

## Supplementary material 1

### Percent whole

Percent whole provides an estimate of patient proximity to attainment of holistic treatment response (e.g., response of at least 1 MCID for all impaired domains equals 100% whole; response of at least 1 MCID for three out of four impaired domains equals 75% whole).

Percent whole was significantly greater at 12-months (mean difference [MD] 15, 95% confidence interval [95% CI]: 2.5-27.5,  $p=0.019$ ) and 24-months (MD 13.7, 95% CI: 1.5-25.8,  $p=0.028$ ) follow-up.

<b>Percent whole, mean (SD)</b>	76.6 (32.2)	66.5 (36.4)	75.4 (33.8)	60.4 (39.1)	71.6 (34.2)	57.9 (36.9)
Mean difference and 95% CI	10.1 (-1.7, 21.8), $P=0.092$		15.0 (2.5, 27.5), $P=0.019$		13.7 (1.5, 25.8), $P=0.028$	

CI=confidence interval; SD=standard deviation

## SUPPLEMENTARY MATERIAL 2

**Table S1. Proportion of responders and cumulative MCIDs at 3-, 12- and 24-months from those patients with impairment in all domains at baseline**

	3-month		12-month		24-month	
	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS
<b>Pain intensity responders (VAS Overall <math>\geq 30\%</math>)</b>	41/44 (93.2%)	25/36 (69.4%)	41/44 (93.2%)	25/36 (69.4%)	38/44 (86.4%)	22/36 (61.1%)
Risk difference (%) and 95% CI, P-value	23.7 (6.9, 40.5), P=0.006		23.7 (6.9, 40.5), P=0.006		25.3 (6.4, 44.1), P=0.009	
Mean (SD) number of MCIDs	2.5 (0.9)	1.9 (1.2)	2.6 (0.8)	1.8 (1.2)	2.4 (1.0)	1.7 (1.2)
Mean difference and 95%CI, P-value	0.6 (0.2, 1.1), P=0.006		0.7 (0.3, 1.2), P=0.003		0.7 (0.2, 1.1), P=0.009	
<b>Physical function responders (ODI Score <math>\geq 10</math>)</b>	36/44 (81.8%)	22/36 (61.1%)	32/44 (72.7%)	21/36 (58.3%)	34/44 (77.3%)	22/36 (61.1%)
Risk difference (%) and 95% CI, P-value	20.7 (1.1, 40.3), P=0.047		14.4 (-6.4, 35.2), P=0.236		16.2 (-4.0, 36.3), P=0.145	
Mean (SD) number of MCIDs	2.7 (1.9)	1.8 (1.8)	2.7 (1.8)	1.6 (1.7)	2.3 (1.6)	1.5 (1.5)
Mean difference and 95%CI, P-value	1.0 (0.2, 1.8), P=0.021		1.1 (0.3, 1.9), P=0.007		0.8 (0.1, 1.5), P=0.022	
<b>QoL responders (EQ-5D-5L Index Score <math>\geq 0.074</math>)</b>	36/44 (81.8%)	22/36 (61.1%)	35/44 (79.5%)	20/36 (55.6%)	34/44 (77.3%)	21/36 (58.3%)
Risk difference (%) and 95% CI, P-value	20.7 (1.1, 40.3), P=0.047		24.0 (3.9, 44.1), P=0.029		18.9 (-1.4, 39.3), P=0.091	
Mean (SD) number of MCIDs	3.5 (2.7)	2.4 (2.4)	3.2 (3.0)	2.0 (2.3)	3.2 (2.4)	1.9 (2.0)
Mean difference and 95%CI, P-value	1.1 (-0.1, 2.2), P=0.065		1.2 (0.0, 2.4), P=0.048		1.3 (0.3, 2.3), P=0.011	
<b>Sleep responders (PSQI <math>\geq 3</math>)</b>	30/44 (68.2%)	16/36 (44.4%)	33/44 (75.0%)	15/36 (41.7%)	27/44 (61.4%)	13/36 (36.1%)
Risk difference (%) and 95% CI, P-value	23.7 (2.5, 45.0), P=0.042		33.3 (12.8, 53.9), P=0.003		25.3 (4.0, 46.5), P=0.042	
Mean (SD) number of MCIDs	1.8 (1.7)	1.1 (1.6)	2.0 (1.5)	1.2 (1.8)	1.6 (1.6)	0.9 (1.6)
Mean difference and 95%CI, P-value	0.7 (-0.1, 1.4), P=0.079		0.8 (0.1, 1.6), P=0.025		0.7 (-0.1, 1.4), P=0.069	
<b>Emotional function responders (POMS TMD Score <math>\geq 10</math>)</b>	31/44 (70.5%)	19/36 (52.8%)	33/44 (75.0%)	14/36 (38.9%)	33/44 (75.0%)	16/36 (44.4%)
Risk difference (%) and 95% CI, P-value	17.7 (-3.5, 38.8), P=0.113		36.1 (15.7, 56.5), P=0.001		30.6 (9.9, 51.2), P=0.006	
Mean (SD) number of MCIDs	2.3 (2.2)	1.2 (1.6)	2.5 (2.1)	0.8 (1.7)	2.3 (2.0)	0.9 (1.7)
Mean difference and 95%CI, P-value	1.1 (0.2, 2.0), P=0.011		1.7 (0.8, 2.5), P<0.001		1.4 (0.5, 2.2), P=0.002	

CI=confidence interval; MCID=minimal clinical important difference; ODI=Oswestry Disability Index; POMS=Profile of Mood States; PSQI=Pittsburgh Sleep Quality Index; QoL=quality of life; SCS=spinal cord stimulation; SD=standard deviation; TMD=total mood disorder; VAS=visual analogue scale

**Table S2. Multimodal and holistic treatment response in patients with impairment in all domains at baseline**

	3-month		12-month		24-month	
	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS
<b>Multimodal treatment responders (MCID in at least 2 impaired domains out of VAS<math>\geq</math>30%, ODI<math>\geq</math>10, EQ-5D<math>\geq</math>0.074, PSQI<math>\geq</math>3, POMS<math>\geq</math>10)</b>						
Responders in $\geq$ 1 impaired domain	43/44 (97.7%)	29/36 (80.6%)	43/44 (97.7%)	28/36 (77.8%)	43/44 (97.7%)	28/36 (77.8%)
Responders in $\geq$ 2 impaired domains	38/44 (86.4%)	25/36 (69.4%)	37/44 (84.1%)	22/36 (61.1%)	37/44 (84.1%)	23/36 (63.9%)
Responders in $\geq$ 3 impaired domains	37/44 (84.1%)	23/36 (63.9%)	34/44 (77.3%)	20/36 (55.6%)	34/44 (77.3%)	21/36 (58.3%)
Responders in $\geq$ 4 impaired domains	31/44 (70.5%)	18/36 (50.0%)	32/44 (72.7%)	15/36 (41.7%)	29/44 (65.9%)	16/36 (44.4%)
Responders in 5 impaired domains	25/44 (56.8%)	9/36 (25.0%)	28/44 (63.6%)	10/36 (27.8%)	23/44 (52.3%)	6/36 (16.7%)
Cumulative responder score, mean (SD)	12.9 (7.7)	8.4 (7.3)	13.1 (7.6)	7.5 (7.6)	11.7 (6.6)	6.9 (6.5)
Mean difference (95%CI)	4.5 (1.1, 7.8), P=0.010		5.6 (2.2, 8.9), P=0.002		4.8 (1.9, 7.8), P=0.002	
Percent whole, mean (SD)	79.1 (29.9)	57.8 (37.9)	79.1 (32.3)	52.8 (39.8)	75.5 (31.7)	52.2 (37.4)
Mean difference (95%CI)	21.3 (6.2, 36.4), P=0.006		26.3 (10.3, 42.3), P=0.002		23.2 (7.9, 38.6), P=0.004	
Holistic treatment responder	25/44 (56.8%)	9/36 (25.0%)	28/44 (63.6%)	10/36 (27.8%)	23/44 (52.3%)	6/36 (16.7%)
Risk difference (%) and 95% CI	31.8 (11.5, 52.2), P=0.006		35.9 (15.5, 56.3), P=0.002		35.6 (16.5, 54.7), P=0.001	

MCID=minimal clinical important difference; ODI=Oswestry Disability Index; POMS=Profile of Mood States; PSQI=Pittsburgh Sleep Quality Index; SCS=spinal cord stimulation; SD=standard deviation; VAS=visual analogue scale

**Table S3. Proportion of responders and cumulative MCIDs at 3-, 12- and 24-months for all patients regardless of baseline impairment**

	3-month		12-month		24-month	
	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS
<b>Pain intensity responders (VAS Overall <math>\geq 30\%</math>)</b>	60/67 (89.6%)	51/67 (76.1%)	61/67 (91.0%)	50/67 (74.6%)	54/67 (80.6%)	46/67 (68.7%)
Risk difference (%) and 95% CI, P-value	13.4 (0.9, 26.0), P=0.036		16.4 (4.0, 28.9), P=0.010		11.9 (-2.7, 26.5), P=0.109	
Mean (SD) number of MCIDs	2.4 (0.9)	2.0 (1.1)	2.5 (0.8)	2.0 (1.2)	2.3 (1.0)	1.8 (1.2)
Mean difference and 95%CI, P-value	0.4 (0.1, 0.8), P=0.024		0.5 (0.1, 0.8), P=0.005		0.5 (0.1, 0.9), P=0.010	
<b>Physical function (ODI Score <math>\geq 10</math>)</b>	53/67 (79.1%)	47/67 (70.1%)	47/67 (70.1%)	43/67 (64.2%)	49/67 (73.1%)	43/67 (64.2%)
Risk difference (%) and 95% CI, P-value	9.0 (-5.7, 23.6), P=0.321		6.0 (-9.9, 21.8), P=0.581		9.0 (-6.7, 24.6), P=0.352	
Mean (SD) number of MCIDs	2.6 (1.8)	2.1 (1.8)	2.4 (1.8)	1.9 (1.7)	2.2 (1.6)	1.6 (1.6)
Mean difference and 95%CI, P-value	0.5 (-0.1, 1.1), P=0.092		0.5 (-0.1, 1.1), P=0.083		0.6 (0.0, 1.1), P=0.036	
<b>QoL (EQ-5D-5L Index Score <math>\geq 0.074</math>)</b>	52/67 (77.6%)	46/67 (68.7%)	50/67 (74.6%)	40/67 (59.7%)	50/67 (74.6%)	41/67 (61.2%)
Risk difference (%) and 95% CI, P-value	9.0 (-6.0, 23.9), P=0.330		14.9 (-0.8, 30.6), P=0.097		13.4 (-2.2, 29.1), P=0.138	
Mean (SD) number of MCIDs	3.1 (2.5)	2.7 (2.4)	2.9 (2.7)	2.2 (2.4)	2.9 (2.2)	2.0 (2.2)
Mean difference and 95%CI, P-value	0.4 (-0.4, 1.3), P=0.330		0.6 (-0.2, 1.5), P=0.143		0.9 (0.2, 1.7), P=0.018	
<b>Sleep (PSQI Global Score <math>\geq 3</math>)</b>	44/67 (65.7%)	35/67 (52.2%)	45/67 (67.2%)	32/67 (47.8%)	39/67 (58.2%)	27/67 (40.3%)
Risk difference (%) and 95% CI, P-value	13.4 (-3.1, 29.9), P=0.160		19.4 (3.0, 35.8), P=0.036		17.9 (1.3, 34.6), P=0.057	
Mean (SD) number of MCIDs	1.6 (1.6)	1.2 (1.3)	1.7 (1.5)	1.1 (1.5)	1.3 (1.5)	0.9 (1.4)
Mean difference and 95%CI, P-value	0.4 (-0.1, 0.9), P=0.080		0.6 (0.1, 1.1), P=0.031		0.4 (-0.1, 0.9), P=0.131	
<b>Emotional function (POMS TMD Score <math>\geq 10</math>)</b>	40/67 (59.7%)	22/67 (32.8%)	40/67 (59.7%)	22/67 (32.8%)	40/67 (59.7%)	20/67 (29.9%)
Risk difference (%) and 95% CI, P-value	26.9 (10.6, 43.1), P=0.003		26.9 (10.6, 43.1), P=0.003		29.9 (13.8, 45.9), P<0.001	
Mean (SD) number of MCIDs	1.7 (2.1)	0.8 (1.3)	1.9 (2.0)	0.6 (1.4)	1.7 (1.9)	0.6 (1.4)
Mean difference and 95%CI, P-value	1.0 (0.4, 1.5), P=0.002		1.2 (0.7, 1.8), P<0.001		1.1 (0.5, 1.7), P<0.001	

CI=confidence interval; MCID=minimal clinical important difference; ODI=Oswestry Disability Index; POMS=Profile of Mood States; PSQI=Pittsburgh Sleep Quality Index; QoL=quality of life; SCS=spinal cord stimulation; SD=standard deviation; TMD=total mood disorder; VAS=visual analogue scale

**Table S4. Multimodal and holistic treatment response in all patients regardless of baseline impairment**

	3-month		12-month		24-month	
	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS
Responders in $\geq 1$ domain	63/67 (94.0%)	58/67 (86.6%)	63/67 (94.0%)	56/67 (83.6%)	63/67 (94.0%)	56/67 (83.6%)
Responders in $\geq 2$ domains	56/67 (83.6%)	51/67 (76.1%)	55/67 (82.1%)	45/67 (67.2%)	53/67 (79.1%)	45/67 (67.2%)
Responders in $\geq 3$ domains	54/67 (80.6%)	46/67 (68.7%)	49/67 (73.1%)	39/67 (58.2%)	47/67 (70.1%)	39/67 (58.2%)
Responders in $\geq 4$ domains	45/67 (67.2%)	35/67 (52.2%)	43/67 (64.2%)	30/67 (44.8%)	40/67 (59.7%)	28/67 (41.8%)
Responders in 5 domains	31/67 (46.3%)	11/67 (16.4%)	33/67 (49.3%)	17/67 (25.4%)	29/67 (43.3%)	9/67 (13.4%)
Cumulative responder score, mean (SD)	11.6 (7.3)	8.9 (6.5)	11.3 (7.1)	7.8 (6.8)	10.4 (6.4)	6.9 (6.1)
Mean difference (95%CI)	2.7 (0.4, 5.1), P=0.023		3.5 (1.1, 5.8), P=0.005		3.5 (1.3, 5.6), P=0.002	

MCID=minimal clinical important difference; ODI=Oswestry Disability Index; POMS=Profile of Mood States; PSQI=Pittsburgh Sleep Quality Index; SCS=spinal cord stimulation; SD=standard deviation; VAS=visual analogue scale

As holistic treatment response considers baseline impairment, the holistic treatment response results in the primary analysis apply to this sensitivity analysis

## SUPPLEMENTARY MATERIAL 3

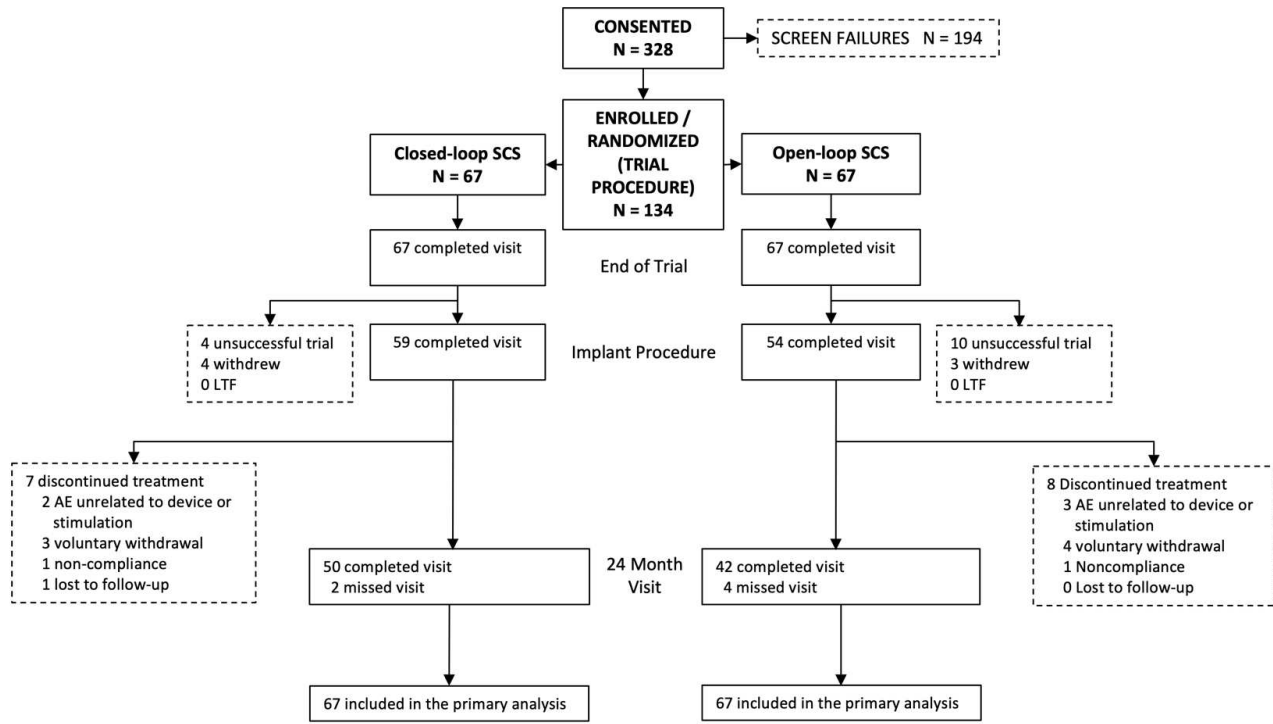


Figure S1. EVOKE study CONSORT flow diagram

## SUPPLEMENTARY MATERIAL 4

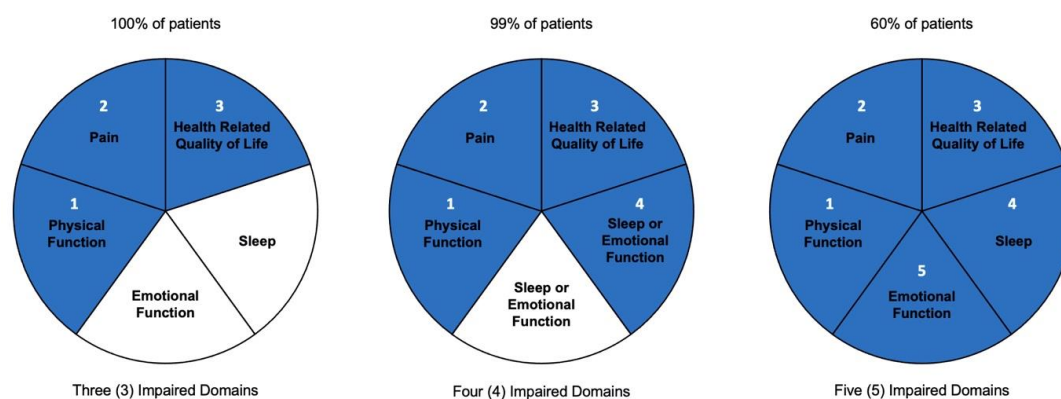


Figure S2. Proportion of combined CL-SCS and OL-SCS patients reporting impairments in the different domains at baseline – pain assessed by VAS, physical function by ODI, HRQoL by EQ-5D-5L, sleep quality by PSQI and emotional function by POMS

## SUPPLEMENTARY MATERIAL 5

**Table S5. Proportion of responders for each impaired outcome domain at 3-, 12- and 24-months**

	3-month		12-month		24-month	
	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS
<b>Pain intensity responders (VAS Overall <math>\geq 30\%</math>)</b>	60/67 (89.6%)	51/67 (76.1%)	61/67 (91.0%)	50/67 (74.6%)	54/67 (80.6%)	46/67 (68.7%)
Risk difference (%) and 95% CI	13.4 (0.9, 26.0), P=0.036		16.4 (4.0, 28.9), P=0.010		11.9 (-2.7, 26.5), P=0.109	
<b>For reference: pain intensity <math>\geq 50\%</math> reduction</b>	56/67 (83.6%)	42/67 (62.7%)	59/67 (88.1%)	43/67 (64.2%)	53/67 (79.1%)	36/67 (53.7%)
Risk difference (%) and 95% CI	20.9 (6.3, 35.5), P=0.005		23.9 (10.0, 37.7), P<0.001		25.4 (10.0, 40.8), P=0.001	
<b>For reference: pain intensity <math>\geq 80\%</math> reduction</b>	37/67 (55.2%)	28/67 (41.8%)	37/67 (55.2%)	25/67 (37.3%)	31/67 (46.3%)	20/67 (29.9%)
Risk difference (%) and 95% CI	13.4 (-3.3, 30.2), P=0.116		17.9 (1.3, 34.5), P=0.035		16.4 (0.2, 32.6), P=0.047	
<b>Physical function responders (ODI Score <math>\geq 10</math>)</b>	53/67 (79.1%)	47/67 (70.1%)	47/67 (70.1%)	43/67 (64.2%)	49/67 (73.1%)	43/67 (64.2%)
Risk difference (%) and 95% CI	9.0 (-5.7, 23.6), P=0.321		6.0 (-9.9, 21.8), P=0.581		9.0 (-6.7, 24.6), P=0.352	
<b>QoL responders (EQ-5D-5L Index Score <math>\geq 0.074</math>)</b>	52/67 (77.6%)	46/67 (68.7%)	50/67 (74.6%)	40/67 (59.7%)	50/67 (74.6%)	41/67 (61.2%)
Risk difference (%) and 95% CI	9.0 (-6.0, 23.9), P=0.330		14.9 (-0.8, 30.6), P=0.097		13.4 (-2.2, 29.1), P=0.138	
<b>Sleep responders (PSQI <math>\geq 3</math>)</b>	43/66 (65.2%)	34/64 (53.1%)	45/66 (68.2%)	32/64 (50.0%)	38/66 (57.6%)	27/64 (42.2%)
Risk difference (%) and 95% CI	12.0 (-4.8, 28.8), P=0.212		18.2 (1.6, 34.8), P=0.049		15.4 (-1.6, 32.4), P=0.114	
<b>Emotional function responders (POMS TMD Score <math>\geq 10</math>)</b>	31/44 (70.5%)	20/38 (52.6%)	33/44 (75.0%)	15/38 (39.5%)	33/44 (75.0%)	16/38 (42.1%)
Risk difference (%) and 95% CI	17.8 (-3.0, 38.6), P=0.114		35.5 (15.4, 55.7), P=0.002		32.9 (12.6, 53.1), P=0.003	

The denominator for the number of patients varies according to whether the domains were impaired at baseline.

CI=confidence interval; MCID=minimal clinical important difference; ODI=Oswestry Disability Index; POMS=Profile of Mood States; PSQI=Pittsburgh Sleep Quality Index; SCS=spinal cord stimulation; SD=standard deviation; TMD=total mood disorder; VAS=visual analogue scale



## SUPPLEMENTARY MATERIAL 6

**Table S6. Cumulative MCIDs – depth of response**

	3-month		12-month		24-month	
	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS
<b>Pain intensity (VAS Overall <math>\geq 30\%</math>), mean (SD)</b>	2.4 (0.9)	2.0 (1.1)	2.5 (0.8)	2.0 (1.2)	2.3 (1.0)	1.8 (1.2)
Mean difference and 95%CI	0.4 (0.1, 0.8), P=0.024		0.5 (0.1, 0.8), P=0.005		0.5 (0.1, 0.9), P=0.010	
<b>Physical function (ODI Score <math>\geq 10</math>), mean (SD)</b>	2.6 (1.8)	2.1 (1.8)	2.4 (1.8)	1.9 (1.7)	2.2 (1.6)	1.6 (1.6)
Mean difference and 95%CI	0.5 (-0.1, 1.1), P=0.092		0.5 (-0.1, 1.1), P=0.083		0.6 (0.0, 1.1), P=0.036	
<b>QoL (EQ-5D-5L Index Score <math>\geq 0.074</math>), mean (SD)</b>	3.1 (2.5)	2.7 (2.4)	2.9 (2.7)	2.2 (2.4)	2.9 (2.2)	2.0 (2.2)
Mean difference and 95%CI	0.4 (-0.4, 1.3), P=0.330		0.6 (-0.2, 1.5), P=0.143		0.9 (0.2, 1.7), P=0.018	
<b>Sleep (PSQI Global Score <math>\geq 3</math>), mean (SD)</b>	1.6 (1.6)	1.2 (1.3)	1.7 (1.5)	1.2 (1.5)	1.3 (1.5)	1.0 (1.4)
Mean difference and 95%CI	0.4 (-0.1, 0.9), P=0.119		0.5 (0.0, 1.0), P=0.048		0.3 (-0.2, 0.9), P=0.186	
<b>Emotional function (POMS TMD Score <math>\geq 10</math>), mean (SD)</b>	2.3 (2.2)	1.2 (1.5)	2.5 (2.1)	0.8 (1.6)	2.3 (2.0)	0.9 (1.7)
Mean difference and 95%CI	1.1 (0.3, 2.0), P=0.009		1.7 (0.8, 2.5), P<0.001		1.4 (0.6, 2.2), P=0.001	
<b>Cumulative responder score, mean (SD)</b>	11.4 (7.2)	8.7 (6.5)	11.1 (7.2)	7.7 (6.6)	10.2 (6.4)	6.8 (5.9)
Mean difference and 95%CI	2.6 (0.3, 5.0), P=0.028		3.4 (1.0, 5.7), P=0.005		3.4 (1.3, 5.5), P=0.002	
<b>Holistic MCID, mean (SD)</b>	2.4 (1.5)	2.0 (1.4)	2.3 (1.4)	1.7 (1.4)	2.2 (1.3)	1.5 (1.3)
Mean difference and 95%CI	0.5 (0.0, 0.9), P=0.070		0.6 (0.1, 1.1), P=0.015		0.6 (0.2, 1.1), P=0.005	

CI=confidence interval; MCID=minimal clinical important difference; ODI=Oswestry Disability Index; POMS=Profile of Mood States; PSQI=Pittsburgh Sleep Quality Index; SCS=spinal cord stimulation; SD=standard deviation; TMD=total mood disorder; VAS=visual analogue scale

## SUPPLEMENTARY MATERIAL 7

Table S7. Neural activation and system utilization in closed-loop and open-loop SCS

	3-month		12-month		24-month	
	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS	Closed-loop SCS	Open-loop SCS
<b>Neural Activation (mode ECAP elicited, <math>\mu</math>V)</b>	32.3 [11.5-52.0]	4.0 [1.5-10.5]	24.0 [12.5-67.5]	4.3 [1.3-19.5]	21.3 [5.5-49.0]	4.5 [1.0-15.0]
P-value †	<0.001		<0.001		<0.001	
<b>Neural Activation Accuracy (RMSE, <math>\mu</math>V) ‡</b>	3.1 [1.8-4.8]	11.4 [7.2-26.1]	4.2 [2.4-5.9]	26.8 [11.2-51.7]	3.4 [2.3-5.8]	24.3 [14.4-56.9]
P-value †	<0.001		<0.001		<0.001	
<b>System Utilization (% time on)</b>	87.7 [65.597.3]	91.7 [77.5-96.9]	81.5 [52.4-95.7]	83.3 [33.2-98.7]	86.2 [35.1-96.3]	82.4 [21.7-98.0]
P-value †	0.321		0.714		0.390	

Data are medians [IQR]

† difference between medians

‡ Lower values equal greater neural activation accuracy