BDNF Provides Many Routes Toward STN DBS-Mediated Disease Modification

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ABSTRACT: The concept that subthalamic nucleus deep brain stimulation (STN DBS) may be disease modifying in Parkinson's disease (PD) is controversial. Several clinical trials that enrolled subjects with late-stage PD have come to disparate conclusions on this matter. In contrast, some clinical studies in early- to midstage subjects have suggested a disease-modifying effect. Dopaminergic innervation of the putamen is essentially absent in PD subjects within 4 years after diagnosis, indicating that any neuroprotective therapy, including STN DBS, will require intervention within the immediate postdiagnosis interval. Preclinical prevention and early intervention paradigms support a neuroprotective effect of STN DBS on the nigrostriatal system via increased brain-derived neurotrophic factor (BDNF). STN DBS-induced increases in BDNF provide a multitude of mechanisms capable of ameliorating dysfunction and degeneration in the parkinsonian brain. A biomarker for measuring brain-derived neurotrophic factor-trkB signaling, though, is not available for clinical research. If a prospective clinical trial were to examine whether STN DBS is disease modifying, we contend the strongest rationale is not dependent on a preclinical neuroprotective effect per se, but on the myriad potential mechanisms whereby STN DBS-elicited brain-derived neurotrophic factor-trkB signaling could provide disease modification. © 2018 The Authors. *Movement Disorders* published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

Key Words: brain-derived neurotrophic factor; deep brain stimulation; disease modification; Parkinson's disease; subthalamic nucleus

The use of subthalamic nucleus deep brain stimulation (STN DBS) to treat the cardinal motor signs of Parkinson's disease (PD) has increased dramatically since its first use was reported in 1994.[1] DBS is a vetted, safe, and efficacious neurosurgical therapy for PD.[2] Once considered a treatment of last resort where patients underwent neurosurgery approximately 10 to 16 years postdiagnosis,[3] STN DBS now is U.S. Food and Drug Administration approved for use as early as 4 years after diagnosis and may be superior to medical therapy at that time.[4] With a trend toward implanting earlier in the course of the disease, questions remain as to whom will best benefit from additional and earlier years of stimulation treatment. The neurologist-patient discussion must weigh symptomatic benefit versus neurosurgical risks over a now longer interval.

There is a strong prevalent opinion in the neurological community that STN DBS is not disease modifying in PD.[5] In light of the lack of direct evidence, this is an appropriate stance in counseling patients considering STN DBS. However, from a scientific perspective, this conclusion may be premature in light of an evolved PD literature. The preclinical evidence still supports pursuing a clinical trial with the addition of newer studies. In addition, we will argue that previous trials that assessed

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the disease-modifying potential of STN DBS were flawed in their designs. Further, we will emphasize that stimulation-induced increases in brain-derived neurotrophic factor (BDNF)[6-10] provide multiple mechanistic avenues for STN DBS to promote the survival of the nigrostriatal system, promote functionality of the basal ganglia-cortical circuitry, and decrease α-synuclein (α-syn) aggregation in the parkinsonian brain.

Current Wisdom on Trial Design for Disease Modification in PD — Timing Is Everything

Dysfunction and degeneration of the nigrostriatal system begin long before diagnosis and the ability to intervene. At the time of motor symptom onset and on prompt diagnosis, it has been estimated that half of striatal dopamine content has been depleted along with 30% of nigral dopamine neurons.[11] However, it was not until the work by Kordower and colleagues published in 2013[12] that the early magnitude of putaminal denervation in the disease process was fully appreciated (schematically represented in Fig. 1). Specifically, this study demonstrated that 50% putaminal denervation had already occurred at the time of diagnosis and that this denervation progressed to approximately 90% loss within 4 years after diagnosis. This loss of putaminal innervation preceded cell body loss; about 50% of melanin-containing nigral dopamine neurons remained at 4 years postdiagnosis, and fewer than a third retained their tyrosine hydroxylase (TH) phenotype. This important revelation of the scope of early dopaminergic terminal loss suggests that neuroprotective therapies that target the nigrostriatal system cannot be adequately evaluated with a clinical trial population with disease duration longer than this 4-year time frame.

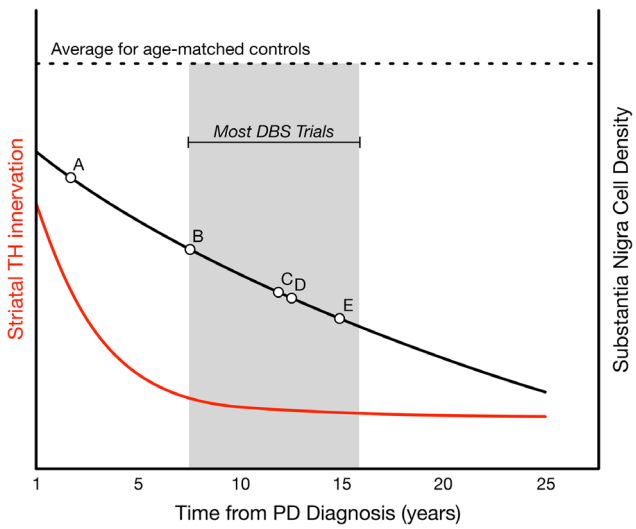

FIG. 1. Timing of nigrostriatal degeneration (adapted from Kordower et al [2013][12]. Average time course for degeneration since diagnosis of PD (*x* axis) is plotted for both putaminal TH immunoreactivity (left *y* axis, red line) and number of melanized neurons in the substantia nigra (right *y* axis, black line) compared with the average from age-matched controls (dashed line). The gray box brackets the window during which the majority of trials examining STN DBS have occurred (compare with Table 1). For illustration, points A, B, C, D, and E correspond to the studies conducted by Charles et al,[36] Schuepbach et al,[4] Tagliati et al,[21] Hilker et al,[22] and Pal et al,[34,35] respectively.

Current wisdom for design of clinical trials to assess for disease modification now includes this perspective on timing.[13] More recent clinical trials enrolled early-stage PD subjects (eg, the NET-PD trials[14-17], and the confound of diagnostic uncertainty in this population was addressed by enrolling a large population. As a separate issue for detecting an effect, early-stage PD subjects also exhibit a long-term effect of L-dopa that may take months to wash out, so the trial design can take this symptomatic effect into account, for example, through a delayed-start design.[13] Other trial designs aimed to detect development of disability over a long period[16] or detect a change in slopes between treatment groups. Of importance, neuroprotection per se is not assessed directly by trial end points, as there is no method to do so; rather, the clinical consequences of an intervention—neuroprotective or not—are used. Ultimately, trial design for neuroprotective therapies for PD is still an area of active research, but standard practice now is to enroll early-stage PD subjects prior to the degeneration of the nigrostriatal system.

Completed Trials Assessing STN DBS Disease-Modifying Potential

Several clinical studies have investigated whether STN DBS has the ability to slow or halt the progression of PD. However, the common thread in all these studies was that motor symptom progression was examined in subjects who were in late-stage PD, that is, about 10 years after diagnosis. Many of these investigations have been retrospective studies, evaluating symptomatic progression in subjects receiving STN DBS and making comparisons with either expectations of symptom progression or best-matched, medication-only cohorts in either the ON or OFF states (or both). One limitation of examination of OFF-state symptoms is the unknown impact of the washout period, which for medication ranged from 12 hours to 7 days (Table 1)—that is, what is truly OFF for either medication or DBS? Given the long disease durations and variability in washout, it is not surprising that results have been mixed. Four retrospective analyses showed STN DBS could maintain subjects' off-medication motor signs several years after electrode implantation.[18-21] In contrast, a prospective study showed equivalent disease progression, as measured by striatal fluorodopa uptake in subjects receiving or not receiving STN DBS.[22]

TABLE 1. Clinical trials assessing STN DBS

Author (year)	Age (SD) at surgery	Disease duration at time of surgery in years (SD)	ON/OFF assessments?	Washout period?	Conclusion(s)
Charles et al. (2014)[36]	60 (6.8)	2.2 (1.4)[c]	MedOFF/ON, StimOFF/ON	7 days for meds and stim	No difference in UPDRS (total) or in part III from STN DBS compared with medication controls over 2 years.
Weaver et al (2017)[24]	65.6 (7.6)	>5	None	N/A	DBS (STN or GPi) associated with increased survival compared with matched controls.
Schuepbach et al (2013)[4] and Lhommee et al (2018)[125]	52.9 (6.6)	7.3 (3.1)	MedOFF/ON, StimOFF/ON	12-48 hours for meds, 2 hours for stim	PDQ-39, UPDRS-II, -III, and -IV improved compared with medication control group; PDQ-39 also improved compared with baseline in DBS group. Improved behavioral outcomes in DBS group compared with medical therapy alone.
Yamada et al (2009)[29]	65.7 (7.8)	9.8 (5.6)	MedOFF/ON, StimON	12 hours for meds	Shorter disease duration at surgery associated with better postoperative S&E ADLs.
Dafsari et al (2017)[30]	53.2-72.3§	10.5-11.1[d]	MedON, StimON	N/A	PDQ-8 improved with STN DBS over 5 months, with larger effect size associated with younger age at time of surgery.
Dafsari et al (2018)[126]	62.3 (7.8)	10.9 (4.8)	MedON, StimON	N/A	Improvement in nonmotor symptom scale over 2 years (compared with baseline) with bilateral STN DBS.
Toft et al (2011)[127]	60.3 (7.8)	11.0 (4.8)	MedOFF/ON, StimON	Not reported	Annual increase of 3.2 points on UPDRS-III scale after STN DBS surgery and a survival of 97% and 90% at 3 and 5 years postoperation, respectively.
Ngoga et al (2014)[23]	60 (53-63)[a]	11.0 (8.8-13.0)[a]	None	N/A	Longer survival and less likely to enter a residential care home with STN DBS compared with medical management.
Trager et al (2016)[33]	61.6 (8.0)	11.0 (3.5)	MedOFF, StimON/OFF	12-72 hours for meds, 60 minutes for stim	Improved UPDRS-III and reduced beta-band power with StimOFF after 12 months of DBS compared with baseline.
Tagliati et al (2010)[21]	60 (12)	12 (4)	MedOFF/ON, StimOFF/ON	~12 hours for meds, 30 minutes for stim	UPDRS-III stable when off medication at baseline compared with off medication and off stimulation over 3-4 years.
Aviles-Olmos (2014)[128]	52.8 (10.1)	12.3 (4)	MedOFF/ON, StimON	12 hours for meds	Over 8 years, STN DBS improved UPDRS-III versus baseline when off medication, and on medication, UPDRS-III scores declined over time.
Merola et al (2012)[25]	54.7-65.5[d]	12.5-19.2[d]	MedOFF/ON, StimOFF/ON	Overnight for meds, 1 hour for stim	Lower incidence of medication- or stimulation-resistant symptoms in young-onset PD compared with non-young-onset PD over 5 years postsurgery.
Hilker et al (2005)[22]	59.8 (7.2)	12.6 (4.2)	MedOFF/ON, StimON	12 hours for meds	No change in rate of decline of F-dopa uptake in caudate nucleus or putamen in association with STN DBS compared with rates in the literature (no matched medication group in study).
Merola et al (2014)[31]	60.11 (5.62)	12.94 (2.15)	MedOFF/ON, StimOFF/ON	12 hours for meds, 1 hour for stim	Decreased off time and disability from dyskinesia with STN DBS but no difference in UPDRS-III between DBS and medication control group over about 6 years.
Lezcano et al (2016)[129]	61.3 (7.4)	13.2 (5.7)	MedOFF/ON, StimON	Not reported	Improved UPDRS-II and -III and S&E ADL scores over 5 years compared with baseline off medication. Worse UPDRS-III versus baseline when on medication.
Castrioto et al (2011)[26]	52.9 (7.9)	13.4 (4.8)	MedOFF/ON, StimOFF/ON	Overnight for meds, 1 hour for stim	UPDRS-III improved compared with baseline when assessed off medication at 10 years.
Fasano et al (2010)[130]	56.9 (7.2)	13.7 (4.8)	MedOFF/ON, StimON	Overnight for meds	Over 8 years, STN DBS improved UPDRS-III versus baseline but not relative to 5 years postsurgery, and UPDRS-II significantly worsened from year 5 to year 8.
Rocha et al (2014)[131]	60 (8)	14 (range, 5-48)	None	N/A	Survival of 99% and 94% at 3 and 5 years, respectively, with DBS (mixed GPi and STN).
Rodriguez-Oroz et al (2005)[20]	59.8 (9.8)	14.1 (5.9)	MedOFF/ON, StimOFF/ON	~12 hours for meds, 1-2 hours for stim	UPDRS-II and UPDRS-III improved compared with baseline when assessed off medication, on stimulation over 3-4 years.
Krack et al (2003)[18]	55 (7.5)	14.6 (5.0)	MedON/OFF, Stim ON	8-12 hours for meds	UPDRS-III and S&E improved compared with baseline when assessed off medication over 5 years.
Pal et al (2017)[34] and Pal et al (2018)[35]	≈ 72	≈14.6	MedOFF/ON, StimON but not specifically reported	Overnight for meds	Increased α-synuclein density scores, equivalent loss of pigmented nigral neurons, and equivalent putaminal dopamine and dopamine metabolite whole-tissue content with STN DBS compared with medically treated controls.

(Continues)

TABLE 1. Continued

Author (year)	Age (SD) at surgery	Disease duration at time of surgery in years (SD)	ON/OFF assessments?	Washout period?	Conclusion(s)
Hilker et al (2003)[132]	61.8 (4.9)	15.3 (4.4)	MedOFF, StimON/OFF	12 hours, allowed 1 adjunctive dose	Using [11C]raclopride PET, no change in binding between on and off stimulation.
Bang Henriksen et al (2016)[133]	59.7 (7.7)	15.7 (6.0)	None	N/A	Postsurgery, 70% of STN DBS subjects survived 10 years (25 total years' disease duration).
Zibetti et al (2011)[134]	61.4 (6.0)	16.4 (4.9)	MedOFF/ON, StimOFF/ON	Overnight for meds, 1 hour for stim	Over 9 years, STN DBS improved UPDRS-III versus baseline without improvement in UPDRS-II and some with cognitive decline.
Rodriguez-Oroz et al (2004)[19]	62	"Advanced PD"	MedOFF, StimON/OFF	Overnight for meds, 2 hours for stim	UPDRS-II and UPDRS-III improved compared with baseline when assessed off medication, on stimulation over 4 years.
Lilleeng et al (2014)[32]	64 (6)	18 (9)[b]	MedON, StimON	N/A	No change in time to death or in rate of decline by UPDRS-III when assessed on medication and on stimulation over several years compared with age-matched group on medication alone.
Strafella et al (2003)[135]	≈59 (9.0)	32.6 (5.9)[b]	MedON, StimON/OFF	No stim overnight	Using [11C]raclopride PET, no change in binding between on and off stimulation.

[a]Median (quartiles).
[b]Reported as UPDRS-III on medication (SD).
[c]Measured in years from start of medication use, not time since diagnosis.
[d]Three groups compared, with means of youngest and oldest groups displayed.
S&E ADLs, Schwab and England activities of daily living.

Not examining disease modification per se but providing corroborating evidence, STN DBS in late-stage PD improved survival and decreased the likelihood of entering a residential care home,[23,24] and when performed in younger patients with late-stage PD, benefits were sustained even 10 years after implantation.[25,26] Shorter disease duration improves outcomes from DBS in primary dystonia[27] and young-onset DYT1 dystonia.[28] Similarly, when examining PD patients from mid- to late-stage disease who elected STN DBS, postoperative independence measured by activities of daily living was greater in those with a shorter disease duration,[29] and a better quality of life, measured by Parkinson's Disease Questionnaire-8 (PDQ-8), after STN DBS was observed with younger age at time of surgery.[30] These results indicate enhanced tolerability for the surgery itself with younger age and earlier disease stage, implying when there is greater cognitive reserve.

A retrospective cohort study found over several years of follow-up that late-stage PD subjects treated with STN DBS had improved outcomes regarding motor fluctuations, OFF time, and dyskinesia, but they did not find any difference overall in motor outcome—measured by Unified Parkinson's Disease Rating Scale part III (UPDRS-III) in both OFF and ON conditions—between subjects treated with DBS or medical therapy alone, concluding no disease-modifying effect.[31] Similarly, another retrospective cohort study of a similar design reported no disease-modifying effect of STN DBS, although it included patients with severe motor complications who were likely in late-stage PD as disease duration was specifically not reported.[32] Of note, a study that used beta-band power, which is associated with PD motor symptoms, showed reduced power after 1 year of DBS even after the stimulator was turned off, suggesting a disease-modifying effect on the circuit.[33] The most recent retrospective cohort study examining the disease-modifying potential of STN DBS examined α-syn density, pigmented nigral neurons, and putaminal dopamine tissue content in late-stage PD subjects (14.5 years) and found no differences compared with medically treated controls.[34,35]

The common thread in all these aforementioned studies is that disease modification, whether measured by motor symptom or pathology progression, was examined in subjects who were in late-stage PD, that is, about 10 years after diagnosis. Because the majority of loss of putaminal innervation occurs by 4 years post diagnosis,[11,12] it is unreasonable to assess the question of disease modification in the context of a PD subject in whom dopaminergic putaminal innervation had long been absent (Fig. 1). Simply put, it is not possible to protect what is no longer there. Granted, a few pigmented neurons may remain, but they no longer contribute to circuit integrity. A more recent clinical trial has employed STN DBS at an earlier time in the disease course (ie, about 7 to 8 years postdiagnosis),[4] but this

TABLE 2. Predictive validity of preclinical models for STN DBS-mediated neuroprotection (adapted from Spieles-Engemann et al [2010][136]

PD model	Major finding	Reference(s)	
		Rat	Nonhuman primate
Intact/unlesioned	STN DBS excites STN output structures	Windels et al (2000),[55] Windels et al (2003)[137]	
	STN DBS inhibits the STN	Tai et al (2003),[138] Zheng et al (2011)[139]	
	STN DBS increases subthalamic glutamate	Lee et al (2007)[140]	
	STN DBS increases striatal DA	Paul et al (2000),[141] Bruet et al (2001)[142]	
	STN DBS increases BDNF in striatum and motor cortex	Spieles-Engemann et al (2011)[8]	
	STN DBS increases rpS6 and Akt phosphorylation in SNpc neurons	Fischer et al (2017)[10]	
6-OHDA, complete lesion	STN DBS inhibits the STN	Tai et al (2003),[143] Shi et al (2006)[144]	
	STN DBS does not increase striatal DA	Meissner et al (2001),[145] Meissner et al (2002)[146]	
6-OHDA, partial lesion	STN DBS increases striatal DA	Bruet et al (2001)[142]	
	STN DBS protects against neurotoxicant	Maesawa et al (2004),[38] Temel et al (2006),[39] Harnack et al (2008),[40] Spieles-Engemann et al (2010),[41] Fischer et al (2017a)[10]	
	STN DBS increases BDNF in SN and motor cortex	Spieles-Engemann et al (2011)[8]	
MPTP	STN DBS inhibits the STN		Hashimoto et al (2003),[147] Meissner et al (2005)[148]
	STN DBS increases striatal DA		Zhao et al (2009)[149]
	STN DBS protects against neurotoxicant		Wallace et al (2007)[42]
α-Synuclein viral overexpression	STN DBS protects SNpc somata	Musacchio et al (2017)[50]	
	STN DBS does not protect SNpc somata or nigrostriatal fibers	Fischer et al (2017b)[52]	
	STN DBS does not increase rpS6 phosphorylation in SNpc neurons	Fischer et al (2017b)[52]	

trial also did not enroll subjects early enough in disease duration to overcome this hurdle in experimental design. The only existing PD cohort that may be able to address the question of disease modification is at Vanderbilt University, although current follow-up may be too short and the cohort too small to provide any definitive evidence.[36] Ergo, the available clinical data (Table 1) are insufficient to evaluate whether STN DBS is disease modifying. Of note, in a retrospective analysis of a subset of the Vanderbilt data, a neuroprotective signal was present. Using a "clinically important worsening" measure—defined as both a 3-point increase in UPDRS part III and a 1-point increase in part IV—early-stage subjects treated with STN DBS had a reduced risk of worsening compared with those subjects managed with medical therapy alone.[37] Although an appropriately designed (and powered) clinical trial has yet to be completed, the aforementioned pilot trial may serve as a template for a future one.

Preclinical Evidence for STN DBS-Mediated Neuroprotection

Several laboratories have examined the effects of STN DBS and whether it is neuroprotective using a variety of animal models of PD that collectively provide support to pursue a clinical trial (Table 2). The neurotoxicant models of PD are able to produce a severely dopamine-depleted striatum and a modestly progressive loss of nigral somata, and these models have been used extensively to investigate the molecular and morphological effects of STN DBS. In rats, STN DBS used immediately after 6-hydroxydopamine (6-OHDA) administration results in a doubling of the remaining tyrosine hydroxylase immunoreactive neurons in the SNpc compared with rats without activated electrodes,[38] and when STN DBS is activated 1 or 2 weeks after 6-OHDA, the SNpc neurons that remain are protected from further degeneration.[39-41] Similar results have been found in nonhuman primate models of PD using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) with either pretreatment with STN DBS or waiting 6 days after MPTP administration.[42]

Whereas 6-OHDA and MPTP are neurotoxicant-based models of PD that primarily rely on the oxidative stress component of PD pathophysiology, models using viral vector-mediated overexpression of α-syn should possess greater construct validity for PD.[43] A large body of evidence points to α-syn's involvement in PD, including that point mutations and multiplications of the *Snca* gene have been linked to onset of familial

forms of PD.[44-46] Subsequent discoveries of the presence of α-syn in the hallmark protein aggregates (Lewy bodies) and dystrophic neurites of PD have linked α-syn to sporadic forms of the disease.[47] Delivery of viral vectors encoding human wild-type or A53T α-syn results in nigrostriatal α-syn overexpression, degeneration of nigral somata and nigrostriatal terminals and motor dysfunction.[43,48,49] Overexpression of α-syn at specific titers results in progressive degeneration over several weeks to months, and the remaining neurons exhibit α-syn-immunoreactive inclusions and dystrophic neurites. In one laboratory's use of this model, overexpression of A53T α-syn, a form with greater propensity for aggregation, via a high viral titer was used to examine STN DBS-mediated neuroprotection. In this study, STN DBS protected nigral neurons[50]; however, nigrostriatal terminals were not examined and may not have been protected.[51] Indeed, vector-mediated overexpression of the human wild-type form of α-syn using a lower titer produces a more progressive model of PD in which STN DBS is not neuroprotective of nigral terminals or somata.[52] Because the use of high levels of α-syn expression to model sporadic PD may produce artifactual results not relevant to the human condition,[53,54] the construct validity of the approach of using α-syn overexpression to model sporadic PD is less than ideal. Moreover, the predictive validity of all animal models of PD to date has been poor. One way to circumvent concerns related to preclinical models is to understand the impact of STN DBS on the brain in general, devoid of parkinsonian manipulations. We contend that the strongest rationale for a prospective clinical trial to examine the disease-modifying potential of STN DBS is not dependent on the preclinical neuroprotective effect per se, but on the mechanism by which STN DBS achieves this.

The Role of BDNF in STN DBS-Mediated Disease Modification

The mechanism for STN DBS-mediated neuroprotection provides insight into how STN DBS may be disease modifying in idiopathic PD. First, it is worth stating that the early hypothesis that DBS decreased glutamate release from the STN, thereby protecting nigral neurons from excitotoxicity, is not supported because stimulation results in the propagation of action potentials leading to *increased* nigral glutamate levels.[55,56] More recent evidence supports a neurotrophic mechanism of neuroprotection by STN DBS, specifically via increased levels of BDNF.[8,10] Specifically, BDNF release can be driven through electrical stimulation. In neuronal cultures, high-frequency stimulation leads to increased BDNF release.[6,57] In addition, glutamatergic signaling at N-methyl-D-aspartate (NMDA) receptors can lead to increased BDNF mRNA expression.[58]

Brain-Derived Neurotrophic Factor

Brained-derived neurotrophic factor (BDNF) is a member of the neurotrophin family. All neurotrophins are secreted proteins that bind tropomyosin-related kinase (trk) receptors, leading to dimerization and receptor activation.[59,60] The effects of BDNF were first described as a factor in glioma-conditioned medium capable of supporting survival and fiber formation of isolated chick sensory neurons,[61] findings that were replicated when examined using rat brain extracts.[62] Identification of the responsible new factor was conducted by the same laboratory group[63] and later became known as brain-derived neurotrophic factor. Of particular importance to STN DBS, BDNF mRNA is expressed by numerous nuclei in the basal ganglia including the subthalamic nucleus, entopeduncular nucleus (rat homologue to the internal globus pallidus), striatal medium spiny neurons (MSNs), and dopaminergic neurons of the substantia nigra (SN).[8,64-67] The receptor for BDNF, tropomyosin-related kinase type 2 (trkB), is similarly expressed throughout the basal ganglia, including by dopaminergic neurons of the SN.[68,69] In addition, BDNF and trkB mRNA are expressed in the motor cortex.[70,71]

On the firing of an action potential, the presynaptic neuron releases neurotransmitter and coreleases vesicular proBDNF into the synaptic cleft.[72] The prodomain is proteolytically cleaved, thereby converting the proBDNF form into the mature form that is referred to simply as BDNF.[57,73] Then, the mature form of BDNF can act via two categories of signaling pathways on the postsynaptic neuron: the canonical and the noncanonical pathways. In the canonical pathway, BDNF binds to its high-affinity trkB receptor. Three canonical trkB intracellular signaling cascades have been identified: (1) the mitogen-activated protein kinase/extracellular signal related-kinase (MAPK/ERK) cascade, (2) the phosphatidylinositol 3-kinase/AKT (PI3K/AKT) cascade, and (3) the phospholipase C gamma (PLCγ) cascade.[74,75] Binding of BDNF to trkB triggers phosphorylation that initiates all three cascades. MAPK/ERK and PI3K/AKT signaling play key roles in both translation and trafficking of proteins, whereas PLCγ regulates intracellular Ca^{2+} that can drive transcription via cyclic adenosine monophosphate and protein kinase.

TrkB signaling affects neuronal survival, growth/arborization, and regulation of synaptic plasticity through mediating long-term potentiation.[76,77] Although the time course for the signaling events is many minutes, the measurable effects take much longer, on the order of hours, as they require alterations in transcription and

translation of specific genes and the production of a complement of new proteins. In the noncanonical pathway, the effects of BDNF are also mediated through TrkB, but the intracellular signaling takes a tangential path. Through PI3K-Akt signaling and a series of phosphorylation events at the NMDA receptor 2B subunit,[78-80] potentiated responses are observed. In addition, BDNF-trkB signaling has been suggested to have effects on presynaptic dopamine release and reuptake.[81] Of importance, because of the involvement of immediate phosphorylation events, the effects mediated via the noncanonical pathway occur at a much faster rate than the translational and transcriptional events in the canonical pathway. Collectively, an increase in BDNF can exert a multitude of effects on the basal ganglia.

Stimulation Results in Increased BDNF In vitro and In Vivo

As mentioned in the previous section, firing of action potentials can cause presynaptic neurons to corelease BDNF in addition to neurotransmitter.[72] Specifically, action potentials elicited by high-frequency stimulation of glutamatergic neurons is associated with release of BDNF.[6] In a similar manner, DBS to the glutamatergic STN in either naive rats (unlesioned) or rats lesioned with 6-OHDA show a stimulation-specific increase in BDNF protein and mRNA in the nigrostriatal system and motor cortex.[8] Specifically, STN DBS drives robust increases in BDNF protein in the SN, striatum, and M1 cortex and enhances *Bdnf* gene expression in the SN and entopeduncular nucleus (rat homologue to the internal globus pallidus; Fig. 2). Within dopaminergic neurons of the SNpc, STN DBS activates trkB signaling cascades, as measured by phosphorylation of ribosomal protein S6 and Akt.[10] Further, STN DBS-mediated neuroprotection from 6-OHDA insult can be specifically linked to BDNF-trkB signaling because this neuroprotection is abolished when trkB is blocked pharmacologically.[10] Similarly, when α-syn overexpression interferes with STN DBS-mediated trkB signaling, nigrostriatal axonopathy cannot be prevented.[52] In addition, other evidence supports a connection between stimulation and increased BDNF, specifically in rodent models of depression.[79,82] These preclinical studies suggest that through increased BDNF, STN DBS may—depending on the ability of trkB survival signaling to occur—provide neuroprotection of the nigrostriatal system.

Potential Functional Effects of Stimulation-Induced BDNF

Our previous STN DBS research illustrated a clear causal link between stimulation of the STN and

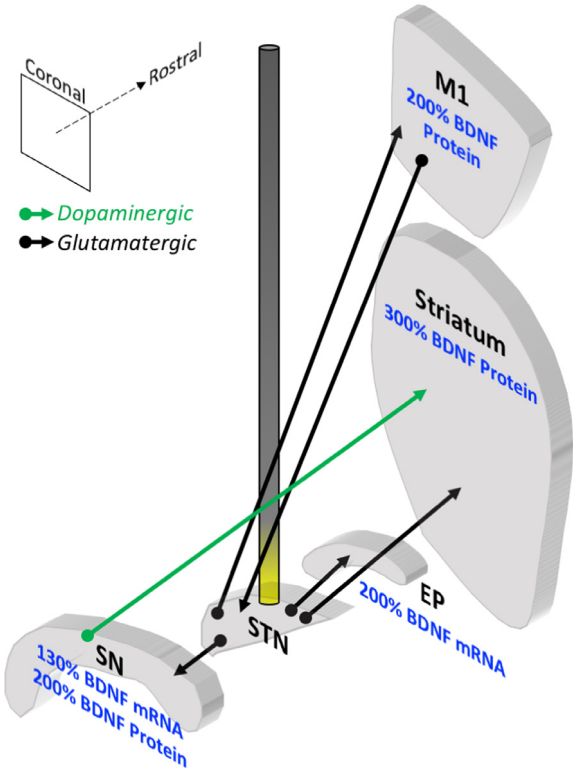

FIG. 2. STN DBS increases BDNF in the basal ganglia in PD animal models. Coronal sections of select basal ganglia structures in the rat are depicted in 3 dimensions relative to one another, and an electrode stimulating the STN is illustrated. Effects of high-frequency stimulation of the STN on BDNF levels in the rat are noted. STN DBS increases BDNF mRNA in the SN and entopeduncular nucleus (EP, rodent homologue to primate GPi). STN DBS also increases BDNF protein in the primary motor cortex (M1) and the striatum of unlesioned animals and the SN of lesioned animals. The green arrow represents dopaminergic fibers; the black arrows represent glutamatergic fibers. Data summarized from Spieles-Engemann et al (2011).[8]

neuroprotection of nigral dopamine neurons from 6-OHDA insult. This neuroprotective effect mirrors what has been shown previously. BDNF application to mesencephalic dopamine neurons in vitro protects against 1-methyl-4-phenylpyridinium (MPP+)- or 6-OHDA-induced cell death.[83] BDNF also has been shown to be neuroprotective in vivo against MPP+, resulting in decreased loss of nigral dopamine neurons,[84,85] results that were essentially replicated in nonhuman primates.[86] Further, BDNF can augment neurite outgrowth from transplanted embryonic DA neurons in a 6-OHDA rodent model.[87] These prosurvival, pro-outgrowth effects of BDNF represent the classic mechanism whereby DBS can be disease modifying. Indeed, the finding that BDNF levels can be reduced in the brains of PD subjects[88,89] lends further credence to the concept that elevated BDNF could be neuroprotective.

The goal of disease modification in PD typically refers to the prevention of worsening of motor symptoms via preservation of nigrostriatal circuitry. However, there are additional compensatory mechanisms beyond

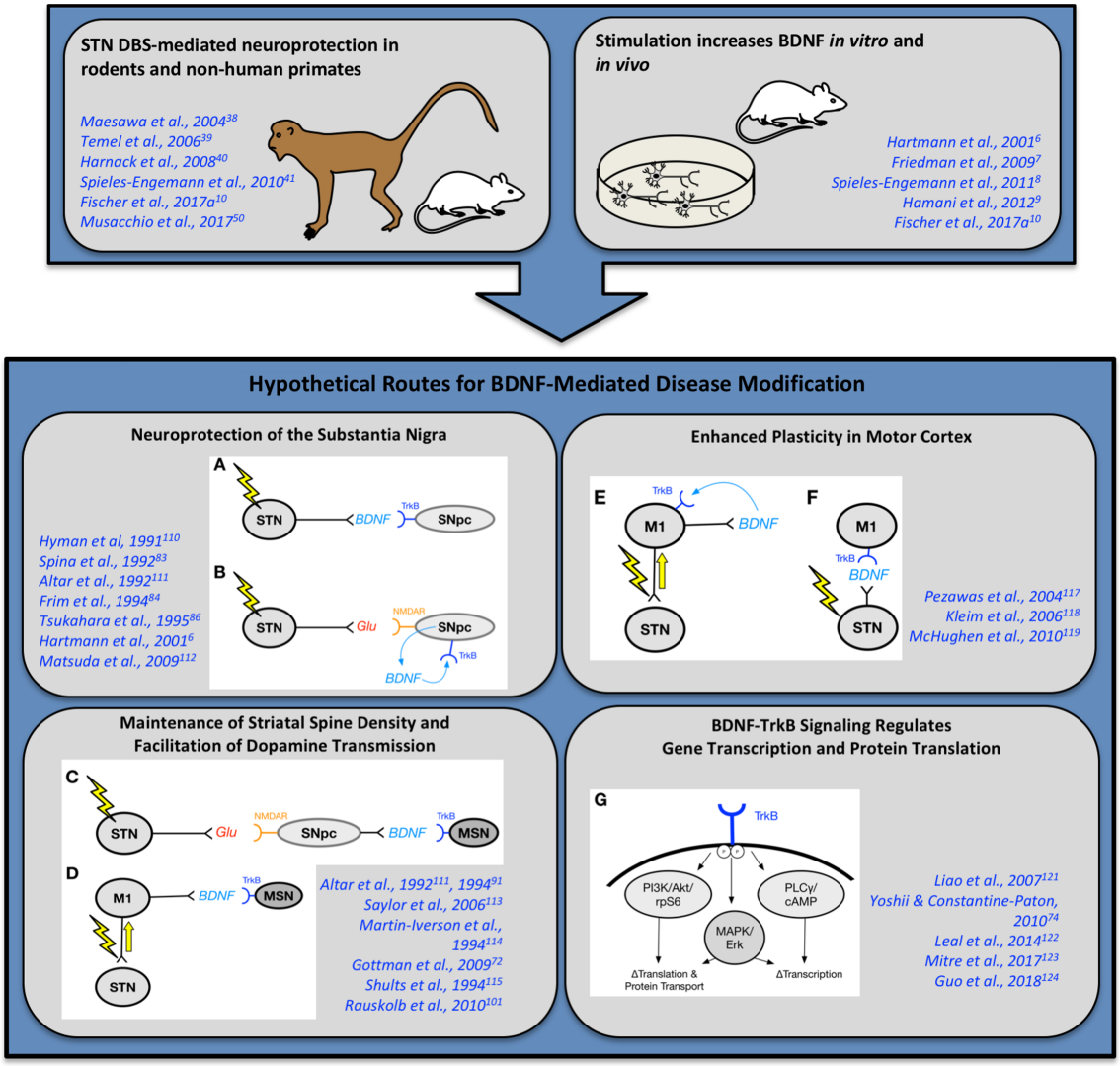

FIG. 3. Hypothetical routes for BDNF-mediated disease modification. Preclinical studies have demonstrated STN DBS-mediated neuroprotection in rodents and nonhuman primates.[10,38-41,50] In addition, high-frequency stimulation increases BDNF in vitro and in vivo.[6-10] In light of these preclinical studies, there are several hypothetical routes for BDNF-mediated disease modification. The SNpc may be protected directly (A,B).[6,83,84,86,110-112] (A) DBS increases STN activity, increases activity-dependent release of BDNF at the SNpc and binding to TrkB for a trophic effect. (B) DBS increases STN activity, increases glutamate (Glu) release at the SNpc and binding to NMDA receptors (NMDAR). SNpc activation results in production of BDNF transcript, translation, and local release of BDNF that binds to TrkB for an autocrine/paracrine trophic effect. BDNF may maintain striatal spine density and facilitate dopamine transmission (C,D).[72,91,101,111,113-115] (C) DBS increases STN activity, increases glutamate (Glu) release at the SNpc and binding to NMDA receptors (NMDAR). SNpc activation results in production of BDNF transcript, translation, and activity-dependent release of BDNF that binds to TrkB on striatal medium spiny neurons (MSNs) for a trophic effect, including maintenance of spine density. (D) DBS results in antidromic activation of corticosubthalamic projections from the motor cortex (M1)[116] and subsequent activity-dependent release of BDNF via corticostriatal fibers to bind to TrkB on MSNs for an ultimately trophic effect. BDNF may enhance M1 plasticity (E,F).[117-119] (E) DBS results in antidromic activation of corticosubthalamic projections from the M1 and activity-dependent release of BDNF by cortical neurons in an autocrine/paracrine manner, thereby enhancing plasticity. (F) DBS activates STN activity and through subthalamocortical projections found in the rat[120] releases BDNF in the M1 and enhancing plasticity. Of importance, BDNF-trkB signaling exerts powerful effects on intracellular signaling pathways (G).[74,121-124] (G) Intraneuronal changes with some shown in the STN DBS paradigm specifically,[10] where TrkB phosphorylation results in phosphorylation of Akt and ribosomal protein S6 (rpS6), as well as MAPK/Erk and PLCγ/cAMP signaling pathways that have been shown to result in changes in transcription, translation, and protein transport.

maintenance of neural architecture[90]—that is, mechanisms capable of maintaining or augmenting dopaminergic transmission at a cellular level—that could be harnessed by BDNF-trkB signaling. BDNF-trkB signaling is associated with increased dopamine release, tyrosine hydroxylase synthesis, enhanced dopamine turnover, and increased dopamine neuron activity.[91-97] Indeed, preclinical and clinical studies have suggested that STN DBS can alter dopamine transmission and dopamine receptors,[98] effects to which enhanced BDNF-trkB signaling may contribute. In addition to augmented survival and function of nigral dopamine neurons, STN DBS-induced increases in BDNF have the potential to exert other disease-modifying effects in both the nigrostriatal system and the motor cortex.[8] BDNF plays a critical role in the maintenance and remodeling of neuronal

circuits. BDNF is a critical modulator of gamma aminobutyric acid-ergic and glutamatergic synapses. BDNF facilitates long-term potentiation and mediates use-dependent plasticity.[72,99,100] Within the striatum, BDNF has the potential to exert a multitude of effects. BDNF plays an essential role in the maintenance of postsynaptic spine density of striatal MSNs that are the targets of dopaminergic innervation.[101] Loss of MSN spines has been demonstrated in both preclinical models of dopamine depletion and postmortem PD patients.[102,103] Striatal MSN spines are the site of interaction for nigral dopamine, glutamatergic cortical, and thalamic neurons, and this interaction is necessary for normal basal ganglia functioning. In the face of dysfunctional and degenerating circuits, BDNF may mitigate the aberrant plasticity present in PD[104] and maintain native circuit integrity. Such a role for BDNF has been described, albeit indirectly: in PD subjects, a BDNF variant conferring decreased BDNF release[105] is associated with earlier development of L-dopa-induced dyskinesia in a gene dose-dependent manner.[106]

Lastly, augmented trkB signaling resulting from STN DBS-induced BDNF may have the potential to attenuate the aggregation of α-syn. One preclinical report described decreased accumulation of α-syn aggregates in the enteric nervous system following a pharmacologically induced increase in BDNF.[107] The same study observed that blockade of trkB signaling increased α-syn aggregation. This finding adds a new dimension to the disease-modifying potential of elevated BDNF induced by STN DBS. Using STN DBS to bolster BDNF levels in a manner that is spatially and temporally controlled by the native circuit(s) provides a multitude of mechanisms capable of positively modifying dysfunction and degeneration in the parkinsonian brain (Fig. 3).

Keys for a Well-Designed STN DBS Trial for Disease Modification

In light of the preclinical evidence supporting STN DBS-mediated neuroprotection and the myriad mechanisms whereby STN DBS-elicited BDNF-trkB signaling could provide disease modification, a prospective clinical trial to assess whether STN DBS may modify the course of PD progression is warranted. Of importance, the trial should only include subjects who are truly early-stage PD, specifically fewer than 3 or 4 years since diagnosis, and as discussed above, employ a trial design that takes into account this unique time frame. With the Vanderbilt clinical trial experience in mind,[36] it is certainly feasible to recruit and retain early-stage PD subjects for such an endeavor. Of note, enrolling early-stage PD subjects reduces a noted selection bias[108] that has affected the validity of DBS studies that included subjects with advanced disease, where exclusion criteria for surgery include factors that negatively affect survival and are more prevalent in the late-stage PD population. The confound of symptomatic benefit from instrumenting the STN versus stimulation should be addressed, possibly by inclusion of a "sham" group in which electrodes are placed but not activated. Given that the course of PD progression has been determined as a decrease by 2 points on the UPDRS (total score) per year,[16] the study should be powered appropriately to detect a change in slope or a similar measure of progression; this will likely require a study of several years' duration. Of note, direct measurement of a neuroprotective effect is not required: STN DBS may be disease modifying through a neuroprotection-independent mechanism, and the result of any neuroprotection would improve the disease course if it were clinically meaningful. Lastly, as such a clinical trial will likely represent a large financial investment, it would be prudent to gather specimens and imaging data for testing other hypotheses using the database that is created. Since PD likely represents the convergence of several unique etiologies,[109] the ability to retrospectively analyze the data set, even if the study does not support a disease-modifying role for PD, cannot go underappreciated.

Conclusions

There is sufficient preclinical evidence to support a clinical trial examining the disease-modifying potential of STN DBS, likely via BDNF-mediated effects and perhaps extending beyond strictly neuroprotective mechanisms. To date, an appropriately designed and statistically powered trial that enrolls early-stage PD subjects has yet to be conducted. The pilot Vanderbilt trial may serve as a template for a larger multicenter trial to assess if STN DBS is disease modifying when applied to early-stage PD subjects whose neural circuitry and physiology still may be most capable of responding to the effects of BDNF. ■

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