January 15, 2020 Version 4

Title of Project

Tandem DBS for Parkinson's Disease: A Pilot Study Utilizing STN/GPi + hypothalamic stimulation

DESCRIPTION

With progression of symptoms, patients with Parkinson's disease (PD) frequently develop significant disability despite optimal medical therapy. Surgical treatments, such as subthalamic or globus pallidal-deep brain stimulation (DBS), offer some benefit for selected patients. However, a large percentage of patients subsequently develop dementia.
Preliminary studies have identified stimulation of the hypothalamus/fornix as potentially useful in improving cognitive functioning acutely and there are theoretical reasons why such stimulation may lead to neurogenesis and potentially obviate future cognitive decline/dementia.

We propose a pilot study of dual hemispheric stimulation of the subthalamic nucleus (STN) and fornix/hypothalamus in 12 PD patients experiencing motor disability despite optimal medical therapy, who would otherwise be undergoing STN-DBS. These individuals may also have mild cognitive impairment. The study will include measures of motor and cognitive function.

PERFORMANCE SITES

Mayo Clinic, Jacksonville, FL

KEY PERSONNEL

Ryan J. Uitti, MD PI
Robert E. Wharen, Jr., MD Co-PI
John A. Lucas, PhD Co-investigator
Amy Grassle, RN Nurse Coordinator
Audrey Strongosky, BA Research Coordinator

Ryan J. Uitti, MD PI
Dr. Uitti will oversee the project, selecting patients for entry into the study, insuring optimization of medical therapy, participating in electrophysiological and clinical guidance of stimulator lead placement in the operating room, regulating stimulators and directing follow-up evaluation and care for all patients. He will perform initial UPDRS scoring in every patient evaluation. He is a fellowship-trained movement disorder specialist who has functioned in this capacity in studies concerning both

lesioning and stimulation procedures. He has provided neurological assistance intraoperatively for Dr. Wharen for nearly every patient undergoing movement disorders surgery at Mayo Clinic in Jacksonville.

Robert E. Wharen, Jr., MD, Co-PI
Dr. Wharen will perform all surgery in study patients and pre- and post-surgical evaluations. He will determine the radiological target in every patient and determine the utility of electrophysiological and clinical guidance on the basis of eventual lead location site. He was the first neurosurgeon to perform MR-electrophysiological-guided movement disorder surgery at the Mayo Clinic and has performed every deep brain stimulation procedure carried out at Mayo Clinic in Jacksonville (in conjunction with Dr. Uitti).

John A. Lucas, PhD
Dr. Lucas, neuropsychology consultant, will oversee collection and interpretation of all neurobehavioral data, including quality of life information. He has served in this capacity in previous studies with Drs. Uitti and Wharen.

Amy Grassle, RN
Amy Grassle is Dr. Uitti's research nurse coordinator. She will coordinate logistics for the study, including pre- and post-surgical evaluations. She will perform nursing duties during each surgery. She will collect and record data during every patient evaluation. She will assist with IRB compliance and clinical data compilation.
Audrey Strongosky, BA
Audrey Strongosky is a clinical research coordinator with the Movement Disorders Group. She will be responsible for IRB documentation and will assist in managing data, data entry into the computerized database, scheduling of patient's visits

Background

Tandem Deep Brain Stimulation for Parkinson's Disease

Abstract

Deep brain stimulation (DBS) targets for Parkinson's disease have been limited to neuronal regions wherein lesions have produced beneficial effects. Improvements in imaging allow placement in small and novel targets. Additionally, due to the ability of impulse generators to accommodate multiple electrodes, simultaneous stimulation in multiple neuronal regions is possible.

Given that the two most disabling clinical features of Parkinson's disease, namely postural instability and dementia, have evaded effective treatment, consideration for new structural targets is warranted. Characteristics of dementia in parkinsonism include progressive deficits in attention and executive function. Additionally, many patients experience pronounced variability in cognition with profound fluctuations/variability in attention and alertness.

Anecdotal and initial trial reports concerning DBS to the fornix/hypothalamus have been associated with improvement in memory function and reductions in expected cognitive decline in patients with early Alzheimer's disease. The fornix constitutes the major inflow and output pathway from the hippocampus and medial temporal lobe.

I hypothesize that tandem DBS, targeting the STN/GPi and fornix/hypothalamus and/or hippocampus may have a positive impact on improving cognitive function and/or reducing risk for subsequent dementia with Lewy bodies/Parkinson dementia. Such targets also pose potential negative ramifications. Nevertheless, given the tremendous disability produced by dementia, new structural targets require systematic study.

Tandem Deep Brain Stimulation for Parkinson's Disease

Deep brain stimulation (DBS) targets for Parkinson's disease (PD) have been limited to neuronal regions wherein lesions have produced beneficial effects. Every DBS target routinely employed at international centers: ventral intermediate nucleus of the thalamus, subthalamic nucleus, or globus pallidus internus, have been historically lesioned with documentation of ensuing motor benefit. The positive ramifications have included predominantly improvement in motor function and functional "on" time. Patients undergoing surgery have been highly selected; PD patients with depression and dementia have consistently been avoided as surgical candidates [1].

While most series of DBS surgery for PD patients find minimal changes in cognition within the first year following surgery, longitudinal series subsequently document that cognitive decline and dementia are still commonplace. Additionally, most DBS series have avoided operating on elderly PD patients who are at most risk for dementia. We

have suggested for some time that unilateral STN-DBS be routinely employed (as opposed to immediate bilateral surgery) in PD, as it may be therapeutically effective and carry fewer cognitive complications, particularly in elderly patients [2].

Most long-term follow-up indicate that speech, axial motor features and cognitive decline frequently become apparent in PD patients receiving DBS [3]. Studies examining specific cognitive outcomes more than two years after surgery indicate that the majority of STN-DBS patients demonstrate significant declines in nonverbal memory, semantic fluency, and processing speed, with the same percentage converting to dementia as those PD who were not surgical patients [4]. Hence, there is no evidence to suggest that current DBS targets, even employed in a selected, non-demented, non-depressed cohort, subsequently minimize the risk for future dementia.

In summary, currently available pharmacological and surgical therapies do not consistently, effectively ameliorate balance and cognitive decline/dementia or reduce their risk, and frequently exacerbate these problems in the short-term.

Dementia and Parkinson's disease

Dementia in Parkinson's disease (PD) represents the most frequent, eventually disabling feature of this common neurodegenerative disorder. It also is a strong predictor of survival [5].

Parkinson dementia/dementia with Lewy bodies represents the second most common form of disabling dementia. Characteristics of dementia in parkinsonism include progressive dementia with deficits in attention and executive function [6]. Recurrent, complex visual hallucinations frequently occur and may be accompanied by REM sleep behavior disorder (concurrently or prior to development of other features). Additionally, many patients experience pronounced variability in cognition with profound fluctuations/variability in attention and alertness. Fluctuations in cognitive functioning and deficits in attention and executive function, often without prominent memory impairment, is a core feature of dementia with Lewy bodies [6], and occurs particularly in early stages. Such variability is a hallmark of dementia with Lewy bodies that differentiates this form of cognitive decline from Alzheimer's disease and aging [7].

Unfortunately, the two most common disabling clinical features of PD, namely postural instability leading to falls and dementia have evaded effective treatment. Additionally, these features are increasingly common in aging PD patients, precisely the demographic who are avoided by most centers performing DBS surgery.

Could DBS potentially impact cognitive decline/dementia in PD?

DBS with high-frequency stimulation of the limbic circuitry, namely the anterior thalamic nuclei, demonstrates neurogenesis of neurons in the dentate gyrus of the hippocampus, a component of the limbic circuit.

The ability to produce adult hippocampal neurogenesis has also been associated with effective antidepressant treatments. Studies in mice have demonstrated that stimulation of the ATN may produce increases in neural progenitors in the dentate gyrus of the same variety that can be stimulated by fluoxetine and physical exercise [8]. This suggests that ATN stimulation might be useful for limbic circuitry activation and influence on cognition and mood. While most clinical studies in PD patients do not suggest that cognition is negatively impacted by DBS per se, this may also be possible. DBS of the anterior thalamus at high current has shown the ability to impair memory in rat animal models [9].

An anecdotal report concerning DBS in the fornix and hypothalamus in a patient being treated for obesity included descriptions of impressive memory enhancement [10]. While on the operating table, this patient was able to provide detailed memory recollections from 30 years previous. Subsequent evaluation disclosed that there were EEG effects in the hippocampal formation and medical temporal lobe in conjunction with high-intensity stimulation (3-5 V, 60-microsecond pw, 130 Hz). Additionally, performance on neuropsychological testing after chronic hypothalamic stimulation demonstrated improvements in attention, verbal learning (short- and long-delay recall) and spatial associative learning. This testing suggested that hypothalamic stimulation induced enhanced recollection in the memory process. The mechanism thought to be responsible was driving activity of the hippocampal memory circuit through stimulation of the fornix. The fornix represents the major axonal bundle from the hippocampus and medial temporal lobe. Lesions in the fornix are also well known to produce memory deficits in humans. In contrast in this instance, apparent driving of activity in the ipsilateral medial temporal lobe to unilateral hypothalamic stimulation ("on" state), was associated with increased memory ability.

A subsequent trial has ensued examining the impact of DBS on memory circuits in Alzheimer's disease (AD) [11]. This trial recruited six patients with early AD. All had Clinical Dementia Rating scores of 0.5 or 1.0 [12] and scores between 15-26 on the Mini Mental State Examination (MMSE)[13]. Each were implanted bilaterally in the vertical portion of the fornix within the hypothalamus. Assessments with the Alzheimer's Disease Assessment Scale, Cognitive Subscale (ADAS-Cog)[14] took place at baseline and 6 and 12-months post-operatively. After 6 months of stimulation, 4 of 6 patients showed improvement, with lowering of 1.3-4.0 points in the ADAS-Cog scores. This magnitude compares favorably to the reported impact of donepezil in mild cognitive impairment, which is 0.5 points [15].

After 12 months, one patient had 4.4 points lower than baseline, 2 patients a 2-point increase, 1 patient a 5-point increase, and 2 patients >5 point increases. The expected change in the cohort of 6 was: 2 patients had less than expected increases, 1 more, and 3 within the expected range. Interestingly the patient with the greatest improvement experienced the most vivid experiential experience with stimulation during surgery, as had been the case with the original anectodal patient reported. Functional imaging carried out in this trial also suggested that fornix/hypothalamic-DBS produced changes in the

cognitive and limbic brain areas (improved glucose metabolism), were the basis for observed changes in some of the AD patients. These authors also suggest that DBS may drive greater delivery of neurotrophin brain-derived neurotrophic factor and influence neurogenesis in the diseased hippocampus.

Hypothesis: Tandem DBS for PD

Given that 1) the most disabling and common negative consequence of PD is dementia for which there is no means to avoid or beneficial treatment, and 2) there is some evidence that DBS can potentially safely impact upon memory, I suggest that tandem DBS, namely targeting both STN (or GPi) and the fornix/hypothalamus and/or hippocampus may improve both motor and cognitive function (immediate and future). As such, tandem DBS with STN/GPI + fornix/hypothalamus for PD patients should be considered for systematic study.

DBS of the fornix/hypothalamus and/or hippocampus may have a positive impact on cognitive function and/or reducing risk for subsequent dementia with Lewy bodies/Parkinson dementia.

Potential studies could include PD patients with:

- normal cognition
- mild cognitive impairment
- mild dementia

Studies with patients who have normal cognition could determine if DBS of the fornix/hypothalamus had any impact on the natural course of the disorder and likelihood of subsequent development of dementia. Studies engaging patients with cognitive dysfunction could test whether DBS of the fornix/hypothalamus was capable of providing symptomatic improvement through improved alertness, attention, memory and other performance metrics.

Logistical Possibilities

Originally, impulse generators for deep brain stimulation electrodes accommodated only single quadric-polar brain electrodes. Consequently, deep brain stimulation was necessarily constrained by the lack of pulse generator flexibility. Currently available impulse generators readily accept multiple brain electrodes. Therefore, it is logistically possible to consider utilizing multiple brain electrodes simultaneously. The studies suggested would require at least two electrodes to be placed in one cerebral hemisphere (one for motor improvement and one for potential cognitive implications). Trials would need to include designs to determine the impact of DBS in targets considered singly (e.g. STN or fornix/hypothalamus) and in combination (e.g. STN and fornix/hypothalamus).

I propose controlled studies implanting PD patients who are otherwise undergoing unilateral DBS-GPi or DBS-STN with a unilateral DBS electrode with stimulation to the

fornix/hypothalamus region, i.e. tandem DBS. Such patients would receive a single IPG, as would otherwise be required for such surgery. Patients subsequently undergoing second-sided surgery for motor parkinsonism would concurrently also receive a second electrode with stimulation for the fornix/hypothalamus. Stimulation to the fornix/hypothalamus would be accomplished with either the same rate/frequency as for the unilateral basal ganglia structure or utilize 3.0-3.5 V with a frequency of 130 Hz and pulse width of 90 microseconds.

Neuropsychological studies and dementia status immediately prior to and years post-operatively would form the primary outcome measure for these tandem DBS studies. Historical results, with single hemispheric electrodes (either unilateral or bilateral) could serve as potential comparative data for secondary analyses.

MRI scans will be completed for serial hippocampal volume measures. Scans will be evaluated by Erik Middlebrooks, MD.

Pathological studies of brain from patients at death would subsequently help to determine the nature of results, including ability to ascertain whether neurogenesis or other mechanism might be associated with fornix/hypothalamus-DBS/tandem DBS.

Summary

DBS utilizing "traditional motor targets" for PD patients has provided improvement in functional "on" time and reduced tremor compared to standard medical therapy. However, subsequent risk for cognitive decline/dementia remains and development of these features leads to early disability and death. Potential improvements in cognitive function and neurogenesis are conceivable with tandem DBS targeting STN/GPi and the fornix/hypothalamus and should now be considered for systematic study in PD.

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Acknowledgments
RJU is partially supported by the NIH/NINDS P50-NS072187 and NIH/NINDS NS057567, research funding from Advanced Neuromodulation Systems, Inc./St. Jude Medical, and a gift from Carl Edward Bolch, Jr., and Susan Bass Bolch (MCF #90052031/PAU #90052).

RESEARCH DESIGN AND METHODS

Experimental Subjects
Inclusion/Exclusion Criteria

All patients will be enrolled from the practice of the primary investigator. It is anticipated that PD patients eligible for this study will range from 40-80 years and will have been symptomatic with parkinsonism for 7-20 years.

The study will include PD patients in whom optimal medical therapy has failed to relieve the patient from significant disability owing to parkinsonism. PD will be diagnosed by the principal investigator on the basis of the presence of at least 2 of 3 cardinal features of parkinsonism (resting tremor, rigidity, and bradykinesia) without known cause. Patients with prominent and early dysautonomia or ataxia or downgaze palsy or pyramidal signs will be excluded. Response to levodopa should be specified as more than minimal (reductions in UPDRS motor scoring of 20% or greater when "off" scores are compared to "on" scores during the drug motor response profile) and as sustained (e.g. for at least five years).

All patients will have responsivity to levodopa (as defined by UPDRS changes above). Common causes for significant disability will be intractable tremor, levodopa-induced dyskinesias and other motor fluctuations. Optimal medical therapy will consist of appropriate use of levodopa and at least one dopamine agonist under the direction of the principal investigator. Common causes for significant disability will be motor fluctuations, levodopa-induced dyskinesias, intractable tremor, other motor disability including gait disturbances. Individuals with normal or mild cognitive impairment as a diagnosis following neuropsychological study will be eligible for the study.

Exclusionary criteria will include clinically significant dementia (MMSE $\leq$23), Hoehn & Yahr [Hoehn, 1967 #1839] stage I or V disease, other significant neurological or psychiatric disease, previous pallidotomy or thalamotomy, previous placement of other implantable devices, and secondary parkinsonism (non-idiopathic parkinsonism). Patients with the aforementioned characteristics (without exclusionary criterion) are defined as surgical candidates.

The study will seek to include women and members of minority groups.

The principal investigator will discuss the study with surgical candidates. Patients will not incur any financial charges or responsibility relating to this study.
Consent for participation in this study will be sought and obtained by the primary investigator and study coordinator. The information provided to prospective subjects will include the details regarding each surgical procedure and the risks inherent with surgery (as listed below) will be that included on the IRB-approved consent form with consent being documented by written or econsent signature of the patient.

Potential risks for participation in this study include death, stroke, hemiparesis, and visual field deficits, and all other risks related to stereotactic brain surgery. The likelihood of such occurrences is generally reported to be approximately 2%. At our institution there have been no such serious adverse events in the >100 procedures performed during the past 2 years. Should patients expect greater improvement than obtained they may experience depression and frustration with outcome. Patients in this study would by definition have failed to experience significant relief of parkinsonism despite best medical therapy. Alternatives to treatment in this study would include no additional treatment or other surgery, such as pallidotomy, thalamotomy, and subthalamotomy (significant additional risk for bilateral procedures).

The risks to subjects are reasonable in relation to the anticipated benefits to subjects as these patients have no predictably successful alternatives and would be expected to continue to decline functionally without treatment.

Patient-related data will remain confidential, with only numerical patient identification numbers being placed on data collection sheets. In the event of adverse effects to the subjects, patients would be cared for, including all appropriate specialty out-patient and in-patient care at Mayo Clinic in FL. Any unexpected or untoward outcomes encountered in this study would be reported to the IRB. Clinical data will be obtained both for research purpose and for clinical care as indicated. The medical record will be recorded in the Mayo Clinic electronic record. Data exclusive to this study will not be recorded in the Mayo Clinic electronic record but will be stored on paper record before being transcribed into electronic computer record form.

Surgical Technique

Surgical implantation of DBS leads will be carried out employing techniques previously reported (Uitti, Wharen et al. 1997) (Wharen, Uitti et al. 1996) as described below. Patients will have antiparkinsonian medication withheld for 12-48 hours prior to surgery. During this time, patients will be constantly accompanied by a caregiver to insure their safety.

After application of a stereotactic headframe under IV sedation in the operating room to maximize patient comfort, MR imaging is performed using a 1.5-T magnet (General Electric, Milwaukee, WI). The MRI scanner in our facility is located adjacent to the operating room. Images are acquired using a 3-D volumetric spoiled GRASS sequence in the sagittal and axial planes. The sagittal acquistion is a 2 cm volume of 1 mm thick contiguous slices obtained in 3 minutes. This sequence will be used to define the anterior (AC) and posterior (PC) commissures. The second acquisition uses an identical sequence in the axial plane consisting of a 12 cm volume of 1mm thick contiguous slices obtained in 10 minutes. This sequence will be used to construct multiplanar (axial, sagittal, and coronal) viewing of the target point and trajectory. Axial images are used because this data is least vulnerable to any magnetic distortion. Additionally, a directly acquired axial fast spin echo inversion recovery sequence

(T1=200, TR=2200, TE=24, slice thickness=2mm) is obtained. This sequence is used to construct coronal images for direct visualization of the subthalamic nucleus (STN) and substantia nigra (SN). Targeting of the fornix/hypothalamus will take place utilizing the same computer software/imaging.

MR accuracy is verified by weekly quality assurance evaluations of the MR magnet using stereotactic phantoms. MR data is transferred over a network directly to the stereotactic planning computer in the OR computer room. The COMPASS software is used to define the AC and PC, the AC-PC line, and its midpoint.

The initial target is chosen using standard coordinates for the STN (3 mm posterior, 4 mm inferior, and 12 mm lateral to the midpoint of the AC-PC line). Final anatomic target adjustments are made based on correlation with the visualization of both SN and STN on the T2 weighted coronal images. A trajectory is chosen to include the target site, the midpoint of the AC-PC line and to avoid the lateral ventricles.

Microelectrode recording (MER) is then performed to verify the borders of the STN. STN has a characteristic electrophysiological activity that may be recognized by the discharge pattern within high background noise. The background noise diminishes distinctly at the inferior border of the STN into the SNR. Single units are recorded, both in the STN and SNR. In STN, cells fire with high activity (50-60 Hz), the spikes being almost symmetrical. They may respond to passive movements of the limbs with an increased firing rate. Cells in SNR typically produce larger potentials with slower firing rates (15-20Hz) and are irregular. They may be less likely to vary with limb movement. The medial and lateral borders of the STN formed by the lemniscal and corticospinal fibers respectively are identified by microstimulation-evoked sensory and motor responses. The MERs are again correlated to the tri-planar MR anatomy in the COMPASS software to assist in verification of the borders of the STN. We will perform MER using 1-5 microelectrodes placed simultaneously with our linear array (separated 3 mm apart center-to-center) aligned with the long axis of the STN as judged by its location immediately superior to SNR.

Microstimulation (0.5-5 uA, 130 Hz, 60usec pulse width) is carried out over the length of the STN to determine clinical response based on measurement of rigidity at the contralateral wrist to passive movement, as well as bradykinesia. Additionally, increasing microstimulation-induced side effects (such as paresthesias, vertigo, diplopia, eye deviation, etc.) are determined at each level. The final target will be determined by selecting the microelectrode track with the largest inferior-superior span of STN recording, the optimal clinical response in terms of reduction of rigidity and the highest threshold for side effects (particularly eye deviation and diplopia).

After the final STN target is selected, a Medtronic or Boston Scientific multipolar electrode is stereotactically placed at the target site and macroelectrode stimulation is performed. Adjustments in the final electrode placement are made based upon clinical response of parkinsonian symptoms and sensory and motor thresholds, selecting the

location that provides the greatest reduction in parkinsonian signs without significant side effects.

The initial electrode will be placed on the appropriate side contralateral to the most severe symptoms, or the dominant hand. If stimulation demonstrates improvement in parkinsonian symptoms at acceptable thresholds, the electrode will be secured in the burr hold and placed in a subgaleal pocket. Immediately thereafter, the hypothalamic electrode will be placed, with similar stimulation being employed to confirm proper placement.

Both hemispheric electrodes will subsequently be joined to extension leads which will be connected to an ipsilateral IPG placed in an infraclavicular superficial location.

Follow-Up

All patients will be seen preoperatively and at, 3, , 12, , 24months, and yearly intervals in order to adjust medications and stimulation parameters optimally. MRI scanning will be completed at baseline, and at yearly follow up visits. During year 4 and 5 a member of the study team will call the patient to see if they require additional evaluations.

Evaluations will be performed as outlined in the Summary – Evaluation Protocol table.

We will attempt to optimize the use of antiparkinsonian medications following surgery in conjunction with DBS parameters. Patients will be seen up to daily within the first week post-operatively for such adjustments and for suture removal.

Data Handling

Data obtained from all evaluations will be recorded on electronic data sheets or in Epic by the principal investigator (R. Uitti) and study coordinator (A. Grassle);

Brain Bank Registry

Clinicopathological studies in individuals who have undergone BSUBSTIM may be extremely informative and every attempt will be made to obtain autopsy in the unlikely event of death during the study. All patients in the study will be strongly encouraged to participate in the registry although this participation is not mandatory.

Motor Function Testing

Evaluations

Patients' motor function will be evaluated pre-operatively and at, 312, 24months, and yearly thereafter with quantitative outcome measures, employing standardized motor rating scales as have been previously reported by the investigators. (Uitti, Wharen et al. 1997) Changes in motor function of both sides of the body will be quantitated. Gait assessments may be videotaped if patient agrees, but it is not required.

Motor Function Testing – Drug and Stimulation Profile

During all post-operative visitspatients will be seen "ON" stimulation and "ON" medication. Time of last dose of antiparkinsonian medication will be collected.

The following motor function testing battery consists of: modified UPDRS, modified Hoehn & Yahr (Hoehn and Yahr 1967) scoring.

The motor function tests will be scored while patient is adhering to normal medication schedule and optimal "on" DBS settings.

Neuropsychological testing

A short test of mental status utilizing the Kokmen test will be completed on patients at 3 month follow up. The full neuropsychological test battery (see below) will be administered at baseline, and at yearly follow-up evaluations. Per normal clinical care Testing will take place annually (within 6-month windows of the exact date).

Post-operative testing will be completed with the patient in an "ON" setting.

Assessment and Statistical Analyses

The primary method of assessing treatment effects will be paired t-tests at the various post-operative intervals.

The primary efficacy parameters are neuropsychological battery scores over time in comparison with pre-operative scoring.

Secondary efficacy parameters will include UPDRS scoring (motor and activity of daily living subscores).

The primary endpoints will be the change in neuropsychological scoring from baseline to 12 and 36 months, expressed as a percentage change from baseline (employing "on"/"on" post-operative status versus "on" pre-operative values. Two-sided two-sample t-tests will compare post-operative changes to pre-operative data. Such

comparisons will take place when the full contingent of patients are accrued and have completed such assessments.

The effect of stimulation on cognitive functioning and mood state will be assessed using t-tests for dependent samples to compare performance on neuropsychological tests and POMS scores in the "on" and "off" condition at each follow-up evaluation. Changes in cognitive functioning, mood, and HRQOL from presurgical baseline will be analyzed using repeated-measures ANOVAs, with neuropsychological test scores as the DV and time of testing as the repeated measure. Demographic variables and measures of social support and locus of control will be entered into analyses of covariance whenever appropriate.

Hierarchical multiple regression analyses will be used to determine the relationship between presurgical psychosocial and neuropsychological variables and postsurgical outcome, as measured by HRQOL.

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Summary – Evaluation/Data Collection Protocol

	Pre-op	Post-op	3 mo	12 mo	24 mo	36 mo	Yr 4	YR5
Entry criteria	x							
Medical history	x							
Medications	x	x	x	x	x	x		
Lead Implant Data		x						
Settings			x	x	x	x		
Therapy side effects		x	x	x	x	x		
System complications		x	x	x	x	x		
Physician evaluation	x	x	x	x	x	x		
Drug profile motor function testing:								
motor rating scale	x			x	x	x		
MRI Imaging	x			x	x	x		
Memory testing	x		x	x	x	x		
Videotaping	x		x	x	x	x		
Questionnaires	x		x	x	x	x		
Brain bank registry	x							
Phone follow-up							X	X

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Summary required by Mayo IRB:

Tandem DBS for Parkinson's Disease: A Pilot Study

Summary

Hypothesis

STN and hypothalamic nucleus deep brain stimulation (Tandem DBS) is a safe and effective method for minimizing motor and cognitive dysfunction in disabling Parkinson's disease.

Basic study plan

This is a prospective study of Parkinson's disease outcome following a deep brain stimulation procedure. Twelve Parkinson's disease patients, with significant disability despite optimal medical therapy, will undergo stereotactic placement of unilateral deep brain stimulation electrodes (Medtronic 3387 electrode) into the subthalamic nucleus or GPi AND the hypothalamus/fornix during a single surgical procedure (Tandem DBS). A single, dual implantable pulse generator will be placed to control both DBS leads. Patients will be evaluated pre- and post-operatively (at, 3, 12, , 24months 36-months (and yearly thereafter) with quantitative outcome measures. The study will include measures of motor function, speech, neurobehavior, socioeconomic impact and quality of life.

Statistical method/rationale

The primary method of assessing treatment effects will be paired t-tests at the various post-operative intervals.

The primary efficacy parameters are neuropsychological scoring. Secondary measures are UPDRS scoring (motor and activity of daily living subscores) and changes in hippocampal volume as measured on MR imaging.

Scientific basis or justification

Parkinson's disease is a common neurodegenerative disorder with no treatment that definitively alters the natural progression of the condition. With progression of symptoms, patients with Parkinson's disease (PD) frequently develop significant disability despite optimal medical therapy. This study is designed to test a new technology for the treatment of severe PD.

Currently available surgical treatments, such as pallidotomy, GPi-DBS, and STN-DBS, offer some benefit for selected patients but do not influence cognitive dysfunction. Reports concerning cognitive benefit have documented potential improvement with

placement of DBS electrodes and stimulation in the fornix/hypothalamus in normal and patients with mild Alzheimer's disease.

We propose a pilot study of tandem DBS in 12 PD patients experiencing disability despite optimal medical therapy. The subthalamic nucleus and substantia nigra reticulata are crucial output nuclei in the cortico-basal ganglia-thalamic anatomy in which abnormal physiological activity have been described in animal models of parkinsonism and confirmed in human PD. DBS of STN bilaterally has been shown to ameliorate parkinsonism in both settings. The substantia nigra reticulata is an output nucleus that shares neurophysiological function with the internal segment of the globus pallidus or medial pallidum. Lesioning or DBS of the medial pallidum have both been shown to improve parkinsonism in animal models and human parkinsonism. We believe that DBS of both STN and hypothalamus would prove optimal in terms of reducing both parkinsonian and cognitive signs and symptoms.

Our surgical technique (MRI-microelectrode-guided procedure) allows for the implantation of bihemispheric DBS leads and pulse generator within the space of 3 hours.

Inclusion/exclusion criteria

Inclusion criteria

All patients will be enrolled from the practice of the primary investigator. It is anticipated that PD patients eligible for this study will range from 40-80 years and will have been symptomatic with parkinsonism for 7-20 years.

The study will include PD patients in whom optimal medical therapy has failed to relieve the patient from significant disability owing to parkinsonism. PD will be diagnosed by the principal investigator on the basis of the presence of at least 2 of 3 cardinal features of parkinsonism (resting tremor, rigidity, and bradykinesia) without known cause. Patients with prominent and early dysautonomia or ataxia or downgaze palsy or pyramidal signs will be excluded. Response to levodopa should be specified as more than minimal (reductions in UPDRS motor scoring of 20% or greater when "off" scores are compared to "on" scores during the drug motor response profile) and as sustained (e.g. for at least five years).

All patients will have responsivity to levodopa (as defined by UPDRS changes above). Common causes for significant disability will be intractable tremor, levodopa-induced dyskinesias and other motor fluctuations. Optimal medical therapy will consist of appropriate use of levodopa and at least one dopamine agonist under the direction of the principal investigator.

Exclusionary criteria

- clinically significant dementia (MMSE $\leq$23)

- Hoehn & Yahr (Hoehn and Yahr 1967) stage V disease
- other significant neurological or psychiatric disease
- previous pallidotomy or thalamotomy
- previous placement of other implantable devices
- secondary parkinsonism (non-idiopathic parkinsonism)
- inability to travel to Jacksonville for post-operative study visits
- women who are not post-menopausal

Monetary considerations

We are requesting provision from Medtronics of twelve (12) 3387 DBS leads and extensions. We may also utilize Boston Scientific electrodes as clinically indicated. Reimbursement for the procedure will be requested from patient medical insurance carriers. Mayo Clinic in FL will absorb all costs associated with the study (physician time and clinic visits). Additional funding has been obtained to cover the costs associated with MRI scanning.