HHS Public Access

Author manuscript

J Parkinsons Dis. Author manuscript; available in PMC 2016 March 29.

Published in final edited form as:

J Parkinsons Dis. 2015 October 17; 5(4): 893–905. doi:10.3233/JPD-150632.

Orthopedic Surgery and Post-Operative Cognitive Decline in Idiopathic Parkinson's Disease: Considerations from a Pilot Study

Catherine C. Price, Ph.D.[1,2,5], **Shellie-Anne Levy, Ph.D.**[1], **Jared Tanner, Ph.D.**[1], **Cyndi Garvan, Ph.D.**[3], **Jade Ward, B.S., ARNP**[1], **Farheen Akbar, M.S., MPH**[1], **Dawn Bowers, Ph.D.**[1,5,6], **Mark Rice, M.D.**[2,4], and **Michael Okun, M.D.**[5,6]

[1]Clinical and Health Psychology, University of Florida

[2]Anesthesiology, University of Florida

[3]College of Nursing, University of Florida

[4]Anesthesiology, Vanderbilt University

[5]Center for Movement Disorders and Neurorestoration, University of Florida

[6]Neurology, University of Florida

Abstract

BACKGROUND—Post-operative cognitive dysfunction (POCD) demarks cognitive decline after major surgery but has been studied to date in "healthy" adults. Although individuals with neurodegenerative disorders such as Parkinson's disease (PD) commonly undergo elective surgery, these individuals have yet to be prospectively followed despite hypotheses of increased POCD risk.

OBJECTIVE—To conduct a pilot study examining cognitive change pre-post elective orthopedic surgery for PD relative to surgery and non-surgery peers.

METHODS—A prospective one-year longitudinal design. No-dementia idiopathic PD individuals were actively recruited along with non-PD "healthy" controls (HC) undergoing knee replacement surgery. Non-surgical PD and HC controls were also recruited. Attention/processing speed, inhibitory function, memory recall, animal (semantic) fluency, and motor speed were assessed at baseline (pre-surgery), three-weeks, three-months, and one-year post- orthopedic surgery. Reliable change methods examined individual changes for PD individuals relative to control surgery and control non-surgery peers.

RESULTS—Over two years we screened 152 older adult surgery or non-surgery candidates with 19 of these individuals having a diagnosis of PD. Final participants included 8 PD (5 surgery, 3 non-surgery), 47 Control Surgery, and 21 Control Non-Surgery. Eighty percent (4 of the 5) PD surgery declined greater than 1.645 standard deviations from their baseline performance on

Correspondence: Catherine Price, Ph.D., ABPP/CN, Department of Clinical and Health Psychology, PO Box 100165, Gainesville, Florida, 32610, cep23@phhp.ufl.edu.

measures assessing processing speed and inhibitory function. This was not observed for the non-surgery PD individuals.

CONCLUSION—This prospective pilot study demonstrated rationale and feasibility for examining cognitive decline in at-risk neurodegenerative populations. We discuss recruitment and design challenges for examining post-operative cognitive decline in neurodegenerative samples.

Keywords

Orthopedics; arthroplasty; neurodegenerative; memory; executive function

---

The term “Post-Operative Cognitive Dysfunction” – or POCD - denotes post-operative memory and/or thinking problems that have been corroborated by neuropsychological testing [1]. While not yet recognized as a clinical diagnosis, clinicians are beginning to use the term POCD as a general description of postoperative patients who complain of memory and thinking problems. Typically, these problems include reduced attention and concentration, word finding problems and difficulty learning information relative to pre-surgery abilities. Researchers show that post-operative cognitive change associates with increased post-operative and long-term care costs [2, 3] as well as mortality [4, 5]. Type of post-operative cognitive change predict functional limitations; older adults with isolated executive changes experience more functional limitations and increased caregiver burden[6].

Despite numerous attempts to identify anesthetic or surgical mechanisms for operative related cognitive decline, there are no definitive explanations for POCD. General anesthesia remains an unconfirmed influence on cognitive decline in numerous randomized trials [7–9], despite animal studies suggesting that inhalational anesthetics enhance oligomerization and cytotoxicity of amyloid β peptides (a protein change associated with Alzheimer’s Disease) [10, 11], tau phosphorylation[12], and associated neuroinflammatory responses in humans [13, 14]. Surgery-related mechanisms on post-operative cognitive dysfunction (POCD), most often studied in cardiac populations, remain equally inconclusive. [4, 15–17].

Pre-operative patient characteristics are, by contrast, important predictors for post-operative cognitive decline and complications [5, 6, 18–22]. A large scale non-cardiac study prospectively examining age differences shows significantly higher rates of POCD for older adults (i.e., 3-month post-operative cognitive decline involving two standard deviations below baseline performance: young=5.7%, middle=5.6%, older=12.7%[5]). Lower education is a risk, as well[5, 20], with higher education and better outcome attributed to better brain status (being resistant to disease), better test-taking abilities, and the interrelationships between educational advancement, social support, and better postoperative medical care. Other proposed risk factors are lower pre-surgery executive function[23], higher rates of pre-surgical depression [23], greater vascular disease state (e.g., renal disease, congestive heart failure; [24]), pre-surgical evidence of non-symptomatic stroke [5, 25], and pre-surgical evidence of small vessel vascular disease [26].

Furthermore, there appear to be varying types of cognitive decline, with some individuals primarily experiencing executive based changes, others declarative memory difficulties, and others mixed cognitive profiles[6]. Our research group [6, 26, 27] as well as others [10, 23,

28] hypothesize that pre-operative cognitive profiles and disease risk states could indicate cognitive reserve deficiencies that may be accelerated by operative related events. Retrospective studies suggest that evidence of pre-surgery mild cognitive impairment may increase the risk for developing post-operative cognitive decline and Alzheimer's disease (AD)[29]. Prospective post-operative cognitive studies to date, however, have been limited to non-dementia adults without known neurodegenerative disease(citations here). Thus, the magnitude of risk that a pre-existing neurodegenerative disease may pose on post-surgery cognitive outcome remains largely unknown [30].

Individuals with Parkinson's disease (PD) may be at particular increased risk for acceleration of motor and cognitive dysfunction after surgery. PD impacts at least 1.5 million people in the United States alone, with most patients diagnosed after age 60. The disease is not only associated with motor changes, but also cognitive, mood, pain, and fatigue disturbances. Like their non-PD peers, individuals with PD may seek orthopedic joint replacement for quality of life improvement (e.g., total knee replacement), pain management, or for urgent events such as falls and fractures. We know of no studies examining how individuals with PD change cognitively after major surgery. There are only a few retrospective studies examining changes in range of motion or pain in PD patients after orthopedic surgery[31]. Since PD is associated with a 1.7–5.9 greater risk for dementia relative to non-PD peers [32–34], it appears prudent to examine how operative events may contribute to PD cognitive decline.

The primary aim of this pilot study was to examine post-operative cognitive decline in patients with PD. Reliable change methods examined individual changes in PD patients relative to control surgery and control non-surgery peers. Non-surgical PD participants were also recruited. Outcome measures included markers of processing speed, inhibitory function, memory, semantic fluency, and motor function. We hypothesized that surgery related cognitive changes in PD would be primarily apparent on measures assessing processing speed and inhibitory function. This hypothesis is based on previous work showing that PD initially alters frontal-subcortical cognitive pathways associated with processing speed, working memory and inhibitory function [35] which may place these patients at a resource disadvantage during operative events and/or stressors.

Methods

Study Design

The study was a prospective longitudinal pilot study with control arms involving a baseline (pre-surgery) neuropsychological assessment, with repeat assessments at 3-weeks, 3-months, and 1 year post-surgery. Patients were assessed for delirium, and followed during inpatient surgery related hospitalizations. The study was approved by the University of Florida Institutional Review Board (315–2002). It required a participant consenting process and followed guidelines from the Declaration of Helsinki.

Participants

Potential surgery participants were referred from the UF Center for Movement Disorder and Neurorestoration, as well as the Departments of Orthopedics and the Anesthesiology within the University of Florida as well as from private orthopedic surgery centers throughout Florida. Surgery participants underwent joint replacement surgery (total knee, hip, or spinal fusion) that required general anesthesia. Non-surgery non-PD control participants were referred from the same departments, and also recruited through newspaper advertisements, radio announcements, speaking engagements, and community memory screenings. Individuals with idiopathic PD had to be diagnosed by a movement disorder specialist and were required to meet the United Kingdom PD Society Brain Research Criteria for diagnosis, with “on” medication Hoehn and Yahr scale range of 1–3. Individuals with PD had to be non-demented and were required to be receiving dopaminergic treatment. Exclusion criteria included the intention to obtain another surgery during the study period (including deep brain stimulation; although DBS acquired 6 months or more prior to surgery was permitted), evidence of a learning disorder, evidence of secondary or atypical parkinsonism or other disorder as suggested by the presence of any of the following: 1) history of major stroke(s); 2) exposure to toxins or neuroleptics; 3) history of encephalitis; or 4) neurological signs of upper motor neuron disease, cerebellar involvement, supranuclear palsy, or significant orthostatic hypertension. A substantial portion of the surgery and non-surgery non-PD participants are reported upon in another publication [26] and are not commented upon here in this manuscript.

Enrollment required two study phases. After informed consent, there was an initial screening for eligibility and for cognitive function via a telephone-based assessment (Telephone Interview for Cognitive Status, [36]). This was followed by an in-person cognitive assessment to identify patients who met inclusion/exclusion criteria. For the knee and hip surgery patients, a standardized anesthetic protocol was used that involved ropivacaine for nerve blocks and postoperative infusion, pre-medication with intravenous midazolam, induction with fentanyl and thiopental (mechanically ventilated with an air/oxygen mixture to maintain an end-tidal CO_2 at 35 ± 5 mm anesthesia maintained with inhaled isoflurane and a Bispectral Index Monitor (BIS™) maintained between 40 and 50) and intravenous fentanyl and rocuronium. Delirium was assessed each post-operative day until discharge [37]. With the exception of one surgery (hip surgery) that involved communication to the anesthesiology and surgery team via telephone correspondence and fax, all surgeries were conducted within the same hospital.

Neuropsychological Protocol

A trained psychometrician administered all cognitive measures. For the current study, learning/memory, attention/processing speed, inhibition, semantic fluency, and motor function were analyzed. For each cognitive domain, z-scores were created from standardized scores referenced to published test norms [38, 39]. Two neuropsychologists (CP, DB) reviewed the baseline data. Data were double scored and entered by trained individuals who were blinded to diagnosis or condition.

Measures—The Hopkins Verbal List Learning-Revised (HVLT-R;[40]) is a 12-item word list that assesses learning and memory. The words were orally presented at the rate of one word per 2 seconds. After three learning trials, participants were instructed to recall the words immediately and after a 20-minute delay. Dependent variable = the total correct after the 20-minute delay.

The Digit Symbol Coding subtest of the WAIS-III [41]was used to assess attention/ concentration and processing speed. Participants were instructed to quickly match digits with their corresponding symbols without making errors within a 120 second time limit. Dependent variable = total correct within this time limit.

The Stroop Color Word Test, Part 3 [42, 43] was used to assess inhibitory function. In part 3 of this test, the participant views words that are printed in different color ink (e.g., *red* is printed in blue ink) and are instructed to name the color of the ink and not read the word. Dependent variable = total correct in 45 seconds.

Animal Fluency (Animals; [44]) required participants to name as many animals as possible within 60 seconds. Dependent variable = total correct exemplars.

The Finger Tapping Test [45] assessed fine motor speed in the dominant and non-dominant hand. Dependent variable = mean speed of both dominant and non-dominant hands.

Statistical Analysis

Descriptive statistical analyses for POCD were based on reliable change analyses using a modification of Jacobson and Truax's Reliable Change Index (RCI; see ISPOCD publications, e.g.,[1, 26]): $(\Delta X - \Delta X_c)/ SD_{(\Delta Xc)}$. Two RCI scores were computed for each PD participant at each time point (2 weeks, 3 months, and 1 year) using mean change (ΔX_c) and standard deviation of the mean change ($SD_{(\Delta Xc)}$) calculated from the HC surgery group and the HC non-surgery group. HCs change means were stratified by age (i.e., 60–70 and ≥71) to appropriately match age ranges of the participants with PD. Reliable change was defined by setting alpha at 0.10 (two-tailed), which corresponds to a 90% confidence level. Reliable decline was determined as a z-score ≤ −1.65 and improvement as a z-score ≥ +1.645. Changes at these cutoffs occur randomly in only 5 percent of cases in each direction, and is thus considered a clinically significant change [46]. Chi-square analyses were conducted to explore group frequency by type of cognitive decline for PD surgery relative to PD non-surgery peers.

Results

Enrollment

Over a two-year period, we screened 152 older adult surgery or non-surgery candidates with 19 of these individuals having a diagnosis of PD. Of the individuals with PD, 8 met inclusion/exclusion criteria and elected to participate in the study. The remaining individuals with PD chose not to participate due to surgery location (surgery at another hospital), travel concerns, or choosing to postpone the surgery. The final sample included 5 PD orthopedic surgery, 3 PD non-surgery, 47 surgery and 21 non-surgery. For the PD surgery group, none

dropped out at 2 weeks and 3 months. One participant did not return for 1-year follow up. There were no dropouts in the PD non-surgery group. For the control surgery and non-surgery participants, the rate of attrition was 0% at three weeks, 8% (3 of 40) at 3 months, and 15% (6 of 40) at 1 yr. Of these controls, two were unavailable at the 3-month time point but were tested at 1 yr. Of the PD participants having surgery, three had total knee replacement, one had hip replacement, and one had spinal surgery. All of the HC participants had elective total knee replacement surgery. No participant experienced delirium.

Demographics

Table 1. PD patients (n = 8) and controls (n = 68) were similar regarding general demographic variables and general cognitive status (all $p > 0.05$). Aside from having PD, all were considered healthy, with low comorbidities, and there were no statistically significant group baseline differences in cognitive measures with the exception of memory (PD < HC, $p = .03$).

Table 2. PD surgery and PD non-surgery patients were statistically different in age (PD-S < PD-NS, $p = .011$). All other demographic variables were similar. Data regarding the PD surgery characteristics are shown in Table 3.

Frequency of PD Cognitive Changes Based on HC Non-Surgery Change Scores (Table 4)

At the three week post-surgery time point, four out of five PD surgery individuals (80%) experienced significant decline (at or greater than the −1.645 reliable change score). Three PD surgery participants experiencing significant decline at three-month and one year post-surgery assessments. By contrast, only one (33.33%) non-surgery PD participant experienced decline at three-month and one-year post baseline assessments.

A review of Table 4 shows that the majority of these PD surgery cognitive changes occurred on measures of processing speed and inhibitory function. Exploratory analyses in this sample comparing group type (PD surgery, PD nonsurgery) supports a trend for three weeks [$x^2(2)=4.80$, $p=0.09$]. Group mean reliable change measures are shown in Table 7.

Frequency of PD Cognitive Changes Based on HC Surgery Change Scores (Table 5)

Four out of five (80%) PD individuals experienced significant decline (at or greater than the −1.645 reliable change score) at three weeks post-surgery. Three PD surgery participants experienced significant decline at three-months and one year. Only one non-surgery PD participant (33.3%) experienced reliable decline at three-month post baseline assessment.

Similar to PD cognitive changes found relative to HC Non-Surgery group, exploratory analyses comparing group type (PD surgery, PD non-surgery) by domain relative to HC Surgery group supports a trend for greater processing speed changes at 3-wks post-surgery ([$x^2(2)=4.80$, $p=0.09$]. Group mean reliable change measures can be seen in Supplementary Table 8.

Discussion

This prospective pilot study demonstrates the importance of studying POCD in neurologically at-risk populations. Our data show the majority individuals with PD electing surgery experienced greater cognitive decline relative to the non-PD “healthy” surgery and non-surgery peers. These findings are significant given that the healthy surgery peers have been reported in a separate paper to have cognitive changes of their own [26]. For the PD participants, these changes were significant for the domains of processing speed and inhibitory functions. Based on the comparison group of PD non-surgery peers, the severity of cognitive change after surgery may be more pronounced than would be expected by PD progression alone. If these findings are confirmed by a larger investigation, the collective findings will support the concept of a threshold effect; i.e., pre-operative cognitive and brain status heralds a type of post-operative insult. A larger, potentially multicenter study is clearly needed to investigate this topic in detail. With the global presence and increase in PD [47–51], it is important that we understand how to provide medical and surgical care and support to those with PD without further accelerating neurodegeneration.

It is not known why some individuals experience cognitive changes after surgery. In 1955, Bedford [52] published findings suggesting that anesthesia induced cognitive changes. This publication reported upon a chart review of 1,193 adults over the age of 65 who had received a variety of surgical interventions under general anesthesia. Of these patients, 120 individuals (10%) were reported to have experienced postoperative changes. A subset of 120 patients (n=18, 1%) was described as “human vegetables” in the medical records. Since the publication by Bedford, research on POCD has been steadily increasing yet, we still do not know the mechanism(s) that cause POCD. It has been postulated that anesthesia does not contribute to the syndrome at all [8]. Long standing changes have not been traditionally blamed on lingering pharmacologic effects of anesthetic drugs because of the relatively short half-lives of these agents[53]. Most patients affected by POCD recover in a matter of months [54], which evokes the picture of a slow-healing injury. The fact that not every patient is affected raises a question about genetic influence. The elderly are at greater risk than younger patients [5]and it is known that with age the central nervous system, as with many other physiological systems, is more susceptible to damage. Within our study, the findings suggest that this may be even more pronounced for individuals with a neurodegenerative disease that has been described by some [55] as accelerated aging (i.e., PD).

Studies are beginning to suggest that there are subtypes of POCD among older adults and that by studying type of cognitive decline we can improve our understanding of mechanisms. Price, Garvan, and Monk (2008) showed that within older adults who have POCD after orthopedic surgery, 34% experienced primary executive impairment involving difficulties with mental flexibility and processing speed, 54% experienced primary learning/memory impairment, and 12% showed combined both executive and memory impairment. These findings suggest that adults over 60 years of age can exhibit different variants of cognitive impairment at three months following surgery. Although these findings require replication, they appear to suggest that there are likely different regions of the brain that can be influenced or associated with POCD. Follow-up investigations e.g.,[26] are continuing to

show differences in types of post operative cognitive decline, and that executive changes can be predicted at least partially by the integrity of frontal-subcortical systems *prior* to surgery.

In patients with PD, selective impairment in postoperative processing speed symptoms may be primarily linked to a disturbance in the direct and indirect cortical-subcortical network systems. The current pilot study findings of primary processing speed and inhibitory impairment for the PD participants speak to PD based frontal-striatal neuronal vulnerabilities[35]. It has been theorized that individuals can remain above a critical threshold due to cognitive[56] or brain reserve[57] until some combination of factors (e.g., brain damage, neuronal stress) summates to accelerate symptom manifestation (threshold theory' [57]. Operative events or "stressors" may serve to accelerate frontal-subcortical deficits already developing due to the neurodegenerative disease course. Stressful events include at minimum (a) emboli (b) damage to the subcortical nuclei due to alteration of the small vessel vascular supply, and (c) neurochemical changes associated with anesthesia.

Certain surgical procedures are associated with venous emboli (e.g., air or clot). Emboli can occur during total knee replacement surgery; e.g., immediately after femoral tourniquet release [58] [59, 60]. The comforting image that venous emboli are filtered by the lung - and thus not gain access to the cerebral circulation – needs to be abandoned. On one hand, up to 30% patients can have a patent foramen ovale that allows material from the right atrium to traverse to the left atrium when atrial pressure on the right exceeds that on the left [61]. This increase in right heart pressure is observed with pulmonary emboli (either air or debris). On the other hand, Sulek and colleagues have observed emboli to pass through the lungs and into the brain even in patients with closed atrial septums [60]. Emboli during surgery present a risk for stroke. Moreover, arterioles supplying the subcortical nuclei (thalami, basal ganglia, caudate) are particularly vulnerable to blood flow alterations [62] and may be especially prone to operative hemodynamic changes[63]. For all of these reasons, we speculate that embolic insults to individuals with PD may be particularly disruptive due to their already compromised striatal integrity [35]. We encourage future researchers studying POCD in PD to monitor intraoperative emboli and venous pressure changes throughout surgery.

It is also unknown how anesthesia may contribute to post-operative outcome for older adults - and particularly those with Parkinson's disease. General anesthesia alters activation and blood flow to the brain [64]. Communication between the frontal and posterior brain regions (frontoparietal network) may be disrupted [65] with cerebral blood flow reduction to the frontal cortex, parietal cortex, cingulate, and thalamus [64]. Anesthesia induction is also uniquely associated with decreased spontaneous neuronal firing within the gray matter of the cortex, [66] with later firing changes occurring in the subcortical gray regions involved in sensory gating (i.e., thalamic network) [67]. Within these regions, high-frequency rhythms reduce thereby resulting in the sleep of anesthesia [68]. Interestingly, severely depressed patients under propofol sedation and anesthesia have shown greater reductions in global cerebral blood flow, with particular reduction in inferior prefrontal region relative to studies of healthy adults [64, 69]. There is some suggestion that depression at time of surgery associates with an abnormal response to anesthesia during the induction phase [27]. These studies, combined with growing appreciation for the rate of depression, apathy, and frontal-

subcortical dysfunction in PD, [70, 71] supports the argument for investigations on PD and anesthesia responsiveness. Understanding how to predict risk, control the interaction of pre-surgery factors and operative events, and treat POCD will depend on advancing our understanding of the brain, anesthesia and other operative events in at risk and healthy adults.

Our current study suggests potential for prospective investigations. This is despite our difficulty recruiting individuals with PD who were planning orthopedic surgery. Retrospectively, we consider the recruitment issue largely due to communication difficulties (i.e., often individuals with PD did not consider it necessary to inform their neurologist about the likelihood of surgery and we would learn about the surgery post-hoc). Hence, we did not acquire many referrals from our movement disorder center. Addressing communication issues between neurologists and other providers is an important issue for a) reducing complications post hospitalization[72] and b) building prospective team based studies that target complex medical issues related to medical care. We encourage a large multicenter effort (where each center concentrates on recruiting a small number of participants), and that includes an organized communication system between neurology, surgery departments, and the preoperative anesthesia screening clinic. The downside of a multicenter study would be the variation in surgical technique, but the upside of a properly powered study would outweigh this negative.

We recognize study limitations. First, our sample size is a clear limitation for generalizing rates of POCD in PD. We statistically address this issue by examining change at the PD individual level relative to a group of surgery and non-surgery peer groups. Second, we have an unequal sample size for individuals diagnosed with PD versus PD non-surgery controls. As shown with other diseases [73], an essential study design characteristic for post-operative cognitive research is a comparison group of disease matched peers. These peers help clarify if the cognitive change over time can be attributed partially to operative events after controlling for age and disease progression. We encourage future researchers to match surgery and non-surgery participants on demographics but also disease based severity. In a much larger sample it may also be feasible to examine PD clinical type (i.e., tremor dominant, primary gait disturbance) and whether the presence of a deep brain stimulator contributed negatively or positively to post-operative outcome. Third, we did not acquire the Unified Parkinson's Disease Rating Scale[74] (UPDRS) scores for the PD participants, but encourage this for future investigations as well. Fourth, we recognize that our PD orthopedic surgery group included a mixture of knee, hip, and back procedures, while our healthy surgery control group included those having total knee replacement. Orthopedic surgery is not uniform across these surgery types; e.g., knee surgery is associated with emboli from the tourniquet, hip surgery with potential more blood loss, and back surgery with surgery based on and anesthesia time. Examining orthopedic surgery in general, however, is advantageous to studying post-operative cognitive decline. Orthopedic surgeries are often elective. This allows for prospective enrollment and completion of baseline cognitive assessments. Orthopedic surgeries generally use a routine procedure and rehabilitation approach thereby introducing less bias when compared to non-cardiac surgeries such as abdominal procedures that may vary widely based on patients' illness. These surgeries are also associated with concerning rates of POCD in older adults [5]as well as associated with negative

perioperative events such as emboli and anemia. While we recognize that it would have been more controlled to have the PD participants with only one type of orthopedic surgery (i.e., knee) this was not possible due to difficulties recruitment options in our current investigation. We encourage an improved study design to include a similar proportion of PD and non-PD peers within each orthopedic surgery type. Future studies should also examine severity of PD cognitive change after type of orthopedic surgery, if possible. Fifth, we did not assess non-cognitive features that play a significant role in PD such as quality of life or symptoms of depression, apathy, anxiety, and pain. There is a possibility that for some individuals a subtle change in cognitive function after elective surgery may be outweighed by decreased pain, improved mobility, and improved quality of life. Given the complexity of PD motor and non-motor related symptoms, we acknowledge that post-operative cognitive decline in PD may be best studied holistically rather than isolated on cognitive function alone.

Despite these weaknesses, we consider our study well organized from a group design perspective and an appropriate pilot study for identifying challenges and stimulating future research. Our findings that the majority (80%) of the PD surgery sample experienced cognitive decline greater than that of the healthy surgery and non-surgery peers is noteworthy, particularly given our previous findings that the healthy surgery adults in our sample had decline relative to the non-surgery healthy peers[26]. Given the pilot nature of the study, however, we strongly caution clinicians to avoid using these data as a foundation for clinical decisions regarding surgery for individuals with PD.

In summary, this pilot study supports the feasibility and rationale for investigating surgical risk for individuals with PD. We encourage future larger scale multicenter prospective studies to investigate cognitive change associated with operative events in older adults, but in particular those with neurodegenerative diseases such as PD.

Acknowledgments

This paper is dedicated to the memory of J.S. Gravenstein, M.D., who was a mentor to many of us regarding the importance of post-operative cognitive decline research. We are very grateful to each participant for his/her time and efforts associated with this investigation. We are grateful to Peter Gearen, M.D., Dr. Thomas Wright, Dr. Richard Vlasak, and Dr. Timothy Lane, within the Department of Orthopedic Surgery, for their assistance with research recruitment and study enthusiasm. We sincerely thank Hubert Fernandez, M.D., for assistance with study initiation and his enthusiasm regarding the topic of POCD in Parkinson's disease, as well as Gang Zheng, M.D., Anesthesiology, for his assistance with the anesthesia protocol. We want to acknowledge the support of the NPF Center of Excellence located at the University of Florida. We acknowledge Lordes Lasagna, B.S., Katherine Moyses, B.A., Kristen Moffett, M.S., and Ida Kellison, Ph.D., Departments of Clinical and Health Psychology, University of Florida, for their assistance with recruitment, data entry, and study management. We thank Ann Horgas, Ph.D., and Laura Anderson, B.S., for their manuscript review and comments. We thank Neil and Nancy Crenshaw for their editoral review.

Disclosure of Funding: Supported by the National Parkinson Foundation Center of Excellence Grant (CP), Alzheimer Association NIRG-05-14502 (CP), I. Herrmann Anesthesia Foundation, Gainesville, Florida (*CP)*, NIH General Clinical Research Center Grant # MO1-RR00082, NIA F32AG021363, NIH K23NS60660, NIH R01NR014181 and R01 NS082386.

Literature Citations

1. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT. The assessment of postoperative cognitive function. Acta Anaesthesiol Scand. 2001; 45:275–289. [PubMed: 11207462]
2. Shourt CA, Crowson CS, Gabriel SE, Matteson EL. Orthopedic surgery among patients with rheumatoid arthritis 1980–2007: a population-based study focused on surgery rates, sex, and mortality. J Rheumatol. 2012; 39:481–485. [PubMed: 22247350]
3. Fernandez J, Chen C, Anolik G, Brdlik OB, Laub GW, Anderson WA, McGrath LB. Perioperative risk factors affecting hospital stay and hospital costs in open heart surgery for patients > or = 65 years old. Eur J Cardiothorac Surg. 1997; 11:1133–1140. [PubMed: 9237599]
4. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med. 2001; 344:395–402. [PubMed: 11172175]
5. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology. 2008; 108:18–30. [PubMed: 18156878]
6. Price CC, Garvan CW, Monk TG. Type and severity of cognitive decline in older adults after noncardiac surgery. Anesthesiology. 2008; 108:8–17. [PubMed: 18156877]
7. Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME. Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. Jama. 1995; 274:44–50. [PubMed: 7791257]
8. Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, Jolles J, Papaioannou A, Abildstrom H, Silverstein JH, Bonal JA, Raeder J, Nielsen IK, Korttila K, Munoz L, Dodds C, Hanning CD, Moller JT. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand. 2003; 47:260–266. [PubMed: 12648190]
9. Somprakit P, Lertakyamanee J, Satraratanamai C, Wanicksamban S, Silapadech A, Chainchop P, Muangsuay V. Mental state change after general and regional anesthesia in adults and elderly patients, a randomized clinical trial. J Med Assoc Thai. 2002; 85(Suppl 3):S875–883. [PubMed: 12452224]
10. Eckenhoff RG, Johansson JS, Wei H, Carnini A, Kang B, Wei W, Pidikiti R, Keller JM, Eckenhoff MF. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. Anesthesiology. 2004; 101:703–709. [PubMed: 15329595]
11. Perucho J, Rubio I, Casarejos MJ, Gomez A, Rodriguez-Navarro JA, Solano RM, De Yebenes JG, Mena MA. Anesthesia with isoflurane increases amyloid pathology in mice models of Alzheimer's disease. J Alzheimers Dis. 2010; 19:1245–1257. [PubMed: 20308791]
12. Le Freche H, Brouillette J, Fernandez-Gomez FJ, Patin P, Caillierez R, Zommer N, Sergeant N, Buee-Scherrer V, Lebuffe G, Blum D, Buee L. Tau phosphorylation and sevoflurane anesthesia: an association to postoperative cognitive impairment. Anesthesiology. 2012; 116:779–787. [PubMed: 22343471]
13. Tang JX, Baranov D, Hammond M, Shaw LM, Eckenhoff MF, Eckenhoff RG. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. Anesthesiology. 2011; 115:727–732. [PubMed: 21857497]
14. Kapila AK, Watts HR, Wang TL, Ma DQ. The Impact of Surgery and Anesthesia on Post-Operative Cognitive Decline and Alzheimer's Disease Development: Biomarkers and Preventive Strategies. Journal of Alzheimers Disease. 2014; 41:1–13.
15. Selnes OA, McKhann GM, Borowicz LM Jr, Grega MA. Cognitive and neurobehavioral dysfunction after cardiac bypass procedures. Neurol Clin. 2006; 24:133–145. [PubMed: 16443135]
16. Lund C, Sundet K, Tennoe B, Hol PK, Rein KA, Fosse E, Russell D. Cerebral ischemic injury and cognitive impairment after off-pump and on-pump coronary artery bypass grafting surgery. Ann Thorac Surg. 2005; 80:2126–2131. [PubMed: 16305857]

17. Diegeler A, Hirsch R, Schneider F, Schilling LO, Falk V, Rauch T, Mohr FW. Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. Ann Thorac Surg. 2000; 69:1162–1166. [PubMed: 10800812]
18. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet. 1998; 351:857–861. [PubMed: 9525362]
19. Frye RL, Kronmal R, Schaff HV, Myers WO, Gersh BJ. Stroke in coronary artery bypass graft surgery: an analysis of the CASS experience. The participants in the Coronary Artery Surgery Study. Int J Cardiol. 1992; 36:213–221. [PubMed: 1512060]
20. Newman MF, Croughwell ND, Blumenthal JA, Lowry E, White WD, Spillane W, Davis RD Jr, Glower DD, Smith LR, Mahanna EP, et al. Predictors of cognitive decline after cardiac operation. Ann Thorac Surg. 1995; 59:1326–1330. [PubMed: 7733762]
21. Tuman KJ, McCarthy RJ, Najafi H, Ivankovich AD. Differential effects of advanced age on neurologic and cardiac risks of coronary artery operations. J Thorac Cardiovasc Surg. 1992; 104:1510–1517. [PubMed: 1453714]
22. Gardner TJ, Horneffer PJ, Manolio TA, Pearson TA, Gott VL, Baumgartner WA, Borkon AM, Watkins L Jr, Reitz BA. Stroke following coronary artery bypass grafting: a ten-year study. Ann Thorac Surg. 1985; 40:574–581. [PubMed: 3878134]
23. Greene NH, Attix DK, Weldon BC, Smith PJ, McDonagh DL, Monk TG. Measures of executive function and depression identify patients at risk for postoperative delirium. Anesthesiology. 2009; 110:788–795. [PubMed: 19326494]
24. Carrier M, Perrault LP, Jeanmart H, Martineau R, Cartier R, Page P. Randomized trial comparing off-pump to on-pump coronary artery bypass grafting in high-risk patients. Heart Surg Forum. 2003; 6:E89–92. [PubMed: 14721990]
25. Goto T, Baba T, Honma K, Shibata Y, Arai Y, Uozumi H, Okuda T. Magnetic resonance imaging findings and postoperative neurologic dysfunction in elderly patients undergoing coronary artery bypass grafting. Ann Thorac Surg. 2001; 72:137–142. [PubMed: 11465168]
26. Defreitas GA, Lemack GE, Zimmern PE, Dewey RB, Roehrborn CG, O'Suilleabhain PE. Distinguishing neurogenic from non-neurogenic detrusor overactivity: a urodynamic assessment of lower urinary tract symptoms in patients with and without Parkinson's disease. Urology. 2003; 62:651–655. [PubMed: 14550436]
27. Price CC, Pereira DB, Andre R, Garvan CW, Nguyen P, Herman M, Seubert C. Prospective Pilot Investigation: Presurgical Depressive Symptom Severity and Anesthesia Response in Women Undergoing Surgery for Gynecologic Mass Removal. Int J Behav Med. 2014
28. Terrando N, Eriksson LI, Eckenhoff RG. Perioperative neurotoxicity in the elderly: summary of the 4th International Workshop. Anesth Analg. 2015; 120:649–652. [PubMed: 25695580]
29. Bekker A, Lee C, de Santi S, Pirraglia E, Zaslavsky A, Farber S, Haile M, de Leon MJ. Does mild cognitive impairment increase the risk of developing postoperative cognitive dysfunction? American Journal of Surgery. 2010; 199:782–788. [PubMed: 20609722]
30. Vanderweyde T, Bednar MM, Forman SA, Wolozin B. Iatrogenic risk factors for Alzheimer's disease: surgery and anesthesia. J Alzheimers Dis. 2010; 22(Suppl 3):91–104. [PubMed: 20858967]
31. Kryzak TJ, Sperling JW, Schleck CD, Cofield RH. Hemiarthroplasty for Proximal Humerus Fractures in Patients with Parkinson's Disease. Clin Orthop Relat Res. 2010; 468:1817–1821. [PubMed: 20387015]
32. Marder K, Tang MX, Cote L, Stern Y, Mayeux R. The frequency and associated risk factors for dementia in patients with Parkinson's disease. Arch Neurol. 1995; 52:695–701. [PubMed: 7619026]
33. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson disease. J Neurol Sci. 2010; 289:18–22. [PubMed: 19733364]

34. Goldman JG, Stebbins GT, Bernard B, Stoub TR, Goetz CG, Detoledo-Morrell L. Entorhinal cortex atrophy differentiates Parkinson's disease patients with and without dementia. Mov Disord. 2012
35. Bohnen NI, Albin RL, Muller ML, Petrou M, Kotagal V, Koeppe RA, Scott PJ, Frey KA. Frequency of Cholinergic and Caudate Nucleus Dopaminergic Deficits Across the Predemented Cognitive Spectrum of Parkinson Disease and Evidence of Interaction Effects. JAMA Neurol. 2014
36. Cook SE, Marsiske M, McCoy KJ. The use of the Modified Telephone Interview for Cognitive Status (TICS-M) in the detection of amnestic mild cognitive impairment. J Geriatr Psychiatry Neurol. 2009; 22:103–109. [PubMed: 19417219]
37. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990; 113:941–948. [PubMed: 2240918]
38. Lezak, MD. Neuropsychological assessment. Oxford University Press; Oxford; New York: 2012.
39. Strauss, E.; Sherman, EMS.; Spreen, O. A compendium of neuropsychological tests : administration, norms, and commentary. Oxford University Press; Oxford; New York: 2006.
40. Rosewell A, Clark G, Mabong P, Ropa B, Posanai E, Man NW, Dutta SR, Wickramasinghe W, Qi L, Ng JC, Mola G, Zwi AB, MacIntyre CR. Concurrent outbreaks of cholera and peripheral neuropathy associated with high mortality among persons internally displaced by a volcanic eruption. PLoS One. 2013; 8:e72566. [PubMed: 24023752]
41. Wechsler, D. Wechsler Adult Intelligence Scale – Third Edition. The Psychological Corporation; San Antonio, Texas: 1997.
42. Golden, CJ.; Freshwater, SM. The Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Stoelting; Chicago, IL: 2002.
43. Stroop JR. Studies of Interference in Serial Verbal Reactions. Journal of Experimental Psych. 1935; 18:643–660.
44. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol. 1999; 14:167–177. [PubMed: 14590600]
45. DIKMEN. et al. Test–retest reliability and practice effects of Expanded Halstead–Reitan Neuropsychological Test Battery. Journal of the International Neuropsychological Society. 1999; 5:346–356. [PubMed: 10349297]
46. Duff K. Evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods. Arch Clin Neuropsychol. 2012; 27:248–261. [PubMed: 22382384]
47. Wong SL, Gilmour H, Ramage-Morin PL. Parkinson's disease: Prevalence, diagnosis and impact. Health Rep. 2014; 25:10–14. [PubMed: 25408491]
48. Blin P, Dureau-Pournin C, Foubert-Samier A, Grolleau A, Corbillon E, Jove J, Lassalle R, Robinson P, Poutignat N, Droz-Perroteau C, Moore N. Parkinson's disease incidence and prevalence assessment in France using the national healthcare insurance database. Eur J Neurol. 2015; 22:464–471. [PubMed: 25389031]
49. Durmus H, Gokalp MA, Hanagasi HA. Prevalence of Parkinson's disease in Baskale, Turkey: a population based study. Neurol Sci. 2015; 36:411–413. [PubMed: 25351343]
50. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2014; 29:1583–1590. [PubMed: 24976103]
51. Ma CL, Su L, Xie JJ, Long JX, Wu P, Gu L. The prevalence and incidence of Parkinson's disease in China: a systematic review and meta-analysis. J Neural Transm. 2014; 121:123–134. [PubMed: 24057652]
52. Bedford P. Adverse cerebral effects of anaesthesia on old people. Lancet. 1955; 2:758–861.
53. Price, C.; Gravenstein, JS. Post Operative Cognitive Dysfunction. In: Lobato, EB.; Gravenstein, N.; Kirby, RR., editors. Complications in Anesthesia: Second Edition. Lippincott-Williams & Wilkins; Hagerstown, MD: 2007. p. 276-290.
54. Abildstrom H, Rasmussen LS, Rentowl P, Hanning CD, Rasmussen H, Kristensen PA, Moller JT. Cognitive dysfunction 1–2 years after non-cardiac surgery in the elderly. ISPOCD group.

International Study of Post-Operative Cognitive Dysfunction. Acta Anaesthesiol Scand. 2000; 44:1246–1251. [PubMed: 11065205]

55. Sandyk R. The accelerated aging hypothesis of Parkinson's disease is not supported by the pattern of circadian melatonin secretion. Int J Neurosci. 1997; 90:271–275. [PubMed: 9352432]
56. Stern Y. Cognitive reserve. Neuropsychologia. 2009; 47:2015–2028. [PubMed: 19467352]
57. Satz P. Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. Neuropsychology. 1993; 7:273–295.
58. Berman AT, Parmet JL, Harding SP, Israelite CL, Chandrasekaran K, Horrow JC, Singer R, Rosenberg H. Emboli observed with use of transesophageal echocardiography immediately after tourniquet release during total knee arthroplasty with cement. J Bone Joint Surg Am. 1998; 80:389–396. [PubMed: 9531207]
59. Parmet JL, Horrow JC, Berman AT, Miller F, Pharo G, Collins L. The incidence of large venous emboli during total knee arthroplasty without pneumatic tourniquet use. Anesth Analg. 1998; 87:439–444. [PubMed: 9706947]
60. Sulek CA, Davies LK, Enneking FK, Gearen PA, Lobato EB. Cerebral microembolism diagnosed by transcranial Doppler during total knee arthroplasty: correlation with transesophageal echocardiography. Anesthesiology. 1999; 91:672–676. [PubMed: 10485777]
61. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first ten decades: A necropsy study of 965 normal hearts. Mayo Clin Proc. 1987; 59:17. [PubMed: 6694427]
62. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke. 1997; 28:652–659. [PubMed: 9056627]
63. Baumbach GL. Effects of increased pulse pressure on cerebral arterioles. Hypertension. 1996; 27:159–167. [PubMed: 8567036]
64. Fiset P, Paus T, Daloze T, Plourde G, Meuret P, Bonhomme V, Hajj-Ali N, Backman SB, Evans AC. Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. J Neurosci. 1999; 19:5506–5513. [PubMed: 10377359]
65. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA. Disruption of Frontal-Parietal Communication by Ketamine, Propofol, and Sevoflurane. Anesthesiology. 2013; 118:1264–1275. [PubMed: 23695090]
66. Velly LJ, Rey MF, Bruder NJ, Gouvitsos FA, Witjas T, Regis JM, Peragut JC, Gouin FM. Differential dynamic of action on cortical and subcortical structures of anesthetic agents during induction of anesthesia. Anesthesiology. 2007; 107:202–212. [PubMed: 17667563]
67. Nicoll RA, Madison DV. General anesthetics hyperpolarize neurons in the vertebrate central nervous system. Science. 1982; 217:1055–1057. [PubMed: 7112112]
68. Steriade M. Corticothalamic resonance, states of vigilance and mentation. Neuroscience. 2000; 101:243–276. [PubMed: 11074149]
69. Ogawa K, Uema T, Motohashi N, Nishikawa M, Takano H, Hiroki M, Imabayashi E, Ohnishi T, Inoue T, Takayama Y, Takeda M, Matsuda H, Andoh T, Yamada Y. Neural mechanism of propofol anesthesia in severe depression: a positron emission tomographic study. Anesthesiology. 2003; 98:1101–1111. [PubMed: 12717131]
70. Richard IH. Depression and apathy in Parkinson's disease. Curr Neurol Neurosci Rep. 2007; 7:295–301. [PubMed: 17618535]
71. Cohen ML, Aita S, Mari Z, Brandt J. The Unique and Combined Effects of Apathy and Depression on Cognition in Parkinson's Disease. J Parkinsons Dis. 2015
72. Aminoff MJ, Christine CW, Friedman JH, Chou KL, Lyons KE, Pahwa R, Bloem BR, Parashos SA, Price CC, Malaty IA, Iansek R, Bodis-Wollner I, Suchowersky O, Oertel WH, Zamudio J, Oberdorf J, Schmidt P, Okun MS. Management of the hospitalized patient with Parkinson's disease: Current state of the field and need for guidelines. Parkinsonism Relat Disord.
73. Selnes OA, Grega MA, Bailey MM, Pham L, Zeger S, Baumgartner WA, McKhann GM. Neurocognitive outcomes 3 years after coronary artery bypass graft surgery: a controlled study. Ann Thorac Surg. 2007; 84:1885–1896. [PubMed: 18036903]

74. Fahn, S.; Elton, RL., et al. Unified Parkinson's Disease Rating Scale. In: Fahn, S.; Marsden, CD.; Goldstein, M.; Calne, DB., editors. Recent Developments in Parkinson's Disease. Macmillan Publishing Company; New York: 1987. p. 153-164.

75. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987; 40:373–383. [PubMed: 3558716]

76. Yesavage JA. Geriatric Depression Scale. Psychopharmacol Bull. 1988; 24:709–711. [PubMed: 3249773]

77. Spielberger, CD. State-trait anxiety inventory : a comprehensive bibliography. Consulting Psychologists Press; Palo Alto, CA (577 College Ave., Palo Alto 94306): 1989.

78. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]

79. Wechsler, D. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation; San Antonio, Tx: 1999.

Table 1

Baseline demographics, mood, and cognition for individuals with Parkinson's disease and "Healthy" controls.

Measure	PD (N=8)	Controls (N=68)	*p*
Age (years)	69.13 (9.34)	71.60 (6.00)	0.30
Education (years)	16.13 (2.17)	15.02 (3.50)	0.39
Sex (M: F)	5:3	35:33	
Charlson Combordity	.00 (.00)	1.21 (1.42)	**0.02***
GDS	5.25 (3.01)	3.88 (4.26)	0.38
State Anxiety	28.63 (6.23)	32.34 (10.53)	0.33
Trait Anxiety	31.14 (8.49)	30.13 (7.40)	0.75
MMSE	29.63 (0.52)	28.99 (1.70)	0.30
Stroop CW	0.19 (0.69)	−0.09 (1.15)	0.53
Digit Symbol	0.33 (0.89)	0.28 (0.87)	0.86
HVLT Delay	−1.37 (1.44)	−0.41 (1.09)	**0.03***
Animal Fluency	0.51 (0.92)	0.44 (0.98)	0.83
Finger Tapping	−1.71 (0.65)	0.65 (0.96)	**0.00***

* <0.05 compared to controls

Charlson Comorbidity range (0–30; 30=worst)[75]; GDS = Geriatric Depression Scale[76]; State Anxiety = State Trait Anxiety Inventory [77]State Raw Score ; Trait Anxiety = State Trait Anxiety Trait Raw Score; MMSE = Mini Mental State Examination[78], Stroop CW = Stroop Color Word Test (Color Word Condition), HVLT Delay = Hopkins Revised Verbal Learning Test (HVLT-R) Delay Condition

Table 2

Baseline demographics for PD groups and healthy control groups

Measure	PD-S N = 5	PD-NS N=3	HC-S N = 47	HC-NS N = 21
Age	63.80 (6.76)	78.00 (5.00)*	71.53 (6.38)	71.76 (5.20)
Education	16.00 (2.00)	16.00 (2.49)	14.29 (3.53)	16.67 (2.85)**
Charlson Comorbidity	0.00 (0.00)	0.00 (0.00)	1.19 (1.31)	1.24 (1.67)
MMSE	29.67 (0.58)	29.60 (0.55)	28.81 (1.93)	29.40 (0.88)
GDS	6.00 (4.00)	4.80 (2.68)	3.79 (4.11)	4.10 (4.67)
State Anxiety	30.67 (6.35)	27.40 (6.54)	32.07 (10.17)	32.95 (11.55)
Trait Anxiety	30.33 (4.93)	30.00 (9.14)	30.36 (7.13)	32.81 (10.87)

* $p<0.05$ PD Comparisons

** $p< 0.05$ HC Comparisons

PD-S = PD-Surgery; PD-NS = PD-Non surgery; HC-S = Healthy Control- Surgery; HC-NS = Healthy Control Non Surgery; Charlson Comorbidity range (0–30; 30=worst)[75]; MMSE = Mini Mental State Examination [78]; GDS = Geriatric Depression Scale [76], State Anxiety = State Trait Anxiety Inventory [77] State Raw Score ; Trait Anxiety = State Trait Anxiety Trait Raw Score

Table 3

Demographic and surgery variables for five Parkinson's disease surgery participants

	PD-01	PD-02	PD-03	PD-04	PD-05
Demographics					
Age	55	72	67	66	59
Sex	M	F	M	M	F
Education	16	14	20	17	14
PD Type	L Tr	R Tr	L Tr	R Tr	L Tr
DBS Placement	Y	N	N	Y	N
Disease Duration (years)	6	6	5	17	16
Pre-Surgery Data					
Weight (pounds)	235	164	165	195	117
Baseline Blood Pressure	130/80	100/64	131/66	129/87	–
Comorbidity score	0	2	0	0	0
WASI Standardized Score	96	121	130	118	99
Surgery Data					
Surgery Type	L	L	R	R	R
Surgery Site	knee	knee	spine	knee	hip
General Anesthesia	Y	Y	Y	Y	Y
Regional Anesthesia	Y	Y	Y	Y	–
Surgery Duration (minutes)	117	–	240	111	–
Anesthesia Duration (minutes)	145	–	300	161	–
BL Hematocrit	39.30	49.00	44.0	–	–
Post-Op Hematocrit	28.80	35.00	31.0	–	–
Post-Surgical Complications					
Inpatient Complications	Blood unit	None	None	None	None
Postoperative Delirium	None	None	None	None	None

M=male; F=female; L= left; R=Right; Tr = tremor; Y=yes; N=no; DBS = Deep Brain Stimulation; Premorbid IQ = WASI = Wechsler Abbreviated Scale of Intelligence[79]; Post-Op = Post Operative; – stands for missing data due to unavailable medical record information.

Table 4

Participant reliable change index test scores relative to **healthy control <u>non-surgery</u>** peer reference group (n=21). RCI ≤ −1.645 SD are in bold.

		3 Weeks					3 Months					1 Year				
ID	**Group**	**Stroop CW**	**Digit Symbol**	**Hopkins Delay**	**Animal Fluency**	**Finger Tapping**	**Stroop CW**	**Digit Symbol**	**Hopkins Delay**	**Animal Fluency**	**Finger Tapping**	**Stroop CW**	**Digit Symbol**	**Hopkins Delay**	**Animal Fluency**	**Finger Tapping**
PS-01	PD-S	.06	−.22	−1.19	.21	2.47	−.97	−.17	.53	.37	3.30	**−1.82**	**−2.97**	**−4.53**	−.30	1.10
PD-02	PD-S	**−8.78**	**−3.09**	2.83	.70	.43	1.04	**−2.51**	3.35	−.36	.44	−.43	**−1.90**	2.31	−.75	−.73
PD-03	PD-S	.	**−2.71**	−1.21	−.59	.57	.	**−4.25**	−.13	−1.06	−.12	.	−1.54	.17	−.61	−.64
PD-04	PD-S	**−2.89**	**−2.08**	2.09	−.95	.	**−2.42**	**−3.57**	**−2.77**	−.07	.	−.01	**−2.50**	2.86	.07	.
PD-05	PD-S	.06	−.22	−1.19	−.08	**−2.03**	−.26	1.25	1.20	.15	.04	.	.	.	.	.
119	PD-NS	−.01	−.16	1.03	−.41	3.09	.41	1.60	−.18	−1.43	2.75	−.43	−.14	.95	.10	.89
120	PD-NS	1.03	−1.33	−1.12	.48	1.37	−.85	**−2.51**	**−3.69**	−.04	2.75	−1.07	−1.32	−.85	.62	−.58
121	PD-NS	−1.05	−.75	.18	−.86	.	−.22	−.06	−.18	.39	.34	**−1.71**	−.16	1.40	**−1.97**	−.58

*Note: PD-S = PD surgery participant; PD-NS = PD non-surgery participant; . denotes missing data

Table 5

Participant reliable change index test scores relative to **healthy control surgery** peer reference group (n=47). RCI ≤ −1.645 SD are in bold.

		3 Weeks					3 Months					1 Year				
ID	**Group**	**Stroop CW**	**Digit Symbol**	**Hopkins Delay**	**Animal Fluency**	**Finger Tapping**	**Stroop CW**	**Digit Symbol**	**Hopkins Delay**	**Animal Fluency**	**Finger Tapping**	**Stroop CW**	**Digit Symbol**	**Hopkins Delay**	**Animal Fluency**	**Finger Tapping**
024-PD	PD-S	.48	.27	−.16	.44	2.33	−.08	.09	.42	.22	3.29	**−2.37**	**−2.98**	**−4.56**	−.30	3.08
025-PD	PD-S	**−4.72**	**−2.56**	2.35	.73	−.09	.57	**−1.94**	2.13	−.35	−.09	−.36	**−1.94**	1.86	−.61	−.85
027-PD	PD-S	.	**−2.30**	−.17	−.42	.57	.	**−4.25**	−.03	−1.24	.12	.	−1.38	−.27	−.79	−.50
028-PD	PD-S	−.65	**−1.65**	1.61	−.80	.	−.75	**−3.53**	**−1.80**	−.22	.	.18	**−2.45**	2.19	.28	.
029-PD	PD-S	.48	.27	−.16	.12	**−1.86**	.25	1.61	.87	.00	.26	.	.	.	.	.
119	PD-NS	−.31	.35	.61	−.25	2.17	.16	1.44	−.07	−1.36	1.48	−.36	.10	.68	.00	1.04
120	PD-NS	.24	−.81	−1.47	.53	.71	−.66	**−1.94**	**−2.26**	−.05	1.48	−.66	−1.27	−.88	.37	−.67
121	PD-NS	−.85	−.24	−.21	−.64	.	−.25	.08	−.07	.35	−.16	−.96	.08	1.08	−1.47	−.67

*Note: PD-S = PD surgery participant; PD-NS = PD non-surgery participant; see method section for test dependent variable summaries; . denotes missing data

Table 6

Mean reliable change z-scores relative to the **healthy control <u>non-surgery</u>** peers (n=21).

	PD Non-Surgery (n = 3)		PD Surgery (n = 5)	
	M (SD)	**Min/max**	**M (SD)**	**Min/max**
2 weeks				
Stroop CW	−0.01 ±1.04	−1.05/1.03	−2.89 ± 4.17	−8.78/0.06
Digit Symbol	−0.75 ± 0.59	−1.33/−.16	−1.66 ± 1.37	−3.09/−.22
HVLT Delay	0.03 ± 1.08	−1.12/1.03	0.27 ± 2.02	−1.21/2.83
Animal Fluency	−0.26 ± 0.68	−0.86/0.48	−0.14 ± 0.65	−0.95/0.70
Finger Tapping	2.23 ± 1.21	1.37/3.09	0.36 ± 1.85	−2.03/2.47
3 months				
Stroop CW	−0.22 ± 0.63	−0.85/0.41	−0.65 ± 1.44	−2.42/1.04
Digit Symbol	−0.32 ± 2.07	−2.51/1.60	−1.85 ± 2.32	−4.25/1.25
HVLT Delay	−1.35 ± 2.03	−3.69/−0.18	0.44 ± 2.22	−2.77/3.35
Animal Fluency	−0.36 ± 0.95	−1.42/0.39	−0.19 ± .55	−1.06/0.37
Finger Tapping	1.94 ± 1.39	0.34/2.75	0.91 ± 1.61	−0.12/3.30
1 year				
Stroop CW	−1.07 ± 0.64	−1.71/−0.43	−0.75 ± 0.95	−1.82/−0.01
Digit Symbol	−0.54 ± 0.67	−1.32/−0.14	−2.23 ± 0.64	−2.97/−1.54
HVLT Delay	0.50 ± 1.19	−0.85/1.40	0.20 ± 3.36	−4.53/2.86
Animal Fluency	−0.42 ± 1.37	−1.97/0.62	−0.40 ± .36	−0.75/0.07
Finger Tapping	−0.09 ± 0.85	−0.58/0.89	−0.09 ± 1.03	−0.73/1.10

See method section for summary descriptions of the test dependent variables.

Table 7

Mean reliable change z-scores relative to the **healthy control surgery** peers (n=47).

	PD Non-Surgery (n = 3)		PD Surgery (n = 5)	
	M (SD)	**Min/max**	**M (SD)**	**Min/max**
2 weeks				
Stroop CW	−0.31 ± −.55	−0.85/0.24	−1.10 ± 2.46	−4.72/0.48
Digit Symbol	−0.23 ± 0.58	−0.81/0.35	−1.19 ± 1.38	−2.56/0.27
HVLT Delay	−0.35 ± 1.05	−1.47/0.61	0.69 ± 1.20	−0.17/2.35
Animal Fluency	−0.12 ± 0.60	−0.64/0.53	0.01 ± 0.62	−0.80/0.73
Finger Tapping	1.44 ± 1.03	0.71/2.17	0.24 ± 1.73	−1.86/2.33
3 months				
Stroop CW	−0.25 ± 0.41	−0.66/0.16	−0.00 ± 0.56	−0.75/0.57
Digit Symbol	−0.14 ± 1.70	−1.94/1.44	−1.61 ± 2.45	−4.25/1.61
HVLT Delay	−0.80 ± 1.26	−2.26/−0.07	0.32 ± 1.43	−1.80/2.13
Animal Fluency	−0.35 ± 0.90	−1.36/0.35	−0.32 ± 0.55	−1.24/0.22
Finger Tapping	0.93 ± 0.94	−0.16/1.48	0.89 ± 1.60	−0.09/3.29
1 year				
Stroop CW	−0.66 ± 0.30	−0.96/−0.36	−0.85 ± 1.34	−2.37/0.18
Digit Symbol	−0.36 ± 0.45	−1.27/0.78	−2.18 ± 0.69	−2.98/−1.38
HVLT Delay	0.29 ± 1.03	−0.88/1.08	−0.19 ± 3.11	−4.56/2.19
Animal Fluency	−0.37 ± 0.97	−1.47/0.37	−0.36 ± 0.46	−0.79/0.28
Finger Tapping	−0.10 ± 0.99	−0.67/1.04	0.58 ± 2.18	−0.85/3.08

See method section for summary of test dependent variables