Supplementary material

Supplementary Table 1: Univariate logistic regression analysis for baseline characteristics Responder vs. not responder (n=158)

Variable	Responder (n=95)	Non-responder (n=63)	P value	Odds Ratio	95% CI	
					Lower	Upper
Age, y; median (Range)	25(6-71)	27 (6-65)	0.223	0.987	0.967	1.008
Epilepsy duration, y; median (Range)	14 (1-53)	16 (2-50)	0.427	0.990	0.966	1.015
Disabling seizure frequency at baseline, sz/mo; median (IQR)	16 (6-60)	6.5 (3-30)	0.182	1.002	0.999	1.005
Number of ASD at baseline	3 (1-6)	3 (1-7)	0.996	1.001	0.750	1.336
ANT-DBS; n(%)	21 (55)	17 (45)	0.483	1.302	0.623	2.723
CM-DBS; n(%)	11 (58)	8 (42)	0.832	0.900	0.341	2.380
RNS; n(%)	17 (57)	13 (43)	0.667	0.838	0.375	1.874
CSS; n(%)	**25 (81)**	**6 (19)**	**0.012**	**3.393**	**1.303**	**8.836**
VNS; n(%)	21 (53)	19 (47)	0.256	0.657	0.319	1.356
Frontal onset; n(%)	12 (80)	3 (20)	0.222	2.571	0.564	11.724
Temporal onset; n(%)	27 (63)	16 (37)	0.878	1.085	0.383	3.072
Paracentral onset; n(%)	12 (63)	7 (37)	0.774	1.157	0.429	3.119
Posterior onset; n(%)	2 (33)	4 (67)	0.193	0.317	0.056	1.786
Multifocal onset; n(%)	19 (51)	18 (49)	0.215	0.625	0.297	1.313
Generalized onset; n(%)	9 (60)	6 (40)	0.992	0.994	0.336	2.945
Mixed onset; n(%)	14 (61)	9 (39)	0.937	1.037	0.419	2.565
Lesional MRI; n(%)	56 (58)	41 (42)	0.439	0.770	0.398	1.490
Prior epilepsy surgery; n(%)	16 (47)	18 (53)	0.082	0.506	0.235	1.090
Prior invasive EEG; n(%)	50 (62)	31 (38)	0.673	1.147	0.606	2.169

ANT-DBS, anterior thalamic nuclei deep brain stimulation; ASDs, anti-seizure drugs; CM-DBS, centromedian thalamic nuclei deep brain stimulation; CSS, chronic subthreshold stimulation; IQR, interquartile range; RNS, responsive neurostimulation; sz/mo, seizures per month; sz/y, seizures per year; VNS, vagus nerve stimulation; y, years.

Supplementary Table 2: Multivariate logistic regression analysis **Responder vs. not responder; AUC 0.67 (0.5876 to 0.7566)**				
Variable	**P value**	**Odds Ratio**	**95% CI**	
			Lower	**Upper**
Neuromodulation strategy (VNS as reference)	0.176			
• ANT-DBS	0.318	1.696	0.602	4.781
• CM-DBS	0.778	1.197	0.343	4.184
• RNS	0.891	0.920	0.278	3.048
• CSS	0.025	6.029	1.249	29.093
Prior epilepsy surgery	0.146	0.527	0.222	1.250
Disabling seizure frequency at baseline	0.292	1.002	0.999	1.005
Seizure onset (Mixed onset as reference)	0.296			
• Frontal onset	0.513	1.801	0.310	10.474
• Temporal onset	0.758	1.230	0.330	4.584
• Paracentral onset	0.183	0.287	0.046	1.799
• Posterior onset	0.140	0.202	0.024	1.690
• Multifocal onset	0.278	0.502	0.144	1.744
• Generalized onset	0.833	0.861	0.213	3.474
ANT-DBS, anterior thalamic nuclei deep brain stimulation; CM-DBS, centromedian thalamic nuclei deep brain stimulation; CSS, chronic subthreshold stimulation; RNS, responsive neurostimulation; VNS, vagus nerve stimulation				

The predictors for the multivariate model were chosen if their P-value was less than 0.25 in the univariate analysis. Since Neuromodulation type and Seizure onset were families of mutually exclusive variables, dummy coding using VNS and Mixed onset as reference, respectively was used.

Adverse effects and deaths

A total of 16 patients required surgery due to AEs. Regarding ANT-DBS, one person requested IPG explant due to local pain, one patient had a lead break requiring replacement and one patient had a pocket infection that ascended through the leads causing intracranial infection requiring whole system explant. For CM-DBS, two patients requested IPG explantation due to lack of perceived benefit. One patient had erosion of the leads in the neck with local infection requiring whole system removal, and one patient had an initially malpositioned IPG that required revision surgery to allow device recharging. For RNS, one patient developed a local infection without intracranial spread requiring whole system explant. One patient had a local infection in the soft tissue and skull surrounding the IPG that failed washout surgery and antibiotics. There was intracranial spread requiring whole system explant. That patient went on to have another RNS implanted and has tolerated it without other side effects. Two RNS patients required early battery replacement (<1.5 years since implant) for premature battery depletion of unclear reasons. Two CSS patients requested whole system removal explanation due to lack of perceived benefit. Two VNS patients were explanted at their parents' request due to lack of perceived benefit. One VNS patient had two IPG-related infections, the first one resolved with antibiotics alone. She then went on to have a VNS replacement and had another IPG infection requiring washout surgery. The overall infection rate for the whole cohort was 3% (5 patients total).

Six patients had immediate postprocedural complications. One ANT-DBS patient had transient focal seizures due to edema surrounding the thalamic lead that resolved with a short course of steroids. Another ANT-DBS patient had transient worsening of chronic left hemiparesis that

improved with physical therapy; post op CT scan showed only expected post-operative changes. Two CM-DBS patients had motor symptoms without associated changes in postoperative CT scan that resolved with physical therapy. One had right sided hemiparesis and one had difficulty with ambulation. One CSS patient had transient right hemiparesis without associated changes in postoperative CT scan that resolved with physical therapy. Another CSS patient had an asymptomatic right subdural hematoma that did not require drainage. No lasting deficits were noted for either of these six patients.

A total of 4 deaths occurred during the follow-up period. One ANT-DBS patient died due to SUDEP; this was diagnosed by autopsy fulfilling Definite SUDEP criteria. One RNS patient died from status epilepticus; RNS recorded continuous seizure activity at the time of death. One RNS patient committed suicide. The patient had a history of major depressive disorder that seemed well-controlled according to a PHQ-2 score five months prior (Score=1). Between that assessment and death there was no mention of active depressive symptoms in the medical record. One VNS patient died without any details available as to the circumstances. None of the deaths were thought secondary to neurostimulation.

Supplementary Table 3 – Adverse Effects						
	Total n=159	ANT n=38	CM n=19	RNS n=30	CSS n=32	VNS N=40
Patients with stimulation related AEs %, (n)	**32 (51)**	**21 (8)**	**10 (2)**	**6 (2)**	**28 (9)**	**75 (30)**
All stimulation related AEs	76	9	3	2	12	50
Headache	4 (6)	8 (3)	5 (1)		3 (1)	2 (1)
Paresthesia/dysesthesia head/face	4 (7)	3 (1)	5 (1)		9 (3)	5 (2)
Paresthesia/dysesthesia body	5 (8)	3 (1)	5 (1)		6 (2)	10 (4)
Photopsia	<1 (1)			3 (1)		2 (1)
Head and neck involuntary muscle contractions	1 (2)			3 (1)	3 (1)	
Body involuntary muscle contractions	2 (3)				9 (3)	
Limb weakness/clumsiness	<1 (1)				3 (1)	
Device making sounds while turned on	<1 (1)				3 (1)	
New onset depression/anxiety	<1 (1)	3 (1)				
Word finding difficulties	2 (3)	8 (3)				
Dysphonia/hoarseness/throat discomfort	14 (23)					57 (23)
Dysphagia	<1 (1)					2 (1)
Hiccups	1 (2)					5 (2)
Cough	2 (3)					7 (3)
Exertional dyspnea	7 (9)					22 (9)
Sleep-disordered breathing induction or exacerbation	2 (3)					7 (3)
Patients referring device related AEs	**38 (24)**	**6 (16)**	**4 (21)**	**5 (17)**	**10 (31)**	**13 (33)**
All device related AEs	49	9	5	5	14	16
Other device related AEs	1 (2)		5 (1)			2 (1)
IPG discomfort	9 (14)	11 (4)		3 (1)	16 (5)	10 (4)
Lead discomfort	10 (16)	8 (3)	5 (1)		19 (6)	15 (6)
Lead break/dysfunction	1 (2)	3 (1)				2 (1)
Local infection (soft tissue/bone)	3 (4)		5 (1)	3 (1)		5 (2)
CNS infection	1 (2)	3 (1)		3 (1)		
Early battery depletion	1 (2)			7 (2)		
Overall dissatisfaction with device	4 (7)		11 (2)		9 (3)	5 (2)
Patients with implant AEs	**6 (4)**	**6 (2)**	**11 (2)**	**0 (0)**	**6 (2)**	**0 (0)**
Other implantation related AEs	<1 (1)	3 (1)				
Asymptomatic intracranial hemorrhage	<1 (1)				3 (1)	
Motor deficit with normal postoperative scan	3 (4)	3 (1)	6 (2)		3 (1)	
Empty cells indicate that no patients reported such adverse effect. AEs, adverse effects; ANT-DBS, anterior thalamic nucleus deep brain stimulation; CM-DBS, centromedian thalamic nucleus deep brain stimulation; CNS, central nervous system; IPG, implantable pulse generator; CSS, chronic subthreshold stimulation; RNS, responsive neurostimulation; VNS, vagus nerve stimulation.						

Charge per hour per lead calculation

Charge per hour per lead was calculated to compare the amount of charge delivered per unit time across the different neuromodulation strategies and is reported as millicoulombs per hour (mC/h).

For voltage-based devices we assumed a uniform resistance of 1000 Ω and converted voltage to current per lead in mA. For current-based devices, we used the current per lead as indicated by the device.

$$Current(mA) \times Pulse\ Width(s) \times Frequency(Hz) \times 3600\ s$$

When the device had an active duty cycle, the time was adjusted as follows:

$$Current(mA) \times Pulse\ Width(s) \times Frequency(Hz) \times 3600\ s\ \times \left(\frac{On\ time}{(On\ time(s) + Off\ time\ (s)}\right)$$

In case of responsive neurostimulation (RNS) that stimulates on an as-needed basis, we corrected for burst duration and therapies delivered per day. Since RNS has 2 programmable bursts, when only one lead was used per burst the following formula was used.

$$\frac{Current(mA) \times Pulse\ Width(s) \times Frequency(Hz) \times Burst\ Duration(s) \times 1.27 \times Terapies\ Delivered\ per\ Day}{24}$$

When the same lead was used for both burst 1 and burst 2, the charge was multiplied by 2:

$$\frac{\left(Current(mA) \times Pulse\ Width(s) \times Frequency(Hz) \times Burst\ Duration(s)\right) \times 2 \times 1.27 \times Terapies\ Delivered\ per\ Day}{24}$$

The 1.27 factor in the above formulae represents the average number of burst sets (Burst 1 + Burst 2) delivered per therapy. This information derives from calculations provided by Melinda Marthaler Neuropace field engineer.