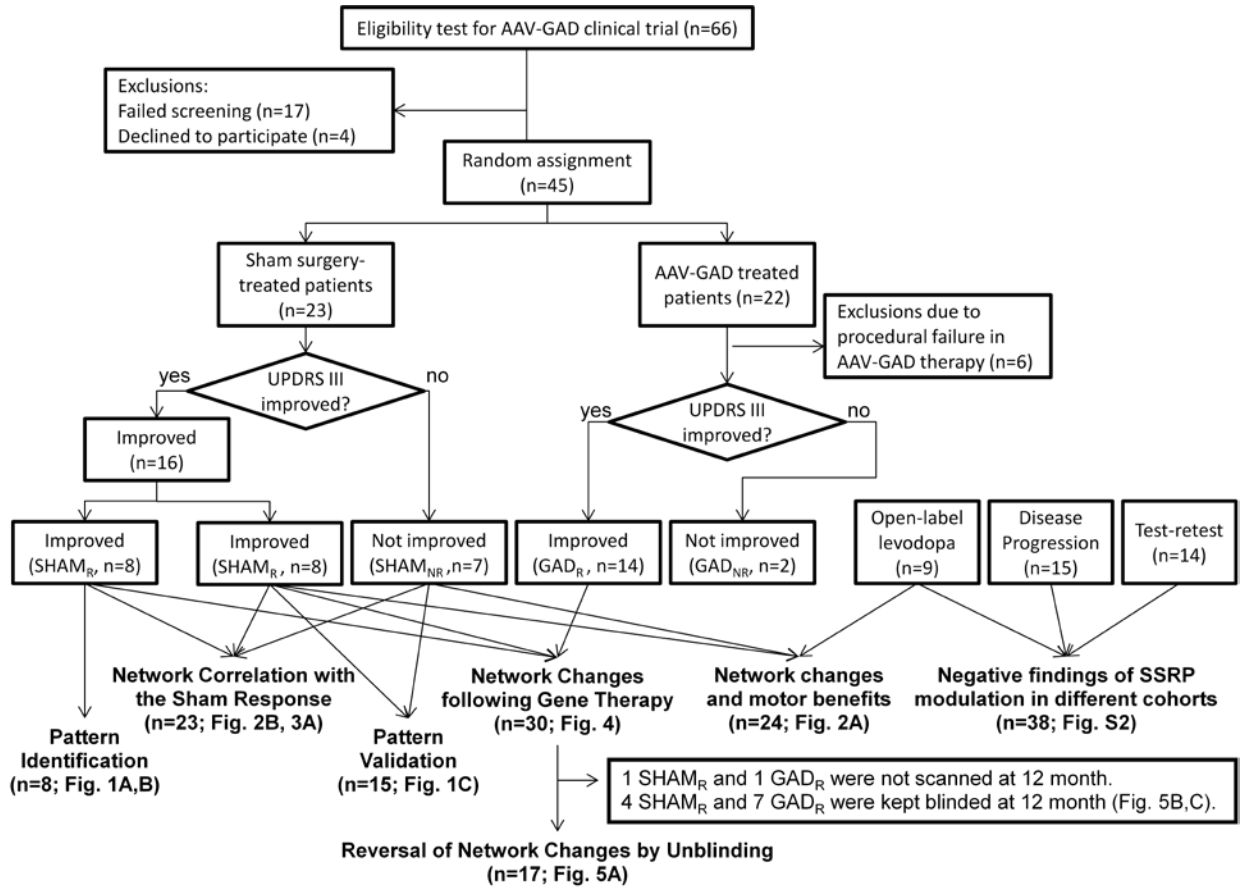
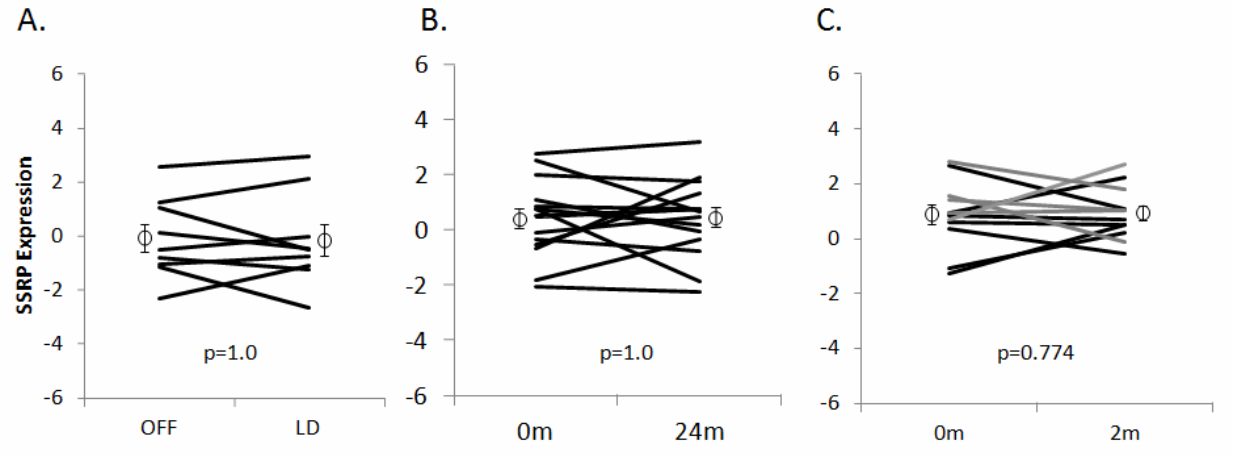
Supplemental Material



Supplemental Figure 1. Study design.
Sixty six subjects with advanced Parkinson's disease (PD) were screened, of which 45 were enrolled in a double-blind Phase II study of adeno-associated viral vector-glutamic acid decarboxylase (AAV-GAD) gene therapy for medication refractory motor symptoms (1). Of these, 23 subjects were randomized to sham surgery group (bilateral burr hole placement) and 22 to subthalamic gene therapy. Six of the gene therapy subjects were excluded because of failed viral vector delivery (see (1) for details). Sixteen of the sham surgery (SHAM) subjects were classified as placebo "responders" based upon the presence of a reduction (improvement) in motor Unified Parkinson's Disease Rating Scale (UPDRS) ratings $\leq$ -2 points under the blind between baseline and 6 months. Fourteen of the gene therapy (GAD) subjects were also classified as "responders" under the same clinical criteria. ^{18}F-fluorodeoxyglucose (FDG) PET scans acquired under the blind were selected in eight of the SHAM responders ($SHAM_R$) and used with supervised principal component analysis (PCA) to identify a significant sham surgery-related metabolic covariance pattern (SSRP). For validation, SSRP expression was computed in the baseline and 6 month scans acquired in the remaining eight $SHAM_R$ subjects, and in the seven "sham non-responders" ($SHAM_{NR}$), who exhibited either no change or deterioration in blinded UPDRS motor ratings. SSRP expression values were computed in the SHAM subjects and correlated with clinical outcomes under the blind. Blinded SSRP values from these subjects were additionally compared with corresponding measures from nine other PD subjects who were

scanned with FDG PET before and during open-label levodopa treatment titrated to produce an improvement in motor UPDRS ratings observed in the $SHAM_R$ testing group. Additional open label SSRP comparisons were performed in serial FDG PET data from PD subjects scanned two months apart in a test-retest paradigm (2) and from a longitudinal two-year natural history cohort (3). Lastly, we assessed the effects of unblinding on SSRP expression in the 12-month scans of the $SHAM_R$ and GAD_R subjects.



Supplemental Figure 2. Changes in SSRP expression: Additional testing sets
(**A**) No consistent trend in treatment-mediated SSRP responses was seen in nine PD subjects (4) receiving open-label levodopa (LD) infusions (4/9 violations, p=1.0; binomial test).
(**B**) No change in SSRP expression was observed in 15 PD subjects (5) scanned at baseline and after 24 months of unblinded follow-up (8/15 violations, p=1.0; binomial test).
(**C**) No change in SSRP expression was observed in 12 PD subjects (6) scanned at baseline and after 2 months of daily oral placebo as part of a randomized, blinded clinical trial for the treatment of cognitive symptoms of the disorder (7/12 violations, p=0.774; binomial test).
[Symbols indicate the mean SSRP expression at each time point±1SE.]

Supplemental Table 1. Physical characteristics of the PET instruments used in the multicenter STN AAV-GAD Phase II study

Site	Scanner	Z (mm)	Slice	Reconstruction Method	Transverse Resolution (mm)	Axial Resolution (mm)	N of patients	
							GAD	SHAM
A	GE Advance (7)	4.25	35	3D REPRJ	3.8/5.6*	4.0/5.3*	10	10
B	SIEMENS HR+ (8)	2.50	61	3D Iterative	4.4/6.2*	4.1/5.9*	3	4
C	SIEMENS HR (9)	3.13	47	3D FBP	3.6/5.5*	4.0/5.4*	3	3
D	GE Advance Nxi (10)	4.25	35	3D REPRJ	4.8/5.6	6.1/6.7	3	4
E	GE Discovery LS (10)	4.25	35	3D FORE Iterative	4.8/5.6	6.1/6.7	2	2

Resolution represents the full width at half maximum (FWHM) at the center and 10 cm from the center of the field of view (FOV).

*Data estimated from the published values at 0 and 20 cm from the center of FOV.

Supplemental Table 2. Clinical and neuropsychological measures in the sham surgery cohort

			UPDRS (motor)		BDI		HVLT		Stroop Interference		SDMT (written)		SDMT (oral)	
	sex	age	0m	6m	0m	6m	0m	6m	0m	6m	0m	6m	0m	6m
$SHAM_R$ (derivation)	M	54	43	23	14	12	21		4.3		34	44	44	45
	M	69	45	36	7	6	17	25	1.3	0.5	42	50		49
	F	52	25	17	13	9	25	32	6.0	4.3	54	51	64	67
	M	63	37	29	1	3	26	25	-2.2	-9.9	44	40	45	42
	M	74	36	29	17	13	19	15	6.2	12.3	12	14	17	12
	F	61	29	23	16	9	14	14	5.3	-4.2	20	20	31	28
	M	65	34	28	16	18	22	21	4.1	9.0	34	36	42	41
	M	58	56	54	8	6	19	21	2.8	0.6	43	48	59	50
$SHAM_R$ (testing)	F	60	48	30	5	3	17	33	5.3	14.0	37	40	49	53
	M	47	31	22	15	10	19	24	4.1	5.7	47	51	52	60
	M	71	33	25	10	10	26	22	5.0	-1.0		60	59	
	F	62	31	24	3	14	28	29	5.6	11.6	42	50	33	49
	M	54	39	33	5	5	28	24	2.2	-2.5	57	56	56	58
	M	56	33	29	5	4	22	28	3.5	-10.0	50	51	49	46
	M	62	49	45	13	15	27	22	4.8	-1.7	39	41	51	38
	M	56	47	43	17	29	31	28	6.0	5.1	45	40	48	51
$SHAM_{NR}$	M	58	37	37	11	7	24	17	1.3	5.0	39	31	52	47
	F	69	55	55	13	20	27	25	5.0	2.1	29	27	37	34
	M	59	42	43	7	10	20	21	11.4	5.6	35	43	50	50
	M	75	48	52	16	26	11	14	0.3	2.1	28	30	40	35
	F	64	30	34	12	13	28	20	-6.1	-5.1	33	44	42	52
	M	47	43	47	4	1	33	30	-6.9	1.4	45	40	49	43
	M	52	35	45	5	8	22	23	14.2	9.2	50	53	57	61
mean		60.3	39.4	34.9	10.1	10.9	22.9	23.3	3.63	2.45	39.0	41.7	46.6	46.0
SE		1.63	1.77	2.32	1.06	1.48	1.14	1.15	0.96	1.41	2.28	2.38	2.28	2.56

Sham responders ($SHAM_R$); Sham non-responders ($SHAM_{NR}$); Unified Parkinson's Disease Rating Scale (UPDRS); Beck Depression Inventory (BDI); Hopkins Verbal Learning Test (HVLT); Symbol Digit Modality Test (SDMT)

Supplemental Table 3. Demographic information

(**A**) Trial participants

	Gene Therapy		**Sham Surgery**		
	Responders	Non-responders	Responders (derivation)	Responders (testing)	Non-responders
Gender (M:F)	12:2	0:2	6:2	6:2	5:2
Age	60.8 ± 1.85	71, 66	62.0 ± 2.62	58.5 ± 2.49	60.6 ± 3.64
Disease Duration	10.1 ± 1.05	19, 10	13.9 ± 2.29	9.6 ± 1.07	11.7 ± 1.41
UPDRS motor (baseline)	34.8 ± 1.83	30, 39	38.1 ± 3.46	38.9 ± 2.82	41.4 ± 3.17
ΔUPDRS motor (6 month)	-10.0 ± 1.28 (-28.7%)	+1 (+3.3%), +9 (+23.1%)	-8.3 ± 1.97 (-21.8%)	-7.5 ± 1.76 (-19.3%)	3.3 ± 1.32 (+8.0%)

(**B**) Validation cohorts

	Test-retest	**Disease Progression**		**Levodopa (open-label)**
		T1	T2	
Gender (M:F)	7:7	12:3		7:2
Age	65.0 ± 2.30	54.7 ± 2.98		58.8 ± 2.78
Disease Duration	4.8 ± 1.36	<2		7.1 ± 1.67
UPDRS motor (baseline)	24.2 ± 3.39	9.0 ± 1.08	16.5 ± 2.66	24.9 ± 2.79
ΔUPDRS motor (ON-OFF)				-8.2 ± 1.16 (-32.9%)

Supplemental References

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