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LEVODOPA-INDUCED DYSKINESIAS IN PARKINSON'S DISEASE: CURRENT KNOWLEDGE AND FUTURE SCENARIOS

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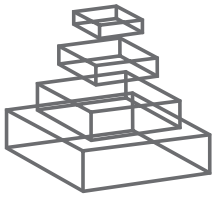

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LEVODOPA-INDUCED DYSKINESIAS IN PARKINSON'S DISEASE: CURRENT KNOWLEDGE AND FUTURE SCENARIOS

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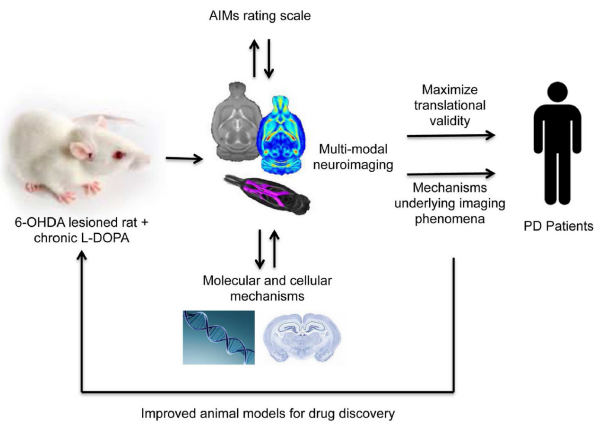
This topic aims to pool the most recent advances in the phenomenology and pathophysiology of levodopa-induced dyskinesias. The papers in this eBook have strongly contributed to reduce the gaps in our knowledge of LIDs pathogenesis.



A translational methodological framework for the combination of rodent models of LID with multimodal imaging, behavior and post-mortem cellular, or molecular analysis to elucidate the mechanisms underlying imaging phenomena associated with levodopa dyskinesia observed in human Parkinson's disease patients

(Front. Neurol. doi: 10.3389/fneur.2014.00095, Brain Morphometry and the Neurobiology of Levodopa-Induced Dyskinesias: Current Knowledge and Future Potential for Translational Pre-Clinical Neuroimaging Studies
Clare J. Finlay, Susan Duty and Anthony C. Vernon)

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EDITORIAL
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Future scenarios for levodopa-induced dyskinesias in Parkinson's disease

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After its first use in clinic since 1960, oral administration of L-3,4-dihydroxyphenylalanine (levodopa) remains the main treatment for Parkinson's disease (PD) patients. Although the vast majority respond positively to treatment, a significant proportion of PD patients develop daily fluctuations in mobility and troublesome involuntary movements known as levodopa-induced dyskinesias (LIDs). The time-to-onset and severity of this motor complication show large individual variability thus limiting the long-term use of levodopa and clinical strategies aimed at reducing LIDs manifestation. In the last few years, a considerable effort has been made to understand the neurobiological basis of this motor complication. In particular, recent evidence coming from human and animal studies has strongly contributed to reduce the gaps in our knowledge of LIDs pathogenesis.

The papers in this research topic highlight several themes relevant to the understanding of the clinical and neurobiological basis of LIDs. From a neuropsychological perspective, Pietracupa et al. (1) have explored the clinical correlated of the poor awareness of LIDs in PD patients; since the few studies conducted so far have used different methods and different patient populations, several hypotheses have been postulated, which suggest that several possible mechanisms may be implicated. One of the most recently proposed mechanisms emphasizes the role of proprioceptive and sensorimotor deficits associated with the impairment of the posterior parietal-ponto-cerebellar pathways, as nicely tested in a sample of PD patients with and without LIDs in the study by Stevenson et al. (2). Furthermore, using a top-down approach, the present topic firstly presents the latest neurophysiological findings in human models obtained using neuroimaging techniques and then moves toward cellular and molecular mechanisms of LIDs in animal model.

Finlay et al. (3) systematically adopted this approach in reviewing the recent literature with the scope to define a translation strategy that can bridge animal studies (that allow to assess the precise effects of drug treatment) with neuroimaging data on humans. These authors also discussed the last evidence provided by our works (4, 5), where we demonstrated that LIDs patients are characterized by anatomical and functional abnormalities of the prefrontal cortex involving the supplementary motor area (SMA) and the inferior frontal cortex (IFC). This notion has been recently confirmed by two independent groups investigating LIDs patients during the ON phase of levodopa therapy (6, 7). In particular, Herz et al. (6) investigated brain functional activity of LIDs during a motor task, continuously for 45 min after levodopa intake before the beginning of peak-dose dyskinesias. They found that PD patients with dyskinesias display an immediate hypersensitivity of the SMA and putamen to levodopa. Moreover, abnormal resting-state functional connectivity between the IFC and the putamen was demonstrated in PD patients with LID at 60 min after levodopa intake, consistent with the expected time peaks of dyskinesia (7).

Beyond the multiple phenomenology of LIDs in PD patients, further insights on the pathophysiology of hyperkinetic movement disorders derive from studies conducted in patients with idiopathic dystonia, tardive dyskinesia (TD), and Gilles de la Tourette syndrome (GTS). Dystonia is a hyperkinetic movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both (8). The term TD referred to abnormal movements produced by the chronic exposure to dopamine receptor blocking agents. GTS is a childhood-onset complex neurobehavioral disorder defined by motor and phonic tics, which can be often complicated by comorbid conditions that could progress to behavioral changes. Recent neuroimaging papers demonstrate the presence of anatomical abnormalities involving the IFC in all these disorders (9–11). That is, we have hypothesized a common pathophysiological mechanism for all these hyperkinetic disorders, including LIDs, based on the inability by specific prefrontal areas to suppress involuntary movements (12, 13). Accordingly, other papers in this topic addressed this hypothesis (14, 15). Overviewing PET-related findings, Alongi et al. (14) discussed how this neuroimaging technique has demonstrated, both in idiopathic dystonia and GTS, metabolic and neurotransmission abnormalities not limited to the cortico-striato-pallido-thalamo-cortical pathway and also within the cerebello-thalamo-cortical network. Tessitore et al. (15) highlight a similar application for fMRI technique in PD

patients, mainly discussing the usefulness of resting-state connectivity analysis. Blood oxygen level-dependent functional MRI signal recorded while the subject lies at rest with eyes closed represents an important tool for understanding brain disorders in patients with PD. Brain regions with similar functions have been shown to display robust functional connectivity during rest, which reflects the presence of direct and indirect anatomical pathways. For this reason, these authors proposed that in the near future, the practical application of this technique might provide a reliable MRI biomarker for an early diagnosis of PD.

Involvement of cortical areas (motor areas and prefrontal cortices) as well of the cerebellum in patients with LIDs has been also suggested by transcranial magnetic stimulation (TMS) studies, specifically using protocols to probe synaptic plasticity in humans (7, 16, 17). In the current research topic, Kishore et al. (18) propose a pathophysiological model of LIDs in PD in which aberrant impaired plasticity in the motor cortex might be sustained by deficient cerebellar modulation of sensory afferents to the motor cortex itself. In this comprehensive review, the authors outline functional and anatomical studies on basal ganglia circuits and their reciprocal connection with the cerebellum, as well the role of dopamine on the basal ganglia, the cortical motor areas and the cerebellum. The model proposed by Kishore et al. (18) allows to understand why non-invasive cerebellar stimulation may be efficacious in treating LIDs in PD (17). Notably, this notion parallels the aforementioned involvement of cortico-cerebellar pathways in the pathological processes of predictive motor control in LIDs (2).

The role of cortical areas such the IFC and the primary motor cortex and well of the cerebellum in the generation of LIDs is a novel concept supported by several recent studies reviewed in this research topic. Nevertheless, the cortico-striato-pallido-thalamocortical loop represents a critical network for the generation of LIDs as supported by the long-term beneficial effect of ablative surgery and deep brain stimulation (DBS) of the globus pallidus internus (GPi) and the subthalamic nucleus (STN) (19). Accordingly, one of the reviews of the present research topic is focused on the role of stereotactic surgery as a powerful tool to treat LIDs in PD (20). From ablative techniques (pallidotomy and subthalamotomy) to DBS of the GPi and the STN, the authors discuss the evidence for a direct anti-dyskinetic effect by techniques involving the GPi or the anteromedial portion of the STN, likely by current spreading to the pallido-thalamic bundle.

The current research topic is also enriched by three intriguing reviews related to the experimental models of LIDs. Animal models provide the unique opportunity to investigate in depth the molecular and cellular machinery involved in the pathophysiology of LIDs. Cenci (21) provides a comprehensive overview of the presynaptic mechanisms of LIDs, focusing on the central notion that the breakdown of pre-synaptic dopaminergic homeostasis predisposes to large fluctuations in therapeutic levels of dopamine upon treatment with levodopa (21). She also underlines the relevance of molecular, physiological, and morphological changes at postsynapatic level produced by dopaminergic denervation (21). One of the main concepts addressed in this review is the role of serotonin neurons in pathophysiological mechanisms of LIDs. Indeed, during the past few years, an abundant literature has support the hypothesis, although quite controversial, that LIDs may depend upon dopamine release from serotonin neurons. This hypothesis is the also the main subject of the review by Carta and Tronci (22). These authors revised the experimental evidence pointing to the role of serotonin neurons in producing dyskinesia, also discussing the clinical implications. Indeed, over the course of PD, other cellular compartments can substitute the lost dopaminergic neurons in mediating levodopa conversion to dopamine. In this context, the serotonergic system has emerged, in recent years, as a key player. In comparison to dopaminergic neurons, serotonin neurons share the same enzymatic machinery required to convert levodopa to dopamine and to store dopamine after exogenous administration of levodopa. However, serotonin neurons lack a feedback control mechanism able to fine-tune the synaptic levels of dopamine. Carta and Tronci (22) propose that this form of dopamine is released in an uncontrolled manner, leading to excessive synaptic dopaminergic peaks, and contributing to swings in synaptic dopaminergic levels following oral administration of levodopa. Although the authors discuss the vast body of evidence providing support for a major role of the serotonergic system in the appearance of LIDs in animal model, they also point out how clinical evidence for a role of serotonin modulation in attenuating LIDs in PD patients are still scarce and generally disappointing.

With a different perspective, Morin and Di Paolo report relevant studies investigating glutamate receptor subtypes in relation to motor complications in PD patients and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys (23). MPTP-lesioned primates are very useful to test potential antidyskinetic and/or anti-parkinsonian pharmacological agents. Glutamate receptors are reported to interact with numerous neurotransmitters and neuromodulators implicated in the development of LIDs including dopaminergic neurotransmission. The authors put the accent on the evidence that nigrostriatal denervation in PD leads to increased glutamatergic transmission in the basal ganglia and that glutamate receptor stimulation is involved in the pathogenesis of levodopa-induced motor complications in PD and glutamate receptor subtypes, such as mGlu5 and NMDA receptors, are potential selective targets for treatment of these adverse effects.

In conclusion, the contributions included in this research topic highlight the role of different cortical and subcortical areas as well as of other neurotransmitters beyond dopamine in the pathophysiology of LIDs. We hope that this research will stimulate new thinking about neurobiological mechanisms of LIDs.

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OPINION ARTICLE
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Parkinsonian patients and poor awareness of dyskinesias

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The question of whether the awareness of levodopa-induced dyskinesias (LID) is reduced, or altogether missing, in patients with Parkinson's disease (PD) has been attracting growing interest. Why is this topic important? Firstly, as studies addressing the efficacy of drugs on LID employ patients' motor diaries as an outcome measure, poor LID self-awareness might interfere with data collection in clinical trials; secondly, poor LID self-awareness may result in increased doses of dopaminergic drugs, which could in turn be associated with an enhanced risk of side effects such as LID. Lastly, understanding this phenomenon may shed light on some pathophysiological aspects of LID in PD.

The few studies conducted so far concluded that at least a proportion of PD patients are either partially or totally unaware of the presence of LID. These studies used different methods to ascertain LID awareness as well as different patient populations. Consequently, several hypotheses have been postulated to explain poor self-awareness of LID, which suggest that several possible mechanisms may be implicated.

An impairment in the experience of moving abnormally was suggested by Vitale et al. (1) in a pilot study conducted on PD patients (and on patients with Huntington disease). The authors found that poor LID self-awareness was more marked in PD patients with mild LID, and therefore suggested that poor LID self-awareness merely reflects the fact that when LID are mild, their interference with normal activities is limited and patients tend to underestimate them. These results, however, were not confirmed in the study conducted by Sitek et al. (2), who instead observed, by means of a video protocol, that poor self-awareness of LID was more pronounced in patients with longer symptom duration (and therefore with possibly more severe LID). This finding reported by Sitek et al. (2) thus suggests that other mechanisms are likely to play a role in the phenomenon of poor self-awareness of LID. Amanzio et al. (3) believed that factors linked to the cognitive domain might be involved. In a well planned study, they investigated whether awareness of different movement disorders in cognitively intact PD patients differs in the *on* and *off* states. The results of their study revealed a significant difference between awareness of LID measured in the *on* state and awareness of hypo-bradykinesia assessed in the *off* state. In particular, while 22 of the 25 patients enrolled in their study displayed a reduced awareness of LID, a reduced awareness of hypo-bradykinetic movement disorders was found in only 6 of the 25 patients. On the basis on these findings, the authors suggested that dopaminergic therapy may, by stimulating mesocortical–limbic pathways, exert a detrimental effect on the function of the orbitofrontal and cingulated frontal–subcortical loops, thereby contributing to a poor self-awareness of LID. Supporting this view, recent papers indeed showed that frontal cortex studied by advanced neuroimaging techniques differ between patients with or without LID. In one study, PD patients with LID had significant overactivity in the supplementary motor area and underactivity in the right inferior prefrontal gyrus during execution of motor tasks when compared with PD patients without LID (4). In addition, in another study cortical thickness analysis revealed a pronounced increase of thickness in the right inferior frontal sulcus in PD patients with LID with respect to PD patients without LID (5). The hypothesis of Amanzio et al. is not, however, supported by the observations of other authors, who found that poor self-awareness is not only associated with LID, but also with motor symptoms assessed in the *off* state, and that awareness of *off* motor symptoms improved, at least in part, during the *on* state following dopaminergic stimulation (1, 6, 7). Maier et al. (7) also found that the severity of impairment of motor self-awareness was unrelated to dopamine-dependent executive functioning. These authors also reported that impaired awareness of abnormal movements (and therefore of LID) was significantly associated with the postural instability gait disorder phenotype of PD to a greater extent than with the hyperkinetic phenotype. Although the postural instability gait disorder phenotype is frequently associated with cognitive decline, it is noteworthy that the severity of the impaired awareness of movement in the study by Maier et al. (7) was not correlated with either disease duration or cognitive outcome. Other authors have proposed alternative or complementary hypotheses. For example, one noteworthy finding comes from the work by Jenkinson et al. (8), who highlighted the fact that normal motor awareness entails a correct comparison of intended vs. actual movement, and predicted in their work that anosognosia of LID in PD arises from a failure to detect discrepancies between intended movement and visual feedback. To test their hypothesis, they used a mirror to reverse the expected visual consequence of an executed movement. PD patients with poor self-awareness of LID did not

detect any differences between congruent and incongruent movement, whereas non-anosognosic PD patients and healthy volunteers reported incongruent movement as being stranger than congruent movement. The findings of Jenkinson et al.'s (8) work thus support the hypothesis that normal motor awareness entails a comparison of intended and actual movement. Indeed, the intactness of the comparator in non-anosognosic PD patients and healthy volunteers is demonstrated by the finding that incongruent movement was reported to be stranger than congruent movement by both these groups, as well as by the fact that there were no significant differences between non-anosognosic PD patients and healthy volunteers. These results are in keeping with the hypothesis of a breakdown of the comparator mechanism in PD patients with anosognosia. According to this hypothesis, if reduced or lack of awareness of LID in PD is a form of anosognosia, then a dysfunction of the right hemisphere is presumably involved. If we bear in mind that PD is usually characterized by asymmetric motor involvement, this paradigm may prove useful as a means of verifying whether patients with more severe symptoms on the left side of the body suffer from a greater degree of anosognosia of LID than patients with more severe symptoms on the right side of the body. Indeed, dysfunction of the right hemisphere seems to contribute to impaired self-awareness of motor symptoms. By studying non-demented PD patients who were tested prior to a unilateral pallidotomy, Leritz et al. (6) found not only that PD patients as a group rated themselves as being less impaired than their caregivers did, but also that PD patients with right-sided symptoms (left pallidotomy patients) rated themselves as being more impaired on two ADL measures than patients with left-sided symptoms (right pallidotomy patients). In other words, patients with more severe symptoms on the left side of the body were less aware of their motor and functional deficit than patients with more severe symptoms on the right side of the body. In a recent work, we investigated awareness of LID in 30 PD patients who had no cognitive dysfunction (9). In that study, which was based on a video protocol, we initially found that 23.3% of the patients investigated were unaware of the presence of their LID. However, when patients were asked to recognize LID while watching video-recordings of themselves, most of them recognized their own LID. Moreover, the same patients recognized LID in video-recordings of reference PD patients. None of the clinical variables (e.g., age, duration of symptoms, severity of disease, duration, and dose of dopaminergic drugs) or neuropsychological variables we took into consideration correlated with poor self-awareness of LID. The only clinical feature that did correlate with poor self-awareness of LID was a prevalence of motor symptoms on the left side of the body. These results led us to hypothesize that LID unawareness is indeed predominantly a form of anosognosia. Might anosognosia of LID be another form of anosognosia due to right subcortical lesions, as has been reported in patients with hemichorea/hemiballism following contralateral infarction of the caudate nucleus (10)? It is more likely that PD patients with left hemi-body involvement are less aware of LID than patients with right hemi-body involvement because of an abnormal interaction in the complex network involving the posterior parietal cortex, the supplementary motor area, the premotor cortex, and the dorsolateral prefrontal cortex, all of which are regions that play a role in the awareness of voluntary movements (11, 12).

Awareness, in general, may also be linked to network activity, as demonstrated recently by Ham et al. (13) who investigated whether self-awareness deficits are associated with network dysfunction after traumatic brain injury. In this study, resting-state and event-related functional magnetic resonance imaging showed that neural activity within the fronto-parietal control network and the dorsal anterior cingulate cortex was abnormal in patients with impaired self-awareness. It could be worth exploring by means of resting-state and event-related functional magnetic resonance whether network dysfunction is also present in PD patients with poor awareness of LID.

Another question that warrants consideration is whether LID awareness varies depending on the body part examined. In this regard, we observed that PD patients are less aware of LID in the trunk (9). Although there is no clear explanation for this finding, some neurophysiological observations may help to shed light on the issue. In a noteworthy experimental study, Wright et al. (14) demonstrated that PD patients control the direction of axial twisting in both the hips and trunk less accurately than normal subjects. Another interesting observation that emerged from the study by Wright et al. (14) was that the proprioceptive deficit in the trunk may be exacerbated by levodopa administration. It is tempting to speculate, therefore, that mechanisms underlying this body site-specific poor awareness of LID may be due to the complex interplay between anosognosia and the impairment in axial kinesthesia observed in PD patients (14). Supporting this hypothesis is the observation that PD patients may also display poor awareness of other trunk abnormalities, such as bent trunk (camptocormia) and lateral deviation of the trunk (Pisa syndrome) (15). Poor awareness of LID in the trunk may be of considerable relevance in PD patients because it might contribute to the lack of control over balance and worsen the postural instability of PD patients, thereby predisposing patients in more complicated stages of the disease to falls during the *on* phases. Although much has yet to be understood regarding the intriguing phenomenon of poor motor and LID awareness in PD and other movement disorders, the studies we have analyzed in this brief review may be considered a starting point.

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Excessive sensitivity to uncertain visual input in L-DOPA-induced dyskinesias in Parkinson's disease: further implications for cerebellar involvement

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When faced with visual uncertainty during motor performance, humans rely more on predictive forward models and proprioception and attribute lesser importance to the ambiguous visual feedback. Though disrupted predictive control is typical of patients with cerebellar disease, sensorimotor deficits associated with the involuntary and often unconscious nature of L-DOPA-induced dyskinesias in Parkinson's disease (PD) suggests dyskinetic subjects may also demonstrate impaired predictive motor control.

Methods: We investigated the motor performance of 9 dyskinetic and 10 non-dyskinetic PD subjects on and off L-DOPA, and of 10 age-matched control subjects, during a large-amplitude, overlearned, visually guided tracking task. Ambiguous visual feedback was introduced by adding "jitter" to a moving target that followed a Lissajous pattern. Root mean square (RMS) tracking error was calculated, and ANOVA, robust multivariate linear regression, and linear dynamical system analyses were used to determine the contribution of speed and ambiguity to tracking performance.

Results: Increasing target ambiguity and speed contributed significantly more to the RMS error of dyskinetic subjects off medication. L-DOPA improved the RMS tracking performance of both PD groups. At higher speeds, controls and PDs without dyskinesia were able to effectively de-weight ambiguous visual information.

Conclusion: PDs' visually guided motor performance degrades with visual jitter and speed of movement to a greater degree compared to age-matched controls. However, there are fundamental differences in PDs with and without dyskinesia: subjects without dyskinesia are generally slow, and less responsive to dynamic changes in motor task requirements, but in PDs with dyskinesia, there was a trade-off between overall performance and inappropriate reliance on ambiguous visual feedback. This is likely associated with functional changes in posterior parietal–ponto–cerebellar pathways.

Keywords: L-DOPA-induced dyskinesias, Parkinson's disease, dynamical system models, visually guided tracking, visual uncertainty

INTRODUCTION

Prediction is a fundamental component of motor control. For instance, when catching a baseball it is necessary to predict where the ball will be at a given instant and how much force its impact will generate in order to prepare the hand for the catch. Central to motor prediction is the forward model, which enables prediction of the sensory effects of movement (1). Substantial evidence indicates that humans use forward models to predict the sensory consequences of their own actions (1–6), as well as to predict the dynamics of objects in the external environment (4, 7–11). Furthermore, forward models of object dynamics are necessary to guide visuo-motor coordination tasks, and can even override observed kinematic feedback (12, 13).

Predictive forward modeling becomes even more imperative as the reliability of visual feedback is compromised, for example in dim lighting, or disease states such as Parkinson's disease (PD) where the visual system may be affected (14). Normally, human subjects account for the degree of sensory uncertainty during motor performance by de-weighting their reliance on sensory feedback when it is ambiguous (1, 6, 15–20), and instead more heavily rely on predictive forward models (6, 18, 20). However, when subjects are unable to use predictive motor control, the

motor response no longer anticipates sensory feedback but rather reacts to it in an uncoordinated manner (21–24).

Motor performance in PD, at least in the early stages of the disease, is greatly improved by pharmacotherapy, and L-DOPA remains the gold standard of treatment in PD (25). However, L-DOPA-induced dyskinesias (LIDs) – excessive choreoathetoid involuntary movements – are a relatively common side effect of L-DOPA of which peak-dose LIDs are the most common type (26). Though LID pathophysiology remains unclear, behavioral studies suggest that rather than being a purely motor phenomenon, LIDs may be associated with deficits in sensorimotor control (27–29). For example, dyskinetic subjects have demonstrated increased variation in tracking velocity during a visually guided tracking task that was significantly reduced when visual feedback was withdrawn, suggesting an exaggerated motor response to sensory input (27). As dyskinetic subjects are often unaware of their involuntary movements (30), and have been shown to underestimate the distance their limb has moved (28), a component of sensorimotor deficits associated with LIDs may be attributed to impaired predictive motor control. For instance, a mismatch between predicted movement and actual movement may drive dyskinetic subjects to compensate for the sensory discrepancy with excessive movement. Deficits in predictive motor control are typically seen in diseases of the cerebellum (31–36), yet such deficits have also been demonstrated in PD (37, 38). There is evidence to support cerebellar involvement in LIDs (39), and altered activity and plasticity in the prefrontal cortex in dyskinetic subjects (40, 41) may contribute to altered sensorimotor control in LIDs.

If inadequate predictive motor control is an underlying feature of dyskinetic subjects' motor performance, then a heightened reliance on sensory feedback should be especially prominent in conditions where healthy subjects rely more heavily on predictive forward models, such as when confronted with ambiguous visual feedback (6). Accordingly, we hypothesized that dyskinetic subjects would demonstrate an impaired ability to de-weight ambiguous visual feedback during a visually guided tracking task. We have purposely chosen a motor adaptation task, whereby subjects had to adapt to changing sensory information. We have recently demonstrated that overall, PD subjects are susceptible to sensory uncertainty during visually-guided tracking (42), but in that study we did not dichotomize dyskinetic and non-dyskinetic subjects. We have since recruited additional PD subjects while employing the same tracking task to assess the reliance on uncertain visual feedback of dyskinetic and non-dyskinetic PD (NDPD) subjects. As previous work has demonstrated linear dynamical system (LDS) models to be a sensitive marker of motor performance in PD (42, 43), here we use LDS models in addition to quantifying tracking error to assess tracking performance. By extracting the decay rate parameter from the LDS models during ambiguous tracking, we quantified subjects' relative reliance on uncertain visual feedback.

MATERIALS AND METHODS

SUBJECTS

The Ethics Board of the University of British Columbia approved the study and all subjects gave written, informed consent. We recruited 19 patients with probable PD according to diagnostic criteria (44) and 10 age-matched control subjects without active neurological disorders. Exclusion criteria included known PD with dementia. PD subjects were Hoehn and Yahr stage 1–3 (45), and 9 subjects were dyskinetic PD (DPD) subjects and 10 were NDPD subjects. We did not screen subjects for the presence of depression or anxiety, however we excluded PD subjects with dementia and all subjects were cognitively able to follow the instructions and complete the tasks. Subject characteristics are shown in **Table 1**. All patients had overnight withdrawal of medications before the study for at least 12 h for L-DOPA and 18 h for dopamine agonists. We calculated the converted L-DOPA daily dosage as 100 mg L-DOPA = 125 mg of controlled-release L-DOPA, which was then added to the equivalents of dopamine agonists to give the L-DOPA equivalent daily dosage (LEDD), where 100 mg of L-DOPA = 1 mg of pramipexole, 6 mg of ropinirole, 10 mg of bromocriptine, 75 mg of L-DOPA plus entacapone. The presence of peak-dose LIDs was assessed up to 1.5 h after the L-DOPA challenge, where subjects received the equivalent of their morning L-DOPA dose given in the immediate release form. Peak-dose LIDs were defined by the presence of involuntary choreiform movements in any of the head/neck, trunk, and upper limbs of variable duration and in some cases were accompanied by dystonia. LID severity was assessed according to the Goetz Dyskinesia Rating Scale (46), and all DPD subjects had mild LID that were of minimal severity and did not interfere with voluntary motor acts (Goetz score = 1). Disease severity was assessed according to the Unified Parkinson's Disease Rating Scale (UPDRS) motor score in the off medication state.

STUDY PARADIGM

The large-amplitude tracking task used here has been previously described (42). Briefly, a Lissajous figure was presented on a screen measuring 1.62 m × 1.22 m with a red circular target (12 cm in diameter) in the center of the screen. Subjects stood approximately 55 cm in front of the screen, and tracked the moving target with their index finger, requiring movement about the wrist, elbow, and shoulder joints. We tested subjects in the standing position in order to facilitate larger amplitude movements more representative of everyday life that are often precluded in imaging studies. Additionally, evidence suggests LIDs may be of greater amplitude in the standing compared to the sitting position (47). In the baseline trials the target smoothly followed the Lissajous path, either at a slow tracking speed (average speed of 56.2 cm/s) or a fast tracking speed (average speed of 78.3 cm/s). In subsequent visually ambiguous conditions, the target jittered about the path while maintaining the path's overall trajectory. In the ambiguous tracking conditions, subjects were instructed to attempt not to chase the jitter, but rather to attempt to track the desired target's position, which maintained the overall Lissajous trajectory. Four levels of visual ambiguity were tested (0, 0.03, 0.05, 0.07) – representing the jitter root mean square (RMS) amplitude with respect to screen height (0, 0.0191, 0.0318, and 0.0445°), at two speeds, giving a total of eight conditions. The jitter was obtained by first starting with random Gaussian noise sampled at the frame rate of 60 Hz. Because we did not want excessive discontinuities in the visual pattern caused by high-frequencies, we then low-passed the random series at 20 Hz. Each condition was tested in three different trials, where a trial consisted of 30 s of tracking, a 12 s rest, followed

Table 1 | Subjects' characteristics.

Subject	Age	Disease duration	Motor exam UPDRS	Converted daily L-DOPA dosage (mg)	Other Parkinson's medications	Type of LID chorea (C) dystonia (D)	L-DOPA equivalent daily dose (mg)
DPD							
D1	65	22	65	650	Rop, amant	C, D	750
D2	64	7	42	880	Entac, amant	C	1173.3
D3	68	13	51	660	Entac	C	880
D4	65	15	57	720	Entac	C, D	960
D5	66	5	45	1020	None	C	1020
D6	64	4	22	1280	Pram	C	1580
D7	51	7	37	800	Bromo	C, D	1000
D8	55	13	40	640	Pram, amant	C, D	665
D9	75	8	47	600	None	C	600
DPD (mean ± SD)	63.7 ± 7	10.44 ± 5.8	45.11 ± 12.3	805.56 ± 223.33			958.7 ± 296.27
NDPD							
ND1	63	5	8	320	Pram	None	620
ND2	68	4	19	400	None	None	400
ND3	64	9	69	860	None	None	860
ND4	59	9	14	740	None	None	740
ND5	45	4	11	780	None	None	780
ND6	65	9	51	640	Entac, pram	None	1003.3
ND7	63	10	54	800	Pram	None	1000
ND8	66	7	22	640	Rop	None	673.3
ND9	62	5	31	400	None	None	400
ND10	59	12	47	400	Pram	None	775
NDPD (mean ± SD)	61.4 ± 6.4	7.4 ± 2.8	32.6 ± 21.2	598 ± 200.3			725.2 ± 211.3
Control (mean ± SD)	61.6 ± 7.9						
p Value	0.75	0.16	0.14	0.047			0.062

Rop, ropinirole; pram, pramipexole; amant, amantadine; bromo, bromocriptine; entac, entacapone.

by 30 s of tracking. The order of the trials began with the slow non-ambiguous condition followed by the fast non-ambiguous condition. The order of the remaining six ambiguous conditions was randomly selected. This same trial order of all eight tracking conditions was then repeated for the second and third trials. The trial order was the same for every subject. Subject DPD 9 was an exception and completed two trials of each condition due to complaints of fatigue. PD subjects performed this motor task in the morning when in the "off" medication state, and after a break for lunch subsequently repeated the task in the "on" medication state that same day.

QUANTIFICATION OF MANUAL TRACKING

We used a Polhemus Fastrak (Polhemus, Colchester, VT, USA) six-degrees-of-freedom electromagnetic tracking system to record subject tracking. A stylus sensor was held in the palm of the subjects' dominant hand and secured with tape. The tip of the stylus was aligned with the tip of the index finger in order to record subjects' index finger position. A time series for displacement was recorded in the *x*, *y*, and *z* directions, and data was recorded at 10 Hz. We performed a robust linear regression analysis on the *x* and *y* sensor data during non-ambiguous tracking to determine the optimum affine transformation to map the sensor data coordinates to the Lissajous figure coordinates. We subsequently applied the same transformation to the ambiguous conditions on a subject-by-subject basis.

QUANTIFICATION OF TRACKING PERFORMANCE

Root mean square tracking error was calculated by subtracting the processed *x* and *y* sensor data of the index finger from the *x* and *y* target position along the baseline track, squaring the result for each time point, taking the mean for the squared values for each trial, and computing the square root of the result.

Analysis of motor performance using LDS models is being increasingly utilized in sensorimotor studies (16, 48–51) and has been previously used to rigorously characterize tracking performance in PD (42, 43). We computed LDS models of subjects' tracking using system identification techniques (52) and extracted the decay rate parameter, which describes how quickly tracking performance returns to equilibrium after a perturbation. Intuitively, a higher decay rate can be considered akin to the tighter suspension of a sports car: tighter turning on a good road may be desirable, but when an uneven gravel (noisy) road is encountered, the ability to smooth out the bumps (i.e., de-weight the noise) is diminished. Thus during ambiguous tracking, higher decay rates can intuitively be interpreted as a greater response to ambiguous visual feedback (see Figure S1 in Supplementary Material). The natural logarithm of the decay rates were used to make the results

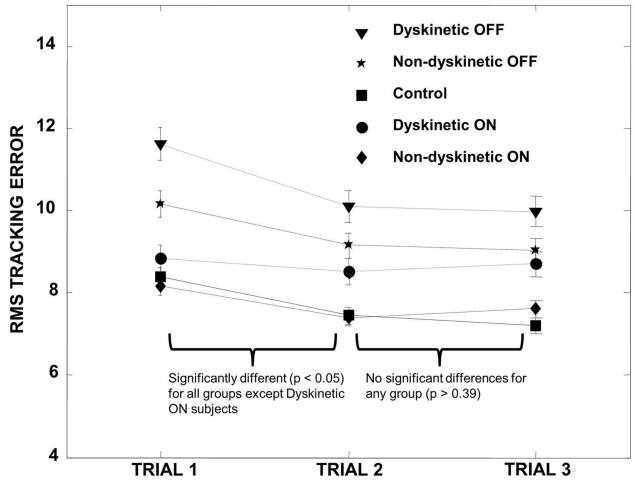

FIGURE 1 | Training effect. All groups demonstrated a significant decrease in RMS error between trial 1 and trial 2 except for the DPD ON group (where the decrease was not significant), and the RMS error subsequently stabilized for all groups between trials 2 and 3. We therefore omitted trial 1 data in all subsequent calculations. Error bars represent the standard error.

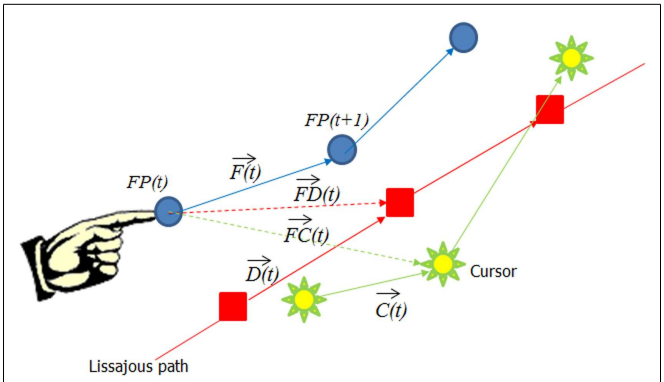

FIGURE 2 | The decomposition of the finger movement vector into different constituent vectors. The blue arrow represents the finger velocity [$\vec{F}(t)$], the green arrow the cursor velocity [$\vec{C}(t)$], the red arrow the desired velocity [$\vec{D}(t)$], the green dotted arrow from the finger position to the cursor [$\vec{FC}(t)$], and the red dotted arrow represents the vector from the finger to the desired point [$\vec{FD}(t)$].

more Gaussian distributed and this was subsequently used in all statistical analyses.

STATISTICAL ANALYSES

MatLab (The MathWorks Inc., MA, USA) was used for all statistical analyses. In order to control for a training effect between tracking trials, we first performed paired t-tests on the pooled RMS error of all groups (DPD and NDPD off and on medication and control) between trial sets 1 and 2 and trial sets 2 and 3. We observed a training effect between trial set 1 and 2 that stabilized between trial set 2 and 3 (**Figure 1**), and trial 1 data were therefore omitted from all subsequent data analysis to ensure we were not examining motor learning in our visually guided tracking task but rather the effect of visual uncertainty after learning had occurred and stabilized.

We used mixed-model analysis of variance (ANOVA) to assess different effects on both overall RMS error as well as decay rate. In the first instance, we examined the effect of ambiguity, tracking speed, and drug status (i.e., ON or OFF L-DOPA), PD group (i.e., DPD or NDPD), and subject number as factors in the ANOVA. Since the same PD subjects were assessed before and after L-DOPA, ambiguity, tracking speed, and drug status were considered within subject factors and subject number was nested within the PD group factor.

To compare the PD subjects with Normal subjects, we also used a mixed-model analysis of variance (ANOVA), where ambiguity, tracking speed, group (i.e., N, DPD ON or OFF L-DOPA, or NDPD ON or OFF L-DOPA) and subject number were used as factors in the ANOVA. As before, ambiguity and tracking speed were considered within subject factors and subject number was nested within the group factor. We then repeated the above two ANOVA analyses with log(decay rate) instead of RMS error.

In order to examine the relationship between UPDRS and the effect of ambiguity on tracking performance, we calculated Spearman's rank correlation coefficients between UPDRS and the difference in RMS error between the non-ambiguous and maximum ambiguous tracking conditions for each PD group, as well as between UPDRS and decay rate in each of the ambiguous tracking conditions. In order to better visualize the results of the ANOVA, a robust multivariate regression analysis was also performed, using RMS error or log(decay rate) as the dependent variable, and speed and ambiguity as the independent variables. Regression coefficients were obtained to indicate the portion of dependent variable explained by speed and ambiguity amplitude. Quality of LDS models' was assessed by the Akaike information criterion (AIC) with a model quality score based on a trade-off between matching the data well and penalizing the use of an excessive number of model parameters. Significance for all comparisons was declared at $p < 0.05$. We estimated the stability of the regression coefficients and the group-wise RMS and log(decay rate) values by leave-one-out validation.

In order to further evaluate what features in visual input influenced finger movement, we decomposed finger velocity into its projection along different vectors. As shown in **Figure 2**, we looked at Finger velocity $\vec{F}(t)$ [i.e., the vector from FP(t) to FP($t+1$)], depicted as a Blue arrow; the cursor movement on the screen $\vec{C}(t)$: green arrow, the desired velocity along the Lissajous path, $\vec{D}(t)$; the path from finger point to cursor point, $\overrightarrow{\mathrm{FC}}(t)$ green dotted arrow; and $\overrightarrow{\mathrm{FD}}(t)$ the path from the finger to the desired point: red dotted arrow. We used the "robustfit" function of MatLab to estimate the coefficients of a multivariate linear regression equation:

$$\begin{pmatrix} F_x(1) \\ F_y(1) \\ F_x(2) \\ F_y(2) \\ \dots \end{pmatrix} = F_o + \begin{pmatrix} FC_x(1) & FD_x(1) & C_x(1) & D_x(1) \\ FC_y(1) & FD_y(1) & C_y(1) & D_y(1) \\ FC_x(2) & FD_x(2) & C_x(2) & D_x(2) \\ FC_y(2) & FD_y(2) & C_y(2) & D_y(2) \\ \dots & \dots & \dots & \dots \end{pmatrix} \begin{pmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta 4 \end{pmatrix} + \in$$

We then compared DPD subjects before medication and after medication (i.e., D-pre vs. D-post), NDPD before and after medication (ND-pre vs. ND-post), as well as the difference in finger

Table 2 | Mixed-model analysis of variance (ANOVA) table to assess different effects on overall RMS error in PD subjects.

RMS: dyskinetic vs. non-dyskinetic PD					
Source	**Sum sq.**	**df**	**Mean sq.**	***F***	**Prob > *F***
Ambiguity	1764.544	1	1764.544	246.2379	1.5×10^{-11}
Speed	125.1352	1	125.1352	76.27172	2.9×10^{-11}
L-DOPA	10.50281	1	10.50281	2.544744	0.12
PD group	2.378259	1	2.378259	0.841198	0.37
Subject (PD group)	48.0629	17	2.827229	0.588631	0.87
Ambiguity × speed	18.34189	1	18.34189	19.12748	1.8×10^{-05}
Ambiguity × L-DOPA	28.59159	1	28.59159	29.81618	1.2×10^{-07}
Ambiguity × PD group	39.13004	1	39.13004	5.460503	0.03
Ambiguity × subject (PD group)	121.8222	17	7.166014	7.472938	1.6×10^{-14}
Speed × L-DOPA	3.5044	1	3.5044	3.654495	0.057
Speed × PD group	0.791581	1	0.791581	0.257766	0.62
Speed × subject (PD group)	52.20574	17	3.070926	3.202455	3.7×10^{-05}
L-DOPA × PD group	0.15373	1	0.15373	0.014268	0.90
L-DOPA × subject (PD group)	183.1669	17	10.77452	11.236	6.7×10^{-22}
Error	215.7589	225	0.958929		
Total	4069.522	303			

Root mean square error was taken as the dependent variable and the effect of ambiguity, tracking speed, and drug status (i.e., ON or OFF L-DOPA), PD group (i.e., DPD or NDPD), and subject number were used as factors in the ANOVA. Subject number was nested within the PD group factor, since the same PD subjects were assessed before and after L-DOPA. RMS, root mean square; Sum sq., sum of squares; df, degrees of freedom; Mean sq., mean squares; F, F statistic; Prob, probability.

Table 3 | Mixed-model analysis of variance (ANOVA) table to assess different effects on overall RMS error in all subjects.

RMS: all subjects					
Source	**Sum sq.**	**df**	**Mean sq.**	***F***	**Prob > *F***
Ambiguity	1975.723	1	1975.723	451.6872	1.9×10^{-24}
Speed	152.2342	1	152.2342	149.8938	1.0×10^{-23}
Group	21.47974	4	5.369934	3.660012	0.01
Subject (group)	63.08918	43	1.46719	1.445266	0.058
Ambiguity × speed	18.13801	1	18.13801	25.40773	9.1×10^{-7}
Ambiguity × group	99.69423	4	24.92356	5.69799	9.0×10^{-4}
Ambiguity × subject (group)	188.0861	43	4.374096	6.127235	1.1×10^{-20}
Speed × group	10.30256	4	2.57564	1.562198	0.20
Speed × subject (group)	70.89532	43	1.648728	2.309539	3.7×10^{-5}
Error	170.6168	239	0.713878		
Total	4707.803	383			

Root mean square error was the dependent variable and ambiguity, tracking speed, group (i.e., N, DPD ON or OFF L-DOPA, or NDPD ON or OFF L-DOPA), and subject number were used as factors in the ANOVA, with subject number nested within the group factor. RMS, root mean square; Sum sq., sum of squares; df, degrees of freedom; Mean sq., mean squares; F, F statistic; Prob, probability.

movement trajectories with and without noise for all groups of patients.

RESULTS

Subjects' characteristics are shown in **Table 1**. There were no significant differences between age, UPDRS, disease duration, and LEDD ($p > 0.05$), though converted daily L-DOPA dosage was significantly higher for the DPD group. Analysis of RMS error between trials revealed that there was a significant decrease in the pooled RMS error between trial set 1 and trial set 2 ($p < 0.00001$) that stabilized between trial sets 2 and 3 ($p = 0.7$). The individual groups' RMS error by trial is shown in **Figure 1**.

The results of the mixed-model ANOVA tests on RMS error are shown in **Tables 2** and **3**. When comparing DPD and NDPD subjects, ambiguity and tracking speed were significant independent factors on RMS error, as well as the interaction terms between ambiguity and tracking speed, PD group and drug status. When normal subjects were included in the analysis (**Table 3**), ambiguity,

Table 4 | Mixed-model analysis of variance (ANOVA) table to assess different effects on overall log(decay rate) in PD subjects.

Log(decay rate): dyskinetic vs. non-dyskinetic PD					
Source	**Sum sq.**	**df**	**Mean sq.**	***F***	**Prob > *F***
Ambiguity	8.197592	1	8.197592	109.5405	0
Speed	0.483603	1	0.483603	6.462162	0.01
L-DOPA	0.14046	1	0.14046	1.876896	0.17
PD group	0.062757	1	0.062757	0.365946	0.56
Subject (PD group)	18.32016	17	1.077656	14.40021	0
Ambiguity × speed	0.084005	1	0.084005	1.122517	0.29
Ambiguity × L-DOPA	0.107382	1	0.107382	1.434896	0.23
Ambiguity × PD group	0.422255	1	0.422255	5.642388	0.01
Speed × L-DOPA	0.052067	1	0.052067	0.695753	0.40
L-DOPA × PD group	1.581883	1	1.581883	21.13796	7.5×10^{-6}
Error	15.04207	201	0.074836		
Total	61.64793	227			

*The factors used were identical to that of **Table 2**, only log(decay rate) was used as opposed to overall RMS error as the dependent variable. Sum sq., sum of squares; df, degrees of freedom; Mean sq., mean squares; F, F statistic; Prob, probability.*

Table 5 | Mixed-model analysis of variance (ANOVA) table to assess different effects on overall log(decay rate) in all subjects.

Log(decay rate): all subjects					
Source	**Sum sq.**	**df**	**Mean sq.**	***F***	**Prob > *F***
Ambiguity	168.2415	1	168.2415	652.8348	0
Speed	0.644047	1	0.644047	4.313921	0.03
Group	2.767405	4	0.691851	3.262799	0.02
Subject (group)	9.117819	43	0.212042	1.420009	0.05
Ambiguity × speed	1.165972	1	1.165972	6.882016	9.2×10^{-3}
Ambiguity × group	5.921167	4	1.480292	5.74404	8.5×10^{-4}
Ambiguity × subject (group)	11.08149	43	0.257709	1.521099	0.027
Speed × group	0.573569	4	0.143392	1.339341	0.270
Speed × subject (group)	4.603654	43	0.107062	0.631919	0.964
Error	40.4921	239	0.169423		
Total	275.5562	383			

*The factors used were identical to that of **Table 3**, only log(decay rate) was used as opposed to overall RMS error as the dependent variable. Sum sq., sum of squares; df, degrees of freedom; Mean sq., mean squares; F, F statistic; Prob, probability.*

tracking speed, and group were all significant factors, as well as the interaction terms between ambiguity, speed, group, and subject. Similarly, when determining the effects on log(decay rate), ambiguity and speed were significant when comparing DPD and NDPD (**Table 4**), as well as the interaction between L-DOPA and PD group (**Table 4**). When control subjects were included in the analysis, significances were seen in the main effects of ambiguity, speed, and group, as well as the interaction effects of ambiguity and speed and group (**Table 5**).

The differences in RMS error between non-ambiguous and maximum ambiguous tracking conditions were not significantly correlated with UPDRS scores at either tracking speed for either dyskinetic subjects or for non-dyskinetic subjects and $p > 0.05$.

The overall effect of increasing ambiguity and speed on overall tracking performance, and the L-DOPA effect, is illustrated in **Figure 3**. As expected, there were increases in RMS error with both speed and visual ambiguity. DPD subjects had the highest error, which was partially ameliorated by L-DOPA. In NDPD subjects, after medication, the tracking error approached that of control subjects.

The effect of visual ambiguity on the log of decay rate is shown in **Figure 4**. At slow speeds and higher levels of ambiguity, NDPD subjects had lower log(decay rates) than controls (left panel). However, at higher tracking speeds the NDPD subjects had similar or higher log(decay rates) as controls. In contrast, DPD subjects had higher values for log(decay rate) at high ambiguity levels at both speeds, a situation not ameliorated by medication.

The regression analysis illustrates the relative contribution of increasing ambiguity and speed to RMS error (**Figure 5**) and log(decay rate) (Figure S1 in Supplementary Material) by group. The speed and ambiguity regression coefficients captured by the model were highly significant for all groups ($p < 10–5$), and the

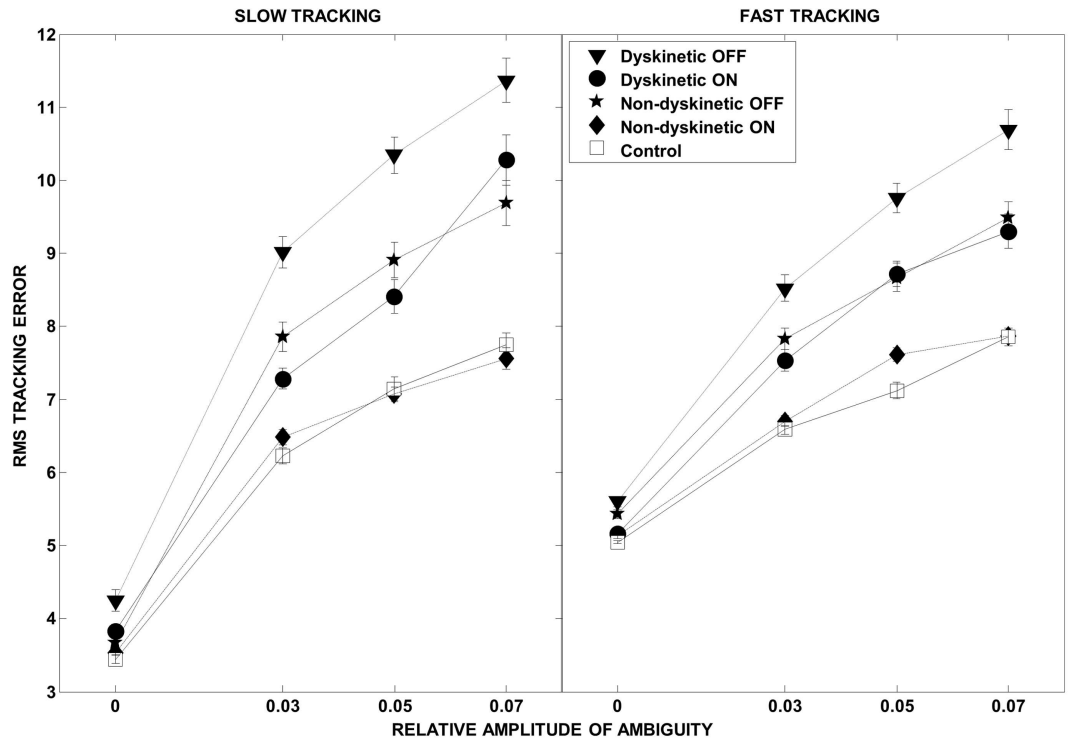

FIGURE 3 | Root mean square error as a function of visual ambiguity and tracking speed. Differences in RMS error in the low tracking speed condition (left panel) and high tracking speed condition (right panel) are shown. Error bars were estimated by leave-one-out-validation.

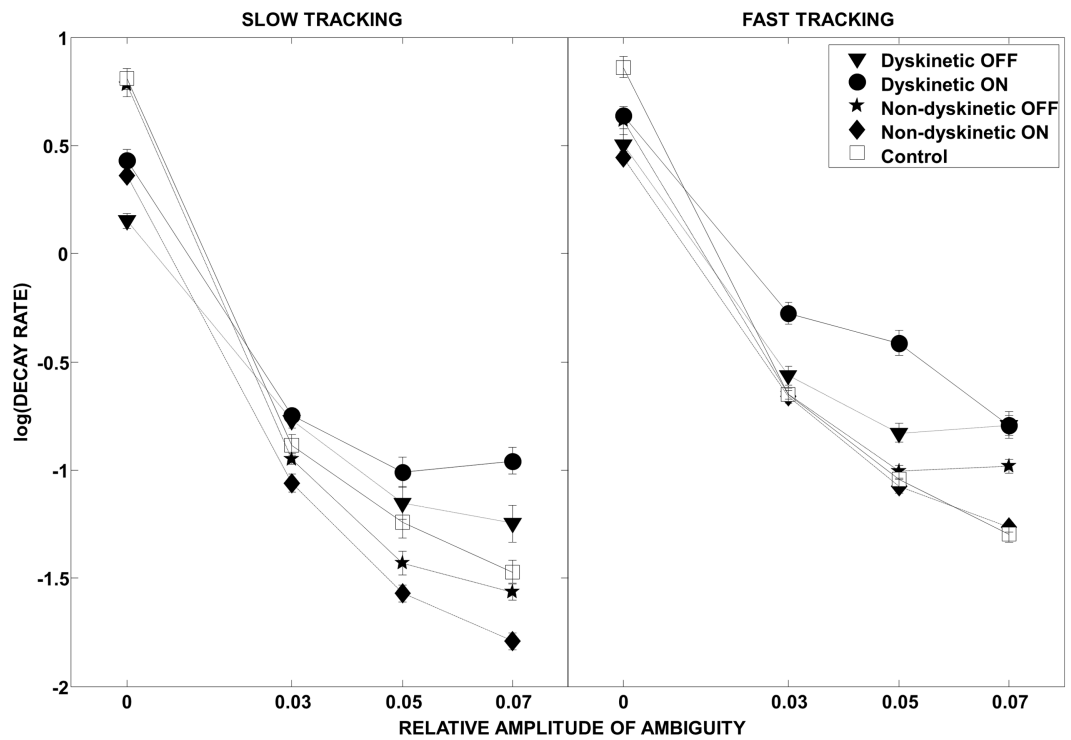

FIGURE 4 | Log(decay rate) as a function of visual ambiguity and tracking speed. Differences in RMS error in the low tracking speed condition (left panel) and high tracking speed condition (right panel) are shown. Error bars were estimated by leave-one-out-validation.

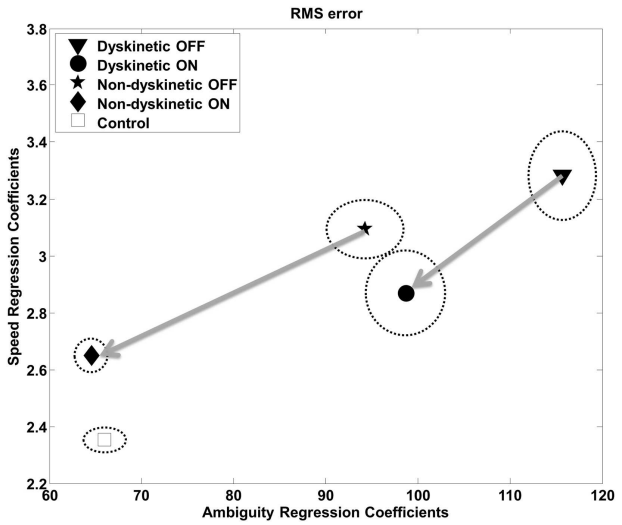

FIGURE 5 | Regression analysis – RMS. The relative contribution of increasing target ambiguity and speed to RMS error is demonstrated. The design matrix for the regression included tracking speed, ambiguity columns, as well as nuisance covariates corresponding to individual subject and overall mean. The units can be considered arbitrary. The vertical and horizontal radii of the ellipses represent the standard error of the regression coefficients as estimated by leave-one-out validation. The arrows are from the same PD subjects OFF medication to ON medication, and thus show the effects of L-DOPA medication.

between group differences in both speed and ambiguity regression coefficients were also highly significant ($p < 10–5$). **Figure 5** demonstrates that increasing tracking speed and ambiguity contributed to the RMS error of DPD OFF subjects significantly more than for all other groups. Additionally, the susceptibility to speed and visual ambiguity is not normalized with medication for DPD ON subjects, but is roughly normalized for NDPD ON subjects. Figure S1 in Supplementary Material suggests that log(decay rate) is significantly affected by visual ambiguity in PD, but especially so for DPD subjects. L-DOPA had less of an effect on the sensitivity of log(decay rate) to tracking speed in DPD compared to NDPD subjects.

The Akaike's final prediction error (FPE) and AIC used to assess the LDS models from ambiguous tracking conditions revealed robust tracking models. The means and standard deviations of the estimated LDS models' FPE and AIC scores were $\leq 3.1 \pm 2.0$ and $\leq 1.8 \pm 0.4$ respectively, for all groups across all conditions, which is indicative of high model quality/fit. Furthermore, there were few outliers in the FPE and AIC values indicating validity of the modeling framework across subject groups.

In order to get an intuitive interpretation of the significantly different decay rates, we interrogated typical models from each group (i.e., models with eigenvalues close to the mean for each group) with one-dimensional sinusoidal inputs and additive noise similar to the experiment to determine the predicted tracking performance. Ideal tracking performance would occur in systems that ignore the noisy input and faithfully maintain sinusoidal tracking. Consistent with the RMS error results, the sinusoidal tracking improved with post-medication models in both dyskinetic and non-dyskinetic subjects. However, consistent with the statistical results, the dyskinetic model had an impaired ability to ignore the noisy visual cue, and was excessively reliant on noisy ambiguous visual feedback (**Figure 6**).

We observed the significant differences in the decomposition of the finger tracking data, depending upon whether or not jitter was present (Figure S2 in Supplementary Material). For only the DPD (D-pre and D-post) group, we found that contribution of $\overrightarrow{FD}(t)$ – the vector from finger position to the desired position – increased ($p = 0.036$ and $p = 0.026$), while the contribution of $\vec{D}(t)$ – the desired trajectory – decreased when jitter was present ($p = 0.002$ and $p = 0.005$).

DISCUSSION

We examined the ability of 9 dyskinetic and 10 NDPD subjects, as well as that of 10 age-matched control subjects, to de-weight uncertain sensory feedback and instead rely more heavily on predictive motor control during visually guided tracking. The relative contributions of increasing target ambiguity and speed (examined independently) to the RMS tracking error were the greatest for DPD subjects off medication (**Figure 3**). As expected, L-DOPA medication improved overall tracking performance for both PD groups, as evidenced by reduced RMS error with medication (**Figure 3**).

Dyskinetic subjects' gross motor performance was worse in the Parkinsonian state than in the "on" medication state despite the presence of LIDs. This is consistent with the presence of mild LIDs experienced by DPD subjects that did not interfere with the completion of motor tasks, and the increased movement in the on-state compared to the Parkinsonian state that enabled improved overall motor performance. However in dyskinetic subjects, improved overall tracking performance came at a price: they were also more responsive to and reliant on non-informative visual cueing (**Figure 6**, right lower panel). We interpret our results in the context of established performance trade-offs in control theory, in which controllers that produce exceptionally fast, high-performance tracking under ideal circumstances are also extremely poor at disturbance rejection (that is, they experience high sensitivity to external or un-modeled noise processes). In a biological context, this is indicative of a system that relies more heavily on ambiguous sensory feedback and less on predictive motor control. This interpretation is further supported by the decomposition of the finger velocity $\dot{\vec{F}}(t)$. For DPD group only (i.e., D-pre and D-post), the contribution of the desired trajectory $\vec{D}(t)$, to finger velocity, $\dot{\vec{F}}(t)$, was significantly reduced during jitter cases, implying that finger movement velocity was significantly degraded by jitter in these subjects. Interestingly, $FD(t)$, i.e., where their finger was to where it should have been, significantly increased in the DPD group only, possibly reflecting an compensatory corrective motor movement after the realization that they had been misled by the jitter. The trends we observed in the LDS are consistent with the trends we observed through the regression analysis. The LDS model separates the contribution of the output due to the desired trajectory from the contribution of the output due to the additive jitter. The decreased reliance on $\vec{D}(t)$ in DPD subjects is consistent with the increased decay rate in the LDS – that is, the subjects are following the noise more than they were in the no-noise case.

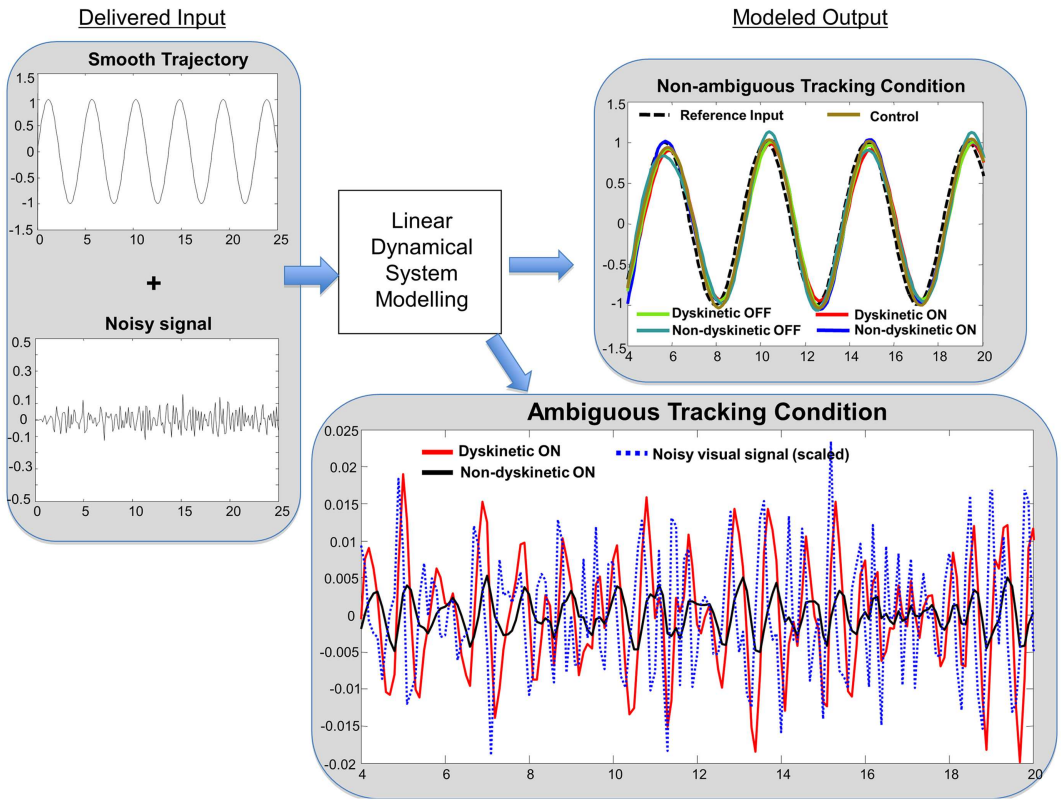

FIGURE 6 | Linear dynamical system model simulation results. Left panel: tracking input is a combination of a smooth sinusoidal reference trajectory and bandpass filtered white noise. Right panel: subjects modeled tracking output in a smooth non-ambiguous tracking condition (*upper box*) and in a "noisy" ambiguous tracking condition (*lower box*). In the upper box, the modeled tracking output of a representative subject from each group is shown. The subjects' output in non-ambiguous conditions is similar across groups. In the lower box, the effect of "noisy" ambiguous input on modeled output of a dyskinetic and a non-dyskinetic subject is shown. The increased decay rate of dyskinetic subjects on medication leads them to attempt to track the noise more significantly. The noisy visual signal is reduced to 15% of the actual magnitude for visualization purposes.

It is important to note that the LDS models utilized here are deterministic. The numerical algorithm used to identify the LDS model, in fact, minimizes the residual between the actual output and the predicted output, in essence capturing as much information as possible from the input–output relationship and leaving only white noise. What would we see if the only differences between DPD and NDPD were that the DPD subjects had the same tracking performance but superimposed dyskinesias that were truly random fluctuating movements? The parameters of the models would be the same, but the residuals of the model, which reflect the part of the movement not accurately captured by the deterministic model, would be much higher in the DPD case. Yet we observed the opposite: the model residuals were not significantly higher in the DPD subjects (as reflected by the lack of significant differences in their model scores) and the parameters of the model were appreciably different. In fact, this raises an important issue, that a key interpretation of our findings is that LIDs may not be "random" at all as is normally assumed, but a deterministic response to various endogenous and exogenous stimuli that is normally appropriately de-weighted. This may explain why increasing sensitivity to stimuli such as that seen in anxiety (53), or increased vigilance due to cognitive or motor load (54) may increase dyskinesias.

Normally, forward models are used to predict sensory feedback, and the predicted feedback is subsequently compared to actual feedback when it becomes available after an inherent delay (55, 56). The difference between the actual and predicted sensory feedback is known as the sensory discrepancy or error, which is then used to update the forward model and in turn improve motor performance (1, 56). In fact, the concept of forward modeling has been extended from predicting the sensory consequences of movement to predicting the external environment (4, 7–13). For example, evidence indicates that human subjects utilize forward models of visual cues (11), of target motion during interception tasks (12, 13), and of the physical laws of gravitational acceleration (4, 9, 15). We quantified RMS tracking error as the difference between the subjects' index finger position and the target position along the smooth Lissajous path at any given time point. During the non-ambiguous conditions of our tracking task, the sensory discrepancy is likely minimal as the predicted sensory feedback relating the subjects' index finger position and the target position would be congruent, which is supported by the lack of differences in RMS tracking error between the groups in the baseline conditions (**Figure 3**). However, in the ambiguous tracking conditions the sensory discrepancy would be large due to the ambiguous

jitter of the target. Human subjects have been shown to reliably predict the mean perturbation delivered from a variable distribution in reaching tasks (50, 57), and to do so according to Bayesian inference (17).

Though we did not explicitly test the use of Bayesian statistics in this study, the strategy of more heavily weighting the mean jitter amplitude and de-weighting the instantaneous uncertain jittering position of the target in order to predict the desired tracking position, corresponds to the optimal motor response in our task that minimizes RMS tracking error.

As expected, in our study, normal controls had the lowest overall tracking error of all groups (**Figure 3**). However, **Figure 4** provides interesting insight into how this is achieved. During slow tracking and in high ambiguous situations, NDPD subjects had even lower decay rates than controls, suggesting that they were robust to the ambiguity – so much so that they excessively de-weighted the (still partially meaningful) visual information. However, in the high speed tracking condition, it becomes more critical to de-weight the visual information and the originally sluggish approach of the NDPD becomes the appropriate response – this is why NDPD patients ON medication and controls had essentially the same decay rates. These observations are consistent with other studies demonstrating that NDPD subjects do not overly respond to visual feedback (58), and that healthy human subjects internally account for sensory uncertainty and de-weight uncertain feedback during motor performance (1, 18, 20). In contrast, in both slow and fast tracking conditions, the DPD subjects demonstrated excessively high decay rates (**Figure 4**), implying faster dynamics, even though this resulted in excessive overall tracking error (**Figure 2**).

Thus, the inability of DPD subjects to de-weight ambiguous visual data that we observed may be based on excessive sensitivity to discrepancies between a (accurate) forward model and sensory feedback and/or an impaired forward model. The effect of L-DOPA medication may provide insight on this. In addition to reducing overall tracking error (**Figure 3**), L-DOPA medication made overall tracking error less susceptible to tracking speed and visual ambiguity (**Figure 5**), but had minimal effect on the log(decay rate)'s sensitivity to tracking speed and visual ambiguity (Figure S1 in Supplementary Material). If we assume that decay rate is related to corrective sub-movements and hence responses to discrepancy between models, this would imply that L-DOPA largely improves forward model accuracy (and hence reduced RMS error's sensitivity to visual ambiguity and speed) while having minimal effect on the dynamics of the response to the errors between the forward model and sensory estimates (**Figure 5**).

A possible functional neuroanatomical correlate of the inability of DPD subjects to de-weight ambiguous visual feedback demonstrated in the present study is inadequate predictive cerebellar forward modeling. There is growing evidence of functional cerebellar changes occurring in PD (59–64) and in DPD (39) that supports this possibility. Furthermore, the cerebellum is known to have an integral role in predictive motor control, and predictive deficits that lead subjects to excessively respond to feedback are typically seen in cerebellar disease (21, 24, 31–34). Extensive evidence supports the use of forward models in human subjects (2–6), and neuroimaging, electrophysiology, and transcranial magnetic stimulation (TMS) studies provide strong evidence for the role of the cerebellum in forward modeling (31, 65–75). Interestingly, evidence from neuroimaging studies demonstrates significantly increased cerebellar activity in conditions of mismatch between predicted and actual feedback (66), and the degree of mismatch imposed by temporal delays has been correlated with cerebellar activity (76). Further evidence indicates that the cerebellar climbing fiber-Purkinje cell synapse may signal the error between the predicted and actual sensory feedback (71, 72, 77–80).

In addition to the cerebellum, the posterior parietal cortex (PPC) is believed to have an important role in predictive motor control (65). The role of the PPC in making on-line corrections (a process that requires forward models) during movement has been demonstrated in patients with lesions to this area and through the use of TMS (81, 82). TMS applied to the PPC of healthy human subjects prevented them from making fast on-line corrective movements to a target perturbation in a reaching task when vision of their arm was occluded, and they instead continued to reach to the initial target (81). As DPD subjects in our study were found to be overly responsive to the ambiguous visual feedback (as opposed to unresponsive PPC subjects), this may argue against altered PPC function explaining our results. Moreover, PPC stimulation has been related to motor awareness (83), and interestingly DPD patients can be unaware of their involuntary movements (30). Nonetheless it is possible that altered PPC activity contributed to the impaired predictive motor control of dyskinetic subjects, and as the PPC and cerebellum have reciprocal neuroanatomical connections (84, 85), it is likely that these two structures work together in using forward models to guide motor performance. Given that frontal "executive" dysfunction is well described in PD (86), it is tempting to speculate whether or not impaired frontal lobe dysfunction may contribute to the our observation of impaired forward models in PD. While this may explain, at least in part, the differences between PD subjects as a whole and controls, we do not believe that it could explain the differences between NDPD and DPD subjects we observed.

There is increasing evidence that although dyskinesias are present when DPD subjects are on medications, changes in motor function persist off medication (42). For example, **Figure 3** demonstrates that DPD subjects OFF medication were significantly worse in overall tracking compared to NDPD subjects OFF medication. Animal models of PD suggest that unnatural pulsatile stimulation of dopaminergic receptors, occurring with intermittent dosing of L-DOPA, may induce plastic changes that contribute to the development of LIDs (87, 88). Interestingly, younger patients are more prone to developing LIDs (89), and this may be related to a greater degree of plasticity occurring in the younger brain. Additionally, neurochemical changes related to LIDs (90) are not limited to the basal ganglia. Nimura and colleagues (91) demonstrated that the binding potential of the cerebellar sigma receptors was positively correlated with LID scores but not with disease severity of PD patients undergoing pallidotomies; while Koch and colleagues (39) have demonstrated altered cerebellar plasticity in DPD subjects using TMS. Furthermore, we have found behavioral differences that differentiate dyskinetic from non-dyskinetic subjects in the off medication state that may be related to altered cerebellar functioning (42). Thus, the dyskinetic brain may exhibit

altered cerebellar plasticity that manifests functionally as inadequate predictive motor control. Direct neuroanatomical pathways connecting the basal ganglia and the cerebellum have been found in primates (92, 93), providing a direct route for the administration of L-DOPA to interact with altered cerebellar structures.

There are a number of potential limitations to our study. First, there was a trend toward greater disease severity of dyskinetic than NDPD subjects, though the difference was non-significant (**Table 1**). Nonetheless, in order to fully address this, we examined the relationship between UPDRS and the increase in RMS between the non-ambiguous and maximum ambiguous tracking conditions, and no significant correlation for either DPD or NPDP subjects was found. Thus, the worsening of motor performance with increasing visual ambiguity was not associated with disease severity. Furthermore, UPDRS was not significantly correlated with decay rate for either PD groups, except for in the slow tracking condition (ambiguity level = 0.03), which was the only ambiguous tracking condition that lacked significant differences in mean decay rate between groups. Second, in addition to testing while on medication, we also tested PD subjects in the practically defined off medication state with 12 h of L-DOPA withdrawal and 18 h for dopamine agonists, and subjects were symptomatic upon study commencement. We note that this method of examining the practically defined off medication state in PD is universally utilized (94, 95), though we acknowledge that this may not reflect a truly depleted dopaminergic state. Furthermore, non-motor complications can occur with the off medication state (96), as well as pain that can be experienced by DPD patients (97), and such non-motor complications were not accounted for in this study. However, none of the subjects complained of pain and none of the subjects experienced non-motor complications requiring them to stop the study. Third, dyskinetic subjects can experience postural instability while on medication and experiencing LIDs (98), and we did not quantify postural instability between groups. However none of the subjects from either PD group complained of postural problems, and the lack of difference in overall accuracy in the baseline tracking condition of our task indicates that PD subjects were able to perform the task while standing equally well as healthy control subjects, and suggests any potential differences in postural instability did not significantly affect motor performance. Fourth, we did not examine potential differences in visual acuity between dyskinetic, non-dyskinetic, and control subjects. However, once again a lack of difference in RMS error in the baseline non-ambiguous conditions of the task suggests that any differences in visual acuity were not great enough to impact baseline motor performance. Fifth, it is theoretically possible that L-DOPA affected DPD and NDPD subjects with respect to eye movements. However, we note that (99) we found no changes in smooth pursuit gain during dose-related on–off fluctuations, so believe that this was not a factor here.

In conclusion, we demonstrate that DPD subjects are significantly more susceptible to visually ambiguous sensory input during a visually guided tracking task, and that the improvement in overall tracking performance with L-DOPA medication comes at a price for DPD subjects: an increased reliance on ambiguous visual feedback. The results indicate inadequate weighting of predictive motor control in DPD, which may be a significant contributor to pathophysiology of LIDs. We discuss possible cerebellar dysfunction in DPD as a neuroanatomical substrate of inadequate weighting of predictive motor control.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/Journal/10.3389/fneur.2014.00008/abstract

Figure S1 | Regression analysis – log(decay rate). The regression was the same as for **Figure 4**, only the dependent variable used in the regression was log(decay rate).

Figure S2 | Regression weights of the vector decomposition in Figure 2, comparing the situations with and without "jitter."

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Brain morphometry and the neurobiology of levodopa-induced dyskinesias: current knowledge and future potential for translational pre-clinical neuroimaging studies

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Dopamine replacement therapy in the form of levodopa results in a significant proportion of patients with Parkinson's disease developing debilitating dyskinesia. This significantly complicates further treatment and negatively impacts patient quality of life. A greater understanding of the neurobiological mechanisms underlying levodopa-induced dyskinesia (LID) is therefore crucial to develop new treatments to prevent or mitigate LID. Such investigations in humans are largely confined to assessment of neurochemical and cerebrovascular blood flow changes using positron emission tomography and functional magnetic resonance imaging. However, recent evidence suggests that LID is associated with specific morphological changes in the frontal cortex and midbrain, detectable by structural MRI and voxel-based morphometry. Current human neuroimaging methods however lack sufficient resolution to reveal the biological mechanism driving these morphological changes at the cellular level. In contrast, there is a wealth of literature from well-established rodent models of LID documenting detailed *post-mortem* cellular and molecular measurements. The combination therefore of advanced neuroimaging methods and rodent LID models offers an exciting opportunity to bridge these currently disparate areas of research. To highlight this opportunity, in this mini-review, we provide an overview of the current clinical evidence for morphological changes in the brain associated with LID and identify potential cellular mechanisms as suggested from human and animal studies. We then suggest a framework for combining small animal MRI imaging with rodent models of LID, which may provide important mechanistic insights into the neurobiology of LID.

Keywords: levodopa, magnetic resonance imaging, T_1 relaxation, voxel-based morphometry, plasticity, prefrontal cortex

INTRODUCTION

Parkinson's disease (PD) is a multi-system neurodegenerative disorder that affects 1 in 100 people aged over 60 in the United Kingdom. The disease is characterized pathologically by the progressive degeneration of nigrostriatal dopamine (DA) containing neurons in the substantia nigra (1) and the accumulation of phosphorylated α-synuclein in Lewy bodies, ascending from the brain stem to the higher area association cortices as the disease progresses (2). The subsequent depletion of DA in the caudate and putamen of PD patients manifests itself as the classical triad of PD motor symptoms, akinesia, resting tremor, and rigidity/postural instability.

Some 44 years since its first use in the clinic (3), the first-line treatment for many PD patients to alleviate their motor symptoms remains pharmacological DA replacement with the DA precursor levodopa (L-DOPA) (4). Although most patients respond positively to L-DOPA treatment, after ~4–6 years of L-DOPA therapy, a significant proportion of patients (~40%) exhibit a decline in the therapeutic efficacy of L-DOPA and develop debilitating dyskinesias (5). This phenomenon, termed levodopa-induced dyskinesia (LID), is characterized by involuntary dystonic and/or choreic movements of the trunk, limbs, and face, most commonly when the plasma concentration of DA is high ("peak dose" dyskinesia) (5). The expression of LID severely limits the long-term clinical utility of L-DOPA in this sub-set of PD patients and thus significantly impacts on patient quality of life. As such, strategies to mitigate or prevent LID onset are the subject of intense research efforts to address this serious unmet medical need. In the clinic, these efforts are currently centered on modifying the timing, formulation, and mode of administration for L-DOPA. In particular, emphasis is placed on delaying L-DOPA treatment where possible by use of direct-acting DA receptor agonists (6) and if not possible, using continuous intestinal L-DOPA infusion rather than intermittent L-DOPA injections (7). Both approaches have met with some success in reducing the incidence and severity of LID. At the pre-clinical level, significant effort is being directed toward understanding the role of other neurotransmitter systems in LID, particularly the role of glutamate and serotonin, as well

as the underlying molecular signaling pathways involved (8–10). Despite these efforts, the neural mechanisms underlying LID in PD remain obscure and the underlying neural correlates are not well understood. This presents a significant barrier to development of novel treatments (11).

In this article, we therefore examine current clinical evidence that suggests neuroanatomical changes in the brain are associated with LID, and the caveats associated with this. Second, we identify potential *post-mortem* cellular mechanisms as suggested from human and animal studies, which may explain these abnormalities. Thirdly, we outline the framework for combining small animal imaging with rodent models of LID, which may provide important mechanistic insights into the neurobiology of LID.

NEURAL CORRELATES OF LEVODOPA-INDUCED DYSKINESIA: functional MRI STUDIES

Research efforts to unravel the neural correlates of LID in the clinic and in relevant animal models of LID are critical to address the gaps in our knowledge of LID pathogenesis (12, 13). A fruitful and translational strategy that can bridge clinical and pre-clinical studies to achieve this is the application of neuroimaging tools to both human patients and relevant animal models. In particular, the latter can provide a mechanistic framework to underpin neuroimaging observations in patients.

To date, such investigations have typically focused on the use of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). These studies have identified changes in brain network activity, metabolism and molecular changes related to LID onset and severity, as described elsewhere (14–17). In brief, it is clear from these studies that LID is associated with bi-directionally altered neuronal firing patterns between the basal ganglia and the neocortex, the net result of which is dis-inhibition of thalamo-cortical neurons, leading to over-activation of frontal cortical areas, particularly in the motor, pre-motor, and prefrontal cortices. These data have been confirmed in PD patients with LID using PET (14, 18), transcranial magnetic stimulation [TMS; Ref. (19)], task-based and resting state fMRI (17, 20, 21).

NEUROANATOMICAL CORRELATES OF LEVODOPA-INDUCED DYSKINESIA: STRUCTURAL MRI STUDIES

Functional magnetic resonance imaging studies have revealed several important insights into LID pathophysiology. However, it is also true that human neuroimaging studies consistently demonstrate a linear relationship between the functional activity of the brain, assessed by fMRI and the shape, volume, or thickness of brain gray matter (22–24). These findings hold true for rodents as well (25, 26). This structure–function relationship is most likely driven by neuroanatomical remodeling at the cellular, synaptic (neuronal dendrite), or vascular level as a consequence of altered brain functional or metabolic activity (23, 27, 28). In other words, changes in brain function usually lead to or are concurrent with changes in the structure of the brain. Taking this into consideration, it is perhaps surprising that the use of structural MRI (sMRI) to probe whether there are neuroanatomical differences between patients with LID and those who are not dyskinetic has not been widely investigated.

In a recent study, the first of its kind to address this issue, Cerasa et al. (29) utilized optimized voxel-based morphometry (VBM) to analyze T_1-weighted MR images from PD patients with LID ($n = 36$), non-dyskinetic PD patients ($n = 36$), and age- and sex-matched controls ($n = 32$). Compared to healthy controls, both dyskinetic and non-dyskinetic PD patients showed no significant differences in gray matter volume (GMV), somewhat consistent with other VBM findings in PD patients of a similar age and disease duration, although the sample size was small (29). However, when comparing dyskinetic versus non-dyskinetic PD patients directly, a significant *increase* in GMV was observed in the bilateral inferior frontal gyrus of the dyskinetic patients (29). This increase was negatively correlated to age at onset, such that the greatest increases in inferior frontal gyrus GMV were in LID expressing PD patients with younger age of onset (29). These data suggest a hypothesis that aberrant striato-frontal and/or thalamo-cortical neural plasticity associated with LID consequently leads to morphological remodeling of the prefrontal cortex (29), findings which have sparked an interesting debate (30, 31).

The normalization and smoothing processes inherent to the VBM pipeline may however lead to reduced sensitivity in assessing cortical pathology, since individual sulci and gyri cannot be accurately anatomically resolved (32, 33). As such, VBM therefore provides a mixed measure of gray matter reflecting two components, cortical surface area and cortical thickness. A direct measure of cortical thickness therefore represents a topographical measurement that might provide a more sensitive indicator of the integrity of the cytoarchitecture in the cortex (32, 33).

To address this, Cerasa et al. (34) used surface-based investigation of cortical thickness in PD patients with LID ($n = 29$), without LID ($n = 30$), and age- and sex-matched controls ($n = 24$). This analysis revealed a pronounced *increase* in the thickness of the right inferior frontal sulcus in the dyskinetic, as compared to non-dyskinetic patients (34). These data support their original VBM findings (29) and delineate with greater precision the anatomical abnormalities characterizing dyskinetic PD patients (34). A third study *combining* VBM and cortical thickness measurements in PD patients with LID ($n = 33$) or without LID ($n = 33$), stratified by their PD age-of-onset ($<$ or >50 years of age), compared to age- and sex-matched healthy controls ($n = 40$) reveals further insights (35). Independent of the age of PD onset, dyskinetic patients were characterized by increased GMV and thickness in the inferior frontal cortex (35). Interestingly, early-onset PD patients with dyskinesia also demonstrated increased GMV in the substantia nigra and the red nucleus when compared to non-dyskinetic patients (35). In contrast, late-onset PD patients with dyskinesia were characterized by GMV increases in the supplementary motor area (SMA) only (35). Taken together, these data support the previous observations of anatomical abnormalities associated more generally with LID in the prefrontal cortex. Moreover, they demonstrate that different spatial patterns of brain abnormalities occur in patients with LID according to their age of PD onset. In particular, nigral pathology may be important in early-onset patients and in contrast, cortical pathology in late-onset patients (35).

LEVODOPA, GRAY MATTER, AND MAGNETIC RESONANCE IMAGING SIGNAL

When interpreting VBM results, it is important to eliminate artificial causes for differences between processed images that do not originate from genuine biological differences. In particular, MR image contrast between tissue classes on T_1-weighted MR images is inversely proportional to the T_1 relaxation time. Cerebrospinal fluid (CSF) is dark, reflecting a long T_1; whereas the much shorter T_1 of white matter renders it bright; and gray matter is intermediate between these. When the brain is segmented into these different tissue classes for volumetric analysis, VBM (and other automated techniques, including cortical thickness) utilizes voxel signal intensity profile (36). Each voxel has its own distinct intensity profile and there is substantial overlap in the voxel intensity histograms linked to gray and white matter. This renders precise tissue class segmentation difficult, particularly in the presence of partial volume effects, wherein a single voxel contains a mixture of tissue types (37). This is particularly common when a voxel spans distinct tissues, in cortical sulci (38). Such voxels are usually excluded or allocated to a particular tissue type on a probabilistic basis. As such, this segmentation process has the potential to go awry in the presence of unrecognized changes in voxel intensity profiles, leading to spurious volumetric findings (37). In other words, a reported volume change might in fact be an artifact of the signal acquisition and image analysis process (37).

This has recently been advanced as a biophysical explanation for the effects of lithium, a mood stabilizer, to apparently *increase* GMV (37). Whilst this notion is debated (39–41) and has yet to be explored in detail, it is certainly important and warrants attention (40, 41).

Interestingly, L-DOPA is associated with shortening of T_1 (and T_2) relaxation time *in vitro*, although this may be influenced by the presence of iron (42). This raises the possibility that changes in T_1 in the human brain after L-DOPA administration may lead to an adjustment in the number of voxels that are attributed to gray matter. These would then be detected by VBM analysis as an apparent increase in GMV. Consistent with this hypothesis, VBM analysis reports an increase in voxels attributed to gray matter in the substantia nigra, ventral tegmental area, and subthalamic nucleus following *acute* L-DOPA administration in healthy volunteers (43). Unfortunately, this study did not include quantitative T_1 parametric mapping to assess the impact of L-DOPA on T_1 *in vivo*.

These findings following a single administration of L-DOPA to healthy people may lead to the suggestion differences in anatomical MRI data acquired from dyskinetic and non-dyskinetic PD patients (29, 34, 35), are driven by simple changes in signal intensity (grounded in increases in proton T_1), which may be misinterpreted as a volume increase in the gray matter. Importantly, therefore, the gray matter volume increases reported in dyskinetic PD patients were detected only in dyskinetic patients compared to non-dyskinetic patients. All of these patients were receiving L-DOPA therapy at the time of scanning, with no significant difference in the duration of L-DOPA treatment (29, 34, 35).

Taken together, this does not support a general influence of L-DOPA on the MRI signal driving the observed results, since such an effect would be predicted to be present in both L-DOPA treated patient groups. The fact that the anatomical abnormalities are only present in the dyskinetic group strongly suggests these are inherently linked to the pathogenesis of LID. We note however that Lewis and colleagues report an accumulation of iron in the red nucleus of patients with L-DOPA-induced dyskinesia (44). Iron is paramagnetic and causes a reduction in both T_2 and T_1 relaxation time in brain regions where brain iron is deposited in the form of ferritin and hemosiderin (45). As such, whilst there is no evidence currently to suggest that neuroanatomical brain changes in dyskinetic PD patients are the result of an MR image artifact, quantitative T_1 and T_2 mapping may be recommended for future MRI studies in dyskinetic and non-dyskinetic patients. This would help to more accurately probe the exact origins of MRI signal changes in these groups. Alternatively, controlled animal studies may be important as MRI volume changes can be verified *post-mortem*, as we have shown previously (28, 39, 46, 47), and discussed later in this article.

WHAT IS THE MECHANISM UNDERLYING NEUROANATOMICAL CHANGE IN GRAY MATTER FOLLOWING CHRONIC L-DOPA TREATMENT?

Assuming that dyskinesia following L-DOPA treatment is associated with physical neuroanatomical changes in the brain, the next obvious issue is the identification of the underlying biological mechanism. However, neuroimaging measures are difficult to relate unambiguously to underlying biology (23). In particular, human neuroimaging studies cannot establish if the morphological abnormalities in the prefrontal cortex of dyskinetic PD patients are a cause or consequence of dyskinesia, following chronic L-DOPA treatment (29). One very plausible hypothesis is that these morphological changes reflect heightened activity within the neuronal circuitry implicated in LID pathogenesis (29). In other words, the detected pattern of brain abnormalities reflects altered neurobiological mechanisms central to the pathogenesis of LID. This hypothesis is supported by observations in hyperkinetic movement disorders such as dystonia. Indeed, dystonia is associated with exaggerated increases in GMV of specific brain regions involved in somatosensory processing, such as the basal ganglia, prefrontal cortex, and somatosensory cortex (35, 48). Furthermore, it is suggested that L-DOPA, when applied in a pulsatile and non-physiological manner may perturb the normal physiological mechanisms that mediate motor control (49). This process may lead to aberrant increases in synaptic plasticity, remodeling of neuronal synapses, and changes in the functional connectivity signature of brain activity within circuits responsible for motor control. At the cellular level, this is likely to manifest as increases in the size of neuronal dendritic arbors (50, 51). This phenomenon termed, "L-DOPA-maladaptive plasticity" may be critical to LID pathogenesis (29). Interestingly, this has also been suggested as an explanation for the incidence of tardive dyskinesia following chronic treatment with first generation antipsychotic drugs (52).

Evidence from recent studies using electroencephalography (EEG) and fMRI support this hypothesis. These reveal that brain activity and functional connectivity, defined as spontaneous, temporally coupled blood oxygen level dependent (BOLD) oscillations, is *decreased* in PD patients within the motor circuit in the cortex that receives dopaminergic innervation including the frontal, somatosensory, motor, and SMA (20, 21, 53–55).

Furthermore, these studies confirm that acute and chronic L-DOPA treatment restores this lost connectivity with motor networks and increases neural activity in these brain regions (20, 21, 53–55). In an acute setting, this may explain the therapeutic effects of L-DOPA. However, with chronic treatment and the continued degeneration of the dopaminergic system, this could result in L-DOPA maladaptive plasticity leading to changes in neural arborization, and subsequently the observed neuroanatomical increases in the cortex of dyskinetic PD patients. Alternatively, such neuroanatomical enlargements could equally reflect a structural long-term consequence of the altered neural plasticity in these specific regions.

In reality however, MR phenomena are likely to be driven by several cellular processes; acting potentially in parallel in multiple cell types within the brain (23). Neuronal changes in gray matter as a cause or consequence of chronic L-DOPA treatment may include neurogenesis, synaptogenesis, and changes in neuronal morphology as discussed above. However, extra-neuronal changes may equally be responsible and these could include increases in glial cell size, morphology, number and additionally, angiogenesis. Indeed, the vasculature accounts for about 5% of gray matter (56). Glial cells (astrocytes, microglia, and oligodendrocytes) are believed to outnumber neurons by ~6 to 1, with varying ratios in different brain regions. Any of these cellular changes may influence MRI signals. Importantly, variations in neuronal, glial, and synaptic density may affect modalities sensitive to the proportion of cellular material versus extracellular space in a voxel, such as proton density imaging or relaxometry. Such features would therefore influence commonly used methods to assess gray matter change including VBM and cortical thickness that rely on image intensity boundaries in T_1-weighted images (54).

Addressing this issue is problematic. In patients, one fruitful approach may be to conduct multi-modal neuroimaging in dyskinetic and non-dyskinetic PD patients to study the interrelationships between brain function, metabolism, and structure. This could include, but is not limited to, collection of resting state fMRI, sMRI and quantitative T_1 mapping in the same session. Similarly, angiogenesis could be detected by techniques such as contrast-enhanced imaging of blood volume or perfusion imaging of cerebral blood flow (CBF). Recent advances in simultaneous PET–MRI, the feasibility of which has been demonstrated in rodents (57) and humans (58, 59) make this even more tractable and could provide unparalleled insights into the pathophysiology of LID.

Ultimately, *post-mortem* histological studies are required in order to make direct links between imaging measures and underlying mechanisms. For example, recent studies in our laboratory have established that neuroanatomical changes, including a reduction in the volume of the anterior cingulate cortex due to chronic antipsychotic drug treatment are not due to the loss of neurons or astrocytes (28). Similarly, in a very elegant study, mice subjected to different forms of maze training displayed volume increases in either the hippocampus (spatial maze) or striatum (cued maze), reflecting the distinct brain systems involved in these tasks (27). These MRI-derived measures of growth correlated with growth associated protein-43 (GAP-43) staining *post-mortem*, a marker for axonal growth cones, but not measures of neuronal size or number (27). These data suggest the observed MRI volume change reflected remodeling of neuronal processes, rather than neurogenesis (27). These data highlight the need to study relevant animal models to help unravel the neuroanatomical correlates of LID observed on MRI in patients.

ANIMAL MODELS OF LID

Levodopa-induced dyskinesia can be modeled pre-clinically by recapitulating the conditions required for its development in humans, namely degeneration of the nigrostriatal tract followed by chronic exposure to L-DOPA. The primary dopaminergic cell loss models used for evaluation of dyskinesia are the 6-hydroxydopamine (6-OHDA) lesioned hemi-parkinsonian rat and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated non-human primate (NHP). Repeated exposure of these denervated animals over several weeks to daily treatment with L-DOPA combined with a peripheral DOPA decarboxylase inhibitor such as benserazide or carbidopa, leads to development of abnormal involuntary movements (AIMs), which is considered an experimental proxy for human LID (13, 60–62). This can be scored according to a variety of ratings scales (63, 64). In the 6-OHDA-lesioned rat, AIMs manifest unilaterally as axial (twisting of the head, neck, and trunk), limb (repetitive or dystonic movements involving the forepaw and/or limb), and orolingual (vacuous chewing, tongue protrusion) phenomena on the side of the body contralateral to the lesion (60). In MPTP-treated NHPs, LID is bilaterally expressed and manifests as choreic and dystonic movements of the limbs, especially the lower limbs, and flicking of the fingers, trunk dystonias, and repetitive tongue protrusion (65). The MPTP–NHP model more accurately reflects the human expression of dyskinesia, but ethical and practical considerations mean that the 6-OHDA-lesioned rat model is a very valuable tool for pre-clinical research. Importantly, the mechanisms underlying the development of LID and AIMs appear to be common to both (13). Extensive research in both rat and NHP LID models, including studies to assess the potential of new anti-dyskinetic drug strategies, has identified a plethora of candidate mechanisms in specific brain regions, which may underlie the pathogenesis of LID (5, 66). Both striatal and extra-striatal systems are implicated, as described in brief below.

STRIATAL MECHANISMS UNDERLYING LID

The role of DA in the striatum is to alter the response of medium spiny neurons (MSNs) in both the direct and indirect pathways to excitatory input from the corticostriatal pathway. The classical model of LID suggests the presence of high concentrations of exogenous DA (derived from L-DOPA) causes hyperactivation of the direct pathway (striatonigral) MSNs, which increases thalamocortical feedback and produces exaggerated motor function. Dyskinesia is therefore believed to primarily involve chronic overactivation of striatonigral MSNs (67, 68) and there is a wealth of evidence for a particular role of dopamine D1 receptors (D1R) in the development of LID in both patients and pre-clinical models (69–72). In reality the mechanisms involved are likely to be considerably more complex (73) and a role for the indirect pathway cannot be ruled out, especially as both D1R and dopamine D2 receptor (D2R) agonists can provoke dyskinesia in primed monkeys (74).

The striatonigral GABAergic projection is a point of convergence for, and is therefore modulated by, multiple neurotransmitter systems that may be pathologically altered in dyskinetic PD patients. The major input to the BG involves release of glutamate from corticostriatal neurones, and together with DA and the modulatory activity of other neurotransmitters such as serotonin (5-HT), this determines the activity of the output nuclei: the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNr). There is evidence from animal models that this corticostriatal glutamate release is increased in LID (75, 76), alongside alterations in expression (69, 77–80), phosphorylation (81–83), and distribution (84, 85) of glutamate receptors, including NR1/NR2B NMDA receptors and metabotropic glutamate receptor 5 ($mGlu_5$), that facilitate increased signaling across this synapse. Morphological alterations indicative of increased glutamatergic transmission are also present (86). This is borne out in human LID, where abnormal glutamatergic transmission has been described in the caudate, putamen, and motor cortex (87), alongside increased putaminal expression of NR1/NR2B NMDA receptors (88) and $mGlu_5$ receptors (80). Activation of extrasynaptic NR2B-containing NMDA receptors has particularly been implicated in the development of LID (84).

The effect of this abnormal glutamatergic transmission may be compounded by the consequences of dysregulated release of DA from serotonergic terminals within the striatum (89), leading to abnormal activation of DA receptors. These receptors are expressed on striatonigral MSNs as well as in cortical dopaminergic systems, which have also been implicated in the pathophysiology of dyskinesia (90). There are some reports of altered D1R expression or trafficking in LID (70, 91), but evidence suggests that the key mechanism in dyskinesia is increased functional sensitivity of these receptors (92, 93).

Whatever the exact mechanism behind increased D1R signaling, stimulation of these receptors causes activation of the cyclic AMP (cAMP)/protein kinase A (PKA)/DARPP-32 (DA- and cAMP-regulated phosphoprotein, 32 kDa)/protein phosphatase 1 (PP-1) pathway and the mitogen activated protein kinase (MAPK) pathway, which culminates in phosphorylation of extracellular signal related kinase (ERK1/2) (94). This results in DNA modifications (95, 96) and increased expression of transcription factors, especially ΔFosB/FosB (97), which are indicative of long-term cellular adaptations.

Both NMDA and $mGlu_5$ receptors are known to closely interact with D1R (81, 98) and with each other (99, 100), activating common downstream mediators such as PKA and ERK1/2 (101, 102). Therefore, the increased expression of these receptors alongside enhanced D1R signaling will co-operate to augment striatonigral signaling in LID. In addition, activation of D1R, in combination with enhanced activation of NMDA receptors by glutamate, leads to long-term potentiation-like phenomena. This may explain the lack of depotentiation seen in the dyskinetic versus non-dyskinetic denervated striatum (103), leading to an exaggerated response to normally irrelevant stimuli. The pathological overactivation of the direct pathway leads to GABA bursting in the SNr and GPi (71), thus disinhibiting thalamocortical feedback and leading to the hyperkinetic movements characteristic of LID.

Striatal glutamatergic and dopaminergic transmission can be modulated by several other neurotransmitters. For example, increased serotonergic innervation of the striatum, along with altered expression of several receptor subtypes (104, 105), has been demonstrated in animal and human LID (106, 107). Importantly, activation of serotonin $5\text{-}HT_{1A}$ receptors has been shown to reduce corticostriatal glutamate release (108, 109), and also negatively regulates release of DA as a false neurotransmitter from serotonergic terminals (110). Similarly the endocannabinoid system may play a role in LID as activation of CB_1 receptors has been shown to negatively regulate corticostriatal glutamate release (111, 112) and also reduce D1R-mediated responses (113–115). Consequently, molecules such as serotonin receptor $5\text{-}HT_{1A}$ and $5\text{-}HT_{1B}$ agonists (116–120) and endocannabinoid receptor agonists (121–124) have shown anti-dyskinetic efficacy.

EXTRA-STRIATAL MECHANISMS OF LID

As well as striatal alterations, there is also evidence from pharmacological studies suggesting that modulation of neurotransmission elsewhere in the BG and in areas of the cortex may also contribute to LID. Systemically active drugs could therefore produce anti-dyskinetic effects through actions at more than one key synapse. For example, antagonists of $mGlu_5$, which are currently in clinical trials as anti-dyskinetic agents (125, 126), may exert their effects not only in the striatum but also in the subthalamic nucleus (127). Targeting of $5\text{-}HT_{1A}$ receptors in the subthalamic nucleus (128) or primary motor cortex (129) also attenuates dyskinesia, as does activation of $5\text{-}HT_{1B}$ receptors (130, 131), which are not only present in the striatum but also on GABAergic MSNs terminating in the SNr, where their activation can inhibit GABA release (132). As well as the striatal actions already mentioned, another potential mechanism to explain the efficacy of CB_1 agonists is potentiation of striatopallidal signaling via inhibition of GABA reuptake (121), which would help to rebalance a hyperactivation of striatonigral signaling. Opioid signaling, which is known to be altered in LID (133–135), can modulate transmitter release at several synapses within the BG, for example inhibition of striatopallidal GABA release (136), and inhibition of glutamate and GABA release into the SNr (137). Targeting several opioid receptor subtypes has shown anti-dyskinetic efficacy (138–141), but their role is complex and the effects of opioid-targeted approaches may be dose-dependent (137).

FUTURE DIRECTIONS: A TRANSLATIONAL ROAD MAP TO BRIDGE ANIMAL MECHANISTIC STUDIES WITH BRAIN STRUCTURAL IMAGING TO IDENTIFY THE MORPHOLOGICAL CORRELATES OF LID

These maladaptive plastic changes described above in the striatum and extra-striatal regions may well underlie the morphological changes associated with LID described in humans. Combining well-validated rat and potentially, NHP, models of LID with advanced non-invasive animal MR imaging methods therefore offers an exciting opportunity to integrate currently disparate areas of research and help explain the MR imaging phenomena observed in dyskinetic patients (31) (**Figure 1**). This approach is advantageous for three reasons. First, rodents and primates allow one to assess the precise effects of drug treatment (in this

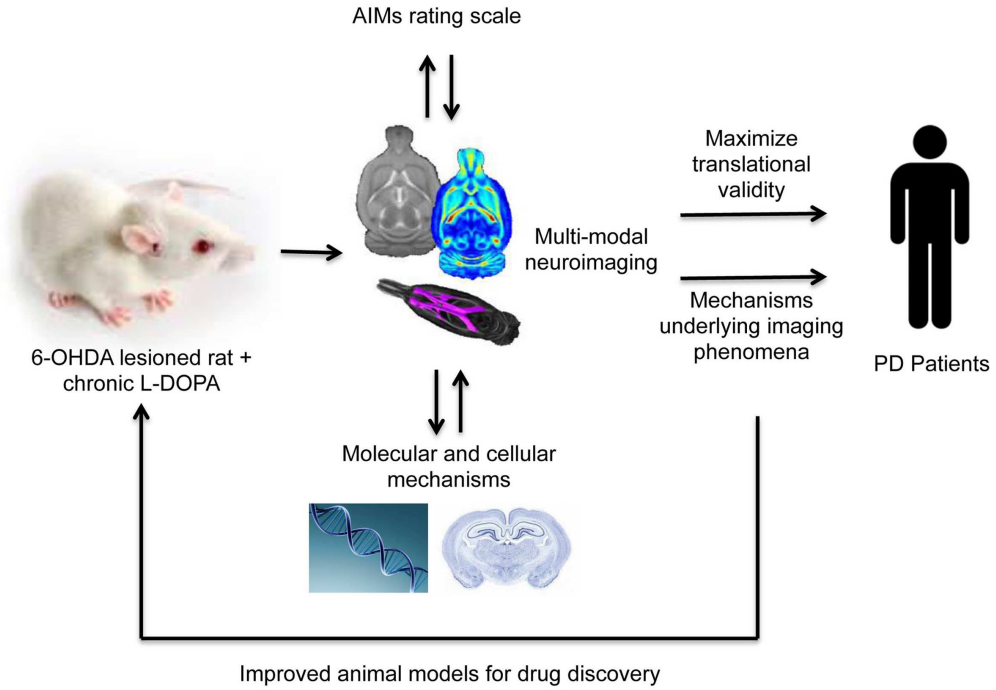

FIGURE 1 | A translational methodological framework for the combination of rodent models of LID (or these could be non-human primates) with multi-modal imaging, behavior and post-mortem cellular, or molecular analysis to elucidate the mechanisms underlying imaging phenomena associated with levodopa dyskinesia observed in human Parkinson's disease patients.

case, L-DOPA) on brain structure and function, disentangled from potential confounding factors present in patient samples. The proof-of-concept for this approach has been recently demonstrated in our laboratory in characterizing the impact of chronic antipsychotic drug treatment on rat brain morphometry (28, 39, 142). Second, the use of MRI/PET (clinically comparable technology) permits the collection of parallel data read-outs in rodents, primates, and humans, maximizing the possibility for translation of basic findings to the clinic. Thirdly, and most importantly, as we have seen in the preceding section, in animals one can measure neurochemical, biochemical, cellular, and molecular aspects of brain structure and function in ways that are impossible in human subjects. Thus neuroimaging and neuropathology may be bridged to identify the biological mechanisms underlying MRI phenomena.

A number of elegant functional imaging studies using small animal micro-PET technology have begun to address this. Studies using PET in 6-OHDA lesioned rats chronically treated with L-DOPA and displaying severe AIMs (the rodent LID phenotype) display regional increases in CBF (measured using [14C]-iodoantipyrine uptake), increases in regional cerebral glucose utilization (rCGU; measured using [14C]-2-deoxyglucose uptake) and DA release (measured using displacement of [11C]-raclopride binding potential), consistent with similar findings in PD patients (143–145). To date however, no studies have assessed the impact of L-DOPA treatment on brain morphometry or relaxation time in either rodent or primates, using advanced structural MR imaging methods. This approach offers a unique opportunity to answer a number of outstanding questions in the emerging field of neuroanatomical alterations linked to L-DOPA and LID pathogenesis. Multi-modal imaging approaches, to study the interrelationships between brain anatomy [sMRI, Diffusion Tensor Imaging (DTI)] metabolism [2-dexoyglucose, ^{1}H-magnetic resonance spectroscopy (MRS)] and fMRI may be of particular relevance. These imaging findings may then serve as a "roadmap" to guide follow-up, region-specific *post-mortem* investigation of the candidate mechanisms already identified in these models, to help explain the imaging phenomena. Excitingly, such studies are now underway in our laboratory.

Combining experimental models of LID with clinically comparable technology may also be particularly important for the assessment of novel anti-dyskinetic drugs, such as antagonists of $mGlu_5$. Indeed, as previously stated, the use of clinically comparable technology (MRI) to conduct parallel assessments in experimental animals and humans is likely to accelerate translation of basic findings to the clinic. Neuroimaging tools may therefore play a critical role in future studies evaluating not only target engagement, but also drug efficacy in models of LID, as evidenced by recent studies using PET (143, 144, 146). No studies as yet have employed MRI methods, but the potential for application of this technology is apparent.

CONCLUSION

Recent human sMRI studies in PD patients with dyskinesia have suggested the presence of neuroanatomical changes in specific brain regions, particularly the frontal cortex, which may have

relevance to the pathogenesis of dyskinesia. It is currently unclear from these studies whether these abnormalities are the cause, or consequence of dyskinesia. Furthermore, it is unclear if these reflect genuine neuroanatomical changes in shape, thickness, or volume of gray matter, or whether these can be explained by a biophysical hypothesis relating to L-DOPA, as recently described for the effects of lithium. Accepting this caveat and presuming these changes to be genuine structural differences in gray matter, the biological mechanism underlying these changes remain unknown, but may be rooted in maladaptive neuronal plasticity, leading to remodeling of synapses and dendrites on neurons and glia alike in the dyskinetic brain. However, a plethora of data for candidate mechanisms underlying the pathophysiology of LID exists from well-validated rodent and NHP pre-clinical models of LID, which display excellent construct, face, and predictive validity to human LID. The combination of these models with advanced, multi-modal small animal MR imaging technology therefore offers a unique opportunity to validate the presence of neuroanatomical changes associated with LID. Furthermore, this will be an important step to bridge neuroimaging and neuropathology to link candidate mechanisms derived from animal models with neuroimaging phenomena in dyskinetic PD patients. Ultimately, this will accelerate our understanding of LID pathogenesis and aid the discovery and evaluation of novel anti-dyskinetic drug treatments.

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Maladaptive plasticity in levodopa-induced dyskinesias and tardive dyskinesias: old and new insights on the effects of dopamine receptor pharmacology

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Maladaptive plasticity can be defined as behavioral loss or even development of disease symptoms resulting from aberrant plasticity changes in the human brain. Hyperkinetic movement disorders, in the neurological or psychiatric realms, have been associated with maladaptive neural plasticity that can be expressed by functional changes such as an increase in transmitter release, receptor regulation, and synaptic plasticity or anatomical modifications such as axonal regeneration, sprouting, synaptogenesis, and neurogenesis. Recent evidence from human and animal models provided support to the hypothesis that these phenomena likely depend on altered dopamine turnover induced by long-term drug treatment. However, it is still unclear how and where these altered mechanisms of cortical plasticity may be localized. This study provides an up-to-date overview of these issues together with some reflections on future studies in the field, particularly focusing on two specific disorders (levodopa-induced dyskinesias in Parkinson's disease patients and tardive dyskinesias in schizophrenic patients) where the modern neuroimaging approaches have recently provided new fundamental insights.

Keywords: levodopa-induced dyskinesias, tardive dyskinesias, hyperkinetic movement disorders, inferior frontal cortex, dopaminergic treatment

INTRODUCTION

Plasticity refers to the ability of the nervous system to change the effectiveness of transmission in neural circuits. This can involve changes at several levels (neuronal, synaptic, protein, or genomic structure) and modulates both the structure and function of neuronal networks. Several human and animal studies demonstrated that exercise and/or behavioral enrichment can increase neuronal survival and resistance to brain insult, promote brain vascularization, stimulate neurogenesis, and enhance learning [for review, see Ref. (1)].

Although neural plasticity is generally viewed as an adaptive process, there is considerable evidence that plasticity can also be maladaptive [for review, see Ref. (2)]. For instance, sensory deprivation, chronic stress, and excessive exercise would reduce variability and impair adaptability. In particular, chronic stress is associated with a loss of neurons and synapses. Furthermore, stress may increase activity in certain brain regions, such as the amygdala and the mesolimbic dopaminergic system, leading to hypertrophy of these structures (3). Again, Byl et al. (4) showed that monkeys that were over-trained to make a particular highly specific hand movement sometimes developed difficulties in moving their hands in a similar manner to focal hand dystonia. The somatosensory cortex of these animals was less organized than that of healthy monkeys, with larger receptive fields and overlapping representations of the individual digits. A change in the pattern of connectivity in the sensory and motor cortices was thought to lead to inappropriate associations between inputs and outputs of the motor areas and cause errors in selecting muscles used in voluntary movement.

However, maladaptive neural plasticity may be triggered not only by exercise and/or behavioral deprivation, but also by other factors, such as chronic drug therapy. In the last few years, several influential authors (5–7) proposed that some hyperkinetic movement disorders [levodopa-induced dyskinesias (LIDs), primary dystonia, Huntington's disease, and tardive dyskinesias (TDs)] are caused by maladaptive synaptic plasticity. The scope of this study is to summarize evidence on the role of dopaminergic replacement in inducing maladaptive neural changes in these hyperkinetic disorders, delineating the presence of shared neural mechanisms. Particular attention will be paid to recent evidence coming from molecular and neuroimaging studies that allow *in vivo* evaluation of neural plasticity.

PARKINSON'S DISEASE WITH LEVODOPA-INDUCED DYSKINESIAS

The classical clinical picture of Parkinson's disease (PD) consists of motor deficits, such as akinesia, rigidity, tremor, and postural dysfunction. These motor symptoms are greatly improved by treatments with dopamine (DA) replacement therapy or DA agonists, but after 4–6 years, the therapeutic window becomes narrow

and patients start to experience very disabling motor symptoms, such as motor fluctuations and LIDs. LIDs in PD has been thought to originate from an imbalance between "direct" and "indirect" pathways regulating neural activity in the striato-frontal network (8, 9). The neurons of the direct pathway project to the globus pallidus pars interna (GPi) and onward to the thalamus. The neurons comprise the indirect pathway project to the globus pallidus pars externa (GPe), where they synapse with more GABAergic projection neurons. In turn, these neurons project to the subthalamic nuclei (STN) and form synapses with the glutamatergic neurons that provide output to the GPi and the substantia nigra pars reticulata (SNr). The essential pathophysiological characteristic of the LIDs state is the presence of under-activity of the indirect pathway and overactivity of the direct pathway. In the last few years, this model has been reinforced and modified to extend knowledge about the interplay between striatal nuclei and the frontal cortex. Indeed, LIDs have also been demonstrated to be associated with a sequence of events that includes presynaptic (i.e., increased synaptic level of DA) and post-synaptic modifications (i.e., downstream changes in proteins and genes), and abnormalities in non-DA transmitter systems (9). Overall, all these events combine to produce alterations in the firing patterns and the coherence between the basal ganglia and the cortex, leading to excessive disinhibition of thalamocortical neurons and overactivation of frontal areas, with specific involvement of motor, premotor, and prefrontal cortices (10, 11). The presence of altered cortical excitability in the motor and prefrontal cortex has also been demonstrated by electrophysiological studies employing transcranial magnetic stimulation (TMS) in patients with PD (12, 13). Moreover, as repetitive TMS applied over the supplementary motor area (SMA), the primary motor cortex (M1) was able to induce a transient reduction of LIDs severity (14, 15). Despite the traditional striato-thalamo-cortical pathways, in the last few years, advances in the neurophysiological field provide alternative scenarios highlighting the involvement of other circuits involved in the pathophysiological mechanisms of LIDs. In particular, reduction of peak-dose dyskinesia for up to 4 weeks was described following repeated sessions of continuous theta burst stimulation (cTBS) delivered bilaterally to the lateral cerebellum (16). This later finding would seem to support the hypothesis that alterations in cerebellar sensory processing function, occurring secondary to abnormal basal ganglia signals reaching it, may be an important element contributing to the maladaptive sensorimotor plasticity of motor cortex and the emergence of abnormal involuntary movements (17).

TARDIVE DYSKINESIAS IN PSYCHIATRIC DISORDERS

Chronic blockage of DA receptors by anti-psychotic drugs in patients with psychiatric disorders has been known to produce another well-known hyperkinetic movement disorder named TDs. Originally, the term TDs referred to abnormal movements produced by long-term DA receptor antagonist therapy, mainly characterized by rapid, repetitive, stereotypic movements affecting mainly the oral, buccal, and lingual areas, and less movements affecting the limb and the trunk; however, other phenomenologies have been described in TDs, such as dystonia and akathisia (18). More than half of TDs cases may persist, even after conventional antipyschotics are switched to atypical ones (19), or anti-psychotics are discontinued (20). The most popular pathophysiological model for TD is based on DA receptor hypersensitivity triggered by anti-psychotic drugs (7, 21, 22). According to this theory, chronic use of DA antagonists, particularly at high levels of antagonism (i.e., haloperidol), results in gradual hypersensitization of DA receptors. Indeed, chronic administration of neuroleptics might cause adaptive changes in DA receptors, causing an increase in the number of D2 receptors (23). D2 receptors being expressed on indirect pathway medium-spiny neurons and being inhibitory, the consequence of D2 hypersensitivity might determine disinhibition of the GPi and the subthalamic nucleus (7). Support for hypersensitivity of DA receptors in TDs mainly comes from rodent models (24). Moreover, further support comes from clinical observations that increasing anti-psychotic dosage temporarily suppresses TD (25) whereas withdrawing anti-psychotics or administering DA agonists exacerbates dyskinetic symptoms in the short term (21). However, although chronic anti-psychotic use is associated with D2 hypersensitivity, the evidence supporting a direct role on TDs generation are not consistent; indeed, DA receptors binding in PET studies was not correlated with severity of dyskinesias and post-mortem studies did not disclose any difference in number of D2 receptors between patients with and without TDs (26).

SHARED MALADAPTIVE NEURAL PLASTICITY IN LIDs AND TDs PATIENTS

Although LIDs and TDs are underlined by drugs acting on the DA receptor in an opposite way and associated with different diseases, there is evidence for shared neurodegenerative mechanisms, likely depending on aberrant neural plasticity in the prefrontal cortex.

The development of LIDs has been attributed in cell studies to dysfunctional cortico-striatal plasticity triggered by the combined effects of DA denervation and chronic pharmacological DA replacement (27) and has also been demonstrated *in vivo* in PD patients with LIDs (12, 13). Chronic non-physiologic stimulation of DA receptors on striatal neurons (23) can induce modifications in NMDA receptors firing and thus the development of aberrant motor patterns leading to motor complications. This has provided the rationale for the use of NMDA receptor antagonists such as amantadine for treating PD patients with LIDs (28). Despite the recent evidence on the efficacious effects of amantadine in ameliorating LIDs [improved motor symptoms in 60–70% of patients; (29)), the restoring of deficient DA with its precursor L-3,4-dihydroxyphenylalanine (levodopa) is again the most effective treatment for PD. In the last decades, concern has been raised that levodopa could have toxic effects on the brain of patients with PD (30). Although some *in vitro* studies support this hypothesis (31), this concern remains uncertain in human studies (32). Recent evidence coming from neuroimaging studies has provided new impetus to unravel the potential effects of levodopa on brain morphometry. Indeed, our group has recently demonstrated that specific morphological alterations are associated with the development of LIDs in PD patients (33). Using unbiased voxel-based morphometry to compare gray matter volume in dyskinetic and non-dyskinetic patients, closely matched for age, duration of medication and age of onset, we observed

significant increases of gray matter volume within the inferior frontal cortex (IFC), the degree of which increased with the severity of motor fluctuations. The IFC is an associative area specifically involved, together with motor and premotor cortices, basal ganglia and STN, in the regulation of motor inhibition (34). The presence of "increased" gray matter volume was in accordance with other neuroimaging studies investigating the neurobiological effects of levodopa treatment in healthy individuals. Indeed, Salgado-Pineda et al. (35) demonstrated an increased gray matter volume in healthy controls 1 week after levodopa administration. All this evidence suggested that levodopa applied in a pulsatile and non-physiological manner can perturb the normal physiological mechanisms that mediate motor control and eventually result in the remodeling of neuronal contacts and pathways, producing long-lasting changes and aberrant neural plasticity (i.e., increased neuronal arborization). The presence of altered anatomy of the IFC has been confirmed using different populations (36) and neuroimaging metrics [i.e., cortical thickness; Ref. (37)] and has raised an interesting scientific debate on the potential effects of levodopa on brain morphometry (38, 39). In particular, the main notion proposed by Vernon and Modo (38) concerned the key role that animal models of PD would play in providing new insight about the hypothesis proposed above. Indeed, although several models of basal ganglia dysfunctions have been proposed to understand the pathophysiological mechanisms underlying motor manifestations in patients with PD (8), these changes cannot completely explain the overall motor symptoms of LIDs in patients. Indeed, a large body of *in vitro* and *in vivo* studies in animal models of parkinsonism have suggested an alternative "glutamatergic" hypothesis for LIDs. Several authors demonstrated that the glutamatergic cortico-striatal projection to medium-spiny neurons might play an important role in the priming and development of LIDs, by induction of abnormal synaptic plasticity at the cortico-striatal level (40–42). The alteration of glutamatergic transmission as causative of LIDs has also been demonstrated *in vivo* by Ahmed et al. (43), who described abnormalities in glutamate transmission in striatal and frontal regions in dyskinetic compared to non-dyskinetic patients with PD. Despite the plethora of studies supporting the glutamatergic contribution to LIDs, there is also a vast consensus that dysfunctions of the serotonergic system are implicated in the development of LIDs and other complications of levodopa therapy. Indeed, serotonin neurons have the ability to synthesize, store, and release DA, formed from exogenous levodopa, but due to the lack of any autoregulatory feedback control, the DA released from serotonin terminals generally show excessive swings in the patients in response to repetitive, intermittent levodopa treatment (44). Such dysregulated release of levodopa-derived DA is likely to be the main trigger of dyskinesia in levodopa-primed animals (44), and may also play a role in PD patients undergoing long-term levodopa therapy (45, 46). Using animal models, Rylander et al. (47) provided the first evidence that levodopa treatment induces sprouting of serotonin axon terminals, with an increased incidence of synaptic contacts and a larger activity-dependent potentiation of DA release in the DA-denervated striatum. This latter finding is of great interest since our reported morphological abnormalities in patients with LIDs (33, 36) highlighted the role of the IFC, a region strongly innervated and regulated by the serotonergic system (48, 49).

Interestingly, similar evidence, highlighting the presence of neural abnormalities in the IFC driven by chronic DA therapy, has also been provided in the psychiatric realm. In particular, chronic psychotropic treatment might cause either adaptive changes in DA receptors (increase in the number of D2 receptors and supersensitivity of D1 receptors) (50) or determine structural remodeling of the brain. Post-mortem studies investigating brains of schizophrenic patients with long duration of anti-psychotic exposure (i.e., haloperidol) showed significant structural abnormalities (51–54), with evidence for slight shrinkage (5%) of the brain in terms of weight, length, and cortical volume and for enlarged (15%) ventricles. Animal studies have confirmed this evidence, demonstrating that chronic (8 weeks) exposure to both haloperidol and olanzapine resulted in significant decreases in whole-brain volume (6–8%) driven mainly by a decrease in frontal cerebral cortex volume (8–12%) (55). Finally, a recent *in vivo* neuroimaging study investigating the neuroanatomical differences between schizophrenic patients with TDs with respect to patients without TDs (closely matched for age at onset of illness, duration of illness, or antipsychotic chlorpromazine equivalent dose) demonstrated, for the first time, the presence of volumetric abnormalities in the same prefrontal region described in patients with LIDs: the IFC. The merit of this work (56) was to provide evidence on the presence of maladaptive neural rearrangements in the IFC driven by chronic psychotropic treatment.

CONCLUSION

Although all these findings are pieces of a very difficult puzzle to assemble, what clearly emerged is that all these disorders have been associated with altered DA turnover induced by long-term drug treatment that might ultimately induce maladaptive synaptic plasticity. We believe that further advances in the understanding of the maladaptive mechanisms of synaptic plasticity in other hyperkinetic movement disorders (Tourette syndrome, dystonia, and Huntington's disease) will lead in the next few years to defining the exact biological impact of chronic DA therapy on the neurological and psychiatric brain, which might ultimately stimulate development for new treatments. For instance, in a recent neuroimaging study, Ganos et al. (57) described the presence of gray matter abnormalities of the IFC in patients affected by Tics in Gilles de la Tourette syndrome. So far, evidence emerging from recent molecular and neuroimaging studies would seem to suggest an intriguing hypothesis that some important hyperkinetic movement disorders might share similar pathophysiological mechanisms (7). In particular, part of these shared mechanisms would seem to be localized outside the classical motor pathway (cerebellum-striato-thalamic-motor network), involving a critical region (IFC) taking part in the hyperdirect pathway, a neural circuit playing a critical role in motor control (58), which might become a new potential therapeutic target for future studies (59).

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PET neuroimaging: insights on dystonia and Tourette syndrome and potential applications

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Primary dystonia (pD) is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Gilles de la Tourette syndrome (GTS) is a childhood-onset neuropsychiatric developmental disorder characterized by motor and phonic tics, which could progress to behavioral changes. GTS and obsessive–compulsive disorders are often seen in comorbidity, also suggesting that a possible overlap in the pathophysiological bases of these two conditions. PET techniques are of considerable value in detecting functional and molecular abnormalities *in vivo*, according to the adopted radioligands. For example, PET is the unique technique that allows *in vivo* investigation of neurotransmitter systems, providing evidence of changes in GTS or pD. For example, presynaptic and post-synaptic dopaminergic studies with PET have shown alterations compatible with dysfunction or loss of D_2-receptors bearing neurons, increased synaptic dopamine levels, or both. Measures of cerebral glucose metabolism with ^{18}F-fluorodeoxyglucose PET (^{18}F-FDG PET) are very sensitive in showing brain functional alterations as well. ^{18}F-FDG PET data have shown metabolic changes within the cortico-striato-pallido-thalamo-cortical and cerebello-thalamo-cortical networks, revealing possible involvement of brain circuits not limited to basal ganglia in pD and GTS. The aim of this work is to overview PET consistent neuroimaging literature on pD and GTS that has provided functional and molecular knowledge of the underlying neural dysfunction. Furthermore, we suggest potential applications of these techniques in monitoring treatments.

Keywords: PET, primary dystonia, Tourette syndrome, movement disorders, neuroimaging, statistical parametric mapping, treatment monitoring

INTRODUCTION

The dystonias are a heterogeneous group of hyperkinetic movement disorders characterized by disabling spasms of the body due to sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both (1).

There has been a rationalization of the classification of dystonia and a greater understanding of the causes of dystonic movements from the study of genetics, neurophysiology, and functional imaging in the most prevalent form of dystonia syndrome, primary dystonia (pD) (2). Three basic parallel approaches are used to classify pD: age of onset (early or late), distribution of affected body parts (focal, segmental, or multifocal), and cause (presence or absence of genetic factors) (2).

Gilles de la Tourette syndrome (GTS) is a childhood-onset complex neurobehavioral disorder defined by motor and phonic tics, which can be often complicated by comorbid conditions that could progress to behavioral changes (3, 4). GTS and obsessive–compulsive disorders (OCD) indeed are often seen in comorbidity, also suggesting that a possible overlap in the pathophysiological bases of these two conditions. The exact etiology of GTS remains unknown, but the impairment of cortico-striatal-thalamo-cortical (CSTC) network seems to be the primary site of underlying damage.

PET molecular and functional neuroimaging techniques have been used to investigate the neural basis of movement disorders, as well as to identify potential cerebral targets for medical and surgical therapies. These techniques have provided evidence for specific alterations of both glucose metabolism and neurotransmitter systems in movement disorders, also useful for differential diagnosis (5). A very intriguing and promising application of ^{18}F-fluorodeoxyglucose PET (^{18}F-FDG PET or perfusion ^{15}O-H_2O) is the monitoring of the brain stimulation treatments in movement disorders (i.e., deep brain stimulation – DBS), together with the related assessment of the functional metabolic post-stimulation changes. Also, statistical parametric mapping (SPM) procedures allow robust voxel-based single-subject analysis (6) useful for treatment monitoring. The chance to run voxel-based single-subject analyses is of particular interest, given the low number of patients usually undergoing surgical stimulation treatments. To date, multiple reports have used similar approaches to define how stimulation treatments exert their effects in various movement disorders, like in pD (7, 8), and GTS with PET molecular imaging (9). Since the clinical manifestations of these movement disorders may be very heterogeneous and peculiar, PET monitoring could play a supportive and crucial role in evaluating the effects of the treatments and the progression of the diseases.

Functional (fMRI) and structural magnetic resonance imaging using advanced techniques as diffusion tensor imaging (DTI) have also been applied to the study of brain functional mechanisms and macrostructural abnormalities underlying movement disorders. As for pD, in sporadic cases as well as in genetic mutation carriers, DTI showed changes in the integrity of white matter fiber tracts by means of indices like fractional anisotropy or mean diffusivity (10). Similarly, DTI-based studies in GTS yielded clear evidence of reduced microstructural integrity of white matter extending beyond motor pathways. These studies suggest that alterations of the connecting systems in these diseases, also with evidence for anatomo-clinical correlations (11, 12).

Advances in PET medical technology imaging have helped to further clarify the pathophysiology of specific movement disorders, showing the associated metabolic and molecular alterations. In pD, ^{18}F-FDG PET revealed a consistent pattern of hypermetabolism, encompassing basal ganglia, and sensorimotor pathways (5, 13). In GTS, ^{18}F-FDG PET provided evidence for hypermetabolism occurring at sensorimotor cortex level and hypometabolism in the limbic cortex and striatum (14). In addition, cerebral perfusion activation studies in GTS (by means of ^{15}O-H_2O and PET) have also provided functional evidence for activations in the cerebellum, insula, thalamus, and putamen during tic release. This prominent involvement of cerebellum and insula, suggested that their recruitment in tic initiation and execution (15).

In addition, PET molecular imaging, with specific radiotracers, such as [^{11}C]raclopride, alpha-[^{11}C]methyl-L-tryptophan (^{11}C-AMT), ^{11}C-flumazenil, ^{11}C-WIN (DA transporter antagonist), ^{11}C-MCN (a 5-HT_{2A}-R antagonist), and ^{11}C-MDL (a SERotonine Transporter – SERT – antagonist) have represented a unique tool for *in vivo* evaluation of the biochemical mechanisms underlying motor dysfunctions. Studies of the neurotransmitters pathophysiology revealed multiple and complex underlying biochemical disorders.

All above supports the crucial role of PET investigations in better identifying the underlying pathophysiological mechanisms of pD and GTS disorders, showing also a potential application in treatment monitoring. The main advantage of such techniques is the possibility to *in vivo* investigate the changes in brain metabolism and neurotransmission systems before and after treatment.

This brief overview addresses the functional alterations in the networks and the interactions with neurotransmission systems in pD and GTS. It also discusses the innovative use of PET molecular imaging as a tool for monitoring interventional therapy and its use as an outcome measure.

PRIMARY DYSTONIA

CLINICAL CHARACTERIZATION

Primary dystonia typically begins in late childhood or adolescence and it is traditionally attributed to basal ganglia dysfunction (16). It is of note that no specific pathological lesions of these structures have been consistently evidenced in post-mortem studies (17). pD is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both (1). Dystonic movements are typically patterned and twisting, and may be tremulous too. These movements are often primed or worsened by voluntary actions and associated with overflowing muscle activation. pD can be classified along two axes, as defined by Albanese et al. (18): (1) clinical characteristics including age at onset, body distribution, temporal pattern, and associated features (additional movement disorders or neurological features); and (2) etiology and inheritance. The clinical characteristics fall into several specific dystonia syndromes that might help in a better diagnosis and strategic treatment. In regards to genetic forms, DYT1 and DYT6 are the most common and are inherited as autosomal dominant traits with incomplete penetrance (19–21).

^{18}F-FDG PET EVIDENCE

Several ^{18}F-FDG PET neuroimaging studies have provided knowledge on the functional anatomy of pD. Lehericy et al. (22, 23), in their comprehensive reviews on neuroimaging of dystonia using fMRI and ^{18}F-FDG PET, highlighted the hyperactivity of premotor and prefrontal areas and the hypoactivity of primary sensorimotor areas. Thus, since regions other than the basal ganglia are involved in dystonic movements, neuroimaging evidence supports the hypothesis of pD as a circuit disorder. Coherently, most of the literature converges in supporting the involvement of both basal ganglia-thalamo-cortical and cerebello-thalamo-cortical pathways (19, 23, 24).

More specifically, ^{18}F-FDG PET has been used in different dystonic disorders including primary generalized dystonia and DOPA-responsive dystonia (DRD), as well as in focal dystonic syndromes such as spasmodic torticollis, writer's cramp, and blepharospasm (25–27). Common findings concern functional metabolic abnormalities in the basal ganglia and associated outflow pathways to sensorimotor cortex and to other regions involved with motor control (5). Hutchinson et al. studied the brain metabolic pattern in six subjects with essential blepharospasm compared to normal volunteers. They showed that the clinical manifestations were associated with abnormal metabolic activity in the pons and cerebellum, and with additional abnormalities also in cortical eyelid control regions (27).

Asanuma et al. (10), by studying subjects' torsion dystonia-related pattern, showed a relative increase in the metabolic activity of the posterior putamen, globus pallidus (GP), cerebellum, and supplementary motor area (SMA).

All these results contribute to consider pD as a neurocircuit disorder, involving the cortico-striato-pallido-thalamo-cortical and cerebello-thalamo-cortical pathways, which are recognized as a cause of the clinical manifestations (28, 29). An aberrant motor response is thought to result from abnormal processing at a level of central sensorimotor integration and as a disturbance of sensory input at the level of spinal interneuronal circuits (23).

^{18}F-fluorodeoxyglucose PET imaging applied to manifesting and clinically non-manifesting gene carriers has offered the possibility of identifying alterations in circuit functional connectivity associated with both genotype and penetrance. For example, in regards to torsion dystonia, some authors hypothesized that its related metabolic pattern (TDRP, hypermetabolic at putamen, pallidus, SMA, and cerebellum levels) can potentially be used as a marker in linkage studies to identify potential gene carriers among family members of pD patients (28). Similarly, in patients with

pD due to DYT1 mutation, an abnormal metabolic brain networks was reported, characterized by hypermetabolism in the basal ganglia, SMA, and cerebellum (10). Trost et al. have quantified the metabolic activity of this network in patients carrying different pD mutations, in order to investigate whether this functional abnormality is linked to genotype. Their findings suggest that a consistent abnormal metabolic topography that is not genotype specific, being present in carriers of other pD mutations (30).

Recently, Carbon et al. (31) identified that brain regions with metabolic changes in DYT11 myoclonus-dystonia (DYT11-MD) showed specific patterns of metabolic abnormalities, involving connecting pathways between the cortex, basal ganglia, thalamus, and cerebellum. In addition, they compared metabolic abnormalities in DYT11-MD with those found in other forms of hereditary dystonia and in post-hypoxic myoclonus. They found significant DYT11 genotype-specific metabolic increases in the inferior pons and in the posterior thalamus as well as reductions in the ventromedial prefrontal cortex. Significant phenotype-related increases were also present in the parasagittal cerebellum. This latter abnormality was shared with post-hypoxic myoclonus, but not with other forms of pD. These findings were consistent with the hypothesis of a sub-cortical myoclonus generator presence in DYT11-MD, particularly likely to involve the cerebellum (31). This evidence shows how ^{18}F-FDG PET imaging can help identify different abnormal metabolic networks in specific variants of movement disorders such as in the context of pD.

PET NEUROTRANSMISSION STUDIES

Primary dystonia is a very complex disease spectrum, in which a pathological phenomena elicits a cascade of events encompassing different networks and molecular systems, from dopamine to GABA (32, 33) and also, as recently shown, acetylcholine (ACh) (34). In pD, PET and appropriate radiotracers have been used, in particular, for the assessment of dopaminergic system to investigate whether alterations in striatal receptor binding are showed by patients. Historically (1997), landmark evidence showed alterations of D_2-R binding in putamen in focal dystonias, as measured by ^{18}F-spiperone (reduced by up to 29%) (35). More recently, the adoption of ^{11}C-raclopride (a very specific radioligand for D_2-R) yielded consistent results across various studies in different forms of pD. Künig et al. (36) evaluated in 14 patients with DRD, the dopamine D_2-R binding by ^{11}C-raclopride PET in comparison with 16 levodopa-treated Parkinson's disease (PD) patients and 26 healthy controls (HCs). The DRD patients showed increased ^{11}C-raclopride binding in the putamen and caudate nucleus when compared with both controls and PD patients. The results were interpreted as reflecting reduced tracer displacement by endogenous dopamine, or as an alteration of the receptor's features due to chronic dopamine deficiency. In addition, the differences in ^{11}C-raclopride binding between DRD and PD patients in the caudate nucleus, suggest that this structure may be of pathophysiological relevance in the presentation of the clinical features of both diseases (36). Coherently, Rinne and co-workers investigated the integrity of striatal dopaminergic system in seven patients with DRD using PET with different radiotracers to evaluate dopamine transporter functioning (DAT ligand ^{11}C-CFT), D_1 (^{11}C-NNC756), and D_2-R (^{11}C-raclopride). The results showed increased striatal dopamine D_2-R availability in DRD with unchanged dopamine D_1 receptors and DAT ligand binding. The increased D_2-R availability seems to be due to reduced competition by endogenous dopamine or a compensatory response to dopamine deficiency, or both (37). ^{11}C-raclopride has been also recently used to investigate another focal dystonia, namely, writer's cramp (38). Berman et al. analyzed striatal D_2/D_3 availability at rest and during endogenous dopamine release during sequential finger tapping and speech production tasks in 15 patients with writer's cramp and 15 matched HC subjects. This work showed that patients with writer's cramp may have divergent patterns of striatal dopamine release during both a motor task (involving the dystonic hand) and an unrelated asymptomatic task, like sentence production (38). On the other hand, ^{11}C-raclopride PET showed its efficacy also in investigating commonalities and divergences between different forms of genetic mutation dystonia, like DYT1 and DYT6 (33, 39).

Asanuma et al. (39) studying the DYT1 mutation with ^{11}C-raclopride, found a 15% reduction of tracer binding in caudate and putamen in subjects without clinical manifestations. While this could have been interpreted as a trait feature of DYT1 mutation, later works with the same radiotracer showed similar reductions a in DYT6 mutation as well (33). These changes, which may be present in different degrees in the DYT1 and DYT6 genotypes, are likely to represent susceptibility factors for the development of clinical manifestations in mutation carriers (33). It is of note that a recent study revealed unaltered D_1 receptor binding (by means of ^{11}C-NNC112 PET) in primary focal dystonias when compared with HCs (40).

This suggests that dopaminergic post-synaptic alteration may be an early pathological trait of the condition, not sufficient *per se* in eliciting the full clinical phenotype (5).

Since preclinical and indirect clinical evidence suggest that molecular changes also of the GABAergic control system might represent a key dysfunctional component leading to disinhibition of the sensorimotor system (41, 42). Garibotto et al. used ^{11}C-flumazenil PET in patients with sporadic and DYT1 mutation pD in order to assess the integrity of the GABAergic system. The results revealed a reduction in $GABA_A$ receptor expression or affinity, both in DYT1 carriers and sporadic patients in primary motor and premotor cortex, primary and secondary somatosensory cortex, and in the motor component of the cingulate gyrus. Clearly, a deficit in GABAergic function might indeed result in abnormalities of neuronal inhibition affecting both the motor and somatosensory systems. In particular, the reduced inhibitory control in somatosensory cortices might suggest that the GABA system plays a crucial role in the modulation of the afferent signal to the somatosensory cortex in pD (43). Noteworthy, a MR spectroscopy study in patients with pD, revealed a significant decrease in GABA levels in the sensorimotor cortex and lentiform nuclei contralateral to the affected side, thus, providing indirect evidence supporting the relevant role of this system in pD (44).

As claimed by Tanabe and co-workers, even-though anticholinergic medications are effective in DYT1 and other forms of dystonia, this does not necessarily imply a primary role of ACh in these disorders. In point of fact, the abnormal cholinergic functioning may result as a secondary effect of the altered dopaminergic

neurotransmission in the striatum (34) and this imbalance may have a role in symptom generation, as showed recently in DYT1 animal models (45).

GILLES de la TOURETTE SYNDROME

CLINICAL CHARACTERIZATION

Gilles de la Tourette syndrome is a childhood-onset neuropsychiatric developmental disorder characterized by motor and phonic tics that are defined as involuntary or semivoluntary, sudden, intermittent, repetitive movements (motor tics), or vocalizations (phonic tics) (3). Comorbidities are very common, in particular, OCD and attention deficit hyperactivity disorder (46). It is of note that the exact etiology of GTS remains unknown. Volumetric MRI in GTS provided evidence for correlations between tic severities and volume of specific structures [e.g., caudate, see Ref. (47)] and also for abnormal gray matter volumes in prefrontal cortex in children and adults [see Ref. (48, 49), and for review see Ref. (50, 51)]. Functional neuroimaging techniques, such as single-photon emission computed tomography (SPECT), PET, and fMRI have provided some evidence for the underlying pathological mechanisms in GTS that enabled new hypotheses on its pathophysiology to be formulated (50, 51). In particular, these studies suggest that the involvement of the CSTC network in the pathophysiology of tics and associated psychopathological manifestations in GTS (19).

^{18}F-FDG PET EVIDENCE

^{18}F-fluorodeoxyglucose PET investigations, also through *ad hoc* parametric measurements and/or voxel-wise statistical analysis, have shown that regions other than the basal ganglia circuits may be involved in GTS [see for example Ref. (14, 52)]. It has been hypothesized that abnormal connections between basal ganglia, thalamus, and cortex (within the CSTC circuitry) may be specifically associated to this condition (53). GTS has been significantly characterized by (a) lower metabolic rates in caudate nucleus and thalamus, (b) possible association with hypoactivity in lentiform nuclei and hippocampal formation, and (c) higher metabolic rates in the sensorimotor cortices (14, 15, 54, 55).

Pourfar et al. showed resting-state reduced metabolic activity in the striatum and orbitofrontal cortex, and it was associated with relative metabolic increases in premotor cortex and in cerebellum in GTS-related metabolic pattern. Further analysis of the same cohort, revealed that OCD symptoms in GTS patients were related with a second metabolic pattern, characterized by (a) reduced metabolic activity in the anterior cingulate and dorsolateral prefrontal cortices and (b) associated increases in primary motor cortices and precuneus. The authors conclude that the different clinical manifestations of GTS are associated with the expression of these two distinct abnormal metabolic brain networks (14).

Correlation analysis between glucose metabolism and clinical evidence contributed in characterizing the system networks affected in this neuropsychiatric disease, which might be useful in correct identification of the disorder. ^{18}F-FDG PET studies have shown significant correlations between the presence of tics and hypermetabolism in several brain regions, including the medium and lateral premotor cortices; the primary motor cortices; the inferior parietal cortices; as well as the anterior cingulate cortex, putamen, and caudate and Broca's area (53). These results support hyperactivity of the systems involved in motor planning/structuring and in the processing of sensory inputs at the basis of GTS symptoms. In summary, GTS shows heterogeneity of cortical and sub-cortical metabolic alterations depending on different factors not yet completely identified, thus, hindering the characterization of a specific metabolic pattern. Nonetheless, ^{18}F-FDG PET at single-subject level represents a useful tool for the assessment of brain functional deficits, giving the chance to monitor personalized brain target therapy and to assess the efficacy of treatments.

PET NEUROTRANSMISSION STUDIES

Few PET molecular studies of neurotransmission systems provided insights on the underlying pathophysiology of GTS. Historically, GTS has always been linked to a dysregulation of dopamine neurotransmission system (52, 56), also given the evidence for reductions of TIC severity in treatments with D_2-R antagonists (57). Coherently, early post-mortem studies also provided evidence for alterations in second messenger system (58) and also for a possible relation between clinical phenotypes of GTS and dopamine innervation in the striatum (^{3}H-mazindol showed an increased density of uptake sites) (59). To date, other neurotransmission systems like serotonin or GABA have been investigated in GTS (15, 60, 61).

Singer et al. tested the presynaptic dopamine release from the striatum after amphetamine administration in GTS adult patients using ^{11}C-raclopride PET. Results were consistent with the possibility that the pathologic mechanisms in GTS relate to an abnormal regulation of the phasic dopamine response, resulting in hyper responsive spike-dependent dopaminergic system activation. Thus, a tonic/phasic imbalance in the DA system may help to explain the DA pathophysiology associated with GTS that could be crucial in developing potential pharmacologic treatments (62). Behen et al. used ^{11}C-AMT PET to assess global and focal brain abnormalities of tryptophan metabolism and their relationship to behavioral phenotype in children with GTS and healthy age-matched controls. Their results show cortical and sub-cortical abnormalities of tryptophan metabolism in GTS, in particular, in the dorsolateral prefrontal cortex (DLPFC) and bilateral thalamus levels, providing a strong neuroimaging evidence for a role of serotoninergic mechanisms in the pathophysiology of GTS (60). Saporta et al. (61), using ^{11}C-AMT PET and DTI investigated both structural white matter abnormalities and serotonin synthesis in children with GTS. The authors hypothesized that microstructural alterations and related altered connectivity in CSTC might have been the primary abnormality in GTS, then inducing altered neurotransmission. They found an asymmetric immature microstructure in the caudate nucleus that was associated with abnormally increased serotonin synthesis. The authors suggest that the increased serotonin synthesis in the caudate could be due to cortical disinhibition, in the context of abnormal corticostriatal connectivity. On this basis the authors suggest serotonin system as a possible new therapeutic target in GTS (61). Interestingly, Lerner et al. (63), in the first study of GABA neurotransmission system in GTS patients using ^{11}C-Flumazenil and PET found a consistent decrease of $GABA_a$ receptors in multiple limbic regions such as amygdala, ventral striatum, thalamus, and also

at the insula level. An increase of these receptors was also present in the cerebellum, in the bilateral substantia nigra (SN) at peri-aqueductal gray (PEG) level and in the right posterior cingulate cortex (63).

In addition, besides the evaluation of isolated systems, insights on underlying GTS pathophysiology have been provided by studies on neurotransmitters inter-modulation. Wong et al. (64) studied both dopaminergic and serotoninergic neurotransmitter systems at transporter and at receptor density levels, as measured by, respectively, ^{11}C-raclopride and ^{11}C-WIN (Dopamine Active Transporter – DAT antagonist) or ^{11}C-McN (5-HT_{2a}R antagonist) and ^{11}C-MDL (SERT antagonist). In particular, they tested whether there was a connection between phasic DA release (DA_{REL}) induced by administration of amphetamine and levels of 5-HT in patients with GTS plus OCD comorbidity. They found a strong correlation between DA_{REL} and low levels of 5-HT, suggesting that "DA_{REL} is a primary defect in GTS" (64).

Further investigations in larger patient groups are necessary in order to further elucidate the complex neuromodulation changes in GTS.

Table 1 | Table showing papers in literature (chronological order) adopting PET for effects assessment of stimulation treatment in dystonia.

Reference	Dystonia type	Sample	Stimulation	Region	Tracer
(70)	gD	Case study	DBS	bilGP	^{15}O-H_2O
(7)	pgD	6	DBS	bilGPi	^{15}O-H_2O
(72)	pfD	Case study	DBS + epidural cortical stimulation	GPi + pMC	^{18}F-FDG
(71)	tD	5	DBS	GPi	^{15}O-H_2O
(8)	pfD	7	Epidural cortical stimulation	preMC	^{18}F-FDG

gD, generalized dystonia; pgD, primary generalized dystonia; pfD, primary focal dystonia; tD, tardive dystonia.

PET NEUROIMAGING AND STIMULATION TREATMENT MONITORING: EVIDENCE IN pD AND GTS

As anticipated in the introduction, a promising approach is to use PET techniques (mainly perfusion ^{15}O-H_2O and/or ^{18}F-FDG PET) to monitor therapy efficacy in a variety of conditions and across different type of medical and surgical treatments. For example, PET techniques have shown a high value in monitoring the effects of surgical therapies like DBS, which has been extensively adopted in movement disorders (65). Clinically, recent studies assessing the efficacy of stimulating treatments as DBS or repetitive transcranial magnetic stimulation (rTMS) at specific movement-related regions (such as globus pallidum or premotor cortices) have demonstrated some positive effects in attenuating the symptoms (66–69).

PET with perfusion radiotracers for monitoring treatments in pD and GTS is not routinely used in clinical practice but some authors, even if with a small cohort of patients, have demonstrated the feasibility and the potential role of this approach in specific setting of post-therapy assessment (see **Table 1** for dystonia). Kumar and colleagues (70) studied the effects of bilateral GP DBS, by means of clinical assessment and of ^{15}O-H_2O PET, in a case of medication-refractory generalized dystonia, taking into account different stimulators settings and induced motor conditions. The authors found a positive clinical improvement after 1 year of DBS, also during active condition in terms of reaction times and randomness of movements, "due to suppression of dystonic patterned involuntary movements." Coherently, PET investigation showed that bilateral GP DBS, during the action (moving a joystick), was reducing activity in lentiform nuclei, motor areas (primary, premotor, SMA), and also in control areas such anterior cingulate or prefrontal cortices (70). Detante et al. (7) studied the effects of internal DBS on bilateral GP by assessing regional cerebral blood flow (by means of ^{15}O-H_2O and PET) in a sample of six patients with primary generalized dystonia. Authors designed two test conditions, namely, OFF (no stimulation) and ON (unilateral DBS GPi stimulation). During OFF condition, PET data showed overactivity in DLPFC, medial and superior frontal gyrus (medFG/supFG), OFC, and thalamus. During ON condition, while stimulation was being administered to the contralateral side of the most dystonic hand (assessed during OFF condition), PET data showed a decrease of the overactivity in the same areas and also in the putamen (7). Finally, Thobois et al. studied the effects of DBS with ^{15}O-H_2O PET in GPi in five patients with tardive dystonia (induced by neuroleptics). Differences in brain perfusion induced by GPi stimulation between motor execution and rest condition confirm that the increased activity of prefrontal cortex and premotor areas can be modulated with DBS (71). Besides ^{15}O-H_2O PET, also ^{18}F-FDG PET has been used in monitoring stimulation treatments (8, 72), showing a very high accuracy and reliability.

Notably, the potential of ^{18}F-FDG PET in detecting regional glucose metabolism abnormalities can be improved using voxel-based statistical methods (such as SPM). This parametric approach has been applied in pD to evaluate, at a voxel-level, brain glucose metabolism changes before and after brain stimulation (8, 72). For example, Lalli et al. (8) have assessed the efficacy and safety of epidural premotor stimulation in patients with primary focal dystonia using ^{18}F-FDG PET and SPM8 for statistical voxel-based analysis (VBA). In order to define regional cerebral metabolism differences, patients were compared to HCs at pre-surgery and post-surgery conditions. The authors found that the sensorimotor cortex was specifically involved in focal dystonia, with hypermetabolism (relatively to HCs) at baseline and a reduction of hyperactivity after epidural stimulation, suggesting that a positive effect of brain stimulation (**Figure 1**). These findings confirmed the notable role of PET to elucidate the underlying metabolic mechanisms, together with the chance to track and monitor treatments progression (8). Some years before, Romito et al. (72) used, in a case of primary fixed dystonia, ^{18}F-FDG PET and SPM99 to monitor the effects of an epidural motor cortex stimulation treatment that significantly reduced the severe dystonic symptoms. This patient experienced null benefits during

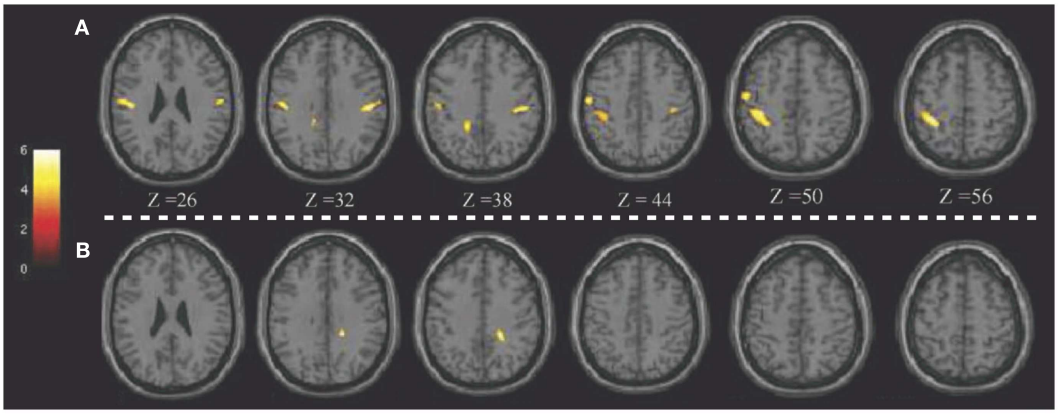

FIGURE 1 | Patients with epidural premotor cortical stimulation in primary focal dystonia. Results of SPM8 group analysis showing increased metabolism in the patient group at **(A)** pre-surgery and **(B)** post-surgery conditions compared to normal controls. Modified from Ref. (8).

internal GP (GPi) stimulation, which is commonly effective in these conditions. Therefore, the authors decided to apply cortical motor areas stimulation that in 6 months, elicited notable improvements in fixed dystonia and in movements. In this study, ^{18}F-FDG PET was then used to characterize the metabolic changes induced by the different treatments, revealing that GPi stimulation was inducing an increase of glucose metabolism in the sensorimotor cortex (L > R), SMA, and anterior cingulate gyri bilaterally. Conversely, motor cortex stimulation was inducing a reduction of glucose metabolism in the bilateral cerebellum. Despite the few earlier reports in literature, the author concluded that motor cortex stimulation may be an effective treatment in focal dystonia (72).

In the previous paragraphs, we have discussed how PET imaging can be useful in characterizing metabolic and neurotransmission abnormalities in GTS, suggesting that its potential application in treatment monitoring in these patients. Notwithstanding, only few reports are currently available in the literature of therapy assessment in GTS. Hopefully, future studies will further apply these techniques, given the urgency of defining effective treatments and provide appropriate safe care. Besides ^{15}O-H_2O and ^{18}F-FDG, PET molecular imaging may be useful too, given all the evidence of multiple neurotransmitters systems alteration in GTS.

For example, Vernaleken et al. studied, in a case study, the effect of thalamic DBS in a GTS patient by means of ^{18}F-Fallypride PET (73). The aim of the authors was to clarify the mechanisms of DBS-induced modulatory effects on GTS symptoms *in vivo*. They found that this stimulation treatment exerted its effects through the modulation of the dopaminergic neurotransmission system. Given the success of this pilot study, some years later, the same group further investigated the dopamine modulation (still with ^{18}F-Fallypride PET) induced by DBS in three GTS patients (9). The authors, evaluating the results, took into account all the possible confounding factors (from anesthesia for the long-PET scan duration to low-subjects number) concluding that DBS may exert its effects modulating the hyperactive dopamine transmission within the basal ganglia circuitry (9).

CONCLUSION: SUMMARY AND FUTURE DIRECTIONS

The most applied PET neuroimaging approaches in movement disorders include functional and molecular imaging using ^{18}F-FDG PET and neurotransmitter-specific tracers. Several studies using PET techniques, also through *ad hoc* parametric measurements or voxel-based statistical analysis (SPM) at both single-subject and group-level, have shown that regions other than the basal ganglia circuits are involved in pD and GTS. This can be used to pinpoint a breakdown of organized trans-synaptic activity, which might distinguish these disorders. Indeed, in GTS and pD, the CSTC circuit seems to play an important role in the generation of tics and dystonia. Nevertheless, the precise localization and mechanisms of these abnormalities remain disputed and are a topic of active debate and research. Finally, despite some authors have proposed the possible value of PET investigations for early and differential diagnosis of movement disorders, further researches and added knowledge on the distinct pathophysiological basis are still necessary. Despite the doubtless value of PET molecular techniques, it should always be taken into account that these results might be undermined by confounding variables, such as age at onset, comorbidities, or ongoing medical treatments.

PET studies involving larger clinical samples to investigate glucose metabolic changes and integrity of neurotransmitter systems (e.g., dopamine system with D_2-R availability, DAT functioning and amphetamine-induced DA_{REL}) and controlling for confounding variables, will surely provide further insights, particularly in the measurement of the pathophysiological abnormalities. The more these factors are evaluated and controlled, the greater the value of the results will be, especially for clinical practice.

In regards to the assessment of therapeutic effects of DBS or cortical stimulations by PET functional neuroimaging, it appears very promising and offers a wide variety of applications. PET techniques can be very useful in correctly identifying potential targets for medical and surgical therapies. These tools can clearly help in defining how the stimulations elicit their effects on the brain functioning, both at treatment site and at whole-brain

circuitry level. Evaluating therapy-induced changes in metabolism or in neurotransmitters systems can be very challenging and heavily dependent on raters' expertise. Semi-quantitative parametric approaches provide very informative data that is less affected by inter-individual observer differences. These voxel-based analyses, especially at single-subject level, have shown high accuracy in monitoring stimulation treatment effects (6, 8, 72). We strongly claim that the adoption of PET molecular and functional imaging, especially with optimized parametric approaches, is of utmost importance for monitoring of both medical and surgical therapies in pD and GTS. Future further studies in this direction are welcome, in order to evaluate the potential of this methodology in clinical practice.

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Sensorimotor connectivity in Parkinson's disease: the role of functional neuroimaging

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The diagnosis of Parkinson's disease (PD) remains still clinical; nevertheless, in the last decades, the rapid evolution of advanced MRI techniques has made it possible to detect structural and, increasingly, functional brain changes in patients with PD. Indeed, functional MRI (fMRI) techniques have offered the opportunity to directly measure the brain's activity and connectivity in patients with PD both in early and complicated stage of the disease. The aims of the following review are (1) to present an overview of recent fMRI reports investigating the activity and connectivity of sensorimotor areas in patients with PD using both task-related and "resting-state" fMRI analysis (2) to elucidate potential pathophysiological mechanisms underlying dyskinetic motor complications in the advanced stage of PD.

Keywords: Parkinson's disease, advanced MRI techniques, task-related functional MRI, resting-state functional MRI, seed approach, independent component analysis, sensorimotor network, dyskinetic motor complications

INTRODUCTION

Parkinson's disease (PD), the second most common neurodegenerative disease worldwide, is characterized by bradykinesia and at least one of tremor, rigidity, and postural instability (1). Although recent advances in neuroimaging have provided new insights into the pathophysiology of the disease, the diagnosis of PD remains still clinical, based upon the presence of cardinal motor symptoms (2). Neuroimaging of PD has been historically dominated by positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies using a variety of dopaminergic radiopharmaceuticals that focus on striatal measures of nigrostriatal neurons (3). Concurrently, fluorodeoxyglucose–PET has been used to image abnormal covariance patterns of cortical and subcortical regional metabolism that correlate with motor and cognitive impairment (4). On the other hand, conventional brain MRI is currently limited to the differential diagnosis between idiopathic PD and atypical or secondary parkinsonism or to prognosticate, and to locate the targets for functional neurosurgery (5). However, the use of 7-T MRI scanners has recently allowed to detect anatomical changes in nigral morphology in PD, which may represent, in the near future, a reliable MRI biomarker of PD diagnosis (6, 7). Nevertheless, in the last decades, the rapid evolution of advanced MRI techniques has allowed us to further investigate the progression of nigral and extra-nigral degeneration with greatly improved spatial resolution and a minimal invasiveness. Moreover, functional MRI (fMRI) techniques have offered the possibility to directly measure the brain's activity and connectivity in patients with PD both in early and complicated stage of the disease. Therefore, morphological and fMRI techniques may shed lights on pathophysiological mechanisms of PD and its disease and treatment-related complications. The most commonly used method, among fMRI techniques, is the measurement of blood oxygen level dependent (BOLD) signal, based on the differences between magnetic characteristics of oxyhemoglobin (diamagnetic) and deoxyhemoglobin (paramagnetic). In the brain, neuronal activity increases consistently with blood flow and oxyhemoglobin and could be hence visualized by changes in the BOLD contrast. This neuroimaging technique enables to explore brain function and connectivity with high temporal and spatial resolution (8). More recently, fMRI in the absence of experimental tasks and behavioral responses, performed with the patient in a relaxed "*resting*" state (RS-fMRI), has allowed for the exploration of brain connectivity between functionally linked cortical regions (9), the so-called resting-state networks (RSNs). The most commonly reported RSNs are the default mode network, the fronto-parietal network, and the sensorimotor network (9), which is crucial for the execution of voluntary movements and functionally connects regions within the supplementary motor area (SMA) and the primary motor cortex (M1) (10, 11). The aims of the following review are (1) to present an overview of recent fMRI reports, which have investigated, in patients with PD, the activity and connectivity of the sensorimotor areas using both task-related and "resting-state" fMRI analysis, respectively, (2) to elucidate potential pathophysiological mechanisms underlying motor complications in the advanced stage of PD.

TASK-RELATED fMRI STUDIES

In the last decades, fMRI studies, employing motor tasks requiring motor selection and initiation (12–14), have consistently shown an abnormal activation of different areas of the motor network

in patients with early and late-stage PD. The integrity of this network is required not only to perform a voluntary movement but also for readiness for a future motor task. These functional changes have been correlated both to bradykinesia and to the severity of the disease (i.e., Hoehn and Yahr stage). Specifically, these studies have commonly revealed hypoactivation of the SMA, and hyperactivation of cerebellum and other cortical motor regions, such as premotor (PMC), primary motor (M1), and parietal cortices in patients with PD compared to age-related healthy controls. It is noteworthy that these results have shown striking similarity with the pattern of altered cerebral metabolic activity observed with PET in patients with PD (15–18). Levodopa or apomorphine administration (12, 19), ventral posterolateral pallidotomy (20), or deep brain stimulation of the subthalamic nucleus (STN) (21) can relatively normalize the reduced activation of the SMA, and decrease the overactivation of other cortical regions. Because the SMA contributes to the preparation and execution of learned motor sequences (22–24), its decreased activation may be an important factor contributing to the lack of readiness and to the difficulty in initiating voluntary movements in patients with PD. Moreover, the hyperactivation of cortico-cerebellar regions may reflect a functional compensation for the defective basal ganglia in motor control. In other words, patients with PD may need compensatory activity of other motor circuits to overcome their difficulty in performing self-initiated movements (25). The compensation operated by the cerebellum could be achieved through the cerebello-thalamo-cortical loop or more directly through direct projections from the cerebellum to the basal ganglia (26, 27). Yu and colleagues (27) have found a significant negative correlation between the BOLD response in the putamen and the contralateral cerebellum, confirming cerebellar compensatory role in patients with PD. On the other hand, no significant correlation between the putamen and M1 was found and M1 hyperactivation was positively correlated only with the severity of upper limb rigidity. The increased connectivity between the M1 and pre-SMA has not only a compensatory role but could also reflect primary pathophysiological changes of PD, as a consequence of the inability to inhibit contextually inappropriate circuits (21, 28). Although several imaging studies on PD have reported similar findings (13, 19, 29), Buhmann and colleagues (19) have observed, in "drug-naïve" patients with PD while performing a simple, auditory-paced random finger-opposition task, a reduced activation of M1, which was partially restored only after levodopa intake. Thus, it is possible that the strengthened connectivity of the M1 and the related compensatory functional reorganization may be induced by the prolonged dopaminergic treatment. Functional reorganization of M1, indeed, is absent in "drug-naïve" patients with PD and hypoactivation of this brain region reflects the decreased input arising from the subcortical motor loop, which is partially restored by dopaminergic treatment.

RESTING-STATE fMRI STUDIES

The interpretation of these functional changes may be confounded by the fact that patients with PD have difficulty with performing motor tasks. RS-fMRI can overcome this problem by providing an index of connectivity across the whole brain. For this reason, a number of studies have applied RS-fMRI technique to investigate sensorimotor network connectivity in patients with PD (30–37). These reports have commonly demonstrated a disrupted functional integration in corticostriatal loops. Wu and colleagues (36), using a regional homogeneity approach, have demonstrated a decreased functional connectivity in the SMA, left dorsal lateral prefrontal cortex (DLPFC), and putamen and an increased cerebellar connectivity in patients with PD without dopaminergic medication for at least 12 h ("off-state"). The decreased SMA and basal ganglia connectivity was negatively correlated with the unified Parkinson's disease rating scale (UPDRS) score, whereas a positive correlation was identified between increased cerebellar connectivity and the UPDRS score. Thus, this suggests that as the disorder progresses, resting-state neuronal activity in the SMA and basal ganglia becomes more abnormal and, at the mean time, the compensatory effect in the cerebellum is more significant. Previous fMRI and PET reports (19, 29, 38, 39) have already highlighted the involvement of DLPFC in patients with PD. The decreased connectivity of this region is probably related to the reduction in the attention to action and in performance monitoring typically observed in patients with PD. In another connectivity study by the same group (37), an increased connectivity in the right M1 and a decreased connectivity in the left putamen were confirmed in patients with PD. Moreover, an inferior parietal lobule (iPL) and a PMC disconnection with the pre-SMA were also detected. Thus, greater PD-related connectivity changes occur in networks linked to preparation and initiation rather than in those involved in motor execution. Indeed, iPL and PMC are related to the integration between motor selection and external information and selection of movements into a precise plan, respectively (22, 40, 41). The increased resting-state connectivity between the pre-SMA and right M1 confirms the potential compensation for the described decreased motor network connectivity in PD. In the first placebo-controlled RS-fMRI study, exploring the intrinsic sensorimotor network functional connectivity in "drug-naïve" patients with PD (42), we have demonstrated a decreased regional connectivity in the SMA in the "off-state," which was partially restored only after levodopa administration. Moreover, a region of interest (ROI) analysis of the sensorimotor network functional connectivity in the basal ganglia and thalamus revealed that levodopa significantly increased the participation of these subcortical regions to the sensorimotor network activity. Finally, no statistically significant differences were detected between the groups in the M1 connectivity, confirming that the compensatory functional reorganization may be related to prolonged dopaminergic treatment rather than PD *per se*. Dopaminergic modulation of resting-state functional connectivity in "drug-naïve" patients with PD has also been evaluated using a correlation analysis with dopamine levels in the striatum, assessed quantitatively by FP-CIT PET (43). Choosing four ROIs, posterior cingulate cortex (PCC), putamen (anterior and posterior), and caudate, the authors found that the DLPC was the primary dopamine-dependent cortical region that was functionally connected with the anterior and posterior putamen. Moreover, patterns of dopamine-dependent positive functional connectivity varied depending on the location of the striatal seeds; dopamine-dependent functional connectivity from the caudate predominantly overlaid pericentral cortical areas, whereas dopamine-dependent structures that were

functionally connected to the posterior putamen predominantly involved cerebellar areas. Finally, there were cortical areas where the cortico-cortical or striato-cortical connectivity were negatively associated with the dopaminergic status in the posterior putamen. Therefore, dopamine deficiency may lead to alterations in resting-state functional connectivity and reorganization of striato-cortical functional network in patients with PD. This may be one of mechanisms underlying impaired sensorimotor integration in PD. According to Braak staging (44), the pathologic process of PD, occurring primarily in the brainstem, pursues an ascending course reaching the neocortex in the final stage; thus, subcortical involvement prevails throughout the course of PD and functional changes in the basal ganglia lie at the heart of PD. Based on this a number of seed based RS-fMRI studies (31, 32, 45), using left and right putamen, caudate, and amygdala as seeds, have shown a significantly reduced connectivity within mesolimbic–striatal and corticostriatal loops in "drug-naïve" PD patients. In these studies, both anterior and posterior putamen showed a decreased connectivity pattern with their contralateral putamen and mesolimbic regions, especially in amygdala, hippocampus, olfactory area, and posterior rectus, whereas the posterior putamen presented a more prominent decreased pattern extending to sensorimotor cortex. The caudate connectivity pattern was relatively spared. Functional connectivity analysis of the amygdala also showed coherent reduced connectivity pattern with the putamen. Moreover, putamen connectivity with amygdala, a limbic region crucial for emotional processing (45) was significantly correlated with non-motor symptom scale (NMSS) total score and NMSS mood subscale score. No compensatory increased functional connectivity was found in this study. Baudrexel and colleagues (30) set out to define the differences of resting-state STN functional connectivity networks between patients suffering from early stage PD and healthy controls using this straightforward seed-region approach. STN was selected as seed region because it is both part of the slow "indirect" and a fast "hyper-direct" functional cortico-subcortical loop, and it is currently the most effective target for DBS in patients suffering from advanced PD (46). The analysis revealed an increased functional connectivity between right and left STN and bilateral M1, PMC, SMA, and also primary sensory regions in patients with PD, confirming the well-established results from electrophysiological recordings, which have demonstrated excessive synchronization in basal ganglia-cortical circuitries at a vastly different temporal scale (47–49). This fMRI resting-state study provides an additional evidence that a pathologic subthalamic–cortical coupling might be a crucial factor in the pathophysiology of PD (50). These results are in line with the original model of BG functioning proposed by Alexander and DeLong (51, 52); dopamine depletion, indeed, causes suppression of the "direct" cortical-BG feedback loop (cortex–striatum–internal globus pallidum/SNr–thalamus–cortex) and a release of the "indirect" loop (cortex–striatum–external globus pallidum–STN–GPi/SNr–thalamus–cortex) both, resulting in hyperactivity of the STN. Although RS-fMRI studies have mainly provided insights into the pathophysiological mechanisms underlying motor and non-motor symptoms of PD, a recent study (53) has demonstrated that changes in basal ganglia network (BGN) connectivity could help us to differentiate patients with PD from healthy controls. Using a BGN template derived from 80 elderly controls, patients with PD showed a reduced functional connectivity in a wide range of BGN areas (such as putamen, caudate, anterior thalamus, DLPC, and precuneus). This functional alteration was clearly improved by levodopa administration. Moreover, average BGN connectivity was able to differentiate patients with PD from controls with 100% sensitivity and 89.5% specificity, confirming the potential role of RS-fMRI connectivity as a biomarker in early PD.

SENSORIMOTOR CONNECTIVITY IN DYSKINETIC PHASE

Long-term levodopa treatment is complicated by the gradual development of involuntary movements referred to as levodopa-induced dyskinesias (LID). Recent studies have evidenced a substantial progress in understanding the cellular and molecular mechanisms, which underlie dyskinesias (54, 55). Hypersensitivity of striatal medium spiny neurons to pulsatile dopamine receptor stimulation during task-related corticostriatal activation of glutamate receptors seem to plays a crucial role to the development of these motor complications (56). Neuroimaging studies of dyskinesias in humans are sparse, because dyskinesias cause movement artifacts impairing data quality. Cerasa and colleagues (57), comparing patients with PD with and without LID during execution of externally and internally triggered visuomotor tasks, showed significant SMA hyperactivity and hypoactivity in the right inferior prefrontal gyrus only in patients with LID. However, it remains unclear how intake of levodopa modulates neural activity in patients with dyskinesias. More recently, Herz and colleagues (58) performed a task-related fMRI experiment in the time window between the intake of levodopa and the onset of motor complication in dyskinetic vs. non-dyskinetic patients with PD, which were asked to produce a mouse click with the right or left hand or no action (No-Go). During No-Go trials, patients with PD, who would later develop dyskinesias, showed an abnormal gradual increase of activity in the pre-SMA and the bilateral putamen during the first 20 min after levodopa intake. This rapidly emerging hypersensitivity of putamen and pre-SMA in the context of movement suppression (No-Go) and in the pre-dyskinesia period might reflect an unphysiological facilitation or impaired inhibition, via striatal D2-type receptors (56), of motor programs, resulting in aberrant activity in interconnected cortical areas.

CONCLUSION

In conclusion, although the diagnosis of PD remains still clinical, functional imaging studies can provide great insights into connectivity changes and pathogenic processes in PD. Task-related fMRI studies have shown an abnormal activation of different areas of the motor network in patients with early and late-stage PD related to cardinal clinical features. More recently, RS-fMRI techniques have been used to investigate sensorimotor network connectivity in patients with PD confirming a disrupted functional integration in corticostriatal loops. Therefore, in the near future, the practical application of these techniques may provide a better understanding of disease- and treatment-related complications and a reliable MRI biomarker for an early diagnosis of PD.

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Cerebellum in levodopa-induced dyskinesias: the unusual suspect in the motor network

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The exact mechanisms that generate levodopa-induced dyskinesias (LID) during chronic levodopa therapy for Parkinson's disease (PD) are not yet fully established. The most widely accepted theories incriminate the non-physiological synthesis, release and reuptake of dopamine generated by exogenously administered levodopa in the striatum, and the aberrant plasticity in the cortico-striatal loops. However, normal motor performance requires the correct recruitment of motor maps. This depends on a high level of synergy within the primary motor cortex (M1) as well as between M1 and other cortical and subcortical areas, for which dopamine is necessary. The plastic mechanisms within M1, which are crucial for the maintenance of this synergy, are disrupted both during "OFF" and dyskinetic states in PD. When tested without levodopa, dyskinetic patients show loss of treatment benefits on long-term potentiation and long-term depression-like plasticity of the intracortical circuits. When tested with the regular pulsatile levodopa doses, they show further impairment of the M1 plasticity, such as inability to depotentiate an already facilitated synapse and paradoxical facilitation in response to afferent input aimed at synaptic inhibition. Dyskinetic patients have also severe impairment of the associative, sensorimotor plasticity of M1 attributed to deficient cerebellar modulation of sensory afferents to M1. Here, we review the anatomical and functional studies, including the recently described bidirectional connections between the cerebellum and the basal ganglia that support a key role of the cerebellum in the generation of LID. This model stipulates that aberrant neuronal synchrony in PD with LID may propagate from the subthalamic nucleus to the cerebellum and "lock" the cerebellar cortex in a hyperactive state. This could affect critical cerebellar functions such as the dynamic and discrete modulation of M1 plasticity and the matching of motor commands with sensory information from the environment during motor performance. We propose that in dyskinesias, M1 neurons have lost the ability to depotentiate an activated synapse when exposed to acute pulsatile, non-physiological, dopaminergic surges and become abnormally receptive to unfiltered, aberrant, and non-salient afferent inputs from the environment. The motor program selection in response to such non-salient and behaviorally irrelevant afferent inputs would be abnormal and involuntary. The motor responses are worsened by the lack of normal subcortico–cortical inputs from cerebellum and basal ganglia, because of the aberrant plasticity at their own synapses. Artificial cerebellar stimulation might help re-establish the cerebellar and basal ganglia control over the non-salient inputs to the motor areas during synaptic dopaminergic surges.

Keywords: levodopa-induced dyskinesias, dopamine, Parkinson's disease, plasticity, motor cortex, cerebellum, basal ganglia

INTRODUCTION

In spite of being the most efficacious drug for the relief of motor symptoms of Parkinson's disease (PD), L-3,4-dihydroxyphenylalanine (also known as levodopa) almost invariably generates disabling involuntary movements. Levodopa-induced dyskinesias (LID) seldom occur with the first dose of levodopa, but chronic exposure to the drug results in LID in 20–30% of PD patients in ∼2 years and in 80% within 5 years (1). The risk to develop LID is enhanced by younger age, longer durations of disease and levodopa treatment, greater disease severity (1), higher levodopa dose (2), genetic etiology of the disease (3–5) and genetic variability in the dopamine metabolizing enzymes (6), dopamine receptor and transporter isoforms (7–9), and brain derived neurotrophic factor (10).

Based on the timing of their appearance in a levodopa cycle, LID are termed as "peak-dose dyskinesia" or "biphasic dyskinesia." Peak-dose dyskinesias are associated with high plasma concentrations of levodopa (11) and the maximum reduction in Parkinsonian signs. Biphasic dyskinesias appear just before the beginning and the end of the relief period of the Parkinsonian

signs, disappear in the phase of maximum clinical response, and occur below a critical, low level of plasma levodopa (12). Peak-dose dyskinesias are often choreic and seldom pure dystonic movements. Biphasic dyskinesias are stereotyped, repetitive, dystonic movements that are usually confined to the legs, and may co-occur with Parkinsonian signs elsewhere in the body. Dystonic movements can also occur in patients not exposed to levodopa and their presence correlates with akinesia of PD (13).

The neural mechanisms of LID, those that determine the clinical type of LID (i.e., choreic or dystonic) and those allowing the co-occurrence of Parkinsonism and biphasic dyskinesias, are still not fully understood (13–16).

The most accepted models of LID implicate pre- and post-synaptic changes at the cortico-striatal synapses and alterations in the activity of dopaminergic and non-dopaminergic (e.g., glutamatergic) neurotransmitter systems. The degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) is associated with a series of changes in the nigro-striatal synapses such as a loss of tonic release of dopamine, diminished dopamine storage, and reuptake capacity [for review see Ref. (17)]. Positron emission imaging studies have demonstrated abnormally high levels of striatal dopamine 1-hour post-medication (18) and reduced dopamine transporter (DAT) levels (19) in dyskinetic patients. Brain concentrations of levodopa after peripheral administration were also found to be higher in dyskinetic rats than non-dyskinetic rats, though plasma levels were not different (20), confirming this association. The availability of extracellular dopamine after exogenous levodopa administration depends significantly on the serotoninergic neurons, which convert it to dopamine and provide vesicular storage (21, 22). These neurons, however, lack the DAT system and pre-synaptic dopamine D2 autoreceptors, which leads to unregulated release and reduced clearance of dopamine (23). Denervation-dependent D1 receptor super-sensitivity causing pronounced activation of the D1-bearing striatal neurons (15) and changes in the dendritic and synaptic morphology (24) are two other important post-synaptic determinants of LID in animal models. Enhanced D1 receptor pathway transmission in dyskinetic animal models can lead to hyperphosphorylation of key enzymes necessary for neural signaling in the direct pathway (25). For example, GluR1, a subunit of AMPA receptors, exhibits high phosphorylation levels of Ser_{831} and Ser_{845} in the membranes of medium spiny neurons (MSNs) after levodopa treatment in dyskinetic rats (26). Thus, advanced PD is a state characterized by the inability to maintain stable, physiological, synaptic and extra-synaptic levels of dopamine, which in turn favors aberrant pre- and post-synaptic plastic responses in the striatum.

Here, we review the theories of LID related to striatal and cortical maladaptive plasticity in PD in the light of (1) the recent studies on motor cortex plasticity in different stages of evolution of PD (27–31), (2) the current knowledge of the physiology and anatomy of basal ganglia circuitry, including the reciprocal subcortical connections between the basal ganglia and the cerebellum (32, 33), and (3) the recent report of the role of cerebellar sensory processing in the bidirectional modulation of primary motor cortex (M1) plasticity (34) and the disturbance of this function in patients with LID (30). We propose a model based on the plasticity changes in PD that considers Parkinsonism, biphasic, and peak-dose dyskinesias as clinical manifestations of the abnormal interaction between M1 and the interlinked subcortical structures including the basal ganglia and cerebellum, during fluctuations in synaptic dopamine levels.

BASAL GANGLIA CIRCUITRY

CORTICO–BASAL GANGLIO–THALAMO-CORTICAL LOOP

Based on current understanding, the cortico–basal ganglia–cortical circuit functions as a complex, integrated network with multiple feed-back and feed-forward loops (35). The motor circuitry that projects from motor cortical areas (primary motor cortex, supplementary cortex, premotor cortex, and parts of the somatosensory dorsal parietal cortex) has a somatotopic, glutamatergic relay with the GABA-ergic MSNs in the dorsolateral portion of the post-commissural putamen and a small rim of the head of the caudate (36). The MSNs are connected to the output nuclei either indirectly, after relay in globus pallidus pars externa (GPe) and subthalamic nucleus (STN), or directly. The globus pallidus pars interna (GPi) and the substantia nigra pars reticulata (SNr) are the output nuclei of the basal ganglia and project to the premotor neurons in the ventral tier of thalamic nuclei (i.e., ventro-anterior, VA and ventro-lateral, VL), the centromedian (CM)/parafascicular (PF) complex, the pedunculo-pontine nucleus, the superior colliculus, and the brain stem (37–39). The VA/VL thalamic nuclei project to the supplementary motor area (SMA) and, to a lesser extent, to M1 and premotor cortex (38). In addition to the afferent input from putaminal MSNs and GPe neurons to STN, a hyper-direct glutamatergic pathway relays input from M1, SMA proper and pre-SMA, and dorsal and ventral premotor cortices to the dorsal aspect of STN (40–42). These hyper-direct glutamatergic cortico–STN connections, along with the STN–GPe and GPe–GPi connections, constitute the cortico–STN–pallidal pathways that bypass the striatum. The STN also receives glutamatergic projections from the thalamic PF and CM nuclei (43, 44). There are direct projections from STN to the cortex (45, 46) and to the thalamus (47). There are also dopaminergic projections from the SNc to STN (48, 49). Thus, dopamine can be seen to influence all glutamatergic synapses within the basal ganglia–thalamo-cortical circuit (**Figure 1**).

RECIPROCAL BASAL GANGLIO–CEREBELLAR CIRCUITRY

A major recent advance has been the identification of topographically organized, reciprocal links between basal ganglia and the cerebellum in non-human primates. Retrograde viral transporter studies in primates showed direct projection from the dentate nucleus, a major output of cerebellum, to the CM/PF complex intralaminar nuclei in the thalamus and subsequently to the dorsolateral putamen (32, 50). This bisynaptic path extends with a third synapse from putamen to GPe (32). It was recently shown in primates that the STN projects not only to the GPi, but also has topographically organized projections to lobule VII B and Crus II in the cerebellum via the pontine nuclei (51). The identification of bilateral subcortical communications between basal ganglia and cerebellum, besides their convergence to partially overlapping cortical areas (52–54), makes it imperative to examine the interaction between the abnormal basal ganglia activity and the

cerebellar circuits in PD that could contribute to the development of Parkinsonism or LID.

DOPAMINERGIC SIGNALING IN THE MOTOR CIRCUITS IN HEALTH

DOPAMINE AND BASAL GANGLIA

Dopaminergic fibers from the SNc innervate the striatum and all structures in the basal ganglia, including the STN and GPi, as well as the prefrontal, motor, and sensory cortices (55). Striatal synaptic and extra-synaptic dopamine levels are maintained at a constant level (56), independent of SNc neuronal firing, due to the efficient dopamine reuptake by the DAT system in the striatum (57) and the auto-inhibition mediated by presynaptic dopamine D2 receptor stimulation (58). The cortex and thalamus send massive glutamatergic input to the GABA-ergic striatal MSNs (59, 60) and dopamine has a pre-synaptic modulatory effect on this excitation (61). Post-synaptically, dopamine also stabilizes the firing rate and excitability of striatal neurons, inhibiting D2-bearing neurons and facilitating D1-bearing striato-pallidal neurons (62). Dopamine also regulates plasticity of striatal neurons by modulating glutamate-mediated long-term potentiation (LTP), long-term depression (LTD), and depotentiation (which is a homeostatic mechanism of reversal of a potentiated synapse to its pre-potentiated state) at the cortico-striatal synapses (63). Striatal LTP and LTD are important for motor learning, while depotentiation is thought to be necessary for removing unnecessary motor information (64). The activation of D1 receptors is necessary for induction of both LTP and depotentiation, while the co-activation of D1 and D2 receptors is required for induction of LTD. Thus, the midbrain dopaminergic neurons [SNc–ventral tegmental area (VTA)], through their projections to multiple basal ganglia nodes that receive glutamatergic inputs, can influence the local neural transmission as well as the induction of plasticity at these nodes (**Figure 1**). Dopamine can also indirectly influence M1 plasticity by regulating the basal ganglia inputs reaching M1.

DOPAMINE AND PRIMARY MOTOR CORTEX

Neuroanatomical studies have confirmed the presence of direct dopaminergic innervations from the midbrain to M1 in rats (65, 66), monkeys (67), and human beings (68), as well as the presence of dopamine D1 and D2 receptors in M1 (69–72). A recent study, using the more specific DAT immunostaining method in mice, confirmed direct dopaminergic innervations of deep layers of M1 (73). D2 receptor agonists that increased the firing rate of pyramidal neurons proved the effect of dopamine on M1 neurons. This effect could be either due to a direct increase of pyramidal neuronal excitability or due to a reduction of inhibitory interneuronal activity (74). An important role of dopamine in M1 is to facilitate motor learning (66, 75) and motor memory encoding (76). In rats, the impaired LTP and motor skills learning following dopaminergic deafferentation of M1 could be corrected by local administration of levodopa within M1 using osmotic mini-pumps (66). However, denervation of SNc resulted in a total loss of motor skills learning, far more severe than direct M1 denervation (77). Vitrac et al. (73) showed that D1 receptors can enhance the associability of the pre- and post-synaptic activity: by increasing the sensitivity and the time-window for LTP induction, they serve as "coincidence modulators" that can determine whether a synapse will undergo LTP in response to a set of activity patterns. Dopamine is also considered necessary for the stability of motor representations within M1, as local injection of D2 receptor blockers results in the collapse of motor representations and of motor cortex excitability (78). This may be because both D1 and D2 receptor-mediated mechanisms within M1 are necessary for the intracortical horizontal connections to form LTP (75).

In human beings, studies in which plastic changes in M1 were artificially induced with non-invasive stimulation techniques (e.g., transcranial direct current stimulation, tDCS, and transcranial magnetic stimulation, TMS) revealed that dopamine has a non-linear dose-dependent effect on M1 plasticity (79–81), which is mediated through both D1 and D2 receptor subtypes (82). In healthy subjects, both low and excessive exogenous dopamine impair both facilitatory and inhibitory cortical plasticity (80, 83), while medium doses of oral levodopa have more stable effects and can even enhance performance in motor learning tasks (76).

DOPAMINE AND CEREBELLUM

Animal studies revealed that there is a small but well-defined dopaminergic system in the cerebellum, which expresses all types of dopamine receptors and whose properties are similar to the striatal dopaminergic system (84). It receives inputs from the SNc and VTA that terminate in the granule and Purkinje cell layers (85–88). This system is important for the optimal development and functioning of both the cerebellum and the basal ganglia. Loss of nigral neurons in neonatal 6-OHDA-treated rats affects postnatal cerebellar development (89) and the expression of $GABA_A$ receptor subtype (90). This highlights the dependency of cerebellar development on dopaminergic input, which could be direct or indirect through the basal ganglia. In addition, both the degeneration of Purkinje cells in a knock-out rat model (84) and kainic acid-induced degeneration of cerebellar cortex with preservation of deep cerebellar nuclei (91) led to up-regulation of D1 receptors and DAT in the striatum. This suggests that the cerebellar cortex, through the deep nuclei and the thalamic relay, down-regulates the striatal D1 receptors.

Besides the modulation of the striatal dopaminergic system, the cerebellum also regulates the cortical dopaminergic system, since electrical stimulation of dentate nucleus can induce dopamine release within the prefrontal cortex in mice (92). This might occur either through dentato-tegmental projections or through dentato-thalamo-cortical projections (93).

In healthy humans, fMRI studies have shown strong connectivity between SNc and cerebellum (94, 95). This connectivity between SNc and cerebellum is lost in PD but is restored by levodopa (96). Thus dopamine has both a direct and indirect influence on the cerebellum.

DOPAMINERGIC SIGNALING IN PARKINSONISM AND LEVODOPA-INDUCED DYSKINESIA

STRIATAL SIGNALING

According to the current models of basal ganglia in PD, dopamine depletion causes under-activation of GPe and disinhibition of STN

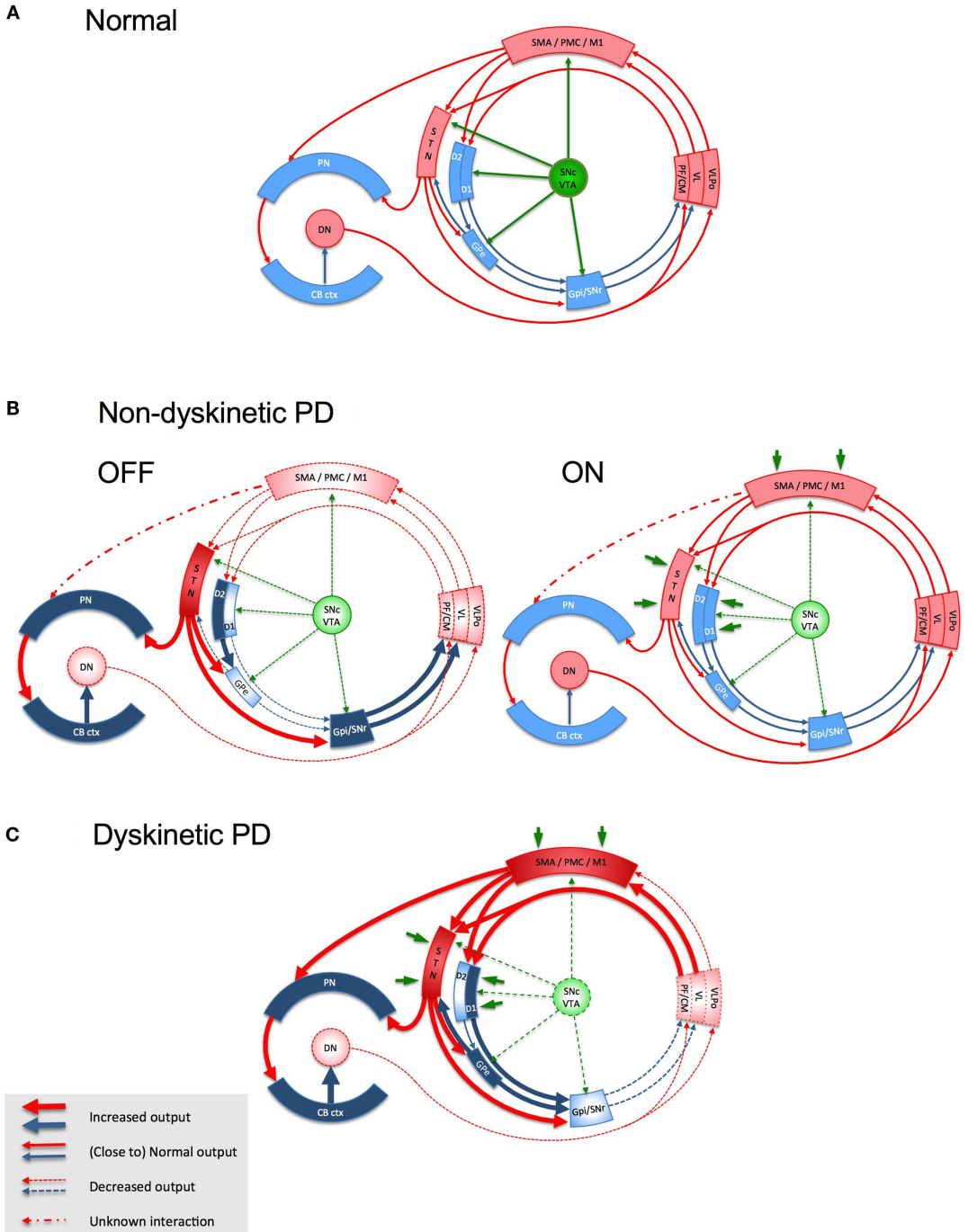

FIGURE 1 | Schematic representation of the basal ganglia-thalamo-cortical loop, the cerebello-thalamo-cortical loop and the interaction between the two in health (A), in non-dyskinetic Parkinson's disease, after levodopa withdrawal (OFF) and after regular dose of levodopa (ON) (B), and in advanced Parkinson's disease with levodopa-induced dyskinesia (C). Red arrows represent glutamatergic projections; blue arrows represent GABA-ergic projections; green arrows represent dopaminergic projections; dark green arrows in panel B and C represent the exogenous dopamine from levodopa. The shades of the blocks represent the activity of the respective network nodes. The STN is overactive because of cortical glutamatergic over activity during dyskinesias and from loss of GPe inhibition in OFF. The STN over activity locks cerebellar cortex in a persistent hyperactive state and interferes with its sensory processing function. The behavior of the cortico-ponto-cerebellar projections in non-dyskinetic PD in ON is not reported so far and is predicted by this model to be close to normal (CB ctx, cerebellar cortex; CM, centromedian thalamic nucleus; D1/D2, dopamine receptor types of the striatal medium spiny neurons (MSNs); DN, dentate nucleus; GPe, globus pallidus externus; GPi, globus pallidus internus; M1, primary motor cortex; PF, parafascicular nucleus; PMC, premotor cortex; PN, pontine nuclei; SMA, supplementary motor area; SNc, substantia nigra, pars compacta; SNr, substantia nigra, pars reticulata; STN, subthalamic nucleus; VL, ventro-lateral thalamic nucleus; VLPo, ventro-latero-posterior thalamic nucleus, pars oralis; VTA, ventral tegmental area).

in the indirect pathway (**Figure 1B**). STN over-activity in PD could not only be due to abnormalities of the indirect pathway, but also to the direct excitatory drive from the motor cortex and thalamus (97, 98). This could lead to excessive activation of GPi, a dysfunction favored also by the reduced input from D1 pathway. The net outcome would be enhanced GABA-ergic inhibition of thalamic projections to motor areas. It is now considered that not only firing rates but also firing patterns are important in maintaining normal signaling within the motor circuit. Intra-operative recordings in PD patients have demonstrated oscillations of local field potentials in the beta band in the STN that are synchronized with beta band oscillations in the cerebral cortex and GPi, indicating that excessive synchronization is a feature of the whole basal ganglia–cortical network. Dopaminergic drugs (99, 100) and STN DBS (101) can suppress the abnormal synchrony between basal ganglia and cortex. Moreover, suppression of beta band synchrony by these interventions positively correlates with improvement in bradykinesia and rigidity.

Levodopa treatment, however, does not restore basal ganglia activity to normal and LIDs are associated with reduced activity in the STN and GPi neurons. For example, peak oscillations at 4–10 Hz associated with dyskinesia were recorded only from the contralateral STN in patients with asymmetrical LID (102). Such abnormal oscillations in Parkinsonian and dyskinetic states could potentially propagate from the STN to the cerebellum in PD.

STRIATAL PLASTICITY IN PARKINSONISM AND LID

In animal studies, striatal LTP and LTD are both impaired if dopaminergic afferents to striatum are lesioned but can be restored by levodopa (103). In human beings, the direct evidence of dopaminergic influence on an extrastriatal site was demonstrated in SNr neuronal plasticity during DBS surgery; local field potential amplitude of SNr neurons showed no enhancement after high frequency stimulation of STN when tested without levodopa, but enhancement was evident following the administration of levodopa (104).

In the rat models of PD and LID, striatal LTP was impaired in both non-dyskinetic and dyskinetic rats and could be restored by levodopa in both groups (64). In contrast, the capacity to depotentiate LTP was preserved only in non-dyskinetic rats. In the rat model, both the presence of dyskinesias and the loss of depotentiation were linked to higher doses of levodopa (105). This shows that loss of depotentiation at the cortico-striatal synapses from levodopa exposure is a marker of LID in animal models.

CORTICAL SIGNALING

A significant loss of dopamine and noradrenaline occurs in the motor cortex of PD patients (36, 55, 68). This postmortem finding was confirmed *in vivo* by PET of the motor cortex (106), motor cortical pathology was therefore proposed to underlie some of the symptoms of PD (106, 107). In line with this hypothesis, anti-PD drugs can modulate the activity of motor cortex (108) and non-invasive stimulation of the motor cortex can help reduce symptoms of PD and LID by reestablishing the homeostasis of some circuits (109). However, the kinetics of cortical dopamine within M1 is yet to be explored in human beings and animal models of LID.

MOTOR CORTEX PLASTICITY

In human PD, changes in motor cortex plasticity have been studied using transcranial magnetic stimulation (TMS), delivered alone as theta-burst (TBS) or as a paired associative stimulation (PAS), in which magnetic pulses delivered over M1 are classically associated with sensory pulses delivered on a peripheral nerve (**Figure 2**). The plastic effects of TBS depend on the stimulation pattern, which will act upon the intracortical synapses within M1. The sensorimotor plastic effects of PAS depend on the coincidence of pre- and post-synaptic neuronal activation within a specific time window (110–112). Using TBS in *de novo* PD, the LTP- and LTD-like plasticity of the intracortical circuits within M1was shown to be symmetrically and severely impaired even though the motor symptoms were unilateral (29). There was also no correlation of the plasticity loss with motor signs of PD, indicating that that M1 changes were more likely the direct consequence of mesocortical denervation than the indirect consequence of striatal denervation, the latter being more correlated with Parkinsonian signs. It also indicates that changes in M1 plasticity occur at a lower level of dopaminergic denervation than the higher threshold of 60–80% striatal dopaminergic denervation necessary for the motor signs to develop. Additionally, the local M1 plasticity in *de novo* patients did not show any short-duration response to a single dose of 100 mg levodopa, while clinical deficits showed significant improvement. This indicated that normalization of plastic mechanisms within M1 needs sustained dopamine replenishment. It was subsequently demonstrated that the propensity of intracortical circuits in the motor cortex to express normal plastic responses was closely linked to the stability of clinical response to levodopa (28):

(1) Patients with stable clinical response to levodopa with no fluctuations in their clinical response to levodopa and without LID could express LTP and LTD even when tested without levodopa. This suggests a beneficial and persistent treatment effect of levodopa therapy on M1 plasticity when compared to the severe loss of plasticity in the untreated state.
(2) Patients with wearing-off motor fluctuation showed a persistent treatment effect of chronic levodopa treatment on LTP, but not on LTD. In these patients, exposure to an acute boost of dopamine, by administering their regular dose of levodopa, revealed a detrimental effect of dopamine on both LTP and LTD.
(3) Patients with both motor fluctuations and dyskinesias have no persistent treatment effect on either LTP or LTD. Acute boost of levodopa did not restore LTP or LTD. Interestingly, acute dopamine boost led to a paradoxical LTP in the motor cortex of these patients in response to an intervention that normally induces LTD in healthy subjects. The paradoxical facilitation was more in those with more severe disease and with higher clinical response to levodopa, suggesting that both are consequences of the acute dopamine replacement. Moreover, PD patients with LID are unable to depotentiate an already established LTP in M1after an acute dosing with even a small dose of levodopa (113). This finding is similar to changes in the striatum of dyskinetic animals (64), but in contrast to non-dyskinetic patients in whom depotentiation was present after

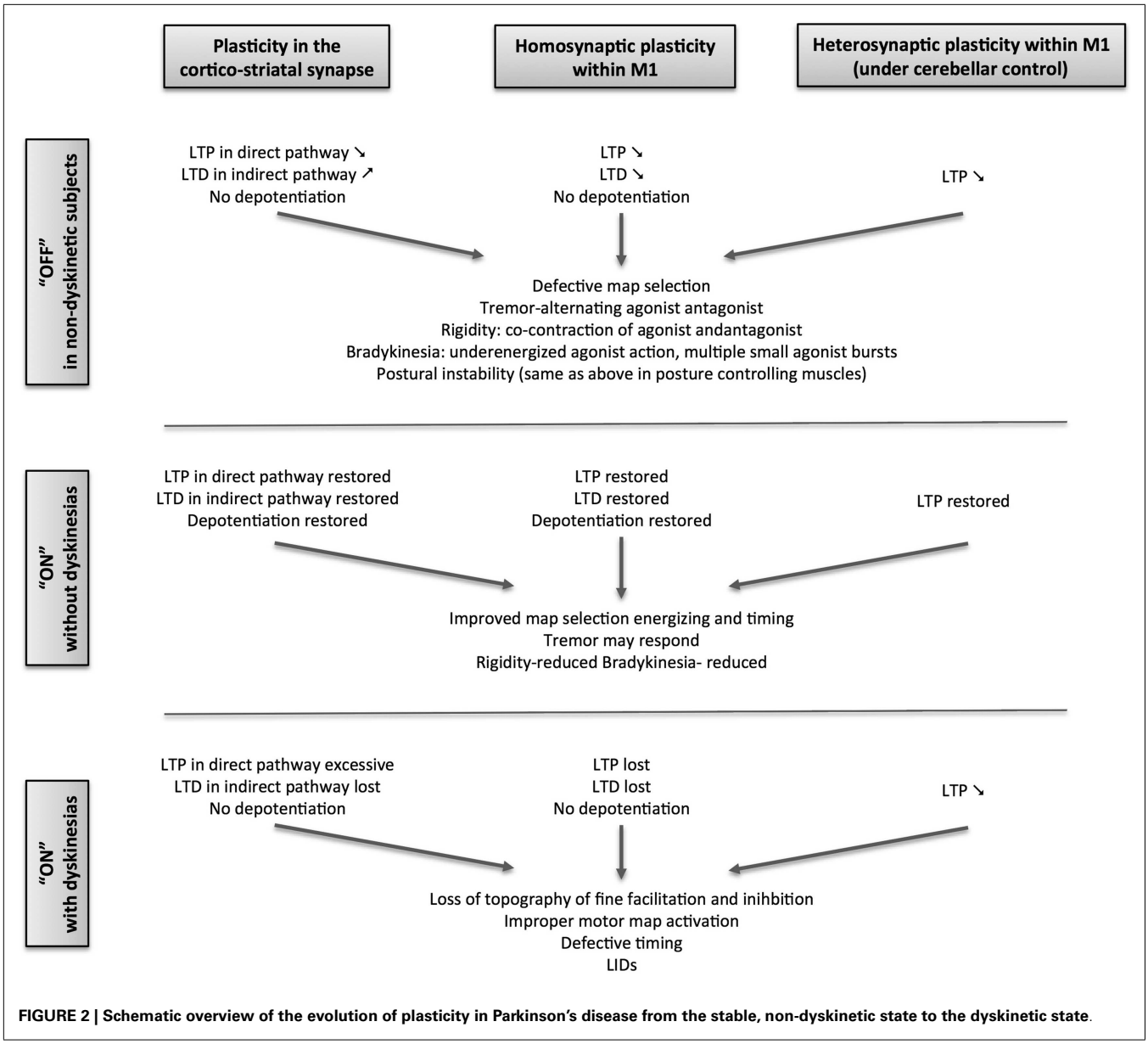

FIGURE 2 | Schematic overview of the evolution of plasticity in Parkinson's disease from the stable, non-dyskinetic state to the dyskinetic state.

their regular dose of levodopa. PD patients with LID could express LTP in M1, but only when given half the regular dose of levodopa, reconfirming the negative effect of the regular dose on LTP. All these findings point to a severe dysregulation of intrinsic plastic mechanisms within M1 of patients with LID.

Additionally, studies using PAS have also revealed severe loss of sensorimotor, associative plasticity of M1 in the more affected hemisphere of *de novo* PD patients (31). Unlike the plastic response of the local intracortical circuits, the impairment in associative plasticity in the more affected hemisphere correlated with the severity of motor signs of PD, indicative of a dependence on striatal denervation underlying both. The short-duration response of associative plasticity to levodopa in *de novo* patients has not been studied so far. However, associative plasticity of M1can be restored by dopaminergic drugs only in chronically treated patients that are non-dyskinetic and not in dyskinetic ones (27).

Besides the plastic responses, intracortical inhibitory circuits are also altered in M1 of treated PD patients. $GABA_A$-mediated, short-interval intracortical inhibition is reduced in PD patients, both dyskinetic and non-dyskinetic, when compared to controls, and levodopa could not correct this (114). In the same study, long interval intracortical inhibition was weaker than in controls in both non-dyskinetic and dyskinetic patients tested without levodopa, but levodopa could weakly correct this in dyskinetic patients. The lack of positive effect of levodopa on intracortical inhibition in M1 and the negative effect of levodopa on short latency afferent inhibition (115) has also been suspected to play a role in LID.

CEREBELLAR LINK TO MOTOR CIRCUITS IN HEALTH, PARKINSONISM AND LID

CEREBELLAR PLASTICITY IN HEALTH

Within the motor control loops, the cerebellum controls and co-ordinates complex movements and is important for adapting movements to changes in feed-back. It receives sensory and motor information from descending cortical pathways and from ascending peripheral pathways. It has also connections to the parietal, premotor, and frontal cortices. The two major excitatory afferents to cerebellum are the climbing fibers and mossy fiber – parallel fiber systems, information from both of which eventually converges on the Purkinje cells that represent the only efferent output from the cerebellar cortex. The exteroceptive and proprioceptive inputs from the spinal cord and the input from pontine nuclei convey information from brainstem nuclei via mossy fibers to the granule cells. The axons of granule cells form the parallel fibers network. Climbing fibers originate in the inferior olive and relay directly to the Purkinje cells. Plastic changes in the strength of synapses relaying from the climbing and parallel fibers to the Purkinje cells are important in motor learning. Plasticity of climbing fibers input bi-directionally adjusts the plasticity of parallel fibers–Purkinje cells synapses. This suggests a role of climbing fibers as an error detector, which signals the need for adjusting the gain of sensory inputs and/or motor output within the cerebellum. Any disturbance in cerebellar plasticity could interfere with this function and result in maladjusted information delivered to M1, leading to abnormal, movement sequences.

CEREBELLAR PLASTICITY DYSFUNCTION IN PARKINSON'S DISEASE AND LID

There are several lines of evidence suggesting that cerebello–thalamo-cortical communication is abnormal in PD. In animal models of PD, the thalamic neurons that receive cerebellar output are underactive, just as those receiving basal ganglia afferents (116), indicative of a reduced dentato-thalamo-cortical excitatory output. In the MPTP mouse model, nigral degeneration is accompanied by loss of Purkinje cells in the cerebellum (117). In the untreated chronic MPTP monkey model of PD, nigral degeneration correlates with persistent hyperactivity in the cerebellum (118). Such a hyperactive state, secondary to striatal dopaminergic denervation, could prevent the efficient processing of the inputs from both parallel and climbing fibers, thus interfering with the plasticity mechanisms within the cerebellar cortex. One potential source of cerebellar hyperactivity could be the pathological hyperactivity in the glutamatergic projections from STN to cerebellum (**Figures 1B,C**). There is now increasing clinical, electrophysiological, and functional imaging evidence to invoke a cerebellar dysfunction in PD – for review see Ref. (119).

In the monkey model of PD, the ventro-lateral posterior nucleus of the thalamus that receives cerebellar output shows oscillations at tremor frequency, while in human PD, cerebellum has been linked to the postural tremor (120, 121). Also in PD patients, tremor-related abnormal oscillatory activity was recorded in the STN and GPi but not in the thalamic nuclei receiving basal ganglia input (122, 123). Considering the newly described anatomical connections between the basal ganglia and the cerebellum, it is conceivable that abnormal oscillations from a cerebellar circuit could propagate either to M1 and subsequently to STN via hyper-direct pathway, or from cerebellum to striatal MSNs projecting to GPe–STN via the indirect pathway. Defects in striatal dopamine release (124) and in cerebellar sensory processing function (125) were recently found in patients with primary focal dystonia. Abnormal signaling between basal ganglia and cerebellum in human PD could therefore potentially cause dystonic symptoms in untreated PD and during low plasma levels of dopamine as in biphasic dyskinesias.

Despite the classical view that LID might be generated exclusively by the disinhibition of cortical motor areas secondary to abnormal output from the basal ganglia in the striato–thalamo-cortical circuit (17), there is indirect evidence that the cerebellum may play a role in it.

In patients with PD, the binding potential of sigma receptors in the cerebellum (as explored with PET) is highly increased with respect to healthy controls and correlates only with LID scores and not with severity scores of Parkinsonian signs (126). Sigma receptor stimulation influences Purkinje cell firing (127) and also plays a role in the modulation of the glutamatergic/NMDA neurotransmission in the dopaminergic systems (128). Successful stereotaxic pallidal surgery (either pallidotomy or deep-brain stimulation) can lower this exaggerated sigma receptor binding in the cerebellum in LID (126).

Further evidence of cerebellar involvement in LID comes from TMS studies. In patients with PD, with mild to moderate LID, repeated sessions of bilateral cerebellar inhibitory stimulation after regular doses of levodopa induce a sustained reduction of dyskinesia lasting at least 2 weeks (30, 129). Repeated cerebellar stimulation can also reduce the cerebellar cortical activity and enhance dentate nuclear activity in imaging studies in PD patients with dyskinesias (130). In such patients, a single session of inhibitory stimulation of the cerebellar cortex combined with levodopa can restore the sensorimotor plasticity tested by PAS, but not the local intracortical plasticity as tested with TBS (30). This effect of cerebellar stimulation would have improved M1 plasticity induced by both PAS and TBS, if cerebellar stimulation was modifying directly M1 excitability. The lack of effects of cerebellar stimulation on intracortical plasticity of M1 and on intrinsic cortical excitability parameters (as reflected by the motor thresholds or intracortical facilitation and inhibition) supports a primarily subcortical mechanism. Recent studies showed that cerebellar stimulation can modulate the M1 associative heterosynaptic plasticity in healthy subjects (131) through the modulation of peripheral sensory afferents (34), eventually scaling the amplitude and topographic specificity of the associative plastic response (34); excitation of the posterior cerebellar cortex led to loss of associative plastic response, while inhibition of the cerebellar cortex led to prolonged facilitatory response to PAS with loss of topographic specificity. These were observed for PAS but not for TBS, suggesting that the target of cerebellar modulation is mainly the afferent input to M1 rather than M1 in itself. Cerebellar cortical excitation (i.e., heightened output of the Purkinje cells) leads to the enhancement of the normal inhibition of the dentate nucleus, which would reduce the normal excitatory

control of dentate nucleus on the afferent inflow to M1, probably at the thalamic or olivary nuclear level, thus blocking the sensorimotor-plasticity within M1. In contrast, cerebellar cortical inhibition (i.e., depressed output of the Purkinje cells) could lead to disinhibition of dentate nucleus, which would facilitate afferent input to M1 (34). This model is in keeping with the adaptive filtering role of the cerebellum on sensory afferents (132). Additionally, repeated sessions of inhibitory stimulation of the posterior cerebellar cortex can restore the levodopa-unresponsive, associative M1 plasticity in dyskinetic PD patients, concurrent with the reduction in LID severity (30). Several findings of this particular study suggested that the reduction in LID could be related to the improvement of responsiveness of M1 to PAS after cerebellar inhibition: (1) larger facilitation of M1 plasticity after a single session of cerebellar inhibitory stimulation in ON predicted greater anti-dyskinetic effect of repeated cerebellar stimulation in the same subjects; (2) the time course of LID improvement was similar to the time-course of the associative plasticity restoration after 10 consecutive sessions of cerebellar stimulation; and (3) patients with more severe LID before the TMS treatment showed larger responsiveness of M1 to cerebellar inhibition suggesting more involvement of the cerebellum in the pathophysiology of dyskinesias as the severity of LID increases. However, cerebellar stimulation did not worsen or enhance the Parkinsonian signs in OFF or beyond the effect of levodopa alone. Patient diaries revealed that the time spent in ON without troublesome dyskinesias, but not the durations of the OFF periods, was improved by cerebellar stimulation. These suggest that combined levodopa replacement therapy and cerebellar inhibition might be required to restore the balance between the two circuits and to concurrently improve Parkinsonian signs and reduce dyskinesias. Exogenously derived dopamine might act by increasing the excitability of M1 neurons (73) and normalizing basal ganglia signaling, whereas inhibition of the cerebellar cortex enhances the gain of the sensory afferent input and allow better sensorimotor integration (34). It remains speculative whether cerebellar hyperexcitation exists in *de novo* human PD as in *de novo* animal model of PD and if this cerebellar defect contributes to the genesis of specific manifestations like tremor or dyskinesias. If it were the case, then this metaplastic state of the cerebellar cortex could be reversed or delayed by early artificial inhibitory stimulation of the cerebellar cortex.

Earlier neuroimaging studies have found increased activity of motor and premotor areas in dyskinetic PD patients when compared to non-dyskinetic patients (133, 134). This led to the classical view that hyperactivity in cortical motor areas might be responsible for LID (17, 135). However, inhibitory stimulation of SMA (135, 136) or of M1 (137) failed to provide sustained improvement of dyskinesias. The results obtained recently with cerebellar stimulation point to an alternative explanation, which reconciles with the observations in these older studies: as SMA, pre-motor cortex, and M1 are all targets of cerebellar output (54). An abnormal input from the cerebellum to SMA or M1 in dyskinetic patients might indeed trigger abnormal fMRI activations, but only as downstream, secondary, phenomena, thus making them unsuitable targets for a direct intervention for the treatment of LID.

PROPOSED MODEL OF PARKINSONISM AND LEVODOPA-INDUCED DYSKINESIA BASED ON ABERRANT PLASTICITY

This model is based on the view that a physiological level of dopaminergic stimulation is critical for maintaining normal plasticity at the glutamatergic terminals in the interconnected large motor network involving the basal ganglia, motor cortices, thalamus, and sensorimotor areas of the cerebellum. This model considers M1 only as the final target of this network and proposes LID as the product of a cascade of changes triggered by the altered dopaminergic signaling in this network. M1 neurons deprived of the ability to depotentiate activated synapses due to abnormally high synaptic dopamine levels during peak-dose, are rendered indiscriminately receptive to non-salient or even aberrant afferent inputs from the environment conveyed by other neural structures (spino-thalamic pathways via ventro-lateral thalamic nuclei, other cortical areas via direct cortico-cortical connections, etc.). This defect may be additionally amplified by the aberrant signals reaching M1 from the thalamic relays erratically modulated by the basal ganglia and cerebellum (**Figure 1C**). The result would be the inappropriate selection of motor programs and the generation of movements that are both unwanted and abnormal. The absence of effective inhibitory control within M1 and the paradoxical facilitation during attempted inhibition would make these movements resistant to voluntary suppression and even exacerbate them. Biphasic dyskinesia co-existing with Parkinsonism may reflect transitory oscillations in the synaptic dopamine levels during the rising and falling phases of release of exogenously derived dopamine. Such oscillations might allow concomitant manifestations of severe Parkinsonism and biphasic dyskinesias. This model needs further experimental validation. It also raises many questions that could be tested in future studies:

(1) Does DBS of the STN influence both STN–thalamo-cortical and STN–cerebellar transmission? Though the exact mechanisms by which DBS of the STN improves PD are not fully established, the fact that effective DBS of the STN improves cerebellar hyperactivity (138, 139) suggests that it may influence both the STN–GPi and the STN–cerebellar projections. Extracellular recordings in MPTP-intoxicated primates have shown that during DBS of the STN, significant change occurs in the pattern of neuronal activity in areas of the motor thalamus receiving both pallidal and cerebellar projections (140).

(2) The dose of administered levodopa has to be reduced after immediately after DBS of the STN to reduce dyskinesia. Does this indicate that DBS of the STN by itself cannot normalize the aberrant plasticity within M1 caused by dopamine surges, which would be necessary to alleviate dyskinesia? Preliminary data showing that sensorimotor cortex plasticity improves only after long-term synergistic combination of DBS with reduced doses of levodopa, but not after DBS alone (141). That long-term stimulation is required for restoring sensory afferent inhibition of M1(142) indicates that cerebellar control of sensory processing may also normalize only after chronic stimulation of STN.

(3) Does selective DBS of the ventral GPi but not of the dorsal GPi or STN simultaneously inhibit the propagation of pro-dyskinetic signals through both cortico-striatal synapses and cerebello-striatal synapses (relayed through CM/PF thalamic nuclei) on D1-bearing MSNs? It is already known that GPi has functional somatotopy (143) and that ventral GPi stimulation has anti-dyskinetic effects while dorsal GPi stimulation improves akinesia and induces dyskinesias (144). In primates, tightly connected functional circuits have been described between basal ganglia and the CM/PF, with a sensorimotor circuit linking the post-commissural putamen, the centrolateral part of the caudal GPi, and the medial two-thirds of the CM nucleus (145). The fact that CM/PF is a target for both pallidal and cerebellar inputs (39) might then explain why DBS of CM/PF is useful for controlling tremor that is resistant to DBS of the STN and also LID that are only partially responsive to DBS of GPi. However, DBS alone of the CM/PF does not change global UPDRS as strongly as DBS of the STN or GPi (146).

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Surgical treatment of dyskinesia in Parkinson's disease

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One of the main indications for stereotactic surgery in Parkinson's disease (PD) is the control of levodopa-induced dyskinesia. This can be achieved by pallidotomy and globus pallidus internus (GPi) deep brain stimulation (DBS) or by subthalamotomy and subthalamic nucleus (STN) DBS, which usually allow for a cut down in the dosage of levodopa. DBS has assumed a pivotal role in stereotactic surgical treatment of PD and, in fact, ablative procedures are currently considered surrogates, particularly when bilateral procedures are required, as DBS does not produce a brain lesion and the stimulator can be programed to induce better therapeutic effects while minimizing adverse effects. Interventions in either the STN and the GPi seem to be similar in controlling most of the other motor aspects of PD, nonetheless, GPi surgery seems to induce a more particular and direct effect on dyskinesia, while the anti-dyskinetic effect of STN interventions is mostly dependent on a reduction of dopaminergic drug dosages. Hence, the *si ne qua non-condition* for a reduction of dyskinesia when STN interventions are intended is their ability to allow for a reduction of levodopa dosage. Pallidal surgery is indicated when dyskinesia is a dose-limiting factor for maintaining or introducing higher adequate levels of dopaminergic therapy. Also medications used for the treatment of PD may be useful for the improvement of several non-motor aspects of the disease, including sleep, psychiatric, and cognitive domains, therefore, dose reduction of medication withdrawal are not always a fruitful objective.

Keywords: Parkinson's disease, dyskinesia, deep brain stimulation, DBS, pallidotomy

INTRODUCTION

Treatment of levodopa-induced dyskinesia (LID) is one of the most common indications for stereotactic surgery in Parkinson's disease (PD). Control of LID can be accomplished by providing significant relief on the motor symptoms of PD through medication optimization, typically through subthalamic nucleus (STN) deep brain stimulation (DBS), or by pallidotomy or globus pallidus internus (GPi) DBS, which are thought to have a direct effect on dyskinesia (1). Currently, DBS has become the preferred stereotactic procedure in PD, however, ablative surgery continues to be performed and can be quite effective especially when dyskinesia are significantly more prominent on one body side. In this review, we will address both forms of surgical techniques, their indications, differentials, and outcomes.

ABLATIVE SURGERY

The indication for any form of stereotactic ablative surgery has always been the symptomatic treatment of certain motor features of PD as identified during a detailed multi-disciplinary workup. As early as the 50s, the inner segment of the GPi and the ansa lenticularis has been the common choice for functional neurosurgeons (2). This approach was advocated and further reinforced following the observation that ligation of the anterior choroidal artery, performed for the treatment of accidental bleeding in a PD patient, resulted in relief of tremor (3, 4). As this technique (ansa – pallidotomy) became more widely utilized, the results for tremor control were mixed, despite the good outcome for rigidity. As a result, pallidotomy was gradually replaced by thalamotomy, which exerted a more optimal tremor control (5). The failure to reduce tremor in some cases was likely due to a failure to target the appropriate postero-ventral pallidum, which was a limitation of early technology. However, with the advent of levodopa in the 1960s, stereotactic surgery became gradually less popular and did not re-emerge again until the early 90s (6).

The renaissance of stereotactic surgery for patients with PD was galvanized by the weaknesses of levodopa therapy that were gradually surfacing (7). The first disappointment was the evidence that it does not interfere positively with disease progression, as it is now well appreciated after decades of use. Additionally, due to the high doses sometimes required to improve tremor, motor fluctuations, and LID started to be noticed. As most clinicians continue to witness today, medical pharmacological management of PD is challenging with the continuous attempt to balance the relief of parkinsonian motor signs against motor fluctuations and induction of dyskinesia, often with neither being managed adequately (8). The setback related to levodopa was allied with advancements from physiological and surgical aspects, and also by the more accurate understanding of the organization of the basal ganglia (BG), better surgical techniques, and the use of neuroimaging for more precise target localization. At that time, thalamotomy was revived, and, in addition to improvements in the motor aspects of PD, several authors reported drastic suppression of LID (9).

Svennilson et al. reported that when the postero-ventral GPi was lesioned additional benefit to general motor function (interpreted as corresponding to relief of akinesia) could be obtained (10). Later, Laitinen et al. returned to the initial target and the postero-ventral GPi became the preferred surgical treatment for PD patients. In the classical report from 1992, Laitinen's group showed favorable outcomes that included not only robust improvements in the cardinal signs of PD, but also significant amelioration of LID (11).

At approximately the same time, anatomic and physiological studies confirmed that the GPi and STN were both overactive in PD. Also, experimental studies demonstrated that lesions in these structures could improve parkinsonism and dyskinesia in animal models (12–14), although the classical BG model predicted that pallidotomy would worsen dyskinesia. This discrepancy between theoretical and practical outcomes is probably the result of interference with abnormal firing patterns (rather than rates) in circuit neurons (15).

Both the clinical report by Laitinen et al. and the pathophysiological laboratory-based developments in PD reinforced the role of pallidotomy for treatment of LID in PD.

PALLIDOTOMY

During the second half of the 90s, many studies reported that unilateral pallidotomy in patients with PD provided successful control of contralateral dyskinesia. At that time, Lozano et al. (15) published the results of pallidotomy in 14 patients with rigid akinetic PD, complicated by severe LID, motor fluctuations, but with intact cognition. Motor improvements in the OFF medication condition were mainly contralateral. The most dramatic improvement was for ON period LID, which were shown to be reduced by 92% in the contralateral side after 6 months. The typical complications of this procedure, homonymous hemianopia, facial paresis, and hemiparesis, were not observed, except for mild and transient facial droop in three cases (noted by clinicians but not the patients). Two years later, the same group published a series of 40 cases, some with a longer follow-up: 27 for 1 year and 11 for 2 years. Short term results were similar to their previous study, however trend analysis revealed a slight worsening of contralateral dyskinesia after the first year, and a loss of benefit for ipsilateral dyskinesia by the second year. Age had an impact on OFF period motor signs, with those older than 65 retaining less improvement after 6 months. LID responded similarly in the two age groups studied. There were no significant reductions in dopaminergic therapy after surgery. Persistent adverse events included facial weakness (two cases), bulbar deficits (three cases), mild dementia (three cases), and worsening of handwriting in four cases (16). The findings in the same cohort were also described after a much longer follow-up (mean 52 months), showing a sustained improvement in OFF period contralateral motor signs and in LID. Other than dyskinesia and levodopa responsive motor signs, no additional characteristics had a significant impact on long-term surgical outcome (17).

In 1998, another group published a preliminary study with a series of 26 PD patients, confirming that the most significant effect following unilateral ventral medial pallidotomy was the reduction of contralateral LID by 67%, while ipsilateral and axial dyskinesia also improved (both around 50%) significantly. The improvement in underlying parkinsonism as measured by comparing the Unified Parkinson's Disease Rating Scale (UPDRS) scores in the OFF state before and 3 months after surgery, was less robust (27%). On medication, no significant post-operative improvements in parkinsonism were detected and antiparkinsonian medication dosages increased by 11% post-operatively. The presence of disabling LID, therefore, was considered the major indication for this surgical procedure. Two (7.7%) patients died due to cerebral hemorrhages directly related to surgery, while another 15% had major complications (significant focal motor and bulbar deficits) (18). In 2003, the first randomized, prospective controlled trial comparing pallidotomy with best medical therapy was published. The study included 18 patients in each group, showing, after 6 months, a 32% improvement of the total UPDRS motor score in the surgical group versus only a 5% deterioration for those randomized for medical therapy. Mean score improvement in the dyskinesia section of the UPDRS (Part IV) for the surgical group was 45%, whereas patients kept on medical therapy worsened by 8%. The study also revealed that LID improved after pallidotomy in all patients, and two-thirds had "complete relief" on the contralateral side. Also, there was a 36% reduction in ipsilateral dyskinesia severity. Levodopa equivalent doses remained unchanged. There were no fatal outcomes and complications occurred in three cases (16.7%). This study also showed that the age had a clear relationship with clinical outcome, independent of disease duration, with younger patients showing more improvement. This effect was continuous, with no apparent threshold (19).

The series with the longest follow-up was by Kleiner-Fisman et al. and included 10 patients, showing a trend toward significance lasting up to 12 years in contralateral LID (20), and by Hariz and Bergenheim who reviewed 13 of the 38 patients described in Laitinen's original study from 1992. Mean follow-up was 10.5 years (up to 13.5), and the effect of surgery remained consistent for contralateral LID, but varied for the appendicular OFF period signs. The authors went as far as to consider pallidotomy as a prophylactic measure against LID (21).

Lesion size does not seem to have a significant effect on response (22), however, the optimal location within the GPi that improved dyskinesia is a matter of controversy. Lesion location and size may be different from that required to ameliorate other PD signs, and some experts still advocate a bigger lesion size for prolonged benefit. While anteromedially placed lesions seems to be better correlated with improvement in contralateral LID, central and posterolateral placed lesions improved OFF parkinsonian signs (23). However, lesions placed in more ventral locations or anywhere in the postero-ventral GPi have been shown to be equally effective (16). Differences in outcome measures as well as in methods of determining lesion location probably account for many of these discrepancies.

Bilateral pallidotomies, staged and simultaneous, produce similar improvements in OFF motor and ON dyskinesia to unilateral procedures, with the possible advantage of improvements in axial dyskinesia, dystonia, and, arguably, selected aspects of gait such as walking speed and freezing (24, 25). These good results were undermined by unacceptable cognitive and bulbar (mainly speech) adverse effects (26). Only a few other studies have shown different perspectives (27, 28). The series by Parkin et al. (29)

Table 1 | Patient selection and point to be considered when indicating stereotactic surgery for dyskinesias in Parkinson's disease.

	Advantages	Disadvantages	Patient profile	Post-operative details
Unilateral pallidotomy	Efficacious Less costly than DBS Does not require post-operative programming No complications related to hardware (infections, malfunction)	Permanent lesion Not reversible Bilateral surgery has higher risk of side effects Does not allow adjustments to control side effects	Unable to travel Live where DBS is too expensive or not available Prefer not to have chronic hardware High infection risk	Ipsilateral dyskinesias may not improve significantly, requiring continuing anti-dyskinetic medical treatment or contralateral GPi DBS
GPi DBS	Direct improvement in dyskinesias Allows *adjustments* in drug regimen May allow for maintaining or introducing higher levels of dopaminergic therapy Synergistic effect with l-DOPA on axial and other symptoms	No significant change in drug regimen in many but not all cases Ventral and dorsal stimulation may induce opposite effects on cardinal motor signs of PD however this has not been replicable on all cases	Needs prompt improvement of severe dyskinesias Responds to low dose l-DOPA, but has low threshold for dyskinesias Has l-DOPA responsive non-motor signs In the right context, may be safer for patients with mild pre-existing cognitive symptoms	Ensure that the beneficial effect of l-DOPA is not antagonized by stimulation
STN DBS	Allows significant *reduction* in dopaminergic drug dosages Effective for OFF period dystonia	Improvements in dyskinesias depend on reduction of levodopa May have negative impact on cognition More laborious post-operative management May worsen or not improve dyskinesia in brittle dyskinetics	Has severe motor fluctuations Uses higher doses of l-DOPA Experiences disabling side effect of dopaminergic treatment Intact cognition	Stimulation induced dyskinesias may appear after a latency of several hours if l-DOPA not adjusted The electrode that induces dyskinesias is usually the most effective

for instance, showed the results in 115 patients who underwent pallidotomy, 53 of which consisted of bilateral procedures. These authors reported significant effectiveness for bilateral pallidotomy, especially for dyskinesia for up to 12 months, at the expense of worsening of speech in 8% and salivation in 13%, figures that were similar to those found for unilateral surgery. **Table 1** shows a summary of the advantages, disadvantages, and other aspects to be considered when a pallidotomy is indicated.

STUDIES COMPARING PALLIDOTOMY AND DEEP BRAIN STIMULATION OF THE GPi OR STN

Few studies have compared the efficacy and safety of pallidotomy and DBS of the GPi or STN. **Table 2** shows the results of the most important clinical parameters described in studies of pallidotomy and DBS techniques. An early, non-randomized trial comparing results of pallidotomy, STN, and GPi DBS concluded that GPi DBS had effects similar effects to pallidotomy, but is safer when bilateral procedures are required. Also, bilateral STN DBS may improve OFF period motor symptoms to a greater proportion than the other procedures, and might also improve ON period motor function (30). In 2004, Esselink et al. (31) compared, in a randomized, observer-blind trial, the effect of unilateral pallidotomy and bilateral STN DBS in patients with PD followed up for 6 months, confirming that stimulation was more effective in reducing OFF period motor signs. In addition, this procedure provided better ON period motor scores and a greater reduction of dopaminergic drug treatment dosages. Both improved LID and functional scales equally, and the number of adverse events was similar in both groups. The same group also published the results after 4 years with similar findings, except for dopaminergic treatment dosage, which did not significantly differ between groups after the first 12 months (32).

Table 2 | Effects of unilateral pallidotomy, bilateral GPi and STN deep brain stimulation (DBS) on general motor improvement (UPDRS III), dyskinesias (UPDRS IV) and levodopa equivalent daily dose (LEDD).

	Motor improvement (%)	Improvement for dyskinesias (%)	Reduction in LEDD
Unilateral pallidotomy	25–45	45–86	n.s. (0–10%)
GPi DBS	26–43	47–88	n.s. (15–17%)
STN DBS	25–54	20–83	31–47%

Mean improvement after a minimum of 6 months compared to preoperative baseline. Scores reflect the medication off condition; for DBS, stimulation on. n.s., non-significant (17, 32–41).

DEEP BRAIN STIMULATION

After DBS was introduced as a treatment option for movement disorders in general, this technique has slowly taken over a pivotal central role in stereotactic surgery. As a matter of fact, ablative procedures are currently regarded as alternatives, only used when DBS is not viable due to technical, travel, patient preference, and economic reasons (42, 43).

Two of the reasons that favor DBS, particularly if bilateral procedures are required, are the facts that it is not intended to produce a brain lesion, and that the stimulator can be programed with respect to several variables, including electrode location, amplitude, frequency, and pulse width, to induce better therapeutic effects while minimizing adverse effects. In the case of PD, DBS electrodes have been placed in two main BG targets: the GPi, and the STN, though other targets are also possible (44).

GPi DBS

The first study to report results of this procedure described three patients in 1994, with the post-operative results described as "excellent," reflecting improvements in all motor signs of the disease, as well as for motor fluctuations and LID (45). During the following decade, descriptions of larger series confirmed these findings. A study with a follow-up of at least 24 months showed that the mean improvements in the UPDRS motor and activities of daily living scores after 12 months were more than 50%, motor fluctuations were reduced from 40 to 10%, and the score for LID was reduced to one third. Doses of levodopa tended to remain unchanged. Half of the patients experienced a slight worsening of levodopa and stimulation resistant gait and bulbar symptoms following 12 months (46). In 2000, a study by Kumar et al. (34) showed the results seen on a cohort of 22 consecutive cases of PD treated with GPi DBS, 17 of whom had bilateral surgeries. Post-operatively, at 6 months, the motor improvement in the OFF condition reached 31 and 66% reduction in LID.

The first double-blind, crossover study evaluating the results of GPi and STN DBS in PD was performed in 2001, showing that both procedures induced significant improvements in motor function and dyskinesia (by 58% for STN and 66% for GPi DBS), however, the average medication used, measured in levodopa equivalents, decreased significantly more for the STN DBS patients (35). A study with longer follow-up, mean 48.5 months, showed a 64% mean improvement in dyskinesia after this period (36). Finally, another study followed up 11 patients with PD who underwent GPi DBS for up to 5 years, showing that, despite a decline on the motor benefit for the OFF period scores after 3 years, the improvement in LID was sustained for up to 5 years (47).

STN DBS

STN DBS for advanced PD was first introduced in the 1990s and is currently the most common form of a surgical treatment applied for this disorder worldwide. The initial series reported significant improvements in OFF period tremor, rigidity, and bradykinesia, as well as attenuation of motor fluctuations and LID, associated with a 50% reduction in dopaminergic treatment dosages (48). Subsequent studies confirmed these findings. In 2001, a prospective study of 91 patients showed, after 6 months, a robust improvement in all motor signs in the OFF condition, in the percentage of time with good mobility and no dyskinesia, mean dyskinesia score, as well as a mean reduction in daily levodopa dose equivalents (approximately 60%) (35). At this point, it became clear that the reduction in dyskinesia could be attributed at least in part to the reduction of levodopa dosage. However, a few studies showed that this may not be the only element in this beneficial effect. A study designed to assess the effect of STN DBS on OFF period dystonia, and on diphasic and peak dose dyskinesia after a levodopa challenge using the same suprathreshold dose as before surgery with the stimulation on, showed a reduction of OFF period dystonia by 90%, and of diphasic dyskinesia by 50%, and of peak dose dyskinesia by 30% (49). The same authors had already reported that chronic STN DBS *per se* tends to reduce dyskinesia, as opposed to chronic activation of the dopaminergic system with levodopa. The authors speculated that this difference may have been due to the pulsatile nature of levodopa stimulation *versus* the more continuous activation provided by chronic STN DBS (50). There was also an important study by Oyama et al. that elegantly showed that dyskinesia could possibly be reduced in both the STN and GPi target. The authors accounted for medication reduction, and showed that in both targets there was a possibility of dyskinesia suppression without medication reduction (51).

Long-term studies of bilateral STN DBS in patients with advanced PD have demonstrated the stability of this therapy over time. A 5-year prospective study of 49 consecutive patients treated with STN DBS noted that OFF medication motor scores at 5 years were still 54% better than baseline (37). Worsening of ON medication akinesia, speech, postural stability, and freezing of gait was interpreted to be consistent with the natural progression of PD. However, LID benefits persisted, with dyskinesia disability and duration at 5 years being improved by 58 and 71%, respectively in comparison with baseline. Similar benefits with respect to dyskinesia were observed in 37 patients followed for 5 years after DBS surgery (52). Finally, a comprehensive meta-analysis of 921 patients who underwent STN DBS between 1993 and 2004 noted an average reduction in LID of 69.1% (53).

MECHANISMS OF ACTION IN REDUCING LEVODOPA-INDUCED DYSKINESIA

Pallidal stimulation

Restoration of the thalamocortical activity by suppression of the inhibitory output from the pallidum to the ventrolateral thalamus is the suspected mechanism for motor improvement underpinning GPi DBS, however, the cellular mechanisms of high-frequency stimulation are still unknown. The mechanism of GPi DBS in reducing dyskinesia is also not completely understood. The current views of the BG physiology suggest that inhibition of ventral GPi activity should induce dyskinesia, however, lesioning of the ventral pallidum provides relief of dyskinesia (54). One of the possible justifications for this apparent paradoxical response is that LID may be more correlated with an abnormal pattern than with the direction and intensity of the neuronal activity within the GPi (54, 55). Surgical modification of this patterned activity might be accomplished by lesioning (direct neuronal inhibition) or with DBS (indirect inhibition through activation of inhibitory axons close to the electrode). Dyskinesia might also arise from an abnormal balance of activity within different functional zones of the nucleus (ventral versus dorsal GPi) and stimulation may suppress this abnormal activity (56, 57). Finally, the anti-dyskinetic effect of GPi DBS maybe mediated through effects on the subthalamopallidal tract, which projects to the dorsal GP externus and GPi. Dorsal GPi stimulation might inhibit this projection and would be expected to improve PD symptoms and induce dyskinesia (58).

STN stimulation

STN DBS mimics the effects of levodopa on parkinsonian motor symptoms and allows reduction of dopaminergic medication, secondarily relieving dyskinesia as medications are reduced or withdrawn post-operatively (51). However, improvement of dyskinesia is also sometimes observed in the early post-operative period after implantation of electrodes in the STN, even in the absence of a reduction of medications (1). This indicates a direct anti-dyskinetic effect of manipulation of the STN (or the vicinity of its dorsal border and perhaps the zona incerta), but long-term relief of dyskinesia generally requires reduction of medications. The specific site of action in stimulation of the STN is unknown. Some data indicate that the best effect can be achieved at the lowest intensity not through stimulation of neurons within the STN, but by stimulation of tissue dorsal to it, which might affect the pallidothalamic bundle, the pallidosubthalamic tract, and/or the zona incerta (59). Other data indicate that the most effective contact location appears to be within the anterodorsal portion of the STN, although current could spread from this location into the directly superior fields of Forel and zona incerta (60). The observation that an active DBS contact dorsal to the STN may provide better control of dyskinesia (indicative of a direct anti-dyskinetic effect) supports the notion that activation of structures dorsal to the STN is important in providing relief of parkinsonian symptoms by DBS of the STN (38). Overall, the specific mechanisms of action of GPi and STN DBS in suppressing dyskinesia are unknown.

STUDIES COMPARING THE EFFECT OF GPi AND STN DBS

A few studies have compared the effect of GPi and STN DBS on PD. **Table 2** shows the results of the most important clinical parameters described in studies comparing these two techniques. The first study to do that was published in 2001, it had a relatively short follow-up period after surgery (3 months), and revealed similar improvements in OFF period motor parameters, as well as for ON dyskinesia, with the caveat that only the STN group was able to significantly reduce the levodopa equivalent dose (35). In 2005, a non-randomized extension of this study with 105 patients followed up for at least 3 years, showed that, in addition to improvements in all motor signs of parkinsonism in the OFF condition, STN DBS significantly improved OFF dystonia and ON dyskinesia, while GPi had a similar effect on ON dyskinesia with no significant improvement on OFF dystonia. In this study, reduction in post-operative levodopa equivalent doses was significant only for the STN group, in which more than 10% of patients stopped taking levodopa. These changes were sustained after up to 4 years of follow-up (36). Moro et al., in an double-blind, non-randomized study with 35 patients who underwent STN DBS and 16 who underwent GPi DBS, found that both procedures induced significant improvements in OFF period motor signs, ADLs, and ON dyskinesia scores, although only the STN group had a significant reduction in the doses of levodopa. These results were sustained after 6 years of follow-up (61). A direct comparison of both procedures was published in 2012 (39). This was a randomized, evaluator-blind study with 198 PD patients followed up for at least 36 months, which concluded that the primary outcome, OFF period motor improvement (including subscales for each motor sign), was significantly improved, but the improvements were similar, stable over time, and with parallel trends for both targets. The scores for complications of levodopa therapy (UPDRS IV), including dyskinesia, as well as the amount of ON period time without troublesome LID were significantly improved for both groups over 36 months, with non-significant, but greater decreases in levodopa dosages in the STN group. Finally, one recent double-blind study of 128 PD patients randomized for either form of treatment, showed that patients who underwent STN DBS had larger improvements in OFF period mean UPDRS motor score, mean change in ADLs scores and mean reduction in medication after surgery. OFF dystonia scores were similarly improved as well as the time in ON phase without dyskinesia. The scores of the dyskinesia rating scales were significantly better 12 months after surgery for those who underwent GPi DBS. This difference probably occurred because the authors assessed patients after 12 months with the same dose of levodopa used at baseline, however in daily life, they may use lower doses, leading to less LID (40).

PRACTICAL ISSUES; SELECTION OF THE SURGICAL TARGET, TECHNIQUE, AND PROGRAMING

Table 1 shows a summary of points that need to be considered when indicating these DBS techniques.

Numerous studies have demonstrated the effectiveness of STN DBS in controlling the appendicular motor signs of PD, however, this procedure is not considered to have as much of a direct effect on the intensity of LID. The anti-dyskinetic effect of STN DBS have been hypothesized to be related to allowing reduction of dopaminergic drug dosages, with consequent improvement in side effects, including LID. The persistence or worsening of LID after STN DBS is common and is, in fact, indicative of the necessity to reduce the dose of levodopa (62). Therefore, the *si ne qua non-condition* for reduction of LID when STN DBS is considered, is its capacity to enable a reduction of levodopa dosage. If, however, an adequate response of motor symptoms does not occur post-operatively, dyskinesia will remain unchanged. Of importance, STN stimulation not uncommonly induces contralateral dyskinesia, which may be persistent, and in some cases lead to the implantation of rescue GPi leads.

On the other hand, GPi DBS seems to have a direct effect on the reduction of dyskinesia. Patients undergoing this procedure typically cannot tolerate significantly lower doses of levodopa after surgery, and still appreciate a marked reduction of dyskinesia. Simplistically, patients who experience a good response of their PD symptoms with levodopa, but whose primary and most significant source of disability are dyskinesia may benefit from GPi DBS (51). In other words, GPi DBS can be especially valuable for cases in which LID are a dose-limiting factor for either maintaining or introducing higher but necessary levels of dopaminergic therapy. In addition, levodopa may have a synergistic effect on GPi DBS, which is not seen after STN stimulation. Burchiel et al., for instance, in a randomized, double-blind study, comparing the effects of STN and GPi DBS, showed that, in combination with levodopa, UPDRS motor scores were significantly more improved for patients who underwent the pallidal procedure. This combination was also more clinically significant for axial symptoms, which are traditionally considered refractory to either form of treatment alone (63). Another more recent meta-regression of

long-term studies of cases who underwent these procedures confirmed that GPi DBS in combination with levodopa was correlated with better scores for postural instability and gait disorder than STN stimulation plus levodopa (64).

Selection of either target may also be influenced by the fact that medications used for the treatment of PD are useful not only for motor, but also for psychiatric, cognitive, sleep, and other non-motor aspects of the disease, therefore, withdrawal or dose reduction may not be a desired goal (65). Selection of the target should be based on the patient's most disabling symptoms, response, and side effects related to levodopa, and the ultimate goals of therapy (66). If LID are a patient's most disabling symptom, especially if they require more immediate improvement due to its severity and potential morbidity, then GPi DBS should be considered with the knowledge that regardless of changes in medication therapy after surgery there is a high likelihood that dyskinesia will improve. On the other hand, patients undergoing STN DBS must hope for a sufficiently good response after surgery that will allow medications to be sufficiently reduced. If change in parkinsonian motor symptoms after STN DBS are insufficient to guarantee reduction of levodopa dosage, or if its reduction worsen or induces non-motor symptoms, the intervention for dyskinesia may be "unfruitful" (1).

In the case of a patient in whom, in addition to motor signs of parkinsonism, medication side effects other than dyskinesia are a primary source of disability (i.e., psychosis, behavioral changes, etc.), STN DBS may be more desirable.

In general, when the presence of LID is the main problem and indication for surgery, there are no formal differences in the procedures when compared to situations when the chief complaint is another motor feature of the disease. However, a few minor variables exist. Implantation of leads is typically performed while patients are in the OFF condition to avoid disabling dyskinesia, leading to motion artifacts during pre operative imaging and to better microelectrode recording during the intraoperative procedure (67). Other variations are used because of possible differential anti-dyskinetic effects of stimulation at different sites within the GPi as stimulation of two different sites within the nucleus induce different effects on dyskinesia and response to dopaminergic treatment. Studies have shown that stimulation of the most dorsal aspects of the GPi in the OFF period usually leads to improvement of the cardinal signs, especially bradykinesia, while inducing dyskinesia, mimicking the action of levodopa. When deeper (ventral) sites within the nucleus were stimulated, signs worsened. In the ON period, stimulation of the ventral GPi reduced dyskinesia but may have worsened bradykinesia. Stimulation of the intermediate area seems to provide a balance between these two extremes. It is unclear whether these findings have a practical significance, but their existence should be kept in mind during surgical planning, positioning of the lead within the GPi, and during programing sessions (56, 57).

Post-operative programing: GPi DBS

As a rule, the evaluation of stimulation-related beneficial effects is typically less reliable during the first weeks after electrode implantation, due to the lesion effect of the procedure. Therefore, the initial programing should be performed after at least 2 weeks of surgery. At this time, the patient should be in the OFF medication condition, after 12 h of dopaminergic drug withdrawal. The first step should focus on achieving the best improvement of the cardinal signs of parkinsonism. The second phase should address the patient during the ON period, under the effect of levodopa, with particular awareness for LID. Therefore, the goal of programing should be attempting to achieve a good relief of PD symptoms in the OFF condition, not associated with the occurrence of dyskinesia in the ON period, and with the highest threshold for side effects of stimulation. This procedure should be performed for all four contacts separately, defining a hierarchy for therapeutic window (68).

In patients whose primary complaint is LID, an additional programing session can be performed in a full ON condition to confirm the adequate beneficial effect of stimulation, but is usually only indicated if there are difficulties suppressing dyskinesia. Special attention must be directed to ensure that beneficial medication effects are not antagonized by stimulation, as well as the OFF medication symptoms are not exacerbated, since different regions within the GPi may have opposite effects on dyskinesia and on the cardinal signs of parkinsonism, when stimulated. Fortunately, the detrimental effects of stimulation on parkinsonism and the response to levodopa have higher thresholds than the beneficial effects on dyskinesia. As ventral GPi areas may provide good relief of dyskinesia at the expense of loss of beneficial effect of levodopa, a better stimulation response can be detected by using more central contacts, which usually provide good relief of dyskinesia as well as tremor, rigidity, and bradykinesia (56, 69). It is important to point out that many experts have been unable to replicate the differential effects of programing different contacts in the GPi, and that in general the GPi has been found to be a much easier target to optimize. The GPi target also allows for more flexibility that the STN target, as was recently shown by Weaver et al. in VA study 36 months outcomes (39, 70).

Post-operative programing: STN DBS

As STN DBS ideally mimics the motor effects of levodopa in many aspects, the main objective of initial programing in cases of dyskinesia relies on providing a significant improvement of the motor signs of parkinsonism and a concomitant decrease in levodopa dosage, which, on average, reaches a 50% reduction (41). Therefore, as in the case of GPi DBS, the first programing session should preferentially be performed in patients during the OFF period, holding all medications for PD for 12 h. In fact, most experts that program STN and GPi DBS have patients report to the clinic in an OFF medication condition, which provides a nearly optimal programing scenario (no bias of medications). This is generally enough for most patients, however some patients may require longer OFF periods. In difficult cases, after programing for reduction of bradykinesia, tremor, and, especially, rigidity, patients should take their regular doses of levodopa and, in the ON state, be assessed for adverse effects with the combination of stimulation and medications, particularly dyskinesia. The patient should be seen during this first session at the peak effect of levodopa, and ideally should have access to expert programing for the next few days, as dyskinesia may appear after a latency period of up to several hours (71, 72). During the first few weeks and months

after surgery, as stimulation is adjusted to provide the best relief of parkinsonian symptoms, medication doses can be slowly titrated downward, and LID tends to improve or resolve. Moreover, dyskinesia has been hypothesized to improve with chronic continuous stimulation due to plastic changes as a direct effect of stimulation, leading to desensitization of the neuronal circuitry underlying to LID. Persistent dyskinesia is generally treated by further reduction of medication (71).

In some instances, especially during the first few weeks after DBS implantation, dyskinesia may be exacerbated and, in fact, the induction of these involuntary movements in the short term predicts a favorable long-term outcome (51). Thus, the particular electrode that induces dyskinesia is usually the most effective contact for long-term therapy. In these cases, if reducing levodopa leads to worsening of PD symptoms, medication doses should be kept at the lowest adequate therapeutic level, and stimulation amplitudes or other parameters should be reduced. Over time, the threshold for induction of dyskinesia typically increases, and amplitude can be gradually increased (73). Finally, if stimulation using the most effective contact precipitates dyskinesia that cannot be controlled except by unacceptable reduction of stimulation intensity, programing the system to use a more proximal contact in a monopolar configuration, or reprograming to a bipolar configuration may be necessary. Addition of a contact dorsal to the STN (perhaps in the zona incerta) may also provide better control of dyskinesia (71).

CONCLUSION

Although STN and GPi procedures have different mechanisms of action, both are effective treatments strategies to control LID. GPi interventions may have a more immediate effect, independent of reduction of levodopa daily dosage. On the other hand, several centers tend to adopt STN DBS as this procedure also brings marginally better improvements in OFF period motor scores than GPI DBS, as indicated by a recent randomized controlled trial (40). Overall, selection of the surgical target should be based on each patient's most disabling symptoms, medication response and regimen, and goals of therapeutic intervention. Currently, the literature is almost entirely focused on results that analyze a combination of the best possible results in regards to global improvements, therefore the ideal stimulation parameters specific for the control of LID are unknown. Also, the anti-dyskinetic effects of additional or combined targets, such as external and internal pallidal stimulation, and the use of adaptive DBS remain largely unexplored.

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Presynaptic mechanisms of L-DOPA-induced dyskinesia: the findings, the debate, and the therapeutic implications

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The dopamine (DA) precursor L-DOPA has been the most effective treatment for Parkinson's disease (PD) for over 40 years. However, the response to this treatment changes with disease progression, and most patients develop dyskinesias (abnormal involuntary movements) and motor fluctuations within a few years of L-DOPA therapy. There is wide consensus that these motor complications depend on both pre- and post-synaptic disturbances of nigrostriatal DA transmission. Several presynaptic mechanisms converge to generate large DA swings in the brain concomitant with the peaks-and-troughs of plasma L-DOPA levels, while post-synaptic changes engender abnormal functional responses in dopaminoceptive neurons. While this general picture is well-accepted, the relative contribution of different factors remains a matter of debate. A particularly animated debate has been growing around putative players on the presynaptic side of the cascade. To what extent do presynaptic disturbances in DA transmission depend on deficiency/dysfunction of the DA transporter, aberrant release of DA from serotonin neurons, or gliovascular mechanisms? And does noradrenaline (which is synthetized from DA) play a role? This review article will summarize key findings, controversies, and pending questions regarding the presynaptic mechanisms of L-DOPA-induced dyskinesia. Intriguingly, the debate around these mechanisms has spurred research into previously unexplored facets of brain plasticity that have far-reaching implications to the treatment of neuropsychiatric disease.

Keywords: neuroplasticity, neuropharmacology, neuropsychiatry, neurovascular unit, movement disorders, dystonia, basal ganglia, monoamines

Parkinson's Disease (PD) is defined by a set of motor signs and symptoms that are caused by dopamine (DA) deficiency and respond well to dopaminergic therapies. Accordingly, functional imaging studies have established a close link between the onset and severity of PD motor features and the loss of dopaminergic markers in the putamen (1, 2). Oral administration of the DA precursor, L-DOPA has provided the backbone of PD treatment for over 40 years [recently reviewed in Ref. (3, 4)]. However, this treatment leads to complications.

After a few years of L-DOPA pharmacotherapy, most PD patients will exhibit a shorter motor response to each medication dose ("wearing-off fluctuation"), often associated with choreiform abnormal involuntary movements (AIMs) that appear when plasma and brain levels of L-DOPA are high ("peak-dose dyskinesias") (**Figure 1**). More complex response patterns may also occur, for example, dyskinesias appearing when plasma L-DOPA levels rise or decline after each dose ("diphasic dyskinesia"), or abrupt fluctuations between a good antiparkinsonian response and a severe parkinsonian motor state ("unpredictable on–off fluctuations") [reviewed in Ref. (3, 5)]. It has recently been established that oral L-DOPA therapy produces non-motor complications too, particularly, fluctuations in mood and cognitive performance (3, 6).

Factors associated with a higher incidence and/or early development of L-DOPA-induced dyskinesia (LID) include, L-DOPA dosage, severity and duration of PD (7, 8, 9), and a young age at PD onset [reviewed in Ref. (8, 9)]. Some autosomal recessive forms of PD also entail a high risk of LID (10), possibly because they share many features with young-onset idiopathic PD, in particular, a severe loss of DA neurons with relative preservation of non-dopaminergic systems and slow progression of Lewy-related brain pathology (11, 12). The reasons underlying a high risk for LID in young-onset PD patients have not been resolved, and several valid hypotheses have been put forward, including a faster DA turnover (13) or a larger potential for neuroplasticity in a younger brain (14). Moreover, the relative integrity of non-dopaminergic systems in younger subjects may contribute to a higher risk for LID. These systems may include corticostriatal and/or serotonergic projections, as will be discussed in this article.

"PRE- OR POST-SYNAPTIC MECHANISMS?" A BRIEF HISTORICAL PERSPECTIVE

In the most typical cases, dyskinesias and motor fluctuations are temporally related to rises and declines in plasma L-DOPA levels (**Figure 1**). In advanced stages of PD, the same dosage of L-DOPA that is required to relieve parkinsonian features may also induce AIMs [reviewed in Ref. (3, 15) and schematically illustrated in **Figure 1**].

Whether this altered response pattern depends on presynaptic or post-synaptic changes in nigrostriatal DA transmission has been a matter of major debate. The presynaptic hypothesis, which prevailed in the 80s, held that the progressive degeneration of

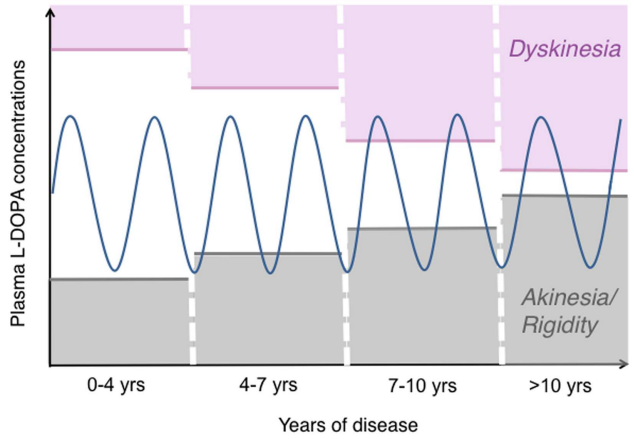

FIGURE 1 | The pattern of motor response to L-DOPA changes during the progression of PD. This drawing illustrates how the therapeutic window of L-DOPA narrows during the progression of PD [based on (172, 173)]. While oral L-DOPA therapy achieves a stable symptomatic control during the first years, it causes motor fluctuations and dyskinesias in more advanced disease stages. Dyskinesias are most commonly associated with high plasma levels of L-DOPA (peak-dose LID), as shown here. The blue sinuous line represents peaks-and-troughs in plasma L-DOPA levels concomitant with oral L-DOPA therapy. The empty area at the centre represents the range of L-DOPA concentrations that induce relief of PD motor features without causing dyskinesia.

nigral neurons causes a loss of DA storage capacity in nigrostriatal nerve terminals (16). Under these conditions, L-DOPA would be immediately converted to DA by a variety of cells in the brain, and rapidly eliminated. Peak-dose LID and wearing-off fluctuations would thus be the clinical counterparts of swift rises and declines in central DA levels, respectively [reviewed in Ref. (17)].

During the 90s, the presynaptic hypothesis appeared to decrease in popularity as many investigators turned one's attention to the post-synaptic consequences of DA depletion. The attention shift was prompted by studies in 6-hydroxydopamine (6-OHDA)-lesioned rats, which revealed striking effects of chronic L-DOPA treatment on the expression of GABA-biosynthetic enzymes, neuropeptides, and opioid precursors in striatal neurons (18). In addition, studies in PD patients revealed that the therapeutic window of apomorphine, a direct DA agonist, narrowed with the progression from a DOPA-naive to a DOPA-treated dyskinetic state (19). Because apomorphine acts independently of presynaptic nigrostriatal terminals, these results were used to suggest that altered signal-transduction mechanisms in striatal neurons are the main culprit of motor complications to PD therapy (19).

Presynaptic factors were brought back into the limelight by human positron emission tomography (PET) studies using the reversible D2 receptor ligand, [^{11}C] raclopride to estimate DA release. This approach takes advantage of a competition between endogenous DA and [^{11}C] raclopride for binding to D2 receptors. Increased DA levels in the striatum are thus seen as a reduction in [^{11}C] raclopride binding potential compared to baseline values. Using this technique, De la Fuente Fernandez and colleagues showed that standard oral doses of L-DOPA caused larger swings in striatal DA levels in PD patients experiencing motor complications compared to patients with a stable response to treatment (20, 21). Moreover, Piccini and collaborators found a positive linear relationship between putaminal changes in [^{11}C] raclopride binding and AIM scores "on" L-DOPA (22). These human studies provided a strong support to the presynaptic hypothesis of LID, and prompted a new wave of clinical and preclinical research aimed at shedding light on the mechanisms involved.

During the past 10 years, different groups of investigators have continued to debate on whether or not presynaptic factors can by themselves drive the development of LID (23, 24), and experimental evidence has been put forward to either support or reject this standpoint [cf., e.g., Ref. (25, 26)]. Because a disruption of presynaptic DA homeostasis will certainly have post-synaptic consequences (27) (**Figure 2**), this debate may appear artificially contentious at first glance. However, it is becoming clear that the relative weight of presynaptic versus post-synaptic mechanisms in generating the involuntary movements will condition the response to antidyskinetic interventions (28).

This review article will summarize both the terms of the debate and the valuable research that has stemmed from it. Thanks to this research, conspicuous progress has been made toward understanding specific players on the "presynaptic side" of the cascade (summarized in **Figures 2** and **3**).

NIGROSTRIATAL DA DENERVATION AND L-DOPA DOSAGE ARE CRITICAL TO LID

Clinical observations suggest that the loss of nigrostriatal DA neurons plays an important role in the development of LID (8, 9, 29). But PD has a complex pathology, and it is difficult to demonstrate the causal link between dopaminergic denervation and LID in human studies. This type of information can however be inferred from experimental models of the movement disorder.

In all the most common animal models of PD–LID, the loss of nigrostriatal neurons is obtained using specific neurotoxins. 6-Hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have been the most commonly used toxins in rodents and non-human primate species, respectively. In all the current animal models, the AIMs induced by L-DOPA mimic the peak-dose variant of human LID [reviewed in Ref. (30)].

Non-human primate studies examining the relationship between LID and extent of nigrostriatal DA lesion have been sparse and, at first glance, conflicting. A seminal study in MPTP-lesioned macaques reported that therapeutic doses of L-DOPA produced dyskinesia only in monkeys having ≥95% striatal DA loss (31). Accordingly, a study in MPTP-lesioned marmosets reported that only animals with >85% striatal DA loss developed choreoathetoid dyskinesias with therapeutic doses of L-DOPA, and that the most severely parkinsonian animals displayed the most severe LID (32). However, studies in squirrel monkeys reported choreoathetoid dyskinesias in animals with partial striatal DA denervation (33), and even in intact animals treated with a therapeutic L-DOPA regimen (15 mg/kg twice daily for 2 weeks) (34). Furthermore, intact macaque monkeys were reported to develop choreoathetoid dyskinesias if treated with very high doses of L-DOPA (80 mg/kg/day for 13 weeks) (35). Thus, the impact of

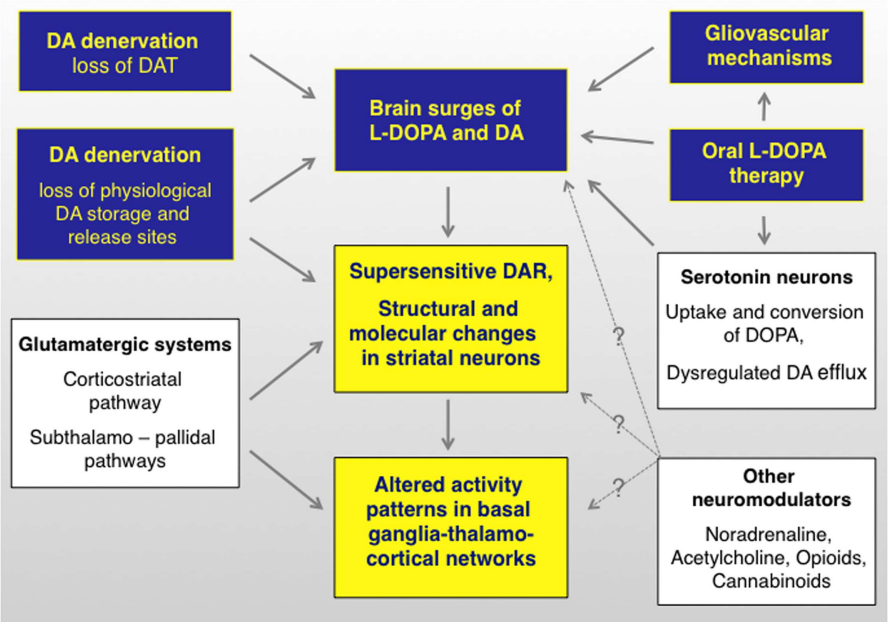

FIGURE 2 | L-DOPA-induced dyskinesia depends on both pre- and postsynaptic disturbances of DA transmission that are modulated by non-dopaminergic transmitter systems. The term "presynaptic" refers to all factors that contribute to generating fluctuating levels of L-DOPA and DA in the brain (blue boxes). The term post-synaptic refers to mechanisms that occur at the level of dopaminoceptive cells (yellow boxes). Non-dopaminergic modulatory systems are shown in white boxes. It is not well understood how these systems modulate different levels of the pathophysiological cascade (hence the question marks). DAR, dopamine receptors. Studies supporting this pathophysiological cascade have been reviewed in Ref. (3, 27, 174, 175). An updated review on the presynaptic factors is presented in this article.

nigrostriatal DA denervation on the susceptibility to LID differs between non-human primate species, some of which can develop involuntary movements even in the absence of dopaminergic denervation, if given sufficiently high doses of L-DOPA.

The largest rodent study addressing the relationship between nigrostriatal DA lesion and LID severity is the one by Winkler and colleagues (36). In this study, rats sustained partial or complete lesions of the nigrostriatal pathway, and were then treated with L-DOPA at a low therapeutic dose (6 mg/kg/day) for 4 weeks. Only rats with >80% loss of striatal dopamine transporter (DAT) or nigral DA neurons developed dyskinetic behaviors, and involuntary movements of maximal severity occurred only in the subgroup exhibiting >90% loss of dopaminergic markers (36). However, some of the completely DA-denervated animals remained free from dyskinetic behaviors throughout the L-DOPA treatment period (**Figure 4**). Thus, although a large nigrostriatal DA lesion was necessary for L-DOPA to induce involuntary movements, the severe dopaminergic denervation was not by itself sufficient (36). A similar conclusion was reached by Bezard and collaborators in a study using MPTP-lesioned macaques (37). It should be added, however, that high doses of L-DOPA will induce dyskinesia in all animals exhibiting >90% loss of dopaminergic markers throughout the caudate-putamen, although the actual doses will vary depending on species [c.f. ≥25 mg/kg/day in the rat (38, 39) versus ≥3 mg/kg/day in mice (40, 41)].

In summary, the bulk of experimental data indicate that, if L-DOPA is given at a therapeutic dosage, involuntary movements develop only when the loss of DA afferents to the motor striatum exceeds a threshold level of 80–85%. Despite these large lesions, some animals will however remain free from LID during the chronic treatment. Intriguingly, these experimental observations are in keeping with the clinical experience, whereby a proportion of PD patients never develop dyskinesias during their lifetime exposure to L-DOPA (9). Autoradiographic studies of DAT binding in the post-mortem striatum have not detected a difference between dyskinetic and non-dyskinetic PD cases (42, 43), indicating that a severe dopaminergic denervation is not sufficient for some patients to develop LID. Thus, although presynaptic DA depletion predicts the risk of LID (29), the susceptibility to this therapy complication must also depend on additional factors. These factors are likely to include some of the mechanisms discussed in the following sections.

PRESYNAPTIC CONSEQUENCES OF NIGROSTRIATAL DA DENERVATION

The degeneration of nigrostriatal DA neurons in PD implies a severe depletion of the presynaptic compartment that physiologically converts L-DOPA to DA, releases DA in a regulated fashion, and clears DA from the extracellular space via high-affinity reuptake (**Figure 3**). The nigrostriatal system has a high capacity to mount compensatory mechanisms after partial lesions through, e.g., increased DA turnover, sprouting of residual DA terminals, and downregulation of the DAT [reviewed in Ref. (15, 44)]. Accordingly, parkinsonian motor symptoms have been estimated

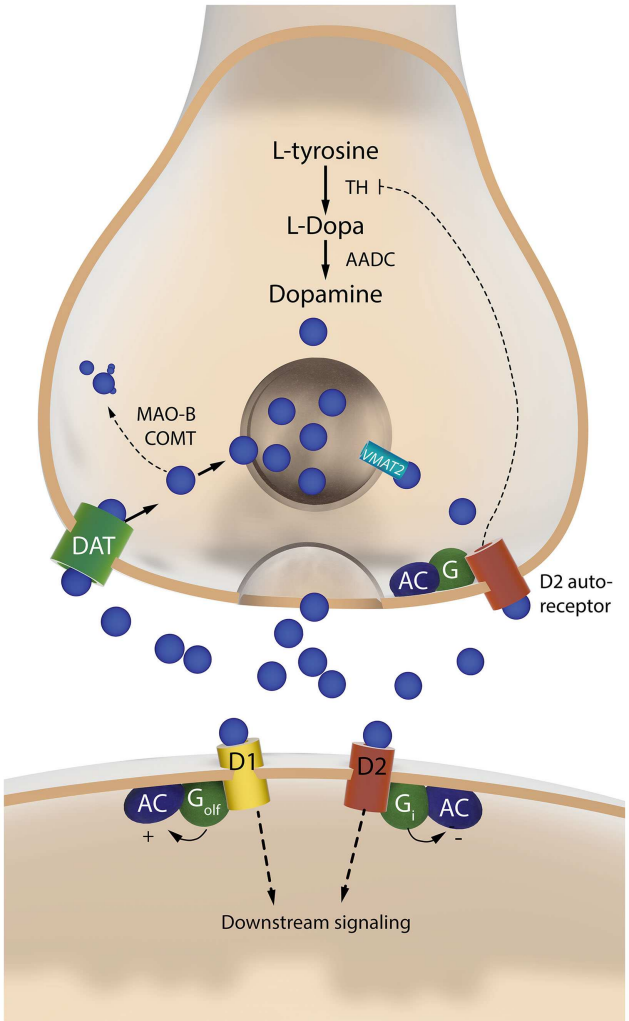

FIGURE 3 | The two sides of a dopaminergic synapse. The drawing illustrates components of the nigrostriatal dopaminergic synapse that are discussed in this article. The presynaptic nigrostriatal terminal releases DA (blue circles), and regulates extracellular DA levels through several mechanisms: DA reuptake from the extracellular fluid (via the DAT), DA transport into synaptic vesicles (via VMAT-2), DA synthesis (which is subjected to autoregulatory control via presynaptic D2 receptors), and DA metabolism (via MAO-B and COMT). The post-synaptic neuron responds to DA via two main types of receptors. The D1 receptor is coupled to G_{olf} and activates c-AMP-dependent intracellular signaling pathways. The D2 receptor is coupled to G_i and inhibits the same pathways. AADC, aromatic L-amino acid decarboxylase; AC, adenylate cyclase; COMT, catechol-O-methyl-transferase; DAT, dopamine transporter; MAO-B, monoamine oxidase B; TH, tyrosine hydroxylase; VMAT-2, vesicular monoamine transporter 2.

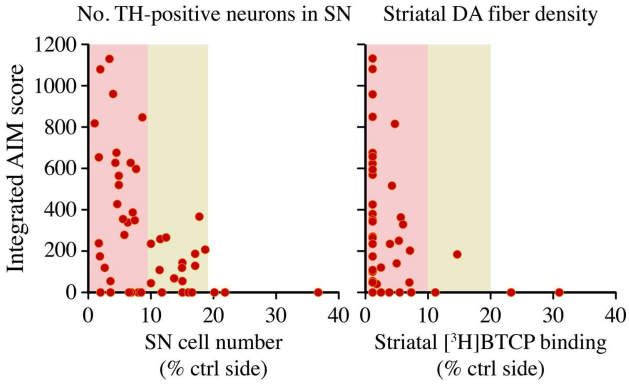

FIGURE 4 | A large nigrostriatal DA lesion is necessary but not sufficient for therapeutic L-DOPA doses to induce dyskinesia. Rats sustained unilateral nigrostriatal DA lesions of varying severity, and were then treated with L-DOPA (6 mg/kg/day) for 4 weeks. Diagrams plot the animals cumulative Abnormal Involuntary Movement (AIM) scores (*y* axis) on presynaptic markers of DA neuron integrity, that is, tyrosine hydroxylase-positive cells in the substantia nigra (SN) or striatal innervation density, estimated with DAT radioligand binding using [^{3}H]-BTCP. Data collected on the side ipsilateral to the lesion are expressed as a percentage of the values on the contralateral (ctrl) intact side. With either measure, AIM scores were found to occur only in animals that had lost more than 80% of presynaptic dopaminergic markers, and maximally severe AIMs occurred only when this loss exceeded 90%. Note however that some of the completely DA-denervated animals did not develop any dyskinesia. The dataset is derived from Ref. (36).

to appear only after a loss of 50% nigral DA neurons and 70% striatal DA contents [reviewed in Ref. (15)]. Similar phenomena have been observed in 6-OHDA-lesioned rodents, where the compensatory capacity of the nigrostriatal system appears to break down only after a >70% loss of nigral DA neurons (45, 46).

The breakdown of presynaptic DA homeostasis predisposes to large fluctuations in central levels of DA upon treatment with L-DOPA. In a seminal microdialysis study, Abercrombie and collaborators showed that a peripheral injection of L-DOPA results in significantly higher extracellular DA levels in rats with large 6-OHDA lesions compared to intact animals (47). The L-DOPA-induced increase in striatal extracellular DA concentrations (ΔDA) was 30- to 80-fold larger in 6-OHDA-lesioned animals compared to intact controls (the striking difference being partly dependent on the lower baseline DA concentrations in lesioned animals) (47). This study also established a causal relationship between ΔDA and the lesion-induced loss of DAT. Indeed, combined treatment of intact rats with L-DOPA and nomifensine, a DAT inhibitor, produced increases in extracellular DA approaching the magnitude of those in 6-OHDA-lesioned animals (47). More recent studies have confirmed the crucial importance of DAT deficiency in determining large increases in extracellular DA "on" L-DOPA (48). However, these studies have also indicated that, when the nigrostriatal lesion is very severe, the magnitude of such increases depends on factors other than DAT deficiency. Thus, animals with less than 90% DA denervation exhibit a significant negative correlation between ΔDA and striatal DAT binding levels. However, in rats with >90% denervation, DAT levels no longer predict ΔDA (48). What factors may then condition the magnitude of ΔDA in animals with severe nigrostriatal DA lesions?

In addition to the loss of DAT, a severe degeneration of the nigrostriatal pathway inevitably entails a shift in the routes of L-DOPA metabolism from nigrostriatal DA neurons to other sites (15). The conversion of L-DOPA to DA is a one-step enzymatic reaction catalyzed by aromatic L-amino acid decarboxylase

(AADC, also called DOPA decarboxylase, DDC) (**Figure 3**). This enzyme is expressed by catecholaminergic neurons (49), but also by astrocytes (50) and blood vessel-associated cells (51).

A seldom appreciated fact is that AADC and 5-hydroxytry ptophan decarboxylase (which synthetizes 5-hydroxytryptamine, serotonin) are the same enzyme (see, e.g., http://omim.org/entry/107930). Serotonin neurons therefore express relatively high levels of AADC, and they also express vesicular monoamine transporter 2 (VMAT-2), which packages DA into synaptic vesicles and protects it from rapid cytosolic degradation [reviewed in Ref. (15)] (cf. **Figure 3**). Although AADC and VMAT-2 also are expressed by noradrenergic neurons, these are unlikely to provide a major source of DA upon L-DOPA treatment, because the DA formed from L-DOPA in these neurons is rapidly converted to noradrenaline (NA) by the enzyme, dopamine-beta-hydroxylase.

Thus, serotonin neurons can both synthetize DA from L-DOPA, store the formed DA in synaptic vesicles, and release it in an activity-dependent manner. During the past few years, an abundant literature has documented that serotonin neurons indeed provide a source of DA release in L-DOPA-treated parkinsonian subjects. An intense debate has grown around the extent of this phenomenon and its significance to the occurrence of LID, as will be detailed in the following sections of this review. But before approaching this topic, we need to briefly consider the post-synaptic consequences of DA denervation, which are likely to be crucial to the development of LID.

POST-SYNAPTIC CONSEQUENCES OF NIGROSTRIATAL DA DENERVATION

Although this article focuses on the presynaptic mechanisms of LID, it is important to keep in mind that a loss of nigrostriatal DA input also entails profound adaptations at the post-synaptic level (**Figure 2**). In particular, DA-denervating lesions cause pronounced molecular, physiological, and morphological changes in striatal neurons, as demonstrated by a large body of experimental literature, briefly reviewed below.

Already in the 70s, a deafferentation-induced supersensitivity of post-synaptic DA receptors was hypothesized to play a role in the development of LID (52). Today we know that this supersensitivity depends on complex changes in the signal-transduction properties of DA receptors. The changes include, an increased coupling efficiency of both D1 and D2 receptors to their corresponding G proteins, a large activation of downstream intracellular signaling molecules, changes in DA receptor trafficking, and also a striking activation of non-canonical signaling pathways [reviewed in Ref. (52–54)]. Gerfen and collaborators were the first to propose that the denervation-induced supersensitivity of D1 receptors leads to an activation of intracellular pathways that are not recruited under physiological conditions (55). In their seminal study (55), treatment of 6-OHDA-lesioned rats with D1 receptor agonists was found to cause a pronounced striatal activation of extracellular signal regulated kinases 1 and 2 (ERK1/2), a pathway traditionally associated with the stimulation of tyrosine-kinase or glutamate receptors, not $G_{s/olf}$-coupled receptors (cf. **Figure 2**). A link between L-DOPA-induced ERK1/2 activation and the development of dyskinetic behaviors was later demonstrated in both rodent (40, 56–58) and non-human primate models of LID (40).

In addition to altered DA receptor-mediated signaling, an abnormal corticostriatal synaptic plasticity (59) and structural changes of striatal neurons associated with the progression of PD (60) predispose to a dyskinetic response to therapy. Post-mortem investigations of striatal tissue from PD patients have revealed conspicuous loss of spines and dendritic atrophy in medium-sized spiny neurons (61, 62). Similar phenomena have been found to occur in both rodent and non-human primate models of PD (63, 64). The results so far available indicate that treatment with L-DOPA does not normalize the dendritic structure of striatal neurons, but instead superimposes a new layer of changes that are associated with the development of dyskinetic behaviors (65–67).

It has been hypothesized that striatal dendritic atrophy has a major impact on the response to PD treatment favoring the emergence of complications because, "expecting a normal reaction to dopaminergic drugs under these circumstances is like expecting a four-cylinder car engine to turn over normally on three cylinders" (68). Further investigations are however needed to clarify the precise contribution of an altered striatal dendritic morphology to the genesis of LID (69).

L-DOPA-INDUCED DA RELEASE IN THE DYSKINETIC BRAIN

PET imaging studies in PD patients have established a link between L-DOPA-induced motor complications and large fluctuations in striatal DA levels (20). In a seminal study using [^{11}C] raclopride PET, De La Fuente Fernandez and coworkers compared the dynamics of striatal DA release between PD patients affected by LID and patients with a stable response to therapy (20). One hour after L-DOPA administration, dyskinetic patients exhibited significantly greater changes in striatal DA levels than did stable L-DOPA responders (21). Similar results were obtained by Piccini's group, who also established a positive correlation between changes in striatal DA levels and severity of peak-dose LID (22). One limitation of these human studies is that the absolute extracellular concentrations of DA, hence their impact on changes in [^{11}C] raclopride binding, were not accessible to investigation. This concern is relevant because the dyskinetic PD patients in these studies had a longer disease duration than did stable L-DOPA responders (21, 22). A longer disease duration may potentially lead to lower striatal DA levels at baseline.

Microdialysis studies in rodent models of LID have been very useful in clarifying the relationship between dyskinesia and absolute striatal DA concentrations "on" and "off" L-DOPA. In a seminal study, Meissner and colleagues compared striatal extracellular DA levels in 6-OHDA-lesioned rats exposed to a prior course of treatment with L-DOPA or saline (70). L-DOPA was given at a high dose (50 mg/kg/day per 10 days), which induced AIMs in all of the treated animals. A striking result of this study is that the same peripheral dose of L-DOPA elicited a larger increase in striatal extracellular DA levels in L-DOPA-primed animals compared to saline-treated ones (70). Other microdialysis studies were performed in 6-OHDA-lesioned rats that had been chronically treated with a lower dose of L-DOPA (6 mg/kg/day), upon which some of the animals remained free from AIMs. These studies reported larger striatal levels of L-DOPA (71) or DA (72,

73) in dyskinetic animals compared to non-dyskinetic cases. The most pronounced between-group difference in striatal DA levels occurred at the peak of the L-DOPA-induced surge, i.e., 40–60 min after L-DOPA administration. DA concentrations did not however differ between dyskinetic and non-dyskinetic animals either at baseline or at later time points post drug dosing (72, 73). Although dyskinetic animals showed a larger increase above baseline (ΔDA), their absolute DA concentrations never exceeded the values measured in intact control animals (72). Interestingly, a similar pattern of group differences was observed in the substantia nigra, which was monitored simultaneously with the striatum in one study (72).

Taken together, these results show that both ΔDA and absolute DA concentrations at the peak of the L-DOPA effect are larger in animals affected by involuntary movements compared to non-dyskinetic cases, despite similar baseline DA levels. The larger ΔDA values in dyskinetic rats are in keeping with the results of [^{11}C] raclopride-PET studies in dyskinetic PD patients, though apparently at variance with other experimental data. In particular, a recent microdialysis study in the macaque model of LID has failed to detect a significant increase in striatal extracellular DA levels after L-DOPA administration, whereas striatal levels of DOPA showed a robust increase (74). According to the authors interpretation, these data indicate that a low DOPA decarboxylase activity in parkinsonian primates limits the production of DA from exogenous L-DOPA, differently from the situation encountered in 6-OHDA-lesioned rodents (74). These unexpected results prompt the interim reflection that the rat model of LID is more suitable than the macaque one to reproduce the presynaptic disturbances seen in the human condition. Indeed, [^{11}C] raclopride binding is displaced by DA, and not by L-DOPA itself.

SEROTONIN NEURONS AS AN ABERRANT SOURCE OF DA RELEASE "ON" L-DOPA

The first report implicating serotonin neuron as a source of DA release "on" L-DOPA was provided by Tanaka and colleagues (75). These authors compared extracellular DA levels in the striatum of 6-OHDA-lesioned rats that had sustained or not an additional chemical lesion of serotonin neurons. Rats in the double-lesion group exhibited a dramatic 80% reduction in L-DOPA-induced DA efflux (75). Another important early study used a similar approach to show that a serotonin lesion completely suppressed the induction of both rotational behavior and striatal c-Fos expression by L-DOPA in 6-OHDA-lesioned rats (76). The authors of these studies suggested that the action of L-DOPA in PD critically depends on its conversion to DA in serotonin neurons.

As explained above, serotonin neurons are endowed with the enzymes that convert L-DOPA to DA, and package this DA into synaptic vesicles. A double-labeling immunofluorescence study in rats treated with L-DOPA has indeed revealed immunoreactivity for DA in serotonin-positive dorsal raphe neurons and their striatal projections (77).

It is therefore hardly surprising that serotonin neurons become an important source of L-DOPA-derived DA release in a situation where nigrostriatal neurons are severely damaged. A relationship between LID severity, on one hand, and morphological or autoradiographic measures of striatal serotonin innervation, on the other hand, has been detected in both rat and non-human primate models of PD by several studies (78–81). These results fit well with our observation that chronically L-DOPA-treated rats with larger ΔDA values "on" L-DOPA show higher striatal levels of serotonin and its metabolite at baseline, suggestive of a denser 5-HT innervation (72).

Supporting the notion that 5-HT neurons release DA "on" L-DOPA, several studies in 6-OHDA-lesioned rats have shown that L-DOPA-induced peak DA efflux can be blunted by agonists of the serotonin autoreceptors, 5-HT1a and 5-HT1b (72, 82, 83). Agonists at these receptors dampen the activity of serotonin neurons, measured as either firing rate or neurotransmitter release (84). 5-HT1a and 5-HT1b receptor agonists have marked antidyskinetic effects in both rodent and non-human primate models of LID [reviewed in Ref. (3, 85)]. However, doses of 5-HT1a/b agonists that improve LID do not improve dyskinesias that are induced by apomorphine (86) or D1 receptor agonists (28). This pattern of effects indicates that low-medium doses of 5-HT1a and 5-HT1b agonists [cf. doses in (28, 72, 86)] interfere with presynaptic mechanisms of dyskinesia that are exclusively recruited by L-DOPA, not by dopaminergic agents acting directly on DA receptors. The efficacy of 5-HT1a and 5-HT1b agonists in reducing LID further indicates that DA release from serotonin neurons plays a causal role in LID. A compelling demonstration of this concept was provided by Carta and collaborators using selective lesions of 5-HT neurons (86). These lesions completely suppressed L-DOPA-induced AIMs in previously dyskinetic rats (86). Other studies applied a chemical lesion of 5-HT neurons to 6-OHDA-lesioned rats before treating them with L-DOPA, and demonstrated a positive association between the levels of residual striatal 5-HT innervation and the severity of dyskinetic movements induced by the treatment (87).

Why would DA release from 5-HT neurons be so prone to induce LID? Serotonin neurons lack presynaptic mechanisms that can sense and regulate their DA release, such as DA autoreceptors and DAT [reviewed in Ref. (15)]. Thus, in situations where both baseline DA levels and DAT activity are severely reduced (which is the case in advanced PD), DA release from serotonin neurons is bound to produce large swings in DA levels. Moreover, DA efflux from 5-HT neurons will be ectopic in terms of both subcellular release sites and anatomical distribution. Accordingly, an elegant microdialysis study in 6-OHDA-lesioned rats reported very large increases in DA levels "on" L-DOPA in many brain structures (including hippocampus and prefrontal cortex), and the increases were totally abolished by a complete lesion of serotonin neurons (88). These large extrastriatal DA surges induced by L-DOPA most likely contribute to the development of both motor and non-motor complications to therapy (89). With respect to LID, a recent study in the rat has linked the stimulation of cortical D1 receptors to the expression of involuntary movements through a local generation of high-frequency oscillatory activities (90).

DEBATE ON THE INVOLVEMENT OF 5-HT NEURONS IN LID

Although the studies reviewed above are quite consistent, the concept that 5-HT neurons provide a major source of DA release in LID has met some resistance. Here follows a summary of common objections presented to us in the form of scientific correspondence. First, it is pointed out that the role of 5-HT neurons in LID has been studied in animals with relatively intact serotonin

projections, which would be unlike the situation in the advanced stages of PD. Second, it is pointed out that a degree of striatal DA denervation as dramatic as in these animals would occur only in the very terminal stages of PD, implying that there would always be some nigrostriatal fibers ready to release DA in dyskinetic PD patients. Third, the comment has been put forward that astrocytes represent a much more abundant compartment than 5-HT projections to take up L-DOPA and convert it to DA in the striatum. All these objections are warranted, but also quite addressable with data available in the published literature.

As to the first point, post-mortem biochemical studies of 5-HT markers in PD have revealed that the loss of serotonergic innervation is more severe in the caudate than the putamen. In the latter structure, detectable levels of serotonergic markers persist until the terminal stages of PD (91). Accordingly, PET imaging studies in patients with advanced PD have detected only 30% reduction in putaminal serotonin transporter (SERT) binding (92), whereas, dopaminergic markers may be reduced by over 75% in the same structure (93). Post-mortem autoradiographic studies of SERT and DAT binding activities in the PD putamen are in keeping with the PET imaging investigations (42, 43, 80, 94). Furthermore, a post-mortem autoradiographic study has revealed larger SERT binding density in the post-commissural putamen in PD cases with LID compared to non-dyskinetic subjects (80).

Regarding the extent of DA denervation in the human disease, a recent pathological study has reported a virtual absence of DA fiber markers in the posterior putamen already at 4–5 years from PD diagnosis (95). Thus, the levels of DA denervation occurring in the dorsolateral striatum in animal models of LID are comparable to those in the post-commissural putamen (the motor part of the striatum) in mid-advanced stages of PD. And these are the stages where motor complications to therapy start to appear (cf. **Figure 1**).

As to the role of non-neuronal cells in handling L-DOPA, while this phenomenon certainly deserves further investigation (see below), it should be pointed out that neither glia nor vessel-associated cells have a capacity for vesicular storage and release of neurotransmitters. This is an important point, because microdialysis studies in 6-OHDA-lesioned rats have shown that L-DOPA-induced DA release is significantly reduced by reserpine, a VMAT blocker (96), and also by tetrodotoxin (TTX) (72, 97), a sodium channel blocker inhibiting the generation of action potentials. Thus, the bulk of DA efflux "on" L-DOPA has a neuronal origin even in animals with complete nigrostriatal DA lesions. Some authors have proposed that striatal interneurons expressing TH may provide a source of DA production and L-DOPA conversion in PD (98–100). However, it is as yet unclear whether these neurons can actually release DA [cf. (101)], and the expression of AADC in these cells appears to be very low, at least in rodents (41).

A proof-of-concept that 5-HT neurons release DA in patients affected by LID has been recently provided by Politis and coworkers using PET imaging techniques (102). In this study, dyskinetic PD patients were compared to patients with a stable response to therapy ("stable responders") using both a SERT ligand ([^{11}C]-DASB PET) and [^{11}C] raclopride. In agreement with previous studies (see above), a standard dose of L-DOPA induced a larger displacement of [^{11}C] raclopride binding in the dyskinetic group. Interestingly, the magnitude of [^{11}C] raclopride displacement was positively correlated with the striatal levels of [^{11}C] DASB binding, suggesting a relationship between peak DA efflux "on" L-DOPA and the density of striatal 5-HT innervation. Further to these observations, the authors evaluated the effects of buspirone, a compound with 5-HT1a agonistic activity, on the change in [^{11}C] raclopride binding induced by L-DOPA administration. Intriguingly, buspirone reduced the magnitude of raclopride displacement only in dyskinetic PD patients, while having no effect at all in the stable responders. Furthermore, dyskinetic patients exhibiting a greater response to buspirone displayed a larger signal on the [^{11}C] DASB PET scans, indicating larger striatal levels of serotonergic terminals. Finally, a strong positive correlation between AIM ratings and [^{11}C] DASB binding density was found in the group of patients with peak-dose LID of mild-moderate severity (102). The authors concluded that striatal serotonergic terminals contribute to LID in human PD via aberrant processing of exogenous L-DOPA and release of DA as false neurotransmitter, quite in agreement with the results obtained in rat studies (102).

DEBATE ON THE PLASTICITY OF THE SEROTONIN SYSTEM IN LID AND ITS ANIMAL MODELS

The serotonin system is highly vulnerable to age-related degenerative changes, but also highly plastic (103–105). Functional and structural adaptations of the serotonin projections may therefore impact on their role in LID.

In many toxin-based animal models of PD, the neurotoxic lesion induces partial damage of ascending 5-HT projections, followed by a long-term compensatory sprouting of 5-HT axon fibers (81, 106–108). Furthermore, chronic dyskinesiogenic treatment with L-DOPA has a growth-promoting effect on serotonin axon terminals (78, 80, 81), which is likely dependent on the treatment-induced upregulation of BDNF (80). The treatment-induced sprouting of 5-HT axon terminals requires a previous severe DA denervation of the affected region, as well as a partial lesion of 5-HT afferents, as it does not seem to occur when LID is produced in animal models of PD having intact serotonin projections [cf. (109)].

The striking plasticity of the 5-HT system in animal models of PD–LID has raised concerns that the importance of this system may be overestimated in the experimental models relative to the human disease, because serotonin neurons are expected to degenerate, not to grow new axon terminals, in PD. However, in the study by Politis and coworkers (102), the dyskinetic patients with longest disease duration exhibited a remarkably preserved serotonin terminal function. Thus, striatal levels of [^{11}C]-DASB binding did not differ between the severely dyskinetic patients and the subjects with a stable response to therapy, who had a significantly shorter disease duration (102). These results are at variance with the expected loss of [^{11}C]-DASB binding during the progression of PD (92), and may in fact suggest that serotonin axon terminals mount a long-term sprouting response in human LID, analogous to that seen in the animal models. Further support to this interpretation comes from an autoradiographic study of SERT radioligand binding density in the human post-mortem putamen and pallidum, showing larger SERT binding levels in PD patients with clinical records of LID compared to non-dyskinetic cases (80). In this study, a linear correlation was found between SERT binding

density and number of SERT-immunoreactive axonal varicosities, at least in the pallidum (80).

At variance with the evidence above, some recent studies in 6-OHDA-lesioned rats have suggested that chronic L-DOPA treatment may have deleterious effects on serotonin neurons. In one study, animals were treated with L-DOPA (12 mg/kg/day) for 28 days, after which tissue levels of DA and serotonin were measured in several brain regions at various intervals following the last L-DOPA dose (89). A reduced ratio between serotonin and DA concentrations occurred for up to 4 h post L-DOPA administration in all the structures examined. The authors concluded that L-DOPA treatment had increased DA levels while reducing 5-HT levels in all brain regions (89). These results may reflect the fact that DA displaces 5-HT from synaptic vesicles within serotonin axon terminals (77, 86). If serotonin is displaced from the vesicles, its degradation will be faster and its tissue contents reduced, at least for a few hours following the administration of L-DOPA. However, Eskow Jaunarajs and colleagues proposed that long-term L-DOPA therapy may be directly detrimental to serotonin neurons through mechanisms involving oxidative stress, an idea supported by some observations *in vitro* (89). Endorsing the above interpretation, a microdialysis study performed in rats previously treated with L-DOPA (12 mg/kg/day for 10 days) reported a lower magnitude of L-DOPA-induced DA efflux in several brain regions compared to that measured in acutely L-DOPA-treated animals (110). The authors concluded that chronic L-DOPA therapy negatively affects the functionality of serotonin neurons, at least if high drug doses are used (110). These results are, however, at variance with those reported by other studies using high doses of L-DOPA (70).

While the debate on the degeneration and plasticity of 5-HT neurons in PD–LID is still ongoing, there is agreement that 5-HT receptors in the brain show pronounced functional adaptations. In particular, increases in striatal and cortical levels of 5-HT1a and 5-HT1b receptors, as well as their adaptor proteins (111), have been reported by several studies performed in animal models of PD and LID [partially reviewed in Ref. (112)]. Further studies are needed to verify the occurrence of these adaptations in the human disease, and to clarify their functional consequences. For example, it is likely that these receptor adaptations may impact on the responsiveness to antidyskinetic treatments targeting 5-HT1a and 5-HT1b receptors.

GLIOVASCULAR MECHANISMS

In addition to high DA levels, dyskinetic animals show a large increase in the extracellular levels of L-DOPA following peripheral drug administration (71, 74, 113). A study in non-human primates has even suggested that L-DOPA does not need to be converted to DA in order to elicit AIMs (74).

The concentrations of L-DOPA in the brain extracellular fluid reflect the balance between drug entry and drug uptake/metabolism by brain cells. There are no indications that the uptake of L-DOPA by brain cells is impaired in dyskinetic animals, and it is therefore warranted to ask whether its entry could be increased. L-DOPA enters the brain from the blood stream via the L-type amino acid transporter system present in endothelial cells of the blood–brain barrier (BBB) (114, 115). Thus, the passage of L-DOPA from blood to brain will depend on the same variables that regulate the extraction of any substance, that is: (1) capillary permeability, (2) the capillary surface area, and (3) the regional blood flow (116). In the case of L-DOPA, a fourth variable should be considered, namely, the possibility of an active drug metabolism at the capillary level.

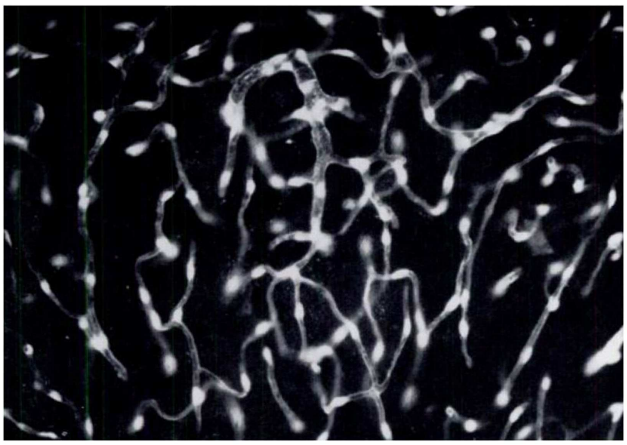

FIGURE 5 | Brain endothelial cells and pericytes produce dopamine following systemic administration of L-DOPA. In the 60s, a group of Swedish pharmacologists led by E. Rosengren discovered that brain endothelial cells and pericytes are a significant site of dopamine production following treatment with L-DOPA. This photomicrograph represents a section of rat cerebellum processed for the Falck–Hillarp catecholamine histofluorescence method to visualize DA-containing cells. The rat had received an injection of L-DOPA (50 mg/kg, combined with the monoamine-B inhibitor nialamide) shortly before being killed. The authors commented, "It was evident that the fluorescent material occurred throughout the capillary walls giving almost a three-dimensional appearance of the capillary tubes. Fluorescence of high intensity (was found) in cytoplasm and nucleus of both endothelial cells and pericytes" [Reproduced with permission from Ref. (51)].

Already in the 60s, studies based on the Falck–Hillarp catecholamine histofluorescence method had indicated that brain capillaries critically regulate the entry of L-DOPA into the brain parenchyma (51). Endothelial cells and pericytes were revealed to be the first site of L-DOPA uptake, conversion, and metabolism in the brain (**Figure 5**), and were found to express very high levels of both AADC and monoamine oxidase B (51). It was thus proposed that cells lining cerebral microvessels form an enzymatic barrier to the entry of L-DOPA (51). Further to these studies, it was recently reported that L-DOPA accumulates not only in the microvessels, but also in astrocyte cell bodies and astrocytic endfeet surrounding cerebral microvessels (117).

Endothelial cells, pericytes, and perivascular astrocytes form a functional unit that controls both capillary permeability and regional cerebral blood flow (rCBF) [reviewed in Ref. (118, 119)]. Both of these parameters are dynamically regulated in the brain to match the metabolic activity of neurons, and this process (termed "neurovascular coupling") is modulated by monoaminergic afferents that innervate cerebral arterioles and microvessels (120–124).

Interestingly, while regional glucose metabolism (which is mainly driven by neuronal activity) and rCBF are well-matched

in PD patients during the "off" medication state, the administration of L-DOPA greatly increases rCBF without elevating glucose metabolism in a brain network that includes putamen, pallidum, and midbrain–pons (125). In this brain network, the dissociation between flow and metabolism is particularly striking in patients affected by LID (125). These findings suggest that L-DOPA exerts hemodynamic effects that are independent of its modulation of neuronal metabolic activity, thus superseding physiological mechanisms of neurovascular coupling in the affected brain regions. 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, often in the absence of large concomitant changes in glucose metabolism (126).

The flow-metabolism dissociation response is a particularly intriguing phenomenon as it may signal a previously overlooked effect of L-DOPA on gliovascular cells (126). Moreover, this phenomenon may result in higher extracellular levels of L-DOPA in dyskinetic subjects (125, 126), impacting on the presynaptic mechanisms of LID. The underlying mechanisms are however unclear. Evidence of flow-metabolism dissociation has thus far been found only in specific regions, and the observed regional pattern cannot be readily explained by regional differences in either DA efflux "on" L-DOPA (88) or gliovascular expression of DA receptors (43, 120, 122, 127). Some interesting mechanistic suggestions have however emerged from studies performed in the rat model of LID. In 6-OHDA-lesioned rats treated with L-DOPA, regions with large increases in blood flow "on medication" exhibit endothelial proliferation and angiogenic activity when the treatment is given chronically (126). Furthermore, some of these regions exhibited an increased microvascular density and upregulation of angiogenesis markers in a post-mortem study of basal ganglia tissue from dyskinetic PD patients (43). These findings suggest that the large increases in rCBF "on" L-DOPA and the angiogenic response to the chronic treatment are interrelated phenomena, which are critically regulated by gliovascular cells in the affected brain regions (126). Investigating this hypothesis is likely to yield important insights into previously overlooked neurovascular effects of L-DOPA, uncovering novel therapeutic targets.

CHANGES IN BBB PERMEABILITY: THE FINDINGS AND THE DEBATE

As mentioned above, capillary permeability is one of the factors determining the central availability of L-DOPA. The BBB is a selective diffusion barrier that relies on specialized properties of the brain's capillary endothelium, such as the presence of tight cell–cell junctions, low levels of pinocytotic activity, and the expression of selective transporter proteins at the plasma membrane [reviewed in Ref. (128)]. Several independent studies suggest that the functionality of the BBB becomes impaired during the progression of PD (129–131). For example, the ratio between albumin concentrations in cerebrospinal fluid (CSF) and plasma is increased in PD patients with advanced disease compared to age-matched controls (131). Interestingly, higher albumin ratio values were measured in patients receiving DA replacement therapy compared with untreated subjects (131).

It has been suggested that the neuroinflammation associated with neurodegeneration leads to an increased BBB permeability due to the vascular effects of proinflammatory cytokines [see Discussion in Ref. (132), and references therein]. However, while neuroinflammation is a widespread finding in PD (133), the permeability problem appears to depend on focal areas of BBB dysfunction within the striatum and the midbrain. These areas show signs of angiogenic activity (43, 126, 132, 134). Several studies in both parkinsonian animals and human PD have indeed detected endothelial proliferation and other markers of active angiogenesis within the substantia nigra and the striatum (43, 134–137). Because active angiogenesis entails a transient increase in vessel permeability, it will inevitably lead to a localized leakage of the BBB when it occurs in the brain (138). Accordingly, studies in rat models of PD have revealed localized leakage of BBB tracer molecules (132) or downregulation of BBB proteins (139) precisely on vessels having angiogenic features.

When treatment with L-DOPA produces dyskinesias, it may aggravate the BBB dysfunction associated with PD, or even induce a new pattern of dysfunction. In the rat model of LID, dyskinetic animals exhibit endothelial proliferation, increased BBB permeability, and upregulation of vascular endothelial growth factor (VEGF) in the lateral striatum and the basal ganglia output nuclei (the substantia nigra pars reticulata and the entopeduncular nucleus, i.e., rodent equivalent of the GPi) (43, 139–141). These phenomena only occur on the DA-denervated side of the brain, and they are positively associated with the development of LID (139, 141). L-DOPA induces this angiogenic activity via stimulation of D1 receptors and activation of ERK1/2 signaling (140). Treatments that antagonize VEGF attenuate the gradual increase in dyskinesia severity during a chronic course of L-DOPA administration (43, 141), while inhibiting the angiogenic activity and BBB dysfunction induced by L-DOPA in the basal ganglia (43). Along with human pathological observations (43, 137), these findings suggest that a treatment-induced, VEGF-dependent angiogenic activity in the basal ganglia contributes to an aggravation and chronicization of LID in the advanced stages of PD (43).

The pathophysiological implications of these findings are, however, poorly understood. We have proposed that the increased BBB permeability associated with angiogenesis may contribute to an increased entry of L-DOPA in the affected regions (i.e., the motor part of the striatum and the basal ganglia output nuclei) (139). Supporting this proposition, dyskinetic animals were found to exhibit increased striatal and nigral uptake of an intravenous tracer molecule (which normally does not cross the BBB) having a molecular weight similar to L-DOPA (126). Importantly, leakage of this tracer into the striatal parenchyma was detected at significant levels at 60 min, but not 24 h after the administration of L-DOPA (126). This observation is interesting because it suggests an association between increased rCBF "on" L-DOPA and BBB hyperpermeability in dyskinetic subjects (126). In other words, the high rCBF associated with LID (125, 126) would cause BBB leakage at the level of immature microvessels, which form in the striatum and its output nuclei because of the combined effect of DA denervation and chronic L-DOPA treatment (126). In keeping with this suggestion, an increased perfusion has been shown to enhance tight-junction opening between endothelial cells in other models of brain disease involving angiogenesis or microvascular pathology (142). Further investigations are needed to clarify the relative importance of an

increased BBB permeability in producing high extracellular levels of L-DOPA in LID.

The suggestion that BBB permeability is enhanced in LID has raised some debate (143). It is often argued that the peripheral DOPA decarboxylase inhibitors included in standard L-DOPA preparations [i.e., carbidopa or benserazide, reviewed in Ref. (3, 4)] are unlikely to enter the brain. If they did, the treatment would not engender an increase in central levels of DA, whereas raclopride–PET studies unequivocally demonstrate striatal DA release after the administration of L-DOPA to PD patients. However, studies in both intact and 6-OHDA-lesioned rats indicate that peripheral DOPA decarboxylase inhibitors significantly reduce central AADC activity only at doses much higher than those given to patients (144, 145). More importantly, doses of benserazide reducing striatal AADC activity by over 50% did not have any effect on either basal DA levels or L-DOPA-induced DA release in the striatum (145, 146). To achieve a significant effect on the above parameters, benserazide had to be administered at the dose of 50 mg/kg, which reduced striatal AADC activity by ≥80% (145, 146). Such a dose is manifold larger than the highest benserazide dosage to which a PD patient will ever be exposed. In a study using 6-OHDA-lesioned rats, not even 50 mg/kg benserazide had any significant effect on the increase in extracellular DA levels induced by L-DOPA, affecting only the time to reach the peak (145).

ROLE OF NORADRENALINE NEURONS

Dopamine is the immediate precursor of NA along the catecholamine biosynthetic pathway, and extracellular NA levels increase in the DA-denervated striatum after a peripheral injection of L-DOPA. Interestingly, this increase is significantly larger when the treatment induces involuntary movements (73). An elevation in striatal NA levels has been suggested to contribute to LID because local infusions of NA in the DA-denervated striatum induce AIMs in the rat (73, 147). Based on these findings, one would expect LID to be improved by lesions of central NA projections. Quite in contrast with this prediction, most studies addressing the impact of noradrenergic denervation on LID have reported a worsening of dyskinesia, which was due either to an increased peak severity (148, 149) or to an increased duration of the involuntary movements (150). Other studies have not, however, detected a significant worsening of LID, even when the noradrenergic denervation resulted in a worsening of motor and cognitive deficits (151, 152). These apparent discrepancies are likely to depend on technical differences regarding NA lesion procedures and/or types of 6-OHDA models used in different studies. In this regard, it is useful to know that injections of 6-OHDA in the medial forebrain bundle (MFB) damage also ascending NA fibers, an effect that cannot be completely prevented by pretreating animals with blockers of NA uptake, such as desipramine (unpublished data by the Cenci's lab). Thus, a large 6-OHDA lesion in the MFB may occlude the effect of a subsequent NA lesion, even more so if the latter is applied using toxins that damage NA projections but leave their cell bodies intact (150).

Despite the above discrepancies, a large amount of data point to an involvement of the NA system in the motor complications of PD therapy. This system is highly vulnerable to the neurodegenerative process in PD (153) and to the neurotoxins that are used to create PD models in animals [reviewed in Ref. (30)]. Moreover, treatment with L-DOPA appears to modulate the activity of brain NA neurons, as indicated by changes in NA cell firing in the locus coeruleus region, and by an increased NA efflux in their projection targets (73, 150). That the NA system in causally involved in LID is suggested not only by the results of lesion studies in the rat (148–150), but also by a vast pharmacological literature investigating the effects of NA receptor modulators.

Several studies in rat and primate models of PD have indeed shown that modulators of NA receptors improve LID. Many studies have evaluated antagonists of $\alpha_{2B/C}$-adrenoceptors, and found that they reduce the severity of L-DOPA-induced AIMs, and that they also can prolong the anti-akinetic effect of single L-DOPA doses (154–158). One potential underlying mechanism may involve a reduction of peak extracellular levels of both DOPA and DA, which the α_{2C} adrenoceptor antagonist idazoxan has been shown to achieve at a dose that significantly reduces the severity of LID (113). The mechanisms by which central NA neurons modulate the effects of L-DOPA remain, however, poorly understood. Given that the NA system has widespread modulatory functions in the brain, these mechanisms are bound to be very complex. Relevant to the presynaptic mechanisms of LID are the modulatory effects of NA on several afferent striatal systems, including 5-HT and DA axon terminals (159–161), and the key role of locus coeruleus neurons in regulating both cerebral blood flow and capillary permeability (124, 162), and in maintaining the integrity of the BBB (163).

CONCLUDING REMARKS

L-DOPA remains the most effective treatment for PD and understanding how this drug is handled by, and in turn affects, a parkinsonian brain, is an undisputed research priority, not least for the sake of developing better treatment options.

In the past few years, research on the presynaptic mechanisms of LID has generated results of great translational importance, but also scientific controversy. In this article, I have reviewed both the findings and the controversies, while highlighting important aspects that call for further investigations.

Some of the concepts presented in this article are, however, quite uncontroversial and have already inspired a clinical development of new treatments. Thus, the concept that large swings in striatal DA levels are the culprit behind motor fluctuations and dyskinesia has prompted the development of new methods of continuous L-DOPA delivery, which are now available in several countries [reviewed in Ref. (3)]. While these therapies have a proven efficacy against the motor fluctuations (164), the extent to which they can eliminate already established dyskinesias remains to be demonstrated.

The concept that LID depends on DA release from serotonin neurons has raised both interest and discussion. That 5-HT neurons can produce and release DA "on" L-DOPA is now widely accepted. A debate, however, persists regarding the relative importance of this phenomenon. PD dyskinesias are conceivably more complex than the models of peak-dose LID obtained in animals with "clean" nigrostriatal lesions. For example, in the advanced stages of PD, the involuntary movements may exhibit a variable and unpredictable relationship with the timing of drug

administration, and they may be induced by dopaminergic agents that do not release any DA in the brain. A point of recent discussion pertains to the role of DA release from 5-HT neurons in inducing involuntary movements as opposed to "good" antiakinetic effects. Two recent studies (165, 166) have suggested that DA release from serotonin neurons not only generates dyskinesia but may also mediate the therapeutic benefit of L-DOPA. An implication of these findings is that antidyskinetic treatments based on the stimulation of 5-$HT_{1A/B}$ receptors (dampening transmitter release from 5-HT neurons) may have an unfavorable risk-benefit profile in the advanced stages of PD, when most L-DOPA-derived DA release is likely to come from 5-HT neurons, at least in the motor regions of the striatum. Accordingly, large clinical trials of 5-HT_{1A} receptor agonists in LID appear to have faced some difficulties in defining a suitable therapeutic window for the investigational drugs [reviewed in Ref. (3)]. It should be noted, however, that the 5-HT_{1A} ligands so far evaluated in PD patients had partial agonist activity and many off-target effects. To really appreciate the potential of this strategy, it will therefore be important to test more potent and selective compounds.

During the past few years, we have learned that L-DOPA pharmacotherapy affects not only neurons, but also microvascular (43, 125, 126, 141) and glial compartments (43, 117, 167) within the basal ganglia and the midbrain. Findings obtained in rat models of LID have revealed a previously unappreciated plastic potential of basal ganglia microvessels, sparking a new interest in the effects of dopaminergic medications on the neurovascular unit. This topic clearly deserves further investigation. An emerging research is uncovering orchestrated actions of gliovascular cells, immune cells, and neurons in the maladaptive plasticity associated with brain diseases and their treatments (168–171). Investigating the interactions between neuronal and gliovascular compartments is therefore required to fully understand the long-lasting plasticity at the basis of LID. Such an understanding will make it possible to devise new preventive strategies. Ultimately, preventive interventions may represent the best approach to this medical problem because, once established, LID is probably impossible to completely eliminate with add-on pharmacological treatments.

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Serotonin system implication in L-DOPA-induced dyskinesia: from animal models to clinical investigations

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In the recent years, the serotonin system has emerged as a key player in the induction of L-DOPA-induced dyskinesia (LID) in animal models of Parkinson's disease. In fact, serotonin neurons possess the enzymatic machinery able to convert exogenous L-DOPA to dopamine (DA), and mediate its vesicular storage and release. However, serotonin neurons lack a feedback control mechanism able to regulate synaptic DA levels. While in a situation of partial DA depletion spared DA terminals can buffer DA released from serotonin neurons, the progression of DA neuron degeneration impairs this protective mechanism, causing swings in synaptic DA levels and pulsatile stimulation of post-synaptic DA receptors. In line with this view, removal of serotonin neurons by selective toxin, or pharmacological silencing of their activity, produced complete suppression of LID in animal models of Parkinson's disease. In this article, we will revise the experimental evidence pointing to the important role of serotonin neurons in dyskinesia, and we will discuss the clinical implications.

Keywords: serotonin, dopamine, L-DOPA, dyskinesia, 5-HT1 receptor, Parkinson's disease

THE ROLE OF STRIATAL PRE-SYNAPTIC NEURONS IN THE APPEARANCE OF LID

L-DOPA, the precursor of dopamine (DA), represents the most effective drug for alleviating motor symptoms in Parkinson's disease (PD) patients. Its efficacy is due to the ability to restore synaptic DA levels, an effect thought to be mediated by the spared dopaminergic neurons. Indeed, it is known that at the time of diagnosis something between 50 and 70% of nigral DA neurons have already degenerated; the remaining neurons, however, have the ability to take up the exogenous L-DOPA, convert it to DA, store DA into vesicles, and mediate its synaptic release (1, 2). The presence of the DA D2 auto-receptor at the pre-synaptic membrane, which activates a feedback control mechanism able to fine-tune the neurotransmitter release, allows the maintenance of physiological-like synaptic DA levels. Thus, preservation of this mechanism of regulation of DA release in spared DA terminals avoids excessive post-synaptic DA receptor stimulation following chronic L-DOPA administration in PD patients. Unfortunately, the so-called *honeymoon period* does not last forever; in fact, it is estimated that about 40 and 90% of patients suffer for motor fluctuations, known as L-DOPA-induced dyskinesia (LID), within the first 5 and 10 years from diagnosis, respectively. Thus, sooner or later, most of the patients experience a significant worsening of the therapeutic effect of L-DOPA and of their quality of life.

The current view on the risk factors underlying the development of dyskinesias suggests that the progression of the dopaminergic degeneration, rather than the duration of L-DOPA treatment, makes the therapeutic effect to deteriorate over-time (3). Accordingly, it has been shown that delaying the initiation of the L-DOPA administration (using direct DA receptor agonists for the first few years), while postpones the onset of dyskinesia compared to L-DOPA monotherapy, does not reduce the severity of dyskinesia once L-DOPA is introduced (4).

Interestingly, in a positron emission tomography (PET) study, it has been demonstrated that dyskinetic patients present higher synaptic DA levels 1 h after administration of L-DOPA compared to stable responders (5). Thus, dyskinesias appear to be associated to the inability to maintain synaptic DA levels within certain limits, which is likely caused by the progression of DA neuron degeneration and consequent reduced ability to mediate controlled DA release. In fact, in parkinsonian animals, severe dyskinesias develop only in subjects with extensive DA lesion, while partial lesioned animals show either none, or only mild dyskinesias. Elegant support to this view was provided by Ulusoy and collaborators (6); in this study, a significant DA deficiency was induced in rats by viral vector delivery of short hairpin RNA for the tyrosine hydroxylase (TH) enzyme. Interestingly, DA-depleted rats were completely resistant to the induction of dyskinesias following administration of a high dose of L-DOPA (even after being primed with apomorphine), opposite to control animals with similar striatal DA depletion. These results can be explained by the fact that striatal DA terminals were largely preserved after inhibition of DA synthesis, providing a buffering system for the exogenous administered L-DOPA. In this situation, synaptic levels of DA can be maintained within a physiological range by the presence of D2 auto-receptors and DA transporter (DAT) on striatal DA terminals. The ability of the pre-synaptic DA compartment to prevent excessive DA receptor stimulation, even in presence of supersensitive striatal DA receptors, is also confirmed in rat transplantation studies. In fact, L-DOPA-primed dyskinetic rats tend to normalize their response to L-DOPA after receiving ventral mesencephalic DA grafts into the lesioned striatum, which reconstitute the pre-synaptic buffering capacity. The reduction of LID is achieved despite post-synaptic DA receptors remain supersensitive, as shown by the abnormal dyskinetic response of these animals to amphetamine administration (7, 8).

As further support pointing to similar mechanisms underlying the appearance of dyskinesia in patients and animal models, dyskinetic rats have been shown to present higher extracellular DA levels compared to non-dyskinetic animals after administration of L-DOPA, as measured in microdialysis experiments (9, 10), similar to what seen by de la Fuente-Fernandez et al. (5) in dyskinetic patients, in the aforementioned PET-imaging study.

Due to the intermittent oral administration of L-DOPA, synaptic DA peaks are rapidly followed by minimal neurotransmitter levels, resulting in continuous fluctuations of synaptic DA concentration; this determines a pulsatile stimulation of post-synaptic striatal DA receptors which is considered to be the driving force for the induction of post-synaptic alterations at the level of striatal neurons (5, 11).

In agreement with the key detrimental role of synaptic DA swings in the appearance of LID, systems of continuous delivery of dopaminergic drugs, such as the continuous intraduodenal infusion of L-DOPA (known as DuoDopa), are less susceptible of inducing dyskinesias (11, 12). In fact, this treatment strategy is adopted in cases of advanced disease, where motor fluctuations are no longer manageable by modifying the regimen of the oral therapy.

THE SEROTONERGIC SYSTEM IN LID: PRE-CLINICAL EVIDENCE

Although the efficacy of the treatment is partly compromised in advanced stage of disease, as it is in animal models of complete DA denervation, L-DOPA still produces clear motor effects, of which dyskinesias represent an abnormal manifestation; this suggests that other cellular compartments can substitute the lost DA neurons in mediating L-DOPA conversion to DA, and neurotransmitter release. In this context, the serotonergic system has emerged, in recent years, as a key player (1). In fact, serotonin neurons share with the DA ones, the same enzymatic machinery required to convert L-DOPA to DA and mediate vesicular storage, the aromatic amino acid decarboxylase, and monoamine vesicular transporter, respectively. In agreement, early studies have demonstrated the ability of serotonin neurons to store DA after exogenous administration of L-DOPA (13, 14). However, serotonin neurons lack a feedback control mechanism able to fine-tune the synaptic levels of DA. As consequence, L-DOPA-derived DA is released in an uncontrolled manner, leading to excessive synaptic DA peaks, and contributing to swings in synaptic DA levels following oral administration of L-DOPA; this will eventually determine pulsatile stimulation of striatal post-synaptic DA receptors, and changes in signaling cascades at striatal neurons (5, 9, 15–18).

Serotonin neurons are supposed to be involved in the releasing of DA also in early stages of disease; however, such contribution may initially be beneficial due to the presence of the spared DA terminals that can buffer serotonin neuron-derived DA and avoid excessive DA receptor stimulation (1). In support of this view, it has recently been shown that a 30% reduction of striatal L-DOPA-derived DA release is induced upon removal of serotonin nerve fibers in DA neuron-intact rats (19).

Hence, as the DA neuron degeneration progresses, serotonin neurons are expected to contribute more and more to conversion of exogenously administered L-DOPA to DA, eventually producing excessive DA receptor activation. In line with this view, removal of serotonin innervation by 5,7-dihydroxytryptamine (5,7-DHT) administration reduced L-DOPA-derived extracellular DA levels by about 80% in the striatum of complete DA-lesioned rats (20). Most importantly, removal of forebrain serotonin innervation leads to near-complete suppression of LID in L-DOPA-primed parkinsonian rats (15).

The involvement of serotonin neurons in the appearance of LID in animal models has also been demonstrated with a pharmacological approach. In fact, silencing of serotonin neurons can be achieved by targeting the serotonin auto-receptors with selective agonists. Accordingly, several studies have shown a reduction of LID induced by selective 5-HT1 receptor agonists in pre-clinical animal models of PD (15, 16, 21–24). Moreover, co-administration of 5-HT1A and 5-HT1B receptor agonists (8-OHDPAT and CP-94253, respectively) in parkinsonian rats has been demonstrated to produce a synergistic effect on reduction of LID, with complete suppression at doses of the drugs that were ineffective when given individually (15). Most importantly, this result was achieved also in dyskinetic MPTP-treated macaques (24). In line with this hypothesis, reduction of extracellular DA levels was found to account for the potent anti-dyskinetic effect of 5-HT1A and 5-HT1B receptor agonists on LID in a following rat microdialysis study (9).

Interestingly, similar results were also obtained with mixed 5-HT1A/1B receptor agonists, such as eltoprazine and anpirtoline in both rats and macaques, albeit a partial worsening of the therapeutic effect of L-DOPA was seen at effective doses (25, 26). In further support of a pre-synaptic action of 5-HT1A/1B receptor agonists, doses able to fully suppress LID were ineffective against dyskinesia produced by the DA direct agonist apomorphine (26, 27). This is relevant as 5-HT1A and 5-HT1B receptors are also located post-synaptically, and their activation has been shown to reduce striatal glutamate and GABA release, respectively (28, 29), which is known to produce anti-dyskinetic effects; indeed, higher doses of these compounds have been demonstrated to also reduce dyskinesia induced by apomorphine (23).

The involvement of the serotonin neurons in the appearance of LID has also been demonstrated in a rat PET-imaging study; in fact, Nahimi and co-workers have shown that administration of 8-OH-DPAT could reverse L-DOPA-induced decrease of [(11) C]raclopride binding and increase of extracellular DA in 6-OHDA-lesioned rats (30).

The interaction between L-DOPA and serotonin neurons has been shown in another recent study, where administration of the serotonin immediate precursor 5-hydroxy-tryptophan (5-HTP) has produced anti-dyskinetic effect in parkinsonian rats; this effect has been demonstrated to be partly mediated by activation of serotonin auto-receptors and partly by displacement of DA from serotonergic vesicles produced by the exogenous 5-HTP-derived serotonin (31).

Even more striking results were obtained using selective serotonin reuptake inhibitors (SSRIs), such as citalopram or fluoxetine (32, 33), which are known to exert their anti-depressant effect by increasing synaptic serotonin levels. In these studies, the authors observed complete suppression of LID at relatively low doses of drugs, while a 5-HT1 receptor antagonist appeared to counteract this effect, suggesting that increased activation of

serotonin auto-receptors is involved in the mechanisms of the anti-dyskinetic effect of SSRIs in parkinsonian rats.

It should be noted that SSRIs and 5-HTP were found to produce clear anti-dyskinetic effect without compromising the therapeutic efficacy of L-DOPA in specific motor tasks. This is highly relevant as it may suggest that worsening of the efficacy of L-DOPA seen with selective 5-HT1 receptor agonists in parkinsonian rats may be due to a transient reduction of the serotonergic tone. In fact, selective 5-HT1 receptor agonists are expected to reduce both DA and serotonin release from serotonin neurons; by contrast, 5-HTP and SSRIs are likely to reduce DA release without dampening synaptic serotonin levels. This is mostly important when thinking that many advanced PD patients also suffer for symptoms of depression, and administration of selective 5-HT1 receptor agonists may exacerbate this complication.

It should be noted that dampening of serotonin neuron release by 5-HT1 receptor agonists did not only reduce LID, but it has also been shown to prevent induction of post-synaptic alterations at striatal neurons, such as increased expression of FosB and altered synaptic NMDA receptor subunits distribution (24). This confirms that false transmitter release of DA from serotonin neurons plays a key role in driving the maladaptive alterations that associate with dyskinesia.

THE SEROTONERGIC SYSTEM IN LID: CLINICAL EVIDENCE

Whereas an overwhelming body of evidence proves a major role of the serotonergic system in the appearance of LID in animal model, clinical evidence are still scarce.

A large clinical study was conducted in the past years to investigate the efficacy sarizotan, a partial 5-HT1A receptor agonist, in dyskinetic patients. Despite the promising results obtained in pre-clinical experiments, and in an open-label study, the double-blind investigation was terminated for lack of efficacy (34, 35). While disappointing, these results may be due to the fact that sarizotan also exerts antagonistic activity at the level of the D2 receptor (36). Moreover, it should be noted that sarizotan acts only on the 5-HT1A receptor, while experimental evidence demonstrated that a potent synergistic effect on suppression of LID is obtained by simultaneous targeting of the 5-HT1A and 5-HT1B auto-receptors (24, 26). Indeed, the mixed 5-HT1A/1B receptor agonist eltoprazine, which we recently proved to be highly potent on suppression of LID in animal models, is currently under clinical investigation in a small group of dyskinetic patients, with encouraging preliminary results (see http://www.psychogenics.com/press2012.html).

Although it does not provide direct evidence for the involvement of the serotonin system in LID, the results of the PET-imaging study performed by de la Fuente-Fernandez et al. (5), support the concept that dyskinesia is associated to dysregualted DA release; in fact, in this study, dyskinetic patient showed higher synaptic DA levels 1 h after L-DOPA administration compared to stable responders.

In the same line, a key study has recently been performed by Politis and co-workers (37). First, these authors showed that PD patients with LID had relative preservation of serotonergic terminals compared to patients with stable response to L-DOPA, which correlated with the severity of LID, in agreement with a previous post-mortem investigation (38). Moreover, in patients with LID the same L-DOPA dose induced significant higher striatal synaptic DA levels than in non-dyskinetic patients, as already seen by de la Fuente-Fernandez et al (5). Most importantly, the partial 5-HT1A receptor agonist buspirone, administered orally 15 min before L-DOPA, significantly reduced the L-DOPA-evoked rises in striatal synaptic DA release and attenuated LID (37). Whereas a previous report has shown a partial reduction of LID following buspirone administration (39), the study of Politis and colleagues provides the first direct evidence that such reduction is linked to decreased synaptic DA levels.

Whereas these results are extremely encouraging, a major concern that emerged from animal studies is the preservation of the L-DOPA therapeutic effect following dampening of serotonin neurons activity. Thus, larger clinical studies should be performed to address whether the therapeutic window is sufficient to take full advantage from this approach to counteract LID in parkinsonian patients, or to identify the subset of patients that are more likely to benefit from 5-HT1 receptor agonists.

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Pharmacological treatments inhibiting levodopa-induced dyskinesias in MPTP-lesioned monkeys: brain glutamate biochemical correlates

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Anti-glutamatergic drugs can relieve Parkinson's disease (PD) symptoms and decrease l-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias (LID). This review reports relevant studies investigating glutamate receptor subtypes in relation to motor complications in PD patients and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys. Antagonists of the ionotropic glutamate receptors, such as *N*-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, display antidyskinetic activity in PD patients and animal models such as the MPTP monkey. Metabotropic glutamate 5 (mGlu5) receptor antagonists were shown to reduce the severity of LID in PD patients as well as in already dyskinetic non-human primates and to prevent the development of LID in *de novo* treatments in non-human primates. An increase in striatal post-synaptic NMDA, AMPA, and mGlu5 receptors is documented in PD patients and MPTP monkeys with LID. This increase can be prevented in MPTP monkeys with the addition of a specific glutamate receptor antagonist to the L-DOPA treatment and also with drugs of various pharmacological specificities suggesting multiple receptor interactions. This is yet to be well documented for presynaptic mGlu4 and mGlu2/3 and offers additional new promising avenues.

Keywords: Parkinson's disease, L-DOPA-induced dyskinesia, motor complications, glutamate receptor, basal ganglia, direct pathway, indirect pathway, receptor interaction

INTRODUCTION

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is likely to increase due to the aging population (1). PD is principally attributed to the death of dopamine (DA) neurons in the substantia nigra, but other neurotransmitters, such as glutamate, are also affected (2). There is no cure for PD but symptomatic treatments are available (3). Restoring lost DA with its precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), remains the most effective treatment (4). However, many patients (≥40%) develop motor complications after 5–10 years of treatment (5). These motor complications include motor fluctuations and abnormal involuntary movements, such as L-DOPA-induced dyskinesias (LID), and contribute to limit the quality of life in PD patients and can be very difficult to manage (6). Motor fluctuations such as "wearing-off" are also common. Wearing-off is defined as a reduced duration of benefit from an individual L-DOPA dose and a recurrence of parkinsonian symptoms before the next normal dose of L-DOPA (7).

No drug is yet available for LID, aside from some benefit with amantadine that has anti-glutamatergic properties (8). Glutamatergic transmission is increased in the basal ganglia in PD (9) and is also believed to be involved in LID (10, 11).

The mechanisms involved in the occurrence of LID are still not fully understood, altered dopaminergic and non-dopaminergic neurotransmission in the basal ganglia are observed in LID (12). A recent strategy is to treat LID with adjunct drugs targeting non-dopaminergic neurotransmitter systems such as glutamate to indirectly modulate basal ganglia DA neurotransmission (13).

Glutamate is involved in many physiological functions through its interactions with ionotropic glutamate (iGlu), ligand-gated channel, and metabotropic G-protein-coupled glutamate (mGlu) receptors. iGlu receptors drugs suppressing glutamate excitatory transmission often create undesirable side effects (14), whereas acting on mGlu receptors could lead to a more subtle and/or circuit-selective modulation of excitatory transmission (15). Pharmacologic characterization of metabotropic glutamate 5 (mGlu5)

Abbreviations: 6-OHDA, 6-hydroxydopamine; Akt, protein kinase B; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cAMP, cyclic adenosine monophosphate; DA, dopamine; DARPP-32, DA and cAMP-regulated phosphoprotein with molecular weight 32; DHA, docosahexaenoic acid; ERK, extracellular-signal-regulated kinase; GABA, γ-aminobutyric acid; GSK3, glycogen synthase kinase-3; GP, globus pallidus; GPe, external globus pallidus; GPi, internal globus pallidus; iGlu, ionotropic glutamate; KA, kainate; L-DOPA, levodopa (L-3,4-dihydroxyphenylalanine); LID, L-DOPA-induced dyskinesias; MAPK, mitogen-activated protein kinase; mavoglurant, AFQ056; mGlu, metabotropic glutamate; MPEP, 2-methyl-6-(phenylethynyl)pyridine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MTEP, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; mTor, mammalian target of rapamycin; NAM, negative allosteric modulator; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PP-1, protein phosphatase-1; STN, subthalamic nucleus; Wnt, wingless/integrated-signaling.

receptors and its selective negative allosteric modulators (NAMs) show therapeutic potential in animal models of PD (16–18) and efficacy in human PD (19, 20). While mGlu5 receptors regulate L-DOPA-induced motor behavior, the mechanisms involved remains to be fully elucidated (21).

This review focuses on relevant studies investigating glutamate receptor subtypes in the pathophysiology of PD and LID. Brain biochemical correlates of motor complications in PD patients and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys are reviewed.

GLUTAMATE NEUROTRANSMISSION IN THE BASAL GANGLIA AND PARKINSON'S DISEASE

Glutamate is the brain's most abundant excitatory neurotransmitter mediating as much as 70% of synaptic transmission (22). Amantadine reduces LID, it also improves akinesia, rigidity, and tremor (3). The non-selective inhibitor of glutamate transmission (riluzole) was shown to block L-DOPA-induced motor complications in 6-hydroxydopamine (6-OHDA) lesioned rat model of PD (23, 24) and the glial glutamate transporter GLT1 is increased in dyskinetic L-DOPA-treated 6-OHDA rats (25, 26). However, riluzole was not effective in humans to relieve LID (27, 28).

LEVODOPA-INDUCED DYSKINESIAS AND NON-HUMAN PRIMATE MODEL

L-DOPA-induced dyskinesias are abnormal involuntary movements seen typically at the peak effect of each dose of L-DOPA in PD patients (3). LID can be viewed quantitatively as an excess of movement or qualitatively as a problem in selecting the appropriate motor program or pattern (3). The mechanisms involved in the occurrence of LID are complex and have been investigated in numerous studies using animal models and parkinsonian patients (29). The loss of nigrostriatal DA and the chronic administration of L-DOPA, or DA agonists, are two necessary conditions for their appearance (30). The development of LID in human usually requires daily treatment for 3–5 years in idiopathic PD (31), whereas for parkinsonism induced by the toxin MPTP it occurs after only weeks or months of treatment (32). The same applies to the MPTP-lesioned monkey where L-DOPA is usually administered daily for weeks before LID appear (33, 34). MPTP-lesioned primates respond to DA therapies as idiopathic PD patients (35, 36) and are currently the best model for studying LID (37).

MPTP-lesioned primates are very useful to test potential anti-dyskinetic and/or anti-parkinsonian pharmacological agents (37). The primates are rendered parkinsonian and then chronically treated with L-DOPA for several weeks or months until they express stable and well-established LID. Then, acute or chronic effects of compounds are tested when co-administered with L-DOPA (17, 18, 38, 39). This model is widely used since it allows rapid testing of new compounds and animals may be used for several studies. This paradigm is useful to find new treatments for advanced parkinsonian patients with already established LID (37).

Another paradigm uses *de novo* animals rendered parkinsonian with MPTP and then treated with L-DOPA alone or in combination with the agent under investigation (37). This latter paradigm allows the study of specific effects of the test compound on the development of LID and to assess if the effects diminish with long-term use, also called "wearing-off" (40–44). Furthermore, it allows to investigate the post-mortem brains of these monkeys the mechanisms associated with the behaviors and relate it to the specific treatments (42, 44–47). This experiment models newly diagnosed parkinsonian patients when L-DOPA treatment is initiated and could be used to test adjunct drugs to L-DOPA to avoid development of LID while having a good anti-parkinsonian effect (37). Docosahexaenoic acid (DHA) and cabergoline were shown to reduce the severity or delay the development of LID in MPTP-lesioned monkey (41, 48).

IONOTROPIC GLUTAMATE RECEPTORS AND LEVODOPA-INDUCED DYSKINESIAS

Ionotropic glutamate receptors mediate fast excitatory neurotransmission, whereas mGlu receptors mediate slower modulatory neurotransmission. iGlu receptors are classified into *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate (KA) receptors (49). An increase in striatal NMDA and AMPA receptor binding levels in PD patients with L-DOPA-induced motor complications (11) and dyskinetic MPTP monkeys was observed (50, 51). Moreover, NMDA and AMPA receptor antagonists block the development of L-DOPA-induced motor complications in 6-OHDA rats (23). The NMDA antagonist, CI-1041 can prevent the development of LID in parkinsonian monkeys (40), and associated brain molecular changes (52). In these monkeys, CI-1041 also prevented the increased of striatal mGlu5 receptor levels (53). Clinical trials show the antidyskinetic profile of amantadine, known to block NMDA receptors (8, 54, 55). Kynurenic acid antagonizes glycine b site of NMDA receptors, AMPA, and KA receptors (56, 57) and inhibits glutamate release (58). RO 61-8048, an inhibitor of kynurenine hydroxylase activity, can increase kynurenic acid levels (59); it acutely reduced dyskinesias in MPTP monkeys with LID (60) and reduced their development in *de novo* treated MPTP monkeys (61). Abundant recent literature focused on the role of NMDA and AMPA receptor subunits in rodent and non-human primate models of PD in LID including the glycine site, NMDA GluN2D subunits, AMPA receptor subunit composition, and NMDA/AMPA receptor ratio (49, 62–66). Nevertheless, iGlu receptors can cause significant adverse effects such as cognitive impairment in many patients (67, 68).

METABOTROPIC GLUTAMATE RECEPTORS AND LEVODOPA-INDUCED DYSKINESIAS

Metabotropic glutamate receptors are divided into Group I (mGlu1, 5) coupling to Gq and promoting polyphosphoinositide hydrolysis, Group II (mGlu2, 3) and III (mGlu4, 6, 7, 8) coupling to Gi/Go and inhibiting Forskolin-induced increase in cyclic adenosine monophosphate (cAMP) (69). All mGlu receptors are present in the brain basal ganglia except mGlu6 receptor found primarily in the retina (70). The majority (>90%) of Group I mGlu receptor, including mGlu5, are located postsynaptically on the perisynaptic annulus of dendritic spines (71). Presynaptically localized Group II and Group III mGlu receptors are thought to represent the classical inhibitory autoreceptor mechanism suppressing excess glutamate release from presynaptic terminals (72).

The prototypal mGlu5 receptor antagonist, 2-methyl-6-(phenylethynyl)pyridine (MPEP) and a more selective analog 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) (73) improve motor performance (74) and show antidyskinetic activity in 6-OHDA rats (75, 76), but not the other Group I mGlu receptor, such as mGlu1 receptor drugs (77, 78). mGlu5 receptor levels were increased in the putamen of dyskinetic compared to non-dyskinetic MPTP monkeys (42) and parkinsonian patients with motor complications (LID or wearing-off) compared to those without motor complications (53). MPEP and MTEP were shown to have antidyskinetic activity in MPTP monkeys (17) and the mGlu5 receptor antagonist mavoglurant (AFQ056) in MPTP monkeys (18) and humans (19). We reported that development of LID over a month of treatment were lower by overall ~70% with addition of MPEP to the L-DOPA treatment in *de novo* MPTP monkeys (44) and this was associated with a normalization of glutamate (46) and DA neurotransmission (47). Similarly, chronic administration of fenobam to drug-naïve monkeys attenuated the development of dyskinesia without compromising the anti-parkinsonian effect of L-DOPA (43).

Group II mGlu receptor agonists have proven effective in animal models of PD (79). A decrease in mGlu2/3 receptor density in dyskinetic compared to non-dyskinetic MPTP-lesioned monkeys was observed (46). In post-mortem brains of parkinsonian patients, changes in mGlu2/3 receptors were only observed in relation to wearing-off (80).

Recently, agonists of Group III receptors have shown robust efficacy in rodent models of PD (70). mGlu4 receptor agonists reduce γ-aminobutyric acid (GABA)ergic transmission at striatopallidal synapse that is overactive in PD (81, 82). In 6-OHDA-lesioned rats, a combined treatment with L-DOPA and the mGlu4 receptor agonist Lu AF21934 reduced the effective dose of L-DOPA and minimizing the development of LID (83).

Metabotropic glutamate 8 receptor is expressed at lower levels than mGlu4 and mGlu7 receptors but widely distributed in the brain; mGlu7 receptor has low affinity for glutamate only becoming active when glutamate levels are high thus serving as a brake for glutamate overstimulation (70). AMN082, an mGlu7 receptor agonist, was shown to reverse motor dysfunction associated with reduced DA activity in rodent models (84). However, the contribution of mGlu7 and mGlu8 receptors in LID is not yet reported.

DISCUSSION

Denervation-induced supersensitivity of DA receptors is generally recognized as a plausible mechanism of LID. Post-mortem studies have shown that DA receptors, particularly D2 subtype, are increased in the striatum of parkinsonian patients (85–87) as well as D1 and D2 receptors in MPTP monkeys (33, 34, 88, 89). However, treatment with L-DOPA can reverse this increase in humans (85, 87) and monkeys (34, 88, 90). LID are clearly more complex than hypersensitivity due to a simple increase in the density of striatal DA receptors (30), hence changes are sought in signaling pathways activated by DA receptors. Various adjunct drugs that can modulate basal ganglia dopaminergic neurotransmission have been shown to treat LID (13, 67, 91–94). Glutamate receptors are reported to interact with numerous neurotransmitters and neuromodulators implicated in the development of LID including dopaminergic neurotransmission (22, 47). Hence, close interactions are described between mGlu5 and NMDA receptors, mGlu5 with D2 receptors, and adenosine A2A receptors (39, 46, 47, 95, 96). **Figure 1** shows interactions of striatal DA, adenosine, glutamate and opioids in GABAergic neurons and possible sequence of events leading to LID.

Dopamine receptors are associated with regulation of cAMP–protein kinase A (PKA) through G-protein mediated signaling (97). Downstream from PKA, DA, and cAMP-regulated phosphoprotein with molecular weight 32 (DARPP-32) has important functions in regulating DA receptor signaling and its integration with other signaling modalities (98). Extracellular-signal-regulated-kinase (ERK) is also an important mediator of cAMP signaling involved in responses to DA drugs and might be involved in the development of LID (99–101). Rats with abnormal involuntary movements have abnormally high levels of striatal phospho[Thr34]-DARPP-32 (102). DA receptors also exert their effect through protein kinase B (Akt) and glycogen synthase kinase-3 (GSK3) signaling (97) that might serve to integrate signaling of different receptors such as glutamate. Akt can phosphorylate GSK3β at Ser9 [pGSK3β(Ser9)] and inactivate it (103). GSK3 is a juncture of at least three pathways, mitogen-activated protein kinase (MAPK) (104), phosphoinositide 3-kinase (PI3K) (105), and wingless/integrated-signaling (Wnt) (106). Prolonged stimulation of D2 DA receptors in rodents leads to specific dephosphorylation/inactivation of striatal Akt on Thr308 residue [pAkt(Thr308)], Ser473 [pAkt(Ser473)], remaining unaffected (107). Another downstream protein is mammalian target of rapamycin (mTor) recently reported to be implicated in LID (108).

D1 receptor supersensitive response was shown to result from a switch from normal activation of the PKA cascade to aberrant activation of ERK1/2–MAP kinase in lesioned striata and is suggested to underlie LID (109). Interestingly, in a chronic *de novo* treatment with non-human primates, we observed increases in both striatal pERK1/ERK1 and pERK2/ERK2 ratios of L-DOPA-treated MPTP monkeys whereas MPEP prevented this increase (47). Moreover, there were positive correlations between mean dyskinetic scores and striatal pERK1/ERK1 and pERK2/ERK2 ratios (47). These results suggest that antagonists of mGlu5 receptor can potentially inhibit the excessive striatal activation of nuclear signaling pathways and gene expression that is produced by L-DOPA, which might be related to the interaction with DA receptors.

An association between Akt1 gene and PD was also shown (110). In post-mortem substantia nigra, a large reduction of pAkt(Thr308) and pAkt(Ser473) in PD patients was observed compared to controls (111). L-DOPA-treated MPTP monkeys with LID show elevated pAkt(Ser473) and pGSK3β(Ser9) whereas MPTP monkeys treated with L-DOPA + cabergoline with no LID have lower values (112). In MPTP-lesioned monkeys treated with L-DOPA + CI-1041 that did not develop LID, changes in Akt and GSK3 were modest suggesting implication of other pathways, such as ERK. As in the substantia nigra of parkinsonian patients (111), we observe decreases of striatal pAkt with the MPTP lesion in monkeys (112) whereas in 6-OHDA rats, the lesion did not change or increased phosphorylation of Akt (Ser473 and Thr308) (113). In 6-OHDA rats, pGSK3α and pGSK3β were also unchanged or increased with the lesion (113) while we

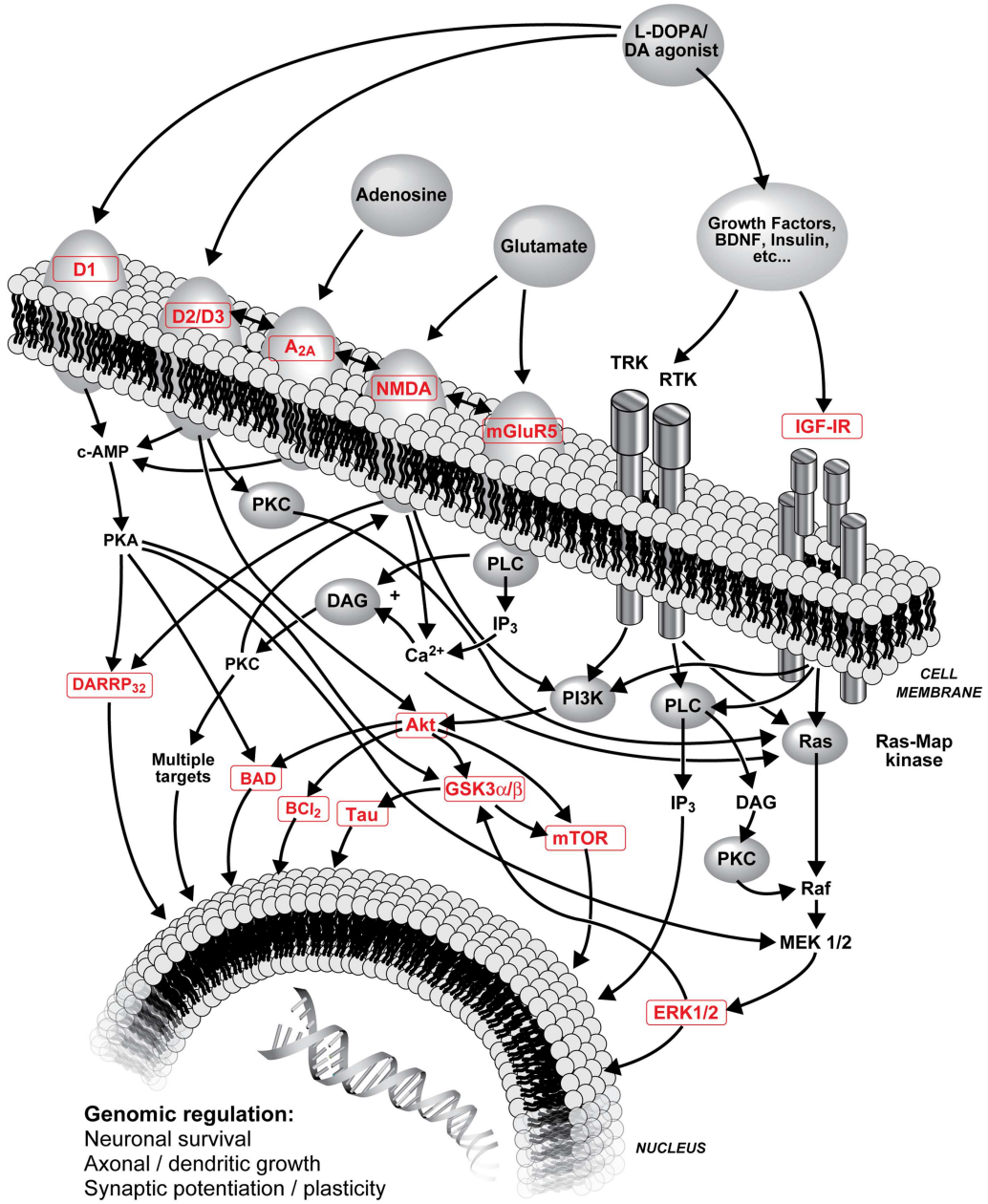

FIGURE 1 | Schematic representation of L-DOPA (metabolized into DA) and DA agonist treatments on striatal DA neurotransmission, interactions of striatal DA, adenosine, glutamate, and opioids in GABAergic neurons and possible sequence of events leading to LID. Numerous interactions are known and are not all included; the focus of this figure is on PI3K and MAPK pathways. A_{2A}, adenosine A2A receptor; Akt, protein kinase B; BAD, Bcl-2-associated death promoter; Bcl-2, B-cell lymphoma 2; Ca^{2+}, calcium ion; cAMP, cyclic adenosine monophosphate; D1/D2/D3, D1/D2/D3 DA receptor; DA, dopamine; DARPP-32, DA and cAMP-regulated phosphoprotein with molecular weight 32; DAG, diacylglycerol; ERK, extracellular-signal-regulated kinase; GSK3, glycogen synthase kinase-3; IGF-IR, type 1 insulin-like growth factor receptor; IP_3, inositol 1,4,5-trisphosphate; L-DOPA, levodopa (L-3,4-dihydroxyphenylalanine); MEK, mitogen-activated protein kinase; mGlu5, metabotropic glutamate type 5 receptor; mTor, mammalian target of rapamycin; NMDA, *N*-methyl-d-aspartate receptor; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; Ras, proto-oncogene protein p21; Raf, proto-oncogene serine/threonine-protein kinase; RTK, receptor tyrosine kinases; Tau, microtubule-associated protein tau; TRK, tropomyosin receptor kinase.

observed no change or decreases in MPTP monkeys (112). However, both in MPTP-lesioned monkeys (112) and in 6-OHDA rats (113), L-DOPA increased pAkt and pGSK3. Moreover, increase in pAkt(Ser473)/Akt and pGSK3β(Ser9)/GSK3β ratios was observed in the L-DOPA-treated MPTP group, this was prevented with the addition of MPEP and positive correlations were observed between

these levels and mean dyskinesia scores (47). This supports a possible involvement of Akt/GSK3β in the mechanisms associated with the development of LID. MPEP might prevent changes in this kinase pathway associated with L-DOPA and could provide new avenues to probe potential novel targets to treat LID.

This mini review focused on glutamate neurotransmission in LID and presented some of its interaction with other neurotransmitter systems showing the complexity of this motor complication and its treatment. Indeed, altered dopaminergic and non-dopaminergic neurotransmission, including also serotonergic, adenosine, cannabinoid, opioid, GABAergic, adrenergic, histaminergic, and cholinergic systems are observed in LID (12, 51). For example, serotoninergic dysfunctions in LID are well documented (114, 115) and serotonin neurotransmission can interact with iGlu (116–118) and mGlu receptors (119).

CONCLUSION

Nigrostriatal denervation in PD leads to increased glutamatergic transmission in the basal ganglia; increased glutamate neurotransmission is also observed in LID. These observations suggest that glutamate receptor stimulation is involved in the pathogenesis of L-DOPA-induced motor complications in PD and glutamate receptor subtypes, such as mGlu5 and NMDA receptors, are potential selective targets for treatment of these adverse effects. Recent studies point to changes in activation of DA receptor signaling in LID rather than changes in DA receptor density. Post-mortem brains of dyskinetic MPTP-lesioned monkeys and PD patients treated with anti-glutamatergic drugs and inhibiting LID show multiple brain molecular changes suggesting various receptors interactions. Thus, ionotropic and metabotropic glutamate receptors represent interesting targets to reduce and prevent LID as well as to prevent associated molecular changes beyond their specific receptor target.

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