A Randomized Controlled Trial of Bilateral Deep Brain Stimulation of the Subthalamic Nucleus versus Globus Pallidus for Parkinson's Disease

Presented on behalf of the CSP 468 Study Group

Frances M. Weaver, PhD

Director, Ctr for Management of Complex Chronic Care & Spinal Cord QUERI, Hines VA Hospital
Professor, Dept of Medicine & Director, Program in Health Services Research
Stritch School of Medicine, Loyola University

CSP #468: A Comparison of Best Medical Therapy and Deep Brain Stimulation of Subthalamic Nucleus and Globus Pallidus for the Treatment of Parkinson's Disease

- Primary endpoint:
  - Compare outcomes of patients undergoing bilateral GPi DBS to those of patients undergoing bilateral STN DBS at 2 years post-surgery
  - UPDRS III by raters blinded to target
- Sponsored by:
  - Department of Veterans Affairs, Cooperative Studies Program and the National Institute of Neurologic Disorders and Stroke
    - Additional funding from Medtronic Neurological, Inc.

CSP #468 Study Sites

- VA Parkinson's Disease Research Education and Clinical Care Centers (PADRECCs)
  - Philadelphia, PA
  - Richmond, VA
  - Houston, TX
  - West Los Angeles, CA
  - San Francisco, CA
  - Portland, OR/Seattle WA
- University Affiliated Sites
  - University of Pennsylvania
  - Medical College of Virginia
  - Baylor School of Medicine
  - UCLA
  - UCSF
  - Oregon Health Sciences

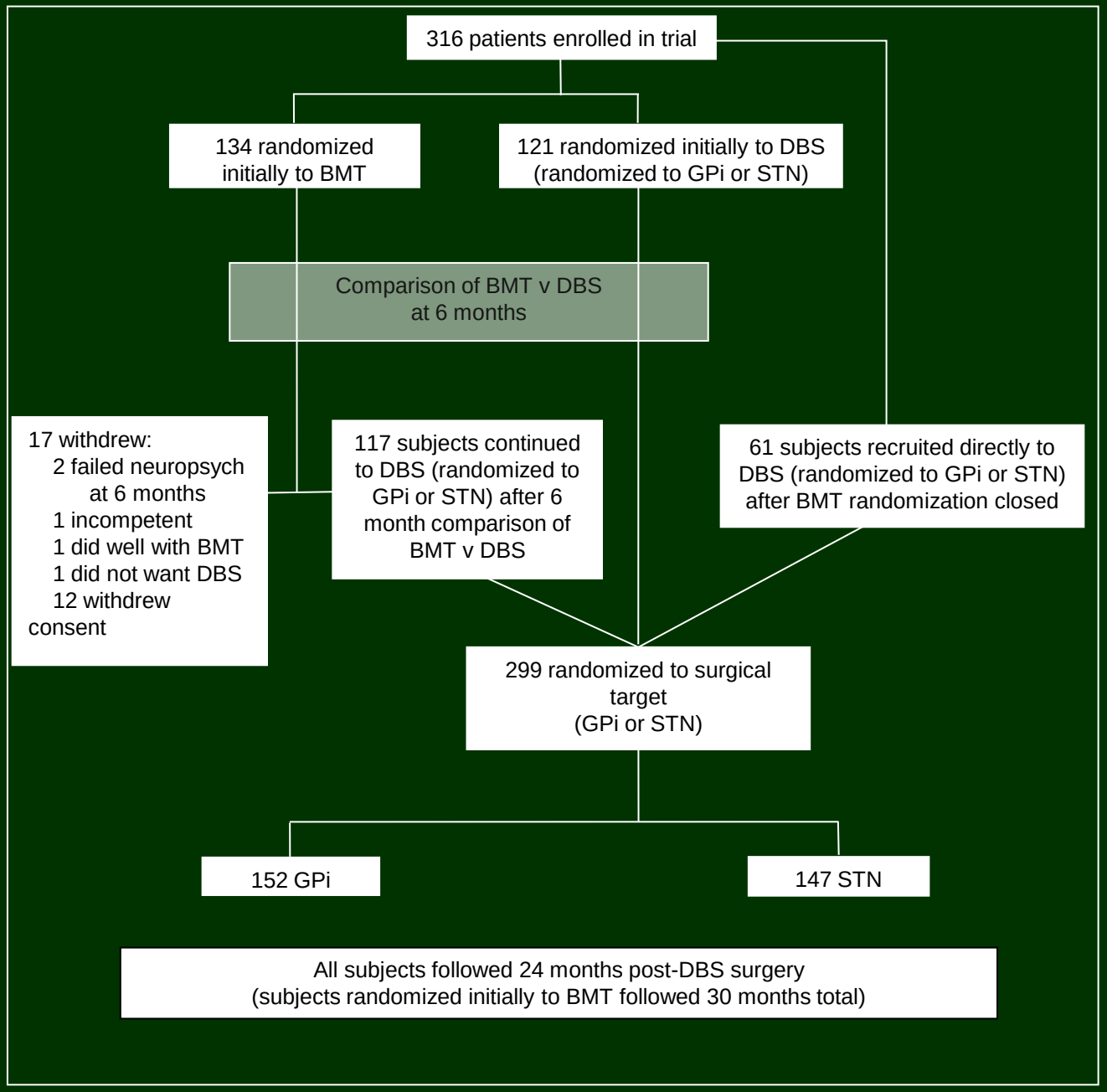
Sites selected competitively, required comprehensive movement disorders program including neuropsychology and surgeon experience with STN and GPi DBS with microelectrode recording

CSP #468 Inclusion Criteria

- Idiopathic Parkinson's disease
- Hoehn & Yahr ≥ stage 2 off medications
- L-dopa responsive with clearly defined "on" periods
- Persistent disabling symptoms despite medication therapy (e.g., motor fluctuation)
- 3 hours or more per day in "off" state or 3 hours in on state with troubling dyskinesias (motor diaries)
- Stable on medication therapy for ≥ 1 month
- Age ≥ 21
- Available for follow-up

CSP #468 Exclusion Criteria

- Parkinson's plus syndromes, secondary or atypical Parkinson's syndromes
- Previous PD surgery
- Medical contraindications to surgery
- Contraindication to MRI
- Active alcohol or drug abuse
- Mini-Mental Status examination score $\leq$ 24 or other neuropsychological dysfunction (neuropsych testing)
- Intracranial abnormalities that contraindicate surgery
- Pregnancy
- Current participation in another research study


316 patients enrolled in trial
134 randomized initially to BMT
121 randomized initially to DBS (randomized to GPi or STN)
Comparison of BMT v DBS at 6 months
17 withdrew:
2 failed neuropsych at 6 months
1 incompetent
1 did well with BMT
1 did not want DBS
12 withdrew consent
117 subjects continued to DBS (randomized to GPi or STN) after 6 month comparison of BMT v DBS
61 subjects recruited directly to DBS (randomized to GPi or STN) after BMT randomization closed
299 randomized to surgical target (GPi or STN)
152 GPi
147 STN
All subjects followed 24 months post-DBS surgery
(subjects randomized initially to BMT followed 30 months total)

Baseline Characteristics

	GPi (N=152)	STN (N=147)	P-value
Age (yrs)	61.8	61.9	0.92
Male	87.5%	78.9%	0.06
Years on PD medications	11.5	11.1	0.47
White	97.4%	94.6%	0.25
Married	71.7%	66.0%	0.63

Baseline Characteristics

	GPi (N=152)	STN (N=147)	P-value
Hoehn and Yahr scale (off medication)	3.3	3.4	0.47
Schwab and England scale (off medication)	51.2	50.7	0.85
On time without troublesome dyskinesia (hrs/d) [c]	6.5	7.0	0.15
On time with troublesome dyskinesia (hrs/d) [c]	4.4	4.0	0.28

[c] On time without or with troublesome dyskinesia was calculated as hours per day based on motor diary. “ON” is defined as “good or practically normal mobility” and “ON with troublesome dyskinesia” is defined as “troubled by involuntary twisting, turning movements different from tremor”

Baseline Characteristics – Motor Function

	GPi (N=152)	STN (N=147)	P-value
UPDRS III (motor function while not taking medication, blinded assessment; scale range 0-108)	41.8	43.0	0.46
UPDRS I (mentation, behavior, and mood; scale range 0-16)	2.5	2.9	0.07
UPDRS II (activities of daily living; scale range 0-52)	19.1	19.0	0.92
UPDRS IV (complication of therapy; scale range 0-23)	8.8	9.0	0.51

Baseline Characteristics – Quality of Life (PDQ-39)*

	GPi (N=152)	STN (N=147)	P-value
Mobility	57.0	61.6	0.06
ADL	55.0	55.7	0.77
Emotional well being	36.5	41.1	0.04
Social support	23.8	30.1	0.003

* Range 0-100

Yellow indicates statistically significant difference, GPi v STN

Baseline Characteristics – Quality of Life (PDQ-39)*

	GPi (N=152)	STN (N=147)	P-value
Stigma	38.7	42.1	0.24
Cognition	39.8	44.1	0.03
Communication	44.7	47.8	0.16
Bodily discomfort	48.1	52.8	0.07

* Range 0-100

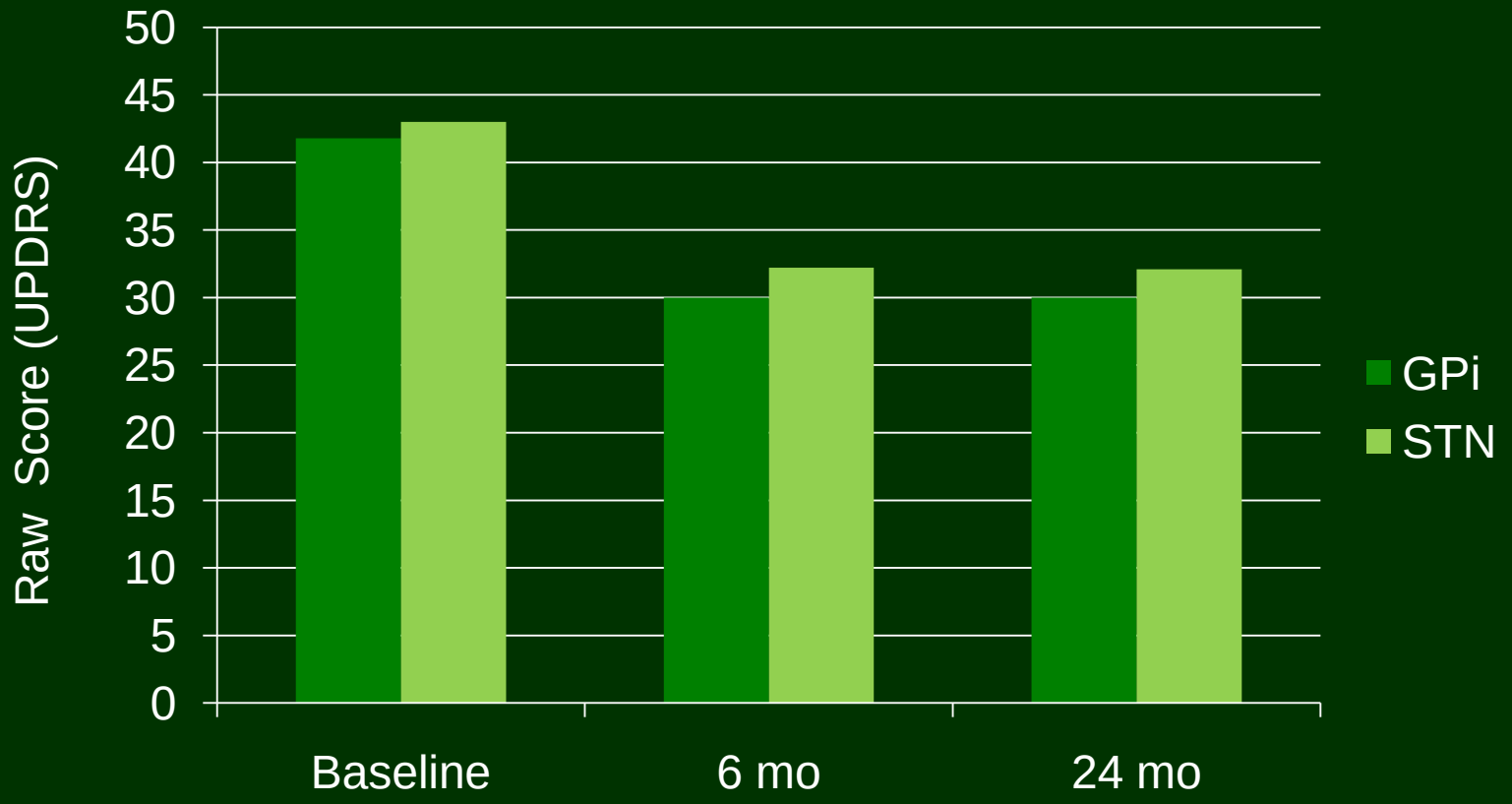
Yellow indicates statistically significant difference, GPi v STN

Baseline Characteristics – Neurocognition and Mood

	GPi (N=152)	STN (N=147)	P-value
Mattis Dementia rating scale	137.5	137.2	0.60
Category Fluency (Animal)	50.4	47.0	0.01
HVLT total (learning/memory)	40.7	38.0	0.04
10 other neuropsychology assessments (see results)	No	significant	difference
Beck depression inventory (range 0-63)	10.4	11.2	0.40

Yellow indicates statistically significant difference, GPi v STN

Primary Study Outcome: UPDRS III (Blinded) at 24 Months (on stimulation/off medication)



No significant difference GPi v STN at any timepoint
No significant difference between 6 and 24 month outcomes

UPDRS III motor scores by raters blinded to stimulation target*

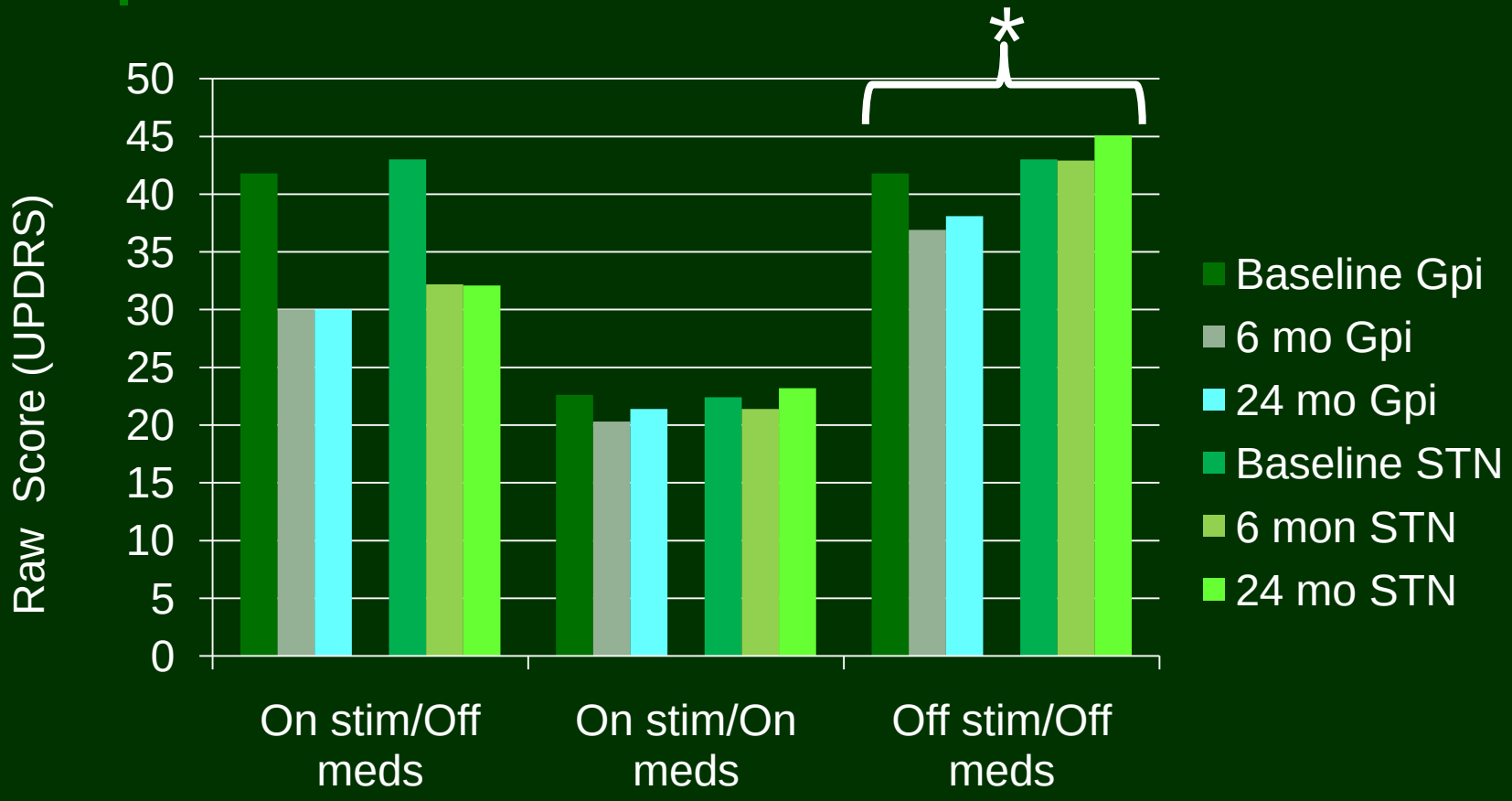
	Score		Changes from Baseline			Changes from 6-Month		
	GPi	STN	GPi	STN	P Value	GPi	STN	P Value
On Stimulation / Off Medication								
Baseline	41.8 ± 13.1	43.0 ± 15.0						
6 Month	30.0 ± 13.7	32.2 ± 16.2	-11.7 (-13.8, -9.6)	-10.6 (-12.8, -8.5)	0.48			
24 Month	30.0 ± 14.2	32.1 ± 15.6	-11.8 (-14.1, -9.5)	-10.7 (-12.9, -8.5)	0.50	-0.0 (-1.5, 1.5)	-0.0 (-1.5, 1.4)	0.97
On Stimulation / On Medication								
Baseline	22.6 ± 11.9	22.4 ± 11.9						
6 Month	20.3 ± 10.4	21.4 ± 12.5	-2.3 (-3.9, -0.6)	-1.0 (-2.4, 0.4)	0.25			
24 Month	21.4 ± 11.8	23.2 ± 12.0	-1.2 (-2.8, 0.4)	0.8 (-0.9, 2.4)	0.09	1.1 (-0.3, 2.5)	1.8 (0.5, 3.0)	0.46
Off Stimulation / Off Medication								
Baseline	41.8 ± 13.1	43.0 ± 15.0						
6 Month	36.9 ± 13.8	42.9 ± 16.0	-4.8 (-6.9, -2.7)	0.0 (-1.9, 2.0)	<0.001			
24 Month	38.1 ± 14.6	45.1 ± 14.6	-3.7 (-5.9, -1.4)	2.2 (-0.0, 4.5)	<0.001	1.2 (-0.6, 3.0)	2.2 (0.5, 3.8)	0.43

* Results are presented as Means ± SD or Means (95% Confidence Interval).

Primary Study Outcome: UPDRS III (Blinded) at 24 Months (on stimulation/off medication)

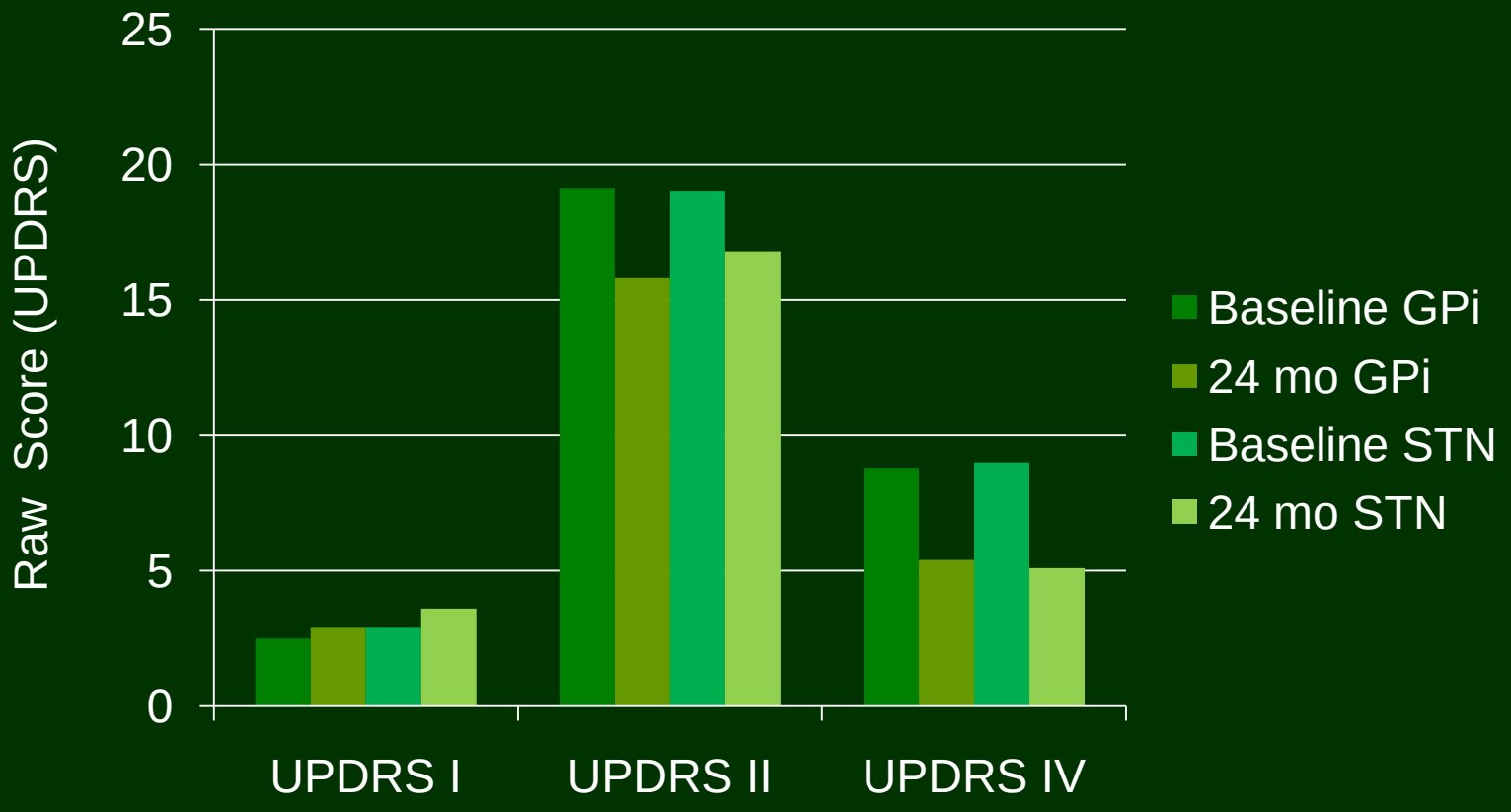
- Primary outcome analysis used intent-to-treat method
- Mixed-effects models for longitudinal analysis and other statistical approaches [analysis of complete data only, assigning zero (no change) to cases with any missing data, applying worst-case scenario (best score at baseline and worst score at 24 month)] yielded similar results
- The finding of no difference between GPi and STN is robust

UPDRS III (Blinded) at 24 Months (secondary stim/med conditions)



*GPi – STN difference at 6 mo = -4.8 and at 24 mo = -5.9; p< 0.001

UPDRS I, II, IV at 24 Months



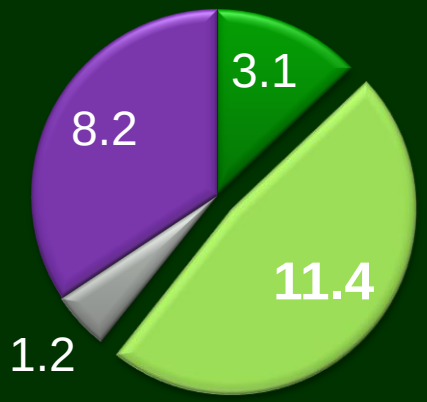
No significant difference GPi v STN on any measures

Motor Diary Data (24 Hours)

GPi Baseline

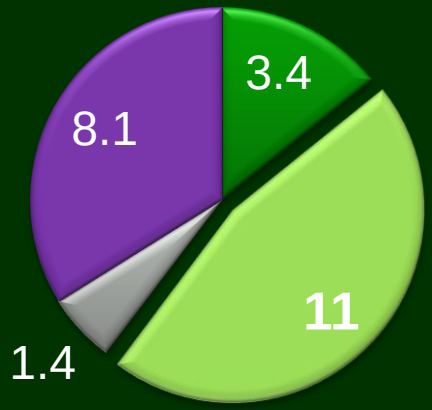
Off
On without dyskinesia
On with dyskinesia
Asleep

Gpi 24 months



STN Baseline

STN 24 months

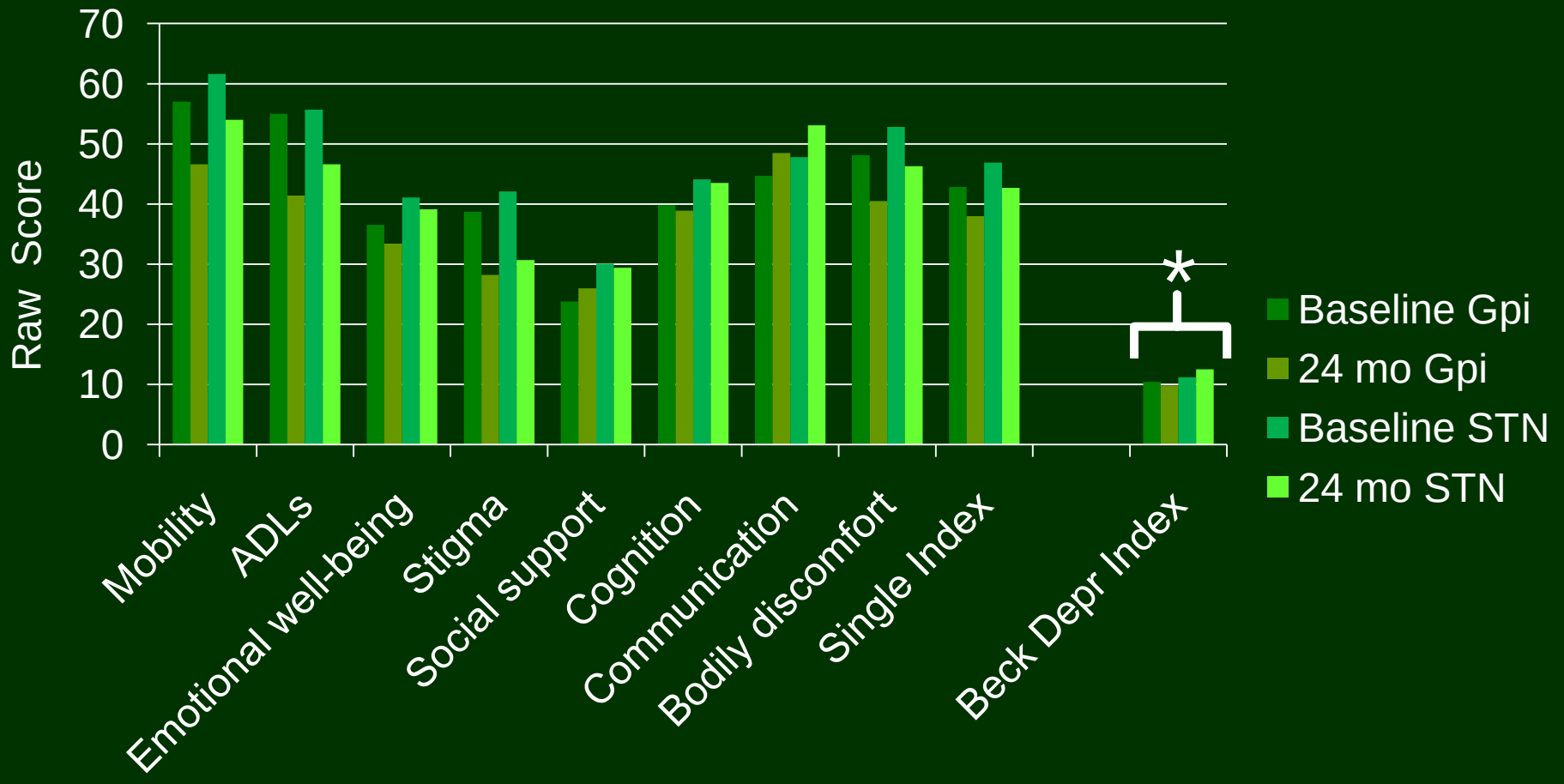


Other functional status outcomes at baseline and 24 months by treatment group

	GPi (n =152)		STN (n = 147)		GPi – STN	
Outcome	Baseline	24 Months	Baseline	24 Months	Diff (95% CIs)	P-value
UPDRS I –Mentation/ Behavior/Mood (0-16)*	2.5	2.9	2.9	3.6	-0.2 (-0.7 to 0.3)	0.39
UPDRS II – ADL (0-52)*	19.1	15.8	19.0	16.8	-1.1 (-2.6 to 0.4)	0.15
UPDRS IV – complications of therapy (0-23)*	8.8	5.4	9.0	5.1	0.5 (-0.3 to 1.3)	0.26
Hoehn and Yahr – off meds (0-5)*	3.3	3.0	3.4	3.1	-0.0 (-0.3 to 0.2)	0.77
Schwab and England – off meds (0-100)ǂ	51.2	66.0	50.7	62.9	2.6 (-2.9 to 8.2)	0.35
Stand-walk-sit – on stim/on meds Ω (seconds)	18.0	18.5	17.4	19.4	-2.0 (-4.6 to 0.6)	0.13
Stand-walk-sit – on stim/off meds Ω (seconds)	27.2	22.9	26.1	22.9	-2.3 (-5.2, 0.6)	0.12
Stand-walk-sit – off stim/off meds Ω (seconds)	27.2	22.7	26.1	26.6	-3.9 (-6.5 to -1.2)	0.005

Ω On stim/off stim conditions only apply to 24 month examinations as baseline evaluations were conducted prior to DBS surgery

PDQ-39 and BDI at 24 Months



*Gpi – STN diff = -1.9; p=0.02

Quality of life at baseline and 24 months by treatment group

	GPi (n =152)		STN (n = 147)		GPi – STN	
Outcome	Baseline	24 Months	Baseline	24 Months	Diff (95% CIs)	P-value
Quality of Life						
PDQ-39 Mobility (0-100)	57.0	46.6	61.6	54.0	-2.3 (-7.6 to 3.1)	0.40
PDQ-39 ADLs (0-100)	55.0	41.4	55.7	46.6	-4.4 (-9.3 to 0.5)	0.08
PDQ-39 Emotional well-being (0-100)*	36.5	33.4	41.1	39.1	-1.2 (-5.6 to 3.2)	0.58
PDQ-39 Stigma (0-100)	38.7	28.2	42.1	30.7	1.0 (-4.5 to 6.4)	0.73
PDQ-39 Social Support (0-100)	23.8	26.0	30.1	29.4	3.1 (-1.2 to 7.4)	0.16
PDQ-39 Cognition (0-100)	39.8	38.9	44.1	43.5	-0.4 (-4.2 to 3.5)	0.85
PDQ-39 Communication (0-100)	44.7	48.5	47.8	53.1	-1.5 (-6.3 to 3.3)	0.54
PDQ-39 Bodily Discomfort (0-100)	48.1	40.5	52.8	46.3	-1.0 (-5.6 to 3.5)	0.65
PDQ-39 Single Index (0-100)*	42.8	38.0	46.9	42.7	-.6 (-3.6 to 2.4)	0.69

Neurocognitive function baseline and 24 months by treatment group (Part 1)

	GPi (n =152)		STN (n = 147)		GPi – STN	
Outcome	Baseline	24 Months	Baseline	24 Months	Diff (95% CIs)	P-value
Mattis Dementia Total Score (0-144)	137.5	135.0	137.2	133.6	1.0 (-0.9 to 3.0)	0.29
WAIS-III Working memory index (50-150)[1]	100.8	97.0	99.3	94.1	1.1 (-0.8 to 3.0)	0.27
WAIS-III Processing speed index (54-150)[2]	91.3	88.3	90.0	84.1	2.5 (0.3 to 4.7)	0.03
Category Fluency (Animal) T-score (0-100)[3]	50.4	44.7	47.0	41.2	-0.0 (-2.8 to 2.8)	>0.99
Phonemic Fluency (F.A.S) T-score (7-100)[3]	46.6	41.8	44.9	39.0	1.1 (-1.2 to 3.4)	0.33
BVMT Total T-score (19-77)	40.2	38.6	39.7	38.3	-0.2 (-2.7 to 2.3)	0.87
BVMT Delayed Recall T-score (19-68)	44.8	41.0	43.0	41.4	-1.9 (-4.7 to 0.8)	0.17

[1] Working Memory Index (Mean = 100, SD = 15) = Arithmetic + Letter-Number + Digit Span tests.
[2] Processing Speed Index (Mean = 100, SD = 15) = Symbol Search + Digit Symbol tests.
[3] T -scores have a norm of 50 and SD = 10.

Yellow indicates statistically significant difference, GPi v STN

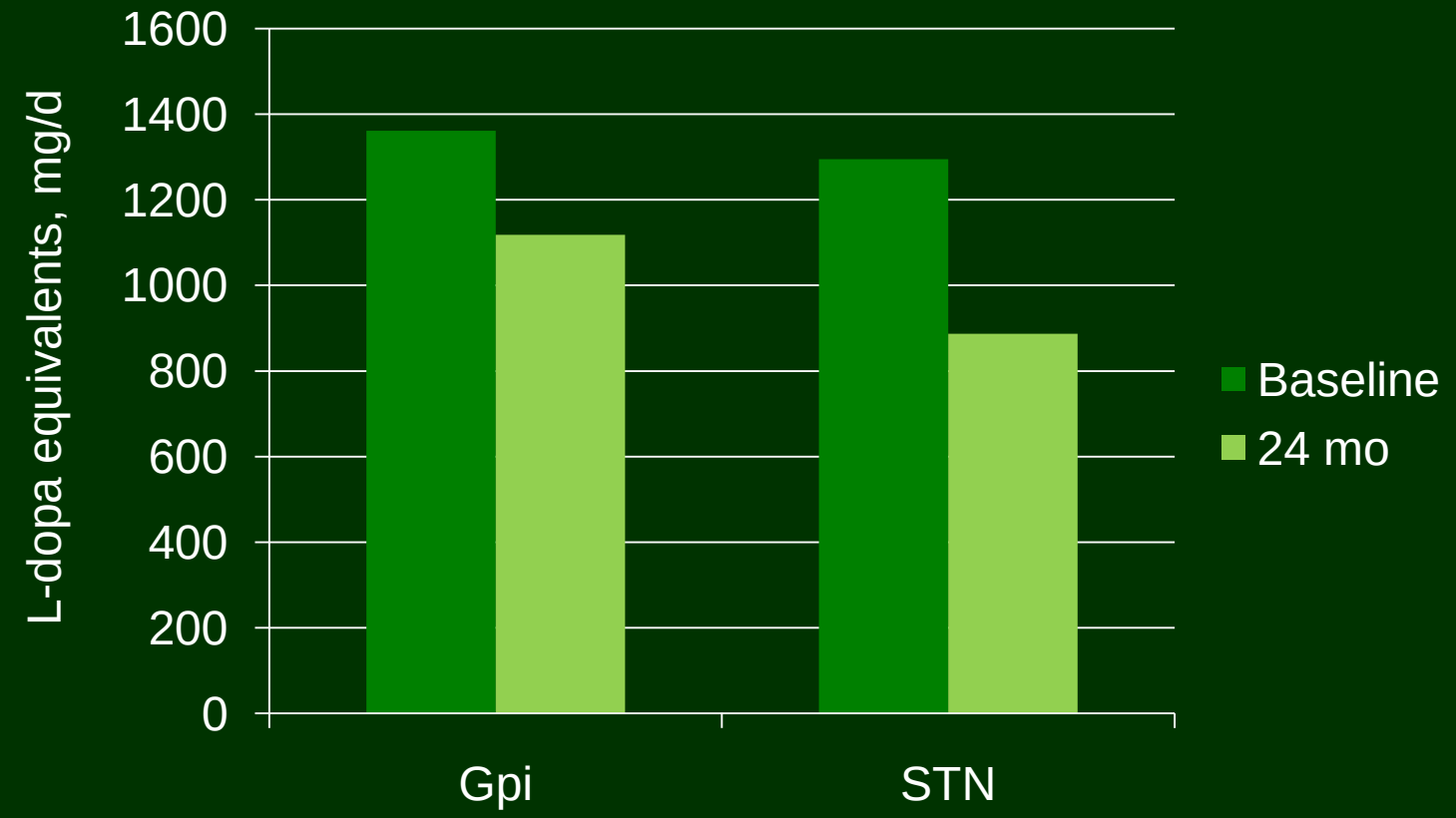
Neurocognitive function baseline and 24 months by treatment group (Part 2)

	GPi (n =152)		STN (n = 147)		GPi – STN	
Outcome	Baseline	24 Months	Baseline	24 Months	Diff (95% CIs)	P-value
Boston Naming Test (0-60)	55.9	55.7	55.6	55.5	0.2 (-0.5 to 0.8)	0.57
Finger Tapping T-score (1-100)	38.2	38.0	38.1	35.9	1.9 (-0.9 to 4.8)	0.18
Stroop Interference T-score (19-81)	51.1	51.0	51.0	50.1	0.8 (-1.0 to 2.7)	0.38
WCST Perseveration response T–score (19-81)	45.3	43.0	44.5	43.4	-1.3 (-4.3 to 1.6)	0.38
HVLT delayed recall T-score (19-65)	35,8	37.5	37.0	36.3	-0.3 (-3.1 to 2.5)	0.84
HVLT Total (learning/memory) T-score (19-75)[3]	40.7	38.5	38.0	37.3	-1.4 (-3.7 to 0.9)	0.24
Beck Depression Inventory (0-63)	10.4	9.8	11.2	12.5	-1.9 (-3.6 to -0.2)	0.02

[1] Working Memory Index (Mean = 100, SD = 15) = Arithmetic + Letter-Number + Digit Span tests.
[2] Processing Speed Index (Mean = 100, SD = 15) = Symbol Search + Digit Symbol tests.
[3] T -scores have a norm of 50 and SD = 10.

Yellow indicates statistically significant difference, GPi v STN

Medication Change



Gpi – STN diff = 165.4; p=0.02

Serious adverse events by number of patients affected over 24 months

	GPi (N=152)	STN (N=147)	P-value
Serious Adverse Events (MedDRA classification)	77	83	0.35
Implant site infection	12	11	>0.99
Falls	5	13	0.053
Pneumonia	8	4	0.38
Confusional state	2	5	0.28
Medical device complication	2	4	0.44
Lumbar spine stenosis	3	2	>0.99
Mental status changes	4	1	0.37
Osteoarthritis	3	2	>0.99
Syncope	1	4	0.21

Serious adverse events by number of patients affected over 24 months

	GPi (N=152)	STN (N=147)	P-value
Depression	4	1	0.37
Adverse Drug Reaction	2	2	>0.99
Coronary Artery Disease	1	3	0.36
Dyskinesia	1	3	0.36
Gastroesoph reflux disease	2	2	>0.99
Inguinal hernia	2	2	>0.99
Depression-suicidal	2	1	>0.99
Cerebral hemorrhage	1	2	0.62
Cerebrovascular accident	0	3	0.12
Intracranial hemorrhage	3	0	0.25

Adverse events by number of patients affected over 24 months

	GPi (N=152)	STN (N=147)	P-value
Moderate and Severe Adverse Events+ (MedDRA classification)			
Falls	58	63	0.41
Gait disturbance	49	45	0.80
Depression	40	54	0.06
Balance disorder	47	44	0.90
Speech problems	43	51	0.26
Freezing phenomena	48	35	0.16
Bradykinesia	36	32	0.78
Motor dysfunction	36	31	0.68
Dyskinesia	34	38	0.50
Dystonia	34	31	0.89
Confusional state	30	33	0.57

+The most common (affected ≥ 20% of subjects over 24 months) moderate and severe adverse events are reported.

Conclusions

- UPDRS “on stim/off meds” 2 years post-surgery does not differ significantly for GPi and STN DBS groups
  - Scores are stable from 6 months to 24 months
- Small decreases in all neurocognitive measures
  - visuomotor processing speed slightly worse for STN
- Mood slightly improved for GPi, slightly worse for STN
- Medication reduction greater for STN
- Interpret secondary outcomes cautiously
- Longer-term outcomes pending
  - 3 year follow-up (n=159)
  - 5 year follow-up (CSP 468F, B. Marks – PI)

Conclusions

- Clinicians may comfortably take into consideration factors other than motor function in selecting a target
- Consider preferences for
  - Ease of targeting
  - Ease of programming
  - Symptoms
    - E.g., dyskinesias vs medication side-effects
  - Medication reduction
    - Is it desirable for all patients?

CSP Study Group

- Site Investigators:
  - Jeff Bronstein, M.D., Ph.D.; John Duda, M.D.; Penelope Hogarth, M.D.; Kathryn Holloway, M.D.; Stacy Horn, D.O.; Eugene C. Lai, M.D., Ph.D.; William J. Marks, Jr., M.D.; Ali Samii, M.D.
- Neurosurgeons:
  - Gordon Baltuch, M.D., Ph.D.; Kim Burchiel, M.D.; Antonio De Salles, M.D., Ph.D.; Jorge Eller, M.D.; Kathryn Holloway, M.D.; Paul Larson, M.D.; Richard Simpson, M.D.; Philip Starr, M.D., Ph.D.
- Many others

CSP 468 Study Leadership

- Kenneth Follett, MD, PhD – chairperson
  - Iowa VAMC/University of Nebraska Medical Center
- Frances Weaver, PhD – co-chair
  - Hines VA Hospital/Loyola University
- Matthew Stern, MD – co-chair
  - University of Pennsylvania/Philadelphia VAMC
- Kwan Hur, PhD & Ping Luo, PhD – biostatisticians
  - Hines VA Hospital /University of Illinois, Chicago
- Johannes Rothlind, PhD – neuropsych consult
  - San Francisco VAMC/UCSF