



# From the Gut to the Brain and Back: Therapeutic Approaches for the Treatment of Network Dysfunction in Parkinson's Disease

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Parkinson's disease (PD) is a complex, multisystem, progressive, degenerative disorder characterized by severe, debilitating motor dysfunction, cognitive impairments, and mood disorders. Although preclinical research has traditionally focused on the motor deficits resulting from the loss of nigrostriatal dopaminergic neurons, up to two thirds of PD patients present separate and distinct behavioral changes. Loss of basal forebrain cholinergic neurons occurs as early as the loss of dopaminergic cells and contributes to the cognitive decline in PD. In addition, attentional deficits can limit posture control and movement efficacy caused by dopaminergic cell loss. Complicating the picture further is intracellular  $\alpha$ -synuclein accumulation beginning in the enteric nervous system and diffusing to the substantia nigra through the dorsal motor neurons of the vagus nerve. It seems that  $\alpha$ -synuclein's role is that of mediating dopamine synthesis, storage, and release, and its function has not been completely understood. Treating a complex, multistage network disorder, such as PD, likely requires a multipronged approach. Here, we describe a few approaches that could be used alone or perhaps in combination to achieve a greater mosaic of behavioral benefit. These include (1) using encapsulated, genetically modified cells as delivery vehicles for administering neuroprotective trophic factors, such as GDNF, in a direct and sustained means to the brain; (2) immunotherapeutic interventions, such as vaccination or the use of monoclonal antibodies against aggregated, pathological  $\alpha$ -synuclein; (3) the continuous infusion of levodopa-carbidopa through an intestinal gel pad to attenuate the loss of dopaminergic function and manage the motor and non-motor complications in PD patients; and (4) specific rehabilitation treatment programs for drug-refractory motor complications.

**Keywords:** Parkinson's disease, enteric nervous system, dopamine, acetylcholine, postural abnormalities, GDNF

## INTRODUCTION

Mammalian brain activities, from executive and motor functioning to memory and emotional responses, are strictly regulated by the integrity of subcortical projections. Among the subcortical structures, the dopaminergic nigrostriatal pathway and the cholinergic innervations from the basal forebrain play pivotal roles in orchestrating motor and cognitive performance under normal circumstances and in degenerative neurological diseases (1, 2). Research using animal models of Parkinson's disease (PD) has typically focused on the

motor deficits resulting from extensive loss of nigrostriatal dopaminergic neurons and on the modeling and treatment of levodopa-induced dyskinesia (3–7). However, up to two thirds of PD patients suffer from a range of non-motor symptoms, including cognitive impairments and mood disorders. Loss of basal forebrain cholinergic neurons occurs as early as the loss of midbrain dopaminergic neurons and likely contributes to the cognitive deficits in PD (8, 9). PD patients also suffer from a propensity for falls, freezing of gait, and associated impairments in posture control and movement efficacy (10) that are not treatable with L-DOPA. These patients have a greater reduction of cortical cholinergic activity relative to PD non-fallers and control subjects (8, 11). Preclinical studies confirm that dual loss in cholinergic and striatal dopamine afferents disrupts posture control and movement efficacy in conditions requiring attention control (12).

In addition to these subcortical changes, increasing evidence suggests that PD pathology can arise in the gut. Clinically, gastrointestinal symptoms often appear in patients before other neurological signs and aggregates of  $\alpha$ -synuclein ( $\alpha$ -syn) have been found in the enteric nerves of PD patients. The mechanisms through which the disease spreads remain unclear, but it is believed to start in the gut and then move retrogradely to the brain via the vagal nerve or begin in the vagal dorsal motor nucleus and move to the gut in an anterograde way (13–15).

Finally, clinical evaluations found rehabilitation strategies, such as a promising non-drug-based approach able to influence the progression of PD lasting long after the program break, therefore suggesting the involvement of the anatomical substrate accompanying the disease (16, 17).

These findings further strain the urge to explore the plastic changes occurring at multiple levels, including cortical and subcortical areas, spinal cord, nerve trunks, and muscles. Understanding the contribution of central and peripheral anatomical rearrangements to the symptoms and recovery could lead to the development of rehabilitation strategies able to counteract the maladaptive changes induced by the disease, ultimately improving patients' quality of life (Figure 1).

## STRIATAL MICROCIRCUIT ALTERATIONS AND BEHAVIORAL OUTCOMES

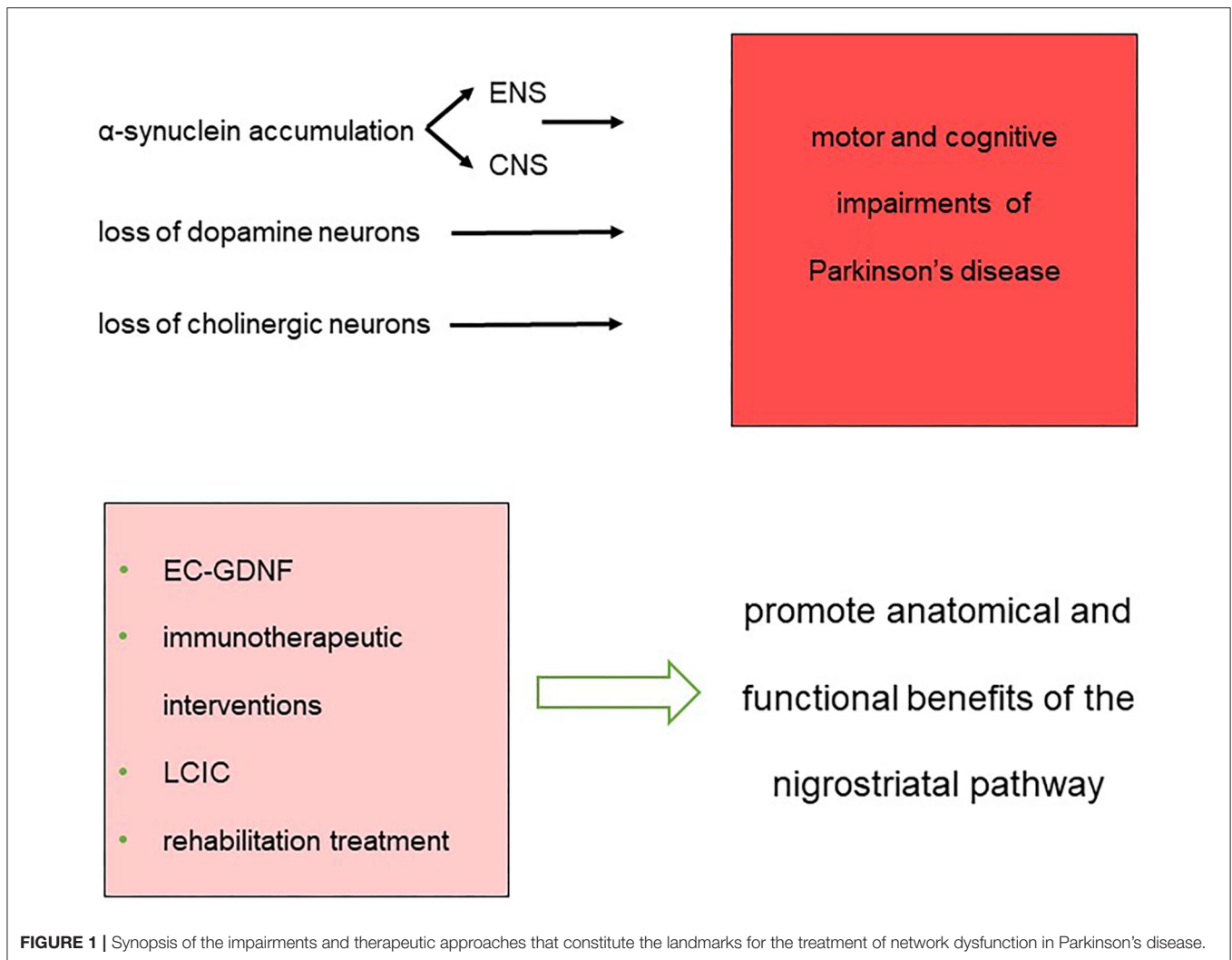
The hallmark of PD is the degeneration of dopaminergic neurons in the substantia nigra *pars compacta* (SNpc) and subsequent reduction of striatal projections. The striatum is a primary nucleus of the basal ganglia involved in motor control, goal-directed action, habit learning, and reward-related processes (18–20). It consists of projection neurons with medium spiny neurons (MSNs) representing 90–95% of the local interneuron population (INs). Among them, cholinergic interneurons (ChINs) represent only 1–2% of the population but play a crucial role in sensory integration and movement control. The lessening of dopaminergic striatal innervation leads to a reduction in inhibition of the tonically active ChINs, significantly altering the local microcircuit and contributing to the major motor symptoms of PD. ChINs express both D1 and

D2 dopaminergic receptors. Activation of D1 receptors induces glutamate co-release and facilitates acetylcholine (ACh) activity (21, 22) while D2 receptor stimulation decreases ChIN activity by sodium current modulation (23, 24). In a reciprocal role, ACh powerfully modulates DA release from terminals originating in the SNpc via nicotinic ACh receptors (nAChRs) on DA axons (25–28). The activation of muscarinic ACh receptors M2 and M4 that are expressed on somatodendritic and axonal sites exert a more complex action on DA release and related motor and reward-related behaviors (29, 30). Although ChINs have traditionally been considered the principle source of striatal cholinergic innervation (31, 32), additional inputs arising from the pedunculo pontine nucleus (PPN) and laterodorsal tegmental nucleus (LDT) have also been identified (33). Although low in numbers, these ChINs play important roles in controlling motor behavior, and prior to the use of L-DOPA, anticholinergic drugs were used to control motor symptoms (34). Of note, Lozovaya et al. (35, 36) report that a subpopulation of striatal ChINs also co-release GABA. Decreased dopaminergic innervation appears to lead to the failure of the GABAergic function in these dual cholinergic/GABAergic cells augmenting the circuits' cholinergic excitatory component.

Post-mortem human brain histology demonstrates that, when the motor symptoms of PD manifest, ~70% of the SNpc DA cells have degenerated (37) together with a marked loss of choline acetyltransferase (ChAT) expressing neurons in the nucleus basalis of Meynert and pedunculopontine nucleus (PPT) and reduced cortical and striatal cholinergic activity (38). Accordingly, a dual-syndrome hypothesis has emerged in which dopaminergic denervation leads to executive/motor function impairments while cholinergic decline underlies learning and attentional goal-driven deficits and poor performance on cognitive neuropsychological tasks (39, 40). Imbalances in striatal activity of these neurotransmitters may impair the normal induction of synaptic plasticity, altering the processing of routine daily experiences and leading to a plethora of cognitive impairments (41). These observations suggest that, rather than having opposite roles, a cooperative, functional interaction occurs between ACh and DA, and therapies targeting both systems may be effective (42, 43).

## THE GUT-BRAIN CONNECTION

The accumulation of intracellular  $\alpha$ -syn is among the major pathological changes associated with neuronal degeneration in PD, including those in the SN and cholinergic cells of the dorsal motor nucleus of the vagus (DMV).  $\alpha$ -syn is a 140 amino acid protein that, when misfolded, has the ability to spread from cell to cell in a prion-like manner, leading to an accumulation of  $\alpha$ -syn aggregates and formation of oligomers that can progress to fibrils and eventually Lewy bodies. Intracellular accumulation of  $\alpha$ -syn likely mediates changes in dopamine synthesis, storage, and release in both the central and enteric nervous systems [C-ENS (44)]. Research into the role of  $\alpha$ -syn in PD suggests that several early stage, non-motor symptoms of PD may not originate in the SN.  $\alpha$ -syn



aggregations evolve in nerve cells of the ENS (13, 14, 45, 46). Shortly thereafter,  $\alpha$ -syn deposition seems to involve the anterior olfactory nucleus and the dorsal motor nucleus of the vagal nerve [medulla oblongata (47–51)]. This deposition progresses to affect additional nuclei of the brainstem, the mid and forebrain, and eventually cortical regions. Anatomical studies have identified lesions in the ENS in both non-symptomatic and clinically diagnosed and neuropathologically confirmed cases (45, 52), making the exact role of gut pathology on brain DA denervation unclear. Improvements in techniques that reliably discriminate misfolded, aggregated  $\alpha$ -syn from physiological  $\alpha$ -syn help clarify the role of this marker for prodromal PD (53).

Brain–gut connectivity and interplay is actually quite deep-rooted in medical history. In 1850, Sydney Whiting (54) in his *Memoirs of a Stomach* wrote, “...and between myself and that individual Mr. Brain, there was established a double set of electrical wires, by which means I could, with the greatest ease and rapidity, tell him all the occurrences of the day as they arrived, and he also could impart to me his own

feelings and impressions.” More recently, Kaelberer et al. (55) report that enteroendocrine cells synapse with the vagus and rapidly transduce gut stimulus signals through glutamatergic neurotransmission. Moreover, catecholamines modulate GI motility by controlling ACh release from motor neurons (56) while the number of DA-positive cells in the meyerteric plexus of patients has been reported to be more than 10 times smaller than in control subjects (57).

## THERAPEUTIC STRATEGIES FOR THE TREATMENT OF PD

Pharmacotherapy with L-DOPA remains a mainstay treatment for PD even though its effectiveness wanes with time. Its use is logically based on the observations of dopaminergic cell loss in patients, but our developing understanding of the multicomponent circuits in PD suggests that multiple treatment avenues might lead to more optimal and longer-lasting efficacy. Some of these avenues are discussed below.

## Neurotrophic Factor Therapy

Delivering trophic factors, such as glial cell line-derived neurotrophic factor (GDNF) to the brain is a potential treatment for PD (58). Although not definitive yet, GDNF may slow or perhaps even reverse the loss of dopaminergic function in PD patients (59, 60). Preclinically, the benefits of GDNF are clear as it prevents the loss of nigral neurons and abnormal motor function that occurs following 6-hydroxydopamine (6-OHDA) lesions in rats (61, 62) and MPTP-lesioned monkeys (63, 64). Direct delivery to the brain is needed for GDNF to be effective, and several approaches are underway to achieve this goal. We have focused on one approach based on implanting GDNF-secreting cells, housed in an immunoprotective membrane, into the brain (65). This approach achieves the goals of selective and long-term delivery to the nigrostriatal system, providing a targeted, continuous, *de novo* synthesized source of high levels of GDNF (66–72). For instance, we recently reported sustained, stable, and selective delivery of high levels of GDNF to the rat striatum implanted with human clonal ARPE-19 cells encapsulated into hollow fiber membranes. Long-term efficacy was evidenced by robust neuroprotection of dopaminergic neurons in the SN and fibers in the striatum in 6-OHDA lesioned rats. In the longest duration studies, GDNF implants produced a significant improvement in motor performance that persisted for over 1 year [62 weeks (73)]. Similarly, impressive distribution of GDNF and positive effects on dopaminergic function were observed when larger, clinical-sized devices were implanted for 3 months into the putamen of Göttingen minipigs. Implantation of GDNF-secreting devices resulted in distribution of GDNF throughout the putamen and caudate that robustly upregulated the expression of tyrosine hydroxylase staining in the regions covered by GDNF diffusion (73, 74). Such an approach may be applicable long term to directly deliver therapeutic molecules, such as GDNF, to the striatum in an attempt to rescue dopaminergic neurons that are otherwise destined to die. GDNF provides substantial anatomical and functional benefits of the nigrostriatal pathway in both rodents and primates, but there is discrepancy in the neuroprotective effects of GDNF in the  $\alpha$ -syn models of PD likely related to poor brain penetration or limited distribution within the brain parenchyma (75).

A member of the same neurotrophic factor family as GDNF (76), Neurturin (NTN) has also demonstrated promoting the survival of dopaminergic neurons. The first time an NTN expression construct was tested in an animal model of PD via a lentiviral *in vivo* gene transfer approach was published in 2005 (77). In this study the authors found that NTN enhanced function and protected dopamine neurons similar to GDNF. Similar findings were reported when an adeno-associated virus type 2 (AAV2) encoding human NTN was administered to aged or MPTP-treated monkeys (78). Although NTN delivery by viral gene transfer provides long-term expression and widespread distribution in the target region of the bioactive protein with a single procedure, benefits have not been observed in double-blind trials in PD patients (79, 80). Quantitative immunohistochemical analyses of post-mortem brain sections of patients enrolled in the studies and survived from 1.5 months to 8 and 10 years post-surgery revealed a mild but

persistent effect of NTN on nigrostriatal neurons, which seem to modestly amplify over time. Unfortunately, the localized responses were less than what had been assessed in animal models and likely were too weak to induce any clinical improvements (81, 82).

## Immunotherapies Directed Against Pathological $\alpha$ -Syn

Immunotherapies were first conceptualized more than 300 years ago (83) and are being used in clinical applications to significantly improve human health and longevity. In the case of degenerative diseases, the use of monoclonal antibodies or vaccination is a means of treating proteopathies across multiple neural populations (84, 85). In transgenic mice, monoclonal  $\alpha$ -syn-specific antibodies increased the degradation of neural and glia accumulation of  $\alpha$ -syn, reduced synaptic loss, slowed neurodegeneration, and improved behavioral deficits. At an intracellular level, immunization promotes the clearance of  $\alpha$ -syn via the lysosomal pathway (78, 86), whereas in the extracellular space, immunization against  $\alpha$ -syn aids microglia in the clearance of the toxic protein, thereby reducing cell-to-cell transmission and local inflammatory response (87, 88). In the PD field, several passive immunization therapies are in preclinical development (89–91), and several others have reached various phases of clinical evaluation (92). One drawback of passive approaches is the necessity for repeated, hospital-based intravenous infusions.

Active immunotherapies elicit a self-produced immune response in the host organism and have the potential advantage of providing long-lasting clearance of the target protein. Recently, Affiris, an Austrian company, completed a Phase I trial with two anti- $\alpha$ -syn vaccines PD01A and PD03A. Although the results from the latter have not yet been published, they have reported about the use of PD01A, which was designed to induce antibodies that selectively target aggregated  $\alpha$ -syn with much lower affinity for monomeric forms. Eighty-seven percent of patients (21 out of 24) received all six immunizations across 259 weeks. Over 5 years of follow-up, the authors found that the vaccine was safe and well-tolerated and induced humoral immune responses against pathological  $\alpha$ -syn. The Phase I clinical trial of the PD01A vaccine was based on a set of preclinical studies using two different transgenic mouse models (93), and although the study was not powered to assess efficacy, patients treated with PD01A showed stabilized clinical scores compared to a placebo group. The results from this study led to the design and initiation of a Phase II clinical trial (94). Though promising, the most critical drawback for  $\alpha$ -syn immunotherapy is the lack of a reliable marker of disease-related proteopathy, and therefore, it becomes difficult to monitor disease progression and establish potential target engagement for anti- $\alpha$ -syn.

## Levodopa–Carbidopa Intestinal Gel Therapy

Administration of oral levodopa–carbidopa is still the most effective drug for PD. However, advanced stage and long-term oral administration leads to disabling motor fluctuations (3, 95) due to pulsatile dopamine release and erratic gastric



emptying (96). To overcome these side effects, the European Medicines Agency (May 2011, EU/3/01/035) and the U.S. FDA (2015) approved levodopa–carbidopa intestinal gel (LCIG) for the treatment of advanced idiopathic PD with severe motor fluctuation in patients unresponsive to oral treatment. LCIG is a fluidic carboxymethylcellulose gel suspension containing four parts of L-DOPA to one part carbidopa monohydrate (same as oral formulations) administered into the duodenum through a percutaneous endoscopic gastrostomy tube and portable infusion pump [PEG (97–99)]. Delivery of L-DOPA via infusion achieves more stable plasma levels relative to oral treatment. As a consequence, striatal dopaminergic neurons are stimulated in a sustained manner that reduces the occurrence of “off” periods while increasing the “on” time without dyskinesia. Although there are few large-scale evaluations of the long-term efficacy and safety of LCIG (87, 90, 91), this treatment may have specific benefits on freezing of gait and global axial signs (100–104). Improvements have also been observed on non-motor symptoms, such as sleep/fatigue, urinary and sexual functions, gastrointestinal motility, and cognitive and affective comorbidities (105, 106). Adverse events occur more frequently during the early stages of implantation, but these appear to be related to the surgical procedure and stoma inflammation (107). The contribution of dopaminergic as well as noradrenergic, glutamatergic, and GABAergic pathways provide insights into the intricacy of the PD phenomenology and the development of novel disease-modifying approaches in addition to dopamine-replacing therapies. Nevertheless, evidence-based and experimental therapeutics continues to expand providing cautious optimism for the treatment of patients with PD (108, 109).

## Motor Abnormalities and Physical Activity

Non-drug-based approaches are emerging with the potential to improve cognitive and motor impairments and slow the progression of PD (110–112). The pre-Socratic philosophical belief *mens sana in corpore sano* or “healthy mind in a healthy body” has developed into a vibrant field exploring the possibilities that physical activity might improve cognitive functions as a consequence of hippocampal neurogenesis (113), brain angiogenesis (114), and augmented neurotrophic factors (115). In rodent models, exposure to treadmill or wheel running improves balance, and motor velocity through activity-induced hippocampal upregulation of BDNF (116), or striatal increased dopaminergic neurotransmission (117).

According to the Movement Disorder Society-PD (MDS-PD), the clinical diagnosis of PD focuses on a defined motor syndrome (Parkinsonism) based on bradykinesia, rigidity, and resting tremor. In addition to these symptoms, patients often report posture impairments. Postural abnormalities (PA) belong to the motor axial component in which posture may be affected in its orientation, such as stooped posture, camptocormia, and Pisa syndrome or in its balance component, which implies loss of postural reflex (118, 119). These disabling, drug-refractory motor complications of PD lead to imbalance, fall-related injuries, and generalized pain, ultimately reducing quality of life and increasing hospitalization. PA are poorly improved

by L-DOPA, which implies that it is unlikely related to the nigrostriatal dopaminergic denervation. However, Schlenstedt and collaborators (120, 121) found that total, upper, and lateral bending were significantly improved when combined medications and deep brain stimulation (DBS) in the subthalamic nucleus were administered.

Factors related to PA associated with PD suggest two mutually non-exclusive pathophysiological pathways involving central (dystonia, rigidity, proprioceptive disintegration) and peripheral (myopathy and soft tissue changes) mechanisms varying between patients and disease progression (122, 123). Although rehabilitation is fundamental in the management of PD, the current approaches only partially improve postural complications. As motor and non-motor components are involved in the neural control of PA, three main elements are fundamental for effective rehabilitation: active self-correction techniques, stabilization exercises, and functional tasks. Based on this, Tinazzi and collaborators (16, 17, 118) have found that a 4-week trunk-specific rehabilitation program improved passive and active control of the trunk and was maintained at 1-month post-treatment. The benefits of training were evident even when PA were assessed through the Unified Parkinson Disease Rating Scale–motor subscale (122, 124).

## CONCLUSION

The results from preclinical models and clinical research reveal the importance of investing in innovative therapies for the treatment of PD and other neurological and degenerative diseases. Targeted, continuous, and sustained delivery of drugs at the level of the C/ENS are efficacious, safe, and promising though each still requires improvements to reach a more stable and predictable titration of the delivered drugs. Although the understanding of the beneficial effects of physical activity and general activities that are stimulating for the CNS and motor system is limited, evidence suggests a bidirectional interaction where brain functionality orchestrates the periphery and is deeply modulated by external inputs. A refined understanding of the complexity of normal and dysfunctional networks in PD should lead to improved multifaceted and more optimal treatments.

## AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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**Conflict of Interest:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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