Changing Gears – DBS For Dopaminergic Desensitization in Parkinson’s Disease?

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In Parkinson’s disease, both motor and neuropsychiatric complications unfold as a consequence of both incremental striatal dopaminergic denervation and intensifying long-term dopaminergic treatment. Together, this leads to ‘dopaminergic sensitization’ steadily increasing motor and behavioral responses to dopaminergic medication that result in the detrimental sequelae of long-term dopaminergic treatment. We review the clinical presentations of ‘dopaminergic sensitization’, including rebound off and dyskinesia in the motor domain, and neuropsychiatric fluctuations and behavioral addictions with impulse control disorders and dopamine dysregulation syndrome in the neuropsychiatric domain. We summarize state-of-the-art deep brain stimulation, and show that STN-DBS allows dopaminergic medication to be tapered, thus supporting dopaminergic desensitization. In this framework, we develop our integrated debatable viewpoint of “changing gears”, that is we suggest rethinking earlier use of subthalamic nucleus deep brain stimulation, when the first clinical signs of dopaminergic motor or neuropsychiatric complications emerge over the steadily progressive disease course. In this sense, subthalamic deep brain stimulation may help reduce longitudinal motor and neuropsychiatric symptom expression – importantly, not by neuroprotection but by supporting dopaminergic desensitization through postoperative medication reduction. Therefore, we suggest considering STN-DBS early enough before patients encounter potentially irreversible psychosocial consequences of dopaminergic complications, but importantly not before a patient shows first clinical signs of dopaminergic complications. We propose to consider neuropsychiatric dopaminergic complications as a new inclusion criterion in addition to established motor criteria, but this concept will require validation in future clinical trials.

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Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| DDS | Dopamine dysregulation syndrome |
| GPi | Globus pallidus internus |
| ICD | Impulse control disorder |
| PD | Parkinson’s disease |
| QOL | Quality of life |
| RCT | Randomized controlled trial |
| STN-DBS | Subthalamic nucleus deep brain stimulation |

Parkinson’s disease (PD) is the second most common neurodegenerative condition after Alzheimer’s disease, with the steepest increase in prevalence among all neurological diseases worldwide. The etiological underpinnings of PD

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neurodegeneration cover a broad spectrum of genetic and environmental factors. These affect the basal ganglia loop, resulting in motor and non-motor manifestations.

Whereas motor symptoms were a traditional focus for treatment, today stronger emphasis is given to non-motor symptoms, including neuropsychiatric, cognitive, and sensory symptoms. These lead to profound psychosocial consequences, including the loss of workforce and dependence on social systems. Quality of life (QOL) is more strongly determined by non-motor than motor domains.

Medical treatment of PD is symptomatic and relies on pharmacological neurotransmitter replacement therapy. After an initial honeymoon phase upon first dopaminergic treatment, medication becomes increasingly intensive as the disease progresses. In particular, the progressive presynaptic dopaminergic lesion, higher dosages of pulsatile non-physiological L-Dopa administration, and non-physiological D3-receptor affinity of dopamine agonists promote dopaminergic sensitization, leading to motor and neuropsychiatric sequelae.

Deep brain stimulation (DBS) for PD was confirmed in several randomized controlled trials (RCTs) as evidence-based therapy to treat dopaminergic complications. In the early years, DBS was offered to patients suffering from the most severe dopaminergic motor complications in the advanced disease stage. The aim was to improve the ‘off-period’ L-Dopa-sensitive bradykinesia, and ‘on-period’ troublesome dyskinesia. However, the past two decades have seen an unprecedented growth in knowledge of the beneficial effects of DBS on motor and non-motor fluctuations, and the neuropsychiatric sequelae of dopaminergic treatment of PD relevant to QOL.

Here, we review the concept and consequences of dopaminergic sensitization, focusing on motor and neuropsychiatric domains. We will then evaluate the present state-of-the-art of DBS therapy to counteract dopaminergic complications. Finally, we develop the integrated viewpoint ‘whether it is time to change gears’, that is whether STN-DBS helps to intervene in the emerging cascade of dopaminergic sensitization by postoperative tapering of dopaminergic medication when the first motor and neuropsychiatric complications appear.

Methods: Search Strategy and Selection Criteria

We identified references through searches of our own files and reference lists of publications in the English language. In addition, we conducted PubMed research using the search terms: (1) “Deep brain stimulation” and “Parkinson’s disease” / “Parkinson disease” (respectively) filtering for randomized controlled trial, human; without time frame; (2) “Parkinson disease” and “deep brain stimulation” and "globe pallidus internus" without time frame; (3) “Parkinson disease” and “deep brain stimulation” and “impulse control disorder / dopamine dysregulation syndrome / dopamine withdrawal / non-motor fluctuations / neuropsychiatric fluctuations / apathy / depression / anxiety / mania / psychosis / hallucinations / non-motor symptoms” from 1998 to present. We selected references based on their originality and relevance to the purpose of this targeted review.

The Enigma of Dopaminergic Sensitization

Dopaminergic sensitization in PD affects the motor, cognitive, and limbic domains (Fig 1). We will focus on sensitization in the neuropsychiatric domain, including neuropsychiatric fluctuations, impulse control disorders (ICD), and dopamine dysregulation syndrome (DDS).

Dopaminergic sensitization was first described in experiments on the monoamine reuptake inhibitor “cocaine,” and refers to the incremental motor and behavioral responses to a single dose after its repeated and chronic administration. As a correlate, increased endogenous dopamine release in the cortico-striatal circuits after a single dose of L-Dopa accounted for sensitization in both motor (dorsal striatum) and neuropsychiatric (ventral striatum) domains. Parallelism between cocaine and L-Dopa exposure exists in terms of the incremental behavioral responses and relate to postsynaptic long-term potentiation. In particular, the depotentiation of synaptic plasticity (ie, the ability to reverse long-term potentiation once induced) is thought to be defective in PD patients with dyskinesia, based on experimental models that do not allow for very long-term follow-up. Nevertheless, desensitization of L-Dopa-induced dyskinesia and ICD was shown in human PD in the long-term follow-up after STN-DBS and postoperative medication reduction.

The Role of Progressive Striatal Dopaminergic Denervation for Dopaminergic Sensitization

In experimental 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) models, the severity of the striatal dopaminergic lesion determined L-Dopa induced dyskinesia and stereotypy punding-like behavior. Human degenerative PD differs from these models because the degeneration of dopaminergic neurons is slowly progressive. With increasing denervation, the capacity to store dopamine in intracellular vesicles of presynaptic dopamine neurons decreases. Nevertheless, even with total denervation idiopathic PD patients continue to respond to L-Dopa. Then, L-Dopa is transformed into dopamine in serotonergic and noradrenergic cells that contain enzymes to metabolize L-Dopa to dopamine. However, these cells do not possess selective dopamine transporters in the presynaptic membrane, nor selective vesicle membrane transporters.
transporters which are essential to store dopamine in the intracellular vesicles.\textsuperscript{19} This ultimately leads to pulsatility of dopamine concentrations in the synaptic cleft,\textsuperscript{4} where dopamine is rapidly metabolized.

There is converging clinical evidence that patients are more susceptible to dopaminergic sensitization as the dopaminergic denervation progresses. Generally, human beings without neurodegeneration of dopamine neurons do not show dyskinesia when exposed to L-Dopa (eg, patients with essential tremor, dystonia, or non-degenerative Parkinsonism).\textsuperscript{20} In degenerative PD, community-based studies suggested that dopaminergic complications occur approximately six to seven years from symptom onset, and independently from the time point of first L-Dopa therapy.\textsuperscript{21,22} Consistently, a constant dosage of L-Dopa led to higher levels of striatal dopamine in more advanced disease.\textsuperscript{23} This most likely reflected the reduced buffering capacity of extracellular dopamine, mirroring experimental findings.\textsuperscript{17} More recently, Cilia and colleagues showed that dopaminergic complications depended on incremental dopaminergic denervation.\textsuperscript{24}

They compared an early treatment PD cohort (within the first 2 years of symptom onset) against a delayed-treatment cohort (4–5 years after symptom onset). Despite this considerable delay, both showed similar motor and neuropsychiatric dopaminergic complications 5 years from symptom onset. Moreover, the initially drug-naïve delayed-treatment patients developed dyskinesias as early as 6 months after introducing L-Dopa. This is comparable with patients from the pre-L-Dopa era: dyskinesias developed within 2 years in those starting treatment 6 to 9 years after disease onset, but within 4 to 6 years when patients are treated early.\textsuperscript{25} Most recently, the LEAP study showed in a delayed-start design that patients experienced the same amount of dyskinesia when L-Dopa was introduced either early after symptom onset or delayed by 40 weeks, arguing against degenerative or protective effects of L-Dopa.\textsuperscript{26}

Together, these comprehensive studies lend clinical evidence that, in human degenerative PD, the progressive dopaminergic denervation is the major pathological prerequisite to dopaminergic sensitization.

**The Role of Pharmacotherapy and the Receptor Profile**

Under physiological conditions, striatal dopamine is mainly released continuously and has equal affinity to both D1 and D2 receptors.\textsuperscript{17} In PD, dopamine replacement therapy differs in two fundamental ways. First, L-Dopa intake leads to increasing and more pulsatile dopamine concentrations in the synaptic cleft as the denervation progresses. Second, the receptor profile of dopamine agonists differs from dopamine. Non-ergoline dopamine agonists (apart from apomorphine) stimulate the D2 receptor family and have high affinity to D3 receptors in the mesocorticolimbic system.\textsuperscript{27} Stimulation of mesolimbic D3 receptors leads to upregulation of D3 receptor expression, unlike stimulation of other receptors. This relates to the role of the mesolimbic system in learning to react to reward by enhancing the behavioral response.\textsuperscript{28} Clinically, preferential stimulation of D3 receptors is associated with the expression of behavioral addictions or ICDs in PD, as reviewed elsewhere.\textsuperscript{1,3}
Early pharmacotherapy after PD diagnosis, that is L-Dopa monotherapy vs. L-Dopa-sparing regimens relying on dopamine agonists with or without combination with L-Dopa, determine the motor and neuropsychiatric symptom profiles months and years from treatment choice.29 While motor symptoms, dyskinesias, and motor fluctuations have been repeatedly compared between the two strategies, neuropsychiatric endpoints were not systematically studied. L-Dopa-weighted therapy has a superior effect on akinesia but requires fractioning of dosages. This circumstance relates to both its pharmacokinetic profile and to progressive dopaminergic denervation. Moreover, there is a role of the L-Dopa dosage in motor sensitization.3,17,30 As such, the ELLDOPA study showed that dyskinesias occur after a delay of 40 weeks following administration of a stable dosage of L-Dopa, but more often with higher dosages.5 Fractioning of L-Dopa is therefore considered for the management of L-Dopa-induced dyskinesia. Similar findings on dose-dependency came from the STRIDE-PD trial31 and from an extended observation of an RCT comparing L-Dopa and pramipexole treatment.32 In this framework, patients would develop dyskinesia to a similar extent and at a similar time, irrespective of whether L-Dopa was introduced early or delayed,24 as monotherapy or as adjunct following a sparing strategy.33 Taken together, this prompted claims for a novel L-Dopa management perspective in terms of ‘don’t delay – start today’ when patients require L-Dopa to achieve satisfactory relief from akinesia.34 However, research into the role of fractioning for prevention or management of neuropsychiatric complications, particularly ICD, has been neglected.

Relying on their long-duration profile, dopamine agonists without or with reduced dosages of L-Dopa may help to stabilize motor and neuropsychiatric fluctuations by reducing uncontrolled off-related akinesia, dystonia, and dysphoria. However, dopamine agonists contribute to more profound neuropsychiatric complications in terms of ICD1,35 and are less efficient for akinesia, such that most patients will require L-Dopa in the long term. Once treated first with dopamine agonists early from diagnosis, the annual ICD incidence rates steadily increased from 8% in year 1, to 18% in year 2, and 25% in year 3, but decreased in those without dopamine-replacement therapy, as suggested from the Parkinson’s Progression Marker Initiative Cohort.36 Beyond pharmacotherapy, risk factors such as younger age, male gender, and others predispose to behavioral addictions and may be considered risk modifiers.35 Importantly, ICD was also observed in patients with L-Dopa monotherapy, which supports the role of L-Dopa pulsatility in ICDs, beyond the role of dopamine agonist D3-receptor affinity. Dopamine agonist withdrawal syndrome may further complicate medication adjustment.

In summary, the pulsatility of L-Dopa contributes to L-Dopa-induced dyskinesia and ICD, whereas the high D3-affinity of dopamine agonists is critical to ICDs. Given that most patients require L-Dopa to achieve satisfactory relief from akinesia as the disease progresses, neuropsychiatric complications occur as a common therapeutic dilemma.

Neuropsychiatric Consequences from Dopaminergic Sensitization

Dopaminergic treatment has marked psychotropic effects by selectively increasing dopamine in the mesolimbic synapse. This is further reinforced by mesolimbic dopaminergic denervation in PD. Together, neuropsychiatric fluctuations are the inevitable consequence.8,37–39 Paralleling motor fluctuations,40 they occur as off-drug and on-drug-related symptoms, with rapid alterations in mood and cognition depending on the dopamine level and degree of sensitization. The off-drug period comes with symptoms such as reduced motivation, sadness, dysphoria, anxiety, empty mind, and cognitive slowing. The on-drug period presents with subjective well-being, increased motivation, creativity, euphoria, racing of thoughts, and hypomania, up to full-scale manic psychosis.

Impulse control disorder relates to a spectrum of behavioral addictions that include pathological gambling and buying, hypersexuality, punding, and binge eating as most common presentations.41 Beyond the L-Dopa dosage, dopamine receptor agonists lead to pronounced susceptibility for ICDs.42 Across different cohorts, 17.6–51.5% of patients treated with dopamine agonists were identified with ICD in the long term, which was remarkably more frequent compared to those without dopamine agonist treatment.35,43 Male gender, younger age, personal history of ICD, and premorbid novelty-seeking behavior were identified as additional risk factors,43,44 as was the degree of dopaminergic denervation as suggested from DAT availability.36 In particular, this latter aspect parallels mechanisms in L-Dopa-induced dyskinesia that resulted from dopaminergic denervation in animal models16 and PD.4 In the limbic domain, on-drug euphoria but not off-period dysphoria correlates with ICD. Therefore, the psychostimulant effects of dopamine treatment during on-drug euphoria have been postulated to drive both behavioral addictions and DDS.

The combination of compulsive dopaminergic medication intake and presence of multiple ICDs was initially referred to as ‘hedonistic homeostatic dysregulation’,45 highlighting the shared mechanism between ICD and drug addiction, and was then renamed DDS.46 DDS was reported in 3–4% of pharmacologically-treated PD populations and up to 16% of candidate DBS patients47; however, generalizable prevalence data is missing.
Compulsive medication intake of the most short-acting dopaminergic medication, such as liquid L-Dopa or subcutaneous apomorphine injections, is the core clinical feature. There is direct experimental evidence that DDS results from dopaminergic sensitization, when single doses of L-Dopa induces larger endogenous dopamine release in the ventral striatum in patients with DDS compared to those without. Detailed reviews on the full clinical spectrum of hyperdopaminergic neuropsychiatric symptoms are provided elsewhere.

Deep Brain Stimulation: State-of-the-Art Evidence in Treating Dopaminergic Complications

In the following, we will first review the available clinical evidence for STN-DBS compared to best medication treatment on motor and QOL outcomes in patients with dopaminergic complications. These trials considered postoperative follow-up periods from several months up to 2 years, whereas the results of long-term outcomes stem from open observations reviewed elsewhere. We will also review the effects of STN-DBS compared to best medical treatment, and how consecutive postoperative medication reductions support desensitization in the neuropsychiatric domain. Therefore, we focus on STN-DBS, which enables postoperative reduction of dopaminergic medication compared to GPi-DBS. From there, we will develop our debatable viewpoint regarding how these insights may integrate with present clinical practice and future clinical trials. For completeness, we provide an additional summary comparing the outcomes of STN-DBS and GPi-DBS as Table S1.

Effects of STN-DBS on Motor Complications and Quality of Life

Subthalamic DBS developed from an experimental surgery to established therapy with the highest level of evidence among PD therapies. In a recent summary of the existing RCTs comparing STN-DBS with best medical treatment in treating motor fluctuations, STN-DBS resulted in a mean off-time reduction of 50.8% (summary of the randomized controlled trials in Table S2). Motor scores ‘off L-Dopa’ improved with stimulation by a mean of 52%. In addition, motor complications were reduced by 49.1%. The reduction in the L-Dopa equivalent daily dose was variable (21–66%), with a mean of 37%, thus accounting as the main determinant for the antidyskinetic effects of STN-DBS. Three of these RCTs reported improvement in QOL as the primary outcome. Of note, motor outcomes with STN-DBS correlated with the preoperative L-Dopa response, whereas patients with an unfavorable preoperative L-Dopa response showed an inferior motor response. In addition to meticulous pre-surgical patient selection, both the precision of stereotactic targeting and postoperative stimulation and medication management are key to favorable outcomes.

Subthalamic DBS is presently considered when patients encounter meaningful motor complications that result in unpredictable daily planning and reduced psychosocial engagement. The EARLYSTIM study aimed to avoid these dopaminergic complications and provided QOL improvement to patients with early dopaminergic complications (disease duration >5 years, fluctuations and dyskinesia present for no longer than 1.5 years). Unrelated work hypothesized a potential neuroprotective effect when introducing STN-DBS early from diagnosis and in the absence of dopaminergic complications. The existing findings were discussed controversially regarding the intended slowing of disease progression, and the concept was carried forward to a larger ongoing prospective multicenter trial to draw more definite conclusions.

Common complications related to surgery and postoperative long-term follow-up include hemorrhage, infections, and device-related complications, neuropsychiatric and cognitive side effects. While global cognitive outcomes were stable after STN-DBS procedures, cognitive side effects were centered around executive functions.

Further preoperative variables need to be considered to balance the benefits and risks of STN-DBS. Generally, an arbitrary age limit of 70 years was respected. Common sense allowed for exceptions, taking into consideration biological age and absence of comorbidities, asymptomatic vascular lesions or atrophy on brain MRI, and minimal cognitive impairment. Even within these arbitrary age limits, higher age seemed to indicate worse motor outcomes, higher surgical complication rates, worse cognitive outcomes, and smaller QOL improvement in some studies. Worse cognitive function in non-demented patients was associated with lower improvement in QOL. Unrealistic preoperative expectations, higher anxiety, and apathy added to less favorable QOL outcomes.

Subthalamic DBS Supports Dopaminergic Desensitization in the Neuropsychiatric Domain

Subthalamic DBS generally led to a substantial decrease in the postoperative L-Dopa-equivalent dosage in previous RCTs, which substantially contributed to the decrease in dyskinesia. Desensitization has been proposed to explain the dyskinesia improvement, and more recently the concept of dopaminergic desensitization has been extended to the behavioral side effects of L-Dopa. Importantly,
desensitization outdates the timepoint of medication adjustment for weeks to months, based on both clinical and experimental findings. ³ The consequence is a reduction in motor and neuropsychiatric clinical signs, such that neuropsychiatric fluctuations, ICDs, and DDS improve in the first months after surgery and show relatively stable outcomes from one to several years after initiation of STN-DBS,⁶⁻⁸,⁶⁵ similar to the stable long-term motor outcomes.⁵⁵

**Neuropsychiatric Fluctuations**

With chronic decrease in dopaminergic treatment, there is desensitization to the psychotropic effects of L-Dopa. As result, on-drug euphoria is reduced.⁷,⁸ Consistently, an acute L-Dopa challenge 1 year after surgery produced a smaller psychotropic effect while using identical drug dosages.¹⁵ STN-DBS by itself has amphetamine-like psychotropic effects on off-period neuropsychiatric symptoms by enhancing well-being and attention and by lowering fatigue, anxiety, and inner restlessness when switching on stimulation in the off-drug condition.⁷⁴ These beneficial effects are also found with chronic STN-DBS, together with marked improvement in neuropsychiatric fluctuations.⁷,⁷⁵ An RCT comparing STN-DBS to best medical treatment confirmed these findings.⁸

**Impulse Control and Related Disorders**

In the absence of a blinded RCT, the effect of chronic STN-DBS on ICD and DDS is estimated from several prospective studies and summaries of the available retrospective and prospective patient series.⁶,⁷⁶ Early case reports described improvements in dopamine addiction⁷⁷ and pathological gambling⁷⁸ in parallel to the postoperative decrease in dopaminergic medication. Since then, larger cohorts from several independent centers followed for periods of up to 7 years supported the overall beneficial long-term effect of STN-DBS on ICD.⁷,⁸,⁴⁷,⁶⁵ The most recent prospective study showed improvement in 95% of patients with preoperative ICD. Dopamine agonist dose reduction was the main driver of ICD improvement.⁶,⁷⁹ Desensitization consequent to a decrease in dopaminergic medications, together with a decrease in on-drug euphoria, seemed to represent the basic mechanism.¹⁵ Systematic improvement of ICD has not been reported in GPI-DBS,⁸⁰ which likely reflects the fact that GPI-DBS generally does not allow for a substantial decrease in dopaminergic medication.

STN-DBS leads to an increase in impulsivity,⁸¹ which is thought to be related to current diffusion to the non-motor parts of the STN. However, this only rarely translates into psychiatric complications such as mania, ICD, or DDS. Mostly, these complications occur in the immediate postoperative period and are potentially reversible after DBS or medication adjustments.⁸² De novo onset of ICD / DDS after STN-DBS surgery has been reported more rarely, and is mostly associated with the lack of decrease or even an increase in the L-Dopa equivalent dosage or alternatively to direct stimulation of the STN non-motor part.⁷⁶,⁸⁰ In the long-term follow-up of patients with STN-DBS, ICD are relatively rare⁶⁵ compared to surgical candidates.⁴⁷

Postoperative management of DDS patients can be challenging when addictive drug-seeking behavior or agonist-withdrawal syndrome conflicts with the intended reduction in L-Dopa and dopamine agonists.⁷⁹ To this end, systematic comprehensive evaluation of behavior, awareness of the neurologist for the slowly progressive nature of dopaminergic desensitization, as well as education and cooperation of the patient are required to improve or revert DDS.

**The Risk of Postoperative Apathy**

Apathy and depression in PD mainly relate to progressive serotonergic and mesolimbic dopaminergic denervation.⁸³,⁸⁴ Apathy in PD is frequent and bothersome to QOL.³⁹ It is observed during prodromal and early PD and increases as the disease progresses. Apathy is common after bilateral STN-DBS, possibly related to the postoperative decrease in dopaminergic medication.⁸² Consistently, the COMPARE trial showed that unilateral STN-DBS, together with a less profound reduction and slow taper of dopaminergic medication, led to relatively stable or only slightly worse outcomes in postoperative mood and apathy.⁸⁵,⁸⁶ In an RCT comparing STN-DBS to best medical treatment and evaluating apathy as secondary endpoint, there were no between-group differences in apathy over 2 years of follow-up, thus supporting the notion that postoperative apathy is not inevitable and is amenable to medical management strategies.⁸

However, apathy increases on average after STN-DBS compared to the preoperative state.⁸⁷,⁸⁸ In the most recent meta-analysis,⁸⁷ postoperative apathy was not statistically correlated with a reduction in dopamine replacement therapy, leading to speculations regarding a direct apathy-inducing effect of STN-DBS per se.⁸⁷ However, meta-analysis of the literature is limited in determining the causal underpinnings. L-Dopa and dopamine agonists do not have the same psychotropic effects; thus, correlation with total L-Dopa equivalent dosage is ambiguous. A series of studies used detailed clinical evaluations, excessive experimental withdrawal of dopaminergic treatment, a randomized placebo-controlled design, and imaging of the dopaminergic system for an in-depth understanding of the mechanisms of postoperative apathy.⁷,⁸³,⁸⁵ Dopamine
agonists were arrested in all patients on the day of surgery, and the L-Dopa dosage was minimized as long as there was no motor worsening. It was found that in 50% of patients followed with monthly apathy evaluations over a year, postoperative apathy occurred after a mean delay of 4 months following drug decrease, and was often accompanied by depression and anxiety. Postoperative apathy was predicted only by the severity of preoperative neuropsychiatric fluctuations, and in an imaging study by the severity of mesocorticolimbic dopaminergic denervation. Improvements in off-period apathy and dysphoria related to STN-DBS per se, while improvements in ICD and On-drug euphoria were explained by drug withdrawal. Finally, piribedil (a D2/D3-selective dopamine agonist) led to improvements in postoperative apathy compared to placebo, suggesting that postoperative apathy occurring in the aftermath of STN-DBS surgery can be explained by postoperative withdrawal of dopaminergic treatment.

Despite these studies favoring dopamine withdrawal as the main contributor to postoperative apathy, there is an ongoing discussion as to whether STN stimulation could induce apathy by itself, independent of the medication decrease. In a recent study, postoperative apathy occurred more frequently in patients with electrodes placed in the sensorimotor STN and its dorsal border zone to the zona incerta. A pro-apathetic effect was attributed to STN-DBS based on correlative evidence in this study. As a limitation, there was no experimental stimulation intervention on apathy outcomes, which remains a source of insecurity when interpreting these findings. A previous study with well-placed electrodes (judged by motor benefit) showed that switching on STN stimulation per se led to acute improvement in apathy. This anti-apathetic effect of STN-DBS was associated with stimulation of the more ventrally-located associative-limbic STN, while the more dorsally-located STN was responsible for improvements in akinesia. Thus, postoperative apathy related to a more dorsally-placed electrode could reflect lower or absent current diffusion to the ventral STN. Another putative explanation would be current diffusion to the pallido-thalamic fibers medially or dorsally from the STN, which may inhibit the prokinetic and psychostimulant effects of L-Dopa. Thus, stimulation of the pallido-thalamic fibers of the zona incerta may mimic the effects of high-frequency stimulation of the ventral GPi or the caudal pallido-thalamic tract leaving the GPi through the ansa lenticularis projecting through the zona incerta dorsally from the STN. This would explain not only the inhibition of L-Dopa-induced dyskinesia, but also of the psychototropic effects of L-Dopa.

Of note, it has been proposed that DBS of the ventral limbic area of the STN might be a target for depressive symptoms in PD and major depression. Future field shaping, including vertical steering, and imaging- and volume-of-tissue-activated-based stimulation, may help deliver more personalized STN-DBS by dissecting both the motor and limbic aspects (apathy/depression) of PD.

Finally, with longer duration of follow up after surgery, ongoing neurodegeneration and more widespread synucleinopathy of non-dopaminergic and non-serotonergic neurotransmitter systems as well as comorbid vascular disease lead to increased cognitive impairment and contribute to L-Dopa resistant apathy.

**Does Continuous Dopaminergic Treatment Play a Role in Dopaminergic Desensitization?**

Whether continuous dopaminergic treatment, in terms of intestinal levodopa-carbidopa or apomorphine pump, would reverse dopaminergic sensitization by changing pulsatile L-Dopa to continuous treatment needs to be studied in greater detail. While it is clear that continuous treatment stabilizes the motor state by increasing ‘on periods without troublesome dyskinesia’, the clinical evidence is incomplete in the neuropsychiatric domain, with first uncontrolled observations that ICDs may improve with either treatment.

**Viewpoint: “Changing Gears – Using Subthalamic Stimulation to Interfere with the Motor or Neuropsychiatric Consequences of Dopaminergic Sensitization?”**

Traditionally, DBS in PD was applied as a ‘last resort’ therapy to attenuate the most severe and advanced motor and non-motor fluctuations. In an individual patient, such severe fluctuations generally build up over years and are driven by both progressive striatal dopaminergic denervation and intensified dopaminergic treatment. However, the period from the first dopaminergic motor or neuropsychiatric sequelae and the time point of ‘last resort’ DBS therapy comes at growing costs for QOL, subjective well-being, and psychosocial functioning. Fig 2 models the temporal evolution of dopaminergic motor and neuropsychiatric complications along the disease progression.

The detrimental effect of progressive dopaminergic sensitization was best illustrated in the EARLYSTIM trial in a 2-year follow-up, albeit in a strictly selected cohort that limited its generalizability. The best medical treatment group showed an approximately 250 mg increase in L-Dopa-equivalent dosage over 2 years, paralleling an increase in hyperdopaminergic behaviors and dyskinesia. In contrast, there was a reduction of approximately 370 mg in the L-Dopa-equivalent dosage in the
STN-DBS group, accompanied by an improvement in motor and neuropsychiatric complications. Consequently, the improvement in motor and neuropsychiatric complications of L-Dopa treatment led to an improvement in QOL only in the STN-DBS group.

From these findings, we posit the core question: Is it time to change gears by using subthalamic stimulation soon after the first clinical signs of dopaminergic sensitization unfold as motor or neuropsychiatric complications? Could this earlier time point of intervention help interrupt the vicious circle of dopaminergic sensitization by allowing sparing of dopaminergic medication, thereby reducing neuropsychiatric consequences and psychosocial costs of the motor and neuropsychiatric dopaminergic complications?

We propose to study the use of STN-DBS at an early time point in the individual disease course, when a patient displays the first clinical signs of dopaminergic sensitization and has entered the vicious circle of increasing dopaminergic complications but has not yet experienced irreversible psychosocial and clinical consequences. Of note, we would like to emphasize that this means widening the indication criteria to the neuropsychiatric domain. Thus, indications may include first motor complications as reflected in the EARLYSTIM study, but also the neuropsychiatric sequelae of dopaminergic sensitization – in particular, neuropsychiatric fluctuations and behavioral addictions in terms of ICD and DDS. These may even occur in the absence of motor complications, although most patients experience motor and neuropsychiatric complications from dopaminergic sensitization in parallel. Moreover, we would like to make it explicit that the earliest time point of intervention in our concept is after the onset of first dopaminergic complications, reflecting the severity of nigrostriatal and mesocorticolimbic dopamine depletion. Importantly, we separate our concept from other unrelated work that considers STN-DBS early after PD diagnosis and in the absence of any dopaminergic complications hypothesizing neuroprotective effects of STN-DBS.61,62 While data from animal models suggested neuroprotection in some of the surviving dopaminergic

FIGURE 2: Motor and neuropsychiatric complications that occur as consequence of both progressive striatal dopaminergic denervation and intensified dopaminergic treatment. During the prodromal phase slowly increasing motor symptoms are often accompanied by depressive mood. After diagnosis and first dopaminergic treatment, there is an initial honeymoon phase without motor and neuropsychiatric complications. Then patients enter a prolonged period of incremental motor and neuropsychiatric fluctuations. We label clinical signs and symptoms upon first appearance; these symptoms are persistent and incremental when patients are treated with oral medications (represented by the dashed and dotted lines). Hypodopamnergic symptoms (color-coded in blue) include both motor and neuropsychiatric wearing off. Hyperdopaminergic symptoms (color-coded in red) include dyskinesia, hypomania, and ICD spectrum disorders. Here, we suggest that STN-DBS may interrupt this vicious circle when the first clinical signs of dopaminergic sensitization occur in the motor or neuropsychiatric domain. Presently, STN-DBS is introduced earliest using EARLYSTIM criteria when motor fluctuations emerge including uncontrolled off-symptoms relevant to quality of life and activities of daily living. Here, we suggest that neuropsychiatric fluctuations and hyperdopaminergic symptoms alone represent an indication for STN-DBS, and that this should be studied in future randomized controlled trials. In our view, STN-DBS should not be introduced before the onset of dopaminergic complications or after late-stage disease milestones occur in med on. Abbreviations: ICD – impulse control disorder; QOL – quality of life; STN-DBS – subthalamic nucleus deep brain stimulation.
neurons, the clinical evidence from long-term follow-up of STN-DBS patients do not presently support conclusions regarding a neuroprotective effect of STN-DBS.\textsuperscript{55} Furthermore, QOL, particularly improved in those patients in whom it was impaired preoperatively impaired by dopaminergic complications.\textsuperscript{100} However, QOL can certainly worsen if surgical complications or management problems occur. Together, we advocate that DBS therapy without the presence of L-Dopa-induced complications should presently not be performed outside clinical trials.

In this framework, we suggest rethinking the use of STN-DBS in future trials. We propose to evaluate STN-DBS in patients with earlier disease onset, who face longer cumulative L-Dopa exposure over their lifetime and who generally have more severe presynaptic dopaminergic lesions (and thereby increased susceptibility to dopaminergic sensitization) – but less tendency to develop L-Dopa-resistant motor and non-motor symptoms. Such a strategy requires identification of patients with dopaminergic sensitization early enough along their individual disease course. Independent from dyskinesia as motor feature, the neuropsychiatric domain needs closer longitudinal evaluation. Assessments of non-motor fluctuations, neuropsychiatric fluctuations, hyperdopaminergic behaviors and of ICDs are needed, and may be validated as future inclusion criteria for clinical trials. If applied in this regard, STN-DBS might enable modification of the longitudinal motor and neuropsychiatric symptom expression – not by changing neurodegeneration, but by interrupting a vicious circle that arises from the combination of the presently inevitable progressive striatal denervation and the potentially reversible intensifying dopaminergic treatment.

We have focused on STN-DBS treatment in this viewpoint because it has the strongest evidence basis to support dopaminergic desensitization among all currently available continuous therapies. This is not to say, however, that continuous dopaminergic treatment does not have the potential to counteract dopaminergic sensitization by reducing pulsatility and D3-receptor stimulation. However, it will remain for future studies to evaluate whether continuous dopaminergic treatment supports desensitization to a similar degree, in particular in the neuropsychiatric domain.

Conclusions
Deep brain stimulation has traditionally evolved as an evidence-based therapy for the treatment of PD patients with motor complications arising from L-Dopa treatment. Intensive clinical research over the last decade supports the notion that DBS therapy in PD – representing a neuropsychiatric disease – must consider both motor and neuropsychiatric symptoms as inclusion criteria in future RCTs, to modify the complications from dopaminergic sensitization. There is a need to validate the best clinical pathways for STN-DBS, when patients encounter the first clinical signs of dopaminergic sensitization in these symptom domains.

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Author Contributions
All authors contributed to the conception and design of this Neurology Grand Round article. D.W., P.K., G.D. conducted literature research and interpretation of the studies. D.W. wrote the first draft. All authors reviewed and edited on the draft, and approved the final version. D.W., G.D., P.K. prepared and drafted the figures.

Potential Conflicts of Interest
DW reports grants and personal fees from Medtronic, Abbott, Boston Scientific, all three manufacturers of DBS equipment; reports personal fees from Abbvie and STADapharm, pharmaceutical companies of intestinal L-Dopa therapy. JV reports grants and personal fees from Medtronic, Boston Scientific. Reports grants and personal fees from Newronika, manufacturer of DBS equipment. AF reports grants and personal fees from Medtronic, Boston scientific, non-financial support from Medtronic, personal fees from Abbott. AK reports personal fees from Medtronic, Boston Scientific, Abbott. “PK reports grants and personal fees paid to employing institution from Boston Scientific, Zambon and Bial” GD reports grants from Medtronic, personal fees from Boston Scientific.

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