DBS Utilization will Expand in the Treatment of PD in the Future: Con

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Deep Brain Stimulation

- Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become the most often practiced neurosurgery for *symptomatic* treatment of motor features of Parkinson's disease (PD).

- Most important development in the treatment of PD since levodopa became available.

Main Points

- DBS has limitations
- Other treatments for PD (potentially superior to DBS) are currently in the pipeline
- Consequence: DBS will eventually be replaced by other treatments IN THE FUTURE
- History supports this notion (e.g. pallidotomy)

Limitations of DBS

- Non-motor symptoms typically do not respond
- Treatment-associated complications
- Cost and access to the therapy
- Exclusion criteria limit the therapy to few

Early non-motor PD features

- Anosmia (loss of smell)
- REM sleep behavior disorder
- Depression
- Constipation
- Restless leg syndrome?

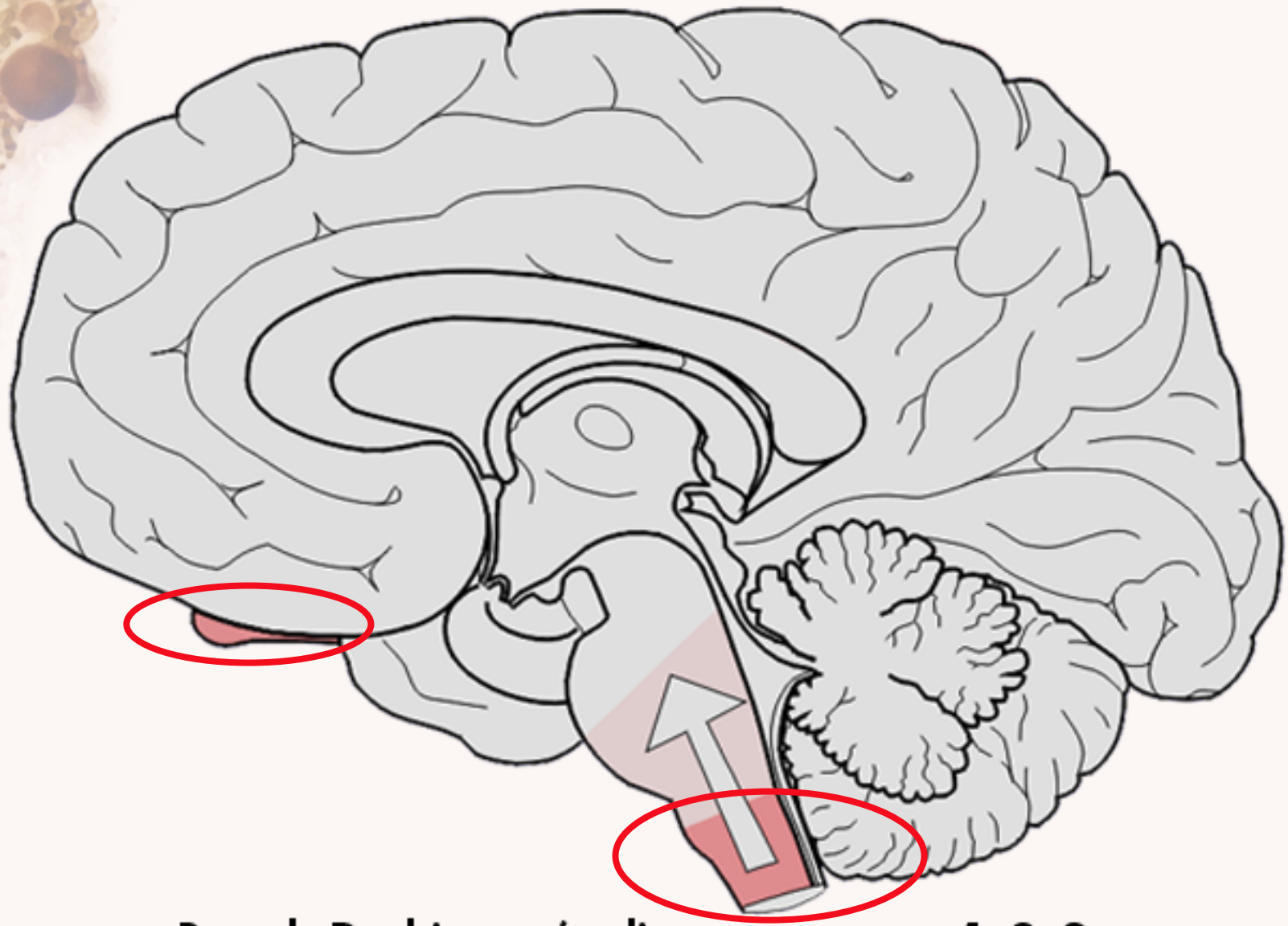
Pre-motor symptoms

Non-Motor Features of PD

- Depression: 45%
- Cognitive impairment: executive dysfunction common; > 40% late dementia
- Sleep disorders: sleep fragmentation, REM-sleep behavior disorder, restless leg syndrome
- Late autonomic dysfunction (i.e., blood pressure decreases when standing)

Lemke MR, et al.. 2005. Witjas T, et al.. 2002; Adler C, 2005

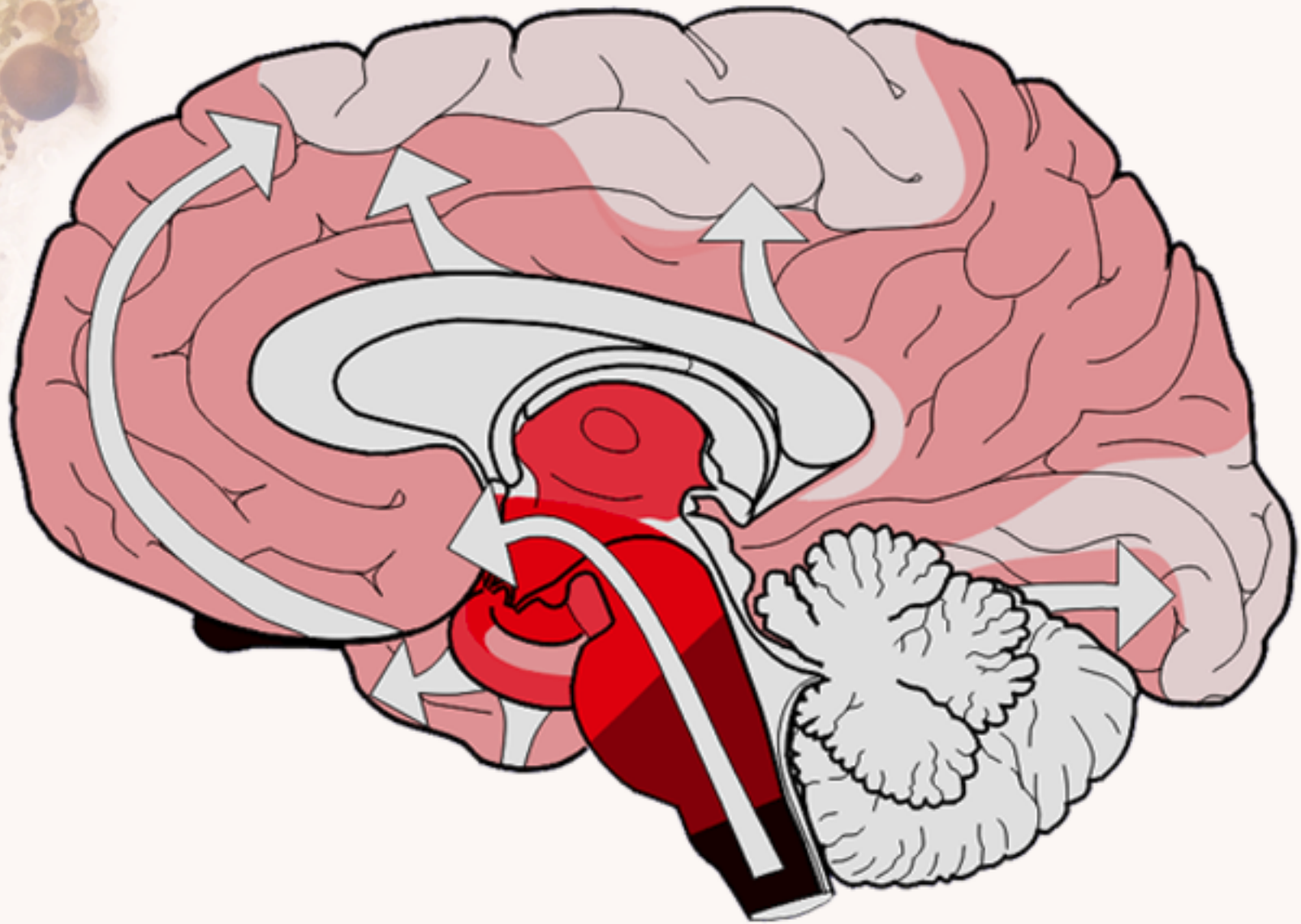
Courtesy of Heiko Braak



Braak Parkinson's disease stages 1 & 2

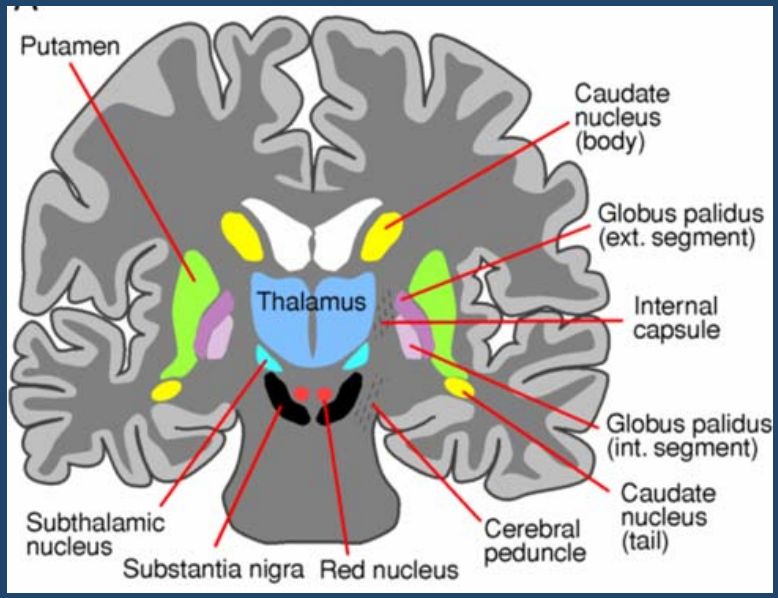
PRECLINICAL

Courtesy of Heiko Braak

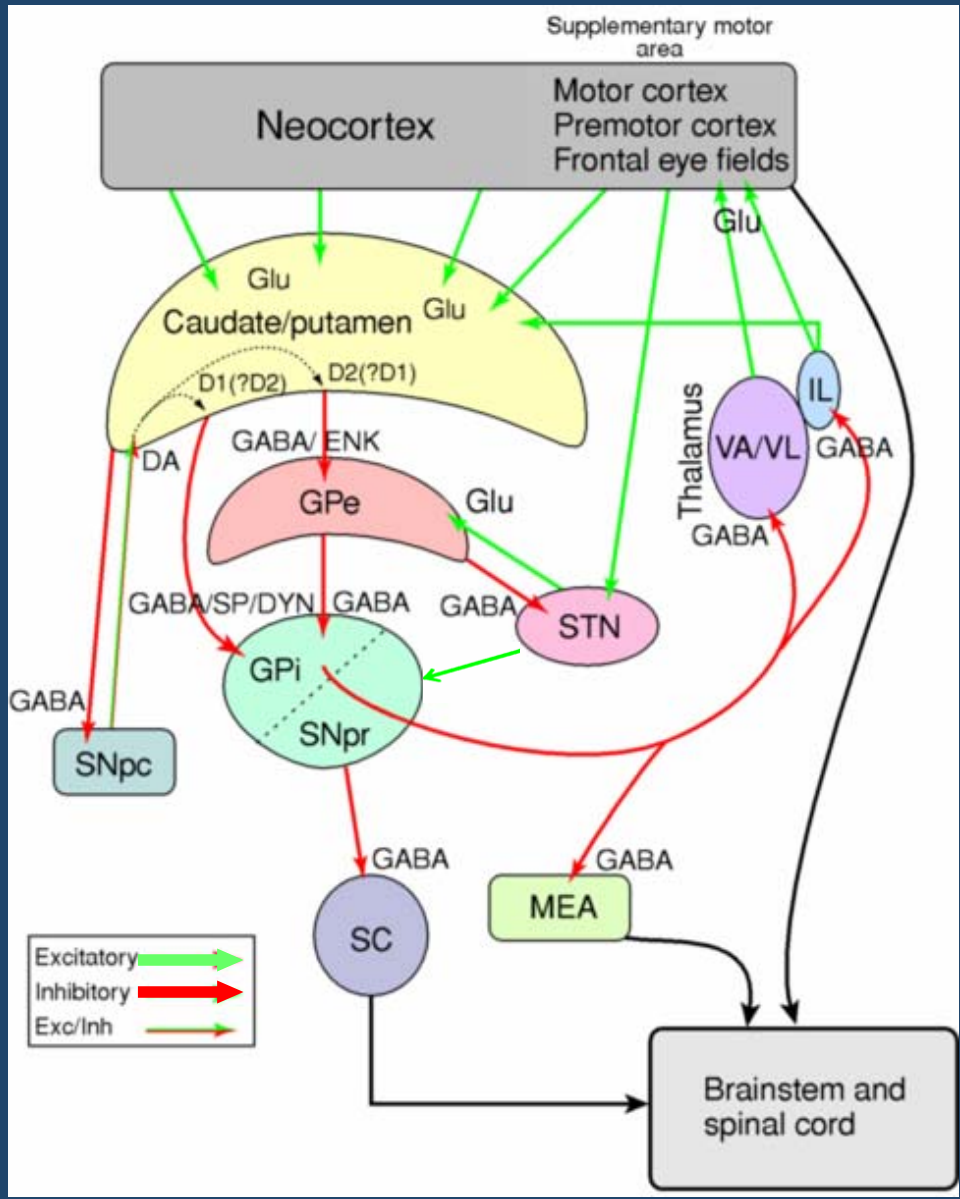


Braak Parkinson's disease stages 5 & 6

COGNITIVE IMPAIRMENT



Basal Ganglia: Anatomy & Physiology



The Challenge: symptoms not responsive to current treatments

- Cognitive function
- Psychiatric difficulties
- Bladder problems
- Constipation
- Sexual dysfunction
- Imbalance and postural instability
- Speech difficulties
- Swallowing difficulties

Cognitive impairment in PD

- Lead to caregiver burden and earlier institutionalization
- Cognitive impairment may increase with disease duration & worsening of motor problems
- Dementia may develop in > 40%
- Psychiatric
  - Depression / Anxiety / Apathy
  - Hallucinations

Green et al. 2002; Uc et al., 2005; Athey et al., 2005; Foltynie et al., 2004

NEUROLOGY 2002;59:1298–1299

Editorial

Penfield revisited?

Understanding and modifying behavior by deep brain stimulation for PD

Helen S. Mayberg, MD; and Andres M. Lozano, MD, PhD

While motor-system abnormalities are the defining features of PD, cognitive and neuropsychiatric symptoms are of major importance.[1,2] Disturbances in mood and motivation, such as depression, apathy, anxiety, impulsivity, and mood lability, are particularly common. These behavior changes can be seen early in the course of PD and may antedate motor dysfunction, providing empirical evidence for an "organic" rather than reactive etiology. Postmortem and in vivo biochemical as well as neuroimaging studies lend support to this hypothesis, with mesolimbic dopamine and serotonin abnormalities and frontolimbic dysfunction demonstrated in affected patient subgroups.[3]

Neuropsychiatric symptoms can also begin later in the illness suggesting that additional factors, acting

abnormalities, further suggesting potential common mechanisms at the neural systems level.[3] Anatomic studies provide additional preclinical evidence of distinct "cognitive" and "affective" pathways, although the picture is far more complex than originally hypothesized.[5,7,8]

As three papers in this issue of *Neurology* report,[9-11] complex neuropsychiatric symptoms also occur with subthalamic nucleus deep brain stimulation (STN DBS) performed for the treatment of refractory PD, thus providing a new avenue to explicitly test these various hypotheses. There are earlier reports of dramatic changes in behavior with STN DBS. In fact, a spectrum of acute and delayed neuropsychiatric symptoms follows this procedure including acute transient depressive and euphoric

Aggressive behavior induced by intraoperative stimulation in the triangle of Sano

B.P. Bejjani, MD; J.L. Houeto, MD; M. Hariz, MD, PhD; J. Yelnik, MD; V. Mesnage, MD; A.M. Bonnet, MD; B. Pidoux, MD; D. Dormont, MD; P. Cornu, MD; and Y. Agid, MD, PhD

Abstract—The authors report a patient with advanced PD, successfully treated by bilateral stimulation of the subthalamic nucleus, who developed acute transient aggressive behavior during intraoperative electrical test stimulation. The electrode responsible for this abnormal behavior was located within the lateral part of the posteromedial hypothalamic region (triangle of Sano). The authors suggest that affect can be dramatically modulated by the selective manipulation of deep brain structures.

NEUROLOGY 2002;59:1425–1427

Bilateral continuous high-frequency stimulation of the subthalamic nucleus (STN) is an efficient treatment for levodopa-responsive forms of PD.[1] During surgery, optimal target selection is performed by test stimulation within the subthalamic region, seeking to obtain the best clinical improvement with the least side effects in awake patients.[2] Stimulation-induced behavioral disturbances such as a transient acute depression and laughter have been reported during periods of test stimulation.[3,4]

left side, typical STN activities[2] were recorded on the central trajectory, with a dramatic improvement in contralateral motor signs and the expected induction of dyskinesias during the test stimulation. During the exploration of the medial track (located 2.2 mm medial to the central trajectory; figure) thalamic reticular cellular activities[2] were recorded at the level of the bicommissural line (AC-PC) and no cellular activity was recorded below that level. When test stimulation using the usual current (140 Hz, 60 μsec, 2 volts) was applied on this track at a level 2 mm below the

Mania following deep brain stimulation for Parkinson's disease

J. Kulisevsky, MD; M.L. Berthier, MD; A. Gironell, MD; B. Pascual-Sedano, MD; J. Molet, MD; and P. Parés, MD

Abstract—Three patients with PD developed manic behavior after bilateral implantation of electrodes for deep-brain stimulation (DBS). Common to all three patients were manic symptoms unremitting after levodopa reduction or stimulation "off," lower electrodes positioning caudal to the subthalamic nucleus area, postoperative DBS with the lower contacts (0) of the quadripolar electrodes, and resolution of the manic episodes coinciding with stimulation through higher contacts.

NEUROLOGY 2002;59:1421–1424

Depression is a relatively frequent adverse effect of functional neurosurgery in PD. Transient depression induced by deep-brain stimulation (DBS) of the left substantia nigra has been reported in a PD patient with electrodes targeting the subthalamic nucleus (STN) area.[1] Among our first 15 consecutive patients with PD receiving STN-DBS (June 1999 to December 2000), we identified three patients who instead developed manic symptoms (elation, inflated self-

tionale for the unusual practice of initially stimulating through the lowest contact in each patient other than the routine taken from our previous experience in DBS of the pars interna of the globus pallidus. Active electrode contacts and stimulation parameters were progressively adjusted in the follow-up and resulted in significant improvement in parkinsonism (see table 1). The initial monopolar stimulation through the lower contacts of the quadripolar electrodes was changed in each patient at the end of the 1st postoperative week because they all showed

CME

Effect on mood of subthalamic DBS for Parkinson's disease

A consecutive series of 24 patients

A. Berney, MD; F. Vingerhoets, MD; A. Perrin, Lic Phil; P. Guex, MD; J.-G. Villemure, MD, FRCSC; P.R. Burkhard, MD; C. Benkelfat, MD, DERBH; and J. Ghika, MD

Abstract—A series of 24 consecutive PD patients were prospectively studied prior to and within 6 months postoperatively for mood, motor, and cognitive status to investigate the effects on mood of subthalamic deep brain stimulation (DBS) in PD. In six patients (25%), mood state worsened significantly, and three were transiently suicidal despite clear motor improvement. Caregivers and patients should be educated about the potential impact of this neurosurgical procedure on mood.

NEUROLOGY 2002;59:1427–1429

Subthalamic nucleus deep brain stimulation (STN-DBS) is a new effective treatment for severe PD resulting in major gains in motor function[1,2] and minimal or no cognitive impairment.[3] Transient acute depression, fulfilling *Diagnostic and statistical manual of mental disorders-IV* (DSM-IV) criteria for a major depression (except duration), has been observed after stimulation of the left substantia nigra pars reticulata.[4] This and other recent reports,[5,6] have raised the possibility that the procedure may have deleterious effects on aspects

Method. We studied 24 consecutive patients with PD (15 men, 9 women, ages 64.2 ± 7.9 years, duration of disease 13.6 ± 5.2 years; mean ± SD) refractory to medical treatment who underwent STN-DBS at Lausanne University Hospital (Switzerland). Exclusion criteria for neurosurgery included dementia, current axis I psychiatric disorder as defined by the DSM-IV, and poor response to a challenging dose of acute L-dopa.[2]

All patients were assessed during the month prior to the operation in their "best on" medication state and within 3 to 6 months under STN-DBS once stimulation

PAPER

Behavioural disorders, Parkinson's disease and subthalamic stimulation

J L Houeto, V Mesnage, L Mallet, B Pillon, M Gargiulo, S Tezenas du Moncel, A M Bonnet, B Pidoux, D Dormont, P Cornu, Y Agid

J Neurol Neurosurg Psychiatry 2002;**72**:701–707

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Objective: to analyse 24 parkinsonian patients successfully treated by bilateral STN stimulation for the presence of behavioural disorders.
Method: patients were evaluated retrospectively for adjustment disorders (social adjustment scale, SAS), psychiatric disorders (comparison of the results of psychiatric interview and the mini international neuropsychiatric inventory) and personality changes (IOWA scale of personality changes).
Results: parkinsonian motor disability was improved by 69.5% and the levodopa equivalent daily dosage was reduced by 60.5%. Social adjustment (SAS) was considered good or excellent in nine patients, moderately (n=14), or severely (n=1) impaired in 15 patients. Psychiatric disorders consisted of amplification or decompensation of previously existing disorders that had sometimes passed unnoticed, such as depressive episodes (n=4), generalised anxiety (n=18), and behavioural disorders with drug dependence (n=2). Appearance of mild to moderate emotional hyperreactivity was reported in 15 patients. Personality traits (IOWA scale) were improved in eight patients, unchanged in seven, and aggravated in eight
Conclusion: Improvement in parkinsonian motor disability induced by STN stimulation is not necessarily accompanied by improvement in psychic function and quality of life. Attention is drawn to the possible appearance of personality disorders and decompensation of previous psychiatric disorders in parkinsonian patients who are suitable candidates for neurosurgery. We suggest that a careful psychological and psychiatric interview be performed before surgery, and emphasise the need for psychological follow up to ensure the best possible outcome.

Journal of the International Neuropsychological Society (2007), **13**, 68–79.

DOI: 10.1017/S1355617707070105

Neuropsychological performance following staged bilateral pallidal or subthalamic nucleus deep brain stimulation for Parkinson's disease

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Abstract

Deep brain stimulation (DBS) has the potential to significantly reduce motor symptoms in advanced Parkinson's disease (PD). Controversy remains about non-motor effects of DBS and the relative advantages of treatment at two brain targets, the globus pallidus internus (GPi) and the subthalamic nucleus (STN). We investigated effects of DBS

Neuropsychological Performance after DBS for PD

- "DBS is associated with small reductions in speeded information processing and working memory. These findings are similar to deficits found to be associated with DBS in previous studies (Burchiel et al., 1999; Fields et al., 1999; Funkiewiez et al., 2004; Rodriguez-Oroz et al., 2005; Temel et al., 2005)"

- "Even subtle decrements in speeded information processing and working memory may impact performance in complex real-world tasks"

Rothlind JC, Cockshott RW, Starr PA, Marks WJ Jr. J Int Neuropsychol Soc. 2007 Jan;13(1):68-79

Stimulation of STN impairs aspects of cognitive control in PD

T. Hershey, PhD; F.J. Revilla, MD; A. Wernle, BSN; P. Schneider Gibson, MS, OT; J.L. Dowling, MD; and J.S. Perlmutter, MD

Abstract—*Objective:* To test the hypothesis that subthalamic nucleus (STN) stimulation in Parkinson disease (PD) patients affects working memory and response inhibition performance, particularly under conditions of high demand on cognitive control. *Methods:* To test this hypothesis, spatial working memory (spatial delayed response [SDR]) and response inhibition (Go–No–Go [GNG]) tasks requiring varying levels of cognitive control were administered to patients with PD with previously implanted bilateral STN stimulators (n = 24). Patients did not take PD medications overnight. Data were collected while bilateral stimulators were on and off, counterbalancing the order across subjects. *Results:* On the SDR task, STN stimulation decreased patients' working memory performance under a high but not low memory load condition (effect of stimulator condition on high load only and condition × load interaction, $p < 0.05$). On the GNG task, STN stimulation reduced discriminability on a high but not medium inhibition condition (effect of stimulator condition on high inhibition level only, $p = 0.05$; condition × inhibition level interaction, $p = 0.07$). *Conclusion:* STN stimulation reduces working memory and response inhibition performance under conditions of greater challenge to cognitive control despite significant improvement of motor function.

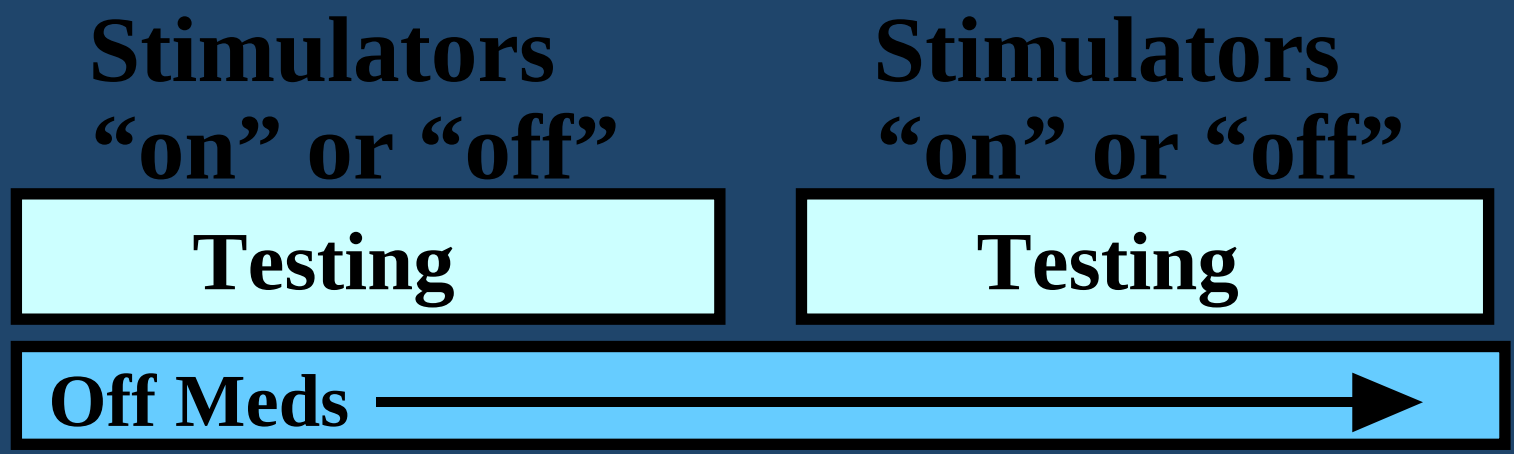
NEUROLOGY 2004;62:1110–1114

Despite the effectiveness of deep brain stimulation (DBS) of the subthalamic nucleus (STN) for motor symptoms of Parkinson disease (PD),[1,2] there has been concern about cognitive impairments following the procedure, as the surgery requires electrode penetrations through the frontal lobe.[3] Some studies have reported that surgery decreased performance on tasks that depend on prefrontal cortex[4,5] and require cognitive control, the active monitoring and manipulation of information in response to internal

Materials and methods. *Subjects.* This study was approved by the Institutional Review Board at Washington University School of Medicine, and all participants gave informed consent. Twenty-four patients with PD with previously implanted bilateral STN stimulators were studied. Patients met the diagnostic criteria for clinically definite PD.[14] The surgical implantation of stimulators (Medtronic model 3389 DBS leads, Minneapolis, MN) targeted STN with a technique that combines conventional stereotactic planning using formulas with reference to the anterior–posterior commissural line, visual targeting on T2-weighted MRI, frame-based targeting using computerized methods (Medtronic Stealth Station, Framelink IV), and microelectrode recording.[15] Intraoperative test stimulation confirmed optimal location of elec-

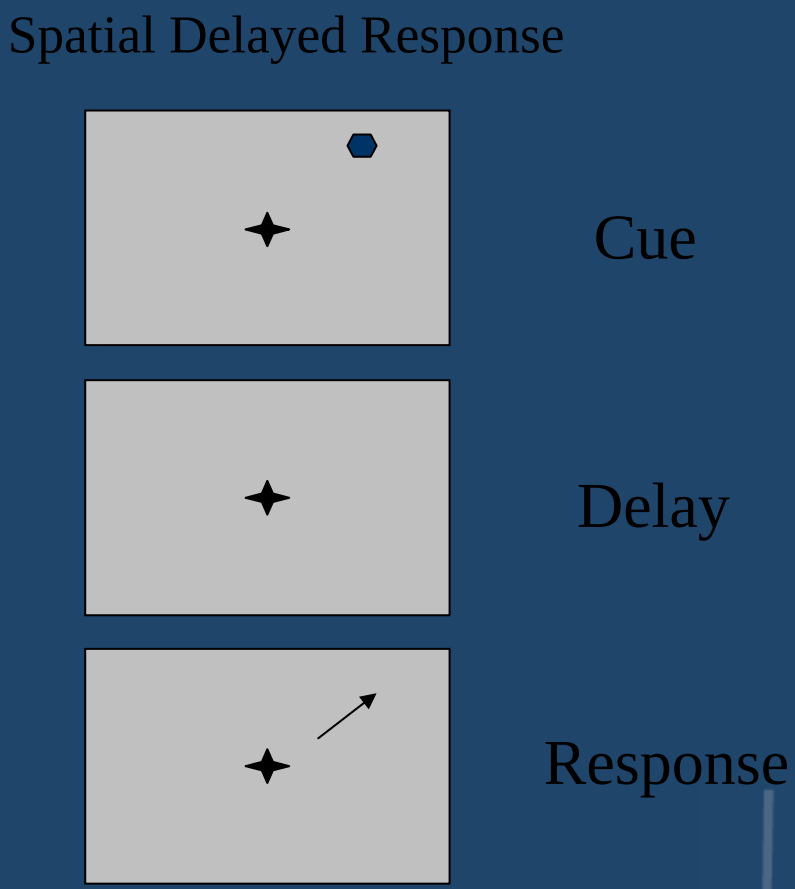
Methods

PD patients with bilateral STN stimulators



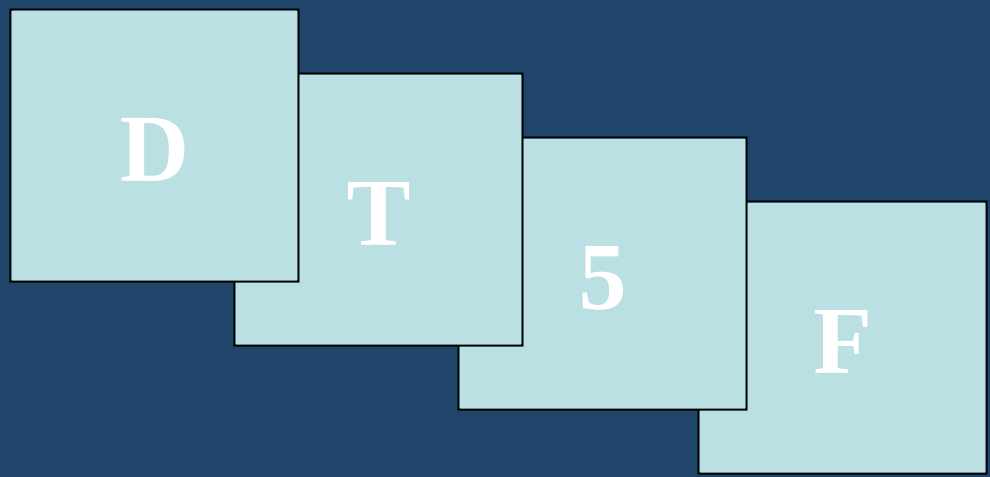
Working Memory

- Spatial Delayed Response Task (SDR)
  - delays: 0, 5 and 15 sec
  - cues: 1 or 2
  - CPT task during delay
  - recall error = mm

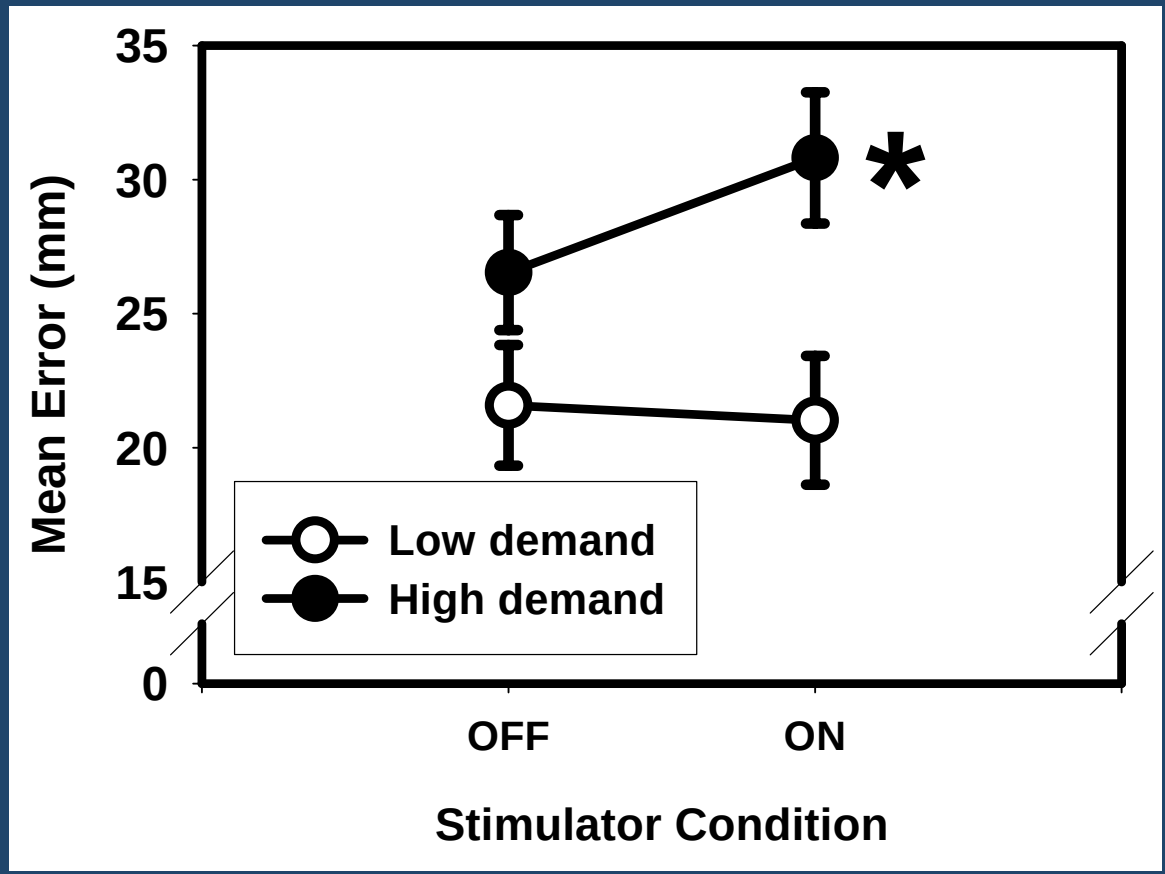


Response Inhibition

- Go No Go (GNG)
  - letters and 5s presented one at a time
  - press button for all letters, but not for 5s
  - frequency of letters and 5s equal (low demand), or more letters than 5s (17%) (high demand).



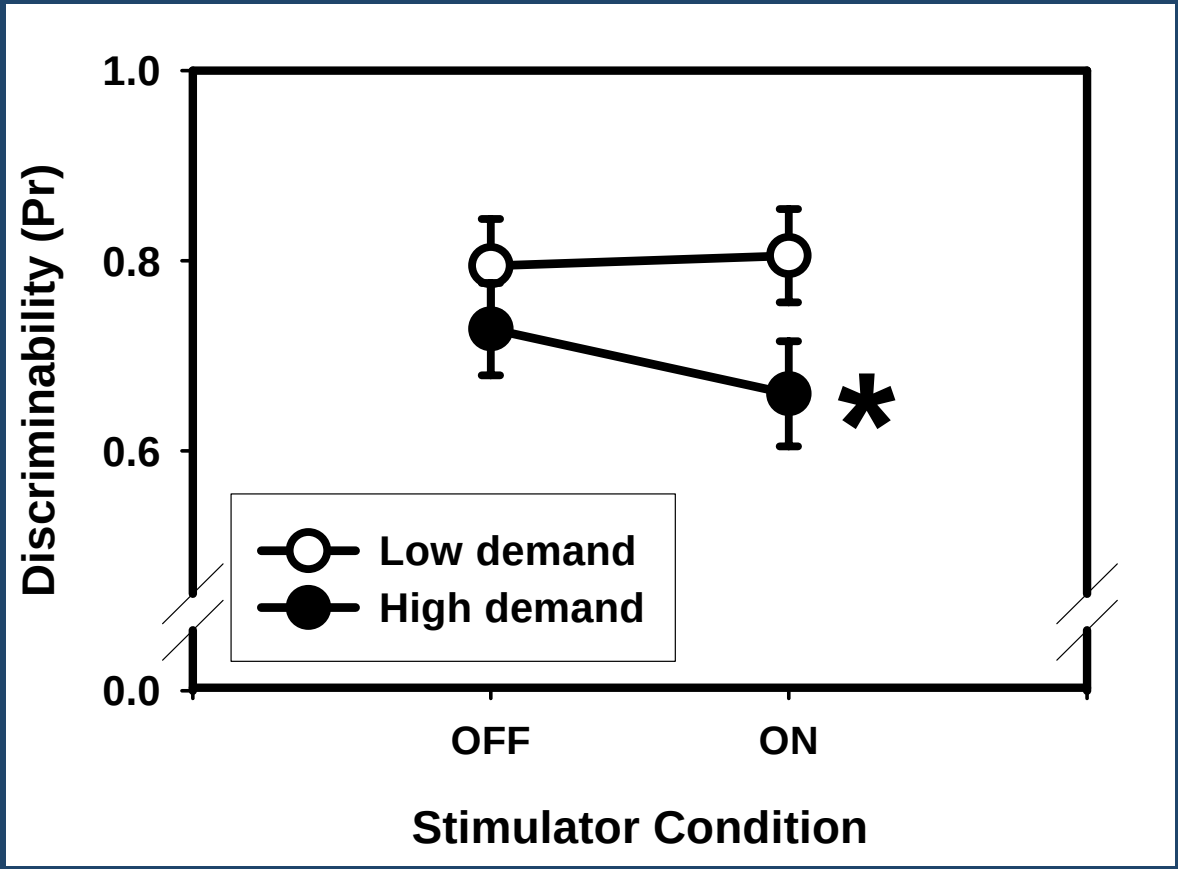
SDR



STN stimulation increased error on high demand ($p<.05$), but not low demand condition

Condition x demand ($p<.01$)

GNG



STN stimulation decreased Pr on high demand (p=.05) but not low demand condition.

Condition x demand (p=.07)

DBS and Suicide

- Suicide risk after DBS: 0.16 % to 4.3 %
- Soulas et al: 200 pts over 10 year-period
  - Completed suicide: 1% of patients
  - Attempted suicide: 2% of patients
- Suicidal behavior is a potential hazard of DBS
- Postoperative factors could include surgical or stimulation parameters

Moriarty J: Editorial in J Neurol Neurosurg Psychiatry. 2008 Aug;79(8):851
Soulas et al: J Neurol Neurosurg Psychiatry. 2008 Aug;79(8):952-4

DBS and Suicide

- Suicide in the general population (French of the same age (between 45 and 74 years) :
  - 16/100,000 for women
  - 37 to 50/100,000 for men

- Authors' conclusion: suicidal behaviour is a serious potential hazard of STN DBS

Soulas et al: J Neurol Neurosurg Psychiatry. 2008 Aug;79(8):952-4

Electrode Placement

- 7 patients with PD without improvement after DBS
- The misplacement of electrodes is a possible explanation for suboptimal response to DBS
- Average misplacement: 5.52 mm (2.89-10.45)

Anheim et al: Arch Neurol. 2008 May;65(5):612-6

ORIGINAL CONTRIBUTION

Improvement in Parkinson Disease by Subthalamic Nucleus Stimulation Based on Electrode Placement

Effects of Reimplantation

Mathieu Anheim, MD; Alina Batir, MD; Valérie Fraix, MD; Madjid Silem, MD; Stéphan Chabardès, MD; Eric Seigneuret, MD; Paul Krack, MD; Alim-Louis Benabid, MD, PhD; Pierre Pollak, MD

Background: The misplacement of electrodes is a possible explanation for suboptimal response to bilateral subthalamic nucleus (STN) stimulation in patients with Parkinson disease.

Objective: To evaluate whether reimplantation of electrodes in the STN can produce improvement in patients with poor results from surgery and with suspected electrode misplacement based on imaging findings.

Design: Prospective follow-up study.

Setting: Academic research.

Patients: A 1-year postoperative study was undertaken in 7 consecutive patients with Parkinson disease who, despite bilateral STN stimulation, experienced persistent motor disability and who were operated on for reimplantation a median of 16.9 months later.

Main Outcome Measures: The [illegible] the STN theoretical effective target, defined as the mean position of the clinically efficient contact from 193 previously implanted electrodes, were compared.

Results: Except for a single patient, all patients displayed improvement following reimplantation. Under off-medication (ie, the patient is taking no medication) condition, STN stimulation improved the basal state UPDRS motor score by 26.7% before reimplantation and by 59.4% at 1 year after reimplantation. The median off-medication Schwab and England score improved from 51% to 76%. The median levodopa equivalent daily dose was reduced from 1202 mg to 534 mg. The stimulation varibles changed from a mean of 2.6 V/73.0 µs/163.0 Hz to 2.8 V/60. 0 µs/140.0 Hz. The mean threshold of the first stimulation-induced adverse effect increased from 2.6 to 4.4 V. The mean distance between the contacts used for chronic stimulation and the theoretical effective target decreased from 5.4 to 2.0 mm. This distance correlated inversely with the percentage improvement in the UPDRS

principal objective of this study was to evaluate whether reimplantation of electrodes in the STN can produce an improved outcome in patients with poor results from surgery and with suspected electrode misplacement based on imaging findings.

Benabid et al[14] defined the theoretical effective target (TET) for STN implantation as the mean position of the contacts for clinical stimulation taken from 193 successfully implanted electrodes; statistically, the mean (SD) location is 5.02 (0.71)–twelfths of the anteroposterior commissure (AC-PC) line anterior to the posterior commissure, 1.5 (0.66)–eighths of the height of the thalamus below the AC-PC line, and 11.98 (1.12) mm lateral to the midline. The coordinates of the TET are reproducible at our center[15] and are similar to those found by other groups.[16,17]

METHODS

DESIGN AND PATIENTS

The first 7 consecutive patients with PD who were treated with bilateral STN stimulation, who demonstrated limited benefits from the method, and who were subsequently reoperated on at our center were studied. Limited benefit was defined as improvement of less than 40% in the UPDRS motor score, despite trials to optimize stimulation variables, for patients in whom the levodopa-induced motor score was higher than 60%. The 7 patients came from different centers, including 1 patient from our center. All patients satisfied criteria to qualify for surgery and for initial STN stimulation treatment.[18] Each patient had a minimal decrease in the LEDD following surgery, an STN stimulation response that was markedly lower than the corresponding levodopa response, and the occurrence of an initial stimulation-induced adverse effect at a voltage prohibitive to obtaining a fair antiparkinsonian effect. Of 14 electrodes implanted, 12 fulfilled criteria characteristic of misplacement (**Figure 1**). These electrodes, visualized with minimal artifact on T1-weighted sequences, were positioned outside of the STN hypointense sig-

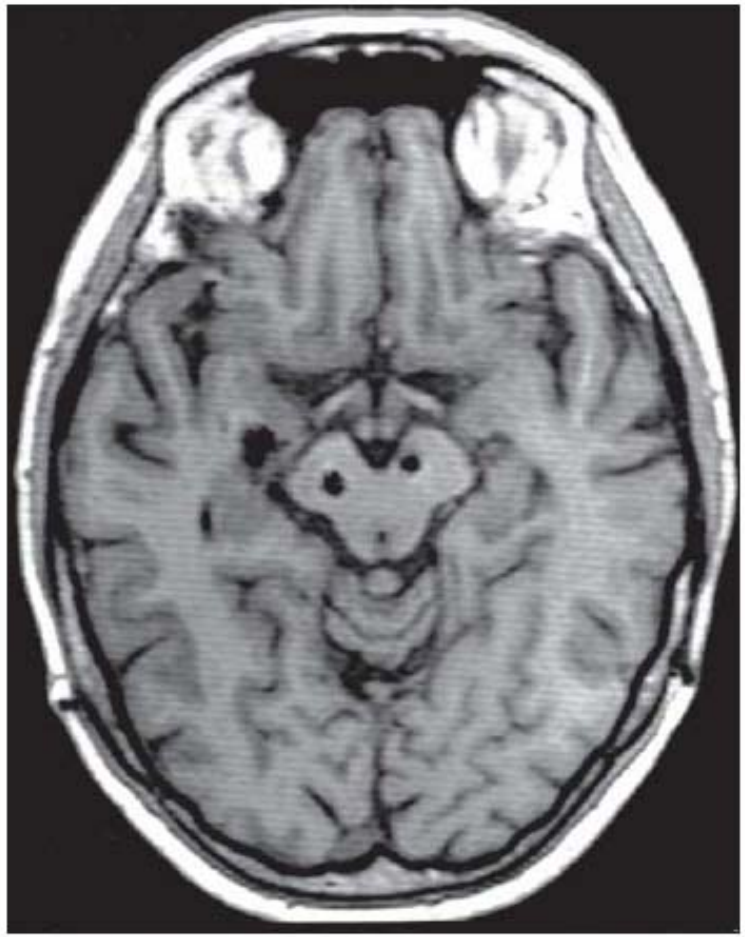


Figure 1. Preimplantation T1-weighted magnetic resonance imaging axial view of a patient revealing anteromedial misplacement of the left electrode.

imaging permitted precise localization of the electrode contacts without electrode-induced artifacts. Electrodes were connected to the extension lead previously established and were linked to a programmable implanted pulse generator (Medtronic).

EVALUATIONS

Surgery-related Limitations of DBS

- Complications associated with the surgical procedure
  - Hemorrhage
  - Infection
  - Stroke
  - Other perioperative complications

New Treatments

- Gene Therapy
- Growth Factors
- Spheramine
- Transplantation
- New “old” treatments
- Neuroprotection

Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics

Advances in Gene Therapy for Movement Disorders

Hideki Mochizuki,*† Toru Yasuda,* and M. Maral Mouradian‡

**Research Institute for Diseases of Old Age and †Department of Neurology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan; ‡Center for Neurodegenerative and Neuroimmunologic Diseases, Department of Neurology, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey 08854*

Summary: After nearly 20 years of preclinical experimentation with various gene delivery approaches in animal models of Parkinson's disease (PD), clinical trials are finally underway. The risk/benefit ratio for these procedures is now generally considered acceptable under approved protocols. The current vehicle for gene delivery to the human brain is recombinant adeno-associated viral vector, which is nonpathogenic and non–self-amplifying. Candidate genes tested in PD patients encode 1) glutamic acid decarboxylase, which is injected into the subthalamic nucleus to catalyze biosynthesis of the inhibitory neurotransmitter γ-aminobutyric acid and so essentially mimic deep brain stimulation of this nucleus; 2) aromatic L-

neurotransmission or providing trophic effects to dopaminergic neurons by delivering a specific missing or defective gene. For example, the parkin gene (PARK2) is linked to recessively inherited PD due to loss of function mutations; it prevents α-synuclein-induced degeneration of nigral dopaminergic neurons in rats and nonhuman primates. On the other hand, for dominantly inherited Huntington's disease (HD), in which an expanded polyglutamine tract imparts to the protein huntingtin a toxic gain of function, repressing expression of the mutant allele in the striatum using RNA interference technology mitigates pathology and delays the phenotype in a mouse model. Here we review the current state of preclinical and clinical gene

Gene Therapy

- Candidate genes tested in PD encode:
  - Glutamic acid decarboxylase (into STN)
  - Aromatic L aminoacid decarboxylase, which converts L-dopa to dopamine
  - Neurturin, a member of the glial cell line-derived neurotrophic factor family

Mochizuki H, Yasuda T, Mouradian MM: Neurotherapeutics. 2008 Apr;5(2):260-9

Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne *GAD* gene for Parkinson's disease: an open label, phase I trial

Michael G Kaplitt, Andrew Feigin, Chengke Tang, Helen L Fitzsimons, Paul Mattis, Patricia A Lawlor, Ross J Bland, Deborah Young, Kristin Strybing, David Eidelberg, Matthew J During

Summary

Background Dopaminergic neuronal loss in Parkinson's disease leads to changes in the circuitry of the basal ganglia, such as decreased inhibitory GABAergic input to the subthalamic nucleus. We aimed to measure the safety, tolerability, and potential efficacy of transfer of glutamic acid decarboxylase (*GAD*) gene with adeno-associated virus (AAV) into the subthalamic nucleus of patients with Parkinson's disease.

Methods We did an open label, safety and tolerability trial of unilateral subthalamic viral vector (AAV-GAD) injection in 11 men and 1 woman with Parkinson's disease (mean age 58·2, SD=5·7 years). Four patients received low-dose, four medium-dose, and four high-dose AAV-GAD at New York Presbyterian Hospital. Inclusion criteria consisted of Hoehn and Yahr stage 3 or greater, motor fluctuations with substantial off time, and age 70 years or less. Patients were assessed clinically both off and on medication at baseline and after 1, 3, 6, and 12 months at North Shore Hospital. Efficacy measures included the Unified Parkinson's Disease Rating Scale (UPDRS), scales of activities of daily living (ADL), neuropsychological testing, and PET imaging with ^{18}F-fluorodeoxyglucose. The trial is registered with the ClinicalTrials.gov registry, number NCT00195143.

Findings All patients who enrolled had surgery, and there were no dropouts or patients lost to follow-up. There were no adverse events related to gene therapy. Significant improvements in motor UPDRS scores (p=0·0015), predominantly on the side of the body that was contralateral to surgery, were seen 3 months after gene therapy and persisted up to 12 months. PET scans revealed a substantial reduction in thalamic metabolism that was restricted to the treated hemisphere, and a correlation between clinical motor scores and brain metabolism in the supplementary motor area,

Lancet 2007; 369: 2097–105

See Comment page 2056

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Spheramine

- Active component of cultured human retinal pigment epithelial (hRPE) cells
- Attached to an excipient part of crosslinked porcine gelatin microcarrriers
- Administered by stereotactic implantation into the striatum of PD patients
- Immunosuppression not required

Stover NP, Watts RL: Neurotherapeutics. 2008 Apr;5(2):252-9

Spheramine

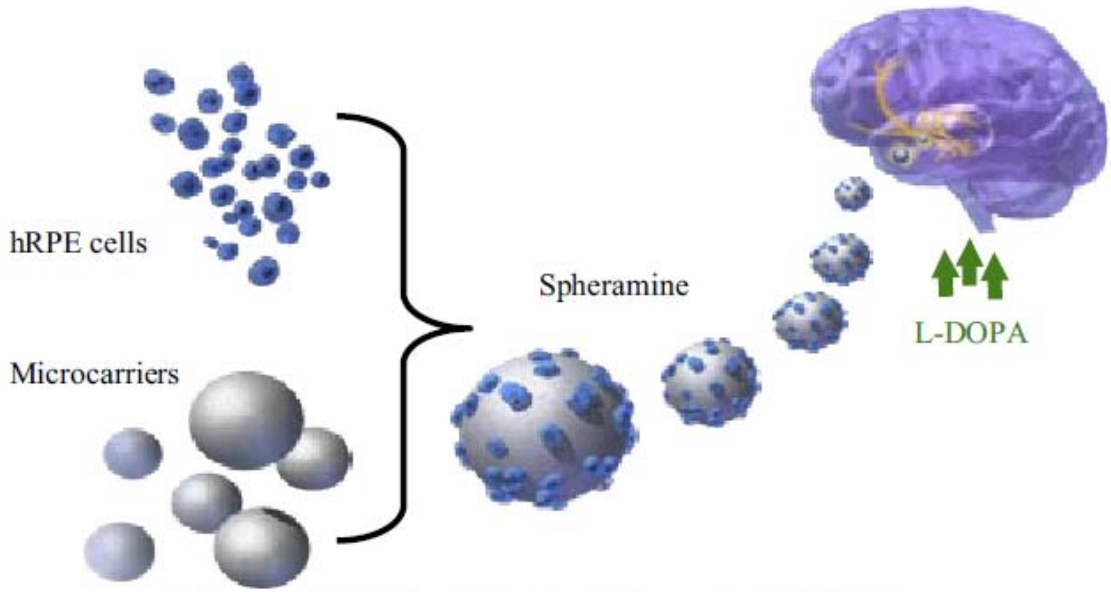

FIG. 1. Schematic depiction of Spheramine and brain implant sites.

Stover NP, Watts RL: Neurotherapeutics. 2008 Apr;5(2):252-9

Spheramine

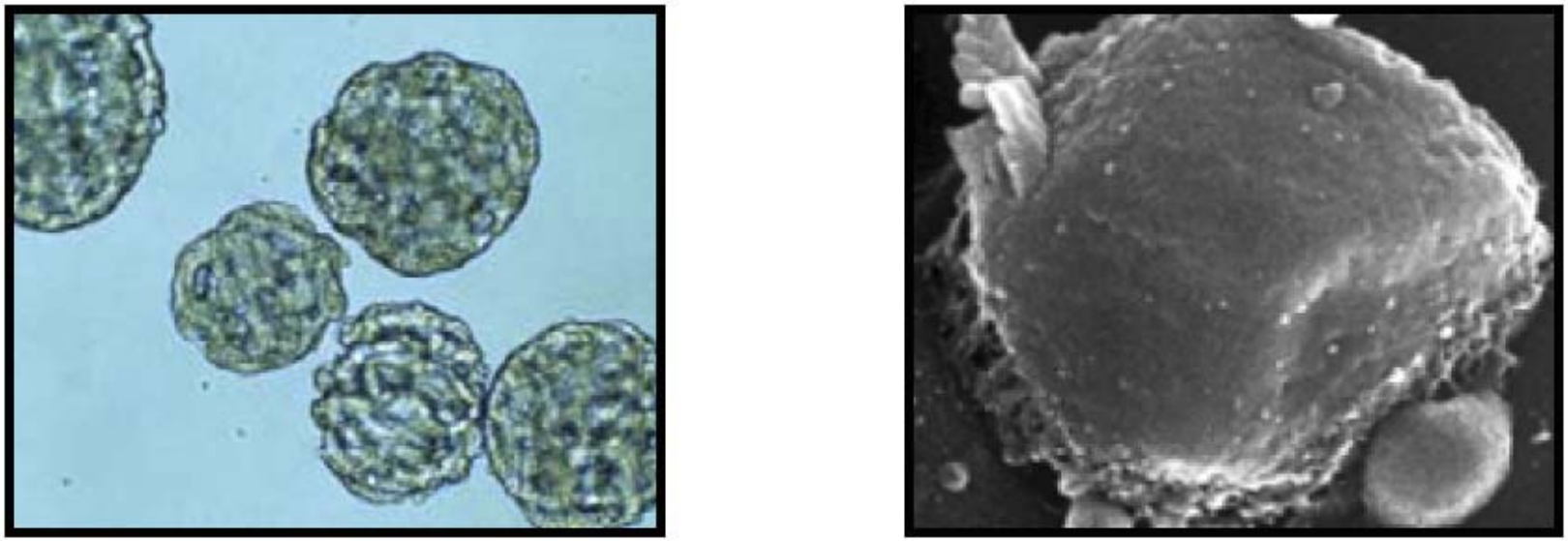

FIG. 2. Micrographs of Spheramine. *Left*: Microcarrier support matrix (MSM) with attached hRPE (human retinal pigment) cells (photomicrograph, 40×). *Right:* A single hRPE cell on an MSM (electron micrograph, 12,000×).

Stover NP, Watts RL: Neurotherapeutics. 2008 Apr;5(2):252-9

Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics

Therapeutic Potentials of Human Embryonic Stem Cells in Parkinson's Disease

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Summary: The loss of dopaminergic neurons of the substantia nigra is the pathological hallmark characteristic of Parkinson's disease (PD). The strategy of replacing these degenerating neurons with other cells that produce dopamine has been the main approach in the cell transplantation field for PD research. The isolation, differentiation, and long-term cultivation of human embryonic stem cells and the therapeutic research discovery made in relation to the beneficial properties of neurotrophic and neural growth factors has advanced the transplantation field beyond dopamine-producing cells. The present review addresses recent advances in human embryonic stem cell experimentation in relation to treating PD, as well as cell transplantation techniques in conjunction with alternative therapeutics.
Key Words: Neurotrophic, microenvironment, cytokines, growth factors, chemokines, progenitor cells, precursor cells, neural stem cells, transplantation, central nervous system, injury, repair.

Embryonic Stem Cells

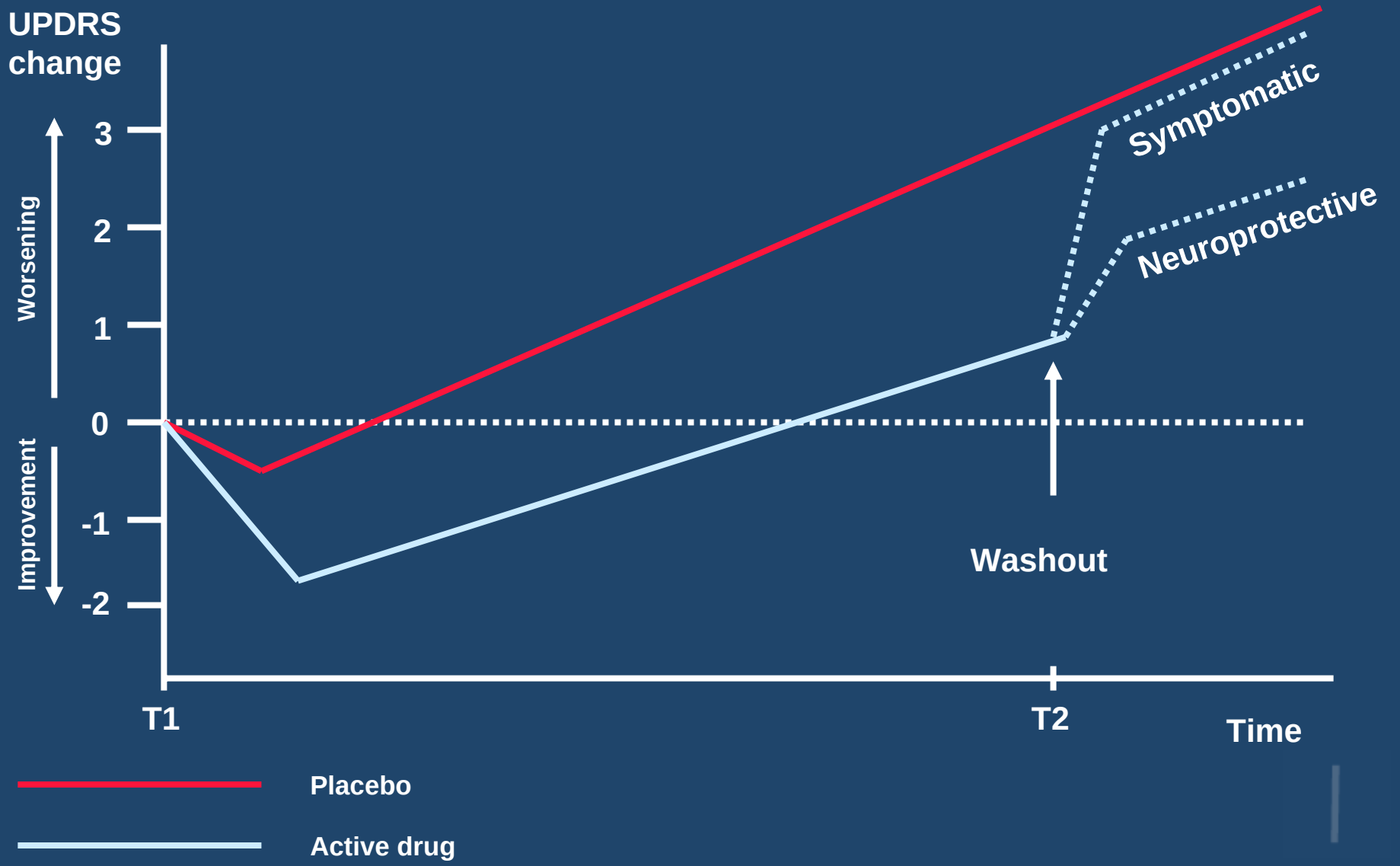
- The effectiveness of stem cells, in general, may have more to do with protecting and repairing the degenerating or injured tissue than with the actual replacement of cells

- Stem cells may also be useful in studying the etiology and pathology, along with new drug treatments, in models of *in vitro* PD

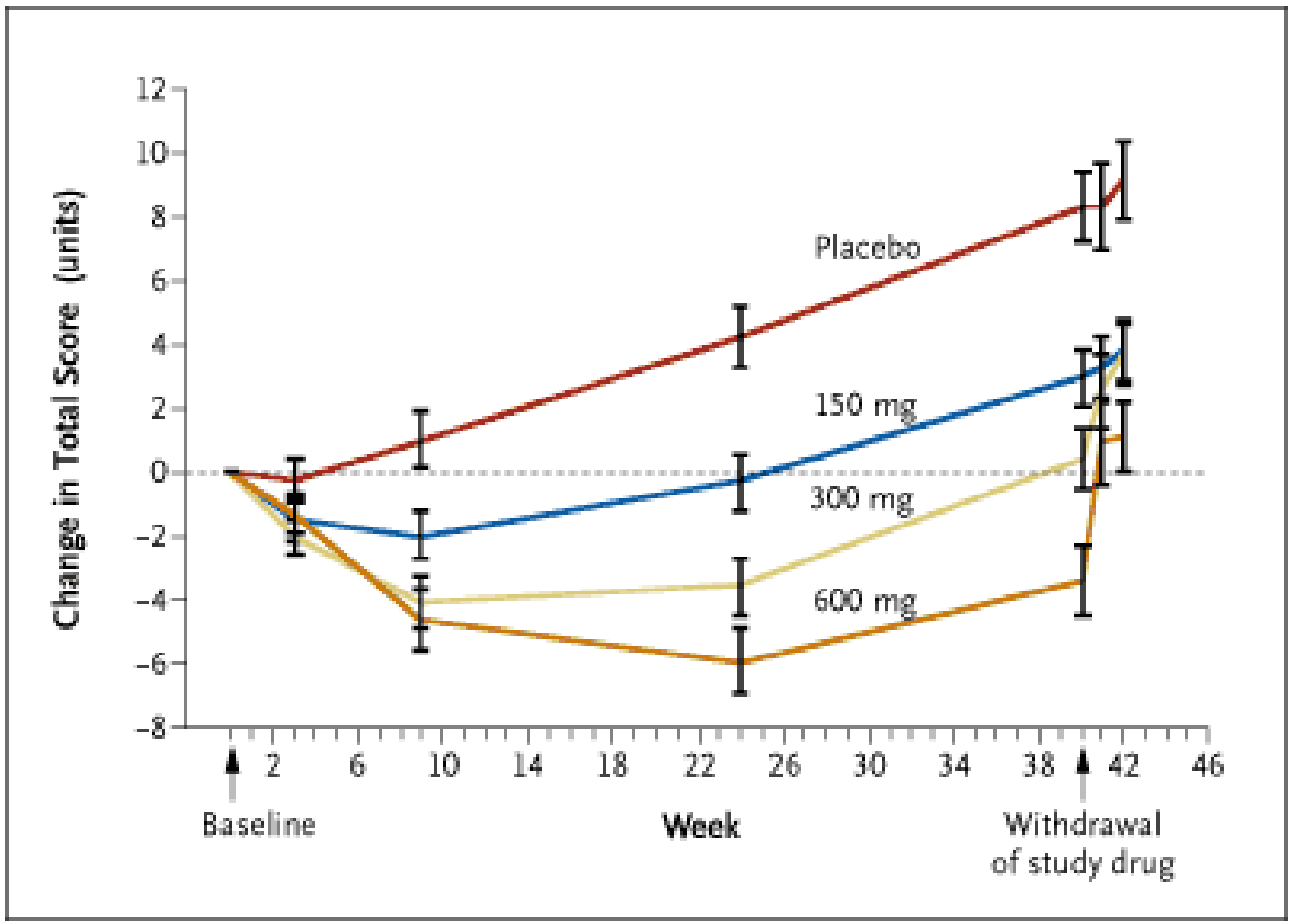
- It is imperative, before clinical application can be considered, to have the capability to predict the behavior of hESCs over a very long period in culture and after differentiation

Newman MB, Bakay RA: Neurotherapeutics. 2008 Apr;5(2):237-51RL

Neuroprotection: wash-out model



ELLDOPA study: Neuprotective behavior of L-dopa



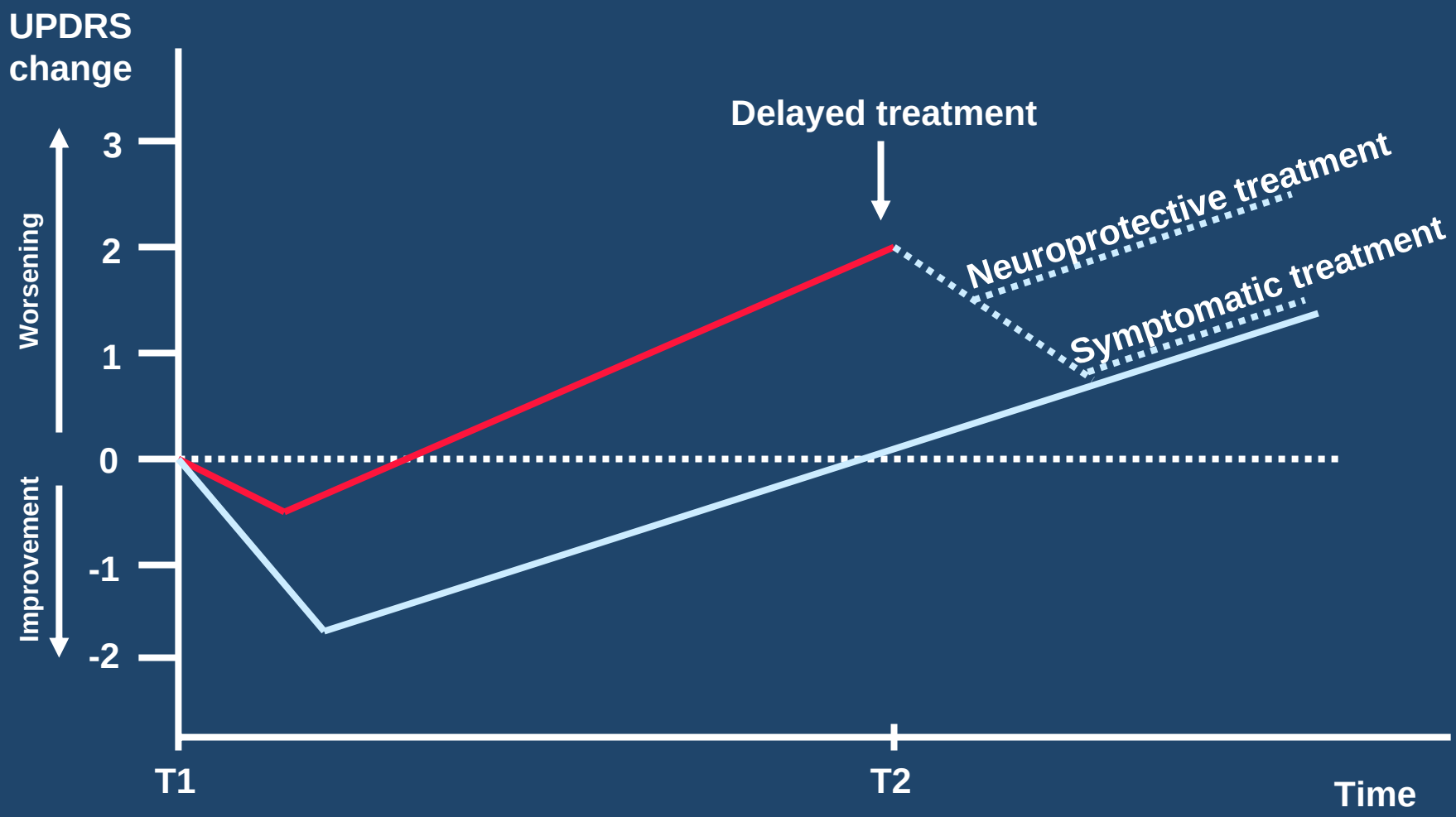
Fahn S et al, N Engl J Med 351:2498, 2004

Levodopa may be “neuroprotective”

- Levodopa does not speed up progression of disease
- Levodopa appears to have a neuroprotective or disease-modifying behavior

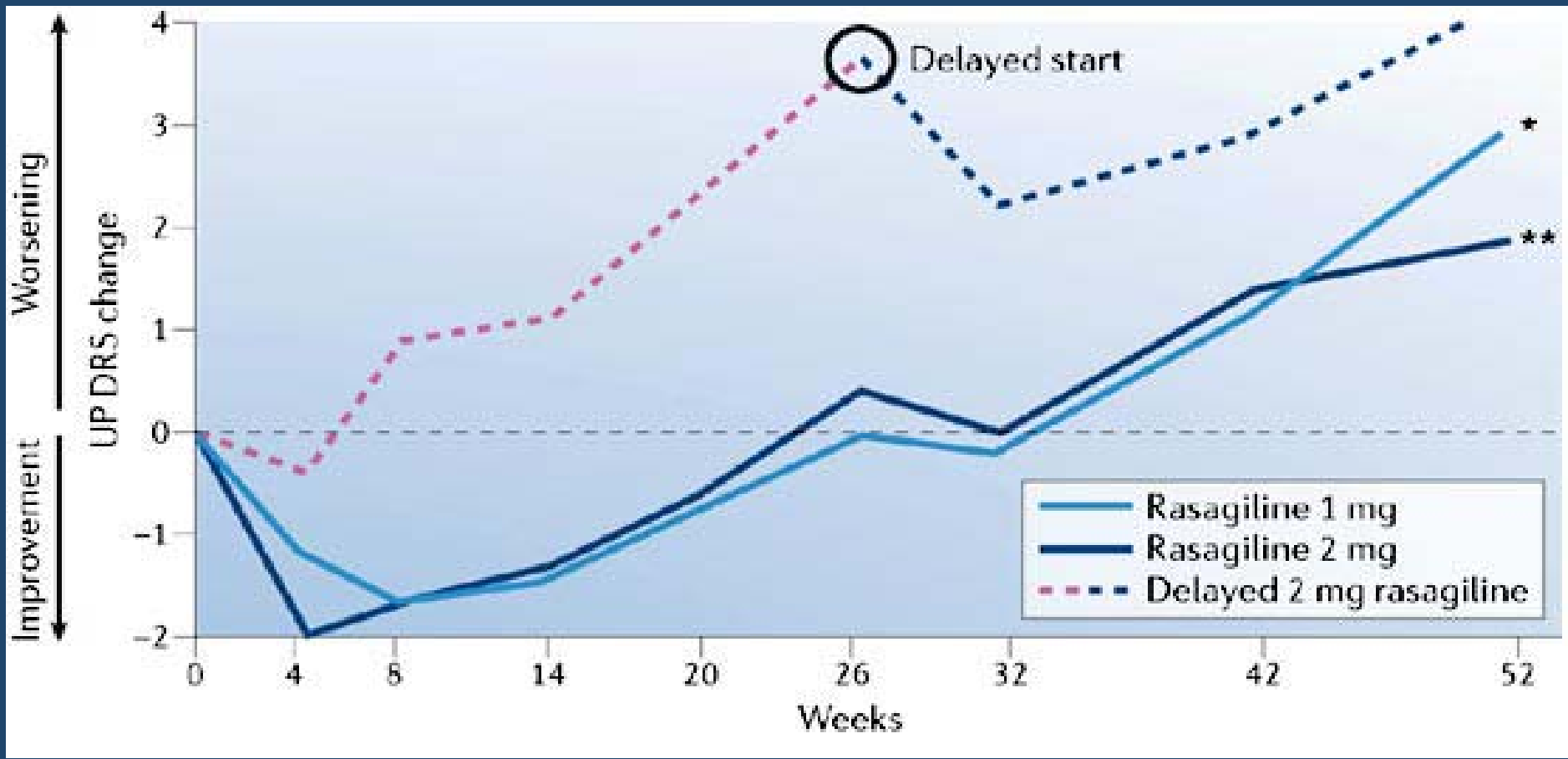
- *Early levodopa may provide greater long-term benefits than delayed levodopa*

Neuroprotection: delayed-start model



Modified from: Leber P. Alzheimer Dis Assoc Disord 1996;10:31-35
Bodick et al. Alzheimer Dis Assoc Disord 1997;11:50

Delayed-treatment design: TEMPO trial



TEMPO study, PSG. Arch Neurol 2004;61:561-566

Neuroprotection in PD

- MAO-B inhibitors:
  - Selegiline
  - Rasagiline
  - Lazabemide
- Dopaminergic medications:
  - CALM-PD
  - REAL-PET
  - ELLDOPA
- Mitochondrial Energy Enhancement:
  - Coenzyme Q10
  - Creatine
- Antiapoptotic Agents: TCH346, CEP-1347
- Antiglutamatergics: riluzole

Neuroprotection in PD

- Legacy of PD neuroprotection studies is a wealth of experience in the challenges and pitfalls of study design and implementation
- Data from clinical trials in early PD provide an important resource for studying the natural history of PD and for designing new studies and interpreting the results of others
- This information, plus experience in using different clinical rating and neuroimaging study outcome measures, has made it possible for studies to be planned with greater precision as to duration and numbers of subjects required.

Acta Neurol Scand 2001: 104: 343–348
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Duodenal levodopa infusion in Parkinson's disease – long-term experience

Nilsson D, Nyholm D, Aquilonius S-M. Duodenal levodopa infusion in Parkinson's disease – long-term experience.
Acta Neurol Scand 2001: 104: 343–348. © Munksgaard 2001.

Motor fluctuations in parkinsonian patients can be reduced by intraduodenal infusion of levodopa. Between 1991 and 1998 continuous daytime administration of levodopa through a transabdominal port has been used in 28 very advanced patients over a total period of 1045 months. A stable suspension of levodopa and carbidopa (Duodopa®) has been developed. Patients were characterized by early onset, long history of disease and levodopa therapy. The reason for infusion was in all cases related to on–off fluctuations. All patients experienced a general improvement after the introduction of continuous treatment. There have been no severe complications. Six patients have taken the decision to curtail their treatment. The mean daily levodopa consumption has been slightly reduced on infusion as compared to oral therapy. Nine of the first group of patients participating in the new therapy have been regularly evaluated by means of rating scales and movement analyses. Short-term results have already been published and a follow-up showing

D. Nilsson, D. Nyholm, S.-M. Aquilonius

Department of Neuroscience, Neurology, Uppsala University, Sweden

Key words: Parkinson's disease; levodopa; carbidopa; duodenal infusion; movement analysis

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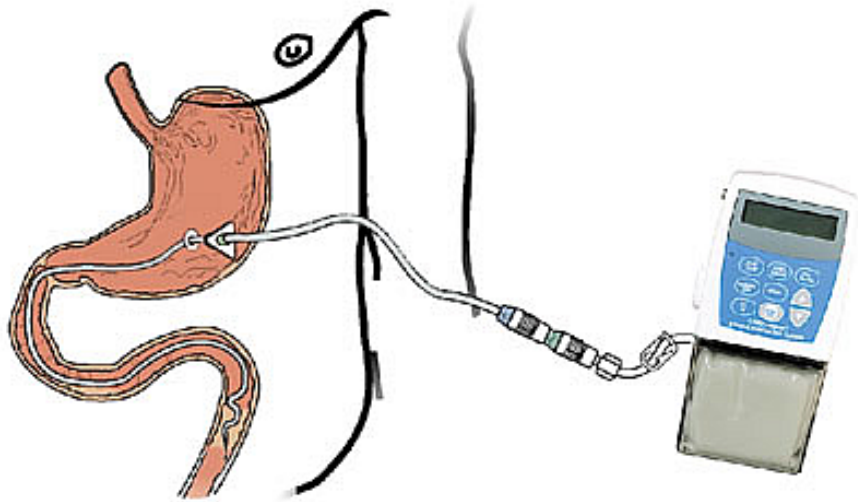

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Dag Nilsson, Department of Neuroscience, Neurology, University Hospital, SE-751 85 Uppsala, Sweden

The Future

- Parkinson's disease is a progressive neurodegenerative disease, impacting many systems, and likely caused by several factors
- Nonetheless, more information, from both clinical and basic research is providing new insight into disease mechanisms and novel treatment modalities
- Continued diverse and creative approaches exploring treatment options for PD are ongoing and are critical for optimizing therapies for this disease

Conclusion

- DBS is an excellent treatment for DBS at the present time

- However, new treatments (possibly neuroprotective) will replace DBS

IN THE FUTURE

I wish I was wrong!


CAUTION