grafts matured the proportion of TH-positive contacts onto the dendrites significantly increased, however this study provided the first direct evidence that a decrease in the number of spine contacts was significantly correlated with an increase in the graft-derived aberrant behaviours (Soderstrom *et al.*, 2008). Perhaps more significantly, ultrastructural evidence in this model indicated that in rats exhibiting these graft-associated dyskinetic behaviours not only were the grafted synapses making contact with the wrong part of the MSN but the type (i.e. symmetry) of synapses was also atypical. So-called "symmetric" synapses are classically associated with inhibitory neurotransmission, and "asymmetric" with excitatory neurotransmission (see Klemann and Roubos, 2011). In the normal striatum, DAergic terminals predominantly make symmetric and rarely asymmetric synapses (Freund *et al.*, 1985). Soderstrom et al. (2008) found that as grafts matured over time the incidence of asymmetric (presumably excitatory) TH-positive synapses was seen to increase from 4% up to 38%. An increase in the number of asymmetric synapses formed by grafted DA neurons has also been reported in the grafted parkinsonian monkey striatum (Leranth *et al.*, 1998). Thus, rather than normal symmetric DAergic input that predominately occurs on the necks of dendritic spines modulating the degree of excitatory corticostriatal input that reaches the dendritic shaft from the same spines, there are asymmetric DAergic inputs directly onto the dendritic shaft in the grafted striatum of animals exhibiting these novel post-graft dyskinesia (Soderstrom *et al.*, 2008). Non-TH (presumably host-derived) asymmetric synapses were noted to contact the soma and proximal dendrites of the grafted cells. These connections also were correlated with an increased incidence of the GID-like behaviours in this model (Soderstrom *et al.*, 2008). Similar to the cortico-striatal re-wiring associated with LID it is possible that these may be new cortico-striatal endings that would be expected to stimulate grafted cells, potentially giving rise to the irregular spontaneous discharge and fast firing rate of grafted DAergic neurons (Fisher *et al.*, 1991; Trulson and Hosseini, 1987) and the generation of graft-associated dyskinetic behaviours.

The interesting paradox of DA grafts in PD is that on one hand they can apparently de-prime the LID brain while inducing a new set of aberrant circuitry resulting in the emergence of GID. The ability to significantly reduce LID for prolonged periods of time suggests that these cells are not simply acting as mini-pumps that elevate striatal DA tone. Indeed, while pharmacological L-dopa can restore DA to the parkinsonian striatum and continue to shape synaptic strength, the manner in which it is shaped is divorced from the normal outcome of action selection because it is not driven phasic DA release/signalling (Fieblinger *et al.*, 2014a). Phasic stimulation or suppression of striatal DA, i) acts to adjust the relative strength of competing inputs critical for normal experience-dependent motor learning and action selection, and ii) is dependent on specific anatomical input to nigral DA neurons (Redgrave *et al.*, 2008). Thus, simply flooding the striatum with DA in the absence of phasic changes to provide saliency to particular situations would be predicted to result in aberrant synaptic plasticity and aberrant motor output. Based on an abundance of preclinical and clinical data, it is clear that DA grafts can restore some degree of physiologically relevant signalling within the basal ganglia that reverses LID behaviours and thus arguably provides a better mechanism of DA replacement than pharmacological approaches. The challenge remains to determine how to prevent GID and tap into the beneficial mechanisms by which new DA neurons can re-store physiological signalling to improve motor dysfunction.

5.4.3. Non-neuronal factor involvement in dyskinesia

Over the past decade, an accumulation of preclinical and clinical evidence has suggested that important non-neuronal morphological variables that appear to participate in the pathophysiology of LID are angiogenesis and alterations in blood flow. Using the 6-OHDA-lesioned rat, Westin and colleagues (2006) first demonstrated that in rats that developed LID there was proliferation of vascular endothelial cells and a significant increase in total blood vessel length. They also found downregulation of an endothelial barrier antigen on vessel walls and visible extravasation of serum albumin. These data indicated that in the brains of rats that developed LID there was an induction of angiogenesis as well as a compromise of the blood-brain barrier. Importantly, these changes were found to be not only specific to dyskinetic rats but also specific to nuclei of the basal ganglia (Westin *et al.*, 2006). An additional series of preclinical studies have investigated mechanisms of LID-associated vascular changes finding differential involvement of D_1R and D_2R (Lindgren *et al.*, 2009) and the involvement and potential therapeutic efficacy of angiotensin type 1 receptor blockade

(Munoz *et al.*, 2014). Congruent findings in both parkinsonian rats and PD patients further demonstrated that there is an upregulation of vascular endothelial growth factor associated with the microvascular changes involved with LID pathophysiology (Ohlin *et al.*, 2011). Alterations in cerebral vasculature and blood flow are uniquely regulated by synaptic activity to ensure that blood delivery matches neuronal energy needs (Ko *et al.*, 2015), and alterations in blood brain barrier occurs in several neurodegenerative disorders. However, as reviewed by Ko and colleagues (2015), a series of complex functional imaging studies involving PET (human studies) or microPET (rodent studies) imaging of [^{18}F]FDG as a marker of synaptic activity and [^{15}]H_2O for blood flow have revealed that there is an uncoupling of cerebral metabolic rate and rCBF that is uniquely and differentially effected in LID compared to non-LID parkinsonian subjects. While the impact of L-dopa in subjects expressing LID is CBF-cerebral metabolic rate uncoupling and compromise of blood brain barrier integrity, the exact mechanism by which these events occur and how these changes are linked to LID expression remains equivocal. As reviewed by Ko and colleagues (2015), L-dopa converted to DA binds to vascular receptors likely resulting in vasodilatation and increase in local blood flow. These authors speculate that the newly formed vessels may be supersensitive to DA and the resultant increase in rCBF after L-dopa administration might lead to "an increase in perfusion pressure, and a treatment state-dependent breach of blood brain barrier in brain regions characterized specifically by increased local dopa decarboxylase expression and comparatively large numbers of vascular DA receptors" (Ko *et al.*, 2015). Understanding the molecular triggers for vascular changes seen in dyskinetic subjects and why some individuals show a more pronounced dissociation of CBF- cerebral metabolic rate, angiogenesis and expression of LID will undoubtedly foster the development of new treatment strategies directed at ameliorating LID in PD.

Puzzlingly enough, the role of astrocytes in such complex pathological changes has almost remained untouched. The current concept of basal ganglia organization and function excludes the most numerous cells in the brain (Tsacopoulos and Magistretti, 1996). For decades, astrocytes have been regarded as passive partners of neurons in the central nervous system, but this view has been challenged and they are now integrated in the concept of "tripartite synapse". Indeed astrocytes have a multitude of processes that are intertwined within the neuropil ensheathing synaptic contacts, they possess receptors and reuptake sites for neurotransmitters, so they sense and integrate synaptic activity. Charron and co-workers therefore characterized anatomically the PD-related modifications in astrocytic morphology, the changes in astrocytic network connections and the consequences on the spatial

relationship between astrocytic processes and asymmetric synapses in normal and PD-like conditions in experimental and human PD (Charron *et al.*, 2014), unravelling a dramatic regulation of striatal astrocytosis supporting the hypothesis of a key role in (dys)regulating corticostriatal transmission. Such PD-related astrocytosis is not diminished by L-dopa treatment in non-dyskinetic or in dyskinetic experimental and human PD (Bortolanza *et al.*, 2014; Charron *et al.*, 2014), shedding light upon a possible role played by astrocytes in LID pathophysiology, notably upon the L-dopa-induced rise in inducible nitric oxide-synthase immunopositive astrocytes (Bortolanza *et al.*, 2014). Consistent with this finding, a number of pharmacological studies show that nitric oxide-synthase inhibition decreases AIMs in L-dopa-treated 6-OHDA lesioned rats (Bortolanza *et al.*, 2014; Padovan-Neto *et al.*, 2015; Takuma *et al.*, 2012) and dyskinesia in aphakia mice (Solis *et al.*, 2015), while such intervention induces akinesia or catalepsy in normal rodents (Del Bel *et al.*, 2004). That nitrinergic neurons participate to this action is envisioned as the main nitric oxide-synthase inhibitor is the 7-nitroindazole, a neuron-specific inhibitor of that enzyme. However, 7-nitroindazole treatment decreases the number of nitric oxide-synthase immunopositive astrocytes and the AIMs in the 6-OHDA-lesioned rat (Bortolanza *et al.*, 2014) suggesting that the drug specificity is not so great and that astrocytes might well be a major site for such development of nitrinergic transmission in the newly formed tripartite synapse.

5.5. Priming leads to LID

The phenomenon of "priming" has often been called into question to explain the onset of dyskinesia in PD patients on DA replacement therapy. Priming can be defined as the presence of neurochemical and functional aberrant modifications in the DA-denervated basal ganglia that eventually lead to the emergence of dyskinesia in response to the repeated administration of L-dopa or DA agonists (Jenner, 2008).

The features of priming have been extensively investigated in experimental models of PD, such as the MPTP-treated primate and the 6-OHDA-lesioned rat (Blanchet *et al.*, 2004; Jenner, 2003; Morelli *et al.*, 1989; Simola, 2007), although it is in the 6-OHDA-lesioned rat that the great majority of information on the behavioural and neurochemical correlates of priming has been obtained. In this model, priming is usually produced by means of a two-step administration of DAergic agonists, which includes an induction phase and an expression phase, the latter being the step where the effects of priming are evident (Morelli *et al.*, 1989). The manifestation of priming is behavioural, and consists in the emergence of a vigorous,

sensitized, contralateral rotational behaviour stimulated by a dose of a D_1R agonist that is otherwise ineffective in unprimed rats (Morelli *et al.*, 1989; Morelli, 1993). Drug-stimulated contralateral rotations in the 6-OHDA-lesioned rat are indicative not only of anti-parkinsonian effects but also of pro-dyskinetic potential (Lane, 2006) (but see (Lundblad *et al.*, 2002)); therefore, the sensitized rotational behaviour featuring priming was considered as an index of an abnormal drug-induced motor response (Morelli, 1993). In addition, several studies have shown that priming is associated with a series of neurochemical maladaptive modifications in the DA-denervated striatum that are similar to those observed in animal models of experimental dyskinesia elicited by the chronic administration of DA replacement therapy. These include changes in the production of cyclic adenosine monophosphate (cAMP), phosphorylation of DARPP-32, and expression of mRNAs encoding for the immediate early genes dynorphin, and glutamate acid decarboxylase 67 KDa (GAD67), which all critically regulate the activity of the striatal output neurons (Barone, 1994; Carta, 2003; Consolo, 1999; Crocker, 1998; Pinna, 1997; van de Witte, 1998). Interestingly, priming is best manifested when D_1R, but not D_2R, are selectively stimulated in the expression phase; moreover, priming is a time-dependent phenomenon, which is only fully expressed after a critical time from its induction has elapsed (Morelli *et al.*, 1989). On the basis of the evidence indicating that D_1Rs play a major role in the emergence of dyskinesia (Aubert *et al.*, 2005; Guigoni *et al.*, 2007), and considering that maladaptive changes produced by DA replacement therapy in the DA-denervated basal ganglia may require some time to develop and thus influence movement performance, the features of priming suggest that this phenomenon could mimic the initial events associated with drug-induced dyskinetic movements.

Further support to this view comes from the finding that both these phenomena are attenuated by the blockade of glutamate receptors, either ionotropic or metabotropic (Hadj Tahar *et al.*, 2004; Morelli, 1990b; Morin, 2013; van de Witte, 2002). In this regard, it is also noteworthy that cortical glutamatergic neurons form synapses onto striatal MSNs of the striatonigral and striatopallidal pathways, and that these synapses demonstrate functional long term changes, with the occurrence of LTP and LTD (Calabresi *et al.*, 2007; Kreitzer, 2008). Abnormalities in synaptic plasticity in the DA-denervated striatum have been suggested to play a critical role in the genesis of dyskinesia, by favouring a pathologic form of motor learning following the stimulation of DA receptors by DA replacement therapy (Picconi *et al.*, 2003; Pisani, 2005). Recent studies have shown that priming in the 6-OHDA-lesioned rat may be relevant to the aberrant modifications in motor learning thought to occur in PD. Thus, it has been demonstrated that the performance of rotations during priming induction is necessary for the

manifestation of the sensitized motor response on priming expression, as this effect was completely abolished when primed rats were prevented from rotating in response to the initial DAergic challenge (Frau, 2013; Simola, 2009). This finding could indicate that the performance of drug-induced movements upon a first pharmacological stimulation of DA receptors may generate an aberrant motor memory trace in the DA-denervated striatum, and that this trace may eventually favour the emergence of an abnormal motor response following a later DAergic pharmacological challenge (Simola, 2009). Of further relevance to this hypothesis, primed 6-OHDA-lesioned rats that could rotate during priming induction, but not rats that were prevented from doing so, displayed a selective increase in the mRNA encoding for the immediate early gene *zif-268* in dynorphin-positive neurons of the striatonigral pathway when challenged with a pro-dyskinetic D_1R agonist on priming expression (Frau, 2013). Remarkably, it has been demonstrated that the expression of *zif-268* is not only induced by drugs with a high dyskinetic potential (Carta, 2010), but is also enhanced in certain forms of learning, or following LTP (Bozon, 2002; Lanahan, 1998; O'Donovan, 1999 ; Tischmeyer, 1999), further supporting the relevance of the results obtained in primed 6-OHDA-lesioned rats to aberrant motor learning.

As mentioned in section (5.4.1), the DAergic denervation itself is the major effector of the maladaptive neurochemical and functional changes that underlie dyskinesia and priming may not be an absolute requirement for their manifestation (Nadjar *et al.*, 2009). This view is supported in the first place by earlier data obtained in 6-OHDA-lesioned rats showing that the neurochemical effects of priming take place only in the DA-denervated striatum, but not in the intact striatum (Consolo, 1999; Morelli, 1990a). Furthermore, it has been observed in the same model that sensitized rotations induced by a D_1R agonist may occur even without prior DAergic stimulation, if this effect is evaluated after a sufficient length of time (e.g. 60 days) from the DAergic denervation (Morelli *et al.*, 1989), thus allowing maladaptive striatal changes to take place. Experiments in MPTP-treated primates have demonstrated that the first administration of L-dopa elicits proteomic changes in the striatum that are superimposable to those observed after chronic exposure to the drug (Scholz *et al.*, 2008). In line with this, studies in rats (Andersson *et al.*, 1999; Cenci *et al.*, 1998; Putterman *et al.*, 2007; Winkler *et al.*, 2002), mice with 6-OHDA lesions (Darmopil *et al.*, 2009; Ding *et al.*, 2011; Won *et al.*, 2014) and aphakia mice with developmental loss of selective nigrostriatal projection (Ding *et al.*, 2007; Li, 2013) have shown that dyskinetic movements can be observed even after the first exposure to either L-dopa or a D_1R agonist, without the need for a previous priming and further increase with repeated exposure. Whether priming is a phenomenon that exists by

itself, being associated with maladaptive neurochemical and functional changes, or it merely consists of the speeding up of aberrant changes that are primarily arising from the DAergic denervation has still to be ascertained. Nevertheless, the possibility may exist that priming associated with DA replacement therapy would affect the propensity of the pharmacologic treatment to elicit dyskinetic movements. Thus, drugs with a marked D_1R component (e.g. L-dopa and apomorphine) have been shown to be the most effective in inducing priming in experimental models, and are also those with the higher dyskinetic potential in the clinical setting, e.g. the stopped ABT-431 D_1R agonist (Rascol *et al.*, 2001b). Conversely, drugs that chiefly stimulate D_2R, e.g. PPX and ropinirole, are less effective in inducing priming, and also have a lower dyskinetic potential, as indicated by clinical evidence showing that the treatment with these agents induces milder dyskinesia than those elicited by L-dopa (Bagetta *et al.*, 2012).

5.6. Presynaptic component of LID pathophysiology

5.6.1. Handling of L-dopa in the striatum

Whereas alterations in signalling cascade of striatal MSNs are ultimately responsible for the appearance of the abnormal motor response to L-dopa, as they affect gene expression, an increasing body of evidence shows that these alterations are secondary to changes in the presynaptic compartment (relative to the striatal neurons), which are induced by the progressive loss of the DAergic terminals. Indeed, progression of DA neuron degeneration represents the first and most important risk factor for development of dyskinesia. Accordingly, L-dopa does not usually induce dyskinesia during the first few years of administration in patients, when sufficient spared DA terminals are present; similarly, partial DA lesioned animals are resistant to development of LID, while complete DA lesioned animals can present dyskinesia already at the first L-dopa administration. Ulusoy and colleagues have confirmed in an elegant study that the state of the nigrostriatal DAergic compartment determines the susceptibility of rats to the induction of LID; in fact, rats in which the DA levels were reduced by about 70% using a short-hairpin RNA-mediated knockdown of the TH enzyme (shTH), without affecting the integrity of presynaptic terminals, were refractory to LID development (Ulusoy *et al.*, 2010). Interestingly, L-dopa failed to induce dyskinesia in shTH-treated rats even when they were previously rendered dyskinetic by sub-chronic apomorphine treatment; this suggests that the preserved presynaptic DAergic terminals provide a buffering system for the exogenously administered L-dopa, and

mediate regulated release and reuptake of DA resulting in physiological DA receptor stimulation at striatal neurons (Carta and Bezard, 2011; Ulusoy *et al.*, 2010). That said, a report by Pons and colleagues (2013) investigated the common phenomenon of LID in patients with TH deficiency, a population of individuals with a structurally intact nigrostriatal DA system. TH deficiency is an autosomal recessive disorder that results in a deficiency in the production of DA, noradrenaline, and epinephrine, which is also treated with L-dopa (Pons *et al.*, 2013). In contrast to the incidence of LID in PD being 30 – 90%, the incidence in TH-deficient patients is 100% with emergence occurring within the first few days to months of onset of treatment (Pons *et al.*, 2013). The occurrence of LID in these patients suggests that while DA depletion is a critical factor involved in the development of LID, loss of presynaptic terminals is not. In a commentary on the report by Pons, Bezard and colleagues (2013b) discuss that data from these dyskinetic TH-deficient patients suggests a scenario where LID may be primarily related to postsynaptic mechanisms including DA receptor super sensitivity and downstream abnormalities in intracellular signalling cascades within MSNs. The critical question posed by Bezard et al. (2013b) is whether dyskinesia in PD and TH-deficiency patients are induced by a similar or by a different mechanism, reasoning that it is possible that LID may develop in different ways, not only by disturbed presynaptic DA release and synaptic kinetics but also by abnormal receptor stimulation.

In PD, there is a well-established relationship of LID to loss of striatal DA terminals. The ability to properly handle exogenous L-dopa is dramatically diminished as the DA neuron degeneration progresses, and fewer and fewer spared DA terminals can mediate L-dopa conversion and feedback control release of DA. Recent experimental evidence indicate that when most of DAergic neurons have degenerated, 5-HT neurons come to play a major role in conversion of L-dopa to DA, and in the appearance of AIMs (Carta and Bezard, 2011; Carta *et al.*, 2007; Munoz *et al.*, 2008) (**Figure 3**). In fact, it is known since early studies that 5-HT neurons are able to take up exogenously administered L-dopa, convert it to DA (Tison *et al.*, 1991), and store it into synaptic vesicles (Arai *et al.*, 1995; Arai *et al.*, 1994); this is due to the presence of the same machinery expressed by DAergic neurons, i.e., the AADC enzyme and VMAT transporter. 5-HT neurons are expected to contribute to DA release also in early stages of disease; such contribution may initially be beneficial due to the presence of the spared DA terminals that can buffer 5-HT neuron-derived DA and avoid excessive DA receptor stimulation (Carta and Bezard, 2011; Carta *et al.*, 2010). In support of this view, it has been shown that a 30% reduction of striatal L-dopa-derived DA release is induced upon removal of 5-HT nerve fibers in intact animals (Nevalainen *et al.*, 2013a).

By contrast, in a situation of advanced DA denervation, the 5-HT neurons become the main site of L-dopa conversion to DA (**Figure 3**). In fact, removal of 5-HT innervation by 5,7-dyhydroxytryptamine administration reduced L-dopa-derived extracellular DA levels by about 80% in the striatum of complete DA-lesioned rats (Tanaka *et al.*, 1999). However, the loss of spared DAergic terminals, which could buffer 5-HT neuron-derived DA release, triggers the appearance of dyskinesia due to the absence of a feedback control mechanism for DA release on 5-HT neurons (**Figure 3**). In fact, DAergic terminals express the D_2R and the DAT, which can regulate the firing rate of these neurons and the reuptake of the neurotransmitter from the synaptic cleft, respectively. The absence of a mechanism of fine regulation of synaptic DA levels in 5-HT neurons makes 5-HT neuron-derived DA release uncontrolled, contributing to swings in synaptic DA levels, and promoting pulsatile stimulation of striatal postsynaptic DA receptors (Carta and Bezard, 2011; Mosharov *et al.*, 2015) (**Figure 3**). In agreement with this view, removal of striatal 5-HT terminals by a selective toxin is able to completely suppress LID in 6-OHDA-lesioned rats (Carta *et al.*, 2007; Eskow *et al.*, 2009).

Silencing of 5-HT neurons firing can also be achieved by pharmacological targeting of 5-HT auto-receptors. According to a major role of 5-HT neurons in mediating DA release and induction of LID, activation of 5-HT_{1A} receptors (which are mostly located on cell bodies) and/or 5-HT_{1B} receptors (located on axon terminals) was shown to produce a dose dependent reduction of LID. In particular, combination of 5-HT_{1A} and 5-HT_{1B} receptor agonists (8-OH-DPAT and CP-94253, respectively) was found to induce a synergistic effect, with suppression of LID at ineffective doses of the individual drugs (Carta *et al.*, 2007; Munoz *et al.*, 2009; Munoz *et al.*, 2008). Reduction of L-dopa-derived DA release was confirmed to account for the anti-dyskinetic effect in following microdialysis (Lindgren *et al.*, 2010) and PET-imaging rodent studies (Nahimi *et al.*, 2012). However, significant reduction of L-dopa-induced DA release was also seen with selective targeting of 5-HT_{1A} receptors (Iderberg *et al.*, 2015b; Kannari *et al.*, 2001).

Dampening of 5-HT release by 5-HT_1 receptor agonists did not only reduce LID, but it has also been shown to prevent induction of postsynaptic alterations at striatal neurons, such as increased expression of ΔFosB and altered NMDA receptor subunits distribution (Munoz *et al.*, 2008).

It should be noted that 5-HT_1 receptors are not only expressed presynaptically, as auto-receptors, but are also present postsynaptically in non-5-HT neurons; activation of these receptors has been shown to reduce striatal glutamate and GABA release and produce anti-

dyskinetic effect (Bishop *et al.*, 2009; Dupre *et al.*, 2008; Zhang *et al.*, 2008). However, it is worth pointing out that combination of 8-OH-DPAT and CP-94253, or administration of the 5-$HT_{1A/1B}$ agonist eltoprazine at doses able to suppress LID, were shown to be ineffective against dyskinesia induced by apomorphine, suggesting that, at least at moderate doses of 5-HT_1 receptor agonists, the anti-dyskinetic effect is due to activation of 5-HT auto-receptors (Bezard *et al.*, 2013c; Munoz *et al.*, 2009).

Experimental 5-HT_1 receptor agonists (8-OH-DPAT and CP-94253) induced striking anti-dyskinetic effect not only in parkinsonian rats, but also in MPTP-treated dyskinetic macaques, without affecting disability score (Munoz *et al.*, 2008), suggesting a possible clinical application of this approach to treat dyskinesia. Similar effect on LID was seen with the mixed 5-$HT_{1A/1B}$ receptor agonist eltoprazine (Bezard *et al.*, 2013c). Albeit partial reduction of the therapeutic efficacy of L-dopa was seen in those animals following eltoprazine administration, this drug is currently under clinical evaluation for treatment of LID.

Interestingly, the first single-single dose, double-blind study in 22 dyskinetic patients has found a significant reduction of LID without exacerbation of motor disability (Svenningsson *et al.*, 2015). However, it should be noted that the reduction of LID in the latter study was not superior to what observed with amantadine in previous clinical studies as pointed in a commentary of the above study (Bezard and Carta, 2015). Therefore, a number of issues remain to be addressed in future studies: first, whether escalation of the eltoprazine doses and/or modification of the time of administration relative to L-dopa could improve the anti-dyskinetic efficacy; second, whether eltoprazine would remain efficacious after weeks of daily treatment; indeed, it is possible that long-term administration may lead to autoreceptor desensitization, and therefore to reduced therapeutic efficacy. Although no tolerance was observed after 6 weeks of daily eltoprazine administration in rodents (Bezard *et al.*, 2013c), the situation may be different in higher species; in fact, the 5-HT autoreceptors are suggested to desensitize upon chronic administration of selective 5-HT reuptake inhibitors (SSRIs), which explains the delayed efficacy of SSRIs in depressed patients, where alleviation of symptoms can be seen only after 2–4 weeks of daily treatment (Hjorth *et al.*, 2000; Pineyro and Blier, 1999). Therefore, it will be extremely important to verify whether similar effects are induced by chronic eltoprazine. This is a critical issue in determining the clinical feasibility of this approach for dyskinesia.

Clinical feasibility of pharmacological silencing of 5-HT neurons to treat dyskinesia in patients raised concerns not only for possible induction of autoreceptor tolerance, but also because it may reduce the therapeutic efficacy of L-dopa, as seen in preclinical studies

(Bezard *et al.*, 2013a; Bezard *et al.*, 2013c). In fact, in advanced stages of disease, 5-HT neurons may not only be responsible for dyskinesia, but also for the residual therapeutic effect of L-dopa, as they represent the main site of conversion to DA; thus, in a situation of advanced DAergic degeneration, reduction of LID may be unavoidably accompanied by parallel reduction of the therapeutic effect. However, it should be noted that Iderberg and co-workers have recently demonstrated that selective targeting of 5-HT1 receptors can yield significant reduction of dyskinesia without reducing the therapeutic effect of L-dopa in parkinsonian rats (Iderberg *et al.*, 2015c). Last but not least, the effect of chronic silencing of 5-HT neurons on mood should be carefully evaluated, particularly as advanced PD patients often present mood disturbances.

An interesting alternative to selective 5-HT_1 receptor agonists may be represented by drugs acting on the 5-HT transporter. Indeed, selective 5-HT transporter inhibitors, such as fluoxetine and citalopram, have been shown to reduce dyskinesia with similar efficacy as 5-HT_1 receptor agonists, without affecting the therapeutic efficacy of L-dopa in rats (Bishop *et al.*, 2012; Conti *et al.*, 2014). Thus, as suggested by two recent works, compounds that indirectly facilitate 5-HT autoreceptor activation may be more effective therapeutics compared to 5-HT_1 receptor agonists as they might reduce LID while better preserving therapeutic action of L-dopa (Lindenbach *et al.*, 2015; Tronci *et al.*, 2015). Moreover, while SSRIs appear to exert their action by activation of 5-HT_1 auto-receptors, as seen with selective 5-HT_1 receptor agonists, they may provide the advantage to dampen dyskinesia without reducing synaptic 5-HT levels. This would be mostly important as SSRIs are widely used to treat symptoms of depression in parkinsonian patients. Moreover, inhibition of neurotransmitter reuptake by 5-HT transporter blockade may also reduce swings in extracellular DA levels. It remains to be established why no anti-dyskinetic effect has been reported in patients under SSRIs treatment, despite their extensive use also in dyskinetic subjects; thus, it is possible that the anti-dyskinetic mechanism is triggered at doses of drugs that are higher than those used to treat depression, as recently suggested by Fidalgo and co-workers, who found full suppression of LID by administration of a high dose of citalopram to MPTP-treated macaques (Fidalgo *et al.*, 2015). Such view should however be balanced by an intriguing clinical finding (Mazzucchi *et al.*, 2014) reporting that SSRI exposure in patients with PD protected them from LID, but showed that SSRI exposure not only delayed LID onset but also appeared to reduce the LID severity.Clinical investigations are warranted to clarify this issue.

Whereas clinical feasibility of 5-HT neuron targeting remains to be fully proved, an imaging

study has provided important evidence that the 5-HT system may play similar role in patients as in animal models. In this study, in agreement with a previous post-mortem investigation (Rylander *et al.*, 2010b), PD patients with LID were shown to have relative preservation of 5-HT terminals compared to patients with stable response to L-dopa, which correlated with the severity of LID. In patients with LID the same L-dopa dose induced significantly higher striatal synaptic DA levels than in non-dyskinetic patients, in agreement with an earlier PET study (de la Fuente-Fernandez *et al.*, 2004). Most importantly, the 5-HT_{1A} receptor agonist buspirone, orally administered 15 min before L-dopa, significantly reduced the L-dopa-evoked rise in striatal synaptic DA levels and attenuated LID (Politis *et al.*, 2014). Although previous studies have already reported a partial reduction of LID by buspirone administration (Bonifati *et al.*, 1994), this study provides the first direct evidence that such reduction is linked to diminished synaptic striatal DA release.

Recently, Smith and co-workers have suggested, in a PET imaging study, a possible pro-dyskinetic role also for the pallidal 5-HT innervation (Smith *et al.*, 2015). In fact, in this study, PD patients without LID showed a significant reduction of pallidal 5-HT transporter binding compared with healthy controls, while this was within the normal range in dyskinetic patients. Levels of pallidal 5-HT transporter binding correlated positively with severity of LIDs. Moreover, ^{11}C-raclopride PET detected a significant rise in pallidal synaptic DA levels of patients with LID after a L-dopa challenge but not in patients with a stable response. Thus, the increased pallidal 5-HT function may result in further dysregulation of thalamocortical signals and therefore contribute to the expression of dyskinesias (Smith *et al.*, 2015).

Overall, an extensive body of evidence points to DA released as false transmitter from 5-HT neurons as the single most important determinant of the postsynaptic alterations that characterize LID development (Carta and Bezard, 2011; Carta and Tronci, 2014; Cenci, 2014).

5.6.2. Handling of L-dopa outside the striatum

Experimental evidence in animal models suggests that false transmitter release of DA from 5-HT neurons is not restricted to the striatum. In fact, L-dopa induces an ectopic release of DA in a pattern that follows the widespread innervation of the entire forebrain by 5-HT raphe neurons (Azmitia and Segal, 1978), as it was demonstrated using a multisite microdialysis approach with four probes implanted simultaneously in the ipsilateral 6-OHDA-lesioned side (Navailles *et al.*, 2013). The increase in DA release induced by an acute administration of L-

dopa also occurs in the prefrontal cortex, hippocampus and SNr (Navailles *et al.*, 2010a; Navailles *et al.*, 2010b, 2011a). This extrastriatal DA release is also sensitive to 5-HT lesion, 5-HT pharmacological manipulation and high-frequency stimulation of the STN, a surgical approach in PD able to inhibit 5-HT neuronal firing (Navailles *et al.*, 2010a; Navailles *et al.*, 2010b; Temel *et al.*, 2007). All these brain regions display various levels of 5-HT terminal density and express DA receptors (Seeman, 1980) on which the newly synthesized DA can exert its numerous effects and promote DA transmission. The magnitude of the increase in extracellular DA concentration induced by a therapeutic dose range of L-dopa (3-12 mg/kg) is far higher in extrastriatal brain regions than in the striatum compared to the physiological situation, due to the denser serotonergic innervation (Navailles *et al.*, 2010b). DA released from 5-HT neurons in extrastriatal territories may contribute to both therapeutic efficacy of L-dopa and side effects.

5.7. Impact of L-dopa on 5-HT transmission and relationship to LID

L-dopa, by entering 5-HT neurons, mediates numerous changes in 5-HT neuron homeostasis (Navailles *et al.*, 2011a; Navailles and De Deurwaerdere, 2012). The production of massive amounts of DA has tremendous impact on 5-HT function at the level of the metabolism, the activity and the morphology of 5-HT neurons (Navailles and De Deurwaerdere, 2012). Some changes in 5-HT indexes have been associated with the emergence of LID and should be taken into consideration to better control 5-HT transmission and L-dopa's side effects (Fox *et al.*, 2009; Navailles and De Deurwaerdere, 2012; Scholtissen *et al.*, 2006).

Most studies have shown that L-dopa reduces striatal 5-HT tissue concentrations in chronic L-dopa-treated rats (Carta *et al.*, 2007; Gil *et al.*, 2010; Gil *et al.*, 2011; Lindgren *et al.*, 2010; Navailles *et al.*, 2011a) although a trend toward an increase was also reported (Carta *et al.*, 2006). These differences may account for the time of sacrifice after the last L-dopa administration, i.e. 1h, 3h, 24h or more. When considering peak-dose dyskinesia, it is consistently observed that L-dopa administered within 1 to 3 hours before sacrifice decreases 5-HT tissue levels, while increasing DA tissue levels in the striatum (Carta *et al.*, 2007; Gil *et al.*, 2011; Navailles *et al.*, 2011a). According to these opposite 5-HT/DA changes (Gil *et al.*, 2010), the severity of LID is both correlated with striatal DA (positively) and 5-HT tissue levels (negatively and more stringently than DA levels) (Gil *et al.*, 2011). Moreover, an acute treatment with the serotonin precursor 5-hydroxytryptophan, which increases 5-HT and decreases DA tissue levels induced by L-dopa, is able to reduce the appearance of LID in the

AIM rat model (Tronci *et al.*, 2013) as well as in the dyskinetic macaque model (Ko *et al.*, 2014a). Some studies have found a positive correlation between LID and 5-HT tissue levels in the striatum (Eskow *et al.*, 2009) and prefrontal cortex (Carta *et al.*, 2006) or no correlation between LID and 5-HT tissue levels in the striatum (Carta *et al.*, 2006). In these studies, biochemical measurements were performed within a timeframe that does not allow for a direct correlation with LID, i.e. either 72h (Carta *et al.*, 2006) or one week (Eskow *et al.*, 2009) after the last L-dopa administration. Regardless of this timeframe, tissue 5-HT levels in the striatum and cortex, but not the SNr, are systematically found to be higher in dyskinetic versus non-dyskinetic rats (Carta *et al.*, 2007; Gil *et al.*, 2011; Lindgren *et al.*, 2010).

When considering 5-HT extracellular levels and LID, two parameters emerge as critical indicators, i.e. the reactivity of 5-HT terminals to L-dopa challenge (indexed by 5-HT release) and basal 5-HT extracellular levels after chronic L-dopa treatment. Firstly, the reactivity of 5-HT terminals is modified in a region-dependent manner that echoes the region-dependent ability of L-dopa to increase DA release after a chronic L-dopa treatment (see above; (Navailles *et al.*, 2011a). Indeed, the lack of sensitivity of striatal 5-HT terminals to L-dopa, i.e. no change of 5-HT release after acute or chronic treatment (Lindgren *et al.*, 2010; Navailles *et al.*, 2010b, 2011a; Navailles *et al.*, 2013), is associated with a relatively preserved effect on DA release. On the other hand, the highest sensitivity of 5-HT terminals to L-dopa observed in the SNr, i.e. potentiation of L-dopa-induced decrease in 5-HT levels after chronic treatment (Navailles *et al.*, 2011a), leads to the most profound loss of efficacy of L-dopa to increase DA release (Navailles *et al.*, 2011a). Secondly, as for 5-HT tissue levels, basal 5-HT extracellular levels are higher in the striatum, but not SNr, of awake dyskinetic compared to non-dyskinetic animals (Lindgren *et al.*, 2010). The authors suggested that the denser 5-HT innervation in the striatum of dyskinetic animals could account for the higher basal 5-HT levels.

Among the different 5-HT indexes explored in relation to LID, the strongest correlations were found between 5-HT tissue levels or 5-HT terminal density and AIMs scores, in line with the idea that the status of the presynaptic DA releasing compartment, namely the integrity of 5-HT neurons, is a critical determinant of both induction and maintenance of LID. The region-dependent effects of L-dopa on 5-HT and DA releases may reflect the regional heterogeneity of 5-HT terminals characterized by the variable expression of numerous regulatory proteins (Navailles *et al.*, 2011b). Beyond this intrinsic 5-HT neuronal heterogeneity, chronic L-dopa treatment by itself is known to modify the morphology of these 5-HT neurons and the

synaptic plasticity in various brain regions (Berthet *et al.*, 2009; Picconi *et al.*, 2010; Picconi *et al.*, 2005; Prescott *et al.*, 2009; Rylander *et al.*, 2010b; Zeng *et al.*, 2010).

5.8. Impact of L-dopa on amino acids: relationship to LID

There are many relationships between LID and amino acids. Anatomically, DA and 5-HT receptive cells are GABAergic neurons, interneurons and glutamatergic neurons. In the basal ganglia, it is postulated that the multiple changes occurring in this network and the increased DA function induced by L-dopa concur to decrease the activity of output GABAergic neurons of the SNr and the GPi (Albin *et al.*, 1989; DeLong, 1990; Nambu, 2008). Clinically, both STN-DBS and GPi-DBS efficiently reduce LID in humans (Bejjani *et al.*, 2000; Krack *et al.*, 2003; Krack *et al.*, 1999; Krack *et al.*, 1997). In animal models, the data are mitigated regarding the efficacy of STN-DBS on LID reporting an exacerbation (Oueslati *et al.*, 2007), a reduction (Simonin *et al.*, 2009) or no alteration (Gubellini *et al.*, 2006).

These differences could account for the fact that the changes of glutamate release induced by L-dopa depend on the dose, the species and the brain region examined. The acute administration of L-dopa at 25 mg/kg increases glutamate release measured by intracerebral microdialysis in the striatum of naïve and 6-OHDA rats (Jonkers *et al.*, 2002). After chronic L-dopa treatment, basal extracellular glutamate levels are consistently increased in the striatum and/or SNr, and associated with an increase in the glial glutamate transporter (Dupre *et al.*, 2011; Robelet *et al.*, 2004). Specifically in dyskinetic animals, basal extracellular levels of glutamate are similar to those reported in non-dyskinetic rats. However, differences in glutamatergic reactivity are observed on glutamate release induced by various doses of L-dopa (4, 12 or 100 mg/kg) or a depolarizing stimulus (Dupre *et al.*, 2011; Nevalainen *et al.*, 2013b; Robelet *et al.*, 2004). It has been reported in peak-dose LID that glutamate release in the GP and SN was not altered by 15 mg/kg L-dopa in mice while it was enhanced in the SNr, but not the GP or dorsolateral striatum of rats after 6 mg/kg (Bido *et al.*, 2011; Mela *et al.*, 2012). Nevertheless, riluzole, a glutamate release inhibitor alleviates established AIMs in the 6-OHDA-lesioned mouse (Lundblad *et al.*, 2005) and rat (Dekundy *et al.*, 2007). In clinical trials, the effects of riluzole or another glutamate release inhibitor naftazone are mitigated (Bara-Jimenez *et al.*, 2006; Merims *et al.*, 1999; Rascol *et al.*, 2012). Overall, these studies bring evidence for a hyperactivity of glutamatergic neurons in response to chronic L-dopa that may operate in a region-dependent manner.

Accordingly, L-dopa is expected to change GABA release in the basal ganglia (Bezard *et al.*, 2001d; Cenci, 2007b). In dyskinetic mice, L-dopa enhances GABA release in the SNr and GP (Bido *et al.*, 2011). Although this effect is reduced by the non-selective NMDA receptor antagonist amantadine, L-dopa does not enhance glutamate extracellular levels in both regions (Bido *et al.*, 2011). In dyskinetic rats, peak-dose LID are also associated with an increase in GABA release in the SNr (but not in the striatum) that is prevented by amantadine in line with a concomitant surge in nigral glutamate levels (Mela *et al.*, 2012; Mela *et al.*, 2007). These data suggest that the STN may facilitate the activity of the striatonigral GABAergic pathway at terminal level. Indeed, STN-DBS induced forelimb dyskinesia associated with glutamate release in the SNr of hemiparkinsonian rats (Boulet *et al.*, 2006). Interestingly, STN-DBS at a lower intensity that did not induce forelimb dyskinesia, also increased nigral GABA release but without altering glutamate release (Boulet *et al.*, 2006). An enhanced reactivity of GABAergic terminals in the SNr of dyskinetic animals, as also proposed from in vitro studies (Rangel-Barajas *et al.*, 2008) is compatible with a consequent inhibition of the nigrothalamic GABAergic tone (Albin *et al.*, 1989; Chevalier and Deniau, 1990). Accordingly, L-dopa decreases GABA release in the thalamus of 6-OHDA rats or MPTP-treated monkeys that displayed severe dyskinesia after 6 months treatment with L-dopa (Marti *et al.*, 2007; Porras *et al.*, 2014). However, it remains to be determined whether the decrease in thalamic GABA release induced by L-dopa is magnified in case of peak-dose LID.

In conclusion, the impact of neurotransmitters on peak-dose LID is a complex mechanism regarding the neurochemical environment created by L-dopa (Navailles and De Deurwaerdere, 2012). It requires a synaptic increase in DA release, even modest, from 5-HT terminals. High magnitude of variations in synaptic DA levels could favour the development of LID. Such swings and/or aberrant release of DA from L-dopa may occur in many brain regions other than the striatum. This is an important point because LID is associated with changes of cellular activity in sensorimotor, associative and limbic territories (Bastide *et al.*, 2014b; Guigoni *et al.*, 2005c). L-dopa also alters 5-HT extracellular levels directly and in a region-dependent manner as well as amino acids transmission. Notably, LID is associated with a higher GABA release in the SNr and a lower GABA release in the thalamus. Regarding the presynaptic release of other neurotransmitters, some preclinical studies indirectly suggest that peak-dose LID could also be associated with putative modifications of release in acetylcholine (Di Chiara *et al.*, 1994; Zhang *et al.*, 2013a), noradrenalin (Delaville *et al.*, 2011), opioidergic peptides or endogenous cannabinoid reactivity (Huot *et al.*, 2013). Such predictions are expected to be validated soon since the behavioural evaluation of LID in

animals has been considerably improved in the past years (see above) and the *in vivo* assessment of neurochemical environment has benefited from the coupling of intracerebral microdialysis with powerful neurochemical method analysis (Cenci and Ohlin, 2009; Navailles *et al.*, 2013).

5.9. Postsynaptic changes in striatal medium spiny neurons

5.9.1. LID is associated with an increased IEG expression

The IEGs are a class of genes rapidly transcribed in response to an external stimulus (McClung *et al.*, 2004; Okuno, 2011). Although there are a lot of genes potentially involved in LID, the IEG encoding the transcription factor FosB has received particular attention. Indeed, FosB and, especially, its alternatively spliced isoform called ΔFosB are highly expressed in the dorsolateral striatum of dyskinetic monkeys and rodents (Andersson *et al.*, 1999; Bastide *et al.*, 2014b; Berton *et al.*, 2009; Cenci and Konradi, 2010; Cenci *et al.*, 1999; Feyder *et al.*, 2011; Feyder *et al.*, 2014; Fisone and Bezard, 2011; McClung *et al.*, 2004). In rodents, increased ΔFosB expression is restricted to dMSNs (Andersson *et al.*, 1999; Darmopil *et al.*, 2009; Fasano *et al.*, 2010; Feyder *et al.*, 2014) where activation of extracellular signal-regulated protein kinase (ERK) is also occurring (Darmopil *et al.*, 2009; Santini *et al.*, 2009a). Indeed, activation of ERK and of its nuclear downstream effector, mitogen- and stress-activated kinase 1 (MSK1), have been involved in the increase in ΔFosB expression associated to LID (Fasano *et al.*, 2010; Fasano and Brambilla, 2011; Feyder *et al.*, 2014). As striatal ΔFosB immunoreactivity is correlated with the severity of LID in rodents (Andersson *et al.*, 1999; Bastide *et al.*, 2014b; Feyder *et al.*, 2014; Pavon *et al.*, 2006), enhanced expression of ΔFosB appears to be causally related to the development of dyskinesia. Thus, striatal infusion of a *fosB* anti-sense oligonucleotide attenuates the development of AIMs over chronic course of L-dopa treatment in the rat (Andersson *et al.*, 1999). In order to regulate the transcription of its targets genes, ΔFosB must form heterodimers with a member of the Jun transcription factor family, most commonly JunD. In the striatum of dyskinetic rats, ΔFosB and JunD were found to be the main contributors to DNA-protein complexes containing CREB responsive elements (CRE) or activator protein 1 (AP-1) enhancers (Andersson *et al.*, 2001). The importance of ΔFosB/JunD heterodimers to the development of LID was demonstrated by Berton and collaborators (Berton *et al.*, 2009). In this study, the authors showed that overexpression of a truncated variant of JunD (ΔJunD),

which acts as a dominant negative inhibitor of ΔFosB, dramatically reduced the severity of LID (Berton *et al.*, 2009). Using a selective inactivation procedure, a recent study further demonstrated both in rat and macaque that the electrical activity of striatal FosB/ΔFosB neurons mediates LID and also blunts the anti-parkinsonian effect of L-dopa (Engeln *et al.*, 2014a). Conversely, in the rat, viral vector-induced overexpression of ΔFosB exacerbates LID (Cao *et al.*, 2010). In line with these observations, it has been recently shown in mice that overexpression of ΔFosB induced specifically in the striatonigral dMSNs, exacerbates LID. In contrast, functional inactivation of ΔFosB in the same neuronal population reduces dyskinesia (Feyder *et al.*, 2014).

Zif268 (or NGFI-A/Krox24/Egr1), another IEG coding for a transcription factor, has been involved in LID pathophysiology. L-dopa administration increases zif268 in the striatum (Bastide *et al.*, 2014b) with an enhanced expression of zif268 mRNA in both striatopallidal and striatonigral MSNs (Feyder *et al.*, 2011). Interestingly, repeated administration of L-dopa to 6-OHDA-lesioned rats normalizes the levels of zif268 mRNA in neurons of the indirect pathway, but not in those of the direct pathway (Carta *et al.*, 2005). The lack of normalization of zif268 expression in the dMSNs may be due to the persistent activation of ERK observed in these cells in association with dyskinesia (Gerfen *et al.*, 2008; Lebel *et al.*, 2010; Pavon *et al.*, 2006; Santini *et al.*, 2007; Westin *et al.*, 2007).

Zif268 promotes the expression of the activity-regulated cytoskeletal-associated protein ARC (or arg3.1) (Li *et al.*, 2005a), an IEG involved in synaptic plasticity (Bramham *et al.*, 2008). Interestingly, LID is also accompanied by increased ARC expression in the striatum (Bastide *et al.*, 2014b; Sgambato-Faure *et al.*, 2005). In the hippocampus, zif268-induced expression of ARC is involved in the induction of the late phase of LTP (Li *et al.*, 2005a). Therefore, it is possible that the persistent overexpression of zif268 and ARC is involved in the suppression of depotentiation at corticostriatal synapses, observed in association with LID (cf. above) (Picconi *et al.*, 2003).

5.9.2. Gene expression signature associated to LID

To date, very few studies have characterized the pattern of gene expression associated with LID. Basically, four main studies have explored this issue in rodents by using a microarray transcriptomic approach; two of them in the rat model of PD (El Atifi-Borel *et al.*, 2009; Konradi *et al.*, 2004) and two more recent ones in 6-OHDA-lesioned mice (Charbonnier-Beaupel *et al.*, 2015; Heiman *et al.*, 2014). Konradi and collaborators examined the pattern of

striatal messenger RNA expression of over 8000 genes in a rat model of PD and LID (Konradi *et al.*, 2004). The authors approached this issue by comparing 6-OHDA-lesioned rats chronically treated with saline or L-dopa, and subdivided the L-dopa-treated animals into dyskinetic and non-dyskinetic cases. The striatum of dyskinetic rats showed a profile of increased transcriptional activity of GABAergic neurons, accompanied by changes in a gene network involved in calcium-dependent signaling, with a particular upregulation of genes involved in calcium homeostasis. A dysregulation of genes involved in structural and synaptic plasticity was also observed. Finally, the pattern of gene expression in dyskinetic rats pointed to an imbalance between high metabolic demand and a reduced capacity for energy production in the striatum.

Using a similar rat model, El Atifi-Borel and collaborators compared the effects of acute versus long-term L-dopa treatment on the profiles of striatal gene expression in the DA-depleted striatum, examining nearly 5000 genes (El Atifi-Borel *et al.*, 2009). Acute and chronic treatments regulated a common set of 16 genes mainly implicated in signal transduction, transcription, translation, homeostasis processes and synaptic transmission. The transcriptomic response was enhanced by long-term L-dopa treatment. The main differences between the two treatments include genes involved in protein synthesis, metabolism, cell proliferation, neurite outgrowth and synaptogenesis. Long-term L-dopa administration was thus proposed to be associated with structural cellular alterations in the striatum. However, in this study, the gene changes were not directly correlated to dyskinetic behavior.

A recent elegant study used a combination of a hemiparkinsonian mouse model of PD and a refined mRNA translational profiling approach called translating ribosome affinity purification (TRAP) to identify cell-type-specific gene-expression changes in dMSNs and iMSNs as induced by DA depletion and pharmacological DA replacement (Heiman *et al.*, 2014). DA depletion followed by chronic low- or high-dose L-dopa treatment was associated with massive changes in mRNA translation in dMSNs, compared with relatively modest changes in iMSNs. Many of the gene-expression changes observed in dMSNs correlated with the severity of AIMs, strongly suggesting that dMSNs are involved in the genesis of LID. The large gene profiling obtained in this study suggests that CREB, AP-1, and ERK signaling are major drivers of the transcriptional response to chronic high-dose L-dopa administration in dMSNs. Interestingly, several homeostatic changes induced by the treatment were observed in dMSNs, such as the up-regulation of MAPK-signaling phosphatases to counteract the abnormal high activity of the MAPK cascade in LID. However, these homeostatic mechanisms failed to dampen the up-regulation of an AP-1–regulated gene network

(including transcription factors of the *Jun* and *Fos family*). The profound molecular adaptations of dMSNs and the limited response of iMSNs during dyskinesiogenic treatment with L-dopa support the use of DAergic agents with preferential D2-like receptor activity as a first-line therapy to prevent dyskinesia in PD.

The molecular signature induced by L-dopa in the DA-depleted striatum was further uncovered by a recent important study performed in 6-OHDA-lesioned mice (Charbonnier-Beaupel *et al.*, 2015). The study focused, in particular, on ERK-dependent gene expression changes induced by the first administration of L-dopa and associated with the early development of AIMs in hemiparkinsonian mice. A time-course analysis (0-6 h after treatment with L-dopa) identified an acute signature of 709 genes, among which genes involved in protein phosphatase activity were over-represented, suggesting that a negative feedback on ERK activation is recruited by L-dopa itself. L-dopa-dependent deregulation of 28 genes was blocked by pretreatment with an inhibitor of ERK activation, SL327, and 26 genes were found differentially expressed between highly and weakly dyskinetic animals following treatment with L-dopa. The intersection list revealed five genes: *FosB*, *Th*, *Nptx2*, *Nedd4l*, and *Ccrn4l*. *Nptx2* encodes neuronal pentraxin II (or neuronal activity-regulated pentraxin, Narp), involved in the clustering of glutamate receptors. The increase in *Nptx2* expression after L-dopa and its blockade by SL327 was confirmed by quantitative RT-PCR. Using an escalating L-dopa dose protocol, LID severity was decreased in Narp knockout mice or after overexpression of a dominant negative form of Narp in the striatum. In conclusion, the authors identified a molecular signature induced by L-dopa in the DA-denervated striatum, dependent on ERK and associated with LID (Charbonnier-Beaupel *et al.*, 2015). Of particular interest was the result that Narp may be considered as a new therapeutic target in the early phases of LID development. These findings further corroborate the suggestion that changes in the composition of glutamate receptors at corticostriatal and/or thalamostriatal synapses are important element of the maladaptive plasticity that leads to LID.

A recent study examined the involvement of chromatin modifications in the aberrant gene expression associated to LID. Using a mouse model it was shown that L-dopa, via D_1R-mediated activation of DARPP-32 and ERK/MSK1, increased the levels of histone H3 phosphorylation at Ser28 (H3S28p), specifically in dMSNs (Sodersten *et al.*, 2014). Notably, this phosphorylation occurred at genomic regions modified by trimethylation of the adjacent Lys27 (K27me3), a mark linked to the repressive control exerted on gene expression by Polycomb group (PcG) proteins (Simon and Kingston, 2013). Previous work showed that phosphorylation of Ser28 in the context of Lys27 trimethylation leads to displacement of PcG

proteins and increased gene transcription (Gehani *et al.*, 2010). In line with this observation, genome wide analysis by ChIP-sequencing, in combination with expression analysis by RNA-sequencing, revealed that L-dopa-induced H3K27me3S28p correlates with increased expression of a subgroup of genes normally repressed by PcG proteins. These genes include transcription factors implicated in synaptic plasticity, such as *Atf3* (Green *et al.*, 2008) and *Npas4* (Ramamoorthi *et al.*, 2011), which controls of the expression of *Arc*, *Egr1* and *c-Fos* (Ramamoorthi *et al.*, 2011). Importantly, it was also found that different subsets of PcG target genes are specifically induced by acute or chronic L-dopa, further suggesting that the development and manifestation of dyskinesia are mediated by the action of distinct molecular components (Sodersten *et al.*, 2014).

In another interesting study, Ruiz-DeDiego et al. showed the involvement of the calcium-binding protein, downstream regulatory element antagonistic modulator (DREAM), in the control of the expression of FosB and dynorphin-B in response to chronic administration of L-dopa (2015). Importantly, these authors also show that AIMs severity is decreased in dominant active DREAM transgenic mice and, conversely, increased in DREAM knockout mice (Ruiz-DeDiego *et al.*, 2015). DREAM acts by binding to downstream regulatory element sites on DNA and repressing gene transcription. Notably, increased calcium, or activation of cAMP signaling counteracts the repressive action of DREAM (Carrion *et al.*, 1999; Ledo *et al.*, 2000). Taken together, these observations indicate that the abnormal activation of cAMP and Ca^{2+} signaling produced by L-dopa may lead to dyskinesia through increased expression of genes normally repressed by DREAM.

5.9.3. Dopamine receptor signalling

The two major families of DA receptors, generally referred to as D1-type and D2-type, are classically defined by their opposite regulation of cAMP synthesis. D_1R and D_5R, which belong to the type-1 group, are coupled to Gαs/Gαolf proteins, which promote adenylyl cyclase activity and cAMP synthesis (**Figure 4A**). Conversely, D_2R, D_3R and D_4R, which constitute the type-2 group, are coupled to Gαi/o proteins, which inhibit adenylyl cyclase and thereby reduce intracellular levels of cAMP (Herve *et al.*, 1993; Stoof and Kebabian, 1981; Zhuang *et al.*, 2000) (**Figure 4B**).

Considerable attention has been devoted to the participation of D_1R-mediated changes produced by the L-dopa-derived DA in the development and manifestation of dyskinesia on the ground that (i) both experimental models and PD patients exhibit a strong behavioural

sensitization at the level of D_1R (Rascol *et al.*, 2001b), that (ii) such sensitization is supported by a huge increase in D1 receptor-mediated canonical and non-canonical signallings (see the sections below), that (ii) blunting the electrical activity of mainly D_1R-expressing MSNs improves dyskinesia severity in experimental models (Engeln *et al.*, 2014a) and that (iii) eliminating direct pathway D_1R-expressing MSNs dramatically reduces AIMs in the 6-OHDA mouse model of LID (Revy *et al.*, 2014).

5.9.3.1. D_1 receptor canonical pathway

Studies in experimental models of PD indicate that the number and affinity of D_1R is unchanged following DA depletion (Aubert *et al.*, 2005; Breese *et al.*, 1987; Joyce, 1991; Marshall *et al.*, 1989; Savasta *et al.*, 1988). Similar results were obtained in post-mortem samples from parkinsonian patients (Hurley *et al.*, 2001; Pimoule *et al.*, 1985; Shinotoh *et al.*, 1993). However, the loss of DAergic input to the striatum and the development of dyskinetic behaviour in response to chronic administration of L-dopa are accompanied by increased recruitment of D_1R at the plasma membrane of MSNs, which may be caused by impaired receptor internalization and trafficking (Berthet *et al.*, 2009; Guigoni *et al.*, 2007).

In addition to this phenomenon, other changes have been proposed to contribute to the increase in D_1R transmission associated with LID. Studies performed in 6-OHDA-lesioned rats and in post-mortem samples from parkinsonian patients showed that loss of striatal DA is accompanied by increased levels of Gαolf (Alcacer *et al.*, 2012; Corvol *et al.*, 2004; Herve *et al.*, 1993; Rangel-Barajas *et al.*, 2011). In 6-OHDA-lesioned rats, Gαolf overexpression subsides during chronic L-dopa administration and does not correlate with the severity of LID (Corvol *et al.*, 2004; Rangel-Barajas *et al.*, 2011). In contrast, elevated Gαolf has been associated with LID in a mouse model of PD (Alcacer *et al.*, 2012) as well as in PD patients who had received a prolonged L-dopa treatment (Corvol *et al.*, 2004). However, in the same mouse model of PD and LID, reduced expression of Gαolf did not affect dyskinetic behaviour (Alcacer *et al.*, 2012) (cf. below).

Another signalling component contributing to the abnormal D_1R-mediated transmission involved in LID is the adenylyl cyclase type 5 (AC5), which is highly expressed in striatal MSNs (Glatt and Snyder, 1993; Mons and Cooper, 1994) and is stimulated in response to D_1R-mediated activation of Gαolf (Herve *et al.*, 1993; Zhuang *et al.*, 2000). Evidence obtained using 6-OHDA-lesioned rats shows that DAergic depletion increases the levels of this enzyme in the striatum (Rangel-Barajas *et al.*, 2011). A similar increase is also observed

in the SNr, which is innervated by the D_1R-expressing striatal dMSNs (cf. above) (Rangel-Barajas *et al.*, 2011). Interestingly, these effects are maintained during repeated administration of L-dopa, but only in animals displaying severe dyskinesia (Rangel-Barajas *et al.*, 2011). Recently, direct evidence of the involvement of AC5 in LID was obtained in genetically modified mice. In particular it was shown that AC5 knock-out mice exhibits attenuated LID. In addition, genetic inactivation of AC5 prevented the ability of L-dopa to activate cAMP as well as ERK signalling (Park *et al.*, 2014).

Taken together the results of the studies described above indicate that a persistent sensitization of canonical signalling downstream of D_1R is implicated in LID (**Figure 4A**). This sensitization is sustained by several features, such as an increased recruitment of D_1R at the cell surface, an increased D_1R-mediated GTPγS activity, an up-regulation of both Gαolf and AC5 in the striatal dMSNs (Aubert *et al.*, 2005; Berthet *et al.*, 2009; Guigoni *et al.*, 2007; Park *et al.*, 2014; Rangel-Barajas *et al.*, 2011). Altogether, these modifications are likely to influence DAergic transmission in the striatum and may underlie the enhancement in the ability of L-dopa to increase the levels of cAMP and to activate cAMP-dependent protein kinase (PKA).

The importance of augmented PKA activity in dyskinesia is indicated by the observation that, in 6-OHDA-lesioned rats, intrastriatal injections of the PKA inhibitor Rp-cAMPS reduces LID (Lebel *et al.*, 2010). Striatal MSNs express high levels of DARPP-32, which is phosphorylated by PKA on a specific threonyl residue (T34). Phosphorylation at T34 converts DARPP-32 into a selective inhibitor of protein phosphatase-1 (PP-1). This, in turn, suppresses the dephosphorylation of numerous downstream targets of PKA, thereby amplifying behavioural responses produced by activation of cAMP signalling (Borgkvist and Fisone, 2007; Fienberg *et al.*, 1998; Greengard, 2001). Several lines of evidence indicate that PKA-mediated phosphorylation of DARPP-32 is implicated in dyskinesia. Experiments performed in rodents and non-human primates show that LID correlates with increased levels of DARPP-32 phosphorylated at T34 (Lebel *et al.*, 2010; Picconi *et al.*, 2003; Santini *et al.*, 2012; Santini *et al.*, 2010a; Santini *et al.*, 2007). Moreover, this effect is exerted specifically in the striatal dMSNs, which express D_1R (Santini *et al.*, 2012). Knock-out of DARPP-32 or mutation of the phosphorylation site for PKA, both attenuate LID (Santini *et al.*, 2012; Santini *et al.*, 2007). A similar reduction of dyskinetic behaviour is also observed in mice in which DARPP-32 is selectively inactivated in the striatal dMSNs (Bateup *et al.*, 2010). Interestingly, in MPTP-lesioned non-human primates, increased phosphorylation of DARPP-32 persists from first ever administration up to three months of L-dopa chronic administration,

suggesting that DARPP-32 is implicated not only in the development but also in the maintenance and manifestation of LID (Santini *et al.*, 2010a).

The abnormal activation of PKA/DARPP-32 signalling observed in experimental models of LID may have profound repercussions on synaptic plasticity. As shown by Picconi et al., LID is associated with blockade of depotentiation at cortico-striatal synapses. Notably, depotentiation is prevented by inhibition of PP-1 (Picconi *et al.*, 2003). Therefore, it is possible that the increase in DARPP-32 phosphorylation associated to LID contributes to the loss of depotentiation by reducing PP-1 activity. Another possible mechanism by which increased PKA/DARPP-32 signalling prevents depotentiation involves changes in the state of phosphorylation of the GluA1 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor. Increased PKA-dependent phosphorylation of GluA1 at Ser845 correlates with dyskinetic behaviour (Santini *et al.*, 2010a; Santini *et al.*, 2007). This effect is strictly dependent on concomitant phosphorylation of DARPP-32, since it is abolished in DARPP-32 knock-out mice (Santini *et al.*, 2007). Phosphorylation of GluA1 at Ser845 promotes glutamatergic transmission (Banke *et al.*, 2000; Mangiavacchi and Wolf, 2004) and may participate in the block of depotentiation observed in dyskinetic rats (Picconi *et al.*, 2003).

In conclusion, sensitized D_1R signalling along the canonical cAMP pathway is required for the development and manifestation of LID (**Figure 4A**). The identification of downstream targets of PKA ultimately responsible for the emergence of dyskinetic behaviour represents a promising avenue with regard to the development of efficacious anti-dyskinetic therapies. Several questions remain to be addressed. For instance, it has been shown that the reduction of L-dopa-induced phosphorylation of DARPP-32 and GluA1, achieved through downregulation of Gαolf, does not affect dyskinesia, possibly because a partial downregulation of this signalling pathway has no effect on the induction of ERK signalling (Alcacer *et al.*, 2012). These findings suggest that supersensitive D_1R in the DA-denervated striatum recruit non-canonical signalling components via alternative routes. Accordingly, a recent study has demonstrated that the D_1R-dependent induction of ERK1/2 signalling in the DA-denervated striatum can be inhibited by antagonizing phospholipase C (PLC), protein kinase C (PKC), or calcium mobilization from internal stores (Fieblinger *et al.*, 2014b). These signalling components are normally associated with the activation of Gq- and not Gαs/αolf-coupled receptors.

Notwithstanding these recent findings it has also been established that a pronounced inactivation of the PKA/DARPP-32 cascade attenuates dyskinesia (Bateup *et al.*, 2010; Lebel *et al.*, 2010; Santini *et al.*, 2012; Santini *et al.*, 2007). Thus, further studies are needed to clarify the relationship between hyperactive cAMP-dependent signalling and the recruitment of non-canonical calcium-dependent signalling components in the dyskinetic striatum. In this regard it is particularly important to consider the cross-talk between cAMP signalling and transduction pathways implicated in activity-dependent synaptic plasticity, such as those controlled by the Ras-dependent activation of extracellular signal-regulated protein kinases (Ras-ERK) and the mammalian target of rapamycin complex 1 (mTORC1).

5.9.3.2. D_1 receptor non-canonical pathways

Newer evidence indicates that D_1R do crosstalk to glutamate signalling (mainly NMDA receptors) and thus can engage additional non-canonical pathways in LID (**Figure 4A**). The best-characterized pathways implicated in LID are the Ras-ERK and the mTORC1 cascades, which also exert important function in a number of neuronal processes, including learning and memory (Costa-Mattioli *et al.*, 2009; Fasano and Brambilla, 2011). In the now classical paper by Gerfen et al, ERK dependent signalling was shown to be aberrantly hyperactivated in the DA depleted striatum, following D_1R activation. Accordingly, this early report also demonstrated that phospho-ERK (pERK) positive signal, a measure of ERK phosphorylation and activation, in the DA depleted brain, was almost entirely restricted to enkephalin negative cells, i.e. dMSNs (Gerfen *et al.*, 2002). Hence, these initial observations led to the hypothesis that the denervation-induced supersensitivity of D_1R leads to the activation of non-canonical signalling responses involving $ERK_{1/2}$ in dMSNs. It should be noted, however, that psychostimulants such as cocaine, which greatly increase extracellular DA levels, can also induce ERK1/2 activation in dMSNs, as originally shown by Caboche and collaborators (Valjent *et al.*, 2000), by favouring the activity of the direct striatal pathway, which promotes action selection (Albin *et al.*, 1989; DeLong, 1990). This cellular response may mediate the motor activation elicited by both psychostimulants in the normal brain and DAergic agonists (including L-dopa) in the DA-depleted brain. However, an excessive striatal activation of ERK1/2 is specifically linked with a dyskinetic motor output, as indicated by the finding that diminishing the striatal levels of $pERK_{1/2}$ selectively diminishes the AIM scores without interfering with the anti-parkinsonian action of L-dopa (Fasano *et al.*, 2010).

The first reports clearly implicating an abnormal ERK activation in LID came in 2006 (Pavon *et al.*, 2006) and 2007 (Westin *et al.*, 2007). Thus, Pavon and co-workers reported that pERK levels were significantly increased in the denervated striatum already by a single administration of L-dopa, and further enhanced with a chronic treatment over 25 days (Pavon *et al.*, 2006). Importantly, pERK enhancement in the chronic L-dopa condition was also associated with a significant upregulation of FosB/ΔFosB immunoreactivity. A positive linear correlation between striatal levels of phosphorylated ERK and the L-dopa-induced AIM scores was then provided by Westin et al. (Westin *et al.*, 2007). The latter study showed that both acute and chronic L-dopa administration rapidly induced the phosphorylation of ERK and MSK-1 in the DA-denervated striatum. Strong cellular immunoreactivity for pERK was detected in both the medial and the lateral striatum in a time interval ranging between 20 and 120 minutes after a single dose of L-dopa, a time window which parallels the time course of the AIMs. Interestingly, at 24h, the cellular immunostaining for pERK was back to the basal levels (Westin *et al.*, 2007). This study also reported that bromocriptine, an anti-parkinsonian drug with low dyskinesiogenic potential, did not induce any significant increase in either pERK or pMSK-1 immunoreactivity, further strengthening the link between a large activation of ERK and the development of involuntary movements. Further to these results, the study reported that the striatal activation of ERK signalling by L-dopa was dependent on the D_1 class of DA receptors. Indeed, the D_1R antagonist, SCH23390, completely suppressed pERK and pMSK-1 induction, as well as FosB/ΔFosB upregulation, in animals treated with L-dopa (Westin *et al.*, 2007). On the contrary, co-treatment with raclopride, a D_2R antagonist, had no effect on the L-dopa-induced response. The direct link between LID, D_1R and ERK activity was later substantiated by the Moratalla group, by showing that genetic ablation of D_1R but not D_2R suppresses AIMs in the mouse and concomitantly prevents ERK phosphorylation, phospho-acetylation of Histone H3 (pAcH3) (a direct substrate of MSK-1) and FosB/ΔFosB accumulation (Darmopil *et al.*, 2009). Finally, upregulation of pERK and pAcH3 levels specifically in the dMSNs was later corroborated using the aforementioned BAC transgenic EGFP expressing mice (Santini *et al.*, 2009a).

These observations did ascribe a pivotal role of ERK signalling in LID. However, they did not demonstrate that a reduction of the activity of this signal transduction pathway could ameliorate the dyskinetic symptoms. Fisone's group provided the initial evidence (Santini *et al.*, 2007). In this paper it was shown that pERK increase well correlated with AIMs severity of 6-OHDA-lesioned mice, as well as the enhancement of phosphorylation of GluA1 (pSer845) and most importantly DARPP-32 (pThr34) (Greengard *et al.*, 1999). Previous work

had proposed that in MSNs, active DARPP-32 (pThr34) could stimulate ERK activity by suppressing the activity of the striatal-enriched protein tyrosine phosphatase (STEP), a direct substrate of PP-1 (Valjent *et al.*, 2005). Hence, in the DARPP-32 knock-out animals, not only AIMs are significantly attenuated but also pERK and pGluA1 are reduced. Finally, systemic administration of SL327, a specific inhibitor of the MEK1/2 kinases upstream of ERK1/2, robustly attenuated LID in mice, providing not only a conclusive demonstration that aberrant ERK activity is part of the pathophysiology of LID but also opening interesting therapeutic possibilities for treating dyskinesia by targeting this signalling pathway (Fasano *et al.*, 2010; Santini *et al.*, 2007). Indeed, an initial attempt to translate these findings in a potential therapy was based on the use of lovastatin, which besides its wide use to treat hyperlipidemia in humans, has also been shown to prevent the membrane localization of Ras proteins, the upstream activators of ERK signalling, effectively reducing the activity of this cascade *in vivo* in the brain (Li *et al.*, 2005b). In the rat model of LID, treatment with lovastatin effectively prevented LID formation and reduced both pERK induction and FosB/ΔFosB levels (Schuster *et al.*, 2008). Unfortunately, while the treatment with another statin, simvastatin, did reduce LID and attenuate ERK signalling in the non-human primate model of PD and LID, a pilot trial with a small group of patients failed to reveal any therapeutic effect (Tison *et al.*, 2013), at a dose of 40 mg per day, i.e. the maximal dose with absence of side-effects that failed in reducing ERK1/2 activation in the periphery while it did achieve reduction in dyskinetic MPTP-lesioned macaques (see Fig. 3Tison *et al.*, 2013). Failure was thus a problem of bioavailability rather than due to the target itself.

Despite this initial negative result, interesting alternative approaches are available to reduce ERK activity in dyskinesia in order to attenuate LID. For instance, indirect manipulation of ERK activity can be achieved either by modulating both group I mGluRs (mGLUR1 and 5) using specific antagonists or negative allosteric modulators or Nociceptin/Orphanin FQ receptors using specific agonists (Marti *et al.*, 2012; Rylander *et al.*, 2009). In both cases, pharmacological treatments in experimental rodent models did not only reduce AIMs but also attenuated pERK.

One of the potential problems in LID research is the fact that targeting certain signalling intermediates or receptors aberrantly altered in the initial phases of L-dopa exposure (priming) may be effective in reducing dyskinetic symptoms but this therapeutic effect may be lost at later stages, a condition more relevant to most PD patients, due to tolerance or additional compensatory cellular mechanisms. Some evidence tends to suggest that ERK activity in dMSNs may decline during chronic L-dopa treatment. In the macaque model,

levels of phosphorylation of both $ERK_{1/2}$ and of the ribosomal protein S6 (pS235/236), an indirect cytoplasmic target of ERK, were found maximal upon initial L-dopa treatment but then declined significantly after 3 months treatment, although did not return to basal level (Santini *et al.*, 2010a). Note however that ribosomal protein S6 phosphorylation was recently found to actually require the cAMP/PKA/DARR-32/PP-1 cascade and not the mTORC1, PKC and ERK signalling (Biever *et al.*, 2015). The decline in activity after chronic treatment was not observed for either DARPP-32 (Thr34) or GluA1 (Ser845) suggesting that, while ERK signalling may be more implicated in priming, cAMP signalling may be still relevant for the expression of dyskinesia. However, this simplistic idea has been complemented by other experimental observations. First, a study performed using both 6-OHDA-lesioned mice and the Pitx3/aphakia mouse model of PD, showed that L-dopa–induced striatal ERK activation does not subside during long-term treatment, but rather shifts from being predominantly localized to MSNs to occurring in cholinergic interneurons (Ding *et al.*, 2011). Ablating those cholinergic interneurons leads to improvement of AIMs (Won *et al.*, 2014). The ERK activation shift has been confirmed in the macaque model of PD and LID (Beard, unpublished). Second, lentiviral vectors (LV)-mediated inactivation of striatal Ras-ERK signalling (predominantly in MSNs) was found to significantly improve LID in already dyskinetic monkeys, which had been treated with L-dopa for several months prior to the LV delivery (Fasano *et al.*, 2010). Third, in heterozygous mice for Gαolf, L-dopa-induced cAMP-dependent signalling was attenuated while ERK activity and AIMs remained high, suggesting that the role of ERK is preponderant over that of canonical Gαolf-mediated signalling in inducing dyskinesia (Alcacer *et al.*, 2012).

Till recently, the investigation of the role of ERK in brain functions in general and in LID in particular has been largely limited to the core components of this signalling pathway, i.e. $MEK_{1/2}$ and $ERK_{1/2}$ protein kinases. However, upstream mechanisms connecting both DA D_1R and glutamate receptors have been proved to be relevant in the onset of dyskinesia. Ras-GRF1, is a neuronal specific and striatal enriched guanine-nucleotide exchange factor for Ras proteins, previously implicated in cognitive processing as well as in synaptic plasticity and acting as a signalling integrator between D_1R and glutamatergic ionotropic receptors (Brambilla *et al.*, 1997; Fasano and Brambilla, 2011; Fasano *et al.*, 2009). In 2010, Brambilla's group showed that the genetic ablation of Ras-GRF1 in the mouse significantly ameliorates AIMs by reducing both pERK and FosB/ΔFosB levels (Fasano *et al.*, 2010). Importantly, suboptimal doses of SL327, the MEK inhibitor, potentiate the anti-dyskinetic effect observed in the Ras-GRF1 knock-out mice, suggesting that a combination therapy

targeting both upstream and downstream components of the Ras-ERK pathway may be more effective for treating LID symptoms. The relevance of these observations was also supported by a gene therapy approach in the non-human primate model, in which fully dyskinetic monkeys were injected with LV expressing a cocktail of Ras-GRF1 and ERK dominant negative constructs. This treatment significantly reverted LID symptoms without attenuating the anti-parkinsonian action of L-dopa, strongly supporting the idea that Ras-ERK inhibition in already affected individuals may provide a valid therapeutic approach for LID. The fact that Ras-GRF1 inhibition does not completely suppress dyskinetic symptoms may imply that other exchange factors for Ras-proteins could also be implicated in this process. Two valid candidates may be CalDAG-GEFI and CalDAG-GEFII, two striatal enriched Ras-ERK regulators, whose levels were shown altered upon DA depletion and L-dopa treatment (Crittenden *et al.*, 2009). In addition, direct coupling of D_1R to ERK signalling is believed to play a crucial role in LID. In this respect, evidence has elucidated a novel mechanism in which the D_1R-mediated $ERK_{1/2}$ activation in the striatum is dependent on the formation of a signalling complex containing the protein tyrosine phosphatase Shp-2 that persists in dyskinetic animals (Fiorentini *et al.*, 2011; Fiorentini *et al.*, 2013). Thus, Shp-2 may become in the near future an additional interesting target associated to the striatal ERK signalling. Moreover, as mentioned above, signalling components traditionally associated with Gq-coupled receptors appear to be involved in the induction of $ERK_{1/2}$ activation downstream of the D_1R in PD models (Fieblinger *et al.*, 2014b). These signalling components could be explored for the treatment of LID in the future.

Very recently, Brambilla and colleagues have elucidated some striatal synaptic mechanisms connecting Ras-GRF1 and ERK to LID. A combination of both ERK pharmacological blockade and Ras-GRF1 deficient mice revealed a complex scenario, involving this signalling cascade in striatal plasticity (Cerovic *et al.*, 2015). First of all, in mouse naïve striatal slices, inhibition of ERK using U0126, a MEK inhibitor, resulted in a complete inhibition of both cortico-striatal LTP induction and of its reversal, depotentiation. On the contrary, ERK activity seems to be not implicated in cortico-striatal LTD and LTP maintenance since U0126 does not block these two processes. Interestingly, in striatal slices from Ras-GRF1 KO mice, only dMSNs do not show LTP while long-term plasticity is unaffected in iMSNs. This evidence strongly argues for relevant differences in the engagement of different components of the Ras-ERK pathway within the two major populations of striatal cells. The relevance of this observation is in line with the previous report showing an involvement of Ras-GRF1 in LID and suggesting a central role of the sole direct striatal pathway in the process (Fasano *et*

al., 2010). Furthermore, analysis in DA depleted slices, using the 6-OHDA mouse model revealed that repeated L-dopa treatments not only render animals highly dyskinetic but also profoundly alter the synaptic responses to Ras-GRF1 and ERK modulation. Indeed, both ERK inhibition and Ras-GRF1 depletion facilitates depotentiation, thus indicating that restoration of this synaptic process correlates with an attenuated dyskinetic profile, as found in both SL327 treated and Ras-GRF1 deficient mice (Fasano *et al.*, 2010; Santini *et al.*, 2007). However, the most striking finding, with potentially relevant clinical implications, relates to the LTP responses in slices obtained from dyskinetic animals and treated with the MEK inhibitor. Differently from the naïve condition, U0126 did not block synaptic potentiation in all cells but only in approximately 50% of cases, in a pathway independent manner. This observation firstly indicates that profound synaptic rearrangements occur in the dyskinetic striatum, and secondly, that ERK signalling is only required in a portion of the MSNs, with an apparent stochastic pattern, suggesting that normal cortico-striatal LTP and L-dopa mediated LTP are rather distinct processes (Thiele *et al.*, 2014). Further work will be necessary to unravel the underlying molecular mechanisms, however it is intriguing to speculate that this derangement of synaptic responses in the dyskinetic condition may be linked to different cellular states, possibly connected to pulsatile L-dopa administration, rapid changes in DA availability and wearing off.

It is well recognized that the Ras-ERK cascade is a crucial transducer transmitting signals from the cytoplasm to the nucleus. One of the main downstream effectors implicated in ERK-dependent transcriptional regulation is MSK1. Recent evidence indicates that MSK1 could be involved in LID. Thus, MSK1 knock out mice develop less severe dyskinesia in response to chronic administration of L-dopa (Feyder *et al.*, 2014). In this study, inactivation of MSK1 affects specifically the axial dyskinesia, suggesting that specific components of LID can be controlled by targeting specific signalling pathways downstream of ERK signalling (Feyder *et al.*, 2014). Interestingly, genetic inactivation of MSK1 is accompanied by concomitant reduction of histone H3 phosphorylated at Ser10 and ΔFosB, further supporting the idea of their involvement in LID (Feyder *et al.*, 2014). However, in another study MSK1 appears not to be necessary for the development of LID (Alcacer *et al.*, 2014). Using the same transgenic mouse line, the authors show that the lack of MSK1 in 6-OHDA-lesioned mice blocks or attenuates some previously described L-dopa effects, including Gαolf up-regulation and increases of histone H3 phosphorylation and ΔFosB accumulation. The decrease of these biochemical changes was however not sufficient to significantly alter the development of LID. Interestingly, the absence of MSK1 had no effect on L-dopa-induced ERK activation,

suggesting an involvement of additional ERK-dependent signaling mechanisms that are independent of MSK1 (Alcacer *et al.*, 2014).

Aside from its role in transcriptional regulation, ERK activity is involved in the modulation of protein translation. This occurs mainly through the control of the mTOR cascade. mTOR is the essential component of mTORC1, which can be activated by ERK and, in turn, phosphorylates S6K1 and the initiation factor 4E-binding protein (Santini *et al.*, 2010b). Through these effectors, mTORC1 promotes initiation of mRNA translation and protein synthesis. mTORC1 is inhibited by rapamycin and rapamycin derivatives (or "rapalogs"). Similarly to ERK, mTORC1 hyperactivation occurs specifically in dMSNs of DA-depleted animals challenged with L-dopa and the degree of phosphorylation of several markers downstream to mTORC1 correlates well with the severity of AIMs (Santini *et al.*, 2009b). The involvement of mTORC1 in dyskinesia was first demonstrated by showing that, in the 6-OHDA mouse model, this condition is strongly attenuated by systemic administration of rapamycin (Santini *et al.*, 2009b). These results were confirmed in the 6-OHDA rat model, using the rapalog, temsirolimus (CCI-779) (Decressac and Bjorklund, 2013). These findings support the idea that excessive *de novo* protein translation may be responsible for LID pathophysiology (see also, Kultima *et al.*, 2006; Scholz *et al.*, 2008). Remarkably, an upstream component of the mTOR pathway, Rhes, has proven to be involved in the development of LID, further expanding the list of potential therapeutic targets (Subramaniam *et al.*, 2012).

In recent years, the idea of combination therapy has risen as an interesting concept in optimizing novel therapeutic approaches, with clinical trials targeting both Ras-ERK and mTOR cascades already ongoing in oncology (Chappell *et al.*, 2011). The data available on non-canonical intracellular signalling pathways certainly suggest that a similar path could also be taken to treat dyskinesia.

5.9.4. Other dopamine receptors

5.9.4.1. D_2 receptor

While critical involvement of the D_1R has clearly been demonstrated, the role of the D_2R has received much less attention, although imbalance in the activity of the two major striatal output pathways supported through over-activation of D_1R and over-inhibition of D_2R on the direct and indirect pathway, respectively, is a classic concept (Bezard *et al.*, 2001a; Calon *et al.*, 2000; Olanow and Tatton, 1999; Tintner and Jankovic, 2002). Years of behavioural

pharmacology, however, undoubtedly show that D_2R agonists induce behavioural sensitization (Morelli and Di Chiara, 1987; Morelli *et al.*, 1989) and dyskinesia in primed animals (Bezard *et al.*, 2001a; Jenner, 2008). D_2R distribution and expression is however not further affected by chronic L-dopa treatment in DA-depleted animals (Aubert *et al.*, 2005; Guigoni *et al.*, 2007), while DA depletion already provokes the classic upregulation. One should admit, however, that D_2R has probably received less attention because the experimental tools are less developed and/or reliable for the D_2R than for the D_1R (antibodies, transmission assays, etc.). The role of the D_2R is therefore only indirectly emphasized, through, for instance, the adenosine A_{2A} receptors localized on D_2R-expressing MSNs (see below the detailed discussion of this class of receptors) (**Figure 4B**). Other indirect evidence comes from the regulation of D_2R signalling by regulatory GPCR signalling proteins (RGS). RGS9-2 is a GTPase accelerating protein of Gα subunits that inhibits D_2R-activated G proteins (Rahman *et al.*, 2003) and is expressed almost exclusively in the striatum (Rahman *et al.*, 1999). Regulation of RGS9-2 expression in various animal models of LID (Gold *et al.*, 2007) and in L-dopa-exposed PD patients (Tekumalla *et al.*, 2001) suggests that the striatum attempts to compensate for increased D_2R-mediated signalling by increasing RGS9-2 levels, i.e. that would result in a better "stop" signal of D_2R-mediated transduction. This mechanism obviously fails as MPTP-lesioned monkeys and L-dopa-treated PD patients do develop LID. Gold et al. hypothesized that such compensatory mechanisms might be boosted by further increasing RGS9-2 levels using viral transfer. In keeping with this hypothesis, although RGS9-2 knockout mice do show worse AIMs than wild-type mice (Gold *et al.*, 2007), both dyskinetic 6-OHDA-lesioned rats and dyskinetic MPTP-treated monkeys transfected with RGS9-2 did show reduced severity of LID (Gold *et al.*, 2007). This positive effect is counterbalanced by the observation that the anti-parkinsonian action of D_2R agonists is abolished, an observation that clearly highlights the complex role of the D_2R in LID pathophysiology.

While the D_1R may interact with glutamate receptors through protein-protein interaction (Cahill *et al.*, 2014; Lee *et al.*, 2002; Scott *et al.*, 2006) or through the MAGUK proteins (Fiorentini *et al.*, 2003; Yao *et al.*, 2008; Zhang *et al.*, 2007), much less is known about interaction between D_2R and the various components of the glutamate receptor machinery. Recently, however, an interaction between the excitatory synapse-enriched Calcium/calmodulin-dependent protein kinase II (CaMKII) and the D_2R has been described and shown to be enhanced in dyskinetic 6-OHDA-lesioned rats. Disruption of such interaction

using either a specific interaction-dead peptide (Zhang *et al.*, 2014d) or pharmacological inhibition of CAMKII (Yang *et al.*, 2013) reduces AIMs in the same experimental model.

Altogether, while the D_2R sensitization certainly plays a role in LID pathophysiology, strategies aiming at modulating its signalling cascade activity or disrupting its partnership seem ultimately to result into emergence of an anti-L-dopa effect upon parkinsonian symptoms, i.e. reduction of LID severity is achieved at cost of resurgence of parkinsonian symptoms.

5.9.4.2. D_3 receptor

Even less studied, but certainly far more interesting from a therapeutic viewpoint, is the DA D_3R. Interestingly, expression level of the D_3R in the dorsal motor-related striatum correlates with experimental analogs of dyskinesia in mouse (Gross *et al.*, 2003), rat (Bordet *et al.*, 1997) and macaque monkey (Bezard *et al.*, 2003). Furthermore, overexpression of the D_3R in the rat dorsal striatum induces dyskinetic behaviours (Cote *et al.*, 2014). To date, this is the only DA receptor, whose expression levels linearly correlate with LID severity (Azkona *et al.*, 2014; Bezard *et al.*, 2003; Bordet *et al.*, 1997). Interestingly, D_1R and D_3R are co-expressed by the dMSNs (Ridray *et al.*, 1998) and have been shown to directly interact (Fiorentini *et al.*, 2008) through an intramembrane D_1R-D_3R cross-talk (Marcellino *et al.*, 2008) (**Figure 4A**). Such cellular co-localization and cross-talk clearly emphasize the putative key role played by the duet in LID pathophysiology.

Attempts have thus been made for dampening the D_3R activity or the cross-talk between the two receptors. Administration of a D_3R-selective partial agonist, BP897, strongly attenuated LID in the MPTP-treated macaque model of dyskinesia, while leaving unaffected the therapeutic effect of L-dopa (Bezard *et al.*, 2003). On the contrary, attenuation of dyskinesia by D_3R antagonists, nafadotride and ST-198, was accompanied by the reappearance of PD-like symptoms (Bezard *et al.*, 2003). These results suggested that the D_3R participates in both dyskinesia and the therapeutic action of L-dopa in the macaque model in which receptor levels and activities were known. Of note, an anti-dyskinetic action of the D_3R antagonists WV10 and PG01037 has been confirmed in the AIM 6-OHDA-lesioned rat model although, in these reports, they did not interfere negatively with anti-parkinsonian action of L-dopa (Kumar *et al.*, 2009a; Kumar *et al.*, 2009b).

In another species, the squirrel monkey, the same partial agonist, BP897, significantly reduced LID, but at the expense of L-dopa's anti-parkinsonian action (Hsu *et al.*, 2004). Thus,

in squirrel monkeys, in contrast to macaques, BP897 exerted both anti-dyskinetic and proparkinsonian effects. The discrepant effect of the partial D_3R agonist in these two nonhuman primate species may relate to a differential distribution and/or regulation of D_3R (Bezard *et al.*, 2003; Hsu *et al.*, 2004). The fact that even normal squirrel monkeys present LID (Togasaki *et al.*, 2001), i.e. in absence of nigrostriatal lesion, suggest that pathophysiology supporting similar symptoms is actually rather different between the two species vis-à-vis DA receptor expression and sensitivity. An alternate hypothesis has been proposed, positing that the partial agonist BP897 might actually mediate its anti-dyskinetic action at sites other than D_3R (Visanji *et al.*, 2006b). Visanji et al. used the L-dopa-induced hyperkinesia in reserpine-treated rats, the vertical component of which (rearing) is attenuated by agents with anti-dyskinetic actions in MPTP-lesioned primates and PD patients (Johnston *et al.*, 2005). While BP897 reduced L-dopa-induced rearing, the D_3R antagonist S33084 had no effect on this behaviour either alone or in combination to BP897 (Visanji *et al.*, 2006b). The selective D_2R L741,626 mimicked the influence of BP897 on L-dopa-induced rearing while the D_3R antagonist S33084 reproduced the BP897 attenuation of L-dopa-induced horizontal activity (Visanji *et al.*, 2006b). Authors concluded that, in this acute rat model, BP897 may reduce LID but that receptors other than D_3R might be involved in this action. These two sets of data emphasize the need for conducting pharmacological studies in experimental models in which the target expression, here the DA receptors, is known. While data in the macaque models are coherent with the expression levels of DA receptors, the reserpine rat and squirrel monkey data raise more questions than they solve because of the lack of knowledge of the models.

Furthering our knowledge of the complex role played by D_3R is the demonstration that the D_3R antagonist ST 198, known to improve dyskinesia severity in rodent and non-human primate analogues of PD (although with anti-L-dopa effect at high dose), restores normal levels of membrane-bound D_1R in dyskinetic 6-OHDA-lesioned rats (Berthet *et al.*, 2009). Interestingly, notwithstanding the impact upon D_3R-mediated signalling, antagonizing the D_3R seems to disrupt the crosstalk between D_1R and D_3R offering an additional mechanism, i.e. release of D_1R, for anti-dyskinetic action of D_3R ligands (Berthet and Bezard, 2009; Berthet *et al.*, 2009).

5.9.4.3. D_4 receptor

The DA D_4R has been largely ignored because of its low density of in the striatum of control subjects and PD patients (Seeman *et al.*, 1993). Both the anatomical localization and the changes in expression induced by DA loss and further L-dopa replacement therapy are unknown in experimental models and PD patients, further highlighting, if needed, the importance for pathophysiological characterization before embarking into pharmacological studies. Despite this lack of knowledge, pharmacological strategies aiming at antagonizing its activity were attempted to address the issue of D_4R involvement in LID. The clozapine analog 8-methyl-6-(4-methyl-1-piperazinyl)-11H-pyrido(2,3-b)(1,4)benzodiazepine (JL-18) possesses affinity for DA D_4R and demonstrated some efficacy against LID in the MPTP-lesioned macaque model of PD and LID (Hadj Tahar *et al.*, 2000). Although JL-18 is a potent D_4R antagonist, it also exhibits high affinity for 5-HT_{2A}, D_2R, and muscarinic receptors with a rather weak D_4R selectivity, rendering dubious the conclusion of a role of D_4R in LID expression. More recently, L-745,870 (3-([4-(4-chlorophenyl)piperazin-1-yl]methyl)- 1H-pyrrolo[2,3-b]pyridine), a potent and selective D_4R antagonist, exhibiting nearly 100-fold selectivity for D_4R over its next target, originally developed to treat schizophrenia, was tested against LID in the AIM 6-OHDA-lesioned rat model (Huot *et al.*, 2015) and the dyskinetic MPTP-lesioned macaque model (Huot *et al.*, 2012a). L-745,870 reduced both AIMs (Huot *et al.*, 2015) and LID (Huot *et al.*, 2012a). It also diminished the L-dopa anti-parkinsonian benefit in the rat model (Huot *et al.*, 2015) but not in the macaque model (Huot *et al.*, 2012a), calling for further investigations. Overall, these data suggest that L-745,870 may have a narrow therapeutic window as an anti-dyskinetic agent in advanced PD, rendering difficult its titration, in addition to the dubious status of D_4R expression in dyskinetic PD patients.

5.9.5. Dysregulation of homologous DA receptor desensitization

As stated above, the deregulation of DA-mediated signalling manifests itself as strongly enhanced responsiveness to DAergic stimulation both at the behavioural and signalling levels via all major striatal DA receptor subtypes (Brown *et al.*, 2005; Bychkov *et al.*, 2007; Cai *et al.*, 2000; Corvol *et al.*, 2004; Gerfen, 2000; Gerfen *et al.*, 2002; Pifl *et al.*, 1992a; Pifl *et al.*, 1992b; Ravenscroft *et al.*, 2004; Sgambato-Faure *et al.*, 2005; Tong *et al.*, 2004; Ungerstedt, 1971b). Although the mechanism of DAergic supersensitivity is undoubtedly complex, deregulation of the receptor desensitization machinery is likely to play an important role in LID.

Would this be the case, DA receptors should thus be less internalized in dyskinesia. This hypothesis is clearly counterintuitive as the DA receptors belong to the superfamily of GPCR, known to desensitize rapidly in presence of their ligand (**Figure 4C**). In the context of LID, extracellular DA levels are increased and should thus lead to DA receptor desensitization, e.g. through internalization. D_1R, but not D_2R, actually appears overrepresented at neuronal membrane (Berthet *et al.*, 2009; Guigoni *et al.*, 2005a; Guigoni *et al.*, 2007), hence leading to persistent overactivity of its signalling (Aubert *et al.*, 2005; Guigoni *et al.*, 2005a). Active anchoring at membrane takes place as direct further agonism of D_1R (Berthet *et al.*, 2009), disruption of receptor-receptor (Berthet *et al.*, 2009) or receptor-scaffold protein interactions (Porras *et al.*, 2012a) are successful strategies for re-instating D_1R internalization resulting into improvement of LID in experimental models.

DA receptors transmit signals in response to a wide variety of stimuli via an uniform mechanism involving coupling of liganded receptors to heterotrimeric G proteins followed by GTP-GDP exchange on α-subunit and dissociation of α-subunit from the ßγ-dimer, both of which activate or modulate effectors (Rasmussen *et al.*, 2011) (**Figure 4C**). Activation of a GPCR by an agonist initiates G protein-mediated signalling and at the same time triggers a shutdown mechanism termed homologous desensitization, or desensitization of the receptors that are being activated. The classic model of homologous desensitization of GPCR posits that agonist-activated receptor is first phosphorylated by a G protein-coupled receptor kinase (GRK) [reviewed in (Gurevich *et al.*, 2012)]. GRKs specifically recognize receptor conformations conducive to G protein binding and, like G proteins, directly bind active receptors (Huang and Tesmer, 2011). Since this interaction of a GRK with an activated receptor activates the kinase (Palczewski *et al.*, 1991), GRKs are selective towards activated GPCRs. The receptor phosphorylation promotes high-affinity binding of uncoupling proteins arrestin. Arrestin shields the cytoplasmic surface of the receptor, precluding further G protein activation (Krupnick *et al.*, 1997; Wilden, 1995). Arrestin binding also promotes receptor internalization by virtue of direct arrestin interaction with clathrin and AP-2, the main components of the coated pit (Goodman *et al.*, 1996; Laporte *et al.*, 1999), leading to the receptor resensitization and recycling or, in some cases, down-regulation (Morrison *et al.*, 1996; Pan *et al.*, 2003; Wu *et al.*, 2008) (**Figure 4C**).

GRK phosphorylation reduces receptor coupling to G proteins (Wilden, 1995), but does not eliminate it. The full signal shutoff is accomplished by the binding of an arrestin to active phosphorylated GPCR (Attramadal *et al.*, 1992; Krupnick *et al.*, 1997; Lohse *et al.*, 1992; Lohse *et al.*, 1990; Wilden, 1995). Arrestin requires more than one phosphate attached to a

receptor for high affinity binding (Vishnivetskiy *et al.*, 2007). Arrestins have been shown to compete with G proteins for active GPCRs (Krupnick *et al.*, 1997; Wilden, 1995). However, because the receptor needs to be phosphorylated multiple times before arrestin can bind with high affinity, G protein has a time window with a clear advantage over arrestin, when it can be activated and transmit the signal before the shutoff is complete. For example, light-activated rhodopsin, a prototypical class A GPCR, is capable of sequentially activating dozens of G protein molecules (Leskov *et al.*, 2000). The receptor phosphorylation by GRK is the rate-limiting step in the homologous desensitization process (Violin *et al.*, 2008) and GRK concentration in cells strongly influences the rate and extent of receptor desensitization, as well as the duration and intensity of G protein-mediated signalling (Gainetdinov *et al.*, 2003; Gainetdinov *et al.*, 1999; Gainetdinov *et al.*, 2004; Iaccarino *et al.*, 1998; Kim *et al.*, 2001; Menard *et al.*, 1997; Pan *et al.*, 2003; Willets *et al.*, 2004; Willets *et al.*, 1999). Active GTP-liganded α-subunits of G proteins are in their turn deactivated via hydrolysis of GTP to GDP by intrinsic GTPase activity of the α-subunits. This intrinsic activity is enhanced by GTPase activating proteins (GAPs) that accelerate G protein deactivation and reduce signalling. The major class of GAPs are RGS (Ross and Wilkie, 2000; Siderovski *et al.*, 1996; Siderovski and Willard, 2005). When the receptor is uncoupled from G protein via GRK-arrestin-dependent desensitization, the signalling is sustained by remaining active G proteins. RGS proteins, by facilitating G protein deactivation, promote complete signal shutoff. RGS availability and function is an important determinant of the signal intensity and duration. Therefore, it is conceivable that RGS function is perturbed in LID contributing to the deregulation of the DA receptor signalling. In some systems, RGSs and not GRKs are rate-limiting for the overall signal shutoff (Krispel *et al.*, 2006). The RGS family is large and diverse (Ross and Wilkie, 2000), with many members expressed in striatal neurons (Gold *et al.*, 2007; Gold *et al.*, 1997). The RGS9-2 isoform is highly enriched in the striatum in comparison with other brain structures (Gold *et al.*, 2007; Gold *et al.*, 1997; Granneman *et al.*, 1998; Kovoor *et al.*, 2005; Rahman *et al.*, 1999; Rahman *et al.*, 2003). The concentration of multiple RGS proteins is responsive to changes in the DAergic environment (Ding *et al.*, 2006; Geurts *et al.*, 2002; Geurts *et al.*, 2003; Ko *et al.*, 2014b). Any deregulation of this complex well-orchestrated mechanism of termination of the GPCR signalling would result in a profound enhancement of signal duration and/or intensity and is likely to bring about multiple behavioural deficits.

Mammals express seven GRK subtypes, with two isoforms, GRK1 and GRK7, being confined to the retinal photoreceptors and one, GRK4, - largely to testes (Gurevich *et al.*, 2012; Mushegian *et al.*, 2012). Four isoforms, GRK2, 3, 5, and 6, are ubiquitously expressed

throughout the brain including the striatum (Ahmed *et al.*, 2007; Ahmed *et al.*, 2008; Bychkov *et al.*, 2010; Bychkov *et al.*, 2011; Bychkov *et al.*, 2013; Bychkov *et al.*, 2008). Since the number of non-visual GRKs is limited and much lower than the number of ~ 700 mammalian GPCRs they serve, it is generally assumed that each isoform phosphorylates numerous GPCRs. However, studies in GRK KO mice brought forward evidence of *in vivo* receptor specificity of GRKs [see discussion in (Gurevich *et al.*, 2012)]. Furthermore, evidence of differential functional consequence of the receptor phosphorylation by different GRKs [the "barcode" concept (Kim *et al.*, 2005; Liggett, 2011; Nobles *et al.*, 2011; Ren *et al.*, 2005; Zidar *et al.*, 2009)] strongly suggests that GRK isoforms are not interchangeable, but each has a defined function. The receptor specificity and functional role of GRKs *in vivo* remains to be elucidated [for in depth discussion see (Gurevich *et al.*, 2012)]. The human and rodent striatum expresses all four ubiquitous non-visual GRKs (Ahmed *et al.*, 2010; Ahmed *et al.*, 2007; Ahmed *et al.*, 2008; Bychkov *et al.*, 2013; Bychkov *et al.*, 2008). In the rat, GRKs 2 and 5 are equally expressed in the direct and indirect pathway MSNs, but GRK2 is highly enriched in cholinergic interneurons, as compared to the output neurons, whereas GRK5 is expressed at similar level in both (Bychkov *et al.*, 2013). Unfortunately, the expression pattern of GRK6, the highest expressed GRK in the rodent striatum, is yet undefined. Experiments with GRK knock-out mice demonstrated that mice lacking GRK6 were supersensitive to behavioural effects of DAergic drugs, whereas mice lacking the closest relative of GRK6, GRK5, were not (Gainetdinov *et al.*, 2003; Gainetdinov *et al.*, 1999; Gainetdinov *et al.*, 2004). The data strongly suggest that GRK6 is primarily responsible for desensitization of DA receptors. Furthermore, the data support the notion that loss of GRK6 results in enhanced responsiveness of DA receptors to DAergic stimulation.

When DAergic neurons degenerate in PD or in animal models of PD, striatal dopaminoceptive neurons put into place a number of adaptive mechanisms aimed at maintaining the failing signalling (Bezard and Gross, 1998). One effective adaptive response would be a reduction in the level of GRKs. Indeed, in hemiparkinsonian rats, the level of GRKs in the lesioned striatum is decreased, as compared to the intact side, most noticeably that of GRK6 and GRK3 (Ahmed *et al.*, 2010; Ahmed *et al.*, 2007). Such effect could be considered adaptive, because it counteracts the effect of the DAergic lesion, allowing, due to resulting DA receptor supersensitivity, for the signal transmission even with the grossly reduced concentration of DA. Importantly, this reduction in the GRK concentration was not reversed by chronic L-dopa treatment (Ahmed *et al.*, 2010; Ahmed *et al.*, 2007). GRK6, presumably the main isoform regulating DA receptors, was consistently reduced by DA

depletion across striatal subdivisions. The decrease of GRK6A, the splice variant most abundant in the rat brain at the mRNA level (Firsov and Elalouf, 1997) (the protein levels were never compared), reached ~40%, whereas GRK6B splice variant was only marginally reduced (Ahmed *et al.*, 2010). The GRK concentration also tended to be lower in post-mortem striatal samples from PD patients without dementia (Bychkov *et al.*, 2008), which might be the result of years of L-dopa treatment and associated with LID, since the samples were mostly from end-stage patients. Interestingly, in MPTP-treated parkinsonian drug-naïve monkeys, GRKs, particularly GRKs 2 and 6, were elevated as compared to control, and chronic L-dopa reduced the expression to normal in both non-dyskinetic and overtly dyskinetic animals (Bezard *et al.*, 2005). It is conceivable that in this case the increase in the GRK concentration was a part of the pathological process aggravating signalling deficiency. The L-dopa treatment reverts the defect by reducing the GRK concentration, but at the same time the GRK availability could have become grossly insufficient during high signalling periods at the peak of L-dopa concentration. Overall, the background of low GRK availability relative to the demand at the time of high DA concentration generated from peak-dose L-dopa is likely to be a contributing factor to signalling abnormalities associated with peak-dose LID.

This idea was tested by studying the effect of *in vivo* knockdown of GRK6 in the lesioned striatum of hemiparkinsonian rats using LV-delivered miRNA (Ahmed *et al.*, 2010). The reduction in the GRK6 achieved by such knockdown was slightly less than 40% for both GRK6A and GRK6B proteins. The GRK6 knockdown strongly enhanced the frequency of L-dopa-induced contralateral rotations and promoted behavioural sensitization to L-dopa, the phenomenon relevant for LID. Furthermore, rats with reduced GRK6 concentration demonstrated increased frequency of AIMs (Ahmed *et al.*, 2010). These data further support the notion that a deficit in GRK availability, specifically that of GRK6, leads to defective desensitization, enhanced signalling, and ultimately, promotes LID-like behaviour. The fact that a relatively modest loss of GRK6 was sufficient to significantly affect behaviour underscores the critical contribution of the GRK-dependent regulation of the DAergic signalling to LID.

If reduced GRK concentration aggravated LID, then increased GRK availability should ameliorate it. The study employing LV-mediated overexpression of GRK6A in the DA-depleted striatum showed that increased GRK6 concentration resulted in reduced frequency of L-dopa-induced rotations and lower AIMs scores (Ahmed *et al.*, 2010; Ahmed *et al.*, 2015). The behavioural improvement was accompanied by amelioration of molecular hallmarks of LID: characteristic upregulation of prodynorphin and preproenkephalin (PPE-A) mRNA and

the D_3R concentration in the caudate-putamen were all significantly reduced in the GRK6-expressing rats as compared to the GFP-expressing control (Ahmed *et al.*, 2010) as well canonical and non cnonical signalling pathways (Ahmed *et al.*, 2015). Furthermore, lentiviral overexpression of GRK6 in the putamen of MPTP-lesioned monkeys rendered dyskinetic by chronic L-dopa treatment significantly ameliorated peak-dose LID (Ahmed *et al.*, 2010). As in the case of the rodent model of LID, the behavioural improvement was accompanied by a reduction in the level of prodynorphin mRNA, which was elevated in L-dopa-treated animals. Thus, the data in both the rodent and monkey models of LID support the anti-LID potential of GRK6.

GRK6 is likely to alter the DA-dependent behaviour by facilitating desensitization of DA receptors. This notion is supported by the fact that trafficking of the D_1R is markedly improved in the lesioned striatum of rats expressing GRK6, whereas the D_2R was unaffected (Ahmed *et al.*, 2010). These data appear to be inconsistent with the previous finding in GRK6 knock-out mice. Indeed, behavioural supersensitivity to psychostimulants in these animals seems provoked through a modified signalling via the D_2R but not the D_1R (Gainetdinov *et al.*, 2003). As explained at length in previous sections, DA depletion and subsequent LID development in the course of L-dopa treatment precipitates dramatic changes in the function of striatal DA receptors that become supersensitive to DAergic stimulation (Brown *et al.*, 2005; Bychkov *et al.*, 2007; Cai *et al.*, 2000; Corvol *et al.*, 2004; Gerfen, 2000; Gerfen *et al.*, 2002; Pifl *et al.*, 1992a; Pifl *et al.*, 1992b; Ravenscroft *et al.*, 2004; Sgambato-Faure *et al.*, 2005; Tong *et al.*, 2004; Ungerstedt, 1971b) see also (Gurevich and Gurevich, 2010) and references therein]. It is generally believed that both major receptor subtypes contribute to LID, but the D_1R seems to play a particularly important role (Aubert *et al.*, 2005; Berthet *et al.*, 2009; Guigoni *et al.*, 2005a; Guigoni *et al.*, 2007), and multiple aberrations in D_1R signalling are readily detectable in the brain of dyskinetic animals (Aubert *et al.*, 2005; Berthet *et al.*, 2009; Gerfen, 2000; Gerfen *et al.*, 1990; Gerfen *et al.*, 1995; Gerfen *et al.*, 1991; Gerfen *et al.*, 2002; Guigoni *et al.*, 2007). In the dyskinetic monkey, LV-mediated expression of GRK6 reduced LID caused by either the selective D_1R agonist SKF 38393 or the D_2R agonist ropinirole, indicating that its anti-LID effect was mediated via both receptor subtypes (Ahmed *et al.*, 2010). The suppression by GRK6 of the L-dopa-induced upregulation of prodynorphin and D_3R receptor mRNA in hemiparkinsonian rats and prodynorphin elevation in parkinsonian monkeys also support the notion of GRK6 acting at the D_1R, since both effects are attributed to the enhanced D_1R signalling (Bordet *et al.*, 1997; Gerfen *et al.*, 1990; Gerfen *et al.*, 1991). Although no GRK6-induced increase in the D_2R internalization

was detected, GRK6 reduced the upregulation of preproenkephalin mRNA expressed in D_2R-bearing neurons (Gerfen *et al.*, 1990; Gerfen *et al.*, 1991; Le Moine and Bloch, 1995; Morissette *et al.*, 1997), which suggests a GRK6 effect at the D_2R. Thus, the data in the rodent and monkey models of LID collectively point to the involvement of both D_1R and D_2R in the anti-LID action of GRK6.

However, studies in living animals cannot prove that the effect is direct. Since the change in the D_1R trafficking in the rat model was observed, this would suggest a direct GRK6-dependent phosphorylation of the D_1R followed by arrestin binding and intracellular trafficking. The lack of a similar effect on the D_2R leaves room for doubt. However, receptor desensitization may not necessarily be accompanied by internalization (Pan *et al.*, 2003) and trafficking measures could be underestimating the degree of desensitization. Alternatively, D_2R could be less affected by GRK6, since they are known to be resistant to desensitization (Kim *et al.*, 2001; Tiberi *et al.*, 1996). The data in the monkey model bears out this suggestion. When the animals were treated with selective D_1R or D_2R/D_3R agonists instead of L-dopa, transgenic GRK6 not only suppressed LID but also shortened the overall duration of their effects, including the anti-parkinsonian activity. This mode of action is likely reflective of faster and more profound receptor desensitization due to increased GRK6 availability. GRK6 had only a marginal effect on the duration of D_2R-mediated effects, whereas it substantially shortened that of the D_1R agonist, which again supports the notion of the D_1R as the prime target of GRK6. It is important to bear in mind that striatal neurons express other non-DA GPCRs that modulate LID and could be affected by GRK6. It is possible that the effect of GRK6 on the D_2R-dependent signalling is in fact indirectly mediated by other receptors, such as, for example, the adenosine A_{2A} receptor. The inactivation or inhibition of the A_{2A} receptor is known to modestly ameliorate LID and/or provides limited anti-parkinsonian benefits in parkinsonian animals and humans (Fredduzzi *et al.*, 2002; Lundblad *et al.*, 2003; Pinna *et al.*, 2001; Xiao *et al.*, 2006) (see *ad hoc* sections). GRK6-dependent desensitization of the A_{2A} receptor would mimic its inactivation bringing about anti-LID and signalling benefits associated with reduced A_{2A} signalling. The inhibition of the lesion-induced upregulation of enkephalin by GRK6 may be the result of such suppression of A_{2A} receptor activity, similarly to the action of the A_{2A} antagonist KW-6002 (Lundblad *et al.*, 2003).

The biggest stumbling block in the development of viable anti-LID therapies has been separating therapeutic and dyskinetic effects of L-dopa. Both functions of the drug are mediated by DA receptors, and over the years of therapy the anti-parkinsonian and dyskinetic

effects become so intertwined, that reducing LID may mean losing anti-parkinsonian effect as well. Remarkably, GRK6 suppresses LID in dyskinetic monkeys without compromising the anti-parkinsonian effects of L-dopa. In fact, GRK6 prolongs the anti-parkinsonian effect, especially at the lower L-dopa dose. The duration of the anti-parkinsonian effect of the half-dose in GRK6-expressing animals was even slightly longer than that of the full L-dopa dose in controls. Importantly, the additional time afforded by GRK6 was LID-free (Ahmed *et al.*, 2010). Mechanistically, preservation of the anti-parkinsonian activity coupled with reduced LID likely stems, at least, in part, from GRK selectivity towards active GPCRs (Boguth *et al.*, 2010; Huang *et al.*, 2011a; Huang and Tesmer, 2011; Huang *et al.*, 2009). This initial signalling may be sufficient for the anti-parkinsonian effect but receptor desensitization process prevents it from rising high enough to cause LID. This is hardly surprising, because the receptor desensitization machinery is designed to achieve precisely this effect: to limit the duration and intensity of the signal following receptor activation but not to prevent the signalling event. Additionally, GRK6-dependent rebalancing of the striatal circuitry may also play a beneficial role. The fact that GRK6 extended the anti-parkinsonian effect of L-dopa while shortening that of both D_1R and D_2R selective agonists may be due to the action of L-dopa-derived DA at both D_1R and D_2R. If GRK6 mostly desensitized D_1R, it would shift the overall signalling balance in favour of the D_2R-mediated signalling, reducing the D_1R-dependent LID but sustaining the beneficial effect through still active D_2R. Thus, the receptor desensitization mechanism seems like a perfect target when there is a need to rebalance the runaway signalling. Indeed, the data in the monkey model of PD prove that targeting the receptor desensitization machinery for anti-LID therapy may help to reach an elusive goal of controlling LID without sacrificing the anti-parkinsonian benefits of L-dopa.

GRK-mediated receptor phosphorylation leads to arrestin binding that shields the cytoplasmic surface of the receptor, precluding further G protein activation (Krupnick *et al.*, 1997; Wilden, 1995). Complete GPCR shutoff is thus achieved only after arrestin binding. In addition to G-protein mediated signalling, many GPCRs, including DA receptors, signal through ß-arrestin dependent mechanisms (Beaulieu *et al.*, 2007; Lefkowitz and Shenoy, 2005). The two isoforms of β-arrestin, β-arrestin1 (βarr1) and β-arrestin2 (βarr2) are widely co-expressed in the brain (Attramadal *et al.*, 1992; Gainetdinov *et al.*, 2004). It is now apparent that β-arrestins regulate physiology and behaviours that are independent of G protein signalling through their ability to scaffold multiple intracellular signalling molecules such as kinases and phosphatases (Beaulieu *et al.*, 2007; Lefkowitz and Shenoy, 2005; Luttrell *et al.*, 1999; Xiao *et al.*, 2007). Studies from Marc Caron's laboratory have shown that through D_1R and D_2R,

βarr2-mediated signalling plays a major role in DA-dependent locomotion (Beaulieu *et al.*, 2007; Beaulieu *et al.*, 2005; Urs *et al.*, 2011), raising the possibility that targeting βarr2 function in the DA system might be ideal since through its scaffolding of kinases it can facilitate locomotion and simultaneously through its desensitization of G protein signalling reduce dyskinesia, without potentially affecting other neurotransmitter systems. In a recent study, Urs and co-workers provided evidence supporting the hypothesis that up-regulating βarr2 expression not only ameliorates LIDs but also enhances the therapeutic effects of L-dopa (Urs *et al.*, 2015). Four different animal models of PD and LIDs were used to support this notion – i) the bilateral DA-deficient DAT-knock-out (DDD) mouse model (cf. section 4.4.) (Sotnikova *et al.*, 2006), ii) the unilateral 6-hydroxydopamine (6-OHDA)-lesioned mouse model (c.f. section 4.3.2.), iii) the unilateral 6-OHDA-lesioned rat model (c.f. section 4.3.1.) and iv) the bilateral MPTP-lesioned macaque model of PD (c.f. section 4.6.2.) (Urs *et al.*, 2015). Using these various animal models, Urs and co-workers showed that deletion of βarr2 enhances LIDs and reduces forward locomotion but that over-expression of βarr2 in the motor striatum reduces AIMs or LIDs and enhances the therapeutic effects of L-dopa both in rodent and primate models (Urs *et al.*, 2015). T understanding of the pleiotropic actions of arrestins upon signalling, which parallel the canonical and non-canonical signallings through G protein, has led to the development and application of the concept of biased signalling or functional selectivity. Evidence from the literature has shown that individual signalling pathways through the same receptor have the ability to mediate distinct physiological responses. Moreover, targeting these specific signalling pathways affects specific physiological outcomes without affecting others. Thus leveraging functional selectivity to exploit this dichotomous signalling might prove to be ideal for PD therapy. In the future, either generating allosteric G protein biased antagonists at D_1Rs as a supplement to L-DOPA or generating β-arrestin biased agonists at D_1R and/or D_2R might mimic the actions of L-dopa without inducing dyskinesia.

When DA receptors are completely desensitized with arrestins preventing further coupling to G proteins, previously generated active G proteins may still persist and activate downstream targets. However, neither DA depletion nor subsequent L-dopa treatment altered the expression of RGS9-2 in the monkey striatum (Gold *et al.*, 2007). No changes were seen in other RGS proteins (RGS2, 7, 4 or in the level of RGS anchoring protein Gß5) abundant in the striatum of this model (but see the increase in RGS4 in dyskinetic unilateral 6-OHDA-lesioned rat (Ko *et al.*, 2014b). Nevertheless, viral upregulation of RGS9-2 resulted in reduced LID coupled with preservation of the anti-parkinsonian effect of L-dopa in dyskinetic MPTP-

lesioned monkeys and in the reduction in AIMs scores in hemiparkinsonian rats (Gold *et al.*, 2007). Importantly, the magnitude of the RGS9-2-dependent effects was considerably smaller than that observed in the experiments with GRK6. The likely reason is that RGS9-2 selectively binds to and accelerates deactivation of Gαi, but not Gαs/olf (Rahman *et al.*, 2003; Ross and Wilkie, 2000). Thus, RGS9-2 quenches the signalling via the Gi-coupled D2 receptor but not via Gs/olf-coupled D_1R, whereas GRK6 apparently acts via both DA receptors. Since the D_1R deregulation is believed to make the leading contribution to molecular mechanisms responsible for LID (Aubert *et al.*, 2005; Berthet *et al.*, 2009; Feyder *et al.*, 2011; Guigoni *et al.*, 2005a; Guigoni *et al.*, 2007), targeting exclusively the D_2R is less effective than targeting both. Nevertheless, facilitating the RGS9-2-dependent quenching of the Gi-dependent signalling offered substantial anti-LID benefits in the monkey model of LID, proving that RGS-dependent desensitization of the DA receptor signalling is a critical component of the signalling homeostasis in striatal neurons, and its deregulation is likely to be a part of LID pathophysiology.

In the same way, although less documented, is the putative role of RGS4. As indicated above, RGS4 mRNA was recently found increased in the striatum of the rat analog of LID, even correlating with peak-dose AIMs (Ko *et al.*, 2014b). Interestingly, suppressing the elevation of RGS4 mRNA levels using an antisense oligonucleotide in the striatum during L-dopa priming attenuates the behavioural and molecular markers of AIMs in 6-OHDA-lesioned rats (Ko *et al.*, 2014b). While the LID severity reduction after overexpression of striatal RGS9-2 in MPTP-lesioned monkeys is specifically related to the attenuation of D_2R (Gold *et al.*, 2007), the question of the identity of the GPCR(s) responsible for this RGS4 effect arises. The effect of RGS4 protein modulation on reduced physiological expression of AIMs may be mediated through mGluR5 receptor interactions (Schwendt and McGinty, 2007). In support of this, a study demonstrated that overexpression of RGS4 proteins in the rat dorsal striatum modulated the mGluR5-mediated activation of p-ERK1/2, mimicking the molecular effects of mGluR5 receptor antagonist, 3-((2-methyl-4-thiazolyl)ethynyl)pyridine (MTEP) on dopaminergic agents (Schwendt *et al.*, 2012). Intriguingly, the molecular effects of suppressing the up-regulation of RGS4 mRNA levels during L-dopa priming i.e. reduced striatal up-regulation of preproenkephalin (PPE)-B, but not PPE-A, mRNA, i.e. indicative of a normalization of LID-related markers in the direct pathway D_1R-expressing neurons are similar to those found following combined de novo treatment of MTEP and L-dopa in 6-OHDA-lesioned rats (Mela *et al.*, 2007). A study also demonstrated that endogenous RGS4 protein levels are involved in striatal LTD, where it was shown that RGS4 proteins mediate

sophisticated cross-talk interactions between several GPCRs, such as mGluR group I, dopamine D_2R and adenosine A_{2a} receptors (Lerner and Kreitzer, 2012). This same study also showed that high levels of RGS4 proteins blocked LTD in striatopallidal neurons. It is therefore reasonable to suggest that the persistent up- regulation of striatal RGS4 in L-dopa priming in 6-OHDA-lesioned rat may contribute to an abnormal striatal plasticity in the development of L-dopa-induced AIMs, i.e. loss of LTD regulation (Belujon *et al.*, 2010), the specific mechanisms of which are worthy of further investigation, notably because of the absence of normalization of LID-enhanced PPE-A mRNA levels .

To summarize, known molecular mechanisms of action of GRKs and arrestins suggest that these proteins play a key role in neuronal adaptations, including changes in signalling caused by DA depletion and subsequent L-dopa therapy. The role of RGS proteins in the signalling aberrations associated with LID also deserves attention. Unfortunately, mechanistic information regarding the precise role of GRKs, arrestins, or RGSs in the physiological processes associated with these signalling adaptations is currently very limited. GRK6 appears to be the best therapeutic target with proven efficacy in both rodent and monkey models of LID. Furthermore, as a kinase, GRK6 is a "druggable" target. As a group, kinases are second only to GPCRs as drug targets (Cohen, 2002; Melnikova and Golden, 2004). At the moment, there are no drugs selectively aimed at GRK6 or even at the whole GRK4 subfamily, which includes GRKs 4, 5, and 6. Furthermore, for this particular purpose an activator rather than inhibitor would be needed. To the best of our knowledge, no drug that enhances the activity of any GRK has been found (yet). This is perhaps not surprising, given the mode of the drug discovery effort for kinases that so far targeted mostly the kinase domain in search for kinase inhibitors (Fischer, 2004; Ma *et al.*, 2008; Melnikova and Golden, 2004; von Ahsen and Bömer, 2005). The approach has now been expanded to incorporate allosteric type regulators that could act as activators as well as inhibitors (Eglen and Reisine, 2011; Simpson *et al.*, 2009). For GRKs, targeting the GRK-receptor interface offers the best opportunity to find isoform-selective modulators enhancing or inhibiting their activity, although this is by no means a trivial task. Alternatively, drugs regulating the expression, and/or stability of GRKs, arrestins, or RGSs could be developed. Pathway biased agonists for DA receptors that preferentially engage GRK-mediated receptor phosphorylation and arrestin binding are becoming available (Shukla *et al.*, 2011; Violin and Lefkowitz, 2007; Zidar *et al.*, 2009) and can be further developed. Since the receptor desensitization system is a natural mechanism designed to adjust GPCR responsiveness to the intensity and duration of receptor

stimulation, manipulation of its capacity is able to yield a precisely fine-tuned regulation of the signalling that could be exploited for efficacious anti-LID therapy.

5.9.6. Dysregulation of lateral diffusion

As reported above, D_1R is actively anchored at membrane despite high extracellular levels of DA. While impairment of homologous desensitization might certainly account for a significant part of the phenomenon, we should envision as well the possibility that surface diffusion of DA receptors, i.e. away from the signalling area on the neck of the spines, plays an important role as well. The membrane distribution of DA and glutamate receptors at the neuronal surface has indeed been found to be highly dependent on their lateral diffusion properties, which in turn has a huge impact upon their function. Schematically, the measurement of receptor trafficking in neurons greatly benefited from both experimental and conceptual advances made in the field of biophysics and high-resolution imaging (Giepmans *et al.*, 2006). Singer and Nicolson proposed in the 1970s that the plasma membrane is a 'two-dimensional oriented solution of integral proteins embedded in a viscous ‘phospholipid bilayer’ (Singer and Nicolson, 1972). Proteins move passively within the plasma membrane, through thermal motion of surrounding molecules (i.e. phospholipids), which randomly and continuously change both direction and speed. Experimental evidences have now shown that interactions with obstacles in or beneath the membrane are mostly responsible for the lower value of diffusion where compared to the theoretical one in reconstituted membrane. Of importance in physiology, temperature is a critical factor that influences diffusion within membrane. For instance, a temperature change of 10-15^{o}C induces approximately a 2-fold change in protein diffusion coefficient within plasma membrane (Axelrod *et al.*, 1976; Tardin *et al.*, 2003). At the experimental level, the surface trafficking of receptors in neurons was demonstrated and monitored by several approaches, ranging from classical electrophysiological recordings to single particle tracking and ensemble imaging approaches (e.g. fluorescent recovery after photobleaching). To date, the lateral diffusion at the neuronal surface has been demonstrated for all explored neurotransmitter receptors or membrane proteins, which include glutamatergic mGlu5, AMPA and NMDA receptors (Ashby *et al.*, 2006; Borgdorff and Choquet, 2002; Groc *et al.*, 2004; Groc *et al.*, 2006; Tardin *et al.*, 2003), glycine receptor (Dahan *et al.*, 2003; Meier *et al.*, 2001), GABA-A receptor (Bouzigues and Dahan, 2007), ß2-adrenergic receptor (Hegener *et al.*, 2004), µ-opioid receptor (Lober *et al.*,

2006). Several reviews have been published on that topic (Bard and Groc, 2011; Choquet and Triller, 2013; Gerrow and Triller, 2010; Ladepeche *et al.*, 2014; Triller and Choquet, 2008).

Regarding the trafficking of surface D_1R, the first study exploring D_1R surface mobility used an ensemble approach in which intracellular and surface D_1R were examined and displayed that the majority of dendritic D_1R diffused in the plane of the membrane and their mobility was confined by interaction with NMDA receptors (Scott *et al.*, 2006). Using single nanoparticle tracking of solely surface D_1R, Porras et al. and directly demonstrated that D1 receptor is indeed quite dynamic at the surface of striatal neurons (Porras *et al.*, 2012a). In basal condition, more than 80% of surface D_1R was mobile at the surface of striatal neurons. D_1Rs explore large dendritic area, exchanging from various membrane compartments, including glutamate synapses, at a rather high frequency. Exposure to NMDA reduced the diffusion coefficient for D1 receptor and caused an increase in the number of D_1R-positive spines (Scott *et al.*, 2006), a situation highly reminiscent of the elevated extracellular levels of glutamate (Robelet *et al.*, 2004) and DA (Lindgren *et al.*, 2010; Meissner *et al.*, 2006) associated with LID. The functional interplay with NMDA receptor can be direct through protein-protein interaction (Cahill *et al.*, 2014; Lee *et al.*, 2002; Scott *et al.*, 2006) or indirect through the PSD-95 protein that interacts and regulates D_1R membrane content (Fiorentini *et al.*, 2003; Yao *et al.*, 2008; Zhang *et al.*, 2007).

The scaffold protein PSD-95 is at the crossroad of glutamate and DA signal modulation (Kim and Sheng, 2004), especially as glutamatergic and DA terminals form the so-called “synaptic triad” at postsynaptic dendritic spines in the striatum (Yao *et al.*, 2004). Lowering PSD-95 levels in neurons increased the overall surface diffusion of D_1R and decreased their surface membrane content (Porras *et al.*, 2012a). Comparable effects were obtained with a TAT-D_1R/PSD95 peptide that prevents the direct interaction between D_1R and PSD-95 (Porras *et al.*, 2012a). This supports the proposition that PSD-95-D_1R interaction governs D_1R surface dynamics in the extrasynaptic compartment. Whether this holds in striatal glutamate synapses remains however unknown. In addition, it cannot be excluded that PSD-95 alters D_1R intracellular trafficking (exocytotic or endocytotic rate) and surface delivery (Fiorentini *et al.*, 2003; Yao *et al.*, 2008; Zhang *et al.*, 2007), which will consequently modulate the dynamics of the surface receptors.

To shed new lights on these issues, studies have been performed, mostly in hippocampal neurons. They schematically demonstrated that D_1Rs laterally diffuse within glutamate synapses, with lower speed (Ladepeche *et al.*, 2013a). The disruption of the interaction between D_1R and PSD95, using variants of PSD95 or D_1R/PSD95 interaction competing

peptides, did however not affect D_1R dynamics in glutamatergic synapses (Ladepeche *et al.*, 2013b). Strikingly, preventing the physical interaction between D_1R and the GluN1 subunit of NMDA receptors, using a competing peptide, fully abolished the synaptic stabilization of diffusing D_1R, indicating that D_1R are dynamically retained in glutamate synapse through a mechanism requiring the interaction of the receptor with NMDA receptor (Ladepeche *et al.*, 2013a; Ladepeche *et al.*, 2013b). Such single nanoparticle studies demonstrate that the physical interaction between D_1R and NMDA receptors participate to this cross-talk since the capacity of a glutamate synapse to retain DA receptors, and thus to express DA receptor-mediated signalling, is dependent on their dynamic interaction. Consistently, the direct interaction between D_1R and NMDA receptors has been shown to regulate glutamate synaptic transmission, plasticity, and working memory in rodents (Ladepeche *et al.*, 2013a; Nai *et al.*, 2010). It will be of great interest to investigate the role of the DA and glutamate release on D_1R synaptic anchoring by NMDA receptor, since this molecular dynamic cross-road could serve as a physiological integrator of the DA and glutamate system overall activities. In addition, whether such molecular mechanisms apply to striatal networks, as a whole or in a specific subset of glutamate synapses are key questions that remain to be addressed. Finally, direct other interactors of D_1R are present at the plasma membrane of neurons, including D_2R, D_3R, adenosine A_1 receptor, and N-type calcium channel (Fiorentini *et al.*, 2008; Gines *et al.*, 2000; Kisilevsky *et al.*, 2008; Marcellino *et al.*, 2008), providing potential other mechanisms for stabilization in different membrane compartments. Dissecting the timing and role of these interacting cascades will likely shed new key lights on the regulation of D_1R surface trafficking and interplay with the glutamatergic signalling in physiology and pathology such as LID.

5.9.7. D_1 receptor stimulation impairs striatal proteasome activity

The above sections presented the complex alterations in DA signalling in D_1R-expressing MSNs supporting the development or expression of LID. Among those, the dysregulation of D_1R expression, lateral diffusion, intraneuronal trafficking, subcellular localization and desensitization that all lead to a pathological anchorage of D_1R at the plasma membrane (Aubert *et al.*, 2005; Berthet *et al.*, 2012; Berthet *et al.*, 2009; Guigoni *et al.*, 2007; Porras *et al.*, 2012a).

Parallel to these efforts, experimental evidence has accumulated suggesting that the proteasome plays a significant role in neurotransmitter response and synaptic plasticity in

physiological and pathological conditions (Bingol and Schuman, 2006; Citri *et al.*, 2009; DiAntonio and Hicke, 2004; Patrick *et al.*, 2003). Interestingly, a reduced proteasome activity has been observed in PD patients under treatment with L-dopa and DA agonists in peripheral blood lymphocytes (Blandini *et al.*, 2006). Building upon this seminal information, Berthet et al. demonstrated that such decreased proteasomal catalytic activity resulted into the D_1R abnormal trafficking, i.e. its exaggerated cell surface abundance (Berthet *et al.*, 2012). In addition, impairment of the ubiquitine-proteasome system at specific nodes (E3 ligase parkin, polyubiquitination, proteasome catalytic activity) in several experimental models of PD led to the same phenomenon, i.e. aberrant behavioural response to DA replacement therapy in PD (Berthet *et al.*, 2012). While those data highlighted the intimate interplay between DA receptor and proteasome activity, the precise mechanisms by which L-dopa affects striatal proteasome activity remained unknown. Such rapid modulation of striatal catalytic activity actually intervenes through D_1R-mediated disassembly of the 26S proteasome in the absence of changes in proteasome subunits expression (Barroso-Chinea *et al.*, 2015), further highlighting the extremely complex impact of L-dopa upon MSNs.

A fascinating resulting hypothesis posits that L-dopa, through impairment of proteasome catalytic activity, would lead to accumulation of undegraded proteins. Scholz et al. hence studied the proteome in DA-depleted striatum of macaque monkeys with and without subsequent acute and chronic L-dopa treatment using two-dimensional difference in-gel electrophoresis and mass spectrometry (Kultima *et al.*, 2006; Scholz *et al.*, 2008). Their data suggested that the DA-depleted striatum is actually so sensitive to *de novo* L-dopa treatment that the first ever administration alone is able (i) to induce rapid post-translational modification-based proteomic changes that are specific to this first exposure and (ii), possibly, lead to irreversible protein level changes that would not be further modified by chronic L-dopa treatment (Kultima *et al.*, 2006; Scholz *et al.*, 2008). The equivalence between first and chronic L-dopa administration suggests that priming would be the direct consequence of L-dopa-driven impairment in catalytic proteasomal activity (Scholz *et al.*, 2008). An alternate and/or complementary hypothesis involves the D_1R-medsiated effect on protein translation discussed above.

5.9.8. Glutamate receptors

In the last decade, several studies indicated that dysfunction of the glutamatergic system plays a key role both in both PD and LID (Calabresi *et al.*, 2010). Alterations in the corticostriatal

glutamatergic transmission have been reported not only in animal models of PD and LID (Mellone and Gardoni, 2013; Sgambato-Faure and Cenci, 2012), but also in PD patients at different disease stages (Ahmed *et al.*, 2011). In particular, the subcellular organization and the functional interactions of glutamate receptors in the striatum appear to be critical both in the pathogenesis of PD and in the onset of LID.

5.9.8.1. NMDA receptors

After chronic treatment with L-dopa, the glutamatergic signalling from the cortex to the striatum undergoes adaptive changes, which lead to an aberrant functioning of NMDA receptors at striatal MSN dendritic spines. NMDA receptor antagonists have been shown to exert a beneficial effect in blocking the development of dyskinesia in experimental models of LID (Hadj Tahar *et al.*, 2004; Nash *et al.*, 2004; Wessell *et al.*, 2004), even though conflicting findings also have been also reported (Nash *et al.*, 2004; Rylander *et al.*, 2009).

Besides NMDA receptor over-activation, alterations in the trafficking and localization of NMDA receptor regulatory subunits at the postsynaptic membrane have been shown in several neurodegenerative disorders (Mellone and Gardoni, 2013; Sanz-Clemente *et al.*, 2013). Consequently, restoring the physiological synaptic NMDA receptor subunit composition could represent an innovative therapeutic strategy to be explored in the close future. A great number of studies have focused on the role of the synaptic distribution and the phosphorylation state of specific NMDA receptor subtypes in animal models of LID. Changes in the localization of NMDA receptor subunits at the striatal synapse have been described in both DA-denervated rats (Picconi *et al.*, 2004) and L-dopa-treated dyskinetic macaques (Hallett *et al.*, 2005), even though the mechanisms regulating NMDA receptor trafficking and function in experimental parkinsonism and LID are far from being elucidated. In physiological conditions, GluN2B-containing NMDA receptors are the major subtype at MSN synapses. However, in L-dopa-treated dyskinetic rats, GluN2B is redistributed to the extrasynaptic membrane, while the synaptic levels of GluN2A are aberrantly increased in the striatum (Gardoni *et al.*, 2006). These events are paralleled by modifications in the association of GluN2B subunit with members of the PSD-MAGUKs family. Moreover, treatment of non-dyskinetic animals with a cell-permeable peptide (CPP) able to reduce the synaptic localization of GluN2B–containing NMDA receptors caused the appearance of dyskinetic behaviours, confirming the importance of a correct balance in NMDA receptor regulatory subunits at synaptic sites (Gardoni *et al.*, 2006). Interestingly, NMDA receptor regulatory

subunits might not be the only ones in the spotlight. Indeed D_1R-GluN1 complexes have been uncovered as a major substrate for DA-glutamate interaction in MSNs, which is usurped by psychostimulants (e.g. L-dopa in PD patients) to lead to abnormal signalling and persistent behavioral alterations (Cahill *et al.*, 2014).

The role of PSD-MAGUKs in dyskinesia has also been investigated. More specifically, Nash et al. suggested that the onset of LID is associated with the increase in PSD-95 and SAP97 proteins at the synaptic membrane (Nash *et al.*, 2005). This result was confirmed later in rodent and primate models of LID (Porras *et al.*, 2012a). Moreover, treatment with a CPP disrupting GluN2A/PSD-MAGUKs interaction demonstrated that a decrease in synaptic GluN2A-containing NMDA receptors induces a significant reduction in the onset of LID in 6-OHDA-lesioned rats (Gardoni *et al.*, 2012).

Early work addressing modifications in the phosphorylation state of NMDA receptor subunits identified increased levels of GluN2B-ptyr1472 in different animal models of LID (Oh *et al.*, 1998; Quintana *et al.*, 2010), and suggested a reduction of AP-2-mediated endocytosis of GluN2B and the consequent increase in its surface content (Sanz-Clemente *et al.*, 2013). For this reason, GluN2B-selective antagonists have been considered a promising tool for the treatment of LID, but thye were proved as difficult to develop due to the induced side-effects.

Overall, the number of studies which are reviewed here strongly substantiate the idea that, in the corticostriatal glutamatergic synapse, molecular disturbances of the NMDA receptor complex initially caused by DA denervation may have a causal role in the development of LID and can represent a target for therapeutic intervention.

5.9.8.2. AMPA receptors

AMPA receptors are highly dynamic in terms of phosphorylation and insertion/endocytosis at the postsynaptic membrane (Shepherd and Huganir, 2007). Therefore, understanding the molecular mechanisms that control the receptor trafficking is essential to determine AMPA receptor involvement in neurological disorders.

Alterations in synaptic AMPA receptor expression, subunit composition and phosphorylation have been observed in animal models of LID and in PD patients. An increase in AMPA receptor binding has been reported in the lateral striatum of dyskinetic animals (Calon *et al.*, 2002; Ouattara *et al.*, 2010b) and in PD patients (Calon *et al.*, 2003). Enhanced AMPA receptor subunit phosphorylation and trafficking to striatal synapses have been also found in experimental models of LID (Ba *et al.*, 2006; Santini *et al.*, 2007; Silverdale *et al.*, 2010). In

particular, increased PKA-dependent phosphorylation of GluA1-S845, which is linked to the surface expression of AMPA receptors, has been also described in rodent (Ba *et al.*, 2006; Errico *et al.*, 2011; Santini *et al.*, 2007) and macaque (Santini *et al.*, 2010a) models of LID.

Modifications of AMPA receptor subunit composition have also been reported. A study described an alteration in the ratio between synaptic membrane-associated and vesicular GluA2/3 versus GluA1 subunits in a macaque model of LID (Silverdale *et al.*, 2010). Notably, no changes in the total striatal levels of any AMPA receptor subunit were observed (Hallett *et al.*, 2005; Silverdale *et al.*, 2010), indicating the redistribution of the receptor subunits, in particular of GluA2/3, from the vesicular fraction to the postsynaptic membrane in dyskinesia (Silverdale *et al.*, 2010). Moreover, calcium-permeable AMPA receptors and an increase in GluA1 and GluA2 flip isoforms have been involved in both the induction and subsequent expression of LID (Kobylecki *et al.*, 2010; Kobylecki *et al.*, 2013).

Finally, aberrant function of AMPA receptors also appears to be involved in the induction of LID. Studies performed in preclinical dyskinesia models indicate that selective AMPA antagonists can be effective in reducing LID (Juranyi *et al.*, 2004; Kobylecki *et al.*, 2010; Konitsiotis *et al.*, 2000), thus confirming a role for overactive AMPA receptor transmission in LID.

5.9.8.3. Metabotropic glutamate receptors (mGluRs)

Considering their ability to finely modulate the excitatory synapse in the brain without blocking fast excitatory neurotransmission, mGluRs may represent a very interesting target for the treatment of LID (Gasparini *et al.*, 2013; Sgambato-Faure and Cenci, 2012). Among the different mGluRs subtypes, mGluR5 is highly expressed in caudate, putamen and other basal ganglia nuclei, it has a postsynaptic subcellular distribution, and it represents one of the most promising targets to reduce the excessive glutamatergic transmission observed in PD and LID. Different experimental approaches have indicated an increase in mGluR5 expression in putamen and pallidum associated with LID in both non-human primate models of PD and patients (Ouattara *et al.*, 2010a; Samadi *et al.*, 2008). In the last 10 years, specific mGluR5 antagonists or Group II mGluR agonists were tested for their efficacy in improving motor behaviour in animal models of LID. Overall, these studies have shown that mGluR5 antagonists or negative allosteric modulators could reduce LID without affecting the therapeutic effect of L-dopa. In particular, several mGluR5 negative allosteric modulators, such as MPEP, MTEP, fenobam, AFQ056, dipraglurant and PF470,14 were found to reduce peak-dose LID in animal models while preserving or even potentiating the anti-parkinsonian

effect of L-dopa (Bezard *et al.*, 2014; Dekundy *et al.*, 2006; Gregoire *et al.*, 2011; Johnston *et al.*, 2010a; Maranis *et al.*, 2012; Mela *et al.*, 2007; Morin *et al.*, 2010; Rylander *et al.*, 2009; Zhang *et al.*, 2014c). Differently from NMDA receptor antagonists, negative modulators of mGluR5 markedly attenuate D_1R-induced $ERK_{1/2}$ activation in the DA-denervated striatum (Fieblinger *et al.*, 2014b; Rylander *et al.*, 2009). The modulatory role of mGluR5 in the striatal signaling in LID provides further rationale for pursuing anti-dyskinetic therapies that antagonize this receptor (Picconi and Calabresi, 2014).

Group III mGlu receptor agonists have also been studied with regard to their potential anti-parkinsonian and anti-dyskinetic properties (Amalric *et al.*, 2013; Rylander *et al.*, 2009). In particular, it was found that LID was attenuated in the mouse by the orthosteric mGlu4 receptor agonist, LSP1-2111 (Lopez *et al.*, 2011), and in the rat by the PAM, Lu AF21934 (Bennouar *et al.*, 2013). An extensive comparative analysis of the behavioural effects produced by the mGlu4 positive allosteric modulator VU0364770 and the mGlu4 orthosteric agonist LSP1-2111 in 6-OHDA rats showed that neither of the two compounds modified the development of dyskinetic responses elicited by chronic treatment with full doses of L-dopa (Iderberg *et al.*, 2015a). In addition, when given together with L-dopa to rats with already established dyskinesias, neither VU0364770 nor LSP1-2111 modified the AIM scores (Iderberg *et al.*, 2015a). Taken together, these results indicate that pharmacological stimulation of mGlu4 lacks intrinsic anti-dyskinetic activity.

5.9.9. Adenosine receptors

Adenosine A_{2A} receptor antagonists have emerged long ago as a potential treatment for PD. An interesting peculiarity of A_{2A} receptors is their selective localization in the indirect GABA/enkephalinergic striatopallidal pathway (Schiffmann *et al.*, 1991), the stimulation of which leads to the inhibition of motor behavior (Ferré *et al.*, 1991). Interestingly, an increase in A_{2A} receptors in the striatum of 6-OHDA-lesioned rats and of MPTP-treated primates, as well as in PD patients chronically treated with L-dopa displaying dyskinesia might produce a prevailing tone of A_{2A} receptors, the activation of which interferes with motor activity (Brooks *et al.*, 2010; Calon *et al.*, 2004; Pinna *et al.*, 2002; Ramlackhansingh *et al.*, 2011; Tomiyama *et al.*, 2004). Therefore, attenuation of the enhanced A_{2A} receptor tone could be one of the factors underlying the positive effects produced by A_{2A} receptor antagonists in PD. However the absence of A_{2A} receptors in the direct GABA/dynorphinergic striatonigral

pathway, the efferent pathway consistently shown to be involved in dyskinesia, questions the relevance for management of established LID.

The results so far obtained with several A_{2A} receptor antagonists in rodent models of PD suggest indeed that A_{2A} receptor antagonists might have symptomatic therapeutic efficacy in early stages of PD when motor complication are not yet present (Pinna *et al.*, 2007). In particular, studies in 6-OHDA-lesioned rats suggest that A_{2A} receptor antagonists, when administered alone, may ameliorate initiation of movement, gait, and muscle rigidity whilst simultaneously improving the sensorimotor integration deficits and tremor that characterize PD (Pinna *et al.*, 2007; Salamone *et al.*, 2008; Simola *et al.*, 2004). While these drugs potentiate the efficacy of L-dopa co-administered at a low sub-threshold dose, A_{2A} receptor antagonists exhibit contrasted results on LID.

In rodents, A_{2A} receptor antagonists do not induce dyskinesia after chronic treatment and do not exacerbate the dyskinesia in rats previously sensitized to L-dopa (Jones *et al.*, 2013; Lundblad *et al.*, 2003). They also prevent the development of the sensitization of rotational behaviour in 6-OHDA-lesioned rats (Hodgson *et al.*, 2009; Pinna *et al.*, 2001; Tronci *et al.*, 2007) as well as in hemiparkinsonian A_{2A}-knock-out mice (Fredduzzi *et al.*, 2002; Xiao *et al.*, 2006). None of these studies however established clearly a major anti-dyskinetic effect of A_{2A} receptor antagonists upon established AIMs (Lundblad *et al.*, 2003) or LID (Bibbiani *et al.*, 2003). Those mixed results were further confirmed in dyskinetic PD patients. While A_{2A} receptor antagonists have generally demonstrated that their addition to a stable L-dopa regimen reduces OFF time and increase ON periods (Hauser *et al.*, 2011; Hauser *et al.*, 2008; LeWitt *et al.*, 2008; Mizuno *et al.*, 2010; Stacy *et al.*, 2008), they do not improve established dyskinesia (Hauser *et al.*, 2011; Hauser *et al.*, 2008).

Several conclusions can be drawn from these studies. Firstly, A_{2A} receptor antagonists do not attenuate LID. Secondly, they may delay LID appearance without affecting L-dopa therapeutic efficacy if L-dopa-sparing doses are used. Therefore A_{2A} receptor antagonists may be envisioned as a class of non-dopaminergic drugs that might act positively on PD motor symptoms and potentiate L-dopa therapeutic efficacy without having dyskinetic potential. Recently, a functional heteromer complex formed by A_{2A}, cannabinoid CB1 and DA D_2R (A_{2A}-CB1-D_2 receptor heteromers) has been unravelled. This heteromer, present in normal and DA-depleted striatum, is however lost following acute or chronic treatment with L-dopa in rats (Pinna *et al.*, 2014) and monkeys (Bonaventura *et al.*, 2014). Losing the heteromer complex would affect the proper signalling through the three receptors, rendering inefficient the A_{2A} antagonists.

A_1 receptor has received much less attention and offers contradictory results probably linked to the striatal expression of the receptor where it can antagonistically control activity of striato-nigral dMSNs. On one hand A_1 receptor-knock-out mice developed less severe AIMs than wild-type littermates (Xiao *et al.*, 2011) and on the other hand, A_1 receptor stimulation reduces D_1R-mediated GABAergic transmission from striato-nigral terminals and attenuates AIMs in 6-OHDA-lesioned mice (Mango *et al.*, 2014).

5.9.10. Acetylcholine (Ach) receptors

Emerging work indicates that the nicotinic ACh system plays a role in LID. Studies in 6-OHDA-lesioned rats or MPTP-lesioned mice showed that nicotine reduced AIMs up to 60%, including axial, oral and forelimb AIMs (Bordia *et al.*, 2008; Bordia *et al.*, 2010; Huang *et al.*, 2011b; Huang *et al.*, 2011c; Quik *et al.*, 2012a). The nicotine-induced decline in L-dopa-induced AIMs persisted with long-term treatment (months) and was observed with varying modes of nicotine treatment including systemic injection, slow-release minipumps or via the drinking water. Notably, there was no worsening of parkinsonism with nicotine administration. In addition, the effect of nicotine on LID has been investigated in MPTP-lesioned squirrel monkeys. These squirrel monkeys were given nicotine in the drinking water, a paradigm that readily lends itself to long-term treatment. Nicotine maximally reduced LID with 60-70% declines in both peak and total LID after several weeks (Quik *et al.*, 2007; Quik *et al.*, 2013c; Quik *et al.*, 2013d). Again, there was no detrimental effect upon parkinsonism. Nicotine led to a similar reduction in LID whether it was given to L-dopa naïve monkeys or animals with established LID; thus, nicotine can be used prophylactically or to reduce existing LID (Quik *et al.*, 2007; Quik *et al.*, 2013d). There was no tolerance to the nicotine-induced decline in LID for the entire study duration (up to 1 year). This is an important point as PD patients generally require life-long treatment with L-dopa (Quik *et al.*, 2007; Quik *et al.*, 2013d). Nicotine's anti-dyskinetic effect remained for several weeks after drug discontinuation, suggesting that long-term molecular changes underlie the improvement. Studies with varying degrees of nigrostriatal damage showed that nicotine best reduced LID in animal models with a moderate nigrostriatal loss (Bordia *et al.*, 2010; Quik *et al.*, 2013c), suggesting it may not be that effective in late-stage PD.

These studies in animal models have been extended to the clinic; a small phase 1/2 trial in PD patients was recently conducted (NCT00957918). Results await publication in a peer-

reviewed journal. Altogether, these findings suggest that nicotine may be useful for the treatment of LID in PD patients.

Nicotine generally exerts its CNS effects by acting at nicotinic ACh receptors (nAChRs), which are ligand-gated ion channel composed of five membrane-spanning subunits. The primary subtypes in mammalian brain are heteromeric β2* and homomeric α7 receptors, with the asterisk indicating the presence of other nAChR subunits in the receptor complex (Albuquerque *et al.*, 2009; Millar and Gotti, 2009; Quik and Wonnacott, 2011). The most populous subtypes in the basal ganglia are the α4β2* and α6β2* nAChRs, with α7 nAChRs expressed to a lesser degree (Albuquerque *et al.*, 2009; Millar and Gotti, 2009; Quik and Wonnacott, 2011).

Studies with nAChR knock-out mice indicate that nicotine's anti-dyskinetic effect is mediated via multiple subtypes. α6 nAChR subunit knock-out mice, which lack α6β2* nAChRs, had reduced baseline L-dopa-induced AIMs (Quik *et al.*, 2012a). Furthermore, there was no decline in remaining AIMs with nicotine treatment in α6 nAChR knock-out mice compared to wild type mice (Quik *et al.*, 2012a). Thus, nAChRs expressing the α6 subunit are important for both the generation of AIMs and the anti-dyskinetic effect of nicotine. Nicotine also did not reduce LID in α4 nAChR null mutant mice, although baseline AIM scores were unaffected in these mice (Quik *et al.*, 2013b). These data indicate that both α6β2* and α4β2* nAChRs regulate AIMs although in a somewhat different fashion.

Experiments with α7 nAChR null mutant mice showed that these receptors modulated LID in a manner distinct from that by α4β2* and α6β2* nAChRs. First, there was an increase in baseline L-dopa-induced AIMs in α7 nAChR knock-out mice, suggesting that α7 nAChRs have an inhibitory impact (Zhang *et al.*, 2013a). Second, nicotine treatment still decreased AIMs in α7 nAChR knock-out. The variable mode of regulation by β2* and α7 nAChRs may arise because of their differential expression, molecular properties and functional characteristics. For instance, α7 nAChRs are more permeable to calcium, desensitize more rapidly and are linked to alternate intracellular signalling pathways compared to β2* nAChRs (Changeux, 2010; Giniatullin *et al.*, 2005; Picciotto *et al.*, 2008; Quik *et al.*, 2012b;

Wonnacott *et al.*, 2005). In summary, studies with genetically modified mice indicate that α4β2*, α6β2* and α7 nAChRs are all involved in the occurrence of LID, although in distinct manners.

The data with nAChR knock-out mice led to studies testing the effect of nAChR drugs on LID. The general nAChR agonist varenicline reduced dyskinesia in both L-dopa-treated rats and squirrel monkeys, providing proof of principle that the effect of nicotine was nAChR-mediated (Huang *et al.*, 2011c; Zhang *et al.*, 2013a). A role for β2* nAChRs is suggested from work with A-85380 and a series of Targacept compounds, which all reduced LID in 6-OHDA-lesioned rats (Huang *et al.*, 2011c; Quik *et al.*, 2013a). In addition, the β2* nAChR agonist TC-8831 reduced LID in parkinsonian macaques and squirrel monkeys, with no worsening of parkinsonism (Johnston *et al.*, 2013; Quik *et al.*, 2013d). Same observation was made with other series with similar pharmacological properties (Zhang *et al.*, 2014a). Determining the precise contribution of the α4β2* and α6β2* nAChRs to LID has not yet been possible using a pharmacological approach since available drugs act at both receptor subtypes. Studies with α7 nAChR agonists show that these drugs also reduce LID, suggesting that multiple nAChR subtypes are involved (Di Paolo *et al.*, 2014; Zhang *et al.*, 2014b).

The somewhat paradoxical finding that nAChR agonists and the antagonist mecamylamine both reduce L-dopa-induced AIMs to a similar extent in parkinsonian rats has led to the suggestion that nAChR agonists reduce AIMs via nAChR desensitization **(Bordia *et al.*, 2010)**. This molecular event leads to a functional blockade similar to that observed with antagonists **(Buccafusco *et al.*, 2009; Corringer *et al.*, 2006; Picciotto *et al.*, 2008)**. Long term nicotine treatment also downregulated α6β2* nAChRs **(Lai *et al.*, 2005)**. Thus both nAChR-induced desensitization and downregulation may underlie the nicotine-mediated reduction in LID. Dyskinesia are thought to arise because of L-dopa-mediated transient increases in striatal DA release, which leads to disproportionate DAergic stimulation (Carta and Bezard, 2011; Cenci, 2007a; Fisone and Bezard, 2011; Lindgren *et al.*, 2010). Long term nicotine treatment has been shown to reduce striatal nAChR-mediated DA release **(Bordia *et al.*, 2013)**. These combined findings suggest that chronic nicotine treatment desensitizes and/or downregulates nAChRs, with a consequent decline in striatal DA release and subsequent improvement in LID **(Bordia *et al.*, 2013)**.

With respect to the localization of the nAChRs involved in regulating LID, α4β2* and α6β2* nAChRs on nigrostriatal DA terminals most likely play an important role. Data supporting this idea stems from experiments showing that the nicotine-mediated decline in LID is

reduced or absent in animals with severe nigrostriatal damage (Bordia *et al.*, 2013; Huang *et al.*, 2011b; Quik *et al.*, 2013b; Quik *et al.*, 2012a). α4β2* nAChRs at other striatal sites, as well as in other brain regions, may also be involved since nicotine is still partially effective in severely lesioned rats (Quik *et al.*, 2013a). The CNS distribution of α7 nAChRs of relevance to the anti-dyskinetic effect of nicotine is currently not known (Quik *et al.*, 2013b). The idea that nAChRs throughout the brain modulate LID expression is not unlikely since the striatal DAergic system is functionally integrated with numerous other neurotransmitter systems.

5.9.11. Peptidergic transmission

5.9.11.1. Classic opioid transmission

A role for enhanced peptidergic transmission, either opioidergic or not, has classically been proposed for the generation of LID on the basis of *in situ* hybridization studies showing that striatal peptidergic precursor expression consistently correlates with LID severity (Aubert *et al.*, 2007; Cenci *et al.*, 1998; Henry *et al.*, 2003; Tel *et al.*, 2002). Parkinsonian and dyskinetic states have been associated with different patterns of expression of precursors of the peptides extensively reviewed in prior contributions (Bezard *et al.*, 2001a; Cenci and Konradi, 2010; Cenci *et al.*, 1998; Jenner, 2008). Parkinsonism is associated with increased expression of the opioid precursor PPE-A mRNA in striatal neurons projecting to the GP in rodents (GPe in primates) and a decreased prodynorphin (PPE-B) mRNA expression in striatal neurons projecting to the SNr in rodents and primates and GPi in primates (Aubert *et al.*, 2007; Cenci *et al.*, 1998; Gerfen *et al.*, 1990; Henry *et al.*, 2003; Morissette *et al.*, 1999; Nisbet *et al.*, 1995; Quik *et al.*, 2002a; Tel *et al.*, 2002; Westin *et al.*, 2001). In the dyskinetic state, expression of PPE-B mRNA is increased whereas PPE-A mRNA is unchanged versus controls, at least when the tissue was taken from animals killed at the peak of dyskinesia severity (Aubert *et al.*, 2007). Interestingly the correlation points out that the striatum and the STN are two key structures, the latter displaying a near ectopic expression of PPE-B mRNA in the dyskinetic state (Aubert *et al.*, 2007), a result in accordance with direct measurement of peptides in the GPi that receives PPE-B-derived peptides from the striatum and the STN (Bourdenx *et al.*, 2014; Nadjar *et al.*, 2006). Only few studies focused on the actual proteome and peptidome of both parkinsonian and dyskinetic states, three were conducted in the 6-OHDA-lesioned-rodent model (Hanrieder *et al.*, 2011; Nilsson *et al.*, 2009; Valastro *et al.*, 2007) and two in the MPTP-treated macaque model (Bourdenx *et al.*, 2014; Scholz *et al.*, 2008). These studies confirmed the results obtained from previous *in situ* hybridization-based

studies. Moreover, the unbiased peptidomic approach lead to the identification of previous unreported peptides deriving from the classic precursors, some of them being specific of a given structure and/or DA-tone dependent (Bourdenx *et al.*, 2014; Klintenberg and Andren, 2005). However, the exact biological functions of these new endogenous peptides remain to be determined.

The peptides processed from the different precursors bind with various affinities to the three classes of opioid peptide receptors, which have an overall inhibitory action (Hollt, 1986; Law *et al.*, 2000; Mansour *et al.*, 1994; Sadee *et al.*, 2005). Studies in rodents and macaques have shown an almost similar brain expression of the opioid peptide receptors in normal and pathological conditions (Aubert *et al.*, 2007; Johansson *et al.*, 2001; Mansour *et al.*, 1994). The total binding of opioid receptors decreases in the brains of DA-denervated animals and patients (Aubert *et al.*, 2007; Fernandez *et al.*, 1994; Johansson *et al.*, 2001) and further decreases in dyskinetic animals. In non-human primates, Aubert and colleagues reported a reduction in μ and κ receptor binding in the GPi correlating with dyskinesia severity (Aubert *et al.*, 2007). It suggests that the more severe the LID, the more profound is the decrease in total opioid receptor, κ, and μ binding in the GPi, as shown in rats (Johansson *et al.*, 2001) and in PD patients (Piccini *et al.*, 1997), reflecting an increased release of peptides.

Despite a large research effort, enthusiasm has been dampened because, on the clinical side, the non-subtype-selective opioid receptor antagonist naltrexone and naloxone have failed in clinical trials, showing almost no anti-dyskinetic effects (Fox *et al.*, 2004; Rascol *et al.*, 1994). However, μ opioid receptor antagonists have been shown to efficiently reduce LID in non-human primate models without affecting the anti-parkinsonian action of L-dopa (Henry *et al.*, 2001; Koprich *et al.*, 2011; Potts *et al.*, 2015), thus suggesting that subtype-selective agents would have a better clinical outcome. Taken together with the recent peptidomic-based results showing that regulation of peptidergic processing is highly structure-specific, this suggests that something more complex than a simple subtype-selective agent may be required to fully reverse the effects of the complex changes that occur in basal ganglia neuropeptide transmission in LID (Bourdenx *et al.*, 2014).

If one imagines that μ opioid receptor antagonists might be beneficial against LID based upon the striking negative correlation between μ opioid receptor binding in GPi of AIM 6-OHDA-lesioned rats (Johansson *et al.*, 2001) and dyskinetic MPTP-treated macaques (Aubert *et al.*, 2007) and the increased presence of μ opioid receptor ligands in the same dyskinetic GPi (Bourdenx *et al.*, 2014), a classic pharmacological treatment would undoubtedly act all over

the brain and not specifically on the GPi. A preliminary study investigating the impact of intrastriatal versus intrapallidal administration of μ opioid receptor modulators unravelled that only intrapallidal administration is capable of improving LID in dyskinetic MPTP-lesioned macaques (Bezard, unpublished). Modulation of the opioid transmission would certainly become of interest when pharmacology would propose delivery methods enabling to target a given structure instead of the whole brain or if dual compounds are used, such as the mixed κ agonist/ μ antagonist analgesic nalbuphine that was reported to show antidyskinetic properties in a primate model of LID (Potts *et al.*, 2015).

Beyond the case of opioid peptides and their receptors, levels in endogenous morphine are regulated by both DA depletion and further L-dopa treatment (Charron *et al.*, 2011). Morphine itself is indeed endogenously synthesized in the central nervous system (Goumon *et al.*, 2009; Stefano *et al.*, 1996) and endogenous dopamine is thought to be necessary for endogenous morphine formation (Goumon *et al.*, 2009; Stefano *et al.*, 1996). The dramatic upregulation of neuronal endogenous morphine-like compound immunoreactivity and levels in experimental and human PD is only partially normalized by L-DOPA treatment (Charron *et al.*, 2011). The functional consequences of such endogenous morphine upregulation in PD and LID are as yet unknown, but morphine being the natural μ opioid receptor ligand, it is tempting to speculate that endogenous morphine further dysregulate the opioid receptor signalling in LID.

5.9.11.2. N/OFQ-NOP system

Nociceptin/orphanin FQ (henceforth N/OFQ) is a new member of the opioid family discovered in mid 1990's by two separate groups of researchers who named it nociceptin (Meunier *et al.*, 1995) or orphanin FQ (Reinscheid *et al.*, 1995). N/OFQ is a heptadecapeptide with structural homologies with classical opioids, in particular dynorphin A, although the presence of a phenylalanine in its amino terminus instead of the "classical" tyrosine (as in opioid sequence) makes it unable to activate classical opioid receptors (μ, δ and κ) with high affinity (Calo *et al.*, 2000b; Mogil and Pasternak, 2001). Indeed, N/OFQ is the endogenous ligand of the so-called Opioid Receptor Like 1 (ORL 1) receptor, renamed N/OFQ peptide (NOP) receptor, which was cloned 1 year before the isolation of N/OFQ (Mollereau *et al.*, 1994) and crystallized (Thompson *et al.*, 2012). The NOP receptor is a classical GPCR which couples to Gi/o, leading to inhibition of cAMP accumulation, closing of voltage gated calcium channels, and opening of inwardly rectifier potassium (K^+) channels. These effects result in

generally inhibitory actions over neuronal firing and neurosecretion. In addition, N/OFQ can activate mitogen-activated protein kinases, among which ERK (New and Wong, 2002).

Relevant to PD, the N/OFQ-NOP receptor system is highly expressed in the basal ganglia (Anton *et al.*, 1996; Neal *et al.*, 1999a; Neal *et al.*, 1999b). High levels of N/OFQ+ neurons and fibers were detected with *in situ* hybridization and immunohistochemistry in the GP, entopeduncular nucleus, and in SNr, while in striatum only few, scattered N/OFQ+ neurons were evident. The distribution of the NOP receptor substantially matches that of N/OFQ, with the exception of the subthalamic nucleus where high levels of NOP but only scattered N/OFQ+ neurons were found. Significant levels of N/OFQ immunoreactivity (Witta *et al.*, 2004) and expression (Peluso *et al.*, 1998), as well as N/OFQ binding and NOP receptor expression (Berthele *et al.*, 2003) were also measured in the human basal ganglia. A notable difference between the human and rodent brain, is the high levels of NOP receptor/N/OFQ binding in the caudate/putamen, also observed in non-human primates (Bridge *et al.*, 2003).

The NOP receptor is expressed in midbrain DAergic neurons of the ventral tegmental area and SNc (Norton *et al.*, 2002), and sorted both to the somatodendritic and nerve terminal compartments. NOP receptor activation inhibits the firing of nigral DA neurons (Marti *et al.*, 2004b) and striatal presynaptic DA release (Flau *et al.*, 2002), an effect correlated with motor inhibition (Marti *et al.*, 2004b).

The NOP receptor is a druggable receptor which has unique pharmacological properties with respect to the classical opioid systems, first of all the insensitivity to naloxone (Calo *et al.*, 2000b). This peculiarity has contributed to the definition of NOP as a non-opioid member of the opioid receptor family. Since the initial structure-activity relation studies on N/OFQ analogues (Guerrini *et al.*, 1997; Reinscheid *et al.*, 1996), several NOP selective ligands have been developed by academic and industrial groups (for reviews see (Calo *et al.*, 2000a; Zaveri *et al.*, 2005) with selective antagonists (Calo *et al.*, 2005), partial agonists (Rizzi *et al.*, 2002), and full agonists (Calo *et al.*, 2011) now available. Evidences linking N/OFQ with PD support a role for the system in parkinsonian symptom pathophysiology (Marti *et al.*, 2005; Marti *et al.*, 2004a) through action at SNr level where extracellular N/OFQ levels rise as a consequence of DA neuron degeneration or functional impairment of DA transmission (Di Benedetto *et al.*, 2009; Gouty *et al.*, 2010; Marti *et al.*, 2005; Marti *et al.*, 2010; Norton *et al.*, 2002).

The question of whether NOP receptor antagonists are dyskinesiogenic was directly addressed in a paper showing that acute systemic administration of J-113397 worsened the severity of AIMs in dyskinetic rats (Marti *et al.*, 2012). This effect was replicated by intracerebroventricular or intranigral injection of UFP-101, consistent with the view that NOP

antagonists act where N/OFQ tone is elevated. In fact, injection of UFP-101 in striatum, an area where N/OFQ tone is low or absent, and NOP receptor up-regulated after DA denervation, was without effect (Marti *et al.*, 2012). Although in rats the prodyskinetic effect was mild and limited to the limb subtype of AIMs, these data substantially confirmed previous findings in marmosets (Visanji *et al.*, 2008) warning on the potential motor side-effects of overdosing NOP antagonists as an adjunct to L-dopa therapy.

The finding that NOP receptor blockade worsened AIM expression, suggested that endogenous N/OFQ might physiologically oppose LID. In fact, acute intracerebroventricular injection of N/OFQ or systemic administration of Ro 65-6570 (a NOP receptor agonist) mitigated LID expression in rats, being equally effective against axial, limb and orolingual AIMs (Marti *et al.*, 2012). The anti-dyskinetic effect was observed at doses that *per se* did not cause hypolocomotion, a typical effect of NOP receptor agonists (Devine *et al.*, 1996; Jenck *et al.*, 1997; Marti *et al.*, 2004a; Marti *et al.*, 2009; Reinscheid *et al.*, 1995), possibly indicating a specific interference with dyskinetic pathways. Opposite to NOP receptor antagonists, N/OFQ attenuated dyskinesia more potently when injected in striatum than SNr.

In vivo microdialysis revealed that N/OFQ prevented LID expression through an action upon striatal GABAergic MSNs projecting to the SNr. In fact, intracerebroventricular administration of N/OFQ markedly attenuated the rise of SNr GABA release associated with LID expression (Mela *et al.*, 2007), a neurochemical response associated with striatal D1 receptor activation (Mela *et al.*, 2012). Consistently, N/OFQ also prevented the reduction of GABA release in ventro-medial thalamus associated with LID, an index of overinhibition of the nigral output (Marti *et al.*, 2012). As previously reviewed, up-regulation of striatal D_1R signalling in LID is associated with an increased activity along the Ras/MEK/ERK kinase pathway (Feyder *et al.*, 2011; Valjent *et al.*, 2005), and a loss of neuron capability to depotentiate striatal synaptic response after LTP induction (Picconi *et al.*, 2003). Consistent with an inhibitory action of N/OFQ upon striatal D_1R signalling (Olianas *et al.*, 2008), application of N/OFQ to striatal slices of naïve animals prevented the increase in ERK phosphorylation induced by a D_1R agonist, and fully restored the depotentiation in slices treated with a D_1R agonist (Marti *et al.*, 2012). The potential of NOP agonists as anti-dyskinetic drugs was further confirmed in MPTP-treated macaques, where the small molecule Ro 65-6570 was able to attenuate LID without compromising the anti-parkinsonian effect of L-dopa (Marti *et al.*, 2012). Although the effect was overall mild (30%) and significant for the dystonic but not the choreiform component, these data provide a solid background for testing

more selective and potent NOP agonists for their ability to acutely rescue motor function under LID.

In conclusion, N/OFQ appears to play an important role in PD. In particular, elevation of N/OFQ transmission in SNr following DA neuron loss might exacerbate the physiological, inhibitory role of N/OFQ over movement, justifying the use of NOP receptor antagonists as symptomatic anti-parkinsonian drugs. Opposite to SNr, DA neuron loss is associated with reduction of N/OFQ expression and up-regulation of NOP receptors in striatum, which might also contribute to dysregulation of D_1R transmission in striato-nigral MSNs. In this case, NOP agonists, by restoring an inhibitory control over D_1R signalling, might work to oppose LID expression. Studies with more selective NOP agonists are needed to confirm these data, and prove that N/OFQ also prevents the development of sensitization to L-dopa, which underlies LID.

5.10. Postsynaptic changes in striatal interneurons

Although MSNs are the majority (about 95%) of the striatal neurons and the major output neurons, they are heavily influenced by interneurons in the striatum. Striatal cholinergic interneurons (ChIs) represent only about 2% of the total striatal neuronal population (Zhou *et al.*, 2002), yet they have richly arborizing axons with large terminal fields within the striatum, suggesting the importance of these neurons in modulating striatal activity (Pisani *et al.*, 2007). The striatum has the highest density of cholinergic markers in the brain (Bolam *et al.*, 1984). ACh tone contributes to DA and glutamate release locally via presynaptic nicotinic receptors on DA and glutamatergic terminals (Kaiser and Wonnacott, 2000; Rice and Cragg, 2004). ChI activity also contributes to plasticity of glutamatergic and GABAergic inputs to this area via both muscarinic and nicotinic receptor activation (Bamford *et al.*, 2010; Pisani *et al.*, 2007; Pisani *et al.*, 2003). Striatal synaptic plasticity is dependent upon endogenous ACh acting specifically on M1 receptors, with high levels of ACh facilitating LTP and lower levels facilitating LTD (Bonsi *et al.*, 2008). DA denervation modulates the cholinergic system as well, causing a reduction in M4 mRNA levels (Kayadjanian *et al.*, 1999), along with M4 autoreceptor malfunction, resulting in a loss of negative feedback inhibition and increased ACh release (Ding *et al.*, 2006).

As noted above in 5.9.3.2., studies show that striatal ERK activation shifts from being predominantly in dMSNs to ChIs with repeated L-dopa exposure concomitant with behavioral LID development/expression in both unilateral 6-OHDA lesioned and aphakia mouse models

of PD (Ding *et al.*, 2011) and in a primate model (Bezard, unpublished). Therefore, this shift of ERK activation from MSN to ChI with chronic L-dopa exposure suggests that priming of LID may occur in MSN initially, but that ChIs "store" and mediate the hypersensitivity to L-dopa. This shift is more dramatic in aphakia mouse model as inhibition of ERK activation in ChIs reduces LID expression (Ding *et al.*, 2011). The selective ablation of striatal ChIs attenuates LID development and expression dramatically (Won *et al.*, 2014).

ChIs have unique membrane properties, exhibiting spontaneous activity with tonic firing patterns (Bennett and Wilson, 1999). ChIs in both dyskinetic aphakia mice and WT mice with 6-OHDA lesions show increase in ERK activation and DA-induced firing rate following repeated L-dopa treatment compared with saline treated non-dyskinetic mice (Ding *et al.*, 2011). Inhibition of ERK activation restores the baseline and DA-induced increases in ChI firing rate in dyskinetic mice to that of non-dyskinetic PD mice (Ding *et al.*, 2011). Together, the electrophysiological data along with biochemical and behavioural results support the hypothesis that expression of LID following repeated L-dopa exposure results from enhanced striatal ChI excitability, and that these changes are mediated by ERK activation (Ding *et al.*, 2011).

The role of antimuscarinic cholinergic drugs in the treatment of LID is controversial, which is in contrast to the role of nicotinic receptors. The best-established treatment for LID is amantadine, which has significant anticholinergic effect as well as anti-NMDA effect. Clinical experience with anticholinergics in PD patients is limited. Parkinsonian symptoms such as tremor and rigidity may improve after treatment with centrally acting antimuscarinics, such as benztropine (Duvoisin, 1967; Katzenschlager *et al.*, 2003). Although anticholinergic benztropine has been reported to decrease LID in human PD patients (Pourcher *et al.*, 1989), others have reported increased dyskinesia with anticholinergic treatment (Birket-Smith, 1974; Hauser and Olanow, 1993; Linazasoro, 1994). In a study of dyskinetic monkeys, the antimuscarinic antagonist atropine changed the nature of dyskinesia from dystonia to chorea (Gomez-Mancilla and Bedard, 1993), suggesting a modulatory role of muscarinic acetylcholine receptor in LID. Thus the controversial results of antimuscarinics on LID in PD likely reflect the complexity of muscarinic systems in the basal ganglia (Lim *et al.*, 2014). Drugs that modulate these receptors are not receptor-subtype specific and can act upon multiple cell types within the striatum in addition to extra striatal sites. As such, the development of more selective muscarinic receptor ligands or other novel approaches to modify striatal cholinergic signalling specifically may provide more effective treatment strategies for LID. Recently, CNS cell subtype-specific gene translation profiling has revealed

that the H2 histamine receptors are relatively selectively expressed on ChIs compared to other neuronal populations, including MSNs (Doyle *et al.*, 2008). In mice with LID, the H2 antagonist famotidine reduces ChI firing, which suggests that development of LID induces hypersensitivity to histamine signal via H2 receptors in ChIs. Famotidine also reduces behavioural manifestation of LID in two mouse models (Lim *et al.*, 2015) and a primate model of PD (Johnston *et al.*, 2010b), in agreement with the notion that reducing ChI hyperactivity by H2 receptor blockade can reduce LID. However, a small clinical study has failed to find an effect of famotidine on reducing expression of LID, although this trial used relatively low doses (Mestre *et al.*, 2014). H2 antagonists with better CNS penetration or other novel targets that specifically target ChI may allow more effective modulation of ChI activity to reduce LID. Finally, blocking ChI function prior to the beginning of chronic L-dopa treatment (via cell-selective ablation) (Won *et al.*, 2014) had a much more dramatic effect in reducing subsequent LID than blocking ChI function after LID has already fully developed (via receptor antagonists) (Ding *et al.*, 2011). These experimental studies raise the possibility that preventing the development of ChI hyperactivity early during L-dopa treatment may be more effective than suppressing the expression of LID that has already fully developed using anticholinergics, and that treatments that prevent the development of ChI hyperactive in response to chronic L-dopa may combine well with other drugs that suppress the expression of LID

5.11. Involvement of additional extrastriatal regions in LID pathophysiology

As the main dopaminoceptive structure of the brain, the striatum, and generally the other basal ganglia nuclei (i.e. GPe, GPi, SNr, STN), have received most attention to understand the pathophysiology of LID. However, little remains known of the adaptations occurring in other structures, including the dopaminoceptive ones and the others, following a chronic L-dopa treatment. For instance (as discussed in 5.3.) (**Figure 5**), resonant cortical oscillations are associated with LID suggesting that cortex is a site of LID genesis (Halje *et al.*, 2012). In keeping with that hypothesis, the authors showed a direct link between the cortical oscillations and the D_1R. Local delivery of a D_1R antagonist (SCH23390) at the surface of the primary motor cortex decreased both cortical oscillations and AIM severity in dyskinetic 6-OHDA-lesioned rats compared to cortically-infused vehicle animals. Such result clearly suggests a key role of cortical oscillations in the generation of AIMs.

Systematic searches unravelled that extra-basal ganglia structures are involved in LID pathophysiology. 2-deoxyglucose studies showed modifications in 2-deoxyglucose accumulation in structures outside of the basal ganglia both in PD and LID (**Figure 5**). Interestingly, Mitchell et al. showed that, besides the classic 2-deoxyglucose uptake pattern in the basal ganglia (Bezard *et al.*, 2001b; Gnanalingham *et al.*, 1995), the lateral habenula (LHb) and the pedunculopontine tegmental nucleus (PTg) stood up among several structures as strongly affected non-basal ganglia nuclei, showing dramatic increases in 2-deoxyglucose accumulation in parkinsonism (Mitchell *et al.*, 1992; Mitchell *et al.*, 1989). Guigoni and co-workers reported a decrease in 2-deoxyglucose uptake in the bed nucleus of the stria terminalis (BST) only in dyskinetic MPTP-treated macaques (Guigoni *et al.*, 2005c). Beyond that specific result, they showed that changes in metabolic activity of non-motor areas of the basal ganglia and outside was the correlate of dyskinesia manifestation as those structures were the only ones to show a difference between the dyskinetic and non-dyskinetic MPTP-lesioned macaques, suggesting that dyskinesia are linked to a pathological processing of limbic and cognitive information. These metabolic changes might actually reflect the underlying neural mechanisms of not simply motor dyskinesias but also affective, motivational and cognitive disorders associated with long-term exposure to L-dopa. An alternate hypothesis is that dysregulation of affective, motivational and cognitive processes involved in motor planning and execution would be key events in the genesis/expression of LID.

Recently, transcriptional responses induced by LID were investigated by an unbiased whole-brain approach (Bastide *et al.*, 2014b). Nine structures outside the basal ganglia were identified, i.e. the oval (oBST), juxta (jBST), medial (mBST) BST, rostral zona incerta, LHb, hippocampus, pontine nuclei (Pn), cuneiform nucleus (CnF) and PTg, that displayed an overexpression of at least 3 IEG (ΔFosB, ARC, FRA2, Zif268/EGR1) in dyskinetic rats. Interestingly, LID severity significantly correlated with at least one IEG expression profile in the oBST, jBST, LHb, Pn and CnF (Bastide *et al.*, 2014b) (**Figure 5**).

In the epithalamus, the LHb receive basal ganglia afferents, especially from the GPi (Hong and Hikosaka, 2008), the main output structure of the basal ganglia (**Figure 5**). The LHb projects mainly to the monoaminergic brain regions like the VTA, the SNc, the serotonergic dorsal and medial raphe and also to the cholinergic laterodorsal tegmentum (Bernard and Veh, 2012; Geisler and Trimble, 2008; Hikosaka *et al.*, 2008). Thus, the LHb acts as an interface connecting the limbic system and the basal ganglia to the monoaminergic centres. As the false transmitter hypothesis involving the serotonergic system in LID pathophysiology addresses

the presynaptic component of LID pathophysiology (Carta and Bezard, 2011; Navailles *et al.*, 2010b), the efferent connectivity of the LHb suggests that it may play a role in controlling serotonergic output. Impaired LHb input would thus participate to the aberrant DA release from 5-HT terminals (Carta *et al.*, 2007; Carta *et al.*, 2008a, b; Navailles *et al.*, 2011a; Rylander *et al.*, 2010b). Recently, LHb involvement in LID was investigated (Bastide *et al.*, 2014a). In this study, the authors demonstrated a LID-related pathologic activity of LHb at different functional levels including metabolic, electrophysiological and transcriptional readouts, indicating that increased LHb activity in response to L-dopa treatment is associated with LID expression. Then, selective inactivation of LHb ΔFosB-expressing neurons using the Daun02 methodology both alleviated LID severity and enhanced L-dopa anti-parkinsonian action, suggesting an involvement of LHb both in LID severity and in the anti-parkinsonian effect of L-dopa therapy (Bastide *et al.*, 2014a). Taken altogether these results highlight a key role of LHb in the genesis of dyskinesia, i.e. the involvement of a structure outside of the basal ganglia.

Similarly, and following the initial identification by Guigoni and co-workers (2005c), the BST received experimental attention (**Figure 5**). The oBST and jBST are two nuclei belonging to the dorsolateral BST (dlBST) which receive robust monoaminergic inputs featuring 5-HT, noradrenaline and DA (Phelix *et al.*, 1992). The known BST DA inputs originate from VTA, the periaqueducal gray region and the retrorubral field. More importantly, in the oBST, data indicate that exogenous DA can reduce the inhibitory synaptic transmission in a D_2R-like-dose-dependant manner in brain slices of drug-naïve rats (Krawczyk *et al.*, 2011). Moreover, rats self-administering cocaine, i.e. another hyperdopaminergic situation reminiscent in many ways of LID context, display an overexpression of the D_1R (Krawczyk *et al.*, 2013), underlying the hypothesis of a potential role of the BST in LID. Selective inactivation of BST ΔFosB-expressing neurons alleviated LID severity suggesting an involvement of BST in mediating expression of LID (Bezard, Bastide, Georges and Dumont, unpublished). Taken together these results highlight a role of BST in the expression of dyskinesia, further highlighting the role played by structures outside the basal ganglia.

In the brainstem, the Pn primarily projects to the cerebellum (Brodal, 1979, 1980) and, thus, could be considered as a relay structure from the basal ganglia through the STN (Bostan *et al.*, 2010; Wu and Hallett, 2013). As the cerebellum is involved in fine tuning of motor behaviour (Bastian, 2006; Thach *et al.*, 1992; Timmann *et al.*, 2010), it should not be surprising that L-dopa-induced modifications of the transcriptional activity of Pn neurons could influence

cerebellum-driven motor functions and impact LID pathophysiology. The CnF, known as a mesencephalic locomotor area, receives DA inputs (Rolland *et al.*, 2009; Takakusaki *et al.*, 2003). Although the origin of its DAergic innervation is still unclear, data indicate that MPTP-treated monkeys undergo a dramatic decrease in CnF DA content (Rolland *et al.*, 2009), providing information about a putative role in parkinsonian symptoms. Moreover, as the CnF projects back to the SNc (Watabe-Uchida *et al.*, 2012), both CnF and SNc/SNr neurons form a direct loop that could play a role in motor-related behaviour, and hence support the involvement of the CnF in LID. Activity modulation of those nuclei and resulting impact upon dyskinesia remain however to be studied.

In the same way, neuronal activity of the locus coeruleus, containing the largest population of central noradrenergic neurons, is altered in dyskinetic 6-OHDA-lesioned rats following *in vivo* single-unit extracellular recordings (Miguelez *et al.*, 2011). Then, studies demonstrated that the prefrontal cortex, the hippocampus and the amygdala displayed a modified monoaminergic neurochemistry both in dyskinetic 6-OHDA-lesioned rats and MPTP-treated macaques following a chronic L-dopa treatment (Engeln *et al.*, 2014b; Navailles *et al.*, 2011a). Taken together, these studies suggest that several structures outside of the basal ganglia nuclei could be involved in LID pathophysiology.

Consequently, the above-mentioned data further support the need to evaluate the functional involvement of regions outside of the basal ganglia to fully uncover the pathophysiology of LID.

6. Development of therapeutics

6.1. Continuous delivery of L-dopa

The fluctuations in DA levels being key in generating LID, a number of attempts have been made for either improving L-dopa delivery (and hence pharmacokinetics), preventing DA catabolism, or producing long-lasting DA agonists. This latter proposal could be achieved either by developing DA agonists with long half-life or by a galenic improvement leading to slow release formulations. The long-standing continuous-versus-intermittent-receptor-stimulation discussion has led to such attempts with however little therapeutic success (Jenner, 2008; Olanow and Obeso, 2000). While the clinical efficacy of DA agonists in delaying dyskinesia onset (Holloway *et al.*, 2004) or in reducing LID severity (Poewe *et al.*, 2007) is unclear (Fox *et al.*, 2011), several approaches to improve the pharmacokinetics and

ways of administration of L-dopa are in different stages of clinical development and include novel formulations as well as non-oral routes of drug delivery (LeWitt, 2014; Poewe and Antonini, 2014).

The principle behind constant L-dopa infusion is to bypass gastric emptying and deliver an optimized dose that can be kept stable within the patient's individual therapeutic window. While intravenous administration was shown to achieve parkinsonism improvement without troublesome dyskinesia in otherwise severely dyskinetic patients (Quinn *et al.*, 1982), such route is not an option in real life, for practical and safety (thrombolysis risk) reasons. A gelified version of L-dopa was developed for intrajejunal administration achieving constant plasma L-dopa concentrations over several days of infusion (Nyholm *et al.*, 2005). Such intrajejunal infusion of a gel formulation of L-dopa/carbidopa has first been developed in Europe and almost routinely clinically used for severe fluctuant or dyskinetic patients (Antonini *et al.*, 2007; Antonini *et al.*, 2013; Honig *et al.*, 2009). The efficacy of such intrajejunal administration to smooth out motor fluctuations has recently been confirmed in a USA/Europe/New-Zealand randomized, controlled trial (Olanow *et al.*, 2014) opening the way to world-wide use of such pertinent formulation.

Modifying the pharmacokinetic of oral L-dopa is receiving a lot of attention from the industry since the intrajujenal administration route is not without practical limitations. IPX066, an extended-release L-dopa capsule (Hauser *et al.*, 2013; Pahwa *et al.*, 2014; Stocchi *et al.*, 2014), XP21279, an extended-release L-dopa prodrug (Lewitt *et al.*, 2012a; LeWitt *et al.*, 2014), Accordion Pill CD/LD, a L-dopa gastric retention formulation (LeWitt, 2014), and DM-1992, a pill combining immediate and extended release with gastric retention (LeWitt, 2014; Poewe and Antonini, 2014), have either successfully completed phase III clinical trial (IPX066) or are still in phase II.

In the same way, novel enzyme inhibitors enhancing L-dopa efficacy and half-life are also still being developed, including a novel catechol-O-methyltransferase inhibitor with once-daily pharmacokinetics, and there are studies testing the effects of increasing the dose of amino acid decarboxylase inhibitors given concomitantly with L- dopa. Clearly more original is the proposal that deuterium substitutions in the L-dopa molecule yield DA that appears more resistant to enzymatic breakdown (Malmlof *et al.*, 2010). After initial rodent experiments, such demonstration however awaits further confirmation in primate models before entering clinical testing.

A great step forward has been reached with Prosavin gene therapy, a LV-based gene therapy aimed at restoring local and continuous DA production in patients with advanced PD, that

was not aimed to reduce LID in the first place (Palfi *et al.*, 2014). While all Prosavin-treated patients displayed improvement in mean UPDRS part III motor scores off medication at 6 and 12 months compared with baseline, this was not accompanied with occurrence of dyskinesia (Palfi *et al.*, 2014) as with grafting of mesencephalic embryonic neurons. Most common adverse events were however increased on-medication dyskinesia (20 events, 11 patients) and ON-OFF phenomena (12 events, nine patients) (Palfi *et al.*, 2014) suggesting that while continuous production of DA does not lead to dyskinesia, adding further oral L-dopa unrelentingly elicits LID. Larger trial with higher dosages of the Prosavin lentiviral vector-based gene therapy is currently on its way (NCT01856439).

6.2. Serotonin 5-HT_{1A} agonists

Increasing evidence points to the serotonergic system as a key player in the induction and expression of LID (Chase, 2014) in both patients with PD (Bonifati *et al.*, 1994; Politis *et al.*, 2014) and animal models of the disorder (Carta *et al.*, 2007; Dupre *et al.*, 2008; Munoz *et al.*, 2008; Navailles *et al.*, 2010b). Oral administration of the 5-HT_{1A} agonist buspirone was first tested (Kleedorfer *et al.*, 1991). Buspirone reduced L-dopa-evoked striatal synaptic DA release and attenuated LID in a recent small scale investigational study (Politis *et al.*, 2014), somewhat confirming earlier results in other small scale trials (Bonifati *et al.*, 1994; Kleedorfer *et al.*, 1991).

Sarizotan was assessed in 18 PD patients with motor fluctuations and peak-dose LID in a randomized pilot study (Bara-Jimenez *et al.*, 2005). 5mg of sarizotan decreased AIMs scores by 40% without modifying UPDRS motor scores during an acute intravenous L-dopa infusion. These encouraging results were not confirmed in a large randomized, placebo-controlled, phase IIb dose finding trial. This trial enrolled 398 PD patients with at least moderately disabling LID for at least 25% of the waking day who either received sarizotan 2, 4, 10 mg/d or placebo for 12 weeks (Goetz *et al.*, 2007). Mean improvements in diary-based "ON" time without dyskinesia (primary outcome measure) and AIMs scores at rest and with activity were not different between groups after 12 weeks of treatment. Patients receiving 2mg/d sarizotan had lower UPDRS IV (Part A: dyskinesias) scores compared to placebo suggesting that sarizotan may have some minor effects that are not perceived by PD patients according to the observations documented in their home-diaries. UPDRS Part A evaluates duration, disability, pain and dystonia of dyskinesias as a composite score. No adverse events

were more common in patients treated with sarizotan compared to placebo except for an increase in "OFF" time in patients receiving 10mg/d sarizotan and a similar trend for 4mg/d. Furthermore, experiments using the 5-$HT_{1A/1B}$ receptor agonists eltoprazine and anpirtoline (Bezard *et al.*, 2013a; Bezard *et al.*, 2013c) (each of which possess different affinity for these two major 5-HT autoreceptors) have shown them to produce complete suppression of LID in rat and monkey models of PD, albeit in association with a partial loss of the therapeutic efficacy of L-dopa. In recent Phase II trial, Svenningsson et al. provide true translational evidence supporting the use of eltoprazine against dyskinesia (Svenningsson *et al.*, 2015). Truly translational (i) because they aimed to identify acute doses of eltoprazine that do not affect the therapeutic response to L-dopa (absence of impairment of UPDRS part III scores after vehicle or eltoprazine doses) as in experimental studies, and (ii) because they scored the patients directly, i.e., as in experimental studies, instead of relying upon patient diaries. The findings are truly exciting in that a replication of experimental data has been possible using the same investigational design. Thus, this study provides important validation of pre-clinical data, supporting the use of animal models to identify the mechanism(s) underlying LID, as well as new pharmacological targets. However, it should be pointed out that the reduction of LID in the present study was neither as striking as that in animal models, nor superior to that seen with amantadine in previous clinical studies. Therefore, a number of issues remain to be addressed, including (i) whether escalation of the eltoprazine doses and/or modification of the time of administration relative to L-dopa could improve the anti-dyskinetic efficacy; (ii) whether eltoprazine would remain efficacious after weeks of daily treatment in a classic phase IIb/phase III patient diary-based trial, and (iii) in conjunction with the last point, whether chronic administration would not lead to desensitization of 5-$HT_{1A/1B}$ receptors, or to emergence of the anti-L-dopa effect often reported in animal studies. This is a critical issue in determining the clinical feasibility of this approach for dyskinesia.

6.3. NMDA antagonists

Beyond amantadine, other NMDA antagonists such as dextromethorphan, remacemide, milacemide, CP-101,606 and memantine were assessed for treating LID (Clarke *et al.*, 2001; Giuffra *et al.*, 1993; Merello *et al.*, 1999b; Nutt *et al.*, 2008; Parkinson Study Group, 2001; Shoulson *et al.*, 2001; Verhagen Metman *et al.*, 1998a). It should be noted that none of the drugs exhibited strong anti-dyskinetic effects in the gold standard experimental models of LID (e.g. for memantine, see Tronci *et al.*, 2014).

Dextromethorphan was assessed in 18 PD patients with motor fluctuations and LID in a placebo-controlled cross-over trial (Verhagen Metman *et al.*, 1998a). 12 patients were excluded because of decreased L-dopa efficacy or no benefit at the highest dose. In the remaining 6 patients, dextromethorphan decreased the severity and duration of dyskinesia and severity of motor fluctuations. An on-going trial using AVP-923, a combination of dextromethorphan and quinidine in PD subjects with LID is underway (NCT01767129).

Memantine was tested in 12 PD patients with motor fluctuations and LID in a placebo-controlled cross-over study (Merello *et al.*, 1999b). UPDRS "ON" and "OFF" motor scores were decreased in patients receiving memantine, while dyskinesia ratings were unchanged (Moreau *et al.*, 2013; Varanese *et al.*, 2010).

Remacemide, a non-competitive NMDA channel antagonist, has been evaluated by the Parkinson Study Group in two randomized, placebo-controlled, parallel group study trials. In a pilot study, doses ranging between 150 and 600 mg of remacemide were tested against placebo in 39 PD patients with motor fluctuations and disabling LID (Parkinson Study Group, 2001). There were no differences between the placebo and remacemide group for any of the dyskinesia measures. Adverse events mainly occurred in the group receiving 600mg remacemide. In a second large scale trial, remacemide was tested against placebo in 279 PD patients with motor fluctuations who experienced more than 25% of the waking day in the "OFF" state (Shoulson *et al.*, 2001). UPDRS motor scores were improved in patients receiving remacemide (only 150 and 300 mg) compared with placebo. No dyskinesia ratings were performed.

CP-101,606 is a selective antagonist of the GluN2B subunit of the NMDA receptor that was assessed in 12 PD patients with motor fluctuations and dyskinesia in a randomized, placebo-controlled cross-over study (Nutt *et al.*, 2008). Patients received either CP-101,606 (low or high dose) or placebo during intravenous L-dopa infusion. Both doses of CP-101,606 similarly reduced dyskinesia scores compared to placebo, while UPDRS motor scores were not different between groups. Many patients receiving CP-101,606 presented dose-dependently abnormal thinking, depersonalization and amnesia limiting the interest of this compound for further development for LID.

Budipine is a NMDA antagonist with widespread action on other neurotransmitter systems. This drug was tested in 7 PD patients with motor fluctuations in an open-labeled trial (Spieker *et al.*, 1999). Motor scores improved and "OFF" time decreased without appearance of dyskinesia in most patients. Larger randomized, controlled clinical studies were stopped or

planned trials were not conducted when a prolongation of the QT interval in the ECG was observed with the risk of fatal polymorphic ventricular tachycardia.

Milacemide, a glycine prodrug that positively modulates NMDA transmission, was tested in a placebo-controlled cross-over study in 6 PD patients with motor fluctuations (Giuffra *et al.*, 1993). Milacemide worsened parkinsonian motor signs, mainly rigidity, without any effect on dyskinesia ratings.

Altogether those drugs are relatively disappointing as none achieve similar results than amantadine. It further suggests that amantadine mediates part of its anti-dyskinetic efficacy through other receptors than NMDA receptors.

6.4. mGluR5 negative allosteric modulators

mGluR5 negative allosteric modulators have emerged as a novel and potentially effective class of compounds for the treatment of LID. Few trials have been conducted so far. Two small randomized, double-blind, placebo-controlled, parallel-group phase IIa studies assessed the safety, tolerability and efficacy of marvoglurant (AFQ056) in patients with moderate to severe LID (study 1) or severe LID (study 2) (Berg *et al.*, 2011). Patients received up to 150 mg bid and were evaluated after a 16-day titration phase. Marvoglurant had significant anti-dyskinetic effects versus placebo on the Lang-Fahn Activities of Daily Living Dyskinesia Scale (study 1) and the modified AIMs Scale (study 2). Another small phase IIb trial was inconclusive with conflicting clinician-rated outcome ratings (Kumar *et al.*, 2013). This study was prematurely halted because of enrolment challenges. The largest reported randomized, double-blind, placebo-controlled, parallel-group phase IIb study enrolled 197 patients who were treated for 12 weeks (Stocchi *et al.*, 2013). The highest dose of 200 mg/d reduced significantly modified AIMs Scale scores, while all other doses failed. The data of two additional phase II trials (NCT01491529 and NCT01385592) have yet to be published but were communicated by the company as negative (Rascol *et al.*, 2014).

Dipraglurant, another potent mGluR5 NAM (Duvey *et al.*, 2013), was tested in a Phase IIa proof-of-concept 4-week, randomized, double-blind, placebo-controlled, parallel-group clinical trial in PD patients with moderate or severe LID. Dipraglurant proved to significantly reduce modified Abnormal Involuntary Movements Scale scores at day 1 and 14, but the difference between active intervention and placebo did not reach significance on day 28. Full disclosure of data in a peer-reviewed publication is pending.

6.5. Antiepileptics

The efficacy of gabapentin on motor severity and activities of daily life was first tested in 19 PD patients with motor fluctuations and dyskinesia in a randomized placebo-controlled cross-over study (Olson *et al.*, 1997). Total UPDRS scores were lower in patients receiving gabapentin. The effect of gabapentin (up to 2,400mg/d) on motor complications was more specifically investigated in a second randomized, placebo-controlled cross-over trial including 15 PD patients with motor complications and dyskinesia (Van Blercom *et al.*, 2004). Secondary outcome measures included dyskinesia measures. No differences were observed between gabapentin and placebo. Dizziness and accidental falls were more frequent in patients receiving gabapentin.

The anti-dyskinetic properties of levetiracetam were assessed in two small open-label studies (Lyons and Pahwa, 2006; Zesiewicz *et al.*, 2005) after demonstration of moderate efficacy in animal models (Bezard *et al.*, 2004; Hill *et al.*, 2003; Hill *et al.*, 2004a; Hill *et al.*, 2004b). One study reported an increase in "ON" time without or with non-troublesome dyskinesia by 18% in 9 PD patients with peak-dose dyskinesia for at least 25% of waking hours who received up to 3,000mg/d of levetiracetam (Zesiewicz *et al.*, 2005). At the same time, ON time with troublesome dyskinesia decreased by 12%. There was a considerable dropout rate with a withdrawal of 56% of the patients, mostly because of somnolence. The second study was also conducted in 9 PD patients experiencing moderate to severe dyskinesia and receiving up to 3,000mg/d of levetiracetam (Lyons and Pahwa, 2006). This study reported a dropout of 44%, mostly due to worsening of PD symptoms or somnolence. Moreover, of the remaining 5 patients, 4 discontinued levetiracetam after the end of the study because of worsening of PD symptoms and somnolence. A randomized, double-blind, placebo-controlled, parallel-group pilot study in 32 PD patients with moderate to severe LID failed to show a significant reduction in modified AIMs Scale scores, while UPRDS IV item 32/33 sum scores were significantly lower after 11 weeks of treatment compared to baseline in patients receiving levetiracetam (Wolz *et al.*, 2010). Tolerance was better than in the open-label trials. Other small randomized controlled treatment trials reported modest or no effects of levetiracetam on LID (Stathis *et al.*, 2011).

Zonisamide (25-100mg) was tested in a randomized, placebo-controlled, parallel-treatment study including 347 PD patients with motor fluctuations (Murata *et al.*, 2007) although no proper preclinical study ever showed a positive effect in an experimental of LID. Preclinical evidences however were collected supporting moderate efficacy against essential tremor (Miwa *et al.*, 2011). Zonisamide (50mg) decreased disabling dyskinesia. However, patients

receiving zonisamide complained dose-dependently about more dizziness, apathy and a decrease in body weight (Iwata *et al.*, 2012).

Another antiepileptic drug, topiramate, previously suggested to modestly reduce LID without exacerbating parkinsonism in animal models (Kobylecki *et al.*, 2011; Silverdale *et al.*, 2005), was tested in a single-dose randomized, double-blind, placebo-controlled crossover trial in dyskinetic PD patients. Interestingly, as in the eltoprazine trial mentioned above, dyskinesia severity was assessed by a blinded rater from video recordings as the primary outcome measure. Such setting was comparable to animal studies. Topiramate-treated patients showed however a significant increase in dyskinesia severity compared to baseline (and placebo-treated ones). Five patients withdrew from the study whilst taking topiramate due to adverse effects (only 7 completed the trial). Although methodologically very similar to preclinical studies, the trial unravelled that topiramate might worsen dyskinesia in PD patients and is poorly tolerated.

6.6. Antipsychotics

The efficacy of clozapine, a DA receptor antagonist with antiserotonergic, antimuscarinic, antiadrenergic and antihistaminergic properties, in decreasing LID was evaluated in several small pilot studies (Bennett *et al.*, 1994; Bennett *et al.*, 1993; Durif *et al.*, 1997; Pierelli *et al.*, 1998) and in one larger randomized, placebo controlled trial (Durif *et al.*, 2004). In the latter, patients treated with clozapine gained 2.4h of ON time without dyskinesia compared to placebo. There was no increase in the duration of OFF periods. Dyskinesia ratings at rest were decreased during the acute L-dopa challenge. However, ratings in the same condition during an activation task were not different. Clozapine had no effect on the anti-parkinsonian action of L-dopa. Adverse events were not more frequent with clozapine except for drowsiness and hypereosinophilia, the latter rapidly resolved after treatment discontinuation.

Olanzapine has shown anti-dyskinetic properties in a small randomized, placebo-controlled cross-over trial (Manson *et al.*, 2000b). However, adverse events were more common with olanzapine, consisting in increased OFF time, increased parkinsonism and increased drowsiness.

Quetiapine, another atypical antipsychotic with few extrapyramidal side effects, was tested in a small randomized, placebo-controlled, cross-over study enrolling 8 PD patients with disabling LID (Katzenschlager *et al.*, 2004). No differences were observed between quetiapine and placebo. The double-blind trial was followed by an open-label period of

around 30 days during which patients received up to 50mg/d of quetiapine. Mild improvement in dyskinesia duration and severity were observed during the open-label period according to patient home diaries.

6.7. Other strategies

Safinamide, a reversible and selective MAO-B inhibitor that also reduces degradation of DA and displays glutamate release inhibitor properties (Caccia *et al.*, 2006), has long been proposed to display anti-dyskinetic properties (Gregoire *et al.*, 2013). A Phase III, multicenter, double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of safinamide as add-on to L-dopa in the treatment of PD patients with motor fluctuations (Borgohain *et al.*, 2014a; Borgohain *et al.*, 2014b). Primary endpoint (i.e. overall improvement in LID) was not reached but add-on safinamide in mid-to-late PD with motor fluctuations showed improvement in dyskinesia in patients at least moderately dyskinetic at baseline as well as increase in ON-time without troublesome dyskinesia (Borgohain *et al.*, 2014b).

Cannabis was examined in a randomized, placebo-controlled cross-over design in 19 PD patients with LID (Carroll *et al.*, 2004). Cannabis tended to worsen dyskinesia. No serious adverse events were observed.

Nabilone, a cannabinoid, has shown anti-dyskinetic properties in a small randomized, placebo-controlled cross-over study in 7 PD patients who experienced LID during 25-50% of waking hours (Sieradzan *et al.*, 2001). Nabilone decreased dyskinesia by 22% compared to placebo, while the duration of ON time and the percentage of dyskinesia during ON time were not modified. Nabilone had no effect on the anti-parkinsonian action of L-dopa. Two patients were withdrawn from the study because of side effects (vertigo, orthostatic hypotension).

The opioid antagonist naltrexone was assessed in 10 PD patients with end-of-dose wearing OFF and 8 PD patients with dyskinesia in a randomized trial (Rascol *et al.*, 1994). Naltrexone had no effect on motor function or dyskinesia severity and duration. Adverse events (digestive, neuropsychiatric) were more frequent in patients under naltrexone.

The anti-dyskinetic properties of the α2-adrenergic receptor antagonist idazoxan were evaluated in a single oral dose randomized, placebo-controlled study in 18 PD patients with peak-dose dyskinesia (Rascol *et al.*, 2001a). There was a trend for lower dyskinesia in patients receiving 10 or 20mg idazoxan. Cardiovascular adverse events were more frequent with idazoxan. A randomized cross-over trial in 7 PD patients failed to show an effect of

idazoxan on LID (Manson *et al.*, 2000a). No differences were observed between idazoxan and placebo in terms of motor function and dyskinesia severity. All patients experienced side effects during idazoxan treatment, which were serious enough in 3 to discontinue study medication.

Fipamezole, another α2-adrenergic receptor antagonist, was tested in a randomized, double-blind, placebo-controlled, dose-escalating 28-day study involving 179 PD patients from the US and India experiencing LID (Lewitt *et al.*, 2012b). The primary outcome based on LID scale, a modification of the AIMs Scale, was negative for the overall cohort. When only looking at the US subpopulation, patients receiving 90 mg fipamezole t.i.d. showed a significant reduction of LID scores at day 28 compared to placebo. Fipamezole treatment was reported safe and well tolerated.

Propranolol, a beta-adrenergic receptor antagonist, has been regularly suggested to exhibit some anti-dyskinetic potential, without affecting L-DOPA's efficacy. Propranolol, in a dose-dependent manner, reduced LID, without affecting motor performance in the AIM rat model of LID (Bhide *et al.*, 2015) but failed to alter dyskinesia produced by the D1 receptor agonist SKF81297 or the D2 receptor agonist Quinpirole. These findings suggested a pre-synaptic mechanism for Propranolol's anti-dyskinetic effects, possibly through modulating L-DOPA-mediated DA efflux, as unravelled demonstration of propranolol-mediated reduction in L-DOPA-induced DA efflux (Bhide *et al.*, 2015). Therefore, Propranolol's anti-dyskinetic properties appear to be mediated via attenuation of L-DOPA-induced extraphysiological efflux of DA, comparably to 5-$HT_{1A/1B}$ agonists.

A ten day treatment with transdermal high dose 17[beta]-estradiol (0.4 mg/d) was studied in 8 female PD patients with LID in a randomized, placebo-controlled cross-over study (Blanchet *et al.*, 1999). The threshold dose of L-dopa to provide anti-parkinsonian efficacy was reduced. By contrast, the duration of the clinical motor response and dyskinesia ratings were not different between groups. While on estradiol, most patients complained of breast/nipple tenderness and 3 patients reported increased dyskinesia.

7. Concluding remarks

The present review describes the unprecedented accumulation of knowledge on the pathophysiology of LID in particular and of L-dopa-induced disorders in general. One can not however fail to notice the discrepancy between such knowledge and the yet limited

therapeutic armoury. We are indeed basically left with amantadine or DBS to manage the severity of dyskinesia and we have no real option for delaying, or even better prevent the appearance of these troublesome side-effects.

How can we have failed so far in translating those basic science discoveries into real treatments? One immediately thinks about the predictive value of animal models that could be, at first look, considered as relatively poor. We would like to challenge this view by paying attention to two major difficulties inherent to translational research and not simply to LID: on one hand the difference between statistical difference and clinical relevance and, one the other hand, the fundamental difference in the assessment tools used in preclinical and clinical settings.

All anti-dyskinetic strategies that have been shown somewhat efficacious in PD patients were tested in the AIM rat model (L-dopa-treated 6-OHDA-lesioned rat; MA Cenci's lab) and in LID macaque model (L-dopa-treated MPTP-lesioned; E Bezard's lab) and shown capable of significantly reducing the severity of AIMs in those two models. While this back-validation effort partially supports our claim of predictivity, it also shed light upon the importance of magnitude of efficacy. Among the several studies that have reported a significant improvement of AIMs or LID in animal models, the vast majority reports statistically significant results of modest amplitude. One should consider that we work in inbred (rodents) or F2-bred (macaques) animals that are genetically and physiologically homogenous, of same sex and body weight, bearing identical lesions (nigro-striatal for 6-OHDA rat (Cenci *et al.*, 2002; Winkler *et al.*, 2002) and widespread monoaminergic lesions for MPTP macaques (Engeln *et al.*, 2014b; Guigoni *et al.*, 2005b)), scrutinized on- or –off-line for the entire duration of pharmacological stimulation (classically from 4 to 10 hours post-L-dopa administration). Therefore, small amplitude effects, although significant and scientifically valid, bear the risk of not being replicable in less controlled situations, i.e. in the clinic where patients are genetically heterogeneous, are of either sex, likely experience various degrees and natures of lesions and are seldom clinically followed during the entire exposure to L-dopa. As we climb the phylogenetic tree, we have noticed an attrition phenomenon of the anti-dyskinetic effect. In other words, a positive effect should be of large amplitude in rodents to be replicated in monkeys, which themselves should present a large improvement of LID for hoping observing it in patients. mGluR5 negative allosteric modulators are a good example of such a differential magnitude and of the attrition effect. There is a class effect upon AIMs in the AIM rat model, a trend for such a class effect upon LID in the macaque models (Bezard *et al.*, 2014; Gregoire *et al.*, 2011; Rylander *et al.*, 2010a; Zhang *et al.*, 2014c) and modest

improvement in PD patients with report of some anti-L-dopa effects (Berg *et al.*, 2011; Kumar *et al.*, 2013). The only available clinical data are however those obtained so far with the drug, AFQ056, that shows the smallest amplitude of improvement in a macaque model of LID in PD (Gregoire *et al.*, 2011).

Puzzlingly, most clinical trials, small or large scales, are conducted based upon patient diaries reporting the number of hours spent per day without troublesome dyskinesia. We fully understand (and agree) that this must be the final endpoint as it reflect the real life but such setting does not "translate" the basic science settings were individuals would be scrutinized and clinically assessed over time by a trained neurologist. Interestingly, such experimental and pilot settings are applied from time to time and prove to replicate the preclinical findings. Two pivotal examples that use two different settings support the case. Amantadine was first shown efficacious in a small trial in which parkinsonian and dyskinesia scores were obtained during a steady-state intravenous L-dopa infusion, i.e. under direct observation by neurologists in a controlled setting where dyskinesia were deliberately elicited by individually rising the L-dopa plasma levels (Verhagen Metman *et al.*, 1998b). The finding was then confirmed in a more classic trial (Metman *et al.*, 1999). Eltoprazine constitutes the most recent example of such direct translation with first demonstration of efficacy in animal studies (see above) followed by a small clinical trial (Svenningsson *et al.*, 2015) demonstrating anti-dyskinetic potential without impairment of therapeutic anti-parkinsonian response to L-dopa on the basis of direct clinical scoring of patients, i.e., exactly as done in experimental studies.

Investigational clinical trials carefully performed on small number of patients knowingly dyskinetic or made dyskinetic by *ad hoc* L-dopa intravenous titration have therefore the potential for supporting or invalidating preclinical findings. An example of such invalidation is provided by the failed attempt to reposition simvastatin, thanks to its property of inhibiting striatal Ras-ERK pathway (Tison *et al.*, 2013). A "n-of-1" design randomized, placebo-controlled, 3 cross-over trial was conducted in 10 PD patients with troublesome dyskinesia. Such exploratory trial design is highly suitable for rapid proof-of-concept challenging of a new indication of available drugs for LID management (Rascol *et al.*, 2012). The lack of simvastatin efficacy was found to be due to the lack of target engagement in PD patients due to dose limitation while such target engagement was found in the monkey model (Tison *et al.*, 2013).

In the past few years, the concept of combined therapies has emerged. Since no single drug is capable to abolish LID, even in experimental models, attempts to do so, while reducing their side-effects or their pro-parkinsonian action, support the validity of the concept, i.e. that

combination of drugs with different mechanisms of action add their efficacy for a better management of established LID (Bezard *et al.*, 2013c; Bibbiani *et al.*, 2005; Hill *et al.*, 2004b; Ko *et al.*, 2014c; Munoz *et al.*, 2008). Although scientifically valid, and to a certain extent clinically valid provided the drugs are on the market, the industrial development of combined or cocktail therapies is seen as problematic. Besides the intellectual property and marketing issues, the development cost for demonstrating safety appears huge unless we consider existing marketed drugs.

Beyond the issues inherent to pharmacology, the condition itself may prevent development of biological therapies. Experimental studies now rely not simply on pharmacology but also on biological tools such as peptides, antibodies, cellular and gene therapy, etc… , for the sake of scientific demonstration, with a clear therapeutic potential. Regulatory agencies (e.g. US Food and Drug Administration and European Medicines Agency) however rightfully consider LID as a side-effect of the PD therapy. Although obvious, this statement is not without consequences, i.e. no “permanent” therapy, e.g. gene therapy, would be approved for treating LID as such approaches are considered only for treating/curing primary conditions, not the side-effects of their treatment.

Altogether, these parameters lead us to propose a simple roadmap for translational therapeutic development for LID in PD. “Efficacy” should be demonstrated in a AIM rodent model (rat or mouse) and then tested in the macaque model of LID, both widely available. Translating experimental findings requires not only jumping from model species to PD patients but also involves using different assessment methods. We strongly suggest, at least in investigational studies, to use very comparable tools for assessing the efficacy, introducing small-scale studies in patients aimed at paving the way to larger scale studies once proof-of-concept is obtained and dose defined. Such small-scale studies should either use the L-dopa intravenous titration or use a "n-of-1" design placebo-controlled, cross-over trial design (provided the test item half-life permits). With these issues in mind, we can confidently envision the development of pharmacological strategies capable of reducing the severity of established dyskinesia in PD patients.

8. Acknowledgements

This review was supported by the Fondation de France and Grant LABEX BRAIN ANR-10-LABX-43. The funders had no role in study design, data collection and analysis, decision to

publish, or preparation of the manuscript. Although extensive, this review cannot be exhaustive. We therefore apologise the many authors whose work has not be quoted.

9. References

Adler, C.H., Singer, C., O'Brien, C., Hauser, R.A., Lew, M.F., Marek, K.L., Dorflinger, E., Pedder, S., Deptula, D., Yoo, K., 1998. Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson disease treated with levodopa-carbidopa. Tolcapone Fluctuator Study Group III. *Arch Neurol* 55**,** 1089-1095.

Ahlskog, J.E., Muenter, M.D., 2001. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 16**,** 448-458.

Ahmed, I., Bose, S.K., Pavese, N., Ramlackhansingh, A., Turkheimer, F., Hotton, G., Hammers, A., Brooks, D.J., 2011. Glutamate NMDA receptor dysregulation in Parkinson's disease with dyskinesias. *Brain* 134**,** 979-986.

Ahmed, M.R., Berthet, A., Bychkov, E., Porras, G., Li, Q., Bioulac, B.H., Carl, Y.T., Bloch, B., Kook, S., Aubert, I., Dovero, S., Doudnikoff, E., Gurevich, V.V., Gurevich, E.V., Bezard, E., 2010. Lentiviral overexpression of GRK6 alleviates L-dopa-induced dyskinesia in experimental Parkinson's disease. *Sci Transl Med* 2**,** 28ra28.

Ahmed, M.R., Bychkov, E., Kook, S., Zurkovsky, L., Dalby, K.N., Gurevich, E.V., 2015. Overexpression of GRK6 rescues L-DOPA-induced signaling abnormalities in the dopamine-depleted striatum of hemiparkinsonian rats. *Exp Neurol* 266**,** 42-54.

Ahmed, M.R., Bychkov, E.R., Gurevich, V.V., Benovic, J.L., Gurevich, E.V., 2007. Altered expression and subcellular distribution of GRK subtypes in the dopamine-depleted rat basal ganglia is not normalized by L-DOPA treatment *J Neurochem* In press.

Ahmed, M.R., Gurevich, V.V., Dalby, K.N., Benovic, J.L., Gurevich, E.V., 2008. Haloperidol and clozapine differentially affect the expression of arrestins, receptor kinases, and extracellular signal-regulated kinase activation. *J Pharmacol Exper Ther* 325**,** 276-283.

Akerud, P., Canals, J.M., Snyder, E.Y., Arenas, E., 2001. Neuroprotection through delivery of glial cell line-derived neurotrophic factor by neural stem cells in a mouse model of Parkinson's disease. *J. Neurosci.* 21**,** 8108-8118.

Albin, R.L., Young, A.B., Penney, J.B., 1989. The functional anatomy of basal ganglia disorders. *Trends Neurosci* 12**,** 366-375.

Albuquerque, E.X., Pereira, E.F., Alkondon, M., Rogers, S.W., 2009. Mammalian nicotinic acetylcholine receptors: from structure to function. *Physiol Rev* 89**,** 73-120.

Alcacer, C., Charbonnier-Beaupel, F., Corvol, J.C., Girault, J.A., Herve, D., 2014. Mitogen- and stress-activated protein kinase 1 is required for specific signaling responses in dopamine-denervated mouse striatum, but is not necessary for l-DOPA-induced dyskinesia. *Neurosci Lett* 583C**,** 76-80.

Alcacer, C., Santini, E., Valjent, E., Gaven, F., Girault, J.A., Herve, D., 2012. Galpha(olf) mutation allows parsing the role of cAMP-dependent and extracellular signal-regulated kinase-dependent signaling in L-3,4-dihydroxyphenylalanine-induced dyskinesia. *J Neurosci* 32**,** 5900-5910.

Alegre, M., Lopez-Azcarate, J., Alonso-Frech, F., Rodriguez-Oroz, M.C., Valencia, M., Guridi, J., Artieda, J., Obeso, J.A., 2012. Subthalamic activity during diphasic dyskinesias in Parkinson's disease. *Mov Disord* 27**,** 1178-1181.

Alonso-Frech, F., Zamarbide, I., Alegre, M., Rodriguez-Oroz, M.C., Guridi, J., Manrique, M., Valencia, M., Artieda, J., Obeso, J.A., 2006. Slow oscillatory activity and levodopa-induced dyskinesias in Parkinson's disease. *Brain* 129**,** 1748-1757.

Alterman, R.L., Shils, J.L., Gudesblatt, M., Tagliati, M., 2004. Immediate and sustained relief of levodopa-induced dyskinesias after dorsal relocation of a deep brain stimulation lead. Case report. *Neurosurgical focus* 17**,** E6.

Amalric, M., Lopez, S., Goudet, C., Fisone, G., Battaglia, G., Nicoletti, F., Pin, J.P., Acher, F.C., 2013. Group III and subtype 4 metabotropic glutamate receptor agonists: discovery and pathophysiological applications in Parkinson's disease. *Neuropharmacology* 66**,** 53-64.

Ambermoon, P., Carter, A., Hall, W., Dissanayaka, N., O'Sullivan, J., 2012. Compulsive use of dopamine replacement therapy: a model for stimulant drug addiction? *Addiction* 107**,** 241-247.

Ambermoon, P., Carter, A., Hall, W.D., Dissanayaka, N.N., O'Sullivan, J.D., 2011. Impulse control disorders in patients with Parkinson's disease receiving dopamine replacement therapy: evidence and implications for the addictions field. *Addiction* 106**,** 283-293.

American-Psychiatric-Association, 2000. *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. American Psychiatric Association: Washington, DC.

American-Psychiatric-Association, 2013. *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*. American Psychiatric Publishing: Arlington, VA.

Andersson, M., Hilbertson, A., Cenci, M.A., 1999. Striatal fosB expression is causally linked with l-DOPA-induced abnormal involuntary movements and the associated upregulation of striatal prodynorphin mRNA in a rat model of Parkinson's disease. *Neurobiol. Dis.* 6**,** 461-474.

Andersson, M., Konradi, C., Cenci, M.A., 2001. cAMP response element-binding protein is required for dopamine-dependent gene expression in the intact but not the dopamine-denervated striatum. *J Neurosci* 21**,** 9930-9943.

Ando, K., Inoue, T., Itoh, T., 2014. L-DOPA-induced behavioral sensitization of motor activity in the MPTP-treated common marmoset as a Parkinson's disease model. *Pharmacology, biochemistry, and behavior* 127**,** 62-69.

Annett, L.E., Rogers, D.C., Hernandez, T.D., Dunnett, S.B., 1992. Behavioural analysis of unilateral monoamine depletion in the marmoset. *Brain* 115 (Pt 3)**,** 825-856.

Anton, B., Fein, J., To, T., Li, X., Silberstein, L., Evans, C.J., 1996. Immunohistochemical localization of ORL-1 in the central nervous system of the rat. *The Journal of comparative neurology* 368**,** 229-251.

Antonini, A., Isaias, I.U., Canesi, M., Zibetti, M., Mancini, F., Manfredi, L., Dal Fante, M., Lopiano, L., Pezzoli, G., 2007. Duodenal levodopa infusion for advanced Parkinson's disease: 12-month treatment outcome. *Mov Disord* 22**,** 1145-1149.

Antonini, A., Odin, P., Opiano, L., Tomantschger, V., Pacchetti, C., Pickut, B., Gasser, U.E., Calandrella, D., Mancini, F., Zibetti, M., Minafra, B., Bertaina, I., De Deyn, P., Cras, C., Wolf, E., Spielberger, S., Poewe, W., 2013. Effect and safety of duodenal levodopa infusion in advanced Parkinson's disease: a retrospective multicenter outcome assessment in patient routine care. *J Neural Transm* 120**,** 1553-1558.

Arai, R., Karasawa, N., Geffard, M., Nagatsu, I., 1995. L-DOPA is converted to dopamine in serotonergic fibers of the striatum of the rat: a double-labeling immunofluorescence study. *Neurosci Lett* 195**,** 195-198.

Arai, R., Karasawa, N., Geffard, M., Nagatsu, T., Nagatsu, I., 1994. Immunohistochemical evidence that central serotonin neurons produce dopamine from exogenous L-DOPA in the rat, with reference to the involvement of aromatic L-amino acid decarboxylase. *Brain Res* 667**,** 295-299.

Ashby, M.C., Maier, S.R., Nishimune, A., Henley, J.M., 2006. Lateral diffusion drives constitutive exchange of AMPA receptors at dendritic spines and is regulated by spine morphology. *J Neurosci* 26**,** 7046-7055.

Attramadal, H., Arriza, J.L., Aoki, C., Dawson, T.M., Codina, J., Kwatra, M.M., Snyder, S.H., Caron, M.G., Lefkowitz, R.J., 1992. Beta-arrestin2, a novel member of the arrestin/beta-arrestin gene family. *J Biol Chem* 267**,** 17882-17890.

Au, W.L., Adams, J.R., Troiano, A.R., Stoessl, A.J., 2005. Parkinson's disease: in vivo assessment of disease progression using positron emission tomography. *Brain Res Mol Brain Res* 134**,** 24-33.

Aubert, I., Guigoni, C., Hakansson, K., Li, Q., Dovero, S., Barthe, N., Bioulac, B.H., Gross, C.E., Fisone, G., Bloch, B., Bezard, E., 2005. Increased D1 dopamine receptor signaling in levodopa-induced dyskinesia. *Ann Neurol* 57**,** 17-26.

Aubert, I., Guigoni, C., Li, Q., Dovero, S., Bioulac, B.H., Gross, C.E., Crossman, A.R., Bloch, B., Bezard, E., 2007. Enhanced Preproenkephalin-B–Derived Opioid Transmission in Striatum and Subthalamic Nucleus Converges Upon Globus Pallidus Internalis in L-3,4-dihydroxyphenylalanine–Induced Dyskinesia. *Biological psychiatry* 61**,** 836-844.

Avanzi, M., Baratti, M., Cabrini, S., Uber, E., Brighetti, G., Bonfa, F., 2006. Prevalence of pathological gambling in patients with Parkinson's disease. *Mov Disord* 21**,** 2068-2072.

Axelrod, D., Ravdin, P., Koppel, D.E., Schlessinger, J., Webb, W.W., Elson, E.L., Podleski, T.R., 1976. Lateral motion of fluorescently labeled acetylcholine receptors in membranes of developing muscle fibers. *Proc Natl Acad Sci U S A* 73**,** 4594-4598.

Aziz, T.Z., Peggs, D., Sambrook, M.A., Crossman, A.R., 1991. Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. *Mov Disord* 6**,** 288-292.

Azkona, G., Sagarduy, A., Aristieta, A., Vazquez, N., Zubillaga, V., Ruiz-Ortega, J.A., Perez-Navarro, E., Ugedo, L., Sanchez-Pernaute, R., 2014. Buspirone anti-dyskinetic effect is correlated with temporal normalization of dysregulated striatal DRD1 signalling in L-DOPA-treated rats. *Neuropharmacology* 79**,** 726-737.

Azmitia, E.C., Segal, M., 1978. An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. *The Journal of comparative neurology* 179**,** 641-667.

Ba, M., Kong, M., Yang, H., Ma, G., Lu, G., Chen, S., Liu, Z., 2006. Changes in subcellular distribution and phosphorylation of GluR1 in lesioned striatum of 6-

hydroxydopamine-lesioned and l-dopa-treated rats. *Neurochemical research* 31**,** 1337-1347.

Bagetta, V., Sgobio, C., Pendolino, V., Del Papa, G., Tozzi, A., Ghiglieri, V., Giampa, C., Zianni, E., Gardoni, F., Calabresi, P., Picconi, B., 2012. Rebalance of striatal NMDA/AMPA receptor ratio underlies the reduced emergence of dyskinesia during D2-like dopamine agonist treatment in experimental Parkinson's disease. *J Neurosci* 32**,** 17921-17931.

Ballard, P.A., Tetrud, J.W., Langston, J.W., 1985. Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): seven cases. *Neurology* 35**,** 949-956.

Bamford, N.S., Zhang, H., Joyce, J.A., Scarlis, C.A., Hanan, W., Wu, N.P., Andre, V.M., Cohen, R., Cepeda, C., Levine, M.S., Harleton, E., Sulzer, D., 2010. Repeated exposure to methamphetamine causes long-lasting presynaptic corticostriatal depression that is renormalized with drug readministration. *Neuron* 58**,** 89-103.

Banke, T.G., Bowie, D., Lee, H., Huganir, R.L., Schousboe, A., Traynelis, S.F., 2000. Control of GluR1 AMPA receptor function by cAMP-dependent protein kinase. *J. Neurosci.* 20**,** 89-102.

Bara-Jimenez, W., Bibbiani, F., Morris, M.J., Dimitrova, T., Sherzai, A., Mouradian, M.M., Chase, T.N., 2005. Effects of serotonin 5-HT1A agonist in advanced Parkinson's disease. *Mov Disord* 20**,** 932-936.

Bara-Jimenez, W., Dimitrova, T.D., Sherzai, A., Aksu, M., Chase, T.N., 2006. Glutamate release inhibition ineffective in levodopa-induced motor complications. *Mov Disord* 21**,** 1380-1383.

Bard, L., Groc, L., 2011. Glutamate receptor dynamics and protein interaction: Lessons from the NMDA receptor. *Mol Cell Neurosci* 48(4)**,** 298-307.

Barone, P., Morelli, M., Popoli, M., Cicarelli, G., Campanella, G., Di Chiara G., 1994. Behavioural sensitization in 6-hydroxydopamine lesioned rats involves the dopamine signal transduction: changes in DARPP-32 phosphorylation. . *Neuroscience* 61**,** 7.

Barroso-Chinea, P., Thiolat, M.L., Bido, S., Martinez, A., Doudnikoff, E., Baufreton, J., Bourdenx, M., Bloch, B., Bezard, E., Martin-Negrier, M.L., 2015. D1 dopamine receptor stimulation impairs striatal proteasome activity in Parkinsonism through 26S proteasome disassembly. *Neurobiol Dis* in press.

Bastiaens, J., Dorfman, B.J., Christos, P.J., Nirenberg, M.J., 2013. Prospective cohort study of impulse control disorders in Parkinson's disease. *Mov Disord* 28**,** 327-333.

Bastian, A.J., 2006. Learning to predict the future: the cerebellum adapts feedforward movement control. *Curr Opin Neurobiol* 16**,** 645-649.

Bastide, M.F., de la Crompe, B., Doudnikoff, E., Fernagut, P.O., Gross, C.E., Mallet, N., Boraud, T., Bezard, E., 2014a. Inhibiting Lateral Habenula Improves L-DOPA-induced Dyskinesia. *Biol Psychiatry*.

Bastide, M.F., Dovero, S., Charron, G., Porras, G., Gross, C.E., Fernagut, P.O., Bezard, E., 2014b. Immediate-early gene expression in structures outside the basal ganglia is associated to l-DOPA-induced dyskinesia. *Neurobiol Dis* 62**,** 179-192.

Bateup, H.S., Santini, E., Shen, W., Birnbaum, S., Valjent, E., Surmeier, D.J., Fisone, G., Nestler, E.J., Greengard, P., 2010. Distinct subclasses of medium spiny neurons differentially regulate striatal motor behaviors. *Proc Natl Acad Sci U S A* 107**,** 14845-14850.

Bearn, J., Evans, A., Kelleher, M., Turner, K., Lees, A., 2004. Recognition of a dopamine replacement therapy dependence syndrome in Parkinson's disease: a pilot study. *Drug and alcohol dependence* 76**,** 305-310.

Beaulieu, J.M., Gainetdinov, R.R., Caron, M.G., 2007. The Akt-GSK-3 signaling cascade in the actions of dopamine. *Trends Pharmacol Sci* 28**,** 166-172.

Beaulieu, J.M., Sotnikova, T.D., Marion, S., Lefkowitz, R.J., Gainetdinov, R.R., Caron, M.G., 2005. An Akt/beta-arrestin 2/PP2A signaling complex mediates dopaminergic neurotransmission and behavior. *Cell* 122**,** 261-273.

Bédard, P.J., Boucher, R., Gomez-Mancilla, B., Blanchette, P. 1992. Primate models of Parkinson's disease. In: *Animal models of neurological disease, I: neurodegenerative diseases*. pp. 159-173. Eds. A.A. Boulton, G.B. Baker, R.F. Butterworth. Humana press: Totowa.

Beeler, J.A., Cao, Z.F., Kheirbek, M.A., Ding, Y., Koranda, J., Murakami, M., Kang, U.J., Zhuang, X., 2010. Dopamine-dependent motor learning: insights into levodopa's long-duration response. *Ann Neurol* 67**,** 639-647.

Bejjani, B.P., Arnulf, I., Demeret, S., Damier, P., Bonnet, A.M., Houeto, J.L., Agid, Y., 2000. Levodopa-induced dyskinesias in Parkinson's disease: is sensitization reversible? *Ann Neurol* 47**,** 655-658.

Belujon, P., Lodge, D.J., Grace, A.A., 2010. Aberrant striatal plasticity is specifically associated with dyskinesia following levodopa treatment. *Mov Disord* 25**,** 1568-1576.

Benazzouz, A., Gross, C., Bioulac, B., 1992. MPTP-induced hemiparkinsonism in monkeys: behavioral, mechanographic, electromyographic and immunohistochemical studies. *Exp. Brain Res.* 90**,** 116-120.

Benazzouz, A., Gross, C., Féger, J., Boraud, T., Bioulac, B., 1993. Reversal of rigidity and improvement in motor performance by subthalamic high frequency stimulation in MPTP-treated monkeys. *Eur. J. Neurosci.* 5**,** 382-389.

Bennett, B.D., Wilson, C.J., 1999. Spontaneous activity of neostriatal cholinergic interneurons in vitro. *J Neurosci* 19**,** 5586-5596.

Bennett, J.P., Jr., Landow, E.R., Dietrich, S., Schuh, L.A., 1994. Suppression of dyskinesias in advanced Parkinson's disease: moderate daily clozapine doses provide long-term dyskinesia reduction. *Mov Disord* 9**,** 409-414.

Bennett, J.P., Jr., Landow, E.R., Schuh, L.A., 1993. Suppression of dyskinesias in advanced Parkinson's disease. II. Increasing daily clozapine doses suppress dyskinesias and improve parkinsonism symptoms. *Neurology* 43**,** 1551-1555.

Bennouar, K.E., Uberti, M.A., Melon, C., Bacolod, M.D., Jimenez, H.N., Cajina, M., Kerkerian-Le Goff, L., Doller, D., Gubellini, P., 2013. Synergy between L-DOPA and a novel positive allosteric modulator of metabotropic glutamate receptor 4: implications for Parkinson's disease treatment and dyskinesia. *Neuropharmacology* 66**,** 158-169.

Berg, D., Godau, J., Trenkwalder, C., Eggert, K., Csoti, I., Storch, A., Huber, H., Morelli-Canelo, M., Stamelou, M., Ries, V., Wolz, M., Schneider, C., Di Paolo, T., Gasparini, F., Hariry, S., Vandemeulebroecke, M., Abi-Saab, W., Cooke, K., Johns, D., Gomez-Mancilla, B., 2011. AFQ056 treatment of levodopa-induced dyskinesias: results of 2 randomized controlled trials. *Mov Disord* 26**,** 1243-1250.

Bergman, H., Raz, A., Feingold, A., Nini, A., Nelken, I., Hansel, D., BenPazi, H., Reches, A., 1998. Physiology of MPTP tremor. *Mov. Disord.* 13**,** 29-34.

Bernard, R., Veh, R.W., 2012. Individual neurons in the rat lateral habenular complex project mostly to the dopaminergic ventral tegmental area or to the serotonergic raphe nuclei. *The Journal of comparative neurology* 520**,** 2545-2558.

Berthele, A., Platzer, S., Dworzak, D., Schadrack, J., Mahal, B., Buttner, A., Assmus, H.P., Wurster, K., Zieglgansberger, W., Conrad, B., Tolle, T.R., 2003. [3H]-nociceptin ligand-binding and nociceptin opioid receptor mrna expression in the human brain. *Neuroscience* 121**,** 629-640.

Berthet, A., Bezard, E., 2009. Dopamine receptors and L-dopa-induced dyskinesia. *Parkinsonism Relat Disord* 15 Suppl 4**,** S8-12.

Berthet, A., Bezard, E., Porras, G., Fasano, S., Barroso-Chinea, P., Dehay, B., Martinez, A., Thiolat, M.L., Nosten-Bertrand, M., Giros, B., Baufreton, J., Li, Q., Bloch, B., Martin-Negrier, M.L., 2012. L-DOPA impairs proteasome activity in parkinsonism through D1 dopamine receptor. *J Neurosci* 32**,** 681-691.

Berthet, A., Porras, G., Doudnikoff, E., Stark, H., Cador, M., Bezard, E., Bloch, B., 2009. Pharmacological analysis demonstrates dramatic alteration of D1 dopamine receptor neuronal distribution in the rat analog of L-DOPA-induced dyskinesia. *J Neurosci* 29**,** 4829-4835.

Berton, O., Guigoni, C., Li, Q., Bioulac, B.H., Aubert, I., Gross, C.E., Dileone, R.J., Nestler, E.J., Bezard, E., 2009. Striatal overexpression of DeltaJunD resets L-DOPA-induced dyskinesia in a primate model of Parkinson disease. *Biol Psychiatry* 66**,** 554-561.

Beurrier, C., Bezard, E., Bioulac, B., Gross, C., 1997. Subthalamic stimulation elicits hemiballismus in normal monkey. *Neuroreport* 8**,** 1625-1629.

Bezard, E., Brotchie, J.M., Gross, C.E., 2001a. Pathophysiology of levodopa-induced dyskinesia : Potential for new therapies. *Nature Rev. Neurosci.* 2**,** 577-588.

Bezard, E., Carta, M., 2015. Could the serotonin theory give rise to a treatment for levodopa-induced dyskinesia in Parkinson's disease? *Brain*.

Bezard, E., Crossman, A.R., Gross, C.E., Brotchie, J.M., 2001b. Structures outside the basal ganglia may compensate for dopamine loss in the presymptomatic stages of Parkinson's disease. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 15**,** 1092-1094.

Bezard, E., Dovero, S., Prunier, C., Ravenscroft, P., Chalon, S., Guilloteau, D., Bioulac, B., Brotchie, J.M., Gross, C.E., 2001c. Relationship between the appearance of symptoms and the level of nigrostriatal degeneration in a progressive MPTP-lesioned macaque model of Parkinson's disease. *J. Neurosci.* 21**,** 6853-6861.

Bezard, E., Ferry, S., Mach, U., Stark, H., Leriche, L., Boraud, T., Gross, C.E., Sokoloff, P., 2003. Attenuation of levodopa-induced dyskinesia by normalizing dopamine D3 receptor function. *Nature Med.* 9**,** 762-767.

Bezard, E., Gross, C.E., 1998. Compensatory mechanisms in experimental and human parkinsonism : towards a dynamic approach. *Prog. Neurobiol.* 55**,** 93-116.

Bezard, E., Gross, C.E., Qin, L., Gurevich, V.V., Benovic, J.L., Gurevich, E.V., 2005. L-DOPA reverses the MPTP-induced elevation of the arrestin2 and GRK6 expression and enhanced ERK activation in monkey brain. *Neurobiol. Dis.* 18**,** 323-335.

Bezard, E., Hill, M.P., Crossman, A.R., Brotchie, J.M., Michel, A., Grimee, R., Klitgaard, H., 2004. Levetiracetam improves choreic levodopa-induced dyskinesia in the MPTP-treated macaque. *Eur. J. Pharmacol.* 485**,** 159-164.

Bezard, E., Imbert, C., Gross, C.E., 1998. Experimental models of Parkinson's disease : from the static to the dynamic. *Rev. Neurosci.* 9**,** 71-90.

Bezard, E., Munoz, A., Tronci, E., Pioli, E.Y., Li, Q., Porras, G., Bjorklund, A., Carta, M., 2013a. Anti-dyskinetic effect of anpirtoline in animal models of L-DOPA-induced dyskinesia. *Neuroscience research* 77**,** 242-246.

Bezard, E., Olanow, C.W., Obeso, J.A., 2013b. Levodopa-induced dyskinesias in the absence of nigrostriatal degeneration. *Mov Disord* 28**,** 1023-1024.

Bezard, E., Pioli, E.Y., Li, Q., Girard, F., Mutel, V., Keywood, C., Tison, F., Rascol, O., Poli, S.M., 2014. The mGluR5 negative allosteric modulator dipraglurant reduces dyskinesia in the MPTP macaque model. *Mov Disord* 29**,** 1074-1079.

Bezard, E., Przedborski, S., 2011. A Tell on Animal Models of Parkinson Disease. *Mov Disord* in press.

Bezard, E., Ravenscroft, P., Gross, C.E., Crossman, A.R., Brotchie, J.M., 2001d. Upregulation of striatal preproenkephalin gene expression occurs before the appearance of parkinsonian signs in 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine monkeys. *Neurobiol Dis* 8**,** 343-350.

Bezard, E., Tronci, E., Pioli, E.Y., Li, Q., Porras, G., Bjorklund, A., Carta, M., 2013c. Study of the antidyskinetic effect of eltoprazine in animal models of levodopa-induced dyskinesia. *Mov Disord* 28**,** 1088-1096.

Bhide, N., Lindenbach, D., Barnum, C.J., George, J.A., Surrena, M.A., Bishop, C., 2015. Effects of the beta-adrenergic receptor antagonist Propranolol on dyskinesia and

L-DOPA-induced striatal DA efflux in the hemi-parkinsonian rat. *J Neurochem* 134**,** 222-232.

Bibbiani, F., Oh, J.D., Kielaite, A., Collins, M.A., Smith, C., Chase, T.N., 2005. Combined blockade of AMPA and NMDA glutamate receptors reduces levodopa-induced motor complications in animal models of PD. *Exp Neurol* 196**,** 422-429.

Bibbiani, F., Oh, J.D., Petzer, J.P., Castagnoli, N.J., Chen, J.F., Schwarzschild, M.A., Chase, T.N., 2003. A2A antagonist prevents dopamine agonist-induced motor complications in animal models of Parkinson's disease. *Exp. Neurol.* 184**,** 9.

Bido, S., Marti, M., Morari, M., 2011. Amantadine attenuates levodopa-induced dyskinesia in mice and rats preventing the accompanying rise in nigral GABA levels. *J Neurochem* 118**,** 1043-1055.

Biever, A., Puighermanal, E., Nishi, A., David, A., Panciatici, C., Longueville, S., Xirodimas, D., Gangarossa, G., Meyuhas, O., Herve, D., Girault, J.A., Valjent, E., 2015. PKA-dependent phosphorylation of ribosomal protein S6 does not correlate with translation efficiency in striatonigral and striatopallidal medium-sized spiny neurons. *J Neurosci* 35**,** 4113-4130.

Biglan, K.M., Holloway, R.G., Jr., McDermott, M.P., Richard, I.H., 2007. Risk factors for somnolence, edema, and hallucinations in early Parkinson disease. *Neurology* 69**,** 187-195.

Bingol, B., Schuman, E.M., 2006. Activity-dependent dynamics and sequestration of proteasomes in dendritic spines. *Nature* 441**,** 1144-1148.

Birket-Smith, E., 1974. Abnormal involuntary movements induced by anticholinergic therapy. *Acta Neurol Scand* 50**,** 801-811.

Birkmayer, W., Hornykiewicz, O., 1961. Der L-Dopa Effekt bei der Parkinson-Akinese. *Wien. klin. Wschr.* 73**,** 787.

Birkmayer, W., Hornykiewicz, O., 1962. Der L-Dopa Effekt beim Parkinson-Syndrom des Menschen. Zur Pathogenese und Behandlung der Parkinson-Akinese. *Arch. Psychiat. Nervenkr.* 203**,** 560-574.

Bishop, C., George, J.A., Buchta, W., Goldenberg, A.A., Mohamed, M., Dickinson, S.O., Eissa, S., Eskow Jaunarajs, K.L., 2012. Serotonin transporter inhibition attenuates l-DOPA-induced dyskinesia without compromising l-DOPA efficacy in hemi-parkinsonian rats. *Eur J Neurosci* 36**,** 2839-2848.

Bishop, C., Krolewski, D.M., Eskow, K.L., Barnum, C.J., Dupre, K.B., Deak, T., Walker, P.D., 2009. Contribution of the striatum to the effects of 5-HT1A receptor stimulation in L-DOPA-treated hemiparkinsonian rats. *J Neurosci Res* 87**,** 1645-1658.

Black, D.W., 2007. A review of compulsive buying disorder. *World Psychiatry* 6**,** 14-18.

Blanchet, P.J., Calon, F., Morissette, M., Hadj Tahar, A., Bélanger, N., Samadi, P., Grondin, R., Grégoire, L., Meltzer, L., Di Paolo, T., Bédard, P.J., 2004. Relevance of the MPTP primate model in the study of dyskinesia priming mechanisms. . *Parkinsonism Relat. Disord.* 10**,** 8.

Blanchet, P.J., Fang, J., Hyland, K., Arnold, L.A., Mouradian, M.M., Chase, T.N., 1999. Short-term effects of high-dose 17beta-estradiol in postmenopausal PD patients: a crossover study. *Neurology* 53**,** 91-95.

Blandini, F., Sinforiani, E., Pacchetti, C., Samuele, A., Bazzini, E., Zangaglia, R., Nappi, G., Martignoni, E., 2006. Peripheral proteasome and caspase activity in Parkinson disease and Alzheimer disease. *Neurology* 66**,** 529-534.

Boguth, C.A., Singh, P., Huang, C.C., Tesmer, J.J., 2010. Molecular basis for activation of G protein-coupled receptor kinases. *EMBO J* 29**,** 3249-3259.

Bolam, J.P., Wainer, B.H., Smith, A.D., 1984. Characterization of cholinergic neurons in the rat neostriatum. A combination of choline acetyltransferase immunocytochemistry, Golgi-impregnation and electron microscopy. *Neuroscience* 12**,** 711-718.

Bonaventura, J., Rico, A.J., Moreno, E., Sierra, S., Sanchez, M., Luquin, N., Farre, D., Muller, C.E., Martinez-Pinilla, E., Cortes, A., Mallol, J., Armentero, M.T., Pinna, A., Canela, E.I., Lluis, C., McCormick, P.J., Lanciego, J.L., Casado, V., Franco, R., 2014. L-DOPA-treatment in primates disrupts the expression of A(2A) adenosine-CB(1) cannabinoid-D(2) dopamine receptor heteromers in the caudate nucleus. *Neuropharmacology* 79**,** 90-100.

Bonfanti, A.B., Gatto, E.M., 2010. Kleptomania, an unusual impulsive control disorder in Parkinson's disease? *Parkinsonism Relat Disord* 16**,** 358-359.

Bonifati, V., Fabrizio, E., Cipriani, R., Vanacore, N., Meco, G., 1994. Buspirone in levodopa-induced dyskinesias. *Clin Neuropharmacol* 17**,** 73-82.

Bonsi, P., Martella, G., Cuomo, D., Platania, P., Sciamanna, G., Bernardi, G., Wess, J., Pisani, A., 2008. Loss of muscarinic autoreceptor function impairs long-term depression but not long-term potentiation in the striatum. *J Neurosci* 28**,** 6258-6263.

Boraud, T., Bezard, E., Bioulac, B., Gross, C., 1996. High frequency stimulation of the internal Globus Pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. *Neurosci Lett* 215**,** 17-20.

Boraud, T., Bezard, E., Bioulac, B., Gross, C.E., 2001. Dopamine agonist-induced dyskinesias are correlated to both firing pattern and frequency alterations of pallidal neurones in the MPTP-treated monkey. *Brain* 124**,** 546-557.

Bordet, R., Ridray, S., Carboni, S., Diaz, J., Sokoloff, P., Schwartz, J.C., 1997. Induction of dopamine D3 receptor expression as a mechanism of behavioral sensitization to levodopa. *Proc Natl Acad Sci U S A* 94**,** 3363-3367.

Bordia, T., Campos, C., Huang, L., Quik, M., 2008. Continuous and intermittent nicotine treatment reduces L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias in a rat model of Parkinson's disease. *J Pharmacol Exp Ther* 327**,** 239-247.

Bordia, T., Campos, C., McIntosh, J.M., Quik, M., 2010. Nicotinic receptor-mediated reduction in L-dopa-induced dyskinesias may occur via desensitization. *J Pharmacol Exp Ther* 333**,** 929-938.

Bordia, T., Michael McIntosh, J., Quik, M., 2013. The nicotine-mediated decline in L-dopa-induced dyskinesias is associated with a decrease in striatal dopamine release. *J Neurochem*.

Borgdorff, A.J., Choquet, D., 2002. Regulation of AMPA receptor lateral movements. *Nature* 417**,** 649-653.

Borgkvist, A., Fisone, G., 2007. Psychoactive drugs and regulation of the cAMP/PKA/DARPP-32 cascade in striatal medium spiny neurons. *Neurosci Biobehav Rev* 31**,** 79-88.

Borgohain, R., Szasz, J., Stanzione, P., Meshram, C., Bhatt, M., Chirilineau, D., Stocchi, F., Lucini, V., Giuliani, R., Forrest, E., Rice, P., Anand, R., Study, I., 2014a. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. *Mov Disord* 29**,** 229-237.

Borgohain, R., Szasz, J., Stanzione, P., Meshram, C., Bhatt, M.H., Chirilineau, D., Stocchi, F., Lucini, V., Giuliani, R., Forrest, E., Rice, P., Anand, R., Study, I., 2014b. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. *Mov Disord* 29**,** 1273-1280.

Bortolanza, M., Cavalcanti-Kiwiatkoski, R., Padovan-Neto, F.E., da-Silva, C.A., Mitkovski, M., Raisman-Vozari, R., Del-Bel, E., 2014. Glial activation is associated with l-DOPA induced dyskinesia and blocked by a nitric oxide synthase inhibitor in a rat model of Parkinson's disease. *Neurobiol Dis* 73C**,** 377-387.

Bostan, A.C., Dum, R.P., Strick, P.L., 2010. The basal ganglia communicate with the cerebellum. *Proc Natl Acad Sci U S A* 107**,** 8452-8456.

Bouhaddi, M., Vuillier, F., Fortrat, J.O., Cappelle, S., Henriet, M.T., Rumbach, L., Regnard, J., 2004. Impaired cardiovascular autonomic control in newly and long-term-treated patients with Parkinson's disease: involvement of L-dopa therapy. *Auton Neurosci* 116**,** 30-38.

Boulet, S., Lacombe, E., Carcenac, C., Feuerstein, C., Sgambato-Faure, V., Poupard, A., Savasta, M., 2006. Subthalamic stimulation-induced forelimb dyskinesias are linked to an increase in glutamate levels in the substantia nigra pars reticulata. *J Neurosci* 26**,** 10768-10776.

Boulet, S., Mounayar, S., Poupard, A., Bertrand, A., Jan, C., Pessiglione, M., Hirsch, E.C., Feuerstein, C., Francois, C., Feger, J., Savasta, M., Tremblay, L., 2008. Behavioral recovery in MPTP-treated monkeys: neurochemical mechanisms studied by intrastriatal microdialysis. *J Neurosci* 28**,** 9575-9584.

Bourdenx, M., Nilsson, A., Wadensten, H., Falth, M., Li, Q., Crossman, A.R., Andren, P.E., Bezard, E., 2014. Abnormal structure-specific peptide transmission and processing in a primate model of Parkinson's disease and l-DOPA-induced dyskinesia. *Neurobiol Dis* 62**,** 307-312.

Bouzigues, C., Dahan, M., 2007. Transient directed motions of GABA(A) receptors in growth cones detected by a speed correlation index. *Biophys J* 92**,** 654-660.

Boyce, S., Rupniak, N.M.J., Stevenson, M.J., Iversen, S.D., 1990a. Nigrostriatal damage is required for induction of dyskinesias by L-Dopa in Squirrel Monkeys. *Clin. Neuropharmacol.* 13**,** 448-458.

Boyce, S., Rupniak, N.M.J., Steventon, M.J., Iversen, S.D., 1990b. Characterisation of dyskinesias induced by L-DOPA in MPTP-treated squirrel monkeys. *Psychopharmacology* 102**,** 21-27.

Bozon, B., Davis,S., Laroche, S., 2002. Regulated transcription of the immediate-early gene Zif268: mechanisms and gene dosage-dependent function in synaptic plasticity and memory formation. . *Hippocampus***,** 8.

Brambilla, R., Gnesutta, N., Minichiello, L., White, G., Roylance, A.J., Herron, C.E., Ramsey, M., Wolfer, D.P., Cestari, V., Rossi-Arnaud, C., Grant, S.G.N., Chapman, P.F., Lipp, H.-P., Sturani, E., Klein, R., 1997. A role for the Ras signalling pathway in synaptic transmission and long-term memory. *Nature* 390**,** 281-286.

Bramham, C.R., Worley, P.F., Moore, M.J., Guzowski, J.F., 2008. The immediate early gene arc/arg3.1: regulation, mechanisms, and function. *J Neurosci* 28**,** 11760-11767.

Breese, G.R., Duncan, G.E., Napier, T.C., Bondy, S.C., Iorio, L.C., Mueller, R.A., 1987. 6-hydroxydopamine treatments enhance behavioral responses to intracerebral microinjection of D1- and D2-dopamine agonists into nucleus accumbens and striatum without changing dopamine antagonist binding. *J Pharmacol Exp Ther* 240**,** 167-176.

Breger, L.S., Dunnett, S.B., Lane, E.L., 2013. Comparison of rating scales used to evaluate L-DOPA-induced dyskinesia in the 6-OHDA lesioned rat. *Neurobiol Dis* 50**,** 142-150.

Breger, L.S., Lane, E.L., 2013. L-DOPA and graft-induced dyskinesia: different treatment, same story? *Experimental biology and medicine* 238**,** 725-732.

Breier, A., Su, T.P., Saunders, R., Carson, R.E., Kolachana, B.S., de Bartolomeis, A., Weinberger, D.R., Weisenfeld, N., Malhotra, A.K., Eckelman, W.C., Pickar, D., 1997. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc Natl Acad Sci U S A* 94**,** 2569-2574.

Breit, S., Schulz, J.B., Benabid, A.L., 2004. Deep brain stimulation. *Cell and tissue research* 318**,** 275-288.

Bridge, K.E., Wainwright, A., Reilly, K., Oliver, K.R., 2003. Autoradiographic localization of (125)i[Tyr(14)] nociceptin/orphanin FQ binding sites in macaque primate CNS. *Neuroscience* 118**,** 513-523.

Brodal, P., 1979. The pontocerebellar projection in the rhesus monkey: an experimental study with retrograde axonal transport of horseradish peroxidase. *Neuroscience* 4**,** 193-208.

Brodal, P., 1980. The projection from the nucleus reticularis tegmenti pontis to the cerebellum in the rhesus monkey. *Experimental brain research* 38**,** 29-36.

Brodsky, M.A., Godbold, J., Roth, T., Olanow, C.W., 2003. Sleepiness in Parkinson's disease: a controlled study. *Movement disorders : official journal of the Movement Disorder Society* 18**,** 668-672.

Brooks, D.J., Frey, K.A., Marek, K.L., Oakes, D., Paty, D., Prentice, R., Shults, C.W., Stoessl, A.J., 2003. Assessment of neuroimaging techniques as biomarkers of the progression of Parkinson's disease. *Exp Neurol* 184 Suppl 1**,** S68-79.

Brooks, D.J., Papapetropoulos, S., Vandenhende, F., Tomic, D., He, P., Coppell, A., O'Neill, G., 2010. An open-label, positron emission tomography study to assess adenosine A2A brain receptor occupancy of vipadenant (BIIB014) at steady-state levels in healthy male volunteers. *Clin Neuropharmacol.* 33**,** 6.

Brown, A.M., Deutch, A.Y., Colbran, R.J., 2005. Dopamine depletion alters phosphorylation of striatal proteins in a model of Parkinsonism. *Eur J Neurosci* 22**,** 247-256.

Buccafusco, J.J., Beach, J.W., Terry, A.V., 2009. Desensitization of nicotinic acetylcholine receptors as a strategy for drug development. *J Pharmacol Exp Ther* 328**,** 364-370.

Burns, R.S., Chiueh, C.C., Markey, S.P., Ebert, M.H., Jacobowitz, D.M., Kopin, I.J., 1983. A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Proc Natl Acad Sci U S A* 80**,** 4546-4550.

Bychkov, E., Ahmed, M.R., ., Dalby, K.N., Gurevich, E.V., 2007. Dopamine depletion and subsequent treatment with L-DOPA, but not the long-lived dopamine agonist pergolide, enhances activity of the Akt pathway in the rat striatum. *J. Neurochem.* 102**,** 699-711.

Bychkov, E., Ahmed, M.R., Gurevich, E.V., 2010. Sex differences in the activity of signalling pathways and expression of G-protein-coupled receptor kinases in the neonatal ventral hippocampal lesion model of schizophrenia. *Int J Neuropsychopharmacol* 17**,** 1-15.

Bychkov, E., Ahmed, M.R., Gurevich, V.V., Benovic, J.L., Gurevich, E.V., 2011. Reduced expression of G protein-coupled receptor kinases in schizophrenia but not in schizoaffective disorder. *Neurobiol Dis* 44**,** 248-258.

Bychkov, E., Zurkovsky, L., Garret, M., Ahmed, M.R., Gurevich, E.V., 2013. Distinct cellular and subcellular distribution of G protein-coupled receptor kinase and arrestin isoforms in the striatum. *PLoS One* 7**,** e48912.

Bychkov, E.R., Gurevich, V.V., Joyce, J.N., Benovic, J.L., Gurevich, E.V., 2008. Arrestins and two receptor kinases are upregulated in Parkinson's disease with dementia. *Neurobiol. Aging* 29**,** 379-396.

Caccia, C., Maj, R., Calabresi, M., Maestroni, S., Faravelli, L., Curatolo, L., Salvati, P., Fariello, R.G., 2006. Safinamide: from molecular targets to a new anti-Parkinson drug. *Neurology* 67**,** S18-23.

Caccia, S., Conti, I., Vigano, G., Garattini, S., 1986. 1-(2-Pyrimidinyl)-piperazine as active metabolite of buspirone in man and rat. *Pharmacology* 33**,** 46-51.

Cahill, E., Pascoli, V., Trifilieff, P., Savoldi, D., Kappes, V., Luscher, C., Caboche, J., Vanhoutte, P., 2014. D1R/GluN1 complexes in the striatum integrate dopamine and glutamate signalling to control synaptic plasticity and cocaine-induced responses. *Molecular psychiatry* 19**,** 1295-1304.

Cai, G., Zhen, X., Uryu, K., Friedman, E., 2000. Activation of extracellular signal-regulated protein kinases is associated with a sensitized locomotor response to D(2) dopamine receptor stimulation in unilateral 6-hydroxydopamine-lesioned rats. *J. Neurosci.* 20**,** 1849-1857.

Calabresi, P., Di Filippo, M., Ghiglieri, V., Tambasco, N., Picconi, B., 2010. Levodopa-induced dyskinesias in patients with Parkinson's disease: filling the bench-to-bedside gap. *Lancet Neurol* 9**,** 1106-1117.

Calabresi, P., Gubellini, P., Centonze, D., Sancesario, G., Morello, M., Giorgi, M., Pisani, A., Bernardi, G., 1999. A critical role of the nitric oxide/cGMP pathway in corticostriatal long-term depression. *J Neurosci* 19**,** 2489-2499.

Calabresi, P., Maj, R., Pisani, A., Mercuri, N.B., Bernardi, G., 1992. Long-term synaptic depression in the striatum: physiological and pharmacological characterization. *J Neurosci* 12**,** 4224-4233.

Calabresi, P., Picconi, B., Tozzi, A., Di Filippo, M., 2007. Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends Neurosci* 30**,** 211-219.

Calabresi, P., Picconi, B., Tozzi, A., Ghiglieri, V., Di Filippo, M., 2014. Direct and indirect pathways of basal ganglia: a critical reappraisal. *Nature neuroscience* 17**,** 1022-1030.

Calne, D.B., Zigmond, M.J., 1991. Compensatory mechanisms in degenerative neurologic diseases. Insights from parkinsonism. *Arch Neurol* 48**,** 361-363.

Calo, G., Bigoni, R., Rizzi, A., Guerrini, R., Salvadori, S., Regoli, D., 2000a. Nociceptin/orphanin FQ receptor ligands. *Peptides* 21**,** 935-947.

Calo, G., Guerrini, R., Rizzi, A., Salvadori, S., Burmeister, M., Kapusta, D.R., Lambert, D.G., Regoli, D., 2005. UFP-101, a peptide antagonist selective for the nociceptin/orphanin FQ receptor. *CNS drug reviews* 11**,** 97-112.

Calo, G., Guerrini, R., Rizzi, A., Salvadori, S., Regoli, D., 2000b. Pharmacology of nociceptin and its receptor: a novel therapeutic target. *British journal of pharmacology* 129**,** 1261-1283.

Calo, G., Rizzi, A., Cifani, C., Micioni Di Bonaventura, M.V., Regoli, D., Massi, M., Salvadori, S., Lambert, D.G., Guerrini, R., 2011. UFP-112 a potent and long-lasting agonist selective for the Nociceptin/Orphanin FQ receptor. *CNS neuroscience & therapeutics* 17**,** 178-198.

Calon, F., Dridi, M., Hornykiewicz, O., Bédard, P.J., Rajput, A.H., Di Paolo, T., 2004. Increased adenosine A2A receptors in the brain of Parkinson's disease patients with dyskinesias. *Brain* 127**,** 9.

Calon, F., Grondin, R., Morissette, M., Goulet, M., Blanchet, P.J., Di Paolo, T., Bedard, P.J., 2000. Molecular basis of levodopa-induced dyskinesias. *Ann. Neurol.* 47**,** S70-S78.

Calon, F., Morissette, M., Ghribi, O., Goulet, M., Grondin, R., Blanchet, P.J., Bedard, P.J., Di Paolo, T., 2002. Alteration of glutamate receptors in the striatum of dyskinetic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys following dopamine agonist treatment. *Progress in neuro-psychopharmacology & biological psychiatry* 26**,** 127-138.

Calon, F., Morissette, M., Rajput, A.H., Hornykiewicz, O., Bedard, P.J., Di Paolo, T., 2003. Changes of GABA receptors and dopamine turnover in the postmortem brains of parkinsonians with levodopa-induced motor complications. *Mov Disord* 18**,** 241-253.

Cao, X., Yasuda, T., Uthayathas, S., Watts, R.L., Mouradian, M.M., Mochizuki, H., Papa, S.M., 2010. Striatal overexpression of DeltaFosB reproduces chronic levodopa-induced involuntary movements. *J Neurosci* 30**,** 7335-7343.

Caparros-Lefebvre, D., Blond, S., Feltin, M.P., Pollak, P., Benabid, A.L., 1999. Improvement of levodopa induced dyskinesias by thalamic deep brain stimulation is related to

slight variation in electrode placement: possible involvement of the centre median and parafascicularis complex. *J Neurol Neurosurg Psychiatry* 67**,** 308-314.

Carlsson, A., Lindquist, M., Magnusson, T., 1957. 3,4-dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature* 180**,** 1200.

Carrion, A.M., Link, W.A., Ledo, F., Mellstrom, B., Naranjo, J.R., 1999. DREAM is a Ca2+-regulated transcriptional repressor. *Nature* 398**,** 80-84.

Carroll, C.B., Bain, P.G., Teare, L., Liu, X., Joint, C., Wroath, C., Parkin, S.G., Fox, P., Wright, D., Hobart, J., Zajicek, J.P., 2004. Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study. *Neurology* 63**,** 1245-1250.

Carta, A.R., Fenu, S., Pala, P., Tronci, E., Morelli, M., 2003. Selective modifications in GAD67 mRNA levels in striatonigral and striatopallidal pathways correlate to dopamine agonist priming in 6-hydroxydopamine-lesioned rats. *Eur. J. Neurosci.* 18**,** 10.

Carta, A.R., Frau, L., Pinna, A., Morelli, M., 2010. Dyskinetic potential of dopamine agonists is associated with different striatonigral/striatopallidal zif-268 expression. . *Exp. Neurol.* 224**,** 8.

Carta, A.R., Tronci, E., Pinna, A., Morelli, M., 2005. Different responsiveness of striatonigral and striatopallidal neurons to L-DOPA after a subchronic intermittent L-DOPA treatment. *Eur J Neurosci* 21**,** 1196-1204.

Carta, M., Bezard, E., 2011. Contribution of pre-synaptic mechanisms to L-DOPA-induced dyskinesia. *Neuroscience* 198**,** 245-251.

Carta, M., Carlsson, T., Kirik, D., Bjorklund, A., 2007. Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesia in parkinsonian rats. *Brain* 130**,** 1819-1833.

Carta, M., Carlsson, T., Munoz, A., Kirik, D., Bjorklund, A., 2008a. Involvement of the serotonin system in L-dopa-induced dyskinesias. *Parkinsonism Relat Disord* 14 Suppl 2**,** S154-158.

Carta, M., Carlsson, T., Munoz, A., Kirik, D., Bjorklund, A., 2008b. Serotonin-dopamine interaction in the induction and maintenance of L-DOPA-induced dyskinesias. *Prog Brain Res* 172**,** 465-478.

Carta, M., Carlsson, T., Munoz, A., Kirik, D., Bjorklund, A., 2010. Role of serotonin neurons in the induction of levodopa- and graft-induced dyskinesias in Parkinson's disease. *Mov Disord* 25 Suppl 1**,** S174-179.

Carta, M., Lindgren, H.S., Lundblad, M., Stancampiano, R., Fadda, F., Cenci, M.A., 2006. Role of striatal L-DOPA in the production of dyskinesia in 6-hydroxydopamine lesioned rats. *J Neurochem* 96**,** 1718-1727.

Carta, M., Tronci, E., 2014. Serotonin System Implication in l-DOPA-Induced Dyskinesia: From Animal Models to Clinical Investigations. *Frontiers in neurology* 5**,** 78.

Castrioto, A., Kistner, A., Klinger, H., Lhommee, E., Schmitt, E., Fraix, V., Chabardes, S., Mertens, P., Quesada, J.L., Broussolle, E., Pollak, P., Thobois, S.C., Krack, P., 2013. Psychostimulant effect of levodopa: reversing sensitisation is possible. *J Neurol Neurosurg Psychiatry* 84**,** 18-22.

Catalan, M.J., de Pablo-Fernandez, E., Villanueva, C., Fernandez-Diez, S., Lapena-Montero, T., Garcia-Ramos, R., Lopez-Valdes, E., 2013. Levodopa infusion improves impulsivity and dopamine dysregulation syndrome in Parkinson's disease. *Mov Disord* 28**,** 2007-2010.

Cenci, M.A., 2007a. Dopamine dysregulation of movement control in L-DOPA-induced dyskinesia. *Trends Neurosci* 30**,** 236-243.

Cenci, M.A., 2007b. L-DOPA-induced dyskinesia: cellular mechanisms and approaches to treatment. *Parkinsonism Relat Disord* 13 Suppl 3**,** S263-267.

Cenci, M.A., 2014. Presynaptic Mechanisms of l-DOPA-Induced Dyskinesia: The Findings, the Debate, and the Therapeutic Implications. *Frontiers in neurology* 5**,** 242.

Cenci, M.A., Konradi, C., 2010. Maladaptive striatal plasticity in L-DOPA-induced dyskinesia. *Prog Brain Res* 183**,** 209-233.

Cenci, M.A., Lee, C.S., Bjorklund, A., 1998. L-DOPA-induced dyskinesia in the rat is associated with striatal overexpression of prodynorphin- and glutamic acid decarboxylase mRNA. *Eur. J. Neurosci.* 10**,** 2694-2706.

Cenci, M.A., Lundblad, M., 2007. Ratings of L-DOPA-induced dyskinesia in the unilateral 6-OHDA lesion model of Parkinson's disease in rats and mice. *Current protocols in neuroscience / editorial board, Jacqueline N. Crawley ... [et al.]* Chapter 9**,** Unit 9 25.

Cenci, M.A., Ohlin, K.E., 2009. Rodent models of treatment-induced motor complications in Parkinson's disease. *Parkinsonism Relat Disord* 15 Suppl 4**,** S13-17.

Cenci, M.A., Tranberg, A., Andersson, M., Hilbertson, A., 1999. Changes in the regional and compartmental distribution of FosB- and JunB-like immunoreactivity induced in the dopamine-denervated rat striatum by acute or chronic L-dopa treatment. *Neuroscience* 94**,** 515-527.

Cenci, M.A., Whishaw, I.Q., Schallert, T., 2002. Animal models of neurological deficits: how relevant is the rat? *Nature reviews. Neuroscience* 3**,** 574-579.

Centonze, D., Gubellini, P., Bernardi, G., Calabresi, P., 1999a. Permissive role of interneurons in corticostriatal synaptic plasticity. *Brain research. Brain research reviews* 31**,** 1-5.

Centonze, D., Gubellini, P., Picconi, B., Calabresi, P., Giacomini, P., Bernardi, G., 1999b. Unilateral dopamine denervation blocks corticostriatal LTP. *Journal of neurophysiology* 82**,** 3575-3579.

Cerasa, A., Koch, G., Donzuso, G., Mangone, G., Morelli, M., Brusa, L., Stampanoni Bassi, M., Ponzo, V., Picazio, S., Passamonti, L., Salsone, M., Augimeri, A., Caltagirone, C., Quattrone, A., 2015. A network centred on the inferior frontal cortex is critically involved in levodopa-induced dyskinesias. *Brain* 138**,** 414-427.

Cerasa, A., Messina, D., Pugliese, P., Morelli, M., Lanza, P., Salsone, M., Novellino, F., Nicoletti, G., Arabia, G., Quattrone, A., 2011. Increased prefrontal volume in PD with levodopa-induced dyskinesias: a voxel-based morphometry study. *Mov Disord* 26**,** 807-812.

Cerasa, A., Morelli, M., Augimeri, A., Salsone, M., Novellino, F., Gioia, M.C., Arabia, G., Quattrone, A., 2013. Prefrontal thickening in PD with levodopa-induced dyskinesias: new evidence from cortical thickness measurement. *Parkinsonism Relat Disord* 19**,** 123-125.

Cerovic, M., Bagetta, V., Pendolino, V., Ghiglieri, V., Fasano, S., Morella, I., Hardingham, N., Heuer, A., Papale, A., Marchisella, F., Giampa, C., Calabresi, P., Picconi, B., Brambilla, R., 2015. Derangement of Ras-Guanine Nucleotide-Releasing Factor 1 (Ras-GRF1) and Extracellular Signal-Regulated Kinase (ERK) Dependent Striatal Plasticity in L-DOPA-Induced Dyskinesia. *Biol Psychiatry* 77**,** 106-115.

Changeux, J.P., 2010. Allosteric receptors: from electric organ to cognition. *Annu Rev Pharmacol Toxicol* 50**,** 1-38.

Chappell, W.H., Steelman, L.S., Long, J.M., Kempf, R.C., Abrams, S.L., Franklin, R.A., Basecke, J., Stivala, F., Donia, M., Fagone, P., Malaponte, G., Mazzarino, M.C., Nicoletti, F., Libra, M., Maksimovic-Ivanic, D., Mijatovic, S., Montalto, G., Cervello, M., Laidler, P., Milella, M., Tafuri, A., Bonati, A., Evangelisti, C., Cocco, L., Martelli, A.M., McCubrey, J.A., 2011. Ras/Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR

inhibitors: rationale and importance to inhibiting these pathways in human health. *Oncotarget* 2**,** 135-164.

Charbonnier-Beaupel, F., Malerbi, M., Alcacer, C., Tahiri, K., Carpentier, W., Wang, C., During, M., Xu, D., Worley, P., Girault, J., Herve, D., Corvol, J.C., 2015. Gene expression analyses identify Narp contribution in the development of L-DOPA-induced dyskinesia. *Journal of Neuroscience* 35**,** 96-111.

Charron, G., Doudnikoff, E., Canron, M.H., Li, Q., Vega, C., Marais, S., Baufreton, J., Vital, A., Oliet, S.H., Bezard, E., 2014. Astrocytosis in parkinsonism: considering tripartite striatal synapses in physiopathology? *Frontiers in aging neuroscience* 6**,** 258.

Charron, G., Doudnikoff, E., Laux, A., Berthet, A., Porras, G., Canron, M.H., Barroso-Chinea, P., Li, Q., Qin, C., Nosten-Bertrand, M., Giros, B., Delalande, F., Van Dorsselaer, A., Vital, A., Goumon, Y., Bezard, E., 2011. Endogenous morphine-like compound immunoreactivity increases in parkinsonism. *Brain* 134**,** 2321-2338.

Chartoff, E.H., Marck, B.T., Matsumoto, A.M., Dorsa, D.M., Palmiter, R.D., 2001. Induction of stereotypy in dopamine-deficient mice requires striatal D1 receptor activation. *Proc Natl Acad Sci U S A* 98**,** 10451-10456.

Chase, A., 2014. Parkinson disease: A role for serotonergic neurons in levodopa-induced dyskinesia. *Nature reviews. Neurology* 10**,** 180.

Chen, L., Togasaki, D.M., Langston, J.W., Di Monte, D.A., Quik, M., 2005. Enhanced striatal opioid receptor-mediated G-protein activation in l-dopa-treated dyskinetic monkeys. *Neuroscience* 132**,** 409-420.

Chen, M.K., Kuwabara, H., Zhou, Y., Adams, R.J., Brasic, J.R., McGlothan, J.L., Verina, T., Burton, N.C., Alexander, M., Kumar, A., Wong, D.F., Guilarte, T.R., 2008. VMAT2 and dopamine neuron loss in a primate model of Parkinson's disease. *J Neurochem* 105**,** 78-90.

Cheshire, P., Bertram, K., Ling, H., O'Sullivan, S.S., Halliday, G., McLean, C., Bras, J., Foltynie, T., Storey, E., Williams, D.R., 2014. Influence of single nucleotide polymorphisms in COMT, MAO-A and BDNF genes on dyskinesias and levodopa use in Parkinson's disease. *Neuro-degenerative diseases* 13**,** 24-28.

Chevalier, G., Deniau, J.M., 1990. Disinhibition as a basic process in the expression of striatal functions. *Trends Neurosci* 13**,** 277-280.

Chiueh, C.C., Markey, S.P., Burns, R.S., Johannessen, J.N., Jacobowitz, D.M., Kopin, I.J., 1984. Neurochemical and behavioral effects of 1-methyl-4-phenyl-1,2,3,6-

tetrahydropyridine (MPTP) in rat, guinea pig, and monkey. *Psychopharmacology bulletin* 20**,** 548-553.

Choi, J.K., Chen, Y.I., Hamel, E., Jenkins, B.G., 2006. Brain hemodynamic changes mediated by dopamine receptors: Role of the cerebral microvasculature in dopamine-mediated neurovascular coupling. *NeuroImage* 30**,** 700-712.

Chondrogiorgi, M., Tatsioni, A., Reichmann, H., Konitsiotis, S., 2014. Dopamine agonist monotherapy in Parkinson's disease and potential risk factors for dyskinesia: a meta-analysis of levodopa-controlled trials. *European journal of neurology : the official journal of the European Federation of Neurological Societies* 21**,** 433-440.

Choquet, D., Triller, A., 2013. The dynamic synapse. *Neuron* 80**,** 691-703.

Cilia, R., Siri, C., Canesi, M., Zecchinelli, A.L., De Gaspari, D., Natuzzi, F., Tesei, S., Meucci, N., Mariani, C.B., Sacilotto, G., Zini, M., Ruffmann, C., Pezzoli, G., 2014. Dopamine dysregulation syndrome in Parkinson's disease: from clinical and neuropsychological characterisation to management and long-term outcome. *J Neurol Neurosurg Psychiatry* 85**,** 311-318.

Citri, A., Soler-Llavina, G., Bhattacharyya, S., Malenka, R.C., 2009. N-methyl-D-aspartate receptor- and metabotropic glutamate receptor-dependent long-term depression are differentially regulated by the ubiquitin-proteasome system. *Eur J Neurosci* 30**,** 1443-1450.

Clarke, C.E., Cooper, J.A., Holdich, T.A., 2001. A randomized, double-blind, placebo-controlled, ascending-dose tolerability and safety study of remacemide as adjuvant therapy in Parkinson's disease with response fluctuations. *Clin Neuropharmacol* 24**,** 133-138.

Clarke, C.E., Sambrook, M.A., Mitchell, I.J., Crossman, A.R., 1987. Levodopa-induced dyskinesia and response fluctuations in primates rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Journal of the neurological sciences* 78**,** 273-280.

Cohen, P., 2002. Protein kinases--the major drug targets of the twenty-first century? *Nat Rev Drug Discov* 1**,** 309-315.

Collins, G.T., Cunningham, A.R., Chen, J., Wang, S., Newman, A.H., Woods, J.H., 2012. Effects of pramipexole on the reinforcing effectiveness of stimuli that were previously paired with cocaine reinforcement in rats. *Psychopharmacology (Berl)* 219**,** 123-135.

Collins, G.T., Woods, J.H., 2007. Drug and reinforcement history as determinants of the response-maintaining effects of quinpirole in the rat. *J Pharmacol Exp Ther* 323**,** 599-605.

Consolo, S., Morelli, M., Rimoldi, M., Giorgi, S., Di Chiara, G., 1999. Increased striatal expression of glutamate decarboxylase 67 after priming of 6-hydroxydopamine-lesioned rats. *Neuroscience* 89**,** 5.

Conti, M.M., Ostock, C.Y., Lindenbach, D., Goldenberg, A.A., Kampton, E., Dell'isola, R., Katzman, A.C., Bishop, C., 2014. Effects of prolonged selective serotonin reuptake inhibition on the development and expression of l-DOPA-induced dyskinesia in hemi-parkinsonian rats. *Neuropharmacology* 77**,** 1-8.

Contin, M., Martinelli, P., 2010. Pharmacokinetics of levodopa. *Journal of neurology* 257**,** S253-261.

Contin, M., Riva, R., Martinelli, P., Cortelli, P., Albani, F., Baruzzi, A., 1993. Pharmacodynamic modeling of oral levodopa: clinical application in Parkinson's disease. *Neurology* 43**,** 367-371.

Corringer, P.J., Sallette, J., Changeux, J.P., 2006. Nicotine enhances intracellular nicotinic receptor maturation: a novel mechanism of neural plasticity? *J Physiol Paris* 99**,** 162-171.

Corvol, J.C., Muriel, M.P., Valjent, E., Feger, J., Hanoun, N., Girault, J.A., Hirsch, E.C., Herve, D., 2004. Persistent increase in olfactory type G-protein alpha subunit levels may underlie D1 receptor functional hypersensitivity in Parkinson disease. *J Neurosci* 24**,** 7007-7014.

Costa, R.M., Lin, S.C., Sotnikova, T.D., Cyr, M., Gainetdinov, R.R., Caron, M.G., Nicolelis, M.A., 2006. Rapid alterations in corticostriatal ensemble coordination during acute dopamine-dependent motor dysfunction. *Neuron* 52**,** 359-369.

Costa-Mattioli, M., Sossin, W.S., Klann, E., Sonenberg, N., 2009. Translational control of long-lasting synaptic plasticity and memory. *Neuron* 61**,** 10-26.

Cote, S.R., Chitravanshi, V.C., Bleickardt, C., Sapru, H.N., Kuzhikandathil, E.V., 2014. Overexpression of the dopamine D3 receptor in the rat dorsal striatum induces dyskinetic behaviors. *Behav Brain Res* 263**,** 46-50.

Cotzias, G.C., Papavasiliou, P.S., Gellene, R., 1969. L-dopa in parkinson's syndrome. *The New England journal of medicine* 281**,** 272.

Cotzias, G.C., Van Woert, M.H., Schiffer, L.M., 1967. Aromatic amino acids and modification of parkinsonism. *The New England journal of medicine* 276**,** 374-379.

Cox, H., Togasaki, D.M., Chen, L., Langston, J.W., Di Monte, D.A., Quik, M., 2007. The selective kappa-opioid receptor agonist U50,488 reduces L-dopa-induced dyskinesias but worsens parkinsonism in MPTP-treated primates. *Exp Neurol* 205**,** 101-107.

Crittenden, J.R., Cantuti-Castelvetri, I., Saka, E., Keller-McGandy, C.E., Hernandez, L.F., Kett, L.R., Young, A.B., Standaert, D.G., Graybiel, A.M., 2009. Dysregulation of CalDAG-GEFI and CalDAG-GEFII predicts the severity of motor side-effects induced by anti-parkinsonian therapy. *Proc Natl Acad Sci U S A* 106**,** 2892-2896.

Crocker, S.J., Morelli, M., Wigle, N., Nakabeppu, Y., Robertson, G.S., 1998. D1-Receptor-related priming is attenuated by antisense-meditated 'knockdown' of fosB expression. *Mol. Brain Res.* 53**,** 9.

Crossman, A.R., 1987. Primate models of dyskinesia: the experimental approach to the study of basal ganglia-related involuntary movement disorders. *Neuroscience* 21**,** 1-40.

Crossman, A.R., Clarke, C.E., Boyce, S., Robertson, R.G., Sambrook, M.A., 1987. MPTP-induced parkinsonism in the monkey: neurochemical pathology, complications of treatment and pathophysiological mechanisms. *The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques* 14**,** 428-435.

Crossman, A.R., Mitchell, I.J., Sambrook, M.A., 1985. Regional brain uptake of 2-deoxyglucose in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the macaque monkey. *Neuropharmacology* 24**,** 587-591.

da Silva-Junior, F.P., Braga-Neto, P., Sueli Monte, F., de Bruin, V.M., 2005. Amantadine reduces the duration of levodopa-induced dyskinesia: a randomized, double-blind, placebo-controlled study. *Parkinsonism Relat Disord* 11**,** 449-452.

Dahan, M., Levi, S., Luccardini, C., Rostaing, P., Riveau, B., Triller, A., 2003. Diffusion dynamics of glycine receptors revealed by single-quantum dot tracking. *Science* 302**,** 442-445.

Darmopil, S., Martin, A.B., De Diego, I.R., Ares, S., Moratalla, R., 2009. Genetic inactivation of dopamine D1 but not D2 receptors inhibits L-DOPA-induced dyskinesia and histone activation. *Biol Psychiatry* 66**,** 603-613.

Davie, M., 2007. Pathological gambling associated with cabergoline therapy in a patient with a pituitary prolactinoma. *The Journal of neuropsychiatry and clinical neurosciences* 19**,** 473-474.

Day, M., Wang, Z., Ding, J., An, X., Ingham, C.A., Shering, A.F., Wokosin, D., Ilijic, E., Sun, Z., Sampson, A.R., Mugnaini, E., Deutch, A.Y., Sesack, S.R., Arbuthnott, G.W., Surmeier, D.J., 2006. Selective elimination of glutamatergic synapses on striatopallidal neurons in Parkinson disease models. *Nature neuroscience* 9**,** 251-259.

de la Fuente-Fernandez, R., Lu, J.Q., Sossi, V., Jivan, S., Schulzer, M., Holden, J.E., Lee, C.S., Ruth, T.J., Calne, D.B., Stoessl, A.J., 2001. Biochemical variations in the synaptic level of dopamine precede motor fluctuations in Parkinson's disease: PET evidence of increased dopamine turnover. *Ann Neurol* 49**,** 298-303.

de la Fuente-Fernandez, R., Pal, P.K., Vingerhoets, F.J., Kishore, A., Schulzer, M., Mak, E.K., Ruth, T.J., Snow, B.J., Calne, D.B., Stoessl, A.J., 2000. Evidence for impaired presynaptic dopamine function in parkinsonian patients with motor fluctuations. *J Neural Transm* 107**,** 49-57.

de la Fuente-Fernandez, R., Sossi, V., Huang, Z., Furtado, S., Lu, J.Q., Calne, D.B., Ruth, T.J., Stoessl, A.J., 2004. Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: implications for dyskinesias. *Brain* 127**,** 2747-2754.

de Lau, L.M., Verbaan, D., Marinus, J., Heutink, P., van Hilten, J.J., 2012. Catechol-O-methyltransferase Val158Met and the risk of dyskinesias in Parkinson's disease. *Mov Disord* 27**,** 132-135.

Decressac, M., Bjorklund, A., 2013. mTOR inhibition alleviates L-DOPA-induced dyskinesia in parkinsonian rats. *Journal of Parkinson's disease* 3**,** 13-17.

Decressac, M., Mattsson, B., Bjorklund, A., 2012a. Comparison of the behavioural and histological characteristics of the 6-OHDA and alpha-synuclein rat models of Parkinson's disease. *Exp Neurol* 235**,** 306-315.

Decressac, M., Mattsson, B., Lundblad, M., Weikop, P., Bjorklund, A., 2012b. Progressive neurodegenerative and behavioural changes induced by AAV-mediated overexpression of alpha-synuclein in midbrain dopamine neurons. *Neurobiol Dis* 45**,** 939-953.

DeJong, G.J., Meerwaldt, J.D., Schmitz, P.I.M., 1987. Factors that influence the occurence of response variations in Parkinson's disease. *Ann. Neurol.* 21**,** 4-7.

Dekker, M.C., Bonifati, V., van Duijn, C.M., 2003. Parkinson's disease: piecing together a genetic jigsaw. *Brain* 126**,** 1722-1733.

Dekundy, A., Lundblad, M., Danysz, W., Cenci, M.A., 2007. Modulation of L-DOPA-induced abnormal involuntary movements by clinically tested compounds: further validation of the rat dyskinesia model. *Behav Brain Res* 179**,** 76-89.

Dekundy, A., Pietraszek, M., Schaefer, D., Cenci, M.A., Danysz, W., 2006. Effects of group I metabotropic glutamate receptors blockade in experimental models of Parkinson's disease. *Brain Res Bull* 69**,** 318-326.

Del Bel, E.A., da Silva, C.A., Guimaraes, F.S., Bermudez-Echeverry, M., 2004. Catalepsy induced by intra-striatal administration of nitric oxide synthase inhibitors in rats. *Eur J Pharmacol* 485**,** 175-181.

Del Dotto, P., Pavese, N., Gambaccini, G., Bernardini, S., Metman, L.V., Chase, T.N., Bonuccelli, U., 2001. Intravenous amantadine improves levadopa-induced dyskinesias: an acute double-blind placebo-controlled study. *Mov Disord* 16**,** 515-520.

Delaville, C., Deurwaerdere, P.D., Benazzouz, A., 2011. Noradrenaline and Parkinson's disease. *Front Syst Neurosci* 5**,** 31.

DeLong, M.R., 1990. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 13**,** 281-285.

Deroche-Gamonet, V., Belin, D., Piazza, P.V., 2004. Evidence for addiction-like behavior in the rat. *Science* 305**,** 1014-1017.

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schafer, H., Botzel, K., Daniels, C., Deutschlander, A., Dillmann, U., Eisner, W., Gruber, D., Hamel, W., Herzog, J., Hilker, R., Klebe, S., Kloss, M., Koy, J., Krause, M., Kupsch, A., Lorenz, D., Lorenzl, S., Mehdorn, H.M., Moringlane, J.R., Oertel, W., Pinsker, M.O., Reichmann, H., Reuss, A., Schneider, G.H., Schnitzler, A., Steude, U., Sturm, V., Timmermann, L., Tronnier, V., Trottenberg, T., Wojtecki, L., Wolf, E., Poewe, W., Voges, J., German Parkinson Study Group, N.S., 2006. A randomized trial of deep-brain stimulation for Parkinson's disease. *The New England journal of medicine* 355**,** 896-908.

Devine, D.P., Taylor, L., Reinscheid, R.K., Monsma, F.J., Jr., Civelli, O., Akil, H., 1996. Rats rapidly develop tolerance to the locomotor-inhibiting effects of the novel neuropeptide orphanin FQ. *Neurochemical research* 21**,** 1387-1396.

Di Benedetto, M., Cavina, C., D'Addario, C., Leoni, G., Candeletti, S., Cox, B.M., Romualdi, P., 2009. Alterations of N/OFQ and NOP receptor gene expression in the substantia nigra and caudate putamen of MPP+ and 6-OHDA lesioned rats. *Neuropharmacology* 56**,** 761-767.

Di Chiara, G., Morelli, M., Consolo, S., 1994. Modulatory functions of neurotransmitters in the striatum: ACh/dopamine/NMDA interactions. *Trends Neurosci* 17**,** 228-233.

Di Monte, D.A., McCormack, A., Petzinger, G., Janson, A.M., Quik, M., Langston, W.J., 2000. Relationship among nigrostriatal denervation, parkinsonism, and dyskinesias in the MPTP primate model. *Mov Disord* 15**,** 459-466.

Di Paolo, T., Gregoire, L., Feuerbach, D., Elbast, W., Weiss, M., Gomez-Mancilla, B., 2014. AQW051, a novel and selective nicotinic acetylcholine receptor alpha7 partial agonist, reduces l-Dopa-induced dyskinesias and extends the duration of l-Dopa effects in parkinsonian monkeys. *Parkinsonism Relat Disord* 20**,** 1119-1123.

DiAntonio, A., Hicke, L., 2004. Ubiquitin-dependent regulation of the synapse. *Annual review of neuroscience* 27**,** 223-246.

Ding, J., Guzman, J.N., Tkatch, T., Chen, S., Goldberg, J.A., Ebert, P.J., Levitt, P., Wilson, C.J., Hamm, H.E., Surmeier, D.J., 2006. RGS4-dependent attenuation of M4 autoreceptor function in striatal cholinergic interneurons following dopamine depletion. *Nat. Neurosci.* 9**,** 832-842.

Ding, Y., Restrepo, J., Won, L., Hwang, D.Y., Kim, K.S., Kang, U.J., 2007. Chronic 3,4-dihydroxyphenylalanine treatment induces dyskinesia in aphakia mice, a novel genetic model of Parkinson's disease. *Neurobiol Dis* 27**,** 11-23.

Ding, Y., Won, L., Britt, J.P., Lim, S.A., McGehee, D.S., Kang, U.J., 2011. Enhanced striatal cholinergic neuronal activity mediates L-DOPA-induced dyskinesia in parkinsonian mice. *Proc Natl Acad Sci U S A* 108**,** 840-845.

Djamshidian, A., Cardoso, F., Grosset, D., Bowden-Jones, H., Lees, A.J., 2011a. Pathological gambling in Parkinson's disease--a review of the literature. *Mov Disord* 26**,** 1976-1984.

Djamshidian, A., Jha, A., O'Sullivan, S.S., Silveira-Moriyama, L., Jacobson, C., Brown, P., Lees, A., Averbeck, B.B., 2010. Risk and learning in impulsive and nonimpulsive patients with Parkinson's disease. *Mov Disord* 25**,** 2203-2210.

Djamshidian, A., O'Sullivan, S.S., Wittmann, B.C., Lees, A.J., Averbeck, B.B., 2011b. Novelty seeking behaviour in Parkinson's disease. *Neuropsychologia* 49**,** 2483-2488.

Dodd, M.L., Klos, K.J., Bower, J.H., Geda, Y.E., Josephs, K.A., Ahlskog, J.E., 2005. Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 62**,** 1377-1381.

Doudet, D., Gross, C., Lebrun-Grandie, P., Bioulac, B., 1985. MPTP primate model of Parkinson's disease: a mechanographic and electromyographic study. *Brain Res* 335**,** 194-199.

Doudet, D.J., Chan, G.L., Holden, J.E., McGeer, E.G., Aigner, T.A., Wyatt, R.J., Ruth, T.J., 1998. 6-[18F]Fluoro-L-DOPA PET studies of the turnover of dopamine in MPTP-induced parkinsonism in monkeys. *Synapse* 29**,** 225-232.

Doyle, J.P., Dougherty, J.D., Heiman, M., Schmidt, E.F., Stevens, T.R., Ma, G., Bupp, S., Shrestha, P., Shah, R.D., Doughty, M.L., Gong, S., Greengard, P., Heintz, N., 2008. Application of a Translational Profiling Approach for the Comparative Analysis of CNS Cell Types. *Cell* 135**,** 749-762.

Drouot, X., Oshino, S., Jarraya, B., Besret, L., Kishima, H., Remy, P., Dauguet, J., Lefaucheur, J.P., Dolle, F., Conde, F., Bottlaender, M., Peschanski, M., Keravel, Y., Hantraye, P., Palfi, S., 2004. Functional recovery in a primate model of Parkinson's disease following motor cortex stimulation. *Neuron* 44**,** 769-778.

Drui, G., Carnicella, S., Carcenac, C., Favier, M., Bertrand, A., Boulet, S., Savasta, M., 2013. Loss of dopaminergic nigrostriatal neurons accounts for the motivational and affective deficits in Parkinson's disease. *Molecular psychiatry*.

Dunnett, S.B., Lelos, M., 2010. Behavioral analysis of motor and non-motor symptoms in rodent models of Parkinson's disease. *Prog Brain Res* 184**,** 35-51.

Dupre, K.B., Eskow, K.L., Barnum, C.J., Bishop, C., 2008. Striatal 5-HT1A receptor stimulation reduces D1 receptor-induced dyskinesia and improves movement in the hemiparkinsonian rat. *Neuropharmacology* 55**,** 1321-1328.

Dupre, K.B., Ostock, C.Y., Eskow Jaunarajs, K.L., Button, T., Savage, L.M., Wolf, W., Bishop, C., 2011. Local modulation of striatal glutamate efflux by serotonin 1A receptor stimulation in dyskinetic, hemiparkinsonian rats. *Exp Neurol* 229**,** 288-299.

Durif, F., Debilly, B., Galitzky, M., Morand, D., Viallet, F., Borg, M., Thobois, S., Broussolle, E., Rascol, O., 2004. Clozapine improves dyskinesias in Parkinson disease: a double-blind, placebo-controlled study. *Neurology* 62**,** 381-388.

Durif, F., Vidailhet, M., Assal, F., Roche, C., Bonnet, A.M., Agid, Y., 1997. Low-dose clozapine improves dyskinesias in Parkinson's disease. *Neurology* 48**,** 658-662.

Duvey, G., Perry, B., Le Poul, E., Poli, S., Bonnet, B., Lambeng, N., Charvin, D., Donovan-Rodrigues, T., Haddouk, H., Gagliardi, S., Rocher, J.P., 2013. A novel series of metabotropic glutamate receptor 5 negative allosteric modulators based on a 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine core. *Bioorganic & medicinal chemistry letters* 23**,** 4523-4527.

Duvoisin, R.C., 1967. Cholinergic-anticholinergic antagonism in parkinsonism. *Arch Neurol* 17**,** 124-136.

Duvoisin, R.C., 1972. Diphenidol for levodopa induced nausea and vomiting. *JAMA : the journal of the American Medical Association* 221**,** 1408.

Duvoisin, R.C., 1974. Variations in the "on-off" phenomenon. *Adv. Neurol.* 5**,** 339-340.

Eglen, R., Reisine, T., 2011. Drug discovery and the human kinome: recent trends. *Pharmacol Ther* 130**,** 144-156.

Ehringer, H., Hornykiewicz, O., 1960. Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. *Klin. Wochenschr.* 38**,** 1236-1239.

El Atifi-Borel, M., Buggia-Prevot, V., Platet, N., Benabid, A.L., Berger, F., Sgambato-Faure, V., 2009. De novo and long-term l-Dopa induce both common and distinct striatal gene profiles in the hemiparkinsonian rat. *Neurobiol Dis* 34**,** 340-350.

Elsworth, J.D., Deutch, A.Y., Redmond, D.E., Jr., Sladek, J.R., Jr., Roth, R.H., 1987. Differential responsiveness to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity in sub-regions of the primate substantia nigra and striatum. *Life Sci* 40**,** 193-202.

Elsworth, J.D., Deutch, A.Y., Redmond, D.E., Jr., Sladek, J.R., Jr., Roth, R.H., 1990. MPTP-induced parkinsonism: relative changes in dopamine concentration in subregions of substantia nigra, ventral tegmental area and retrorubral field of symptomatic and asymptomatic vervet monkeys. *Brain Res* 513**,** 320-324.

Engberg, G., 1989. A metabolite of buspirone increases locus coeruleus activity via alpha 2-receptor blockade. *J Neural Transm* 76**,** 91-98.

Engeln, M., Ahmed, S.H., Vouillac, C., Tison, F., Bezard, E., Fernagut, P.O., 2012. Reinforcing properties of Pramipexole in normal and parkinsonian rats. *Neurobiol Dis* 49C**,** 79-86.

Engeln, M., Bastide, M.F., Toulme, E., Dehay, B., Bourdenx, M., Doudnikoff, E., Li, Q., Gross, C.E., Boue-Grabot, E., Pisani, A., Bezard, E., Fernagut, P.O., 2014a. Selective

Inactivation of Striatal FosB/DeltaFosB-Expressing Neurons Alleviates L-Dopa-Induced Dyskinesia. *Biol Psychiatry*.

Engeln, M., De Deurwaerdere, P., Li, Q., Bezard, E., Fernagut, P.O., 2014b. Widespread Monoaminergic Dysregulation of Both Motor and Non-Motor Circuits in Parkinsonism and Dyskinesia. *Cerebral cortex*.

Engeln, M., Fasano, S., Ahmed, S.H., Cador, M., Baekelandt, V., Bezard, E., Fernagut, P.O., 2013. Levodopa gains psychostimulant-like properties after nigral dopaminergic loss. *Ann Neurol* 74**,** 140-144.

Errico, F., Bonito-Oliva, A., Bagetta, V., Vitucci, D., Romano, R., Zianni, E., Napolitano, F., Marinucci, S., Di Luca, M., Calabresi, P., Fisone, G., Carta, M., Picconi, B., Gardoni, F., Usiello, A., 2011. Higher free D-aspartate and N-methyl-D-aspartate levels prevent striatal depotentiation and anticipate L-DOPA-induced dyskinesia. *Exp Neurol* 232**,** 240-250.

Errico, F., Rossi, S., Napolitano, F., Catuogno, V., Topo, E., Fisone, G., D'Aniello, A., Centonze, D., Usiello, A., 2008. D-aspartate prevents corticostriatal long-term depression and attenuates schizophrenia-like symptoms induced by amphetamine and MK-801. *J Neurosci* 28**,** 10404-10414.

Eskow, K.L., Dupre, K.B., Barnum, C.J., Dickinson, S.O., Park, J.Y., Bishop, C., 2009. The role of the dorsal raphe nucleus in the development, expression, and treatment of L-dopa-induced dyskinesia in hemiparkinsonian rats. *Synapse* 63**,** 610-620.

Evans, A.H., Katzenschlager, R., Paviour, D., O'Sullivan, J.D., Appel, S., Lawrence, A.D., Lees, A.J., 2004. Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. *Mov Disord* 19**,** 397-405.

Evans, A.H., Lawrence, A.D., Cresswell, S.A., Katzenschlager, R., Lees, A.J., 2010. Compulsive use of dopaminergic drug therapy in Parkinson's disease: reward and anti-reward. *Mov Disord* 25**,** 867-876.

Evans, A.H., Lawrence, A.D., Potts, J., Appel, S., Lees, A.J., 2005. Factors influencing susceptibility to compulsive dopaminergic drug use in Parkinson disease. *Neurology* 65**,** 1570-1574.

Evans, A.H., Pavese, N., Lawrence, A.D., Tai, Y.F., Appel, S., Doder, M., Brooks, D.J., Lees, A.J., Piccini, P., 2006. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. *Ann Neurol* 59**,** 852-858.

Fasano, S., Bezard, E., D'Antoni, A., Francardo, V., Indrigo, M., Qin, L., Dovero, S., Cerovic, M., Cenci, M.A., Brambilla, R., 2010. Inhibition of Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1) signaling in the striatum reverts motor symptoms associated with L-dopa-induced dyskinesia. *Proc Natl Acad Sci U S A* 107**,** 21824-21829.

Fasano, S., Brambilla, R., 2011. Ras-ERK Signaling in Behavior: Old Questions and New Perspectives. *Front Behav Neurosci* 5**,** 79.

Fasano, S., D'Antoni, A., Orban, P.C., Valjent, E., Putignano, E., Vara, H., Pizzorusso, T., Giustetto, M., Yoon, B., Soloway, P., Maldonado, R., Caboche, J., Brambilla, R., 2009. Ras-Guanine Nucleotide-Releasing Factor 1 (Ras-GRF1) Controls Activation of Extracellular Signal-Regulated Kinase (ERK) Signaling in the Striatum and Long-Term Behavioral Responses to Cocaine. *Biol Psychiatry*.

Faucheux, B.A., Bonnet, A.M., Agid, Y., Hirsch, E.C., 1999. Blood vessels change in the mesencephalon of patients with Parkinson's disease. *Lancet* 353**,** 981-982.

Faure, A., Haberland, U., Conde, F., El Massioui, N., 2005. Lesion to the nigrostriatal dopamine system disrupts stimulus-response habit formation. *J Neurosci* 25**,** 2771-2780.

Fenelon, G., Goetz, C.G., Karenberg, A., 2006. Hallucinations in Parkinson disease in the prelevodopa era. *Neurology* 66**,** 93-98.

Fenelon, G., Mahieux, F., Huon, R., Ziegler, M., 2000. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain : a journal of neurology* 123 (Pt 4)**,** 733-745.

Fereshtehnejad, S.M., Lokk, J., 2014. Orthostatic Hypotension in Patients with Parkinson's Disease and Atypical Parkinsonism. *Parkinson's disease* 2014**,** 475854.

Fernagut, P.O., Li, Q., Dovero, S., Chan, P., Wu, T., Ravenscroft, P., Hill, M., Chen, Z., Bezard, E., 2010. Dopamine transporter binding is unaffected by L-DOPA administration in normal and MPTP-treated monkeys. *Plos One* in press.

Fernandez, A., de Ceballos, M.L., Jenner, P., Marsden, C.D., 1994. Neurotensin, substance P, delta and mu opioid receptors are decreased in basal ganglia of Parkinson's disease patients. *Neuroscience* 61**,** 73-79.

Ferrante, R.J., Hantraye, P., Brouillet, E., Beal, M.F., 1999. Increased nitrotyrosine immunoreactivity in substantia nigra neurons in MPTP treated baboons is blocked by inhibition of neuronal nitric oxide synthase. *Brain Res* 823**,** 177-182.

Ferré, S., Rubio, A., Fuxe, K., 1991. Stimulation of adenosine A2 receptors induces catalepsy. *Neurosci. Lett.* 130**,** 3.

Feyder, M., Bonito-Oliva, A., Fisone, G., 2011. L-DOPA-Induced Dyskinesia and Abnormal Signaling in Striatal Medium Spiny Neurons: Focus on Dopamine D1 Receptor-Mediated Transmission. *Front Behav Neurosci* 5**,** 71.

Feyder, M., Sodersten, E., Santini, E., Vialou, V., LaPlant, Q., Watts, E.L., Spigolon, G., Hansen, K., Caboche, J., Nestler, E.J., Fisone, G., 2014. A Role for Mitogen- and Stress-Activated Kinase 1 in L-DOPA-Induced Dyskinesia and FosB Expression. *Biol Psychiatry*.

Fidalgo, C., Ko, W.K., Tronci, E., Li, Q., Stancampiano, R., Chuan, Q., Bezard, E., Carta, M., 2015. Effect of serotonin transporter blockade on L-DOPA-induced dyskinesia in animal models of Parkinson's disease. *Neuroscience* 298**,** 389-396.

Fieblinger, T., Graves, S.M., Sebel, L.E., Alcacer, C., Plotkin, J.L., Gertler, T.S., Chan, C.S., Heiman, M., Greengard, P., Cenci, M.A., Surmeier, D.J., 2014a. Cell type-specific plasticity of striatal projection neurons in parkinsonism and L-DOPA-induced dyskinesia. *Nature communications* 5**,** 5316.

Fieblinger, T., Sebastianutto, I., Alcacer, C., Bimpisidis, Z., Maslava, N., Sandberg, S., Engblom, D., Cenci, M.A., 2014b. Mechanisms of Dopamine D1 Receptor-Mediated ERK1/2 Activation in the Parkinsonian Striatum and Their Modulation by Metabotropic Glutamate Receptor Type 5. *J Neurosci* 34**,** 4728-4740.

Fienberg, A.A., Hiroi, N., Mermelstein, P.G., Song, W., Snyder, G.L., Nishi, A., Cheramy, A., O'Callaghan, J.P., Miller, D.B., Cole, D.G., Corbett, R., Haile, C.N., Cooper, D.C., Onn, S.P., Grace, A.A., Ouimet, C.C., White, F.J., Hyman, S.E., Surmeier, D.J., Girault, J., Nestler, E.J., Greengard, P., 1998. DARPP-32: regulator of the efficacy of dopaminergic neurotransmission. *Science* 281**,** 838-842.

Filion, M., Tremblay, L., Bedard, P.J., 1991. Effects of dopamine agonists on the spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. *Brain Res* 547**,** 152-161.

Fine, J., Duff, J., Chen, R., Chir, B., Hutchison, W., Lozano, A.M., Lang, A.E., 2000. Long-term follow-up of unilateral pallidotomy in advanced Parkinson's disease. *The New England journal of medicine* 342**,** 1708-1714.

Finlay, C.J., Duty, S., Vernon, A.C., 2014. Brain morphometry and the neurobiology of levodopa-induced dyskinesias: current knowledge and future potential for translational pre-clinical neuroimaging studies. *Frontiers in neurology* 5**,** 95.

Fiorentini, C., Busi, C., Gorruso, E., Gotti, C., Spano, P., Missale, C., 2008. Reciprocal regulation of dopamine D1 and D3 receptor function and trafficking by heterodimerization. *Mol Pharmacol* 74**,** 59-69.

Fiorentini, C., Gardoni, F., Spano, P., Di Luca, M., Missale, C., 2003. Regulation of dopamine D1 receptor trafficking and desensitization by oligomerization with glutamate N-methyl-D-aspartate receptors. *J Biol Chem* 278**,** 20196-20202.

Fiorentini, C., Mattanza, C., Collo, G., Savoia, P., Spano, P., Missale, C., 2011. The tyrosine phosphatase Shp-2 interacts with the dopamine D(1) receptor and triggers D(1) -mediated Erk signaling in striatal neurons. *J Neurochem* 117**,** 253-263.

Fiorentini, C., Savoia, P., Savoldi, D., Barbon, A., Missale, C., 2013. Persistent activation of the D1R/Shp-2/Erk1/2 pathway in l-DOPA-induced dyskinesia in the 6-hydroxy-dopamine rat model of Parkinson's disease. *Neurobiol Dis* 54**,** 339-348.

Firsov, D., Elalouf, J.M., 1997. Molecular cloning of two rat GRK6 splice variants. *Am J Physiol.* 273**,** C953-961.

Fischer, P.M., 2004. The design of drug candidate molecules as selective inhibitors of therapeutically relevant protein kinases. *Curr Med Chem* 11**,** 1563-1583.

Fisher, L.J., Young, S.J., Tepper, J.M., Groves, P.M., Gage, F.H., 1991. Electrophysiological characteristics of cells within mesencephalon suspension grafts. *Neuroscience* 40**,** 109-122.

Fisone, G., Bezard, E., 2011. Molecular mechanisms of l-DOPA-induced dyskinesia. *International review of neurobiology* 98**,** 95-122.

Flau, K., Redmer, A., Liedtke, S., Kathmann, M., Schlicker, E., 2002. Inhibition of striatal and retinal dopamine release via nociceptin/orphanin FQ receptors. *British journal of pharmacology* 137**,** 1355-1361.

Fleming, S.M., 2011. Cardiovascular autonomic dysfunction in animal models of Parkinson's disease. *Journal of Parkinson's disease* 1**,** 321-327.

Foffani, G., Ardolino, G., Meda, B., Egidi, M., Rampini, P., Caputo, E., Baselli, G., Priori, A., 2005. Altered subthalamo-pallidal synchronisation in parkinsonian dyskinesias. *J Neurol Neurosurg Psychiatry* 76**,** 426-428.

Follett, K.A., Weaver, F.M., Stern, M., Hur, K., Harris, C.L., Luo, P., Marks, W.J., Jr., Rothlind, J., Sagher, O., Moy, C., Pahwa, R., Burchiel, K., Hogarth, P., Lai, E.C., Duda, J.E., Holloway, K., Samii, A., Horn, S., Bronstein, J.M., Stoner, G., Starr, P.A., Simpson, R., Baltuch, G., De Salles, A., Huang, G.D., Reda, D.J., Group, C.S.P.S., 2010. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *The New England journal of medicine* 362**,** 2077-2091.

Foltynie, T., Cheeran, B., Williams-Gray, C.H., Edwards, M.J., Schneider, S.A., Weinberger, D., Rothwell, J.C., Barker, R.A., Bhatia, K.P., 2009. BDNF val66met influences time to onset of levodopa induced dyskinesia in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 80**,** 141-144.

Fox, S., Silverdale, M., Kellett, M., Davies, R., Steiger, M., Fletcher, N., Crossman, A., Brotchie, J., 2004. Non-subtype-selective opioid receptor antagonism in treatment of levodopa-induced motor complications in Parkinson's disease. *Mov Disord* 19**,** 554-560.

Fox, S.H., Brotchie, J.M., 2010. The MPTP-lesioned non-human primate models of Parkinson's disease. Past, present, and future. *Prog Brain Res* 184**,** 133-157.

Fox, S.H., Chuang, R., Brotchie, J.M., 2009. Serotonin and Parkinson's disease: On movement, mood, and madness. *Mov Disord* 24**,** 1255-1266.

Fox, S.H., Johnston, T.H., Li, Q., Brotchie, J., Bezard, E., 2012. A critique of available scales and presentation of the Non-Human Primate Dyskinesia Rating Scale. *Mov Disord* 27**,** 1373-1378.

Fox, S.H., Katzenschlager, R., Lim, S.Y., Ravina, B., Seppi, K., Coelho, M., Poewe, W., Rascol, O., Goetz, C.G., Sampaio, C., 2011. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 26 Suppl 3**,** S2-41.

Fraix, V., Chabardes, S., Krainik, A., Seigneuret, E., Grand, S., Le Bas, J.F., Krack, P., Benabid, A.L., Pollak, P., 2010. Effects of magnetic resonance imaging in patients with implanted deep brain stimulation systems. *Journal of neurosurgery* 113**,** 1242-1245.

Francardo, V., Cenci, M.A., 2014. Investigating the molecular mechanisms of L-DOPA-induced dyskinesia in the mouse. *Parkinsonism Relat Disord* 20 Suppl 1**,** S20-22.

Francardo, V., Recchia, A., Popovic, N., Andersson, D., Nissbrandt, H., Cenci, M.A., 2011. Impact of the lesion procedure on the profiles of motor impairment and

molecular responsiveness to L-DOPA in the 6-hydroxydopamine mouse model of Parkinson's disease. *Neurobiol Dis* 42**,** 327-340.

François, C., Yelnik, J., Bergman, H., Herrero, T., Hirsch, E.C., 1998. Implication of the A8 area in the generation of parkinsonian tremor. *Mov. Disord.* 13 suppl. 2**,** 120.

Frau, L., Morelli, M., Simola, N., 2013. Performance of movement in hemiparkinsonian rats influences the modifications induced by dopamine agonists in striatal efferent dynorphinergic neurons. . *Exp. Neurol.* 247**,** 10.

Fredduzzi, S., Moratalla, R., Monopoli, A., Cuellar, B., Xu, K., Ongini, E., Impagnatiello, F., Schwarzschild, M.A., Chen, J.F., 2002. Persistent behavioral sensitization to chronic L-DOPA requires A2A adenosine receptors. *J Neurosci* 22**,** 1054-1062.

Freed, C.R., Greene, P.E., Breeze, R.E., Tsai, W.Y., DuMouchel, W., Kao, R., Dillon, S., Winfield, H., Culver, S., Trojanowski, J.Q., Eidelberg, D., Fahn, S., 2001. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *The New England journal of medicine* 344**,** 710-719.

Freund, T.F., Bolam, J.P., Bjorklund, A., Stenevi, U., Dunnett, S.B., Powell, J.F., Smith, A.D., 1985. Efferent synaptic connections of grafted dopaminergic neurons reinnervating the host neostriatum: a tyrosine hydroxylase immunocytochemical study. *J Neurosci* 5**,** 603-616.

Gainetdinov, R.R., Bohn, L.M., Sotnikova, T.D., Cyr, M., Laakso, A., Macrae, A.D., Torres, G.E., Kim, K.M., Lefkowitz, R.J., Caron, M.G., Premont, R.T., 2003. Dopaminergic supersensitivity in G protein-coupled receptor kinase 6-deficient mice. *Neuron* 38**,** 291-303.

Gainetdinov, R.R., Bohn, L.M., Walker, J.K., Laporte, S.A., Macrae, A.D., Caron, M.G., Lefkowitz, R.J., Premont, R.T., 1999. Muscarinic supersensitivity and impaired receptor desensitization in G protein-coupled receptor kinase 5-deficient mice. *Neuron* 24**,** 1029-1036.

Gainetdinov, R.R., Premont, R.T., Bohn, L.M., Lefkowitz, R.J., Caron, M.G., 2004. Desensitization of G protein-coupled receptors and neuronal function. *Annual Review of Neuroscience* 27**,** 107-144.

Galati, S., Salvade, A., Pace, M., Sarasso, S., Baracchi, F., Bassetti, C.L., Kaelin-Lang, A., Stadler, C., Stanzione, P., Moller, J.C., 2015. Evidence of an association between sleep and levodopa-induced dyskinesia in an animal model of Parkinson's disease. *Neurobiol Aging* 36**,** 1577-1589.

Gallagher, D.A., O'Sullivan, S.S., Evans, A.H., Lees, A.J., Schrag, A., 2007. Pathological gambling in Parkinson's disease: risk factors and differences from dopamine dysregulation. An analysis of published case series. *Mov Disord* 22**,** 1757-1763.

Garcia, J., Carlsson, T., Dobrossy, M., Nikkhah, G., Winkler, C., 2011. Extent of pre-operative L-DOPA-induced dyskinesia predicts the severity of graft-induced dyskinesia after fetal dopamine cell transplantation. *Exp Neurol* 232**,** 270-279.

Garcia, L., Audin, J., D'Alessandro, G., Bioulac, B., Hammond, C., 2003. Dual effect of high-frequency stimulation on subthalamic neuron activity. *J Neurosci* 23**,** 8743-8751.

Gardoni, F., Picconi, B., Ghiglieri, V., Polli, F., Bagetta, V., Bernardi, G., Cattabeni, F., Di Luca, M., Calabresi, P., 2006. A critical interaction between NR2B and MAGUK in L-DOPA induced dyskinesia. *J Neurosci* 26**,** 2914-2922.

Gardoni, F., Sgobio, C., Pendolino, V., Calabresi, P., Di Luca, M., Picconi, B., 2012. Targeting NR2A-containing NMDA receptors reduces L-DOPA-induced dyskinesias. *Neurobiol Aging* 33**,** 2138-2144.

Gasparini, F., Di Paolo, T., Gomez-Mancilla, B., 2013. Metabotropic glutamate receptors for Parkinson's disease therapy. *Parkinson's disease* 2013**,** 196028.

Gehani, S.S., Agrawal-Singh, S., Dietrich, N., Christophersen, N.S., Helin, K., Hansen, K., 2010. Polycomb group protein displacement and gene activation through MSK-dependent H3K27me3S28 phosphorylation. *Molecular cell* 39**,** 886-900.

Geisler, S., Trimble, M., 2008. The lateral habenula: no longer neglected. *CNS spectrums* 13**,** 484-489.

Gerfen, C.R., 2000. Dopamine-mediated gene regulation in models of Parkinson's disease. *Ann. Neurol.* 47 (Suppl)**,** S42-S50.

Gerfen, C.R., Engber, T.M., Mahan, L., Susel, Z., Chase, T.N., Monsma, F.J., Sibley, D.R., 1990. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 250**,** 1429-1432.

Gerfen, C.R., Keefe, K.A., Gauda, E.B., 1995. D1 and D2 dopamine receptor function in the striatum: Coactivation of D1- and D2-dopamine receptors on separate populations of neurons results in potentiated immediate early gene response in D1-containing neurons. *J. Neurosci.* 15**,** 8167-8176.

Gerfen, C.R., McGinty, J.F., Young, W.S., 1991. Dopamine differentially regulates dynorphin, substance P, and enkephalin expression in striatal neurons: in situ hybridization histochemical analysis. *J. Neurosci.* 11**,** 1016-1031.

Gerfen, C.R., Miyachi, S., Paletzki, R., Brown, P., 2002. D1 dopamine receptor supersensitivity in the dopamine-depleted striatum results from a switch in the regulation of ERK1/2 kinase. *J. Neurosci.* 22**,** 5042-5054.

Gerfen, C.R., Paletzki, R., Worley, P., 2008. Differences between dorsal and ventral striatum in Drd1a dopamine receptor coupling of dopamine- and cAMP-regulated phosphoprotein-32 to activation of extracellular signal-regulated kinase. *J Neurosci* 28**,** 7113-7120.

Gerrow, K., Triller, A., 2010. Synaptic stability and plasticity in a floating world. *Curr Opin Neurobiol* 20**,** 631-639.

Geurts, M., Hermans, E., Maloteaux, J.M., 2002. Opposite modulation of regulators of G protein signalling-2 RGS2 and RGS4 expression by dopamine receptors in the rat striatum. *Neurosci. Lett.* 333**,** 146-150.

Geurts, M., Maloteaux, J.M., Hermans, E., 2003. Altered expression of regulators of G-protein signaling (RGS) mRNAs in the striatum of rats undergoing dopamine depletion. *Biochem. Pharmacol.* 66**,** 1163-1170.

Ghorayeb, I., Loundou, A., Auquier, P., Dauvilliers, Y., Bioulac, B., Tison, F., 2007. A nationwide survey of excessive daytime sleepiness in Parkinson's disease in France. *Movement disorders : official journal of the Movement Disorder Society* 22**,** 1567-1572.

Giepmans, B.N., Adams, S.R., Ellisman, M.H., Tsien, R.Y., 2006. The fluorescent toolbox for assessing protein location and function. *Science* 312**,** 217-224.

Gil, S., Park, C., Lee, J., Koh, H., 2010. The roles of striatal serotonin and L -amino-acid decarboxylase on L-DOPA-induced Dyskinesia in a Hemiparkinsonian rat model. *Cellular and molecular neurobiology* 30**,** 817-825.

Gil, S.J., Park, C.H., Lee, J.E., Minn, Y.K., Koh, H.C., 2011. Positive association between striatal serotonin level and abnormal involuntary movements in chronic L-DOPA-treated hemiparkinsonian rats. *Brain Res Bull* 84**,** 151-156.

Gines, S., Hillion, J., Torvinen, M., Le Crom, S., Casado, V., Canela, E.I., Rondin, S., Lew, J.Y., Watson, S., Zoli, M., Agnati, L.F., Verniera, P., Lluis, C., Ferre, S., Fuxe, K., Franco, R., 2000. Dopamine D1 and adenosine A1 receptors form functionally interacting heteromeric complexes. *Proc Natl Acad Sci U S A* 97**,** 8606-8611.

Giniatullin, R., Nistri, A., Yakel, J.L., 2005. Desensitization of nicotinic ACh receptors: shaping cholinergic signaling. *Trends Neurosci* 28**,** 371-378.

Giorgi, M., D'Angelo, V., Esposito, Z., Nuccetelli, V., Sorge, R., Martorana, A., Stefani, A., Bernardi, G., Sancesario, G., 2008. Lowered cAMP and cGMP signalling in the brain during levodopa-induced dyskinesias in hemiparkinsonian rats: new aspects in the pathogenetic mechanisms. *Eur J Neurosci* 28**,** 941-950.

Giovannoni, G., O'Sullivan, J.D., Turner, K., Manson, A.J., Lees, A.J., 2000. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. *J Neurol Neurosurg Psychiatry* 68**,** 423-428.

Giros, B., Jaber, M., Jones, S.R., Wightman, R.M., Caron, M.G., 1996. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature* 379**,** 606-612.

Giuffra, M.E., Sethy, V.H., Davis, T.L., Mouradian, M.M., Chase, T.N., 1993. Milacemide therapy for Parkinson's disease. *Mov Disord* 8**,** 47-50.

Glatt, C.E., Snyder, S.H., 1993. Cloning and expression of an adenylyl cyclase localized to the corpus striatum. *Nature* 361**,** 536-538.

Gnanalingham, K.K., Milkowski, N.A., Smith, L.A., Hunter, A.J., Jenner, P., Marsden, C.D., 1995. Short and long-term changes in cerebral [14C]-2-deoxyglucose uptake in the MPTP-treated marmoset: relationship to locomotor activity. *Journal of neural transmission. General section* 101**,** 65-82.

Gobert, A., Rivet, J.M., Cistarelli, L., Melon, C., Millan, M.J., 1997. Alpha2-adrenergic receptor blockade markedly potentiates duloxetine- and fluoxetine-induced increases in noradrenaline, dopamine, and serotonin levels in the frontal cortex of freely moving rats. *J Neurochem* 69**,** 2616-2619.

Goetz, C.G., Damier, P., Hicking, C., Laska, E., Muller, T., Olanow, C.W., Rascol, O., Russ, H., 2007. Sarizotan as a treatment for dyskinesias in Parkinson's disease: a double-blind placebo-controlled trial. *Mov Disord* 22**,** 179-186.

Goetz, C.G., Poewe, W., Rascol, O., Sampaio, C., 2005. Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. *Mov Disord* 20**,** 523-539.

Golbe, L.I., 1991. Young-onset Parkinson's disease: a clinical review. *Neurology* 41**,** 168-173.

Gold, S.J., Hoang, C.V., Potts, B.W., Porras, G., Pioli, E., Kim, K.W., Nadjar, A., Qin, C., LaHoste, G.J., Li, Q., Bioulac, B.H., Waugh, J.L., Gurevich, E., Neve, R.L., Bezard, E.,

2007. RGS9-2 negatively modulates L-3,4-dihydroxyphenylalanine-induced dyskinesia in experimental Parkinson's disease. *J Neurosci* 27**,** 14338-14348.

Gold, S.J., Ni, Y.G., Dohlman, H.G., Nestler, E.J., 1997. Regulators of G-Protein Signaling (RGS) Proteins: Region-Specific Expression of Nine Subtypes in Rat Brain. *J. Neurosci.* 17**,** 8024-8037.

Gomez-Mancilla, B., Bedard, P.J., 1993. Effect of nondopaminergic drugs on L-dopa-induced dyskinesias in MPTP-treated monkeys. *Clin Neuropharmacol* 16**,** 418-427.

Goodman, O.B., Jr., Krupnick, J.G., Santini, F., Gurevich, V.V., Penn, R.B., Gagnon, A.W., Keen, J.H., Benovic, J.L., 1996. Beta-arrestin acts as a clathrin adaptor in endocytosis of the beta2-adrenergic receptor. *Nature* 383**,** 447-450.

Goodwin, F.K., Murphy, D.L., Brodie, H.K., Bunney, W.E., Jr., 1970. L-DOPA, catecholamines, and behavior: a clinical and biochemical study in depressed patients. *Biol Psychiatry* 2**,** 341-366.

Goumon, Y., Laux, A., Muller, A., Aunis, D., 2009. Central and Peripheral Endogenous Morphine. *An. R. Acad. Nac. Farm.* 75**,** 389-418.

Gouty, S., Brown, J.M., Rosenberger, J., Cox, B.M., 2010. MPTP treatment increases expression of pre-pro-nociceptin/orphanin FQ mRNA in a subset of substantia nigra reticulata neurons. *Neuroscience* 169**,** 269-278.

Grandas, F., Galiano, M.L., Tabernero, C., 1999. Risk factors for levodopa-induced dyskinesias in Parkinson's disease. *Journal of neurology* 246**,** 1127-1133.

Granneman, J.G., Zhai, Y., Zhu, Z., Bannon, M.J., Burchett, S.A., Schmidt, C.J., Andrade, R., Cooper, J., 1998. Molecular characterization of human and rat RGS 9L, a novel splice variant enriched in dopamine target regions, and chromosomal localization of the RGS 9 gene. *Mol. Pharmacol.* 54**,** 687-694.

Graybiel, A.M., 1995. Building action repertoires: memory and learning functions of the basal ganglia. *Curr Opin Neurobiol* 5**,** 733-741.

Graybiel, A.M., Canales, J.J., Capper-Loup, C., 2000. Levodopa-induced dyskinesias and dopamine-dependent stereotypies: a new hypothesis. *Trends Neurosci* 23**,** S71-77.

Green, T.A., Alibhai, I.N., Unterberg, S., Neve, R.L., Ghose, S., Tamminga, C.A., Nestler, E.J., 2008. Induction of activating transcription factors (ATFs) ATF2, ATF3, and ATF4

in the nucleus accumbens and their regulation of emotional behavior. *J Neurosci* 28**,** 2025-2032.

Greengard, P., 2001. The neurobiology of slow synaptic transmission. *Science* 294**,** 1024-1030.

Greengard, P., Allen, P.B., Nairn, A.C., 1999. Beyond the dopamine receptor: the DARPP-32/Protein phosphatase-1 cascade. *Neuron* 23**,** 435-447.

Gregoire, L., Jourdain, V.A., Townsend, M., Roach, A., Di Paolo, T., 2013. Safinamide reduces dyskinesias and prolongs L-DOPA antiparkinsonian effect in parkinsonian monkeys. *Parkinsonism Relat Disord* 19**,** 508-514.

Gregoire, L., Morin, N., Ouattara, B., Gasparini, F., Bilbe, G., Johns, D., Vranesic, I., Sahasranaman, S., Gomez-Mancilla, B., Di Paolo, T., 2011. The acute antiparkinsonian and antidyskinetic effect of AFQ056, a novel metabotropic glutamate receptor type 5 antagonist, in L-Dopa-treated parkinsonian monkeys. *Parkinsonism Relat Disord* 17**,** 270-276.

Groc, L., Heine, M., Cognet, L., Brickley, K., Stephenson, F.A., Lounis, B., Choquet, D., 2004. Differential activity-dependent regulation of the lateral mobilities of AMPA and NMDA receptors. *Nature neuroscience* 7**,** 695-696.

Groc, L., Heine, M., Cousins, S.L., Stephenson, F.A., Lounis, B., Cognet, L., Choquet, D., 2006. NMDA receptor surface mobility depends on NR2A-2B subunits. *Proc Natl Acad Sci U S A* 103**,** 18769-18774.

Gross, C.E., Ravenscroft, P., Dovero, S., Jaber, M., Bioulac, B., Bezard, E., 2003. Pattern of levodopa-induced striatal changes is different in normal and MPTP-lesioned mice. *J Neurochem* 84**,** 1246-1255.

Gschwandtner, U., Aston, J., Renaud, S., Fuhr, P., 2001. Pathologic gambling in patients with Parkinson's disease. *Clin Neuropharmacol* 24**,** 170-172.

Gubellini, P., Eusebio, A., Oueslati, A., Melon, C., Kerkerian-Le Goff, L., Salin, P., 2006. Chronic high-frequency stimulation of the subthalamic nucleus and L-DOPA treatment in experimental parkinsonism: effects on motor behaviour and striatal glutamate transmission. *Eur J Neurosci* 24**,** 1802-1814.

Guehl, D., Pessiglione, M., Francois, C., Yelnik, J., Hirsch, E.C., Feger, J., Tremblay, L., 2003. Tremor-related activity of neurons in the 'motor' thalamus: changes in firing rate and pattern in the MPTP vervet model of parkinsonism. *Eur. J. Neurosci.* 17**,** 2388-2400.

Guerrini, R., Calo, G., Rizzi, A., Bianchi, C., Lazarus, L.H., Salvadori, S., Temussi, P.A., Regoli, D., 1997. Address and message sequences for the nociceptin receptor: a structure-activity study of nociceptin-(1-13)-peptide amide. *Journal of medicinal chemistry* 40**,** 1789-1793.

Guigoni, C., Aubert, I., Li, Q., Gurevich, V.V., Benovic, J.L., Ferry, S., Mach, U., Stark, H., Leriche, L., Hakansson, K., Bioulac, B.H., Gross, C.E., Sokoloff, P., Fisone, G., Gurevich, E.V., Bloch, B., Bezard, E., 2005a. Pathogenesis of levodopa-induced dyskinesia: focus on D1 and D3 dopamine receptors. *Parkinsonism Relat. Disord.* 11 Suppl 1**,** S25-29.

Guigoni, C., Doudnikoff, E., Li, Q., Bloch, B., Bezard, E., 2007. Altered D(1) dopamine receptor trafficking in parkinsonian and dyskinetic non-human primates. *Neurobiol Dis* 26**,** 452-463.

Guigoni, C., Dovero, S., Aubert, I., Qin, L., Bioulac, B.H., Bloch, B., Gurevich, E.V., Gross, C.E., Bezard, E., 2005b. Levodopa-induced dyskinesia in MPTP-treated macaque is not dependent of the extent and pattern of the nigrostrial lesion. *Eur. J. Neurosci.* 22**,** 283-287.

Guigoni, C., Li, Q., Aubert, I., Dovero, S., Bioulac, B.H., Bloch, B., Crossman, A.R., Gross, C.E., Bezard, E., 2005c. Involvement of sensorimotor, limbic, and associative basal ganglia domains in L-3,4-dihydroxyphenylalanine-induced dyskinesia. *J. Neurosci.* 25**,** 2102-2107.

Gurevich, E.V., Gurevich, V.V. 2010. Dopamine receptors and the treatment of Parkinson's disease. In: *Dopamine Receptors*. pp. 525-584. Ed. K. Neve. Humana Press: New York.

Gurevich, E.V., Tesmer, J.J., Mushegian, A., Gurevich, V.V., 2012. G protein-coupled receptor kinases: more than just kinases and not only for GPCRs. *Pharmacol Ther* 133**,** 40-69.

Guridi, J., Rodriguez-Oroz, M.C., Arbizu, J., Alegre, M., Prieto, E., Landecho, I., Manrique, M., Artieda, J., Obeso, J.A., 2008. Successful thalamic deep brain stimulation for orthostatic tremor. *Mov Disord* 23**,** 1808-1811.

Haber, S.N., Fudge, J.L., McFarland, N.R., 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 20**,** 2369-2382.

Hadj Tahar, A., Belanger, N., Bangassoro, E., Gregoire, L., Bedard, P.J., 2000. Antidyskinetic effect of JL-18, a clozapine analog, in parkinsonian monkeys. *Eur J Pharmacol* 399**,** 183-186.

Hadj Tahar, A., Gregoire, L., Darre, A., Belanger, N., Meltzer, L., Bedard, P.J., 2004. Effect of a selective glutamate antagonist on L-dopa-induced dyskinesias in drug-naive parkinsonian monkeys. *Neurobiol Dis* 15**,** 171-176.

Hagell, P., Piccini, P., Bjorklund, A., Brundin, P., Rehncrona, S., Widner, H., Crabb, L., Pavese, N., Oertel, W.H., Quinn, N., Brooks, D.J., Lindvall, O., 2002. Dyskinesias following neural transplantation in Parkinson's disease. *Nature neuroscience* 5**,** 627-628.

Halje, P., Tamte, M., Richter, U., Mohammed, M., Cenci, M.A., Petersson, P., 2012. Levodopa-induced dyskinesia is strongly associated with resonant cortical oscillations. *J Neurosci* 32**,** 16541-16551.

Hallett, P.J., Dunah, A.W., Ravenscroft, P., Zhou, S., Bezard, E., Crossman, A.R., Brotchie, J.M., Standaert, D.G., 2005. Alterations of striatal NMDA receptor subunits associated with the development of dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. *Neuropharmacology* 48**,** 503-516.

Hammond, C., Bergman, H., Brown, P., 2007. Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci* 30**,** 357-364.

Hanrieder, J., Ljungdahl, A., Falth, M., Mammo, S.E., Bergquist, J., Andersson, M., 2011. L-DOPA-induced dyskinesia is associated with regional increase of striatal dynorphin peptides as elucidated by imaging mass spectrometry. *Molecular & cellular proteomics : MCP* 10**,** M111 009308.

Hantraye, P., Brouillet, E., Ferrante, R., Palfi, S., Dolan, R., Matthews, R.T., Beal, M.F., 1996. Inhibition of neuronal nitric oxide synthase prevents MPTP-induced parkinsonism in baboons. *Nature Med.* 2**,** 1017-1021.

Hantraye, P., Riche, D., Maziere, M., Isacson, O., 1990. A primate model of Huntington's disease: behavioral and anatomical studies of unilateral excitotoxic lesions of the caudate-putamen in the baboon. *Exp Neurol* 108**,** 91-104.

Hantraye, P., Varastet, M., Peschanski, M., 1993. Stable parkinsonian syndrome and uneven loss of striatal dopamine fibres following chronic MPTP administration in baboons. *Neuroscience* 53**,** 169-178.

Hassler, R., 1938. Zur Pathologie der Paralysis Agitans und des postenzephalitischen Parkinsonismus. *J. Psychol. Neurol.* 48**,** 387-476.

Hauser, R.A., Cantillon, M., Pourcher, E., Micheli, F., Mok, V., Onofrj, M., Huyck, S., Wolski, K., 2011. Preladenant in patients with Parkinson's disease and motor fluctuations: a phase 2, double-blind, randomised trial. *Lancet Neurol.* 10**,** 9.

Hauser, R.A., Hsu, A., Kell, S., Espay, A.J., Sethi, K., Stacy, M., Ondo, W., O'Connell, M., Gupta, S., investigators, I.A.-P., 2013. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial. *Lancet Neurol* 12**,** 346-356.

Hauser, R.A., Olanow, C.W., 1993. Orobuccal dyskinesia associated with trihexyphenidyl therapy in a patient with Parkinson's disease. *Mov Disord* 8**,** 512-514.

Hauser, R.A., Rascol, O., Korczyn, A.D., Jon Stoessl, A., Watts, R.L., Poewe, W., De Deyn, P.P., Lang, A.E., 2007. Ten-year follow-up of Parkinson's disease patients randomized to initial therapy with ropinirole or levodopa. *Mov Disord* 22**,** 2409-2417.

Hauser, R.A., Shulman, L.M., Trugman, J.M., Roberts, J.W., Mori, A., Ballerini, R., Sussman, N.M., Group., I.-U.-S., 2008. Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. . *Mov. Disord.* 23**,** 9.

Healy, D.G., Wood, N.W., Schapira, A.H., 2008. Test for LRRK2 mutations in patients with Parkinson's disease. *Practical neurology* 8**,** 381-385.

Hechtner, M.C., Vogt, T., Zollner, Y., Schroder, S., Sauer, J.B., Binder, H., Singer, S., Mikolajczyk, R., 2014. Quality of life in Parkinson's disease patients with motor fluctuations and dyskinesias in five European countries. *Parkinsonism Relat Disord* 20**,** 969-974.

Hegener, O., Prenner, L., Runkel, F., Baader, S.L., Kappler, J., Haberlein, H., 2004. Dynamics of beta2-adrenergic receptor-ligand complexes on living cells. *Biochemistry* 43**,** 6190-6199.

Heiman, M., Heilbut, A., Francardo, V., Kulicke, R., Fenster, R.J., Kolaczyk, E.D., Mesirov, J.P., Surmeier, D.J., Cenci, M.A., Greengard, P., 2014. Molecular adaptations of striatal spiny projection neurons during levodopa-induced dyskinesia. *Proc Natl Acad Sci U S A* 111**,** 4578-4583.

Heimer, G., Bar-Gad, I., Goldberg, J.A., Bergman, H., 2002. Dopamine replacement therapy reverses abnormal synchronization of pallidal neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of parkinsonism. *J. Neurosci.* 22**,** 7850-7855.

Heimer, G., Rivlin-Etzion, M., Bar-Gad, I., Goldberg, J.A., Haber, S.N., Bergman, H., 2006. Dopamine replacement therapy does not restore the full spectrum of normal pallidal activity in the 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine primate model of Parkinsonism. *J Neurosci* 26**,** 8101-8114.

Henry, B., Crossman, A.R., Brotchie, J.M., 1999. Effect of repeated L-DOPA, bromocriptine, or lisuride administration on preproenkephalin-A and preproenkephalin-B mRNA levels in the striatum of the 6-hydroxydopamine-lesioned rat. *Exp. Neurol.* 155**,** 204-220.

Henry, B., Duty, S., Fox, S.H., Crossman, A.R., Brotchie, J.M., 2003. Increased striatal pre-proenkephalin B expression is associated with dyskinesia in Parkinson's disease. *Exp Neurol* 183**,** 458-468.

Henry, B., Fox, S.H., Crossman, A.R., Brotchie, J.M., 2001. Mu- and delta-opioid receptor antagonists reduce levodopa-induced dyskinesia in the MPTP-lesioned primate model of Parkinson's disease. *Exp Neurol* 171**,** 139-146.

Henschen, C.W., Palmiter, R.D., Darvas, M., 2013. Restoration of dopamine signaling to the dorsal striatum is sufficient for aspects of active maternal behavior in female mice. *Endocrinology* 154**,** 4316-4327.

Hershey, T., Black, K.J., Stambuk, M.K., Carl, J.L., McGee-Minnich, L.A., Perlmutter, J.S., 1998. Altered thalamic response to levodopa in Parkinson's patients with dopa-induced dyskinesias. *Proc Natl Acad Sci U S A* 95**,** 12016-12021.

Herve, D., Levi-Strauss, M., Marey-Semper, I., Verney, C., Tassin, J.P., Glowinski, J., Girault, J.A., 1993. G(olf) and Gs in rat basal ganglia: possible involvement of G(olf) in the coupling of dopamine D1 receptor with adenylyl cyclase. *J Neurosci* 13**,** 2237-2248.

Herz, D.M., Haagensen, B.N., Christensen, M.S., Madsen, K.H., Rowe, J.B., Lokkegaard, A., Siebner, H.R., 2014. The acute brain response to levodopa heralds dyskinesias in Parkinson disease. *Ann Neurol* 75**,** 829-836.

Herz, D.M., Haagensen, B.N., Christensen, M.S., Madsen, K.H., Rowe, J.B., Lokkegaard, A., Siebner, H.R., 2015. Abnormal dopaminergic modulation of striato-cortical

networks underlies levodopa-induced dyskinesias in humans. *Brain* 138**,** 1658-1666.

Herzog, J., Volkmann, J., Krack, P., Kopper, F., Potter, M., Lorenz, D., Steinbach, M., Klebe, S., Hamel, W., Schrader, B., Weinert, D., Muller, D., Mehdorn, H.M., Deuschl, G., 2003. Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. *Mov Disord* 18**,** 1332-1337.

Hikosaka, O., Sesack, S.R., Lecourtier, L., Shepard, P.D., 2008. Habenula: crossroad between the basal ganglia and the limbic system. *J Neurosci* 28**,** 11825-11829.

Hill, M.P., Bezard, E., McGuire, S.G., Crossman, A.R., Brotchie, J.M., Michel, A., Grimee, R., Klitgaard, H., 2003. Novel antiepileptic drug levetiracetam decreases dyskinesia elicited by L-dopa and ropinirole in the MPTP-lesioned marmoset. *Mov Disord* 18**,** 1301-1305.

Hill, M.P., Brotchie, J.M., Crossman, A.R., Bezard, E., Michel, A., Grimee, R., Klitgaard, H., 2004a. Levetiracetam Interferes With the L-dopa priming process in MPTP-lesioned drug-naive marmosets. *Clin Neuropharmacol* 27**,** 171-177.

Hill, M.P., Ravenscroft, P., Bezard, E., Crossman, A.R., Brotchie, J.M., Michel, A., Grimee, R., Klitgaard, H., 2004b. Levetiracetam Potentiates the Antidyskinetic Action of Amantadine in the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-Lesioned Primate Model of Parkinson's Disease. *J. Pharmacol. Exp. Ther.* 310**,** 386-394.

Hirano, S., Asanuma, K., Ma, Y., Tang, C., Feigin, A., Dhawan, V., Carbon, M., Eidelberg, D., 2008. Dissociation of metabolic and neurovascular responses to levodopa in the treatment of Parkinson's disease. *J Neurosci* 28**,** 4201-4209.

Hjorth, S., Bengtsson, H.J., Kullberg, A., Carlzon, D., Peilot, H., Auerbach, S.B., 2000. Serotonin autoreceptor function and antidepressant drug action. *J Psychopharmacol* 14**,** 177-185.

Hodgson, R.A., Bertorelli, R., Varty, G.B., Lachowicz, J.E., Forlani, A., Fredduzzi, S., Cohen-Williams, M.E., Higgins, G.A., Impagnatiello, F., Nicolussi, E., Parra, L.E., Foster, C., Zhai, Y., Neustadt, B.R., Stamford, A.W., Parker, E.M., Reggiani, A., Hunter, J.C., 2009. Characterization of the potent and highly selective A2A receptor antagonists preladenant and SCH 412348 [7-[2-[4-2,4-difluorophenyl]-1-piperazinyl]ethyl]-2-(2-furanyl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-

c]pyrimidin-5-amine] in rodent models of movement disorders and depression. *J Pharmacol Exp Ther* 330**,** 294-303.

Holloway, R.G., Shoulson, I., Fahn, S., Kieburtz, K., Lang, A., Marek, K., McDermott, M., Seibyl, J., Weiner, W., Musch, B., Kamp, C., Welsh, M., Shinaman, A., Pahwa, R., Barclay, L., Hubble, J., LeWitt, P., Miyasaki, J., Suchowersky, O., Stacy, M., Russell, D.S., Ford, B., Hammerstad, J., Riley, D., Standaert, D., Wooten, F., Factor, S., Jankovic, J., Atassi, F., Kurlan, R., Panisset, M., Rajput, A., Rodnitzky, R., Shults, C., Petsinger, G., Waters, C., Pfeiffer, R., Biglan, K., Borchert, L., Montgomery, A., Sutherland, L., Weeks, C., DeAngelis, M., Sime, E., Wood, S., Pantella, C., Harrigan, M., Fussell, B., Dillon, S., Alexander-Brown, B., Rainey, P., Tennis, M., Rost-Ruffner, E., Brown, D., Evans, S., Berry, D., Hall, J., Shirley, T., Dobson, J., Fontaine, D., Pfeiffer, B., Brocht, A., Bennett, S., Daigneault, S., Hodgeman, K., O'Connell, C., Ross, T., Richard, K., Watts, A., Parkinson Study, G., 2004. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Arch Neurol* 61**,** 1044-1053.

Hollt, V., 1986. Opioid peptide processing and receptor selectivity. *Annu Rev Pharmacol Toxicol* 26**,** 59-77.

Holman, A.J., 2009. Impulse control disorder behaviors associated with pramipexole used to treat fibromyalgia. *Journal of gambling studies / co-sponsored by the National Council on Problem Gambling and Institute for the Study of Gambling and Commercial Gaming* 25**,** 425-431.

Hong, J.Y., Oh, J.S., Lee, I., Sunwoo, M.K., Ham, J.H., Lee, J.E., Sohn, Y.H., Kim, J.S., Lee, P.H., 2014. Presynaptic dopamine depletion predicts levodopa-induced dyskinesia in de novo Parkinson disease. *Neurology* 82**,** 1597-1604.

Hong, S., Hikosaka, O., 2008. The globus pallidus sends reward-related signals to the lateral habenula. *Neuron* 60**,** 720-729.

Honig, H., Antonini, A., Martinez-Martin, P., Forgacs, I., Faye, G.C., Fox, T., Fox, K., Mancini, F., Canesi, M., Odin, P., Chaudhuri, K.R., 2009. Intrajejunal levodopa infusion in Parkinson's disease: a pilot multicenter study of effects on nonmotor symptoms and quality of life. *Mov Disord* 24**,** 1468-1474.

Hosp, J.A., Luft, A.R., 2013. Dopaminergic meso-cortical projections to m1: role in motor learning and motor cortex plasticity. *Frontiers in neurology* 4**,** 145.

Hsu, A., Togasaki, D.M., Bezard, E., Sokoloff, P., Langston, J.W., Di Monte, D.A., Quik, M., 2004. Effect of the D3 dopamine receptor partial agonist BP897 [N-[4-(4-(2-methoxyphenyl)piperazinyl)butyl]-2-naphthamide] on L-3,4-dihydroxyphenylalanine-induced dyskinesias and parkinsonism in squirrel monkeys. *J. Pharmacol. Exp. Ther.* 311**,** 770-777.

Huang, C.C., Orban, T., Jastrzebska, B., Palczewski, K., Tesmer, J.J., 2011a. Activation of G protein-coupled receptor kinase 1 involves interactions between its N-terminal region and its kinase domain. *Biochemistry* 50**,** 1940-1949.

Huang, C.C., Tesmer, J.J., 2011. Recognition in the face of diversity: interactions of heterotrimeric G proteins and G protein-coupled receptor (GPCR) kinases with activated GPCRs. *J Biol Chem* 286**,** 7715-7721.

Huang, C.C., Yoshino-Koh, K., Tesmer, J.J., 2009. A surface of the kinase domain critical for the allosteric activation of G protein-coupled receptor kinases. *J Biol Chem* 284**,** 17206-17215.

Huang, L., Grady, S.R., Quik, M., 2011b. Nicotine Reduces L-Dopa-Induced Dyskinesias by Acting at {beta}2 Nicotinic Receptors. *J Pharmacol Exp Ther* 338**,** 932-941.

Huang, L.Z., Campos, C., Ly, J., Carroll, F.I., Quik, M., 2011c. Nicotinic receptor agonists decrease L-dopa-induced dyskinesias most effectively in moderately lesioned parkinsonian rats. *Neuropharmacology* 60**,** 861-868.

Huang, Y.Z., Rothwell, J.C., Lu, C.S., Chuang, W.L., Chen, R.S., 2011d. Abnormal bidirectional plasticity-like effects in Parkinson's disease. *Brain* 134**,** 2312-2320.

Hubble, J.P., 2002. Long-term studies of dopamine agonists. *Neurology* 58**,** S42-50.

Huot, P., Johnston, T.H., Koprich, J.B., Aman, A., Fox, S.H., Brotchie, J.M., 2012a. L-745,870 reduces L-DOPA-induced dyskinesia in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned macaque model of Parkinson's disease. *J Pharmacol Exp Ther* 342**,** 576-585.

Huot, P., Johnston, T.H., Koprich, J.B., Espinosa, M.C., Reyes, M.G., Fox, S.H., Brotchie, J.M., 2015. L-745,870 reduces the expression of abnormal involuntary movements in the 6-OHDA-lesioned rat. *Behavioural pharmacology* 26**,** 101-108.

Huot, P., Johnston, T.H., Koprich, J.B., Fox, S.H., Brotchie, J.M., 2012b. L-DOPA pharmacokinetics in the MPTP-lesioned macaque model of Parkinson's disease. *Neuropharmacology* 63**,** 829-836.

Huot, P., Johnston, T.H., Koprich, J.B., Fox, S.H., Brotchie, J.M., 2013. The pharmacology of L-DOPA-induced dyskinesia in Parkinson's disease. *Pharmacol Rev* 65**,** 171-222.

Huot, P., Johnston, T.H., Lewis, K.D., Koprich, J.B., Reyes, M.G., Fox, S.H., Piggott, M.J., Brotchie, J.M., 2011. Characterization of 3,4-methylenedioxymethamphetamine (MDMA) enantiomers in vitro and in the MPTP-lesioned primate: R-MDMA reduces severity of dyskinesia, whereas S-MDMA extends duration of ON-time. *J Neurosci* 31**,** 7190-7198.

Huot, P., Johnston, T.H., Lewis, K.D., Koprich, J.B., Reyes, M.G., Fox, S.H., Piggott, M.J., Brotchie, J.M., 2014. UWA-121, a mixed dopamine and serotonin re-uptake inhibitor, enhances L-DOPA anti-parkinsonian action without worsening dyskinesia or psychosis-like behaviours in the MPTP-lesioned common marmoset. *Neuropharmacology* 82**,** 76-87.

Hurley, M.J., Mash, D.C., Jenner, P., 2001. Dopamine D(1) receptor expression in human basal ganglia and changes in Parkinson's disease. *Brain Res Mol Brain Res* 87**,** 271-279.

Hwang, D.Y., Ardayfio, P., Kang, U.J., Semina, E.V., Kim, K.S., 2003. Selective loss of dopaminergic neurons in the substantia nigra of Pitx3-deficient aphakia mice. *Brain Res Mol Brain Res* 114**,** 123-131.

Hwang, D.Y., Fleming, S.M., Ardayfio, P., Moran-Gates, T., Kim, H., Tarazi, F.I., Chesselet, M.F., Kim, K.S., 2005. 3,4-dihydroxyphenylalanine reverses the motor deficits in Pitx3-deficient aphakia mice: behavioral characterization of a novel genetic model of Parkinson's disease. *J Neurosci* 25**,** 2132-2137.

Hwang, W.J., Calne, D.B., Tsui, J.K., de la Fuente-Fernandez, R., 2001. The long-term response to levodopa in dopa-responsive dystonia. *Parkinsonism Relat Disord* 8**,** 1-5.

Iaccarino, G., Rockman, H.A., Shotwell, K.F., Tomhave, E.D., Koch, W.J., 1998. Myocardial overexpression of GRK3 in transgenic mice: evidence for in vivo selectivity of GRKs. *Am. J. Physiol.* 275**,** 1298-1306.

Iderberg, H., Francardo, V., Pioli, E.Y., 2012. Animal models of L-DOPA-induced dyskinesia: an update on the current options. *Neuroscience* 211**,** 13-27.

Iderberg, H., Maslava, N., Thompson, A., Bubser, M., Niswender, C., Hopkins, C., Lindsley, C., Conn, P., Jones, C., Cenci, M., 2015a. Pharmacological stimulation of metabotropic glutamate receptor type 4 in a rat model of Parkinson's disease and

L-DOPA-induced dyskinesia: comparison between a positive allosteric modulator and an orthosteric agonist. *submitted*.

Iderberg, H., McCreary, A.C., Varney, M.A., Cenci, M.A., Newman-Tancredi, A., 2015b. Activity of serotonin 5-HT receptor 'biased agonists' in rat models of Parkinson's disease and l-DOPA-induced dyskinesia. *Neuropharmacology* 93C**,** 52-67.

Iderberg, H., McCreary, A.C., Varney, M.A., Kleven, M.S., Koek, W., Bardin, L., Depoortere, R., Cenci, M.A., Newman-Tancredi, A., 2015c. NLX-112, a novel 5-HT receptor agonist for the treatment of L-DOPA-induced dyskinesia: Behavioral and neurochemical profile in rat. *Exp Neurol*.

Imbert, C., Bezard, E., Guitraud, S., Boraud, T., Gross, C.E., 2000. Comparison between eight clinical rating scales used for the assessment of MPTP-induced parkinsonism in the macaque monkey. *J. Neurosci. Meth.* 96**,** 71-76.

Ingham, C.A., Hood, S.H., Arbuthnott, G.W., 1989. Spine density on neostriatal neurones changes with 6-hydroxydopamine lesions and with age. *Brain Res* 503**,** 334-338.

Ingham, C.A., Hood, S.H., Taggart, P., Arbuthnott, G.W., 1998. Plasticity of synapses in the rat neostriatum after unilateral lesion of the nigrostriatal dopaminergic pathway. *J Neurosci* 18**,** 4732-4743.

Isacson, O., Riche, D., Hantraye, P., Sofroniew, M.V., Maziere, M., 1989. A primate model of Huntington's disease: cross-species implantation of striatal precursor cells to the excitotoxically lesioned baboon caudate-putamen. *Experimental brain research* 75**,** 213-220.

Iwata, Y., Irie, S., Uchida, H., Suzuki, T., Watanabe, K., Iwashita, S., Mimura, M., 2012. Effects of zonisamide on tardive dyskinesia: a preliminary open-label trial. *Journal of the neurological sciences* 315**,** 137-140.

Jan, C., Pessiglione, M., Tremblay, L., Tande, D., Hirsch, E.C., Francois, C., 2003. Quantitative analysis of dopaminergic loss in relation to functional territories in MPTP-treated monkeys. *Eur J Neurosci* 18**,** 2082-2086.

Jarraya, B., Boulet, S., Ralph, G.S., Jan, C., Bonvento, G., Azzouz, M., Miskin, J.E., Shin, M., Delzescaux, T., Drouot, X., Herard, A.S., Day, D.M., Brouillet, E., Kingsman, S.M., Hantraye, P., Mitrophanous, K.A., Mazarakis, N.D., Palfi, S., 2009. Dopamine gene therapy for Parkinson's disease in a nonhuman primate without associated dyskinesia. *Sci Transl Med* 1**,** 2ra4.

Jenck, F., Moreau, J.L., Martin, J.R., Kilpatrick, G.J., Reinscheid, R.K., Monsma, F.J., Jr., Nothacker, H.P., Civelli, O., 1997. Orphanin FQ acts as an anxiolytic to attenuate behavioral responses to stress. *Proc Natl Acad Sci U S A* 94**,** 14854-14858.

Jenner, P., 2003. The contribution of the MPTP-treated primate model to the development of new treatment strategies for Parkinson's disease. . *Parkinsonism Relat. Disord.* 9**,** 7.

Jenner, P., 2008. Molecular mechanisms of L-DOPA-induced dyskinesia. *Nature reviews. Neuroscience* 9**,** 665-677.

Jenner, P., Rupniak, N.M., Rose, S., Kelly, E., Kilpatrick, G., Lees, A., Marsden, C.D., 1984. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in the common marmoset. *Neurosci Lett* 50**,** 85-90.

Johansson, P.A., Andersson, M., Andersson, K.E., Cenci, M.A., 2001. Alterations in cortical and basal ganglia levels of opioid receptor binding in a rat model of l-DOPA-induced dyskinesia. *Neurobiol Dis* 8**,** 220-239.

Johnson, P.S., Madden, G.J., Brewer, A.T., Pinkston, J.W., Fowler, S.C., 2011. Effects of acute pramipexole on preference for gambling-like schedules of reinforcement in rats. *Psychopharmacology (Berl)* 213**,** 11-18.

Johnson, P.S., Madden, G.J., Stein, J.S., 2012. Effects of acute pramipexole on male rats' preference for gambling-like rewards II. *Experimental and clinical psychopharmacology* 20**,** 167-172.

Johnston, T.H., Fox, S.H., McIldowie, M.J., Piggott, M.J., Brotchie, J.M., 2010a. Reduction of L-DOPA-induced dyskinesia by the selective metabotropic glutamate receptor 5 antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned macaque model of Parkinson's disease. *J Pharmacol Exp Ther* 333**,** 865-873.

Johnston, T.H., Huot, P., Fox, S.H., Koprich, J.B., Szeliga, K.T., James, J.W., Graef, J.D., Letchworth, S.R., Jordan, K.G., Hill, M.P., Brotchie, J.M., 2013. TC-8831, a nicotinic acetylcholine receptor agonist, reduces l-DOPA-induced dyskinesia in the MPTP macaque. *Neuropharmacology*.

Johnston, T.H., Huot, P., Fox, S.H., Wakefield, J.D., Sykes, K.A., Bartolini, W.P., Milne, G.T., Pearson, J.P., Brotchie, J.M., 2011. Fatty acid amide hydrolase (FAAH) inhibition reduces L-3,4-dihydroxyphenylalanine-induced hyperactivity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned non-human primate model of

Parkinson's disease. *The Journal of pharmacology and experimental therapeutics* 336**,** 423-430.

Johnston, T.H., Lee, J., Gomez-Ramirez, J., Fox, S.H., Brotchie, J.M., 2005. A simple rodent assay for the in vivo identification of agents with potential to reduce levodopa-induced dyskinesia in Parkinson's disease. *Exp Neurol* 191**,** 243-250.

Johnston, T.H., van der Meij, A., Brotchie, J.M., Fox, S.H., 2010b. Effect of histamine H2 receptor antagonism on levodopa-induced dyskinesia in the MPTP-macaque model of Parkinson's disease. *Mov Disord* 25**,** 1379-1390.

Jones, N., Bleickardt, C., Mullins, D., Parker, E., Hodgson, R., 2013. A2A receptor antagonists do not induce dyskinesias in drug-naive or L-dopa sensitized rats. *Brain Res Bull* 98**,** 163-169.

Jonkers, N., Sarre, S., Ebinger, G., Michotte, Y., 2002. MK801 suppresses the L-DOPA-induced increase of glutamate in striatum of hemi-Parkinson rats. *Brain Res* 926**,** 149-155.

Joyce, J.N., 1991. Differential response of striatal dopamine and muscarinic cholinergic receptor subtypes to the loss of dopamine. I. Effects of intranigral or intracerebroventricular 6-hydroxydopamine lesions of the mesostriatal dopamine system. *Exp Neurol* 113**,** 261-276.

Juncos, J.L., Fabbrini, G., Mouradian, M.M., Serrati, C., Chase, T.N., 1987. Dietary influences on the antiparkinsonian response to levodopa. *Arch Neurol* 44**,** 1003-1005.

Juranyi, Z., Sziray, N., Marko, B., Levay, G., Harsing, L.G., Jr., 2004. AMPA receptor blockade potentiates the stimulatory effect of L-DOPA on dopamine release in dopamine-deficient corticostriatal slice preparation. *Critical reviews in neurobiology* 16**,** 129-139.

Kaiser, S., Wonnacott, S., 2000. alpha-bungarotoxin-sensitive nicotinic receptors indirectly modulate [(3)H]dopamine release in rat striatal slices via glutamate release. *Mol Pharmacol* 58**,** 312-318.

Kannari, K., Yamato, H., Shen, H., Tomiyama, M., Suda, T., Matsunaga, M., 2001. Activation of 5-HT(1A) but not 5-HT(1B) receptors attenuates an increase in extracellular dopamine derived from exogenously administered L-DOPA in the striatum with nigrostriatal denervation. *J Neurochem* 76**,** 1346-1353.

Kaplan, N., Vituri, A., Korczyn, A.D., Cohen, O.S., Inzelberg, R., Yahalom, G., Kozlova, E., Milgrom, R., Laitman, Y., Friedman, E., Rosset, S., Hassin-Baer, S., 2014. Sequence Variants in SLC6A3, DRD2, and BDNF Genes and Time to Levodopa-Induced Dyskinesias in Parkinson's Disease. *Journal of molecular neuroscience : MN*.

Kaplan, S.L., 1994. A Self-Rated Scale for Obsessive-Compulsive Disorder. *Journal of clinical psychology* 50**,** 564-574.

Katayama, Y., Oshima, H., Kano, T., Kobayashi, K., Fukaya, C., Yamamoto, T., 2006. Direct effect of subthalamic nucleus stimulation on levodopa-induced peak-dose dyskinesia in patients with Parkinson's disease. *Stereotactic and functional neurosurgery* 84**,** 176-179.

Katzenschlager, R., Head, J., Schrag, A., Ben-Shlomo, Y., Evans, A., Lees, A.J., Parkinson's Disease Research Group of the United, K., 2008. Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD. *Neurology* 71**,** 474-480.

Katzenschlager, R., Manson, A.J., Evans, A., Watt, H., Lees, A.J., 2004. Low dose quetiapine for drug induced dyskinesias in Parkinson's disease: a double blind cross over study. *J Neurol Neurosurg Psychiatry* 75**,** 295-297.

Katzenschlager, R., Sampaio, C., Costa, J., Lees, A., 2003. Anticholinergics for symptomatic management of Parkinson's disease. *The Cochrane database of systematic reviews***,** CD003735.

Kayadjanian, N., Schofield, W.N., Andren, J., Sirinathsinghji, D.J., Besson, M.J., 1999. Cortical and nigral deafferentation and striatal cholinergic markers in the rat dorsal striatum: different effects on the expression of mRNAs encoding choline acetyltransferase and muscarinic m1 and m4 receptors. *Eur J Neurosci* 11**,** 3659-3668.

Kim, E., Sheng, M., 2004. PDZ domain proteins of synapses. *Nature reviews. Neuroscience* 5**,** 771-781.

Kim, J., Ahn, S., Ren, X.R., Whalen, E.J., Reiter, E., Wei, H., Lefkowitz, R.J., 2005. Functional antagonism of different G protein-coupled receptor kinases for beta-arrestin-mediated angiotensin II receptor signaling. *Proc. Nat. Acad. Sci. USA* 102**,** 142-1447.

Kim, K.M., Valenzano, K.J., Robinson, S.R., Yao, W.D., Barak, L.S., Caron, M.G., 2001. Differential regulation of the dopamine D2 and D3 receptors by G protein-coupled receptor kinases and beta-arrestins. *J. Biol. Chem.* 276**,** 37409-37414.

Kishima, H., Poyot, T., Bloch, J., Dauguet, J., Conde, F., Dolle, F., Hinnen, F., Pralong, W., Palfi, S., Deglon, N., Aebischer, P., Hantraye, P., 2004. Encapsulated GDNF-producing C2C12 cells for Parkinson's disease: a pre-clinical study in chronic MPTP-treated baboons. *Neurobiol. Dis.* 16**,** 428-439.

Kisilevsky, A.E., Mulligan, S.J., Altier, C., Iftinca, M.C., Varela, D., Tai, C., Chen, L., Hameed, S., Hamid, J., Macvicar, B.A., Zamponi, G.W., 2008. D1 receptors physically interact with N-type calcium channels to regulate channel distribution and dendritic calcium entry. *Neuron* 58**,** 557-570.

Kleedorfer, B., Lees, A.J., Stern, G.M., 1991. Buspirone in the treatment of levodopa induced dyskinesias. *J Neurol Neurosurg Psychiatry* 54**,** 376-377.

Klemann, C.J., Roubos, E.W., 2011. The gray area between synapse structure and function-Gray's synapse types I and II revisited. *Synapse* 65**,** 1222-1230.

Klintenberg, R., Andren, P.E., 2005. Altered extracellular striatal in vivo biotransformation of the opioid neuropeptide dynorphin A(1-17) in the unilateral 6-OHDA rat model of Parkinson's disease. *Journal of mass spectrometry : JMS* 40**,** 261-270.

Klos, K.J., Bower, J.H., Josephs, K.A., Matsumoto, J.Y., Ahlskog, J.E., 2005. Pathological hypersexuality predominantly linked to adjuvant dopamine agonist therapy in Parkinson's disease and multiple system atrophy. *Parkinsonism Relat Disord* 11**,** 381-386.

Ko, J.H., Lerner, R.P., Eidelberg, D., 2015. Effects of levodopa on regional cerebral metabolism and blood flow. *Mov Disord* 30**,** 54-63.

Ko, W.K., Li, Q., Bezard, E., 2014a. Effects of L-tryptophan on L-DOPA-induced dyskinesia in the L-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaque model of Parkinson's disease. *Neurosci Lett* 566**,** 72-76.

Ko, W.K., Martin-Negrier, M.L., Bezard, E., Crossman, A.R., Ravenscroft, P., 2014b. RGS4 is involved in the generation of abnormal involuntary movements in the unilateral 6-OHDA-lesioned rat model of Parkinson's disease. *Neurobiol Dis* 70**,** 138-148.

Ko, W.K., Pioli, E., Li, Q., McGuire, S., Dufour, A., Sherer, T.B., Bezard, E., Facheris, M.F., 2014c. Combined fenobam and amantadine treatment promotes robust

antidyskinetic effects in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primate model of Parkinson's disease. *Mov Disord* 29**,** 772-779.

Kobylecki, C., Cenci, M.A., Crossman, A.R., Ravenscroft, P., 2010. Calcium-permeable AMPA receptors are involved in the induction and expression of l-DOPA-induced dyskinesia in Parkinson's disease. *J Neurochem* 114**,** 499-511.

Kobylecki, C., Crossman, A.R., Ravenscroft, P., 2013. Alternative splicing of AMPA receptor subunits in the 6-OHDA-lesioned rat model of Parkinson's disease and L-DOPA-induced dyskinesia. *Exp Neurol* 247**,** 476-484.

Kobylecki, C., Hill, M.P., Crossman, A.R., Ravenscroft, P., 2011. Synergistic antidyskinetic effects of topiramate and amantadine in animal models of Parkinson's disease. *Mov Disord* 26**,** 2354-2363.

Koffarnus, M.N., Newman, A.H., Grundt, P., Rice, K.C., Woods, J.H., 2011. Effects of selective dopaminergic compounds on a delay-discounting task. *Behavioural pharmacology* 22**,** 300-311.

Konitsiotis, S., Blanchet, P.J., Verhagen, L., Lamers, E., Chase, T.N., 2000. AMPA receptor blockade improves levodopa-induced dyskinesia in MPTP monkeys. *Neurology* 54**,** 1589-1595.

Konradi, C., Westin, J.E., Carta, M., Eaton, M.E., Kuter, K., Dekundy, A., Lundblad, M., Cenci, M.A., 2004. Transcriptome analysis in a rat model of L-DOPA-induced dyskinesia. *Neurobiol Dis* 17**,** 219-236.

Koob, G.F., Le Moal, M., 1997. Drug abuse: hedonic homeostatic dysregulation. *Science* 278**,** 52-58.

Koprich, J.B., Fox, S.H., Johnston, T.H., Goodman, A., Le Bourdonnec, B., Dolle, R.E., DeHaven, R.N., DeHaven-Hudkins, D.L., Little, P.J., Brotchie, J.M., 2011. The selective mu-opioid receptor antagonist ADL5510 reduces levodopa-induced dyskinesia without affecting antiparkinsonian action in MPTP-lesioned macaque model of Parkinson's disease. *Mov Disord* 26**,** 1225-1233.

Koprich, J.B., Huot, P., Fox, S.H., Jarvie, K., Lang, A.E., Seeman, P., Brotchie, J.M., 2013. The effects of fast-off-D2 receptor antagonism on L-DOPA-induced dyskinesia and psychosis in parkinsonian macaques. *Progress in neuro-psychopharmacology & biological psychiatry* 43**,** 151-156.

Kordower, J.H., Herzog, C.D., Dass, B., Bakay, R.A., Stansell, J., 3rd, Gasmi, M., Bartus, R.T., 2006. Delivery of neurturin by AAV2 (CERE-120)-mediated gene transfer

provides structural and functional neuroprotection and neurorestoration in MPTP-treated monkeys. *Ann Neurol* 60**,** 706-715.

Kovoor, A., Seyffarth, P., Ebert, J., Barghshoon, S., Chen, C.-K., Schwarz, S., Axelrod, J.D., Cheyette, B.N.R., Simon, M.I., Lester, H.A., Schwarz, J., 2005. D2 dopamine receptors colocalize regulator of G-protein signaling 9-2 (RGS9-2) via the RGS9 DEP domain, and RGS9 knock-out mice develop dyskinesias associated with dopamine pathways. *J. Neurosci.* 25**,** 2157-2165.

Krack, P., Batir, A., Van Blercom, N., Chabardes, S., Fraix, V., Ardouin, C., Koudsie, A., Limousin, P.D., Benazzouz, A., LeBas, J.F., Benabid, A.L., Pollak, P., 2003. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *The New England journal of medicine* 349**,** 1925-1934.

Krack, P., Hamel, W., Mehdorn, H.M., Deuschl, G., 1999. Surgical treatment of Parkinson's disease. *Curr Opin Neurol* 12**,** 417-425.

Krack, P., Limousin, P., Benabid, A.L., Pollak, P., 1997. Chronic stimulation of subthalamic nucleus improves levodopa-induced dyskinesias in Parkinson's disease. *Lancet* 350**,** 1676.

Krawczyk, M., Georges, F., Sharma, R., Mason, X., Berthet, A., Bezard, E., Dumont, E.C., 2011. Double-dissociation of the catecholaminergic modulation of synaptic transmission in the oval bed nucleus of the stria terminalis. *Journal of neurophysiology* 105**,** 145-153.

Krawczyk, M., Mason, X., Debacker, J., Sharma, R., Normandeau, C.P., Hawken, E.R., Di Prospero, C., Chiang, C., Martinez, A., Jones, A.A., Doudnikoff, E., Caille, S., Bezard, E., Georges, F., Dumont, E.C., 2013. D1 Dopamine Receptor-Mediated LTP at GABA Synapses Encodes Motivation to Self-Administer Cocaine in Rats. *J Neurosci* 33**,** 11960-11971.

Kreitzer, A.C., Malenka, R.C., 2008. Neuron. 60, 543-554., 2008. Striatal plasticity and basal ganglia circuit function. . *Neuron* 60**,** 12.

Krispel, C.M., Chen, D., Melling, N., Chen, Y.J., Martemyanov, K.A., Quillinan, N., Arshavsky, V.Y., Wensel, T.G., Chen, C.K., Burns, M.E., 2006. RGS expression rate-limits recovery of rod photoresponses. *Neuron* 51**,** 409-416.

Krupnick, J.G., Gurevich, V.V., Benovic, J.L., 1997. Mechanism of quenching of phototransduction. Binding competition between arrestin and transducin for phosphorhodopsin. *J Biol Chem* 272**,** 18125-18131.

Kubo, T., Yue, J.L., Goshima, Y., Nakamura, S., Misu, Y., 1992. Evidence for L-dopa systems responsible for cardiovascular control in the nucleus tractus solitarii of the rat. *Neuroscience letters* 140**,** 153-156.

Kultima, K., Scholz, B., Alm, H., Skold, K., Svensson, M., Crossman, A.R., Bezard, E., Andren, P.E., Lonnstedt, I., 2006. Normalization and expression changes in predefined sets of proteins using 2D gel electrophoresis: a proteomic study of L-DOPA induced dyskinesia in an animal model of Parkinson's disease using DIGE. *BMC Bioinformatics* 7**,** 475.

Kumar, N., Van Gerpen, J.A., Bower, J.H., Ahlskog, J.E., 2005. Levodopa-dyskinesia incidence by age of Parkinson's disease onset. *Mov Disord* 20**,** 342-344.

Kumar, R., Hauser, R.A., Mostillo, J., Dronamraju, N., Graf, A., Merschhemke, M., Kenney, C., 2013. Mavoglurant (AFQ056) in combination with increased levodopa dosages in Parkinson's disease patients. *The International journal of neuroscience*.

Kumar, R., Riddle, L., Griffin, S.A., Grundt, P., Newman, A.H., Luedtke, R.R., 2009a. Evaluation of the D3 dopamine receptor selective antagonist PG01037 on L-dopa-dependent abnormal involuntary movements in rats. *Neuropharmacology* 56**,** 944-955.

Kumar, R., Riddle, L.R., Griffin, S.A., Chu, W., Vangveravong, S., Neisewander, J., Mach, R.H., Luedtke, R.R., 2009b. Evaluation of D2 and D3 dopamine receptor selective compounds on L-dopa-dependent abnormal involuntary movements in rats. *Neuropharmacology* 56**,** 956-969.

Kuoppamaki, M., Al-Barghouthy, G., Jackson, M.J., Smith, L.A., Quinn, N., Jenner, P., 2007. L-dopa dose and the duration and severity of dyskinesia in primed MPTP-treated primates. *J Neural Transm* 114**,** 1147-1153.

Ladepeche, L., Dupuis, J.P., Bouchet, D., Doudnikoff, E., Yang, L., Campagne, Y., Bezard, E., Hosy, E., Groc, L., 2013a. Single-molecule imaging of the functional crosstalk between surface NMDA and dopamine D1 receptors. *Proc Natl Acad Sci U S A* 110**,** 18005-18010.

Ladepeche, L., Dupuis, J.P., Groc, L., 2014. Surface trafficking of NMDA receptors: Gathering from a partner to another. *Semin Cell Dev Biol* 27C**,** 3-13.

Ladepeche, L., Yang, L., Bouchet, D., Groc, L., 2013b. Regulation of Dopamine D1 Receptor Dynamics within the Postsynaptic Density of Hippocampal Glutamate Synapses. *PLoS One* 8**,** e74512.

Lai, A., Parameswaran, N., Khwaja, M., Whiteaker, P., Lindstrom, J.M., Fan, H., McIntosh, J.M., Grady, S.R., Quik, M., 2005. Long-term nicotine treatment decreases striatal alpha6* nicotinic acetylcholine receptor sites and function in mice. *Mol Pharmacol* 67**,** 1639-1647.

Laloux, C., Derambure, P., Houdayer, E., Jacquesson, J.M., Bordet, R., Destee, A., Monaca, C., 2008. Effect of dopaminergic substances on sleep/wakefulness in saline- and MPTP-treated mice. *J Sleep Res* 17**,** 101-110.

Lanahan, A., Worley, P., 1998. Immediate-early genes and synaptic function. . *Neurobiol.Learn.Mem.* 70**,** 7.

Lane, E.L., Cheetham, S.C., Jenner, P., 2006. Does contraversive circling in the 6-OHDA-lesioned rat indicate an ability to induce motor complications as well as therapeutic effects in Parkinson's disease? . *Exp. Neurol.* 197**,** 7.

Lane, E.L., Vercammen, L., Cenci, M.A., Brundin, P., 2009. Priming for L-DOPA-induced abnormal involuntary movements increases the severity of amphetamine-induced dyskinesia in grafted rats. *Exp Neurol* 219**,** 355-358.

Lane, E.L., Winkler, C., Brundin, P., Cenci, M.A., 2006. The impact of graft size on the development of dyskinesia following intrastriatal grafting of embryonic dopamine neurons in the rat. *Neurobiol Dis* 22**,** 334-345.

Langston, J.W., Ballard, P., 1984. Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): implications for treatment and the pathogenesis of Parkinson's disease. *Can. J. Neurol. Sci.* 11**,** 160-165.

Langston, J.W., Ballard, P.A., Tetrud, J.W., Irwin, I., 1983. Chronic parkinsonism in human due to a product of meperidine analog synthesis. *Science* 219**,** 979-980.

Langston, J.W., Forno, L.S., Rebert, C.S., Irwin, I., 1984a. Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl 1-1,2,3,6, tetrahydropyridine (MPTP) in the squirrel monkey. *Brain Res.* 292**,** 390-394.

Langston, J.W., Forno, L.S., Rebert, C.S., Irwin, I., 1984b. Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyrine (MPTP) in the squirrel monkey. *Brain Res* 292**,** 390-394.

Langston, J.W., Quik, M., Petzinger, G., Jakowec, M., Di Monte, D.A., 2000. Investigating levodopa-induced dyskinesias in the Parkinsonian primate. *Ann. Neurol.* 47**,** S79-S89.

Laporte, S.A., Oakley, R.H., Zhang, J., Holt, J.A., Ferguson, s.S.G., Caron, M.G., Barak, L.S., 1999. The 2-adrenergic receptor/arrestin complex recruits the clathrin adaptor AP-2 during endocytosis. *Proc. Natl. Acad. Sci. USA* 96**,** 3712-3717.

Law, P.Y., Wong, Y.H., Loh, H.H., 2000. Molecular mechanisms and regulation of opioid receptor signaling. *Annu Rev Pharmacol Toxicol* 40**,** 389-430.

Lawrence, A.D., Evans, A.H., Lees, A.J., 2003. Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? *Lancet Neurol* 2**,** 595-604.

Le Moine, C., Bloch, B., 1995. D1 and D2 dopamine receptor gene expression in the rat striatum: sensitive cRNA probes demonstrate prominent segregation of D1 and D2 mRNAs in distinct neuronal populations of the dorsal and ventral striatum. *J. Comp. Neurol.* 355**,** 418-426.

Lebel, M., Chagniel, L., Bureau, G., Cyr, M., 2010. Striatal inhibition of PKA prevents levodopa-induced behavioural and molecular changes in the hemiparkinsonian rat. *Neurobiol Dis* 38**,** 59-67.

Ledo, F., Carrion, A.M., Link, W.A., Mellstrom, B., Naranjo, J.R., 2000. DREAM-alphaCREM interaction via leucine-charged domains derepresses downstream regulatory element-dependent transcription. *Molecular and cellular biology* 20**,** 9120-9126.

Lee, C.S., Cenci, M.A., Schulzer, M., Bjorklund, A., 2000a. Embryonic ventral mesencephalic grafts improve levodopa-induced dyskinesia in a rat model of Parkinson's disease. *Brain* 123 (Pt 7)**,** 1365-1379.

Lee, C.S., Samii, A., Sossi, V., Ruth, T.J., Schulzer, M., Holden, J.E., Wudel, J., Pal, P.K., de la Fuente-Fernandez, R., Calne, D.B., Stoessl, A.J., 2000b. In vivo positron emission tomographic evidence for compensatory changes in presynaptic dopaminergic nerve terminals in Parkinson's disease. *Ann Neurol* 47**,** 493-503.

Lee, F.J., Xue, S., Pei, L., Vukusic, B., Chery, N., Wang, Y., Wang, Y.T., Niznik, H.B., Yu, X.M., Liu, F., 2002. Dual regulation of NMDA receptor functions by direct protein-protein interactions with the dopamine D1 receptor. *Cell* 111**,** 219-230.

Lee, J.I., Verhagen Metman, L., Ohara, S., Dougherty, P.M., Kim, J.H., Lenz, F.A., 2007. Internal pallidal neuronal activity during mild drug-related dyskinesias in Parkinson's disease: decreased firing rates and altered firing patterns. *Journal of neurophysiology* 97**,** 2627-2641.

Lee, J.Y., Cho, J., Lee, E.K., Park, S.S., Jeon, B.S., 2011. Differential genetic susceptibility in diphasic and peak-dose dyskinesias in Parkinson's disease. *Mov Disord* 26**,** 73-79.

Leenders, K.L., Aquilonius, S.M., Bergstrom, K., Bjurling, P., Crossman, A.R., Eckernas, S.A., Gee, A.G., Hartvig, P., Lundqvist, H., Langstrom, B., et al., 1988. Unilateral MPTP lesion in a rhesus monkey: effects on the striatal dopaminergic system measured in vivo with PET using various novel tracers. *Brain Res* 445**,** 61-67.

Lees, A.J., 1994. Levodopa substitution: the gold standard. *Clin. Neuropharmacol.* 17**,** S1-S6.

Lees, G.J., Stern, G.M., 1983. Sustained low-dose levodopa therapy in Parkinson's disease: a 3-year follow-up. *Adv. Neurol.* 37**,** 9-15.

Lefkowitz, R.J., Shenoy, S.K., 2005. Transduction of receptor signals by beta-arrestins. *Science* 308**,** 512-517.

Lenoir, M., Augier, E., Vouillac, C., Ahmed, S.H., 2013. A choice-based screening method for compulsive drug users in rats. *Current protocols in neuroscience / editorial board, Jacqueline N. Crawley ... [et al.]* Chapter 9**,** Unit 9 44.

Leranth, C., Sladek, J.R.J., Roth, R.H., Redmond, D.E.J., 1998. Efferent synaptic connections of dopaminergic neurons grafted into the caudate nucleus of experimentally induced parkinsonian monkeys are different from those of control animals. *Experimental brain research* 123**,** 323-333.

Lerner, T.N., Kreitzer, A.C., 2012. RGS4 is required for dopaminergic control of striatal LTD and susceptibility to parkinsonian motor deficits. *Neuron* 73**,** 347-359.

Lesage, S., Belarbi, S., Troiano, A., Condroyer, C., Hecham, N., Pollak, P., Lohman, E., Benhassine, T., Ysmail-Dahlouk, F., Durr, A., Tazir, M., Brice, A., French Parkinson's Disease Genetics Study, G., 2008. Is the common LRRK2 G2019S mutation related to dyskinesias in North African Parkinson disease? *Neurology* 71**,** 1550-1552.

Leskov, I.B., Klenchin, V.A., Handy, J.W., Whitlock, G.G., Govardovskii, V.I., Bownds, M.D., Lamb, T.D., Pugh, E.N.J., Arshavsky, V.Y., 2000. The gain of rod phototransduction: reconciliation of biochemical and electrophysiological measurements. *Neuron* 27**,** 525-537.

Lesser, R.P., Fahn, S., Snider, S.R., Cote, L.J., Isgreen, W.P., Barrett, R.E., 1979. Analysis of the clinical problems in parkinsonism and the complications of long-term levodopa therapy. *Neurology* 19**,** 1253-1260.

Levy, R., Dostrovsky, J.O., Lang, A.E., Sime, E., Hutchison, W.D., Lozano, A.M., 2001. Effects of apomorphine on subthalamic nucleus and globus pallidus internus neurons in patients with Parkinson's disease. *Journal of neurophysiology* 86**,** 249-260.

LeWitt, P.A., 2014. Levodopa therapy for Parkinson's disease: Pharmacokinetics and pharmacodynamics. *Mov Disord*.

Lewitt, P.A., Ellenbogen, A., Chen, D., Lal, R., McGuire, K., Zomorodi, K., Luo, W., Huff, F.J., 2012a. Actively transported levodopa prodrug XP21279: a study in patients with Parkinson disease who experience motor fluctuations. *Clin Neuropharmacol* 35**,** 103-110.

LeWitt, P.A., Guttman, M., Tetrud, J.W., Tuite, P.J., Mori, A., Chaikin, P., Sussman, N.M.-U.-S.G., 2008. Adenosine A2A receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). *Ann. Neurol.* 63**,** 8.

Lewitt, P.A., Hauser, R.A., Lu, M., Nicholas, A.P., Weiner, W., Coppard, N., Leinonen, M., Savola, J.M., 2012b. Randomized clinical trial of fipamezole for dyskinesia in Parkinson disease (FJORD study). *Neurology* 79**,** 163-169.

LeWitt, P.A., Huff, F.J., Hauser, R.A., Chen, D., Lissin, D., Zomorodi, K., Cundy, K.C., 2014. Double-blind study of the actively transported levodopa prodrug XP21279 in Parkinson's disease. *Mov Disord* 29**,** 75-82.

Leyton, M., Boileau, I., Benkelfat, C., Diksic, M., Baker, G., Dagher, A., 2002. Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 27**,** 1027-1035.

Li, L., Carter, J., Gao, X., Whitehead, J., Tourtellotte, W.G., 2005a. The neuroplasticity-associated arc gene is a direct transcriptional target of early growth response (Egr) transcription factors. *Molecular and cellular biology* 25**,** 10286-10300.

Li, L., Zhou, F.M., 2013. Parallel dopamine D1 receptor activity dependence of l-Dopa-induced normal movement and dyskinesia in mice. . *Neuroscience.* 236**,** 11.

Li, W., Cui, Y., Kushner, S.A., Brown, R.A., Jentsch, J.D., Frankland, P.W., Cannon, T.D., Silva, A.J., 2005b. The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis type 1. *Curr Biol* 15**,** 1961-1967.

Lieberman, A., Goodgold, A., Jonas, S., Leibowitz, M., 1975. Comparison of dopa decarboxylase inhibitor (carbidopa) combined with levodopa and levodopa alone in Parkinson's disease. *Neurology* 25**,** 911-916.

Lieberman, A.N., Goodgold, A.L., Goldstein, M., 1972. Treatment failures with levodopa in Parkinsonism. *Neurology* 22**,** 1205-1210.

Liggett, S.B., 2011. Phosphorylation barcoding as a mechanism of directing GPCR signaling. *Sci Signal* 4**,** pe36.

Liggins, J., Pihl, R.O., Benkelfat, C., Leyton, M., 2012. The dopamine augmenter L-DOPA does not affect positive mood in healthy human volunteers. *PLoS One* 7**,** e28370.

Lim, S.A., Kang, U.J., McGehee, D.S., 2014. Striatal cholinergic interneuron regulation and circuit effects. *Frontiers in synaptic neuroscience* 6**,** 22.

Lim, S.A., Xia, R., Ding, Y., Won, L., Ray, W.J., Hitchcock, S.A., McGehee, D.S., Kang, U.J., 2015. Enhanced histamine H2 excitation of striatal cholinergic interneurons in L-DOPA-induced dyskinesia. *Neurobiol. Dis.* 76**,** 67-76.

Linazasoro, G., 1994. Anticholinergics and dyskinesia. *Mov Disord* 9**,** 689.

Linazasoro, G., Antonini, A., Maguire, R.P., Leenders, K.L., 2004. Pharmacological and PET studies in patient's with Parkinson's disease and a short duration-motor response: implications in the pathophysiology of motor complications. *J Neural Transm* 111**,** 497-509.

Lindenbach, D., Palumbo, N., Ostock, C.Y., Vilceus, N., Conti, M.M., Bishop, C., 2015. Side effect profile of 5-HT treatments for Parkinson's disease and L-DOPA-induced dyskinesia in rats. *British journal of pharmacology* 172**,** 119-130.

Lindgren, H.S., Andersson, D.R., Lagerkvist, S., Nissbrandt, H., Cenci, M.A., 2010. L-DOPA-induced dopamine efflux in the striatum and the substantia nigra in a rat model of Parkinson's disease: temporal and quantitative relationship to the expression of dyskinesia. *J Neurochem* 112**,** 1465-1476.

Lindgren, H.S., Ohlin, K.E., Cenci, M.A., 2009. Differential involvement of D1 and D2 dopamine receptors in L-DOPA-induced angiogenic activity in a rat model of Parkinson's disease. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 34**,** 2477-2488.

Lindgren, H.S., Rylander, D., Ohlin, K.E., Lundblad, M., Cenci, M.A., 2007. The "motor complication syndrome" in rats with 6-OHDA lesions treated chronically with L-

DOPA: relation to dose and route of administration. *Behav Brain Res* 177**,** 150-159.

Little, S., Pogosyan, A., Kuhn, A.A., Brown, P., 2012. beta band stability over time correlates with Parkinsonian rigidity and bradykinesia. *Exp Neurol* 236**,** 383-388.

Lober, R.M., Pereira, M.A., Lambert, N.A., 2006. Rapid activation of inwardly rectifying potassium channels by immobile G-protein-coupled receptors. *J Neurosci* 26**,** 12602-12608.

Lobo, M.K., Zaman, S., Damez-Werno, D.M., Koo, J.W., Bagot, R.C., Dinieri, J.A., Nugent, A., Finkel, E., Chaudhury, D., Chandra, R., Riberio, E., Rabkin, J., Mouzon, E., Cachope, R., Cheer, J.F., Han, M.H., Dietz, D.M., Self, D.W., Hurd, Y.L., Vialou, V., Nestler, E.J., 2013. DeltaFosB Induction in Striatal Medium Spiny Neuron Subtypes in Response to Chronic Pharmacological, Emotional, and Optogenetic Stimuli. *J Neurosci* 33**,** 18381-18395.

Lohmann, E., Thobois, S., Lesage, S., Broussolle, E., du Montcel, S.T., Ribeiro, M.J., Remy, P., Pelissolo, A., Dubois, B., Mallet, L., Pollak, P., Agid, Y., Brice, A., French Parkinson's Disease Genetics Study, G., 2009. A multidisciplinary study of patients with early-onset PD with and without parkin mutations. *Neurology* 72**,** 110-116.

Lohse, M.J., Andexinger, S., Pitcher, J., Trukawinski, S., Codina, J., Faure, J.P., Caron, M.G., Lefkowitz, R.J., 1992. Receptor-specific desensitization with purified proteins. Kinase dependence and receptor specificity of beta-arrestin and arrestin in the beta 2-adrenergic receptor and rhodopsin systems. *J Biol Chem* 267**,** 8558-8564.

Lohse, M.J., Benovic, J.L., Codina, J., Caron, M.G., Lefkowitz, R.J., 1990. beta-Arrestin: a protein that regulates beta-adrenergic receptor function. *Science* 248**,** 1547-1550.

Lopez, S., Bonito-Oliva, A., Pallottino, S., Acher, F., Fisone, G., 2011. Activation of metabotropic glutamate 4 receptors decreases L-DOPA-induced dyskinesia in a mouse model of Parkinson's disease. *Journal of Parkinson's disease* 1**,** 339-346.

Lopez-Azcarate, J., Tainta, M., Rodriguez-Oroz, M.C., Valencia, M., Gonzalez, R., Guridi, J., Iriarte, J., Obeso, J.A., Artieda, J., Alegre, M., 2010. Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. *J Neurosci* 30**,** 6667-6677.

Lozano, A.M., Lang, A.E., Levy, R., Hutchison, W., Dostrovsky, J., 2000. Neuronal recordings in Parkinson's disease patients with dyskinesias induced by apomorphine. *Ann Neurol* 47**,** S141-146.

Lukins, T.R., Tisch, S., Jonker, B., 2014. The latest evidence on target selection in deep brain stimulation for Parkinson's disease. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia* 21**,** 22-27.

Lundblad, M., Andersson, M., Winkler, C., Kirik, D., Wierup, N., Cenci, M.A., 2002. Pharmacological validation of behavioural measures of akinesia and dyskinesia in a rat model of Parkinson's disease. *Eur J Neurosci* 15**,** 120-132.

Lundblad, M., Picconi, B., Lindgren, H., Cenci, M.A., 2004. A model of L-DOPA-induced dyskinesia in 6-hydroxydopamine lesioned mice: relation to motor and cellular parameters of nigrostriatal function. *Neurobiol. Dis.* 16**,** 110-123.

Lundblad, M., Usiello, A., Carta, M., Hakansson, K., Fisone, G., Cenci, M.A., 2005. Pharmacological validation of a mouse model of l-DOPA-induced dyskinesia. *Exp Neurol* 194**,** 66-75.

Lundblad, M., Vaudano, E., Cenci, M.A., 2003. Cellular and behavioural effects of the adenosine A2a receptor antagonist KW-6002 in a rat model of l-DOPA-induced dyskinesia. *J. Neurochem.* 84**,** 1398-1410.

Luttrell, L.M., Ferguson, S.S., Daaka, Y., Miller, W.E., Maudsley, S., Della Rocca, G.J., Lin, F., Kawakatsu, H., Owada, K., Luttrell, D.K., Caron, M.G., Lefkowitz, R.J., 1999. Beta-arrestin-dependent formation of beta2 adrenergic receptor-Src protein kinase complexes. *Science* 283**,** 655-661.

Lyons, K.E., Pahwa, R., 2006. Efficacy and tolerability of levetiracetam in Parkinson disease patients with levodopa-induced dyskinesia. *Clin Neuropharmacol* 29**,** 148-153.

Ma, H., Deacon, S., Horiuchi, K., 2008. The challenge of selecting protein kinase assays for lead discovery optimization. *Expert Opin Drug Discov* 3**,** 607-621.

Ma, Y., Feigin, A., Dhawan, V., Fukuda, M., Shi, Q., Greene, P., Breeze, R., Fahn, S., Freed, C., Eidelberg, D., 2002. Dyskinesia after fetal cell transplantation for parkinsonism: a PET study. *Ann Neurol* 52**,** 628-634.

Madden, G.J., Johnson, P.S., Brewer, A.T., Pinkston, J.W., Fowler, S.C., 2010. Effects of pramipexole on impulsive choice in male wistar rats. *Experimental and clinical psychopharmacology* 18**,** 267-276.

Mahalik, T.J., Finger, T.E., Stromberg, I., Olson, L., 1985. Substantia nigra transplants into denervated striatum of the rat: ultrastructure of graft and host interconnections. *J Comp Neurology* 240**,** 60-70.

Malmlof, T., Rylander, D., Alken, R.G., Schneider, F., Svensson, T.H., Cenci, M.A., Schilstrom, B., 2010. Deuterium substitutions in the L-DOPA molecule improve its anti-akinetic potency without increasing dyskinesias. *Exp Neurol* 225**,** 408-415.

Manago, F., Espinoza, S., Salahpour, A., Sotnikova, T.D., Caron, M.G., Premont, R.T., Gainetdinov, R.R., 2012. The role of GRK6 in animal models of Parkinson's disease and L-DOPA treatment. *Scientific reports* 2**,** 301.

Mangiavacchi, S., Wolf, M.E., 2004. D1 dopamine receptor stimulation increases the rate of AMPA receptor insertion onto the surface of cultured nucleus accumbens neurons through a pathway dependent on protein kinase A. *J. Neurochem.* 88**,** 1261-1271.

Mango, D., Bonito-Oliva, A., Ledonne, A., Cappellacci, L., Petrelli, R., Nistico, R., Berretta, N., Fisone, G., Mercuri, N.B., 2014. Adenosine A1 receptor stimulation reduces D1 receptor-mediated GABAergic transmission from striato-nigral terminals and attenuates l-DOPA-induced dyskinesia in dopamine-denervated mice. *Exp Neurol* 261**,** 733-743.

Manson, A.J., Iakovidou, E., Lees, A.J., 2000a. Idazoxan is ineffective for levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 15**,** 336-337.

Manson, A.J., Schrag, A., Lees, A.J., 2000b. Low-dose olanzapine for levodopa induced dyskinesias. *Neurology* 55**,** 795-799.

Mansour, A., Fox, C.A., Burke, S., Meng, F., Thompson, R.C., Akil, H., Watson, S.J., 1994. Mu, delta, and kappa opioid receptor mRNA expression in the rat CNS: an in situ hybridization study. *The Journal of comparative neurology* 350**,** 412-438.

Maranis, S., Stamatis, D., Tsironis, C., Konitsiotis, S., 2012. Investigation of the antidyskinetic site of action of metabotropic and ionotropic glutamate receptor antagonists. Intracerebral infusions in 6-hydroxydopamine-lesioned rats with levodopa-induced dyskinesia. *Eur J Pharmacol* 683**,** 71-77.

Maratos, E.C., Jackson, M.J., Pearce, R.K., Jenner, P., 2001. Antiparkinsonian activity and dyskinesia risk of ropinirole and L-DOPA combination therapy in drug naive MPTP-lesioned common marmosets (Callithrix jacchus). *Mov. Disord.* 16**,** 631-641.

Marcellino, D., Ferre, S., Casado, V., Cortes, A., Le Foll, B., Mazzola, C., Drago, F., Saur, O., Stark, H., Soriano, A., Barnes, C., Goldberg, S.R., Lluis, C., Fuxe, K., Franco, R., 2008. Identification of dopamine D1-D3 receptor heteromers. Indications for a role of synergistic D1-D3 receptor interactions in the striatum. *J Biol Chem* 283**,** 26016-26025.

Maries, E., Kordower, J.H., Chu, Y., Collier, T.J., Sortwell, C.E., Olaru, E., Shannon, K., Steece-Collier, K., 2006. Focal not widespread grafts induce novel dyskinetic behavior in parkinsonian rats. *Neurobiol Dis* 21**,** 165-180.

Marsden, C.D., Parkes, J.D., Quinn, N. 1982. Fluctuations of disability in Parkinson's disease - clinical aspects. In: *Movement disorders*. pp. 96-122. Eds. C.D. Marsden, S. Fahn. Butterworth: London.

Marshall, J.F., Navarrete, R., Joyce, J.N., 1989. Decreased striatal D1 binding density following mesotelencephalic 6-hydroxydopamine injections: an autoradiographic analysis. *Brain Res* 493**,** 247-257.

Marti, M., Mela, F., Fantin, M., Zucchini, S., Brown, J.M., Witta, J., Di Benedetto, M., Buzas, B., Reinscheid, R.K., Salvadori, S., Guerrini, R., Romualdi, P., Candeletti, S., Simonato, M., Cox, B.M., Morari, M., 2005. Blockade of nociceptin/orphanin FQ transmission attenuates symptoms and neurodegeneration associated with Parkinson's disease. *J Neurosci* 25**,** 9591-9601.

Marti, M., Mela, F., Guerrini, R., Calo, G., Bianchi, C., Morari, M., 2004a. Blockade of nociceptin/orphanin FQ transmission in rat substantia nigra reverses haloperidol-induced akinesia and normalizes nigral glutamate release. *J Neurochem* 91**,** 1501-1504.

Marti, M., Mela, F., Veronesi, C., Guerrini, R., Salvadori, S., Federici, M., Mercuri, N.B., Rizzi, A., Franchi, G., Beani, L., Bianchi, C., Morari, M., 2004b. Blockade of nociceptin/orphanin FQ receptor signaling in rat substantia nigra pars reticulata stimulates nigrostriatal dopaminergic transmission and motor behavior. *J Neurosci* 24**,** 6659-6666.

Marti, M., Rodi, D., Li, Q., Guerrini, R., Fasano, S., Morella, I., Tozzi, A., Brambilla, R., Calabresi, P., Simonato, M., Bezard, E., Morari, M., 2012. Nociceptin/orphanin FQ receptor agonists attenuate L-DOPA-induced dyskinesias. *J Neurosci* 32**,** 16106-16119.

Marti, M., Sarubbo, S., Latini, F., Cavallo, M., Eleopra, R., Biguzzi, S., Lettieri, C., Conti, C., Simonato, M., Zucchini, S., Quatrale, R., Sensi, M., Candeletti, S., Romualdi, P., Morari, M., 2010. Brain interstitial nociceptin/orphanin FQ levels are elevated in Parkinson's disease. *Mov Disord* 25**,** 1723-1732.

Marti, M., Trapella, C., Viaro, R., Morari, M., 2007. The nociceptin/orphanin FQ receptor antagonist J-113397 and L-DOPA additively attenuate experimental parkinsonism through overinhibition of the nigrothalamic pathway. *J Neurosci* 27**,** 1297-1307.

Marti, M., Viaro, R., Guerrini, R., Franchi, G., Morari, M., 2009. Nociceptin/orphanin FQ modulates motor behavior and primary motor cortex output through receptors located in substantia nigra reticulata. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 34**,** 341-355.

Mazzucchi, S., Frosini, D., Ripoli, A., Nicoletti, V., Linsalata, G., Bonuccelli, U., Ceravolo, R., 2014. Serotonergic antidepressant drugs and L-dopa-induced dyskinesias in Parkinson's disease. *Acta Neurol Scand*.

McClung, C.A., Ulery, P.G., Perrotti, L.I., Zachariou, V., Berton, O., Nestler, E.J., 2004. DeltaFosB: a molecular switch for long-term adaptation in the brain. *Brain Res Mol Brain Res* 132**,** 146-154.

McElroy, S.L., Keck, P.E., Jr., Pope, H.G., Jr., Smith, J.M., Strakowski, S.M., 1994. Compulsive buying: a report of 20 cases. *The Journal of clinical psychiatry* 55**,** 242-248.

McNeill, T.H., Brown, S.A., Rafols, J.A., Shoulson, I., 1988. Atrophy of medium spiny I striatal dendrites in advanced Parkinson's disease. *Brain Res* 455**,** 148-152.

Meier, J., Vannier, C., Serge, A., Triller, A., Choquet, D., 2001. Fast and reversible trapping of surface glycine receptors by gephyrin. *Nature neuroscience* 4**,** 253-260.

Meissner, W., Leblois, A., Hansel, D., Bioulac, B., Gross, C.E., Benazzouz, A., Boraud, T., 2005. Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. *Brain* 128**,** 2372-2382.

Meissner, W., Ravenscroft, P., Reese, R., Harnack, D., Morgenstern, R., Kupsch, A., Klitgaard, H., Bioulac, B., Gross, C.E., Bezard, E., Boraud, T., 2006. Increased slow oscillatory activity in substantia nigra pars reticulata triggers abnormal involuntary movements in the 6-OHDA-lesioned rat in the presence of excessive extracellular striatal dopamine. *Neurobiol Dis* 22**,** 586-598.

Meissner, W.G., Frasier, M., Gasser, T., Goetz, C.G., Lozano, A., Piccini, P., Obeso, J.A., Rascol, O., Schapira, A., Voon, V., Weiner, D.M., Tison, F., Bezard, E., 2011. Priorities in Parkinson's disease research. *Nat Rev Drug Discov* 10**,** 377-393.

Mela, F., Marti, M., Bido, S., Cenci, M.A., Morari, M., 2012. In vivo evidence for a differential contribution of striatal and nigral D1 and D2 receptors to L-DOPA induced dyskinesia and the accompanying surge of nigral amino acid levels. *Neurobiol Dis* 45**,** 573-582.

Mela, F., Marti, M., Dekundy, A., Danysz, W., Morari, M., Cenci, M.A., 2007. Antagonism of metabotropic glutamate receptor type 5 attenuates l-DOPA-induced dyskinesia and its molecular and neurochemical correlates in a rat model of Parkinson's disease. *J Neurochem* 101**,** 483-497.

Mellone, M., Gardoni, F., 2013. Modulation of NMDA receptor at the synapse: Promising therapeutic interventions in disorders of the nervous system. *Eur J Pharmacol* 719**,** 75-83.

Melnikova, I., Golden, J., 2004. Targeting protein kinases. *Nat Rev Drug Discov* 3**,** 993-994.

Menard, L., Ferguson, S.S., Zhang, J., Lin, F.T., Lefkowitz, R.J., Caron, M.G., Barak, L.S., 1997. Synergistic regulation of beta2-adrenergic receptor sequestration: intracellular complement of beta-adrenergic receptor kinase and beta-arrestin determine kinetics of internalization. *Mol. Pharmacol.* 51**,** 800-808.

Merello, M., Balej, J., Delfino, M., Cammarota, A., Betti, O., Leiguarda, R., 1999a. Apomorphine induces changes in GPi spontaneous outflow in patients with Parkinson's disease. *Mov Disord* 14**,** 45-49.

Merello, M., Nouzeilles, M.I., Cammarota, A., Leiguarda, R., 1999b. Effect of memantine (NMDA antagonist) on Parkinson's disease: a double-blind crossover randomized study. *Clin Neuropharmacol* 22**,** 273-276.

Merims, D., Shabtai, H., Korczyn, A.D., Peretz, C., Weizman, N., Giladi, N., 2004. Antiparkinsonian medication is not a risk factor for the development of hallucinations in Parkinson's disease. *Journal of neural transmission* 111**,** 1447-1453.

Merims, D., Ziv, I., Djaldetti, R., Melamed, E., 1999. Riluzole for levodopa-induced dyskinesias in advanced Parkinson's disease. *Lancet* 353**,** 1764-1765.

Merola, A., Zibetti, M., Artusi, C.A., Rizzi, L., Angrisano, S., Lanotte, M., Lopiano, L., Rizzone, M.G., 2013. 80 Hz versus 130 Hz subthalamic nucleus deep brain stimulation: effects on involuntary movements. *Parkinsonism Relat Disord* 19**,** 453-456.

Mestre, T.A., Shah, B.B., Connolly, B.S., de Aquino, C., Al Dhakeel, A., Walsh, R., Ghate, T., Lui, J.P., Fox, S.H., 2014. Famotidine, a histamine h2 receptor antagonist, does not reduce levodopa-induced dyskinesia in parkinson's disease: a proof-of-concept study. *Mov Disord Clinical Practice* 1.

Metman, L.V., Del Dotto, P., LePoole, K., Konitsiotis, S., Fang, J., Chase, T.N., 1999. Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. *Arch Neurol* 56**,** 1383-1386.

Meunier, J.C., Mollereau, C., Toll, L., Suaudeau, C., Moisand, C., Alvinerie, P., Butour, J.L., Guillemot, J.C., Ferrara, P., Monsarrat, B., et al., 1995. Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. *Nature* 377**,** 532-535.

Micallef-Roll, J., Rihet, P., Hasbroucq, T., Possamai, C., Blin, O., 2001. Levodopa-induced drowsiness in healthy volunteers: results of a choice reaction time test combined with a subjective evaluation of sedation. *Clinical neuropharmacology* 24**,** 91-94.

Miguelez, C., Aristieta, A., Cenci, M.A., Ugedo, L., 2011. The locus coeruleus is directly implicated in L-DOPA-induced dyskinesia in parkinsonian rats: an electrophysiological and behavioural study. *PLoS One* 6**,** e24679.

Millar, N.S., Gotti, C., 2009. Diversity of vertebrate nicotinic acetylcholine receptors. *Neuropharmacology* 56**,** 237-246.

Mink, J.W., 1996. The basal ganglia: focused selection and inhibition of competing motor programs. *Progress in neurobiology* 50**,** 381-425.

Mishina, M., Ishiwata, K., Naganawa, M., Kimura, Y., Kitamura, S., Suzuki, M., Hashimoto, M., Ishibashi, K., Oda, K., Sakata, M., Hamamoto, M., Kobayashi, S., Katayama, Y., Ishii, K., 2011. Adenosine A(2A) receptors measured with [C]TMSX PET in the striata of Parkinson's disease patients. *PLoS One* 6**,** e17338.

Misu, Y., Yue, J.L., Goshima, Y., 1995. L-DOPA systems for blood pressure regulation in the lower brainstem. *Neuroscience research* 23**,** 147-158.

Mitchell, I.J., Boyce, S., Sambrook, M.A., Crossman, A.R., 1992. A 2-deoxyglucose study of the effects of dopamine agonists on the parkinsonian primate brain. Implications

for the neural mechanisms that mediate dopamine agonist-induced dyskinesia. *Brain* 115**,** 809-824.

Mitchell, I.J., Carroll, C.B., 1997. Reversal of parkinsonian symptoms in primates by antagonism of excitatory amino acid transmission: potential mechanisms of action. *Neurosci Biobehav Rev* 21**,** 469-475.

Mitchell, I.J., Clarke, C.E., Boyce, S., Robertson, R.G., Peggs, D., Sambrook, M.A., Crossman, A.R., 1989. Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Neuroscience* 32**,** 213-226.

Mitchell, I.J., Cross, A.J., Sambrook, M.A., Crossman, A.R., 1985. Sites of the neurotoxic action of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the macaque monkey include the ventral tegmental area and the locus coeruleus. *Neurosci Lett* 61**,** 195-200.

Mitchell, I.J., Hughes, N., Carroll, C.B., Brotchie, J.M., 1995. Reversal of parkinsonian symptoms by intrastriatal and systemic manipulations of excitatory amino acid and dopamine transmission in the bilateral 6-OHDA lesioned marmoset. *Behavioural pharmacology* 6**,** 492-507.

Miwa, H., Koh, J., Kajimoto, Y., Kondo, T., 2011. Effects of T-type calcium channel blockers on a parkinsonian tremor model in rats. *Pharmacology, biochemistry, and behavior* 97**,** 656-659.

Miyasaki, J.M., Al Hassan, K., Lang, A.E., Voon, V., 2007. Punding prevalence in Parkinson's disease. *Mov Disord* 22**,** 1179-1181.

Mizuno, Y., Hasegawa, K., Kondo, T., Kuno, S., Yamamoto, M., Group., J.I.S., 2010. Clinical efficacy of istradefylline (KW-6002) in Parkinson's disease: a randomized, controlled study. . *Mov. Disord.* 25**,** 7.

Mogil, J.S., Pasternak, G.W., 2001. The molecular and behavioral pharmacology of the orphanin FQ/nociceptin peptide and receptor family. *Pharmacol Rev* 53**,** 381-415.

Mollereau, C., Parmentier, M., Mailleux, P., Butour, J.L., Moisand, C., Chalon, P., Caput, D., Vassart, G., Meunier, J.C., 1994. Orl1, a Novel Member of the Opioid Receptor Family - Cloning, Functional Expression and Localization. *Febs Lett* 341**,** 33-38.

Mons, N., Cooper, D.M., 1994. Selective expression of one Ca(2+)-inhibitable adenylyl cyclase in dopaminergically innervated rat brain regions. *Brain Res Mol Brain Res* 22**,** 236-244.

Moreau, C., Delval, A., Tiffreau, V., Defebvre, L., Dujardin, K., Duhamel, A., Petyt, G., Hossein-Foucher, C., Blum, D., Sablonniere, B., Schraen, S., Allorge, D., Destee, A., Bordet, R., Devos, D., 2013. Memantine for axial signs in Parkinson's disease: a randomised, double-blind, placebo-controlled pilot study. *J Neurol Neurosurg Psychiatry* 84**,** 552-555.

Morelli, M., De Montis, G., Di Chiara, G., 1990a. Changes in the D1 receptor-adenylate cyclase complex after priming. *Eur. J. Pharmacol.* 180**,** 13.

Morelli, M., Di Chiara, G., 1987. Agonist-induced homologous and heterologous sensitization to D-1- and D-2-dependent contraversive turning. *Eur J Pharmacol* 141**,** 101-107.

Morelli, M., Di Chiara, G., 1990b. Stereospecific blockade of N-methyl-D-aspartate transmission by MK 801 prevents priming of SKF 38393-induced turning. . *Psychopharmacology* 101**,** 2.

Morelli, M., Fenu, S., Garau, L., Di Chiara, G., 1989. Time and dose dependence of the 'priming' of the expression of dopamine receptor supersensitivity. *Eur J Pharmacol* 162**,** 329-335.

Morelli, M., Fenu, S., Pinna, A., Cozzolino, A., Carta, A., Di Chiara, G., 1993. "Priming" to dopamine agonist-induced contralateral turning as a model of non-associative sensitization to the expression of the post-synaptic dopamine message. . *Behav. Pharmacol.* 4**,** 9.

Morin, N., Gregoire, L., Gomez-Mancilla, B., Gasparini, F., Di Paolo, T., 2010. Effect of the metabotropic glutamate receptor type 5 antagonists MPEP and MTEP in parkinsonian monkeys. *Neuropharmacology* 58**,** 981-986.

Morin, N., Jourdain, V.A., Di Paolo, T., 2013. Modeling dyskinesia in animal models of Parkinson disease. *Exp Neurol*.

Morin, N., Morissette, M., Grégoire, L., Gomez-Mancilla, B., Gasparini, F., Di Paolo, T., 2013. 73, 216-231., 2013. Chronic treatment with MPEP, an mGlu5 receptor antagonist, normalizes basal ganglia glutamate neurotransmission in L-DOPA-treated parkinsonian monkeys. . *Neuropharmacology.* 73**,** 16.

Morissette, M., Goulet, M., Soghomonian, J.J., Blanchet, P.J., Calon, F., Bédard, P.J., Di Paolo, T., 1997. Preproenkephalin mRNA expression in the caudate-putamen of MPTP monkeys after chronic treatment with the D2 agonist U91356A in continuous or

intermittent mode of administration: comparison with L-DOPA therapy. *Brain Res. Mol. Brain Res.* 49**,** 55-62.

Morissette, M., Grondin, R., Goulet, M., Bédard, P.J., Di Paolo, T., 1999. Differential regulation of striatal preproenkephalin and preprotachykinin mRNA levels in MPTP-lesioned monkeys chronically treated with dopamine D1 or D2 receptor agonists. *Journal of Neurochemistry* 72**,** 682-692.

Moro, E., Lozano, A.M., Pollak, P., Agid, Y., Rehncrona, S., Volkmann, J., Kulisevsky, J., Obeso, J.A., Albanese, A., Hariz, M.I., Quinn, N.P., Speelman, J.D., Benabid, A.L., Fraix, V., Mendes, A., Welter, M.L., Houeto, J.L., Cornu, P., Dormont, D., Tornqvist, A.L., Ekberg, R., Schnitzler, A., Timmermann, L., Wojtecki, L., Gironell, A., Rodriguez-Oroz, M.C., Guridi, J., Bentivoglio, A.R., Contarino, M.F., Romito, L., Scerrati, M., Janssens, M., Lang, A.E., 2010. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. *Mov Disord* 25**,** 578-586.

Morrison, K.J., Moore, R.H., Carsrud, N.D., Trial, J., Millman, E.E., Tuvim, M., Clark, R.B., Barber, R., Dickey, B.F., Knoll, B.J., 1996. Repetitive endocytosis and recycling of the beta 2-adrenergic receptor during agonist-induced steady state redistribution. *Mol Pharmacol* 50**,** 692-699.

Mosharov, E.V., Borgkvist, A., Sulzer, D., 2015. Presynaptic effects of levodopa and their possible role in dyskinesia. *Mov Disord* 30**,** 45-53.

Mounayar, S., Boulet, S., Tande, D., Jan, C., Pessiglione, M., Hirsch, E.C., Feger, J., Savasta, M., Francois, C., Tremblay, L., 2007. A new model to study compensatory mechanisms in MPTP-treated monkeys exhibiting recovery. *Brain* 130**,** 2898-2914.

Muller, S., Walter, H., Christen, M., 2013. When benefitting a patient increases the risk for harm for third persons - The case of treating pedophilic Parkinsonian patients with deep brain stimulation. *International journal of law and psychiatry*.

Munoz, A., Carlsson, T., Tronci, E., Kirik, D., Bjorklund, A., Carta, M., 2009. Serotonin neuron-dependent and -independent reduction of dyskinesia by 5-HT1A and 5-HT1B receptor agonists in the rat Parkinson model. *Exp Neurol* 219**,** 298-307.

Munoz, A., Garrido-Gil, P., Dominguez-Meijide, A., Labandeira-Garcia, J.L., 2014. Angiotensin type 1 receptor blockage reduces l-dopa-induced dyskinesia in the 6-

OHDA model of Parkinson's disease. Involvement of vascular endothelial growth factor and interleukin-1beta. *Exp Neurol* 261**,** 720-732.

Munoz, A., Li, Q., Gardoni, F., Marcello, E., Qin, C., Carlsson, T., Kirik, D., Di Luca, M., Bjorklund, A., Bezard, E., Carta, M., 2008. Combined 5-HT1A and 5-HT1B receptor agonists for the treatment of L-DOPA-induced dyskinesia. *Brain* 131**,** 3380-3394.

Murata, M., Hasegawa, K., Kanazawa, I., 2007. Zonisamide improves motor function in Parkinson disease: a randomized, double-blind study. *Neurology* 68**,** 45-50.

Mushegian, A., Gurevich, V.V., Gurevich, E.V., 2012. The Origin and Evolution of G Protein-Coupled Receptor Kinases. *PLoS One* 7**,** e33806.

Myllyla, V.V., Kultalahti, E.R., Haapaniemi, H., Leinonen, M., Group, F.S., 2001. Twelve-month safety of entacapone in patients with Parkinson's disease. *European journal of neurology : the official journal of the European Federation of Neurological Societies* 8**,** 53-60.

Nadjar, A., Brotchie, J.M., Guigoni, C., Li, Q., Zhou, S.B., Wang, G.J., Ravenscroft, P., Georges, F., Crossman, A.R., Bezard, E., 2006. Phenotype of striatofugal medium spiny neurons in parkinsonian and dyskinetic nonhuman primates: a call for a reappraisal of the functional organization of the basal ganglia. *J Neurosci* 26**,** 8653-8661.

Nadjar, A., Gerfen, C.R., Bezard, E., 2009. Priming for l-dopa-induced dyskinesia in Parkinson's disease: a feature inherent to the treatment or the disease? *Progress in neurobiology* 87**,** 1-9.

Nahimi, A., Holtzermann, M., Landau, A.M., Simonsen, M., Jakobsen, S., Alstrup, A.K., Vang, K., Moller, A., Wegener, G., Gjedde, A., Doudet, D.J., 2012. Serotonergic modulation of receptor occupancy in rats treated with L-DOPA after unilateral 6-OHDA lesioning. *J Neurochem* 120**,** 806-817.

Nai, Q., Li, S., Wang, S.H., Liu, J., Lee, F.J., Frankland, P.W., Liu, F., 2010. Uncoupling the D1-N-methyl-D-aspartate (NMDA) receptor complex promotes NMDA-dependent long-term potentiation and working memory. *Biol Psychiatry* 67**,** 246-254.

Nambu, A., 2008. Seven problems on the basal ganglia. *Curr Opin Neurobiol* 18**,** 595-604.

Nardone, R., De Blasi, P., Holler, Y., Christova, M., Tezzon, F., Trinka, E., Brigo, F., 2014. Repetitive transcranial magnetic stimulation transiently reduces punding in Parkinson's disease: a preliminary study. *J Neural Transm* 121**,** 267-274.

Nash, J.E., Fox, S.H., Henry, B., Hill, M.P., Peggs, D., McGuire, S., Maneuf, Y., Hille, C., Brotchie, J.M., Crossman, A.R., 2000. Antiparkinsonian actions of ifenprodil in the MPTP-lesioned marmoset model of Parkinson's disease. *Exp. Neurol.* 165**,** 136-142.

Nash, J.E., Johnston, T.H., Collingridge, G.L., Garner, C.C., Brotchie, J.M., 2005. Subcellular redistribution of the synapse-associated proteins PSD-95 and SAP97 in animal models of Parkinson's disease and L-DOPA-induced dyskinesia. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 19**,** 583-585.

Nash, J.E., Ravenscroft, P., McGuire, S., Crossman, A.R., Menniti, F.S., Brotchie, J.M., 2004. The NR2B-selective NMDA receptor antagonist CP-101,606 exacerbates L-DOPA-induced dyskinesia and provides mild potentiation of anti-parkinsonian effects of L-DOPA in the MPTP-lesioned marmoset model of Parkinson's disease. *Exp Neurol* 188**,** 471-479.

Navailles, S., Benazzouz, A., Bioulac, B., Gross, C., De Deurwaerdere, P., 2010a. High-frequency stimulation of the subthalamic nucleus and L-3,4-dihydroxyphenylalanine inhibit in vivo serotonin release in the prefrontal cortex and hippocampus in a rat model of Parkinson's disease. *J Neurosci* 30**,** 2356-2364.

Navailles, S., Bioulac, B., Gross, C., De Deurwaerdere, P., 2010b. Serotonergic neurons mediate ectopic release of dopamine induced by L-DOPA in a rat model of Parkinson's disease. *Neurobiol Dis* 38**,** 136-143.

Navailles, S., Bioulac, B., Gross, C., De Deurwaerdere, P., 2011a. Chronic L-DOPA therapy alters central serotonergic function and L-DOPA-induced dopamine release in a region-dependent manner in a rat model of Parkinson's disease. *Neurobiol Dis* 41**,** 585-590.

Navailles, S., Carta, M., Guthrie, M., De Deurwaerdere, P., 2011b. L-DOPA and serotonergic neurons: functional implication and therapeutic perspectives in Parkinson's disease. *Central nervous system agents in medicinal chemistry* 11**,** 305-320.

Navailles, S., De Deurwaerdere, P., 2012. Imbalanced Dopaminergic Transmission Mediated by Serotonergic Neurons in L-DOPA-Induced Dyskinesia. *Parkinson's disease* 2012**,** 323686.

Navailles, S., Lagiere, M., Contini, A., De Deurwaerdere, P., 2013. Multisite intracerebral microdialysis to study the mechanism of L-DOPA induced dopamine and serotonin release in the parkinsonian brain. *ACS chemical neuroscience* 4**,** 680-692.

Neal, C.R., Jr., Mansour, A., Reinscheid, R., Nothacker, H.P., Civelli, O., Akil, H., Watson, S.J., Jr., 1999a. Opioid receptor-like (ORL1) receptor distribution in the rat central nervous system: comparison of ORL1 receptor mRNA expression with (125)I-[(14)Tyr]-orphanin FQ binding. *The Journal of comparative neurology* 412**,** 563-605.

Neal, C.R., Jr., Mansour, A., Reinscheid, R., Nothacker, H.P., Civelli, O., Watson, S.J., Jr., 1999b. Localization of orphanin FQ (nociceptin) peptide and messenger RNA in the central nervous system of the rat. *The Journal of comparative neurology* 406**,** 503-547.

Neale, R., Gerhardt, S., Liebman, J.M., 1984. Effects of dopamine agonists, catecholamine depletors, and cholinergic and GABAergic drugs on acute dyskinesias in squirrel monkeys. *Psychopharmacology (Berl)* 82**,** 20-26.

Nestler, E.J., Barrot, M., Self, D.W., 2001. DeltaFosB: a sustained molecular switch for addiction. *Proc Natl Acad Sci U S A* 98**,** 11042-11046.

Nevalainen, N., Af Bjerken, S., Gerhardt, G.A., Stromberg, I., 2013a. Serotonergic nerve fibers in l-DOPA-derived dopamine release and dyskinesia. *Neuroscience* 260C**,** 73-86.

Nevalainen, N., Lundblad, M., Gerhardt, G.A., Stromberg, I., 2013b. Striatal glutamate release in L-DOPA-induced dyskinetic animals. *PLoS One* 8**,** e55706.

New, D.C., Wong, Y.H., 2002. The ORL1 receptor: molecular pharmacology and signalling mechanisms. *Neuro-Signals* 11**,** 197-212.

Nicholas, A.P., 2007. Levodopa-induced hyperactivity in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Mov Disord* 22**,** 99-104.

Nilsson, A., Falth, M., Zhang, X., Kultima, K., Skold, K., Svenningsson, P., Andren, P.E., 2009. Striatal alterations of secretogranin-1, somatostatin, prodynorphin, and cholecystokinin peptides in an experimental mouse model of Parkinson disease. *Molecular & cellular proteomics : MCP* 8**,** 1094-1104.

Nirenberg, M.J., 2013. Dopamine agonist withdrawal syndrome: implications for patient care. *Drugs & aging* 30**,** 587-592.

Nirenberg, M.J., Waters, C., 2006. Compulsive eating and weight gain related to dopamine agonist use. *Mov Disord* 21**,** 524-529.

Nisbet, A.P., Foster, O.J., Kingsbury, A., Eve, D.J., Daniel, S.E., Marsden, C.D., Lees, A.J., 1995. Preproenkephalin and preprotachykinin messenger RNA expression in normal human basal ganglia and in Parkinson's disease. *Neuroscience* 66**,** 361-376.

Nishijima, H., Suzuki, S., Kon, T., Funamizu, Y., Ueno, T., Haga, R., Suzuki, C., Arai, A., Kimura, T., Suzuki, C., Meguro, R., Miki, Y., Yamada, J., Migita, K., Ichinohe, N., Ueno, S., Baba, M., Tomiyama, M., 2014. Morphologic changes of dendritic spines of striatal neurons in the levodopa-induced dyskinesia model. *Mov Disord* 29**,** 336-343.

Nishioka, K., Kefi, M., Jasinska-Myga, B., Wider, C., Vilarino-Guell, C., Ross, O.A., Heckman, M.G., Middleton, L.T., Ishihara-Paul, L., Gibson, R.A., Amouri, R., Ben Yahmed, S., Ben Sassi, S., Zouari, M., El Euch, G., Farrer, M.J., Hentati, F., 2010. A comparative study of LRRK2, PINK1 and genetically undefined familial Parkinson's disease. *J Neurol Neurosurg Psychiatry* 81**,** 391-395.

Nobles, K.N., Xiao, K., Ahn, S., Shukla, A.K., Lam, C.M., Rajagopal, S., Strachan, R.T., Huang, T.Y., Bressler, E.A., Hara, M.R., Shenoy, S.K., Gygi, S.P., Lefkowitz, R.J., 2011. Distinct phosphorylation sites on the β(2)-adrenergic receptor establish a barcode that encodes differential functions of β-arrestin. *Sci Signal* 4**,** ra51.

Norton, C.S., Neal, C.R., Kumar, S., Akil, H., Watson, S.J., 2002. Nociceptin/orphanin FQ and opioid receptor-like receptor mRNA expression in dopamine systems. *The Journal of comparative neurology* 444**,** 358-368.

Nunes, I., Tovmasian, L.T., Silva, R.M., Burke, R.E., Goff, S.P., 2003. Pitx3 is required for development of substantia nigra dopaminergic neurons. *Proc Natl Acad Sci U S A* 100**,** 4245-4250.

Nutt, J.G., Fellman, J.H., 1984. Pharmacokinetics of levodopa. *Clin Neuropharmacol* 7**,** 35-49.

Nutt, J.G., Gunzler, S.A., Kirchhoff, T., Hogarth, P., Weaver, J.L., Krams, M., Jamerson, B., Menniti, F.S., Landen, J.W., 2008. Effects of a NR2B selective NMDA glutamate antagonist, CP-101,606, on dyskinesia and Parkinsonism. *Mov Disord* 23**,** 1860-1866.

Nutt, J.G., Woodward, W.R., Hammerstad, J.P., Carter, J.H., Anderson, J.L., 1984. The "on-off" phenomenon in Parkinson's disease. Relation to levodopa absorption and transport. *The New England journal of medicine* 310**,** 483-488.

Nyholm, D., Nilsson Remahl, A.I., Dizdar, N., Constantinescu, R., Holmberg, B., Jansson, R., Aquilonius, S.M., Askmark, H., 2005. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 64**,** 216-223.

O'Sullivan, S.S., Djamshidian, A., Evans, A.H., Loane, C.M., Lees, A.J., Lawrence, A.D., 2010a. Excessive hoarding in Parkinson's disease. *Mov Disord* 25**,** 1026-1033.

O'Sullivan, S.S., Evans, A.H., Quinn, N.P., Lawrence, A.D., Lees, A.J., 2010b. Reckless generosity in Parkinson's disease. *Mov Disord* 25**,** 221-223.

O'Donovan, K.J., Tourtellotte, W.G., Milbrandt, J., Baraban, J.M., 1999 The EGR family of transcription-regulatory factors: progress at the interface of molecular and systems neuroscience. . *Trends Neurosci.* 22**,** 7.

Obeso, J.A., Linazasoro, G., Guridi, J., Ramos, E., Rodriguez-Oroz, M.C., 2000. High frequency stimulation of the subthalamic nucleus and levodopa induced dyskinesias in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 68**,** 122-123.

Odekerken, V.J., van Laar, T., Staal, M.J., Mosch, A., Hoffmann, C.F., Nijssen, P.C., Beute, G.N., van Vugt, J.P., Lenders, M.W., Contarino, M.F., Mink, M.S., Bour, L.J., van den Munckhof, P., Schmand, B.A., de Haan, R.J., Schuurman, P.R., de Bie, R.M., 2013. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *Lancet Neurol* 12**,** 37-44.

Oh, J.D., Russell, D.S., Vaughan, C.L., Chase, T.N., 1998. Enhanced tyrosine phosphorylation of striatal NMDA receptor subunits: effect of dopaminergic denervation and L-DOPA administration. *Brain Res* 813**,** 150-159.

Ohlin, K.E., Francardo, V., Lindgren, H.S., Sillivan, S.E., O'Sullivan, S.S., Luksik, A.S., Vassoler, F.M., Lees, A.J., Konradi, C., Cenci, M.A., 2011. Vascular endothelial growth factor is upregulated by L-dopa in the parkinsonian brain: implications for the development of dyskinesia. *Brain* 134**,** 2339-2357.

Ohlin, K.E., Sebastianutto, I., Adkins, C.E., Lundblad, C., Lockman, P.R., Cenci, M.A., 2012. Impact of L-DOPA treatment on regional cerebral blood flow and metabolism in the basal ganglia in a rat model of Parkinson's disease. *NeuroImage* 61**,** 228-239.

Okereke, C.S., Kirby, L., Kumar, D., Cullen, E.I., Pratt, R.D., Hahne, W.A., 2004. Concurrent administration of donepezil HCl and levodopa/carbidopa in patients with Parkinson's disease: assessment of pharmacokinetic changes and safety following multiple oral doses. *British journal of clinical pharmacology* 58 Suppl 1**,** 41-49.

Okuno, H., 2011. Regulation and function of immediate-early genes in the brain: beyond neuronal activity markers. *Neuroscience research* 69**,** 175-186.

Olanow, C.W., Goetz, C.G., Kordower, J.H., Stoessl, A.J., Sossi, V., Brin, M.F., Shannon, K.M., Nauert, G.M., Perl, D.P., Godbold, J., Freeman, T.B., 2003. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Ann Neurol* 54**,** 403-414.

Olanow, C.W., Kieburtz, K., Odin, P., Espay, A.J., Standaert, D.G., Fernandez, H.H., Vanagunas, A., Othman, A.A., Widnell, K.L., Robieson, W.Z., Pritchett, Y., Chatamra, K., Benesh, J., Lenz, R.A., Antonini, A., Group, L.H.S., 2014. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. *Lancet Neurol* 13**,** 141-149.

Olanow, C.W., Kieburtz, K., Stern, M., Watts, R., Langston, J.W., Guarnieri, M., Hubble, J., Team, U.S.S., 2004. Double-blind, placebo-controlled study of entacapone in levodopa-treated patients with stable Parkinson disease. *Arch Neurol* 61**,** 1563-1568.

Olanow, C.W., Obeso, J.A., 2000. Preventing levodopa-induced dyskinesias. *Ann Neurol* 47**,** S167-176; discussion S176-168.

Olanow, C.W., Tatton, W.G., 1999. Etiology and pathogenesis of Parkinson's disease. *Annu. Rev. Neurosci.* 22**,** 123-144.

Olianas, M.C., Dedoni, S., Boi, M., Onali, P., 2008. Activation of nociceptin/orphanin FQ-NOP receptor system inhibits tyrosine hydroxylase phosphorylation, dopamine synthesis, and dopamine D(1) receptor signaling in rat nucleus accumbens and dorsal striatum. *J Neurochem* 107**,** 544-556.

Oliveri, R.L., Annesi, G., Zappia, M., Civitelli, D., Montesanti, R., Branca, D., Nicoletti, G., Spadafora, P., Pasqua, A.A., Cittadella, R., Andreoli, V., Gambardella, A., Aguglia, U., Quattrone, A., 1999. Dopamine D2 receptor gene polymorphism and the risk of levodopa-induced dyskinesias in PD. *Neurology* 53**,** 1425-1430.

Olson, W.L., Gruenthal, M., Mueller, M.E., Olson, W.H., 1997. Gabapentin for parkinsonism: a double-blind, placebo-controlled, crossover trial. *Am J Med* 102**,** 60-66.

Ondo, W.G., Dat Vuong, K., Khan, H., Atassi, F., Kwak, C., Jankovic, J., 2001. Daytime sleepiness and other sleep disorders in Parkinson's disease. *Neurology* 57**,** 1392-1396.

Ondo, W.G., Lai, D., 2008. Predictors of impulsivity and reward seeking behavior with dopamine agonists. *Parkinsonism Relat Disord* 14**,** 28-32.

Ory-Magne, F., Corvol, J.C., Azulay, J.P., Bonnet, A.M., Brefel-Courbon, C., Damier, P., Dellapina, E., Destee, A., Durif, F., Galitzky, M., Lebouvier, T., Meissner, W., Thalamas, C., Tison, F., Salis, A., Sommet, A., Viallet, F., Vidailhet, M., Rascol, O., Network, N.S.-P.C., 2014. Withdrawing amantadine in dyskinetic patients with Parkinson disease: The AMANDYSK trial. *Neurology* 82**,** 300-307.

Ostock, C.Y., Dupre, K.B., Jaunarajs, K.L., Walters, H., George, J., Krolewski, D., Walker, P.D., Bishop, C., 2011. Role of the primary motor cortex in L-Dopa-induced dyskinesia and its modulation by 5-HT1A receptor stimulation. *Neuropharmacology* 61**,** 753-760.

Ouattara, B., Gasparini, F., Morissette, M., Gregoire, L., Samadi, P., Gomez-Mancilla, B., Di Paolo, T., 2010a. Effect of L-Dopa on metabotropic glutamate receptor 5 in the brain of parkinsonian monkeys. *J Neurochem* 113**,** 715-724.

Ouattara, B., Hoyer, D., Gregoire, L., Morissette, M., Gasparini, F., Gomez-Mancilla, B., Di Paolo, T., 2010b. Changes of AMPA receptors in MPTP monkeys with levodopa-induced dyskinesias. *Neuroscience* 167**,** 1160-1167.

Oueslati, A., Sgambato-Faure, V., Melon, C., Kachidian, P., Gubellini, P., Amri, M., Kerkerian-Le Goff, L., Salin, P., 2007. High-frequency stimulation of the subthalamic nucleus potentiates L-DOPA-induced neurochemical changes in the striatum in a rat model of Parkinson's disease. *J Neurosci* 27**,** 2377-2386.

Oyama, G., Foote, K.D., Iyer, S.S., Zeilman, P., Hwynn, N., Jacobson, C.E., Malaty, I.A., Fernandez, H.H., Rodriguez, R.L., Okun, M.S., 2011. Unilateral GPi-DBS as a treatment for levodopa-induced respiratory dyskinesia in Parkinson disease. *The neurologist* 17**,** 282-285.

Padovan-Neto, F.E., Cavalcanti-Kiwiatkoviski, R., Carolino, R.O., Anselmo-Franci, J., Del Bel, E., 2015. Effects of prolonged neuronal nitric oxide synthase inhibition on the

development and expression of L-DOPA-induced dyskinesia in 6-OHDA-lesioned rats. *Neuropharmacology* 89**,** 87-99.

Pahwa, R., Lyons, K.E., Hauser, R.A., Fahn, S., Jankovic, J., Pourcher, E., Hsu, A., O'Connell, M., Kell, S., Gupta, S., Investigators, A.-P., 2014. Randomized trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease. *Parkinsonism Relat Disord* 20**,** 142-148.

Pahwa, R., Tanner, C.M., Hauser, R.A., Sethi, K., Isaacson, S., Truong, D., Struck, L., Ruby, A.E., McClure, N.L., Went, G.T., Stempien, M.J., 2015. Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (EASED Study). *Mov Disord* 30**,** 788-795.

Paille, V., Picconi, B., Bagetta, V., Ghiglieri, V., Sgobio, C., Di Filippo, M., Viscomi, M.T., Giampa, C., Fusco, F.R., Gardoni, F., Bernardi, G., Greengard, P., Di Luca, M., Calabresi, P., 2010. Distinct levels of dopamine denervation differentially alter striatal synaptic plasticity and NMDA receptor subunit composition. *J Neurosci* 30**,** 14182-14193.

Palczewski, K., Buczylko, J., Kaplan, M.W., Polans, A.S., Crabb, J.W., 1991. Mechanism of rhodopsin kinase activation. *J Biol Chem* 266**,** 12949-12955.

Palfi, S., Ferrante, R.J., Brouillet, E., Beal, M.F., Dolan, R., Guyot, M.C., Peschanski, M., Hantraye, P., 1996. Chronic 3-nitropropionic acid treatment in baboons replicates the cognitive and motor deficits of Huntington's disease. *J. Neurosci.* 16**,** 3019-3025.

Palfi, S., Gurruchaga, J.M., Ralph, G.S., Lepetit, H., Lavisse, S., Buttery, P.C., Watts, C., Miskin, J., Kelleher, M., Deeley, S., Iwamuro, H., Lefaucheur, J.P., Thiriez, C., Fenelon, G., Lucas, C., Brugieres, P., Gabriel, I., Abhay, K., Drouot, X., Tani, N., Kas, A., Ghaleh, B., Le Corvoisier, P., Dolphin, P., Breen, D.P., Mason, S., Guzman, N.V., Mazarakis, N.D., Radcliffe, P.A., Harrop, R., Kingsman, S.M., Rascol, O., Naylor, S., Barker, R.A., Hantraye, P., Remy, P., Cesaro, P., Mitrophanous, K.A., 2014. Long-term safety and tolerability of ProSavin, a lentiviral vector-based gene therapy for Parkinson's disease: a dose escalation, open-label, phase 1/2 trial. *Lancet* 383**,** 1138-1146.

Palfi, S., Riche, D., Brouillet, E., Guyot, M.C., Mary, V., Wahl, F., Peschanski, M., Stutzmann, J.M., Hantraye, P., 1997. Riluzole reduces incidence of abnormal movements but

not striatal cell death in a primate model of progressive striatal degeneration. *Exp. Neurol.* 146**,** 135-141.

Pan, L., Gurevich, E.V., Gurevich, V.V., 2003. The nature of the arrestin x receptor complex determines the ultimate fate of the internalized receptor. *J. Biol. Chem.* 278**,** 11623-11632.

Papa, S.M., Desimone, R., Fiorani, M., Oldfield, E.H., 1999. Internal globus pallidus discharge is nearly suppressed during levodopa-induced dyskinesias. *Ann Neurol* 46**,** 732-738.

Park, H.Y., Kang, Y.M., Kang, Y., Park, T.S., Ryu, Y.K., Hwang, J.H., Kim, Y.H., Chung, B.H., Nam, K.H., Kim, M.R., Lee, C.H., Han, P.L., Kim, K.S., 2014. Inhibition of Adenylyl Cyclase Type 5 Prevents l-DOPA-Induced Dyskinesia in an Animal Model of Parkinson's Disease. *J Neurosci* 34**,** 11744-11753.

Parkinson, J., 1817. *An essay on the shaking palsy*. Sherwood, Nelly and Jones: London.

Parkinson, J., 2002. An essay on the shaking palsy. 1817. *The Journal of neuropsychiatry and clinical neurosciences* 14**,** 223-236; discussion 222.

Parkinson Study, G., 2002. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol* 59**,** 1937-1943.

Parkinson Study Group, 2001. Evaluation of dyskinesias in a pilot, randomized, placebo-controlled trial of remacemide in advanced Parkinson disease. *Arch Neurol* 58**,** 1660-1668.

Parkinson Study Group, 2005. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. *Arch Neurol* 62**,** 241-248.

Patrick, G.N., Bingol, B., Weld, H.A., Schuman, E.M., 2003. Ubiquitin-mediated proteasome activity is required for agonist-induced endocytosis of GluRs. *Curr Biol* 13**,** 2073-2081.

Pavese, N., Evans, A.H., Tai, Y.F., Hotton, G., Brooks, D.J., Lees, A.J., Piccini, P., 2006. Clinical correlates of levodopa-induced dopamine release in Parkinson disease: a PET study. *Neurology* 67**,** 1612-1617.

Pavon, N., Martin, A.B., Mendialdua, A., Moratalla, R., 2006. ERK phosphorylation and FosB expression are associated with L-DOPA-induced dyskinesia in hemiparkinsonian mice. *Biol Psychiatry* 59**,** 64-74.

Pearce, R.K., 1999. L-dopa and dyskinesias in normal monkeys. *Mov Disord* 14 Suppl 1**,** 9-12.

Pearce, R.K., Banerji, T., Jenner, P., Marsden, C.D., 1998. De novo administration of ropinirole and bromocriptine induces less dyskinesia than L-dopa in the MPTP-treated marmoset. *Mov. Disord.* 13**,** 234-241.

Pearce, R.K., Heikkila, M., Linden, I.B., Jenner, P., 2001. L-Dopa induces dyskinesia in normal monkeys: behavioural and pharmacokinetic observations. *Psychopharmacology (Berl)* 156**,** 402-409.

Pearce, R.K., Jackson, M., Smith, L., Jenner, P., Marsden, C.D., 1995. Chronic L-dopa administration induces dyskinesias in the MPTP-treated common marmoset (Callithrix Jacchus). *Mov. Disord.* 10**,** 731-740.

Peluso, J., LaForge, K.S., Matthes, H.W., Kreek, M.J., Kieffer, B.L., Gaveriaux-Ruff, C., 1998. Distribution of nociceptin/orphanin FQ receptor transcript in human central nervous system and immune cells. *Journal of neuroimmunology* 81**,** 184-192.

Pessiglione, M., Guehl, D., Agid, Y., Hirsch, E.C., Feger, J., Tremblay, L., 2003. Impairment of context-adapted movement selection in a primate model of presymptomatic Parkinson's disease. *Brain* 126**,** 1392-1408.

Pezzella, F.R., Colosimo, C., Vanacore, N., Di Rezze, S., Chianese, M., Fabbrini, G., Meco, G., 2005. Prevalence and clinical features of hedonistic homeostatic dysregulation in Parkinson's disease. *Mov Disord* 20**,** 77-81.

Phelix, C.F., Liposits, Z., Paull, W.K., 1992. Monoamine innervation of bed nucleus of stria terminalis: an electron microscopic investigation. *Brain Res Bull* 28**,** 949-965.

Piccini, P., Pavese, N., Hagell, P., Reimer, J., Bjorklund, A., Oertel, W.H., Quinn, N.P., Brooks, D.J., Lindvall, O., 2005. Factors affecting the clinical outcome after neural transplantation in Parkinson's disease. *Brain* 128**,** 2977-2986.

Piccini, P., Weeks, R.A., Brooks, D.J., 1997. Alterations in opioid receptor binding in Parkinson's disease patients with levodopa-induced dyskinesias. *Ann Neurol* 42**,** 720-726.

Picciotto, M.R., Addy, N.A., Mineur, Y.S., Brunzell, D.H., 2008. It is not "either/or": Activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors related to nicotine addiction and mood. *Progress in neurobiology* 84**,** 329-342.

Picconi, B., Bagetta, V., Ghiglieri, V., Paille, V., Di Filippo, M., Pendolino, V., Tozzi, A., Giampa, C., Fusco, F.R., Sgobio, C., Calabresi, P., 2011. Inhibition of phosphodiesterases rescues striatal long-term depression and reduces levodopa-induced dyskinesia. *Brain* 134**,** 375-387.

Picconi, B., Calabresi, P., 2014. Targeting metabotropic glutamate receptors as a new strategy against levodopa-induced dyskinesia in Parkinson's disease? *Mov Disord* 29**,** 715-719.

Picconi, B., Centonze, D., Hakansson, K., Bernardi, G., Greengard, P., Fisone, G., Cenci, M.A., Calabresi, P., 2003. Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia. *Nature neuroscience* 6**,** 501-506.

Picconi, B., Gardoni, F., Centonze, D., Mauceri, D., Cenci, M.A., Bernardi, G., Calabresi, P., Di Luca, M., 2004. Abnormal Ca2+-calmodulin-dependent protein kinase II function mediates synaptic and motor deficits in experimental parkinsonism. *J Neurosci* 24**,** 5283-5291.

Picconi, B., Ghiglieri, V., Calabresi, P., 2010. L-3,4-dihydroxyphenylalanine-induced sprouting of serotonin axon terminals: A useful biomarker for dyskinesias? *Ann Neurol* 68**,** 578-580.

Picconi, B., Paille, V., Ghiglieri, V., Bagetta, V., Barone, I., Lindgren, H.S., Bernardi, G., Angela Cenci, M., Calabresi, P., 2008. l-DOPA dosage is critically involved in dyskinesia via loss of synaptic depotentiation. *Neurobiol Dis* 29**,** 327-335.

Picconi, B., Pisani, A., Barone, I., Bonsi, P., Centonze, D., Bernardi, G., Calabresi, P., 2005. Pathological synaptic plasticity in the striatum: implications for Parkinson's disease. *Neurotoxicology* 26**,** 779-783.

Pierelli, F., Adipietro, A., Soldati, G., Fattapposta, F., Pozzessere, G., Scoppetta, C., 1998. Low dosage clozapine effects on L-dopa induced dyskinesias in parkinsonian patients. *Acta Neurol Scand* 97**,** 295-299.

Pifl, C., Nanoff, C., Schingnitz, G., Schütz, W., Hornykiewicz, O., 1992a. Sensitization of dopamine-stimulated adenylyl cyclase in the striatum of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated rhesus monkeys and patients with idiopathic Parkinson's disease. *J. Neurochem.* 58**,** 1997-2004.

Pifl, C., Reither, H., Hornykiewicz, O., 1992b. Functional sensitization of striatal dopamine D1 receptors in the 6-hydroxydopamine-lesioned rat. *Brain Res.* 572**,** 87-93.

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

Pimoule, C., Schoemaker, H., Reynolds, G.P., Langer, S.Z., 1985. [3H]SCH 23390 labeled D1 dopamine receptors are unchanged in schizophrenia and Parkinson's disease. *Eur J Pharmacol* 114**,** 235-237.

Pineyro, G., Blier, P., 1999. Autoregulation of serotonin neurons: role in antidepressant drug action. *Pharmacol Rev* 51**,** 533-591.

Pinna, A., Bonaventura, J., Farre, D., Sanchez, M., Simola, N., Mallol, J., Lluis, C., Costa, G., Baqi, Y., Muller, C.E., Cortes, A., McCormick, P., Canela, E.I., Martinez-Pinilla, E., Lanciego, J.L., Casado, V., Armentero, M.T., Franco, R., 2014. L-DOPA disrupts adenosine A(2A)-cannabinoid CB(1)-dopamine D(2) receptor heteromer cross-talk in the striatum of hemiparkinsonian rats: biochemical and behavioral studies. *Exp Neurol* 253**,** 180-191.

Pinna, A., Corsi, C., Carta, A.R., Valentini, V., Pedata, F., Morelli, M., 2002. Modification of adenosine extracellular levels and adenosine A(2A) receptor mRNA by dopamine denervation. *Eur. J. Pharmacol.* 446**,** 8.

Pinna, A., Fenu, S., Morelli, M., 2001. Motor stimulant effects of the adenosine A2A receptor antagonist SCH 58261 do not develop tolerance after repeated treatments in 6-hydroxydopamine-lesioned rats. *Synapse* 39**,** 233-238.

Pinna, A., Morelli, M., Drukarch, B., Stoof, J.C., 1997. Priming of 6-hydroxydopamine-lesioned rats with L-DOPA or quinpirole results in an increase in dopamine D1 receptor-dependent cyclic AMP production in striatal tissue. *Eur. J. Pharmacol.* 331**,** 4.

Pinna, A., Pontis, S., Borsini, F., Morelli, M., 2007. Adenosine A2A receptor antagonists improve deficits in initiation of movement and sensory motor integration in the unilateral 6-hydroxydopamine rat model of Parkinson's disease. *Synapse* 61**,** 606-614.

Pioli, E.Y., Meissner, W., Sohr, R., Gross, C.E., Bezard, E., Bioulac, B.H., 2008. Differential behavioral effects of partial bilateral lesions of ventral tegmental area or substantia nigra pars compacta in rats. *Neuroscience* 153**,** 1213-1224.

Pirker, W., Tedroff, J., Ponten, H., Gunne, L., Andren, P.E., Hurd, Y.L., 2001. Coadministration of (-)-OSU6162 with l-DOPA normalizes preproenkephalin

mRNA expression in the sensorimotor striatum of primates with unilateral 6-OHDA lesions. *Exp Neurol* 169**,** 122-134.

Pisani, A., Bernardi, G., Ding, J., Surmeier, D.J., 2007. Re-emergence of striatal cholinergic interneurons in movement disorders. *Trends Neurosci* 30**,** 545-553.

Pisani, A., Bonsi, P., Centonze, D., Gubellini, P., Bernardi, G., Calabresi, P., 2003. Targeting striatal cholinergic interneurons in Parkinson's disease: focus on metabotropic glutamate receptors. *Neuropharmacology* 45**,** 45-56.

Pisani, A., Centonze, D., Bernardi, G., Calabresi, P., 2005. Striatal synaptic plasticity: implications for motor learning and Parkinson's disease. . *Mov. Disord.* 20**,** 8.

Poewe, W., Antonini, A., 2014. Novel Formulations and Modes of Delivery of Levodopa. *Mov Disord*.

Poewe, W.H., Deuschl, G., Gordin, A., Kultalahti, E.R., Leinonen, M., Celomen Study, G., 2002. Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). *Acta Neurol Scand* 105**,** 245-255.

Poewe, W.H., Rascol, O., Quinn, N., Tolosa, E., Oertel, W.H., Martignoni, E., Rupp, M., Boroojerdi, B., Investigators, S.P., 2007. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. *Lancet Neurol* 6**,** 513-520.

Politis, M., Wu, K., Loane, C., Brooks, D.J., Kiferle, L., Turkheimer, F.E., Bain, P., Molloy, S., Piccini, P., 2014. The role of serotonergic mechanisms in L-dopa-induced dyskinesias in Parkinson[1]s disease. *Journal of Clinical Investigation* 124**,** 1340-1349.

Politis, M., Wu, K., Loane, C., Quinn, N.P., Brooks, D.J., Rehncrona, S., Bjorklund, A., Lindvall, O., Piccini, P., 2010. Serotonergic neurons mediate dyskinesia side effects in Parkinson's patients with neural transplants. *Sci Transl Med* 2**,** 38ra46.

Pondal, M., Marras, C., Miyasaki, J., Moro, E., Armstrong, M.J., Strafella, A.P., Shah, B.B., Fox, S., Prashanth, L.K., Phielipp, N., Lang, A.E., 2013. Clinical features of dopamine agonist withdrawal syndrome in a movement disorders clinic. *J Neurol Neurosurg Psychiatry* 84**,** 130-135.

Pons, R., Syrengelas, D., Youroukos, S., Orfanou, I., Dinopoulos, A., Cormand, B., Ormazabal, A., Garzia-Cazorla, A., Serrano, M., Artuch, R., 2013. Levodopa-induced dyskinesias in tyrosine hydroxylase deficiency. *Mov Disord* 28**,** 1058-1063.

Pontone, G., Williams, J.R., Bassett, S.S., Marsh, L., 2006. Clinical features associated with impulse control disorders in Parkinson disease. *Neurology* 67**,** 1258-1261.

Porras, G., Berthet, A., Dehay, B., Li, Q., Ladepeche, L., Normand, E., Dovero, S., Martinez, A., Doudnikoff, E., Martin-Negrier, M.L., Chuan, Q., Bloch, B., Choquet, D., Boue-Grabot, E., Groc, L., Bezard, E., 2012a. PSD-95 expression controls L-DOPA dyskinesia through dopamine D1 receptor trafficking. *The Journal of clinical investigation* 122**,** 3977-3989.

Porras, G., De Deurwaerdere, P., Li, Q., Marti, M., Morgenstern, R., Sohr, R., Bezard, E., Morari, M., Meissner, W.G., 2014. L-dopa-induced dyskinesia: beyond an excessive dopamine tone in the striatum. *Scientific reports* 4**,** 3730.

Porras, G., Li, Q., Bezard, E., 2012b. Modeling Parkinson's disease in primates: The MPTP model. *Cold Spring Harbor perspectives in medicine* 2**,** a009308.

Potts, L.F., Park, E.S., Woo, J.M., Dyavar Shetty, B.L., Singh, A., Braithwaite, S.P., Voronkov, M., Papa, S.M., Mouradian, M.M., 2015. Dual kappa-agonist/mu-antagonist opioid receptor modulation reduces levodopa-induced dyskinesia and corrects dysregulated striatal changes in the nonhuman primate model of Parkinson disease. *Ann Neurol* 77**,** 930-941.

Pourcher, E., Bonnet, A.M., Kefalos, J., Dubois, B., Agid, Y., 1989. Effects of etybenzatropine and diazepam on levodopa-induced diphasic dyskinesias in Parkinson's disease. *Mov Disord* 4**,** 195-201.

Prescott, I.A., Dostrovsky, J.O., Moro, E., Hodaie, M., Lozano, A.M., Hutchison, W.D., 2009. Levodopa enhances synaptic plasticity in the substantia nigra pars reticulata of Parkinson's disease patients. *Brain* 132**,** 309-318.

Prescott, I.A., Liu, L.D., Dostrovsky, J.O., Hodaie, M., Lozano, A.M., Hutchison, W.D., 2014. Lack of depotentiation at basal ganglia output neurons in PD patients with levodopa-induced dyskinesia. *Neurobiol Dis* 71**,** 24-33.

Putterman, D.B., Munhall, A.C., Kozell, L.B., Belknap, J.K., Johnson, S.W., 2007. Evaluation of Levodopa Dose and Magnitude of Dopamine Depletion as Risk Factors for Levodopa-Induced Dyskinesia in a Rat Model of Parkinson's Disease. *Journal of Pharmacology and Experimental Therapeutics* 323**,** 277.

Quik, M., Bordia, T., Okihara, M., Fan, H., Marks, M.J., McIntosh, J.M., Whiteaker, P., 2003. L-DOPA treatment modulates nicotinic receptors in monkey striatum. *Mol. Pharmacol.* 64**,** 619-628.

Quik, M., Campos, C., Bordia, T., Strachan, J.P., Zhang, J., McIntosh, J.M., Letchworth, S., Jordan, K., 2013a. alpha4beta2 nicotinic receptors play a role in the nAChR-mediated decline in l-dopa-induced dyskinesias in parkinsonian rats. *Neuropharmacology* 71**,** 191-203.

Quik, M., Campos, C., Grady, S.R., 2013b. Multiple CNS nicotinic receptors mediate l-dopa-induced dyskinesias: Studies with parkinsonian nicotinic receptor knockout mice. *Biochem Pharmacol*.

Quik, M., Cox, H., Parameswaran, N., O'Leary, K., Langston, J.W., Di Monte, D., 2007. Nicotine reduces levodopa-induced dyskinesias in lesioned monkeys. *Ann Neurol* 62**,** 588-596.

Quik, M., Mallela, A., Chin, M., McIntosh, J.M., Perez, X.A., Bordia, T., 2013c. Nicotine-mediated improvement in L-dopa-induced dyskinesias in MPTP-lesioned monkeys is dependent on dopamine nerve terminal function. *Neurobiol Dis* 50**,** 30-41.

Quik, M., Mallela, A., Ly, J., Zhang, D., 2013d. Nicotine reduces established L-dopa-induced dyskinesias in a monkey model of Parkinson's disease. *Movement Disorders* In press

Quik, M., Park, K.M., Hrachova, M., Mallela, A., Huang, L.Z., McIntosh, J.M., Grady, S.R., 2012a. Role for alpha6 nicotinic receptors in l-dopa-induced dyskinesias in parkinsonian mice. *Neuropharmacology* 63**,** 450-459.

Quik, M., Perez, X.A., Bordia, T., 2012b. Nicotine as a potential neuroprotective agent for Parkinson's disease. *Mov Disord* 27**,** 947-957.

Quik, M., Police, S., Langston, J.W., Di Monte, D.A., 2002a. Increases in striatal preproenkephalin gene expression are associated with nigrostriatal damage but not L-DOPA-induced dyskinesias in the squirrel monkey. *Neuroscience* 113**,** 213-220.

Quik, M., Polonskaya, Y., McIntosh, J.M., Kulak, J.M., 2002b. Differential nicotinic receptor expression in monkey basal ganglia: Effects of nigrostriatal damage. *Neuroscience* 112**,** 619-630.

Quik, M., Vailati, S., Bordia, T., Kulak, J.M., Fan, H., McIntosh, J.M., Clementi, F., Gotti, C., 2005. Subunit composition of nicotinic receptors in monkey striatum: effect of treatments with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or L-DOPA. *Mol Pharmacol* 67**,** 32-41.

Quik, M., Wonnacott, S., 2011. {alpha}6{beta}2* and {alpha}4{beta}2* Nicotinic Acetylcholine Receptors As Drug Targets for Parkinson's Disease. *Pharmacol Rev* 63**,** 938-966.

Quinn, N., Critchley, P., Marsden, C.D., 1987. Young onset Parkinson's disease. *Mov Disord* 2**,** 73-91.

Quinn, N., Marsden, C.D., Parkes, J.D., 1982. Complicated response fluctuations in Parkinson's disease: response to intravenous infusion of levodopa. *Lancet* 2**,** 412-415.

Quinn, N.P., 1998. Classification of fluctuations in patients with Parkinson's disease. *Neurology* 51**,** S25-29.

Quintana, A., Melon, C., Kerkerian-Le Goff, L., Salin, P., Savasta, M., Sgambato-Faure, V., 2010. Forelimb dyskinesia mediated by high-frequency stimulation of the subthalamic nucleus is linked to rapid activation of the NR2B subunit of N-methyl-D-aspartate receptors. *Eur J Neurosci* 32**,** 423-434.

Rabinak, C.A., Nirenberg, M.J., 2010. Dopamine agonist withdrawal syndrome in Parkinson disease. *Arch Neurol* 67**,** 58-63.

Rahman, Z., Gold, S.J., Potenza, M.N., Cowan, C.W., Ni, Y.G., He, W., Wensel, T.G., Nestler, E.J., 1999. Cloning and Characterization of RGS9-2: A Striatal-Enriched Alternatively Spliced Product of the RGS9 Gene. *J. Neurosci.* 19**,** 2016-2026.

Rahman, Z., Schwarz, J., Gold, S.J., Zachariou, V., Wein, M.N., Choi, K.-H., Kovoor, A., Chen, C.-K., DiLeone, R.J., Schwarz, S.C., Selley, D.E., Sim-Selley, L.J., Barrot, M., Luedtke, R.R., Self, D., Neve, R.L., Lester, H.A., Simon, M.I., Nestler, E.J., 2003. RGS9 Modulates Dopamine Signaling in the Basal Ganglia. *Neuron* 38**,** 941.

Rajput, A.H., Martin, W., Saint-Hilaire, M.H., Dorflinger, E., Pedder, S., 1997. Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind, placebo-controlled, multicenter trial. *Neurology* 49**,** 1066-1071.

Rajput, A.H., Stern, W., Laverty, W.H., 1984. Chronic low-dose levodopa therapy in Parkinson's disease : an argument for delaying levodopa therapy. *Neurology* 34**,** 991-996.

Ramamoorthi, K., Fropf, R., Belfort, G.M., Fitzmaurice, H.L., McKinney, R.M., Neve, R.L., Otto, T., Lin, Y., 2011. Npas4 regulates a transcriptional program in CA3 required for contextual memory formation. *Science* 334**,** 1669-1675.

Ramanathan, S., Hanley, J.J., Deniau, J.M., Bolam, J.P., 2002. Synaptic convergence of motor and somatosensory cortical afferents onto GABAergic interneurons in the rat striatum. *J Neurosci* 22**,** 8158-8169.

Ramlackhansingh, A.F., Bose, S.K., Ahmed, I., Turkheimer, F.E., Pavese, N., Brooks, D.J., 2011. Adenosine 2A receptor availability in dyskinetic and nondyskinetic patients with Parkinson disease. *Neurology* 76**,** 6.

Rangel-Barajas, C., Silva, I., Garcia-Ramirez, M., Sanchez-Lemus, E., Floran, L., Aceves, J., Erlij, D., Floran, B., 2008. 6-OHDA-induced hemiparkinsonism and chronic L-DOPA treatment increase dopamine D1-stimulated [(3)H]-GABA release and [(3)H]-cAMP production in substantia nigra pars reticulata of the rat. *Neuropharmacology* 55**,** 704-711.

Rangel-Barajas, C., Silva, I., Lopez-Santiago, L.M., Aceves, J., Erlij, D., Floran, B., 2011. L-DOPA-induced dyskinesia in hemiparkinsonian rats is associated with up-regulation of adenylyl cyclase type V/VI and increased GABA release in the substantia nigra reticulata. *Neurobiol Dis* 41**,** 51-61.

Rascol, O., Arnulf, I., Peyro-Saint Paul, H., Brefel-Courbon, C., Vidailhet, M., Thalamas, C., Bonnet, A.M., Descombes, S., Bejjani, B., Fabre, N., Montastruc, J.L., Agid, Y., 2001a. Idazoxan, an alpha-2 antagonist, and L-DOPA-induced dyskinesias in patients with Parkinson's disease. *Mov Disord* 16**,** 708-713.

Rascol, O., Fabre, N., Blin, O., Poulik, J., Sabatini, U., Senard, J.M., Ane, M., Montastruc, J.L., Rascol, A., 1994. Naltrexone, an opiate antagonist, fails to modify motor symptoms in patients with Parkinson's disease. *Mov Disord* 9**,** 437-440.

Rascol, O., Ferreira, J., Negre-Pages, L., Perez-Lloret, S., Lacomblez, L., Galitzky, M., Lemarie, J.C., Corvol, J.C., Brotchie, J.M., Bossi, L., 2012. A proof-of-concept, randomized, placebo-controlled, multiple cross-overs (n-of-1) study of naftazone in Parkinson's disease. *Fundamental & clinical pharmacology* 26**,** 557-564.

Rascol, O., Fox, S., Gasparini, F., Kenney, C., Di Paolo, T., Gomez-Mancilla, B., 2014. Use of metabotropic glutamate 5-receptor antagonists for treatment of levodopa-induced dyskinesias. *Parkinsonism Relat Disord* 20**,** 947-956.

Rascol, O., Nutt, J.G., Blin, O., Goetz, C.G., Trugman, J.M., Soubrouillard, C., Carter, J.H., Currie, L.J., Fabre, N., Thalamas, C., Giardina, W.J., Wright, S., 2001b. Induction by dopamine D-1 receptor agonist ABT-431 of dyskinesia similar to levodopa in patients with Parkinson disease. *Arch. Neurol.* 58**,** 249-254.

Rasmussen, S.G., Choi, H.J., Fung, J.J., Pardon, E., Casarosa, P., Chae, P.S., Devree, B.T., Rosenbaum, D.M., Thian, F.S., Kobilka, T.S., Schnapp, A., Konetzki, I., Sunahara, R.K., Gellman, S.H., Pautsch, A., Steyaert, J., Weis, W.I., Kobilka, B.K., 2011. Structure of a nanobody-stabilized active state of the β(2) adrenoceptor. *Nature* 469**,** 175-180.

Ravenscroft, P., Chalon, S., Brotchie, J.M., Crossman, A.R., 2004. Ropinirole versus L-DOPA effects on striatal opioid peptide precursors in a rodent model of Parkinson's disease: implications for dyskinesia. *Exp. Neurol.* 185**,** 36-46.

Redgrave, P., Gurney, K., Reynolds, J., 2008. What is reinforced by phasic dopamine signals? *Brain Research Review* 58**,** 322-339.

Redmond, D.E., Jr., Vinuela, A., Kordower, J.H., Isacson, O., 2008. Influence of cell preparation and target location on the behavioral recovery after striatal transplantation of fetal dopaminergic neurons in a primate model of Parkinson's disease. *Neurobiol Dis* 29**,** 103-116.

Reese, R., Gruber, D., Schoenecker, T., Bazner, H., Blahak, C., Capelle, H.H., Falk, D., Herzog, J., Pinsker, M.O., Schneider, G.H., Schrader, C., Deuschl, G., Mehdorn, H.M., Kupsch, A., Volkmann, J., Krauss, J.K., 2011. Long-term clinical outcome in meige syndrome treated with internal pallidum deep brain stimulation. *Mov Disord* 26**,** 691-698.

Reinscheid, R.K., Ardati, A., Monsma, F.J., Jr., Civelli, O., 1996. Structure-activity relationship studies on the novel neuropeptide orphanin FQ. *J Biol Chem* 271**,** 14163-14168.

Reinscheid, R.K., Nothacker, H.P., Bourson, A., Ardati, A., Henningsen, R.A., Bunzow, J.R., Grandy, D.K., Langen, H., Monsma, F.J., Civelli, O., 1995. Orphanin-Fq - a Neuropeptide That Activates an Opioid-Like G-Protein-Coupled Receptor. *Science* 270**,** 792-794.

Ren, X.R., Reiter, E., Ahn, S., Kim, J., Chen, W., Lefkowitz, R.J., 2005. Different G protein-coupled receptor kinases govern G protein and beta-arrestin-mediated signaling of V2 vasopressin receptor. *Proc. Nat. Acad. Sci. USA* 102**,** 1448-1453.

Revy, D., Jaouen, F., Salin, P., Melon, C., Chabbert, D., Tafi, E., Concetta, L., Langa, F., Amalric, M., Kerkerian-Le Goff, L., Marie, H., Beurrier, C., 2014. Cellular and behavioral outcomes of dorsal striatonigral neuron ablation: new insights into striatal functions. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 39**,** 2662-2672.

Rice, M.E., Cragg, S.J., 2004. Nicotine amplifies reward-related dopamine signals in striatum. *Nature neuroscience* 7**,** 583-584.

Riddle, J.L., Rokosik, S.L., Napier, T.C., 2012. Pramipexole- and methamphetamine-induced reward-mediated behavior in a rodent model of Parkinson's disease and controls. *Behav Brain Res* 233**,** 15-23.

Ridray, S., Griffon, N., Mignon, V., Souil, E., Carboni, S., Diaz, J., Schwartz, J.C., Sokoloff, P., 1998. Coexpression of dopamine D1 and D3 receptors in islands of Calleja and shell of nucleus accumbens of the rat : opposite and synergistic functional interactions. *Eur. J. Pharmacol.* 10**,** 1676-1686.

Rieck, M., Schumacher-Schuh, A.F., Altmann, V., Francisconi, C.L., Fagundes, P.T., Monte, T.L., Callegari-Jacques, S.M., Rieder, C.R., Hutz, M.H., 2012. DRD2 haplotype is associated with dyskinesia induced by levodopa therapy in Parkinson's disease patients. *Pharmacogenomics* 13**,** 1701-1710.

Rizzi, A., Rizzi, D., Marzola, G., Regoli, D., Larsen, B.D., Petersen, J.S., Calo, G., 2002. Pharmacological characterization of the novel nociceptin/orphanin FQ receptor ligand, ZP120: in vitro and in vivo studies in mice. *British journal of pharmacology* 137**,** 369-374.

Robelet, S., Melon, C., Guillet, B., Salin, P., Kerkerian-Le Goff, L., 2004. Chronic L-DOPA treatment increases extracellular glutamate levels and GLT1 expression in the basal ganglia in a rat model of Parkinson's disease. *Eur J Neurosci* 20**,** 1255-1266.

Rodrigues, J.P., Walters, S.E., Watson, P., Stell, R., Mastaglia, F.L., 2007. Globus pallidus stimulation improves both motor and nonmotor aspects of quality of life in advanced Parkinson's disease. *Mov Disord* 22**,** 1866-1870.

Rodriguez-Oroz, M.C., Lopez-Azcarate, J., Garcia-Garcia, D., Alegre, M., Toledo, J., Valencia, M., Guridi, J., Artieda, J., Obeso, J.A., 2011. Involvement of the subthalamic nucleus

in impulse control disorders associated with Parkinson's disease. *Brain* 134**,** 36-49.

Rokosik, S.L., Napier, T.C., 2012. Pramipexole-induced increased probabilistic discounting: comparison between a rodent model of Parkinson's disease and controls. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 37**,** 1397-1408.

Rolland, A.S., Tande, D., Herrero, M.T., Luquin, M.R., Vazquez-Claverie, M., Karachi, C., Hirsch, E.C., Francois, C., 2009. Evidence for a dopaminergic innervation of the pedunculopontine nucleus in monkeys, and its drastic reduction after MPTP intoxication. *J Neurochem* 110**,** 1321-1329.

Rosin, B., Slovik, M., Mitelman, R., Rivlin-Etzion, M., Haber, S.N., Israel, Z., Vaadia, E., Bergman, H., 2011. Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron* 72**,** 370-384.

Ross, E.M., Wilkie, T.M., 2000. GTPase-activating proteins for heterotrimeric G proteins: regulators of G protein signaling (RGS) and RGS-like proteins. *Annu. Rev. Biochem.* 69**,** 795-827.

Ruiz-DeDiego, I., Mellstrom, B., Vallejo, M., Naranjo, J.R., Moratalla, R., 2015. Activation of DREAM (downstream regulatory element antagonistic modulator), a calcium-binding protein, reduces L-DOPA-induced dyskinesias in mice. *Biol Psychiatry* 77**,** 95-105.

Russmann, H., Ghika, J., Villemure, J.G., Robert, B., Bogousslavsky, J., Burkhard, P.R., Vingerhoets, F.J., 2004. Subthalamic nucleus deep brain stimulation in Parkinson disease patients over age 70 years. *Neurology* 63**,** 1952-1954.

Rylander, D., Iderberg, H., Li, Q., Dekundy, A., Zhang, J., Li, H., Baishen, R., Danysz, W., Bezard, E., Cenci, M.A., 2010a. A mGluR5 antagonist under clinical development improves L-DOPA-induced dyskinesia in parkinsonian rats and monkeys. *Neurobiol Dis* 39**,** 352-361.

Rylander, D., Parent, M., O'Sullivan, S., Dovero, S., Lees, A., Bezard, E., Descarries, L., Cenci, M.A., 2010b. Maladaptive plasticity of serotonin axon terminals in levodopa-induced dyskinesia. *Ann Neurol* in press.

Rylander, D., Recchia, A., Mela, F., Dekundy, A., Danysz, W., Cenci, M.A., 2009. Pharmacological modulation of glutamate transmission in a rat model of L-DOPA-

induced dyskinesia: effects on motor behavior and striatal nuclear signaling. *J Pharmacol Exp Ther* 330**,** 227-235.

Rylander, G., 1972. Psychoses and the punding and choreiform syndromes in addiction to central stimulant drugs. *Psychiatria, neurologia, neurochirurgia* 75**,** 203-212.

Sadee, W., Wang, D., Bilsky, E.J., 2005. Basal opioid receptor activity, neutral antagonists, and therapeutic opportunities. *Life Sci* 76**,** 1427-1437.

Saka, E., Elibol, B., Erdem, S., Dalkara, T., 1999. Compartmental changes in expression of c-Fos and FosB proteins in intact and dopamine-depleted striatum after chronic apomorphine treatment. *Brain Res* 825**,** 104-114.

Sako, W., Miyazaki, Y., Izumi, Y., Kaji, R., 2014. Which target is best for patients with Parkinson's disease? A meta-analysis of pallidal and subthalamic stimulation. *J Neurol Neurosurg Psychiatry*.

Salamone, J.D., Betz, A.J., Ishiwari, K., Felsted, J., Madson, L., Mirante, B., Clark, K., Font, L., Korbey, S., Sager, T.N., Hockemeyer, J., Muller, C.E., 2008. Tremorolytic effects of adenosine A2A antagonists: implications for parkinsonism. *Frontiers in bioscience : a journal and virtual library* 13**,** 3594-3605.

Samadi, P., Gregoire, L., Morissette, M., Calon, F., Hadj Tahar, A., Dridi, M., Belanger, N., Meltzer, L.T., Bedard, P.J., Di Paolo, T., 2008. mGluR5 metabotropic glutamate receptors and dyskinesias in MPTP monkeys. *Neurobiol Aging* 29**,** 1040-1051.

Sanchez-Pernaute, R., Jenkins, B.G., Choi, J.K., Iris Chen, Y.C., Isacson, O., 2007. In vivo evidence of D3 dopamine receptor sensitization in parkinsonian primates and rodents with l-DOPA-induced dyskinesias. *Neurobiol Dis* 27**,** 220-227.

Sankar, T., Lozano, A.M., 2011. Magnetic resonance imaging and deep brain stimulation. *Journal of neurosurgery* 115**,** 849-850; discussion 850-841.

Santini, E., Alcacer, C., Cacciatore, S., Heiman, M., Herve, D., Greengard, P., Girault, J.A., Valjent, E., Fisone, G., 2009a. L-DOPA activates ERK signaling and phosphorylates histone H3 in the striatonigral medium spiny neurons of hemiparkinsonian mice. *J Neurochem* 108**,** 621-633.

Santini, E., Feyder, M., Gangarossa, G., Bateup, H.S., Greengard, P., Fisone, G., 2012. Dopamine- and cAMP-regulated Phosphoprotein of 32-kDa (DARPP-32)-dependent Activation of Extracellular Signal-regulated Kinase (ERK) and Mammalian Target of Rapamycin Complex 1 (mTORC1) Signaling in Experimental Parkinsonism. *J Biol Chem* 287**,** 27806-27812.

Santini, E., Heiman, M., Greengard, P., Valjent, E., Fisone, G., 2009b. Inhibition of mTOR signaling in Parkinson's disease prevents L-DOPA-induced dyskinesia. *Sci Signal* 2**,** ra36.

Santini, E., Sgambato-Faure, V., Li, Q., Savasta, M., Dovero, S., Fisone, G., Bezard, E., 2010a. Distinct changes in cAMP and extracellular signal-regulated protein kinase signalling in L-DOPA-induced dyskinesia. *PLoS One* 5**,** e12322.

Santini, E., Valjent, E., Fisone, G., 2010b. mTORC1 signaling in Parkinson's disease and L-DOPA-induced dyskinesia: A sensitized matter. *Cell Cycle* 9**,** 2713-2718.

Santini, E., Valjent, E., Usiello, A., Carta, M., Borgkvist, A., Girault, J.A., Herve, D., Greengard, P., Fisone, G., 2007. Critical involvement of cAMP/DARPP-32 and extracellular signal-regulated protein kinase signaling in L-DOPA-induced dyskinesia. *J Neurosci* 27**,** 6995-7005.

Sanz-Clemente, A., Nicoll, R.A., Roche, K.W., 2013. Diversity in NMDA receptor composition: many regulators, many consequences. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry* 19**,** 62-75.

Sassin, J.F., Taub, S., Weitzman, E.D., 1972. Hyperkinesia and changes in behavior produced in normal monkeys by L-dopa. *Neurology* 22**,** 1122-1125.

Savasta, M., Dubois, A., Benavides, J., Scatton, B., 1988. Different plasticity changes in D1 and D2 receptors in rat striatal subregions following impairment of dopaminergic transmission. *Neurosci Lett* 85**,** 119-124.

Schiffmann, S.N., Libert, F., Vassart, G., Vanderhaeghen, J.J., 1991. Distribution of adenosine A2 receptor mRNA in the human brain. . *Neurosci. Lett.* 130**,** 5.

Schiorring, E., 1981. Psychopathology induced by "speed drugs". *Pharmacology, biochemistry, and behavior* 14 Suppl 1**,** 109-122.

Scholtissen, B., Verhey, F.R., Steinbusch, H.W., Leentjens, A.F., 2006. Serotonergic mechanisms in Parkinson's disease: opposing results from preclinical and clinical data. *J Neural Transm* 113**,** 59-73.

Scholz, B., Svensson, M., Alm, H., Skold, K., Falth, M., Kultima, K., Guigoni, C., Doudnikoff, E., Li, Q., Crossman, A.R., Bezard, E., Andren, P.E., 2008. Striatal proteomic analysis suggests that first L-dopa dose equates to chronic exposure. *PLoS One* 3**,** e1589.

Schott, B.H., Niehaus, L., Wittmann, B.C., Schutze, H., Seidenbecher, C.I., Heinze, H.J., Duzel, E., 2007. Ageing and early-stage Parkinson's disease affect separable neural mechanisms of mesolimbic reward processing. *Brain* 130**,** 2412-2424.

Schultz, W., Studer, A., Jonsson, G., Sundstrüm, E., Mefford, I., 1985. Deficits in behavioral initiation and execution processes in monkeys with 1-methyl -4- phenyl -1,2,3,6 - tetrahydropyridine - induced parkinsonism. *Neurosci. Lett.* 59**,** 225-232.

Schuster, S., Nadjar, A., Guo, J.T., Li, Q., Ittrich, C., Hengerer, B., Bezard, E., 2008. The 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor lovastatin reduces severity of L-DOPA-induced abnormal involuntary movements in experimental Parkinson's disease. *J Neurosci* 28**,** 4311-4316.

Schwarting, R.K., Huston, J.P., 1996a. The unilateral 6-hydroxydopamine lesion model in behavioral brain research. Analysis of functional deficits, recovery and treatments. *Prog. Neurobiol.* 50**,** 275-331.

Schwarting, R.K.W., Huston, J.P., 1996b. Unilateral 6-hydroxydopamine lesions of meso-striatal dopamine neurons and their physiological sequelae. *Prog. Neurobiol.* 49**,** 216-266.

Schwendt, M., McGinty, J.F., 2007. Regulator of G-protein signaling 4 interacts with metabotropic glutamate receptor subtype 5 in rat striatum: relevance to amphetamine behavioral sensitization. *J Pharmacol Exp Ther* 323**,** 650-657.

Schwendt, M., Sigmon, S.A., McGinty, J.F., 2012. RGS4 overexpression in the rat dorsal striatum modulates mGluR5- and amphetamine-mediated behavior and signaling. *Psychopharmacology (Berl)* 221**,** 621-635.

Scott, L., Zelenin, S., Malmersjo, S., Kowalewski, J.M., Markus, E.Z., Nairn, A.C., Greengard, P., Brismar, H., Aperia, A., 2006. Allosteric changes of the NMDA receptor trap diffusible dopamine 1 receptors in spines. *Proc Natl Acad Sci U S A* 103**,** 762-767.

Seeman, P., 1980. Brain dopamine receptors. *Pharmacol Rev* 32**,** 229-313.

Seeman, P., Guan, H.C., Niznik, H.B., 1989. Endogenous dopamine lowers the dopamine D2 receptor density as measured by [3H]raclopride: implications for positron emission tomography of the human brain. *Synapse* 3**,** 96-97.

Seeman, P., Guan, H.C., van Tohl, H.H., Niznik, H.B., 1993. Low density of dopamine D4 receptors in Parkinson's, schizophrenia, and control brain striata. *Synapse* 14**,** 247-253.

Senard, J.M., Rai, S., Lapeyre-Mestre, M., Brefel, C., Rascol, O., Rascol, A., Montastruc, J.L., 1997. Prevalence of orthostatic hypotension in Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry* 63**,** 584-589.

Sgambato-Faure, V., Buggia, V., Gilbert, F., Levesque, D., Benabid, A.L., Berger, F., 2005. Coordinated and spatial upregulation of arc in striatonigral neurons correlates with L-dopa-induced behavioral sensitization in dyskinetic rats. *J Neuropathol Exp Neurol* 64**,** 936-947.

Sgambato-Faure, V., Cenci, M.A., 2012. Glutamatergic mechanisms in the dyskinesias induced by pharmacological dopamine replacement and deep brain stimulation for the treatment of Parkinson's disease. *Progress in neurobiology* 96**,** 69-86.

Sgroi, S., Kaelin-Lang, A., Capper-Loup, C., 2014. Spontaneous locomotor activity and L-DOPA-induced dyskinesia are not linked in 6-OHDA parkinsonian rats. *Front Behav Neurosci* 8**,** 331.

Shen, W., Flajolet, M., Greengard, P., Surmeier, D.J., 2008. Dichotomous dopaminergic control of striatal synaptic plasticity. *Science* 321**,** 848-851.

Shepherd, J.D., Huganir, R.L., 2007. The cell biology of synaptic plasticity: AMPA receptor trafficking. *Annual review of cell and developmental biology* 23**,** 613-643.

Shin, E., Garcia, J., Winkler, C., Bjorklund, A., Carta, M., 2012a. Serotonergic and dopaminergic mechanisms in graft-induced dyskinesia in a rat model of Parkinson's disease. *Neurobiol Dis* 47**,** 393-406.

Shin, E., Lisci, C., Tronci, E., Fidalgo, C., Stancampiano, R., Bjorklund, A., Carta, M., 2014. The anti-dyskinetic effect of dopamine receptor blockade is enhanced in parkinsonian rats following dopamine neuron transplantation. *Neurobiol Dis* 62**,** 233-240.

Shin, E., Tronci, E., Carta, M., 2012b. Role of Serotonin Neurons in L-DOPA- and Graft-Induced Dyskinesia in a Rat Model of Parkinson's Disease. *Parkinson's disease* 2012**,** 370190.

Shinotoh, H., Inoue, O., Hirayama, K., Aotsuka, A., Asahina, M., Suhara, T., Yamazaki, T., Tateno, Y., 1993. Dopamine D1 receptors in Parkinson's disease and striatonigral degeneration: a positron emission tomography study. *J Neurol Neurosurg Psychiatry* 56**,** 467-472.

Shoulson, I., Oakes, D., Fahn, S., Lang, A., Langston, J.W., LeWitt, P., Olanow, C.W., Penney, J.B., Tanner, C., Kieburtz, K., Rudolph, A., Parkinson Study, G., 2002. Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: a randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of parkinsonism trial. *Ann Neurol* 51**,** 604-612.

Shoulson, I., Penney, J., McDermott, M., Schwid, S., Kayson, E., Chase, T., Fahn, S., Greenamyre, J.T., Lang, A., Siderowf, A., Pearson, N., Harrison, M., Rost, E., Colcher, A., Lloyd, M., Matthews, M., Pahwa, R., McGuire, D., Lew, M.F., Schuman, S., Marek, K., Broshjeit, S., Factor, S., Brown, D., Feigin, A., Mazurkiewicz, J., Ford, B., Jennings, D., Dilllon, S., Comella, C., Blasucci, L., Janko, K., Shulman, L., Wiener, W., Bateman-Rodriguez, D., Carrion, A., Suchowersky, O., Lafontaine, A.L., Pantella, C., Siemers, E., Belden, J., Davies, R., Lannon, M., Grimes, D., Gray, P., Martin, W., Kennedy, L., Adler, C., Newman, S., Hammerstad, J., Stone, C., Lewitt, P., Bardram, K., Mistura, K., Miyasaki, J., Johnston, L., Cha, J.H., Tennis, M., Panniset, M., Hall, J., Tetrud, J., Friedlander, J., Hauser, R., Gauger, L., Rodnitzky, R., Deleo, A., Dobson, J., Seeberger, L., Dingmann, C., Tarsy, D., Ryan, P., Elmer, L., Ruzicka, D., Stacy, M., Brewer, M., Locke, B., Baker, D., Casaceli, C., Day, D., Florack, M., Hodgeman, K., Laroia, N., Nobel, R., Orme, C., Rexo, L., Rothenburgh, K., Sulimowicz, K., Watts, A., Wratni, E., Tariot, P., Cox, C., Leventhal, C., Alderfer, V., Craun, A.M., Frey, J., McCree, L., McDermott, J., Cooper, J., Holdich, T., Read, B., 2001. A randomized, controlled trial of remacemide for motor fluctuations in Parkinson's disease. *Neurology* 56**,** 455-462.

Shukla, A.K., Xiao, K., Lefkowitz, R.J., 2011. Emerging paradigms of β-arrestin-dependent seven transmembrane receptor signaling. *Trends Biochem Sci* 36**,** 457-469.

Siderovski, D.P., Hessel, A., Chung, S., Mak, T.W., Tyers, M., 1996. A new family of regulators of G-protein-coupled receptors?. *Curr. Biol.* 6**,** 211-212.

Siderovski, D.P., Willard, F.S., 2005. The GAPs, GEFs, and GDIs of heterotrimeric G-protein alpha subunits. *Int J Biol Sci* 1**,** 51-66.

Sieradzan, K.A., Fox, S.H., Hill, M., Dick, J.P., Crossman, A.R., Brotchie, J.M., 2001. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. *Neurology* 57**,** 2108-2111.

Silberstein, P., Oliviero, A., Di Lazzaro, V., Insola, A., Mazzone, P., Brown, P., 2005. Oscillatory pallidal local field potential activity inversely correlates with limb dyskinesias in Parkinson's disease. *Exp Neurol* 194**,** 523-529.

Silveira-Moriyama, L., Evans, A.H., Katzenschlager, R., Lees, A.J., 2006. Punding and dyskinesias. *Mov Disord* 21**,** 2214-2217.

Silverdale, M.A., Kobylecki, C., Hallett, P.J., Li, Q., Dunah, A.W., Ravenscroft, P., Bezard, E., Brotchie, J.M., 2010. Synaptic recruitment of AMPA glutamate receptor subunits

in levodopa-induced dyskinesia in the MPTP-lesioned nonhuman primate. *Synapse* 64**,** 177-180.

Silverdale, M.A., Nicholson, S.L., Crossman, A.R., Brotchie, J.M., 2005. Topiramate reduces levodopa-induced dyskinesia in the MPTP-lesioned marmoset model of Parkinson's disease. *Mov Disord* 20**,** 403-409.

Simola, N., Di Chiara, G., Daniels, W.M., Schallert, T., Morelli, M., 2009. Priming of rotational behavior by a dopamine receptor agonist in Hemiparkinsonian rats: movement-dependent induction. *Neuroscience* 158**,** 7.

Simola, N., Fenu, S., Baraldi, P.G., Tabrizi, M.A., Morelli, M., 2004. Blockade of adenosine A2A receptors antagonizes parkinsonian tremor in the rat tacrine model by an action on specific striatal regions. *Exp Neurol* 189**,** 182-188.

Simola, N., Morelli, M., Carta, A.R., 2007. The 6-hydroxydopamine model of Parkinson's disease. . *Neurotox. Res.* 11**,** 17.

Simon, J.A., Kingston, R.E., 2013. Occupying chromatin: Polycomb mechanisms for getting to genomic targets, stopping transcriptional traffic, and staying put. *Molecular cell* 49**,** 808-824.

Simonin, C., Tir, M., Devos, D., Kreisler, A., Dujardin, K., Salleron, J., Delval, A., Blond, S., Defebvre, L., Destee, A., Krystkowiak, P., 2009. Reduced levodopa-induced complications after 5 years of subthalamic stimulation in Parkinson's disease: a second honeymoon. *Journal of neurology* 256**,** 1736-1741.

Simpson, G.L., Hughes, J.A., Washio, Y., Bertrand, S.M., 2009. Direct small-molecule kinase activation: Novel approaches for a new era of drug discovery. *Curr Opin Drug Discov Devel* 12**,** 585-596.

Singer, S.J., Nicolson, G.L., 1972. The fluid mosaic model of the structure of cell membranes. *Science* 175**,** 720-731.

Smidt, M.P., Smits, S.M., Burbach, J.P., 2003. Molecular mechanisms underlying midbrain dopamine neuron development and function. *Eur J Pharmacol* 480**,** 75-88.

Smith, R., Wu, K., Hart, T., Loane, C., Brooks, D.J., Bjorklund, A., Odin, P., Piccini, P., Politis, M., 2015. The role of pallidal serotonergic function in Parkinson's disease dyskinesias: a positron emission tomography study. *Neurobiol Aging*.

Sodersten, E., Feyder, M., Lerdrup, M., Gomes, A.L., Kryh, H., Spigolon, G., Caboche, J., Fisone, G., Hansen, K., 2014. Dopamine signaling leads to loss of Polycomb

repression and aberrant gene activation in experimental parkinsonism. *PLoS genetics* 10**,** e1004574.

Soderstrom, K.E., Meredith, G., Freeman, T.B., McGuire, S.O., Collier, T.J., Sortwell, C.E., Wu, Q., Steece-Collier, K., 2008. The synaptic impact of the host immune response in a parkinsonian allograft rat model: Influence on graft-derived aberrant behaviors. *Neurobiol Dis* 32**,** 229-242.

Soderstrom, K.E., O'Malley, J.A., Levine, N.D., Sortwell, C.E., Collier, T.J., Steece-Collier, K., 2010. Impact of dendritic spine preservation in medium spiny neurons on dopamine graft efficacy and the expression of dyskinesias in parkinsonian rats. *Eur J Neurosci* 31**,** 478-490.

Solis, O., Espadas, I., Del-Bel, E.A., Moratalla, R., 2015. Nitric oxide synthase inhibition decreases l-DOPA-induced dyskinesia and the expression of striatal molecular markers in Pitx3(-/-) aphakia mice. *Neurobiol Dis* 73**,** 49-59.

Solomon, R.L., Corbit, J.D., 1973. An opponent-process theory of motivation. II. Cigarette addiction. *Journal of abnormal psychology* 81**,** 158-171.

Sossi, V., de La Fuente-Fernandez, R., Holden, J.E., Doudet, D.J., McKenzie, J., Stoessl, A.J., Ruth, T.J., 2002. Increase in dopamine turnover occurs early in Parkinson's disease: evidence from a new modeling approach to PET 18 F-fluorodopa data. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 22**,** 232-239.

Sossi, V., de la Fuente-Fernandez, R., Holden, J.E., Schulzer, M., Ruth, T.J., Stoessl, J., 2004. Changes of dopamine turnover in the progression of Parkinson's disease as measured by positron emission tomography: their relation to disease-compensatory mechanisms. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 24**,** 869-876.

Sossi, V., de la Fuente-Fernandez, R., Schulzer, M., Adams, J., Stoessl, J., 2006. Age-related differences in levodopa dynamics in Parkinson's: implications for motor complications. *Brain* 129**,** 1050-1058.

Sossi, V., de la Fuente-Fernandez, R., Schulzer, M., Troiano, A.R., Ruth, T.J., Stoessl, A.J., 2007. Dopamine transporter relation to dopamine turnover in Parkinson's disease: a positron emission tomography study. *Ann Neurol* 62**,** 468-474.

Sossi, V., Doudet, D.J., Holden, J.E., 2001. A reversible tracer analysis approach to the study of effective dopamine turnover. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 21**,** 469-476.

Sotnikova, T.D., Beaulieu, J.M., Barak, L.S., Wetsel, W.C., Caron, M.G., Gainetdinov, R.R., 2005. Dopamine-independent locomotor actions of amphetamines in a novel acute mouse model of Parkinson disease. *PLoS biology* 3**,** e271.

Sotnikova, T.D., Caron, M.G., Gainetdinov, R.R., 2006. DDD mice, a novel acute mouse model of Parkinson's disease. *Neurology* 67**,** S12-17.

Spieker, S., Loschmann, P.A., Klockgether, T., 1999. The NMDA antagonist budipine can alleviate levodopa-induced motor fluctuations. *Mov Disord* 14**,** 517-519.

Stacy, M., Silver, D., Mendis, T., Sutton, J., Mori, A., Chaikin, P., Sussman, N.M., 2008. A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. *Neurology* 70**,** 8.

Stathis, P., Konitsiotis, S., Tagaris, G., Peterson, D., Group, V.-P.S., 2011. Levetiracetam for the management of levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 26**,** 264-270.

Steece-Collier, K., Collier, T.J., Danielson, P.D., Kurlan, R., Yurek, D.M., Sladek, J.R., Jr., 2003. Embryonic mesencephalic grafts increase levodopa-induced forelimb hyperkinesia in parkinsonian rats. *Mov Disord* 18**,** 1442-1454.

Steece-Collier, K., Rademacher, D.J., Soderstrom, K., 2012. Anatomy of Graft-induced Dyskinesias: Circuit Remodeling in the Parkinsonian Striatum. *Basal ganglia* 2**,** 15-30.

Steece-Collier, K., Soderstrom, K.E., Collier, T.J., Sortwell, C.E., Maries-Lad, E., 2009. Effect of levodopa priming on dopamine neuron transplant efficacy and induction of abnormal involuntary movements in parkinsonian rats. *The Journal of comparative neurology* 515**,** 15-30.

Stefano, G.B., Scharrer, B., Smith, E.M., Hughes, T.K., Jr., Magazine, H.I., Bilfinger, T.V., Hartman, A.R., Fricchione, G.L., Liu, Y., Makman, M.H., 1996. Opioid and opiate immunoregulatory processes. *Crit Rev Immunol* 16**,** 109-144.

Stephenson, D.T., Li, Q., Simmons, C., Connell, M.A., Meglasson, M.D., Merchant, K., Emborg, M.E., 2005. Expression of GAD65 and GAD67 immunoreactivity in MPTP-

treated monkeys with or without L-DOPA administration. *Neurobiol. Dis.* 20**,** 347-359.

Stocchi, F., Hsu, A., Khanna, S., Ellenbogen, A., Mahler, A., Liang, G., Dillmann, U., Rubens, R., Kell, S., Gupta, S., 2014. Comparison of IPX066 with carbidopa-levodopa plus entacapone in advanced PD patients. *Parkinsonism Relat Disord* 20**,** 1335-1340.

Stocchi, F., Rascol, O., Destee, A., Hattori, N., Hauser, R.A., Lang, A.E., Poewe, W., Stacy, M., Tolosa, E., Gao, H., Nagel, J., Merschhemke, M., Graf, A., Kenney, C., Trenkwalder, C., 2013. AFQ056 in Parkinson patients with levodopa-induced dyskinesia: 13-week, randomized, dose-finding study. *Mov Disord* 28**,** 1838-1846.

Stoessl, A.J., 2014. Central pharmacokinetics of levodopa: Lessons from imaging studies. *Mov Disord*.

Stoof, J.C., Kebabian, J.W., 1981. Opposing roles for D-1 and D-2 dopamine receptors in efflux of cyclic AMP from rat neostriatum. *Nature* 294**,** 366-368.

Strong, J.A., Dalvi, A., Revilla, F.J., Sahay, A., Samaha, F.J., Welge, J.A., Gong, J., Gartner, M., Yue, X., Yu, L., 2006. Genotype and smoking history affect risk of levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 21**,** 654-659.

Suarez, L.M., Solis, O., Carames, J.M., Taravini, I.R., Solis, J.M., Murer, M.G., Moratalla, R., 2014. L-DOPA treatment selectively restores spine density in dopamine receptor D2-expressing projection neurons in dyskinetic mice. *Biol Psychiatry* 75**,** 711-722.

Subramaniam, S., Napolitano, F., Mealer, R.G., Kim, S., Errico, F., Barrow, R., Shahani, N., Tyagi, R., Snyder, S.H., Usiello, A., 2012. Rhes, a striatal-enriched small G protein, mediates mTOR signaling and L-DOPA-induced dyskinesia. *Nature neuroscience* 15**,** 191-193.

Svenningsson, P., Rosenblad, C., af Edholm Arvidson, K., Wictorin, K., Keywood, C., Shankar, B., Lowe, D.A., Bjorklund, A., Widner, H., 2015. Eltoprazine counteracts L-dopa-induced dyskinesias in Parkinson's disease: a dose-finding study. *Brain* 138**,** 963-973.

Svenningsson, P., Tzavara, E.T., Liu, F., Fienberg, A.A., Nomikos, G.G., Greengard, P., 2002. DARPP-32 mediates serotonergic neurotransmission in the forebrain. *Proc Natl Acad Sci U S A* 99**,** 3188-3193.

Szamosi, A., Nagy, H., Keri, S., 2013. Delay discounting of reward and caudate nucleus volume in individuals with alpha-synuclein gene duplication before and after the development of Parkinson's disease. *Neuro-degenerative diseases* 11**,** 72-78.

Takakusaki, K., Habaguchi, T., Ohtinata-Sugimoto, J., Saitoh, K., Sakamoto, T., 2003. Basal ganglia efferents to the brainstem centers controlling postural muscle tone and locomotion: a new concept for understanding motor disorders in basal ganglia dysfunction. *Neuroscience* 119**,** 293-308.

Takuma, K., Tanaka, T., Takahashi, T., Hiramatsu, N., Ota, Y., Ago, Y., Matsuda, T., 2012. Neuronal nitric oxide synthase inhibition attenuates the development of L-DOPA-induced dyskinesia in hemi-Parkinsonian rats. *Eur J Pharmacol* 683**,** 166-173.

Tanaka, H., Kannari, K., Maeda, T., Tomiyama, M., Suda, T., Matsunaga, M., 1999. Role of serotonergic neurons in L-DOPA-derived extracellular dopamine in the striatum of 6-OHDA-lesioned rats. *Neuroreport* 10**,** 631-634.

Tardin, C., Cognet, L., Bats, C., Lounis, B., Choquet, D., 2003. Direct imaging of lateral movements of AMPA receptors inside synapses. *Embo J* 22**,** 4656-4665.

Tass, P.A., Qin, L., Hauptmann, C., Dovero, S., Bezard, E., Boraud, T., Meissner, W.G., 2012. Coordinated reset has sustained aftereffects in Parkinsonian monkeys. *Ann Neurol* 72**,** 816-820.

Taylor, D.P., 1988. Buspirone, a new approach to the treatment of anxiety. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 2**,** 2445-2452.

Taylor, J.R., Elsworth, J.D., Roth, R.H., Sladek, J.R., Redmond, D.E. 1994. Behavioral effects of MPTP administration in the Vervet monkey: a primate model of Parkinson's disease. In: *Toxin-induced models of neurological disorders*. pp. 139-174. Eds. M.L. Woodruff, A. Nonneman. Plenum press: New York.

Taylor, J.R., Elsworth, J.D., Roth, R.H., Sladek, J.R., Redmond, D.E., 1997. Severe long-term MPTP-induced parkinsonism in the vervet monkey (Cercopithecus aethiops sabaeus). *Neuroscience* 81**,** 745-755.

Tedroff, J., Pedersen, M., Aquilonius, S.M., Hartvig, P., Jacobsson, G., Langstrom, B., 1996. Levodopa-induced changes in synaptic dopamine in patients with Parkinson's disease as measured by [11C]raclopride displacement and PET. *Neurology* 46**,** 1430-1436.

Tekumalla, P.K., Calon, F., Rahman, Z., Birdi, S., Rajput, A.H., Hornykiewicz, O., Di Paolo, T., Bedard, P.J., Nestler, E.J., 2001. Elevated levels of DeltaFosB and RGS9 in striatum in Parkinson's disease. *Biol Psychiatry* 50**,** 813-816.

Tel, B.C., Zeng, B.-Y., Cannizzaro, C., Pearce, R.K.B., Rose, S., Jenner, P., 2002. Alterations in striatal neuropeptide mRNA produced by repeated administration of L-DOPA, ropinirole or bromocriptine correlate with dyskinesia induction in MPTP-treated common marmosets. *Neuroscience* 115**,** 1047-1058.

Tellez, C., Bustamante, M.L., Toro, P., Venegas, P., 2006. Addiction to apomorphine: a clinical case-centred discussion. *Addiction* 101**,** 1662-1665.

Temel, Y., Boothman, L.J., Blokland, A., Magill, P.J., Steinbusch, H.W., Visser-Vandewalle, V., Sharp, T., 2007. Inhibition of 5-HT neuron activity and induction of depressive-like behavior by high-frequency stimulation of the subthalamic nucleus. *Proc Natl Acad Sci U S A* 104**,** 17087-17092.

Thach, W.T., Goodkin, H.P., Keating, J.G., 1992. The cerebellum and the adaptive coordination of movement. *Annual review of neuroscience* 15**,** 403-442.

Thiele, S.L., Chen, B., Lo, C., Gertler, T.S., Warre, R., Surmeier, J.D., Brotchie, J.M., Nash, J.E., 2014. Selective loss of bi-directional synaptic plasticity in the direct and indirect striatal output pathways accompanies generation of parkinsonism and l-DOPA induced dyskinesia in mouse models. *Neurobiol Dis* 71**,** 334-344.

Thiollier, T., Wu, C., Contamin, H., Li, Q., Zhang, J., Bezard, E., 2015. Permeability of blood-brain barrier in macaque model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson disease. *submittted*.

Thobois, S., Ardouin, C., Lhommee, E., Klinger, H., Lagrange, C., Xie, J., Fraix, V., Coelho Braga, M.C., Hassani, R., Kistner, A., Juphard, A., Seigneuret, E., Chabardes, S., Mertens, P., Polo, G., Reilhac, A., Costes, N., LeBars, D., Savasta, M., Tremblay, L., Quesada, J.L., Bosson, J.L., Benabid, A.L., Broussolle, E., Pollak, P., Krack, P., 2010. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain* 133**,** 1111-1127.

Thomas, A., Iacono, D., Luciano, A.L., Armellino, K., Di Iorio, A., Onofrj, M., 2004. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *J Neurol Neurosurg Psychiatry* 75**,** 141-143.

Thompson, A.A., Liu, W., Chun, E., Katritch, V., Wu, H., Vardy, E., Huang, X.P., Trapella, C., Guerrini, R., Calo, G., Roth, B.L., Cherezov, V., Stevens, R.C., 2012. Structure of the nociceptin/orphanin FQ receptor in complex with a peptide mimetic. *Nature* 485**,** 395-399.

Tiberi, M., Nash, S., Bertrand, L., Lefkowitz, R.J., Caron, M.G., 1996. Differential regulation of dopamine D1A receptor responsiveness by various G protein-coupled receptor kinases. *J. Biol. Chem.* 271**,** 3771-3778.

Timmann, D., Drepper, J., Frings, M., Maschke, M., Richter, S., Gerwig, M., Kolb, F.P., 2010. The human cerebellum contributes to motor, emotional and cognitive associative learning. A review. *Cortex; a journal devoted to the study of the nervous system and behavior* 46**,** 845-857.

Tintner, R., Jankovic, J., 2002. Treatment options for Parkinson's disease. *Curr Opin Neurol* 15**,** 467-476.

Tischmeyer, W., Grimm, R., 1999. Activation of immediate early genes and memory formation. . *Cell. Mol. Life Sci.* 55**,** 11.

Tison, F., Mons, N., Geffard, M., Henry, P., 1991. The metabolism of exogenous L-dopa in the brain: an immunohistochemical study of its conversion to dopamine in non-catecholaminergic cells of the rat brain. *J Neural Transm Park Dis Dement Sect* 3**,** 27-39.

Tison, F., Negre-Pages, L., Meissner, W.G., Dupouy, S., Li, Q., Thiolat, M.L., Thiollier, T., Galitzky, M., Ory-Magne, F., Milhet, A., Marquine, L., Spampinato, U., Rascol, O., Bezard, E., 2013. Simvastatin decreases levodopa-induced dyskinesia in monkeys, but not in a randomized, placebo-controlled, multiple cross-over ("n-of-1") exploratory trial of simvastatin against levodopa-induced dyskinesia in Parkinson's disease patients. *Parkinsonism Relat Disord* 19**,** 416-421.

Todd, R.D., Carl, J., Harmon, S., O'Malley, K.L., Perlmutter, J.S., 1996. Dynamic changes in striatal dopamine D_2 and D_3 receptor protein and mRNA in response to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) denervation in baboons. *J. Neurosci.* 16**,** 7776-7782.

Togasaki, D.M., Protell, P., Tan, L.C., Langston, J.W., Di Monte, D.A., Quik, M., 2005. Dyskinesias in normal squirrel monkeys induced by nomifensine and levodopa. *Neuropharmacology* 48**,** 398-405.

Togasaki, D.M., Tan, L., Protell, P., Di Monte, D.A., Quik, M., Langston, J.W., 2001. Levodopa induces dyskinesias in normal squirrel monkeys. *Ann. Neurol.* 50**,** 254-257.

Tomiyama, M., Kimura, T., Maeda, T., Tanaka, H., Kannari, K., Baba, M., 2004. Upregulation of striatal adenosine A2A receptor mRNA in 6-hydroxydopamine-lesioned rats intermittently treated with L-DOPA. *Synapse* 52**,** 5.

Tong, J., Fitzmaurice, p.S., Ang, L.C., Furukawa, Y., Guttman, M., Kish, S.J., 2004. Brain dopamine-stimulated adenylyl cyclase activity in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Ann. Neurol.* 55**,** 125-129.

Triarhou, L.C., Brundin, P., Doucet, G., Norton, J., Bjorklund, A., Ghetti, B., 1990. Intrastriatal implants of mesencephalic cell suspensions in weaver mutant mice: ultrastructural relationships of dopaminergic dendrites and axons issued from the graft. *Experimental brain research* 79**,** 3-17.

Triller, A., Choquet, D., 2008. New concepts in synaptic biology derived from single-molecule imaging. *Neuron* 59**,** 359-374.

Troiano, A.R., de la Fuente-Fernandez, R., Sossi, V., Schulzer, M., Lee, C., Ruth, T.J., Stoessl, A.J., 2006. Positron emission tomography demonstrates reduced dopamine transporter expression in PD patients with dyskinesia [abstract]. *Movement Disorders* 21**,** S634.

Tronci, E., Fidalgo, C., Stancampiano, R., Carta, M., 2015. Effect of selective and non-selective serotonin receptor activation on l-DOPA-induced therapeutic efficacy and dyskinesia in parkinsonian rats. *Behav Brain Res* 292**,** 300-304.

Tronci, E., Fidalgo, C., Zianni, E., Collu, M., Stancampiano, R., Morelli, M., Gardoni, F., Carta, M., 2014. Effect of memantine on L-DOPA-induced dyskinesia in the 6-OHDA-lesioned rat model of Parkinson's disease. *Neuroscience* 265**,** 245-252.

Tronci, E., Lisci, C., Stancampiano, R., Fidalgo, C., Collu, M., Devoto, P., Carta, M., 2013. 5-Hydroxy-tryptophan for the treatment of L-DOPA-induced dyskinesia in the rat Parkinson's disease model. *Neurobiol Dis* 60**,** 108-114.

Tronci, E., Simola, N., Borsini, F., Schintu, N., Frau, L., Carminati, P., Morelli, M., 2007. Characterization of the antiparkinsonian effects of the new adenosine A2A receptor antagonist ST1535: acute and subchronic studies in rats. *Eur J Pharmacol* 566**,** 94-102.

Trulson, M.E., Hosseini, A., 1987. Dopamine neuron transplants: electrophysiological unit activity of intrastriatal nigral grafts in freely moving cats. *Life Sci* 40**,** 2097-2102.

Tsacopoulos, M., Magistretti, P.J., 1996. Metabolic coupling between glia and neurons. *J Neurosci* 16**,** 877-885.

Ueno, T., Yamada, J., Nishijima, H., Arai, A., Migita, K., Baba, M., Ueno, S., Tomiyama, M., 2014. Morphological and electrophysiological changes in intratelencephalic-type pyramidal neurons in the motor cortex of a rat model of levodopa-induced dyskinesia. *Neurobiol Dis* 64**,** 142-149.

Ulusoy, A., Sahin, G., Kirik, D., 2010. Presynaptic dopaminergic compartment determines the susceptibility to L-DOPA-induced dyskinesia in rats. *Proc Natl Acad Sci U S A* 107**,** 13159-13164.

Ungerstedt, U., 1971a. Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta Physiol Scand Suppl* 367**,** 95-122.

Ungerstedt, U., 1971b. Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigrostriatal dopamine system. *Acta Physiol. Scand. Suppl.* 367**,** 69-93.

Urs, N.M., Bido, S., Peterson, S.M., Daigle, T., Bass, C.E., Gainetdinov, R., Bezard, E., Caron, M.G., 2015. Targeting beta-arrestin2 in the treatment of L-DOPA-induced dyskinesia in Parkinson's disease. *Proc Natl Acad Sci U S A* in press.

Urs, N.M., Daigle, T.L., Caron, M.G., 2011. A Dopamine D1 Receptor-Dependent beta-Arrestin Signaling Complex Potentially Regulates Morphine-Induced Psychomotor Activation but not Reward in Mice. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 36**,** 551-558.

Valastro, B., Dekundy, A., Krogh, M., Lundblad, M., James, P., Danysz, W., Quack, G., Cenci, M.A., 2007. Proteomic analysis of striatal proteins in the rat model of L-DOPA-induced dyskinesia. *J Neurochem* 102**,** 1395-1409.

Valjent, E., Corvol, J.C., Pages, C., Besson, M.J., Maldonado, R., Caboche, J., 2000. Involvement of the extracellular signal-regulated kinase cascade for cocaine-rewarding properties. *J Neurosci* 20**,** 8701-8709.

Valjent, E., Pascoli, V., Svenningsson, P., Paul, S., Enslen, H., Corvol, J.C., Stipanovich, A., Caboche, J., Lombroso, P.J., Nairn, A.C., Greengard, P., Herve, D., Girault, J.A., 2005. Regulation of a protein phosphatase cascade allows convergent dopamine and

glutamate signals to activate ERK in the striatum. *Proc Natl Acad Sci U S A* 102**,** 491-496.

Van Blercom, N., Lasa, A., Verger, K., Masramon, X., Sastre, V.M., Linazasoro, G., 2004. Effects of gabapentin on the motor response to levodopa: a double-blind, placebo-controlled, crossover study in patients with complicated Parkinson disease. *Clin Neuropharmacol* 27**,** 124-128.

van de Witte, S.V., Drukarch, B., Stoof, J.C., Voorn, P., 1998. Priming with L-DOPA differently affects dynorphin and substance P mRNA levels in the striatum of 6-hydroxydopamine-lesioned rats after challenge with dopamine D1-receptor agonist. *Mol. Brain Res.* 61**,** 5.

van de Witte, S.V., Groenewegen, H.J., Voorn, P., 2002. 43, 1-11., 2002. MK-801 alters the effects of priming with L-DOPA on dopamine D1 receptor-induced changes in neuropeptide mRNA levels in the rat striatal output neurons. . *Synapse.* 43**,** 11.

van den Munckhof, P., Gilbert, F., Chamberland, M., Levesque, D., Drouin, J., 2006. Striatal neuroadaptation and rescue of locomotor deficit by L-dopa in aphakia mice, a model of Parkinson's disease. *J Neurochem* 96**,** 160-170.

van den Munckhof, P., Luk, K.C., Ste-Marie, L., Montgomery, J., Blanchet, P.J., Sadikot, A.F., Drouin, J., 2003. Pitx3 is required for motor activity and for survival of a subset of midbrain dopaminergic neurons. *Development* 130**,** 2535-2542.

van Eimeren, T., Ballanger, B., Pellecchia, G., Miyasaki, J.M., Lang, A.E., Strafella, A.P., 2009. Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: a trigger for pathological gambling in Parkinson's disease? *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 34**,** 2758-2766.

van Eimeren, T., Pellecchia, G., Cilia, R., Ballanger, B., Steeves, T.D., Houle, S., Miyasaki, J.M., Zurowski, M., Lang, A.E., Strafella, A.P., 2010. Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD. *Neurology* 75**,** 1711-1716.

van Kampen, J.M., Stoessl, A.J., 2003. Effects of oligonucleotide antisense to dopamine D3 receptor mRNA in a rodent model of behavioural sensitization to levodopa. *Neuroscience* 116**,** 307-314.

Varanese, S., Howard, J., Di Rocco, A., 2010. NMDA antagonist memantine improves levodopa-induced dyskinesias and "on-off" phenomena in Parkinson's disease. *Mov Disord* 25**,** 508-510.

Varastet, M., Riche, D., Maziere, M., Hantraye, P., 1994. Chronic MPTP treatment reproduces in baboons the differential vulnerability of mesencephalic dopaminergic neurons observed in Parkinson's disease. *Neuroscience* 63**,** 47-56.

Vasudevan, A., Won, C., Li, S., Erdelyi, F., Szabo, G., Kim, K.S., 2012. Dopaminergic neurons modulate GABA neuron migration in the embryonic midbrain. *Development* 139**,** 3136-3141.

Verhagen Metman, L., Blanchet, P.J., van den Munckhof, P., Del Dotto, P., Natte, R., Chase, T.N., 1998a. A trial of dextromethorphan in parkinsonian patients with motor response complications. *Mov Disord* 13**,** 414-417.

Verhagen Metman, L., Del Dotto, P., van den Munckhof, P., Fang, J., Mouradian, M.M., Chase, T.N., 1998b. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology* 50**,** 1323-1326.

Vezoli, J., Fifel, K., Leviel, V., Dehay, C., Kennedy, H., Cooper, H.M., Gronfier, C., Procyk, E., 2011. Early presymptomatic and long-term changes of rest activity cycles and cognitive behavior in a MPTP-monkey model of Parkinson's disease. *PloS one* 6**,** e23952.

Villalba, R.M., Lee, H., Smith, Y., 2009. Dopaminergic denervation and spine loss in the striatum of MPTP-treated monkeys. *Exp Neurol* 215**,** 220-227.

Violin, J.D., DiPilato, L.M., Yildirim, N., Elston, T.C., Zhang, J., Lefkowitz, R.J., 2008. beta2-adrenergic receptor signaling and desensitization elucidated by quantitative modeling of real time cAMP dynamics. *J. Biol. Chem.* 283**,** 2949-2961.

Violin, J.D., Lefkowitz, R.J., 2007. β-Arrestin-biased ligands at seven-transmembrane receptors *Trends Pharmacol Sci* 28**,** 416-422.

Visanji, N.P., de Bie, R.M., Johnston, T.H., McCreary, A.C., Brotchie, J.M., Fox, S.H., 2008. The nociceptin/orphanin FQ (NOP) receptor antagonist J-113397 enhances the effects of levodopa in the MPTP-lesioned nonhuman primate model of Parkinson's disease. *Mov Disord* 23**,** 1922-1925.

Visanji, N.P., Gomez-Ramirez, J., Johnston, T.H., Pires, D., Voon, V., Brotchie, J.M., Fox, S.H., 2006a. Pharmacological characterization of psychosis-like behavior in the MPTP-

lesioned nonhuman primate model of Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 21**,** 1879-1891.

Visanji, N.P., Millan, M.J., Brotchie, J.M., 2006b. Actions at sites other than D(3) receptors mediate the effects of BP897 on l-DOPA-induced hyperactivity in monoamine-depleted rats. *Exp Neurol* 202**,** 85-92.

Vishnivetskiy, S.A., Raman, D., Wei, J., Kennedy, M.J., Hurley, J.B., Gurevich, V.V., 2007. Regulation of arrestin binding by rhodopsin phosphorylation level. *J Biol Chem* 282**,** 32075-32083.

Volkmann, J., 2004. Deep brain stimulation for the treatment of Parkinson's disease. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society* 21**,** 6-17.

von Ahsen, O., Bömer, U., 2005. High-throughput screening for kinase inhibitors. *ChemBioChem* 6**,** 481-890.

Voon, V., Fernagut, P.O., Wickens, J., Baunez, C., Rodriguez, M., Pavon, N., Juncos, J.L., Obeso, J.A., Bezard, E., 2009. Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. *Lancet Neurol* 8**,** 1140-1149.

Voon, V., Gao, J., Brezing, C., Symmonds, M., Ekanayake, V., Fernandez, H., Dolan, R.J., Hallett, M., 2011a. Dopamine agonists and risk: impulse control disorders in Parkinson's disease. *Brain* 134**,** 1438-1446.

Voon, V., Hassan, K., Zurowski, M., Duff-Canning, S., de Souza, M., Fox, S., Lang, A.E., Miyasaki, J., 2006. Prospective prevalence of pathologic gambling and medication association in Parkinson disease. *Neurology* 66**,** 1750-1752.

Voon, V., Mehta, A.R., Hallett, M., 2011b. Impulse control disorders in Parkinson's disease: recent advances. *Curr Opin Neurol* 24**,** 324-330.

Voon, V., Potenza, M.N., Thomsen, T., 2007a. Medication-related impulse control and repetitive behaviors in Parkinson's disease. *Curr Opin Neurol* 20**,** 484-492.

Voon, V., Reynolds, B., Brezing, C., Gallea, C., Skaljic, M., Ekanayake, V., Fernandez, H., Potenza, M.N., Dolan, R.J., Hallett, M., 2010. Impulsive choice and response in dopamine agonist-related impulse control behaviors. *Psychopharmacology (Berl)* 207**,** 645-659.

Voon, V., Thomsen, T., Miyasaki, J.M., de Souza, M., Shafro, A., Fox, S.H., Duff-Canning, S., Lang, A.E., Zurowski, M., 2007b. Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease. *Arch Neurol* 64**,** 212-216.

Wall, N.R., De La Parra, M., Callaway, E.M., Kreitzer, A.C., 2013. Differential innervation of direct- and indirect-pathway striatal projection neurons. *Neuron* 79**,** 347-360.

Wang, J., Liu, Z.L., Chen, B., 2001. Association study of dopamine D2, D3 receptor gene polymorphisms with motor fluctuations in PD. *Neurology* 56**,** 1757-1759.

Watabe-Uchida, M., Zhu, L., Ogawa, S.K., Vamanrao, A., Uchida, N., 2012. Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron* 74**,** 858-873.

Waters, C.H., Kurth, M., Bailey, P., Shulman, L.M., LeWitt, P., Dorflinger, E., Deptula, D., Pedder, S., 1997. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. The Tolcapone Stable Study Group. *Neurology* 49**,** 665-671.

Weaver, F.M., Follett, K.A., Stern, M., Luo, P., Harris, C.L., Hur, K., Marks, W.J., Jr., Rothlind, J., Sagher, O., Moy, C., Pahwa, R., Burchiel, K., Hogarth, P., Lai, E.C., Duda, J.E., Holloway, K., Samii, A., Horn, S., Bronstein, J.M., Stoner, G., Starr, P.A., Simpson, R., Baltuch, G., De Salles, A., Huang, G.D., Reda, D.J., Group, C.S.P.S., 2012. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology* 79**,** 55-65.

Weintraub, D., David, A.S., Evans, A.H., Grant, J.E., Stacy, M., 2015. Clinical spectrum of impulse control disorders in Parkinson's disease. *Mov Disord* 30**,** 121-127.

Weintraub, D., Koester, J., Potenza, M.N., Siderowf, A.D., Stacy, M., Voon, V., Whetteckey, J., Wunderlich, G.R., Lang, A.E., 2010. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* 67**,** 589-595.

Weintraub, D., Nirenberg, M.J., 2013. Impulse control and related disorders in Parkinson's disease. *Neuro-degenerative diseases* 11**,** 63-71.

Weintraub, D., Papay, K., Siderowf, A., 2013. Screening for impulse control symptoms in patients with de novo Parkinson disease: a case-control study. *Neurology* 80**,** 176-180.

Weintraub, D., Potenza, M.N., 2006. Impulse control disorders in Parkinson's disease. *Current neurology and neuroscience reports* 6**,** 302-306.

Wessell, R.H., Ahmed, S.M., Menniti, F.S., Dunbar, G.L., Chase, T.N., Oh, J.D., 2004. NR2B selective NMDA receptor antagonist CP-101,606 prevents levodopa-induced

motor response alterations in hemi-parkinsonian rats. *Neuropharmacology* 47**,** 184-194.

West, A.R., Tseng, K.Y., 2011. Nitric Oxide-Soluble Guanylyl Cyclase-Cyclic GMP Signaling in the Striatum: New Targets for the Treatment of Parkinson's Disease? *Front Syst Neurosci* 5**,** 55.

Westin, J.E., Andersson, M., Lundblad, M., Cenci, M.A., 2001. Persistent changes in striatal gene expression induced by long-term L-DOPA treatment in a rat model of Parkinson's disease. *The European journal of neuroscience* 14**,** 1171-1176.

Westin, J.E., Lindgren, H.S., Gardi, J., Nyengaard, J.R., Brundin, P., Mohapel, P., Cenci, M.A., 2006. Endothelial proliferation and increased blood-brain barrier permeability in the basal ganglia in a rat model of 3,4-dihydroxyphenyl-L-alanine-induced dyskinesia. *J Neurosci* 26**,** 9448-9461.

Westin, J.E., Vercammen, L., Strome, E.M., Konradi, C., Cenci, M.A., 2007. Spatiotemporal pattern of striatal ERK1/2 phosphorylation in a rat model of L-DOPA-induced dyskinesia and the role of dopamine D1 receptors. *Biol Psychiatry* 62**,** 800-810.

Whone, A.L., Rabiner, E.A., Arahata, Y., Luthra, S.K., Hargreaves, R., Brooks, D.J., 2002. Reduced substance P binding in Parkinson's disease complicated by dyskinesias: an 18F-L829165 PET study [abstract]. *Neurology* 58**,** A488-A489.

Wichmann, T., Bergman, H., Starr, P.A., Subramanian, T., Watts, R.L., DeLong, M.R., 1999. Comparison of MPTP-induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia nigra pars reticulata in primates. *Exp. Brain Res.* 125**,** 397-409.

Wilden, U., 1995. Duration and amplitude of the light-induced cGMP hydrolysis in vertebrate photoreceptors are regulated by multiple phosphorylation of rhodopsin and by arrestin binding. *Biochemistry* 34**,** 1446-1454.

Willets, J.M., Nash, M.S., Challiss, R.A., Nahorski, S.R., 2004. Imaging of muscarinic acetylcholine receptor signaling in hippocampal neurons: evidence for phosphorylation-dependent and -independent regulation by G-protein-coupled receptor kinases. *J. Neurosci.* 24**,** 4157-4162.

Willets, J.M., Parent, J.L., Benovic, J.L., Kelly, E., 1999. Selective reduction in A2 adenosine receptor desensitization following antisense-induced suppression of G protein-coupled receptor kinase 2 expression. *J. Neurochem.* 73**,** 1781-1789.

Williams, D.R., Lees, A.J., 2005. Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study. *Lancet neurology* 4**,** 605-610.

Winkler, C., Kirik, D., Bjorklund, A., Cenci, M.A., 2002. L-DOPA-induced dyskinesia in the intrastriatal 6-hydroxydopamine model of parkinson's disease: relation to motor and cellular parameters of nigrostriatal function. *Neurobiol Dis* 10**,** 165-186.

Witta, J., Palkovits, M., Rosenberger, J., Cox, B.M., 2004. Distribution of nociceptin/orphanin FQ in adult human brain. *Brain Res* 997**,** 24-29.

Wolf, E., Seppi, K., Katzenschlager, R., Hochschorner, G., Ransmayr, G., Schwingenschuh, P., Ott, E., Kloiber, I., Haubenberger, D., Auff, E., Poewe, W., 2010. Long-term antidyskinetic efficacy of amantadine in Parkinson's disease. *Mov Disord* 25**,** 1357-1363.

Wolz, M., Lohle, M., Strecker, K., Schwanebeck, U., Schneider, C., Reichmann, H., Grahlert, X., Schwarz, J., Storch, A., 2010. Levetiracetam for levodopa-induced dyskinesia in Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *J Neural Transm* 117**,** 1279-1286.

Won, L., Ding, Y., Singh, P., Kang, U.J., 2014. Striatal cholinergic cell ablation attenuates L-DOPA induced dyskinesia in Parkinsonian mice. *J Neurosci* 34**,** 3090-3094.

Wonnacott, S., Sidhpura, N., Balfour, D.J., 2005. Nicotine: from molecular mechanisms to behaviour. *Curr Opin Pharmacol* 5**,** 53-59.

Wu, D.F., Yang, L.Q., Goschke, A., Stumm, R., Brandenburg, L.O., Liang, Y.J., Höllt, V., Koch, T., 2008. Role of receptor internalization in the agonist-induced desensitization of cannabinoid type 1 receptors. *J Neurochem* 104**,** 1132-1143.

Wu, T., Hallett, M., 2013. The cerebellum in Parkinson's disease. *Brain* 136**,** 696-709.

Wu, Y.R., Levy, R., Ashby, P., Tasker, R.R., Dostrovsky, J.O., 2001. Does stimulation of the GPi control dyskinesia by activating inhibitory axons? *Mov Disord* 16**,** 208-216.

Wylie, S.A., Ridderinkhof, K.R., Bashore, T.R., van den Wildenberg, W.P., 2010. The effect of Parkinson's disease on the dynamics of on-line and proactive cognitive control during action selection. *Journal of cognitive neuroscience* 22**,** 2058-2073.

Xiao, D., Bastia, E., Xu, Y.H., Benn, C.L., Cha, J.H., Peterson, T.S., Chen, J.F., Schwarzschild, M.A., 2006. Forebrain adenosine A2A receptors contribute to L-3,4-dihydroxyphenylalanine-induced dyskinesia in hemiparkinsonian mice. *J. Neurosci.* 26**,** 13548-13555.

Xiao, D., Cassin, J.J., Healy, B., Burdett, T.C., Chen, J.F., Fredholm, B.B., Schwarzschild, M.A., 2011. Deletion of adenosine A(1) or A((2)A) receptors reduces L-3,4-dihydroxyphenylalanine-induced dyskinesia in a model of Parkinson's disease. *Brain Res* 1367**,** 310-318.

Xiao, K., McClatchy, D.B., Shukla, A.K., Zhao, Y., Chen, M., Shenoy, S.K., Yates, J.R., 3rd, Lefkowitz, R.J., 2007. Functional specialization of beta-arrestin interactions revealed by proteomic analysis. *Proc Natl Acad Sci U S A* 104**,** 12011-12016.

Yahalom, G., Kaplan, N., Vituri, A., Cohen, O.S., Inzelberg, R., Kozlova, E., Korczyn, A.D., Rosset, S., Friedman, E., Hassin-Baer, S., 2012. Dyskinesias in patients with Parkinson's disease: effect of the leucine-rich repeat kinase 2 (LRRK2) G2019S mutation. *Parkinsonism Relat Disord* 18**,** 1039-1041.

Yahr, M.D., Duvoisin, R.C., Hoehn, M.M., Schear, M.J., Barrett, R.E., 1968. L-Dopa : its clinical effects in parkinsonism. *Trans. Amer. Neurol. Ass.* 93**,** 56-63.

Yang, X., Wu, N., Song, L., Liu, Z., 2013. Intrastriatal injections of KN-93 ameliorates levodopa-induced dyskinesia in a rat model of Parkinson's disease. *Neuropsychiatric disease and treatment* 9**,** 1213-1220.

Yao, W.D., Gainetdinov, R.R., Arbuckle, M.I., Sotnikova, T.D., Cyr, M., Beaulieu, J.M., Torres, G.E., Grant, S.G., Caron, M.G., 2004. Identification of PSD-95 as a regulator of dopamine-mediated synaptic and behavioral plasticity. *Neuron* 41**,** 625-638.

Yao, W.D., Spealman, R.D., Zhang, J., 2008. Dopaminergic signaling in dendritic spines. *Biochem Pharmacol* 75**,** 2055-2069.

Yin, H.H., Knowlton, B.J., Balleine, B.W., 2004. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *Eur J Neurosci* 19**,** 181-189.

Yin, H.H., Ostlund, S.B., Knowlton, B.J., Balleine, B.W., 2005. The role of the dorsomedial striatum in instrumental conditioning. *Eur J Neurosci* 22**,** 513-523.

Yue, J.L., Okamura, H., Goshima, Y., Nakamura, S., Geffard, M., Misu, Y., 1994. Baroreceptor-aortic nerve-mediated release of endogenous L-3,4-dihydroxyphenylalanine and its tonic depressor function in the nucleus tractus solitarii of rats. *Neuroscience* 62**,** 145-161.

Zaveri, N., Jiang, F., Olsen, C., Polgar, W., Toll, L., 2005. Small-molecule agonists and antagonists of the opioid receptor-like receptor (ORL1, NOP): ligand-based

analysis of structural factors influencing intrinsic activity at NOP. *AAPS J* 7**,** E345-352.

Zeng, B.Y., Iravani, M.M., Jackson, M.J., Rose, S., Parent, A., Jenner, P., 2010. Morphological changes in serotoninergic neurites in the striatum and globus pallidus in levodopa primed MPTP treated common marmosets with dyskinesia. *Neurobiol Dis* 40**,** 599-607.

Zengin-Toktas, Y., Authier, N., Denizot, H., Chassain, C., Hafidi, A., Llorca, P.M., Durif, F., 2013. Motivational properties of D2 and D3 dopamine receptors agonists and cocaine, but not with D1 dopamine receptors agonist and L-dopa, in bilateral 6-OHDA-lesioned rat. *Neuropharmacology* 70**,** 74-82.

Zesiewicz, T.A., Sullivan, K.L., Maldonado, J.L., Tatum, W.O., Hauser, R.A., 2005. Open-label pilot study of levetiracetam (Keppra) for the treatment of levodopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 20**,** 1205-1209.

Zhang, D., Bordia, T., McGregor, M., McIntosh, J.M., Decker, M.W., Quik, M., 2014a. ABT-089 and ABT-894 reduce levodopa-induced dyskinesias in a monkey model of Parkinson's disease. *Mov Disord* 29**,** 508-517.

Zhang, D., Mallela, A., Sohn, D., Carroll, F.I., Bencherif, M., Letchworth, S., Quik, M., 2013a. Nicotinic receptor agonists reduce L-DOPA-induced dyskinesias in a monkey model of Parkinson's disease. *J Pharmacol Exp Ther* 347**,** 225-234.

Zhang, D., McGregor, M., Decker, M.W., Quik, M., 2014b. The alpha7 Nicotinic Receptor Agonist ABT-107 Decreases l-Dopa-Induced Dyskinesias in Parkinsonian Monkeys. *J Pharmacol Exp Ther* 351**,** 25-32.

Zhang, J., Vinuela, A., Neely, M.H., Hallett, P.J., Grant, S.G., Miller, G.M., Isacson, O., Caron, M.G., Yao, W.D., 2007. Inhibition of the dopamine D1 receptor signaling by PSD-95. *J Biol Chem* 282**,** 15778-15789.

Zhang, L., Balan, G., Barreiro, G., Boscoe, B.P., Chenard, L.K., Cianfrogna, J., Claffey, M.M., Chen, L., Coffman, K.J., Drozda, S.E., Dunetz, J.R., Fonseca, K.R., Galatsis, P., Grimwood, S., Lazzaro, J.T., Mancuso, J.Y., Miller, E.L., Reese, M.R., Rogers, B.N., Sakurada, I., Skaddan, M., Smith, D.L., Stepan, A.F., Trapa, P., Tuttle, J.B., Verhoest, P.R., Walker, D.P., Wright, A.S., Zaleska, M.M., Zasadny, K., Shaffer, C.L., 2014c. Discovery and preclinical characterization of 1-methyl-3-(4-methylpyridin-3-yl)-6-(pyridin-2-ylmethoxy)-1H-pyrazolo-[3,4-b]pyra zine (PF470): a highly potent,

selective, and efficacious metabotropic glutamate receptor 5 (mGluR5) negative allosteric modulator. *Journal of medicinal chemistry* 57**,** 861-877.

Zhang, S., Xie, C., Wang, Q., Liu, Z., 2014d. Interactions of CaMKII with dopamine D2 receptors: roles in levodopa-induced dyskinesia in 6-hydroxydopamine lesioned Parkinson's rats. *Scientific reports* 4**,** 6811.

Zhang, X., Andren, P.E., Greengard, P., Svenningsson, P., 2008. Evidence for a role of the 5-HT1B receptor and its adaptor protein, p11, in L-DOPA treatment of an animal model of Parkinsonism. *Proc Natl Acad Sci U S A* 105**,** 2163-2168.

Zhang, Y., Meredith, G.E., Mendoza-Elias, N., Rademacher, D.J., Tseng, K.Y., Steece-Collier, K., 2013b. Aberrant restoration of spines and their synapses in L-DOPA-induced dyskinesia: involvement of corticostriatal but not thalamostriatal synapses. *J Neurosci* 33**,** 11655-11667.

Zheng, Z., Li, Y., Li, J., Zhang, Y., Zhang, X., Zhuang, P., 2010. Stimulation-induced dyskinesia in the early stage after subthalamic deep brain stimulation. *Stereotactic and functional neurosurgery* 88**,** 29-34.

Zhou, F.M., Wilson, C.J., Dani, J.A., 2002. Cholinergic interneuron characteristics and nicotinic properties in the striatum. *Journal of neurobiology* 53**,** 590-605.

Zhu, K., van Hilten, J.J., Putter, H., Marinus, J., 2013. Risk factors for hallucinations in Parkinson's disease: results from a large prospective cohort study. *Movement disorders : official journal of the Movement Disorder Society* 28**,** 755-762.

Zhuang, X., Belluscio, L., Hen, R., 2000. G(olf)alpha mediates dopamine D1 receptor signaling. *J Neurosci* 20**,** RC91.

Zidar, D.A., Violin, J.D., Whalen, E.J., Lefkowitz, R.J., 2009. Selective engagement of G protein coupled receptor kinases (GRKs) encodes distinct functions of biased ligands. *Proc Natl Acad Sci U S A* 106**,** 9649-9654.

10. Figure legends

Figure 1: Anatomo-functional organization of the basal ganglia brain regions classically involved in Parkinson's disease (PD) and L-dopa induced dyskinesia (LID) pathophysiology. Red corresponds to excitatory glutamate pathways, blue corresponds to inhibitory GABA (γ-aminobutyric acid)-releasing pathway, and green corresponds to the dopamine projections from the substantia nigra pars compacta (SNc). Changes in colour intensity indicate the level of activity of individual projection systems. The upper half of the striatum that is directly connected to the internal part of the Globus Pallidus (GPi)/SNr corresponds to the medium spiny neurons that bear D1 dopamine receptors (direct pathway). The lower half, which is indirectly connected to GPi/SNr through the external part of the Globus Pallidus (GPe) and Subthalamic Nucleus (STN), corresponds to medium spiny neurons that bear D2 dopamine receptors (indirect pathway). In PD, degeneration of SNc neurons (paler green) breaks the striatal dopamine homeostasis, inducing hyperactivity of the GPi (darker blue), which brakes neuronal activity in the supplementary motor area (SMA, paler red). In LID, exogenous supply of levodopa and/or dopamine receptor agonists might act at structures previously innervated by dopamine neurons. The net result would be hypoactivity of the GPi (paler blue), leading to a hyperactivity of SMA neurons (darker red). VL: Ventral lateral thalamus. CM/PF: centromedian (CM) and parafascicular (PF) complex of the thalamus**.**

Figure 2: Bidirectional synaptic plasticity in Parkinson's disease (PD) and L-dopa induced dyskinesia (LID) in striatal medium spiny neurons (MSNs). (A) Long-term depression (LTD) and long-term potentiation (LTP) in MSNs mediated by a high frequency stimulation (HFS). **(B)** Fully dopamine (DA)-denervated rats (black circles) lose both form of synaptic plasticity. Partially denervated rats present a normal LTD (grey circles, left graph) but only a short-term potentiation (grey circles, right graph). **(C)** Chronic L-dopa treatment restores bidirectional synaptic plasticity (LTD, LTP and depotentiation) in Non-Dyskinetic animals (green circles) while the Dyskinetic rats (red circles) lose the capability to depotentiate the previously induced LTP by a low frequency stimulation (LFS) protocol. **(D)** LFS induces the depotentiation of previous HFS-mediated LTP in individual patients, in ON medication without dyskinesias at time of test (green circles, left graph). LFS is not capable of depotentiating previous HFS-mediated LTP in dyskinetic patient during ON phase (red circles, right graph). **(E)** In healthy subjects, continuous theta burst stimulation (cTBSc0)

protocol induces motor evoked potential (MEP) (left graph). cTBS150 applied 1 minute after cTBSc0 is able to depotentiate the potentiation to baseline levels (left graph). In dyskinetic PD patients the same protocol does not modify the potentiation induced by cTBSc0 (right graph).

Figure 3: Handling of L-dopa in L-dopa induced dyskinesia (LID) physiopathology. (A) Normal L-dopa handling. Dopaminergic terminals convert L-dopa into dopamine (DA) which is released in the synaptic cleft in a controlled way due to the expression of a fine regulatory mechanism composed of the dopaminergic D2 receptor (D2R) and the dopamine active transporter (DAT) proteins. Indeed, D2R and DAT can regulate the firing rate of dopaminergic neurons and DA reuptake, respectively, leading to a regulated DA release. **(B)** Aberrant L-dopa handling. In a situation of advanced DA denervation, the serotonergic (5-HT) neurons become the main site of L-dopa conversion to DA. However, the loss of the last spared dopaminergic terminals, which could buffer 5-HT neuron-derived DA release, triggers the appearance of LID due to the absence of the D2R/DAT feedback control mechanism for DA release on 5-HT neurons. The absence of this mechanism makes 5-HT neuron-derived DA release uncontrolled, contributing to swings in synaptic DA levels, and promoting pulsatile stimulation of striatal postsynaptic DA receptors. **(C)** The silencing of serotoninergic neurons through 5-HT1A/1B auto-receptor agonists decreases excessive swings in DA release and related LID.

Figure 4: Dopaminergic receptors signalling pathways. (A) D1 receptor (D1R) signalling. Dopamine-stimulated D1R activates the adenylyl cyclase (AC) which increases the synthesis of cyclic adenosine monophosphate (cAMP) activating the protein kinase A (PKA) in contrast to the D3 receptor (which cross-talks with D1R). PKA then phosphorylates GluA1 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor and the dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32). Phosphorylation at the T34 specific threonyl residue converts DARPP-32 into a selective inhibitor of protein phosphatase-1 (PP-1). This, in turn, suppresses the dephosphorylation of numerous downstream targets of PKA. Activated-D1R, cross talking to N-methyl-D-aspartate (NMDA) receptor, leads also to activation of extracellular signal-regulated protein kinases (ERK) controlling transcriptional and translational mechanisms. PKA/DARPP-32 and ERK/mitogen- and stress-activated kinase 1 (MSK1) signalling lead to phosphorylation of histone H3 in the nucleus, inducing changes in gene expression. **(B) D2**

receptor (D2R) signalling. Adenosine promotes cAMP synthesis through A2A receptors that activates PKA signalling which directly phosphorylates several substrates. In contrast, dopamine-stimulated D2R inhibits cAMP production and PKA signalling. **(C) Mechanism of D1R homologous desensitization**: Dopamine-stimulated D1R activates G proteins (Gαolf). G protein-coupled receptor kinases (GRK) then phosphorylate D1R and reduce G proteins coupling, inducing an increased affinity for arrestins. Arrestin binding on D1R prevents the association of new G proteins, definitely blocking further D1R activation. Arrestins are able to bind clathrins and trigger D1R endocytosis into endosomes. Then, D1R is either driven into lysosomes to be degraded or phosphatases assure D1R recycling to the plasma membrane.

Figure 5: Anatomo-functional organization of extended basal ganglia brain regions. Red corresponds to excitatory glutamate pathways in the basal ganglia, blue corresponds to inhibitory GABA (γ-aminobutyric acid)-releasing pathway in the basal ganglia, and green corresponds to the dopamine projections from the substantia nigra pars compacta (SNc) in the basal ganglia or the ventral tegmental area (VTA) outside of the basal ganglia. Black corresponds to the brain regions outside of the basal ganglia connected to these nuclei through the internal part of the Globus Pallidus (GPi) and the cerebral cortex. GPe: external part of the Globus Pallidus. STN: Subthalamic Nucleus. VL: Ventral lateral thalamus. CM/PF: centromedian and parafascicular complex of the thalamus