Supplementary Materials

Clinical Information: Neurophysiologically-Based Brain State Tracking & Modulation in Focal Epilepsy (NIH UH3 NS095495 & FDA IDE-G180224)

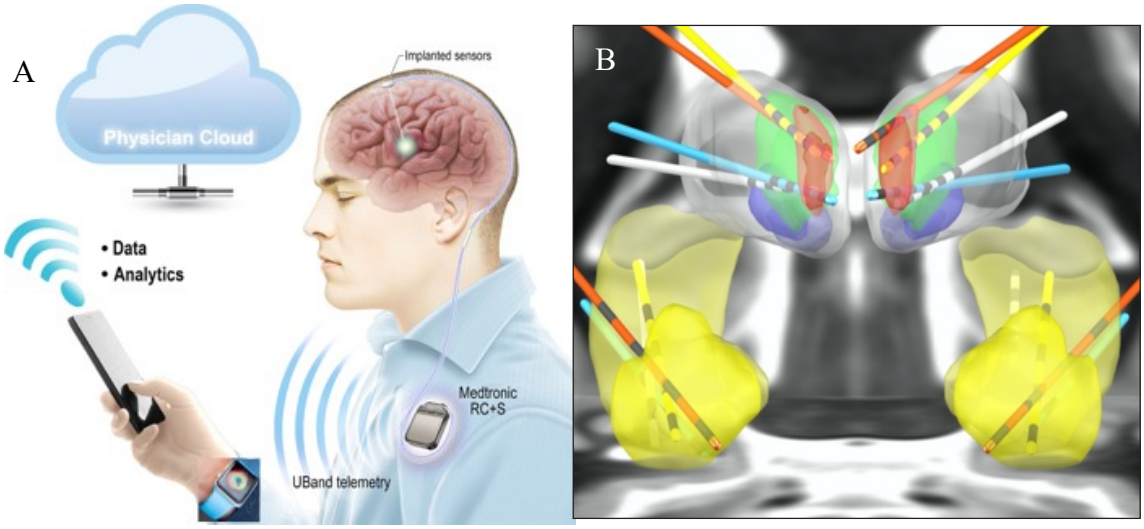
We consented 6 patients and implanted 4 patients with drug resistant mesial temporal lobe epilepsy (mTLE) as part of the NIH Brain Initiative sponsored *Neurophysiologically-Based Brain State Tracking & Modulation in Focal Epilepsy*. Patients are implanted with investigational Medtronic Summit RC+S™ neural sense and stimulation device with bilateral anterior nucleus of thalamus (ANT) and hippocampus (HPC) electrodes. The epilepsy patient assistant device (EPAD) is an application running on a hand-held device provides integration of wearable and implantable devices [28,39]. The FDA IDE protocol investigates electrical deep brain stimulation (DBS) paradigms, including low frequency (2 & 7 Hz) and high frequency (> 100 Hz) electrical stimulation, seizure detection and forecasting, behavioral state tracking, and adaptive DBS control. Supplementary Figure 1 shows a schematic of the implanted system and co-registration of implanted electrodes.

Patient #1. A 57-year-old ambidextrous woman with drug resistant mTLE. History of head trauma with loss of consciousness followed by a generalized tonic-clonic seizure at age 9. She did well until age 21 years, when her seizures became drug resistant. She has both focal impaired awareness seizures (FIAS) and focal aware seizures (FAS). She has comorbid depression and anxiety.

Patient #2. A 20-year-old right-handed woman with type-1 diabetes mellitus and drug resistant mTLE. No epilepsy risk factors. Epilepsy onset at age 7 years, and a prior left temporal lobectomy at age 9 years. She was seizure free until age 17 years when seizures recurred while off all medications. Thereafter, she has been drug resistant. She has both focal impaired awareness seizures (FIAS) and focal aware seizures (FAS). She has comorbid depression and anxiety.

Patient #3. A 41-year-old right-handed woman with drug resistant mTLE. No clear risk factors for epilepsy. Epilepsy diagnosis was at age 31 years. Despite medications and VNS she had continued seizures. She has both focal impaired awareness seizures (FIAS) and focal aware seizures (FAS). She has comorbid depression and anxiety.

Patient #4. A 35-year-old right-handed woman history of diabetes mellitus and drug resistant temporal lobe epilepsy. She has no epilepsy risk factors. Epilepsy onset at age 4 years old. She has both focal impaired awareness seizures (FIAS) and focal aware seizures (FAS). Significant comorbid depression. Elevated GAD-65 that did not respond to immunotherapy.



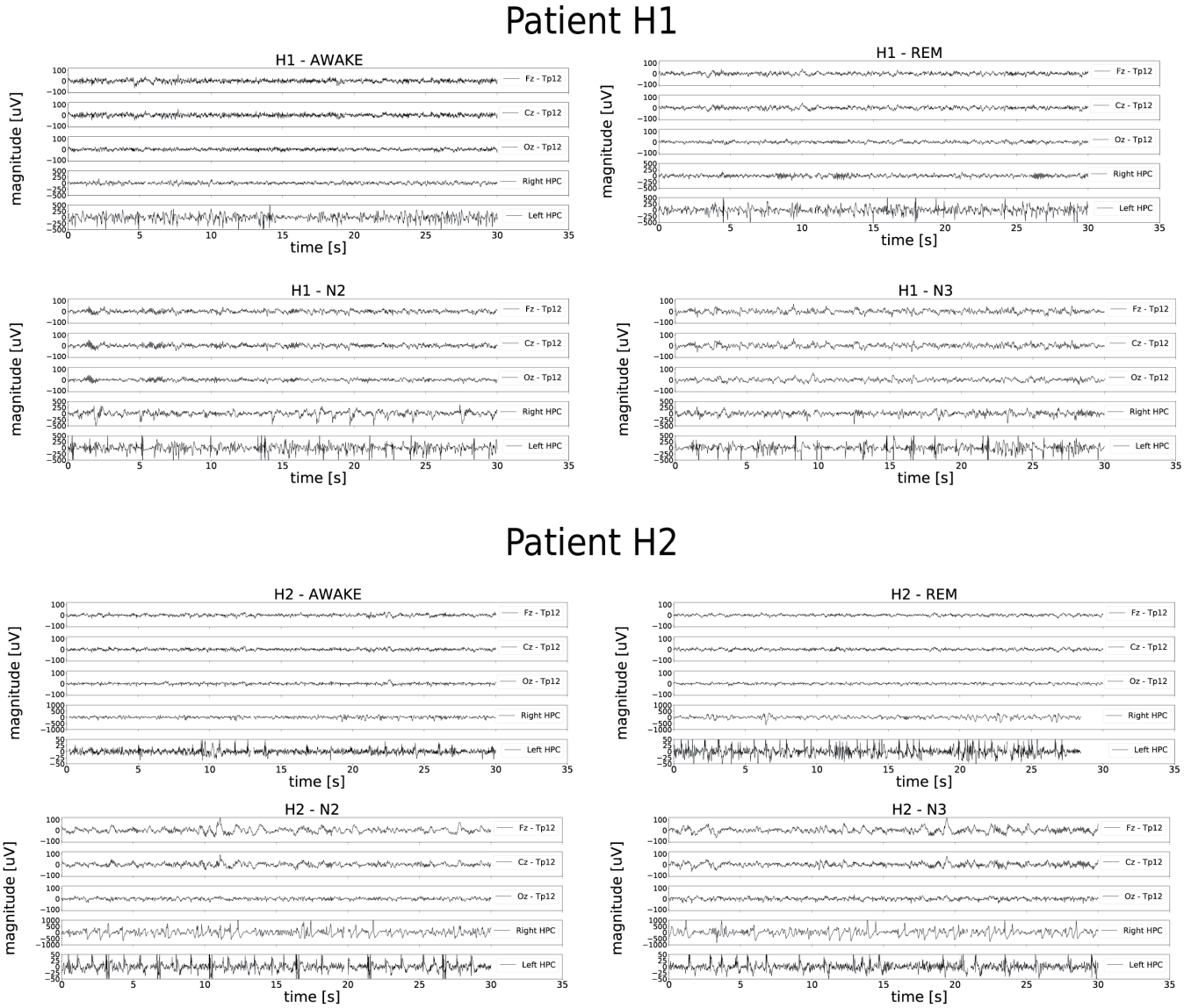
Supplementary Figure 1. **Epilepsy Management System**: A) Implantable neural sensing and stimulating (RC+S) device with bi-directional communication to off-the- body computing on EPAD enabling machine learning analytics. The EPAD system integrates RC+S, wearable sensors (e.g., watch), handheld computing device with cloud computing environment. B) Co-registration of the bilateral ANT and HPC leads (4 electrode contacts on each lead) in the four implanted patients. ANT (red) and HPC (light yellow) and AMG (yellow). Epilepsy patient assistance device (EPAD), Anterior nucleus of the thalamus (ANT), Hippocampus (HPC), Amygdala (AMG).

Supplementary Table S1. Setup of DBS parameters for subjects during three consecutive nights (Day 1-3) in the hospital epilepsy monitoring unit when the iEEG data were acquired simultaneously with PSG data to create the gold standard human expert sleep scoring used for training, validation, and testing. The iEEG data used for classification were acquired from Hippocampus (HPC). Electrical deep brain stimulation was applied bilaterally in the anterior nucleus of thalamus (ANT). Periodic cycling between different DBS setups, that are given by frequency (f), stimulation current (I) and pulse width (PW), was applied to all subjects.

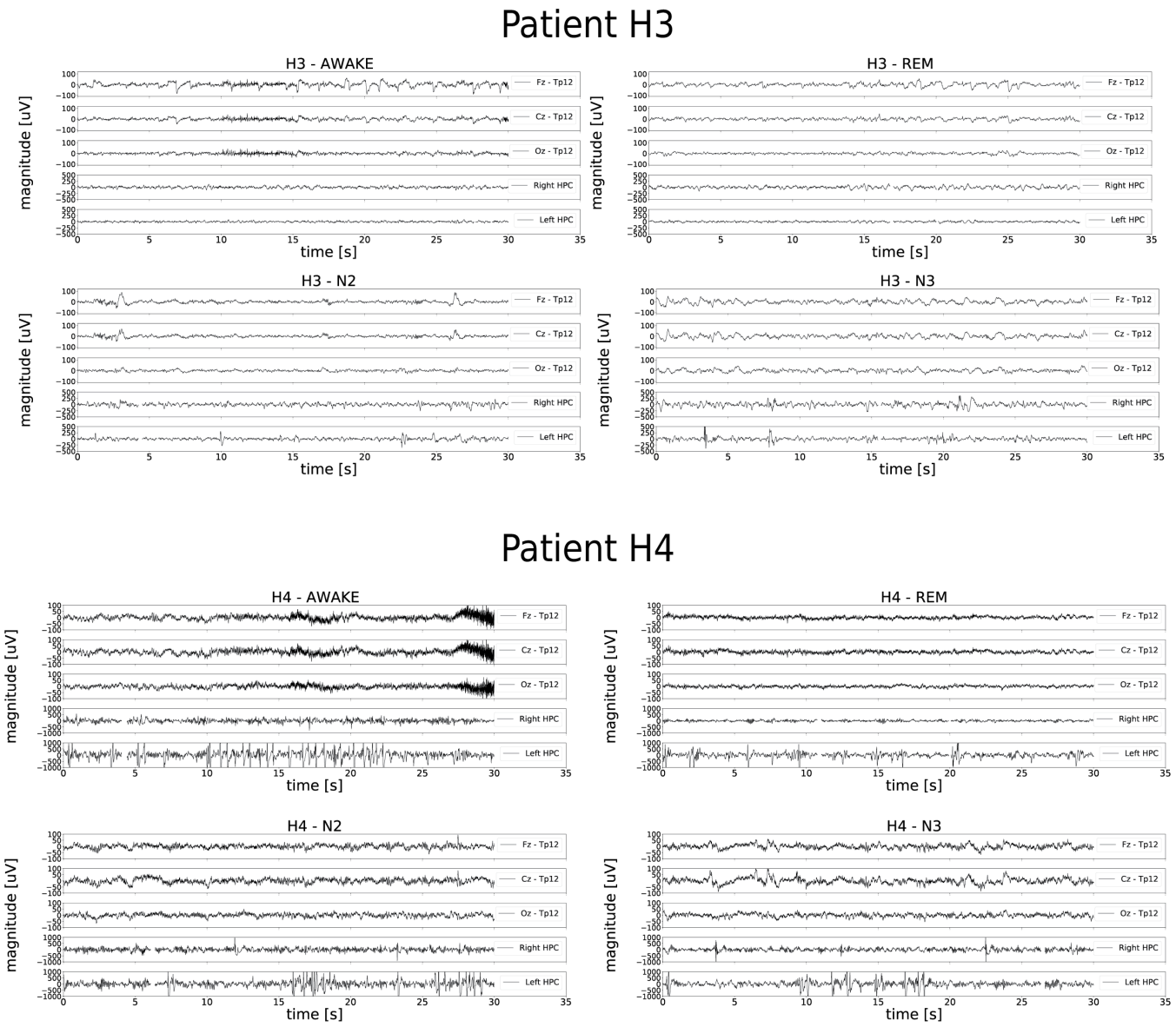
	Day 1			Day 2			Day 3		
	f (Hz)	I (mA)	PW(us)	f (Hz)	I (mA)	PW(us)	f (Hz)	I (mA)	PW(us)
H1	-	-	-	7; HF	3	90	2; HF	3	90
H2	2	6	200	2; 7	5; 6	200	HF	4	200
H3	2	6	200	7; HF	4	200	2; 7	5	200
H4	HF	2	200	2	6	200	7	6	200

Supplementary Table S2. Number of 30-second iEEG epochs collected, DBS parameters, and sleep stage across the three hospital nights. Only epochs with data rate higher than 85% are included. High frequency (HF>100 Hz). Rapid eye-movement (REM) sleep, non-REM (N1, N2, N3) sleep.

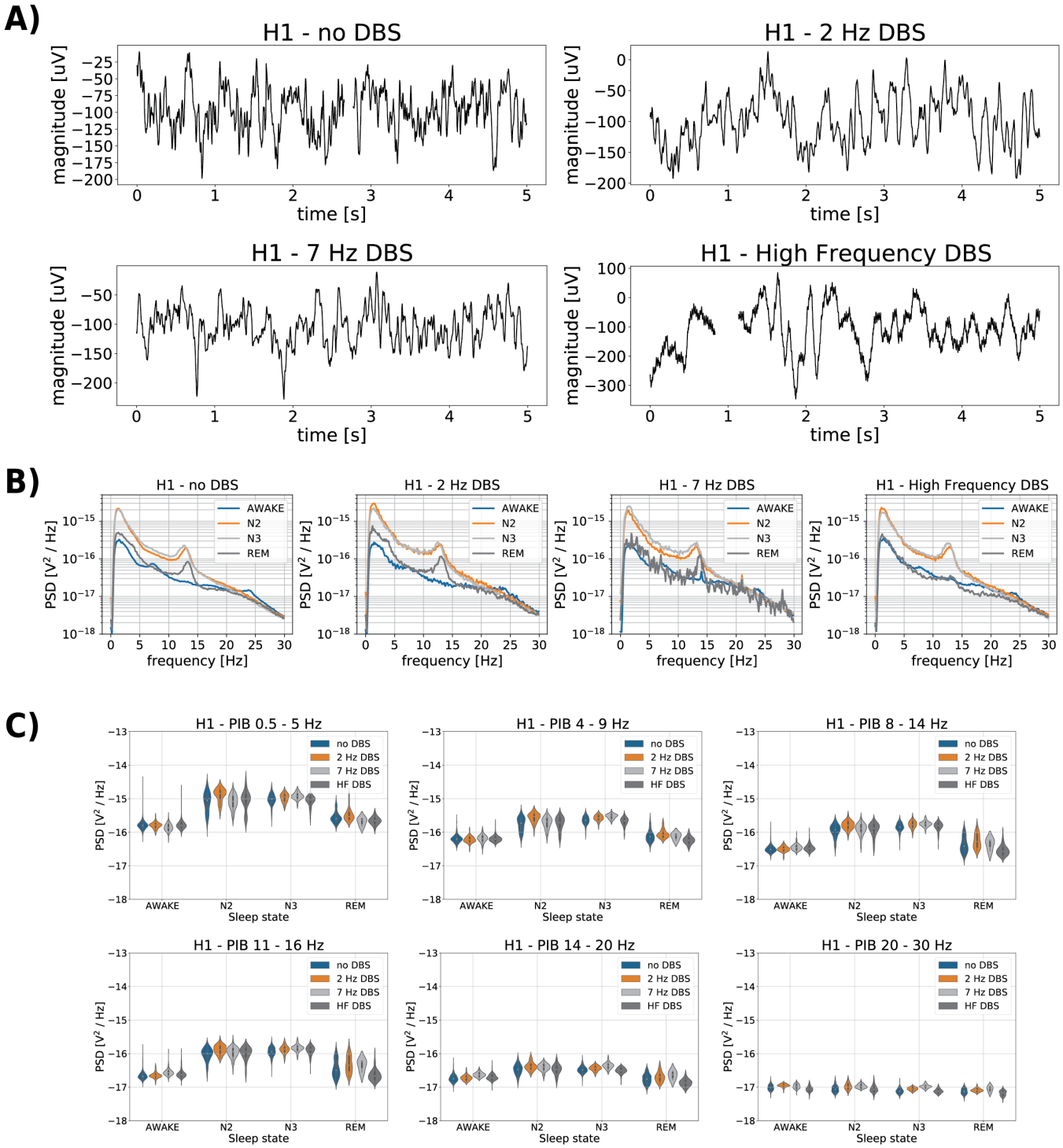
		Night 1					Night 2					Night 3				
	Stim Mode	W	N1	N2	N3	REM	W	N1	N2	N3	REM	W	N1	N2	N3	REM
H1	No stim	421	14	291	266	168	277	6	119	102	91	135	12	75	123	40
	2 Hz	-	-	-	-	-	-	-	-	-	-	48	2	34	50	53
	7 Hz	-	-	-	-	-	148	3	82	30	3	-	-	-	-	-
	HF	-	-	-	-	-	93	5	74	75	38	103	1	46	33	22
	All	**421**	**14**	**291**	**266**	**168**	**518**	**14**	**275**	**207**	**132**	**286**	**15**	**155**	**211**	**115**
H2	No stim	-	-	-	-	-	320	19	113	63	22	72	7	268	34	54
	2 Hz	-	-	-	-	-	115	12	49	71	5	-	-	-	-	-
	7 Hz	-	-	-	-	-	122	1	69	35	17	-	-	-	-	-
	HF	-	-	-	-	-	-	-	-	-	-	89	32	347	33	60
	All	-	-	-	-	-	**557**	**32**	**231**	**169**	**44**	**161**	**39**	**615**	**67**	**114**
H3	No stim	447	16	296	83	180	171	8	46	25	25	327	14	98	42	-
	2 Hz	145	16	282	107	117	-	-	-	-	-	45	14	58	26	-
	7 Hz	-	-	-	-	-	104	-	24	24	23	30	6	80	6	-
	HF Hz	-	-	-	-	-	100	1	25	8	10	-	-	-	-	-
	All	**592**	**32**	**578**	**190**	**297**	**375**	**9**	**115**	**57**	**58**	**402**	**34**	**236**	**74**	**-**
H4	No stim	71	42	183	62	59	90	67	220	40	35	-	-	-	-	-
	2 Hz	-	-	-	-	-	142	144	427	72	43	-	-	-	-	-
	7 Hz	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	HF Hz	111	76	370	120	86	-	-	-	-	-	-	-	-	-	-
	All	**182**	**118**	**553**	**182**	**145**	**232**	**211**	**647**	**112**	**78**	-	-	-	-	-



Supplementary Figure 2. Representative examples of intracranial EEG (iEEG) signal changes between different behavioral states (Awake, REM, N2 and N3) for patients H1 and H2. *Simultaneous scalp-EEG (Fz, Cz and Oz referenced to TP12) and iEEG (bipolar Left ANT, Right ANT, Left HPC, Right HPC) recordings for Awake, rapid eye-movement (REM), non-REM (N2 and N3) sleep.*

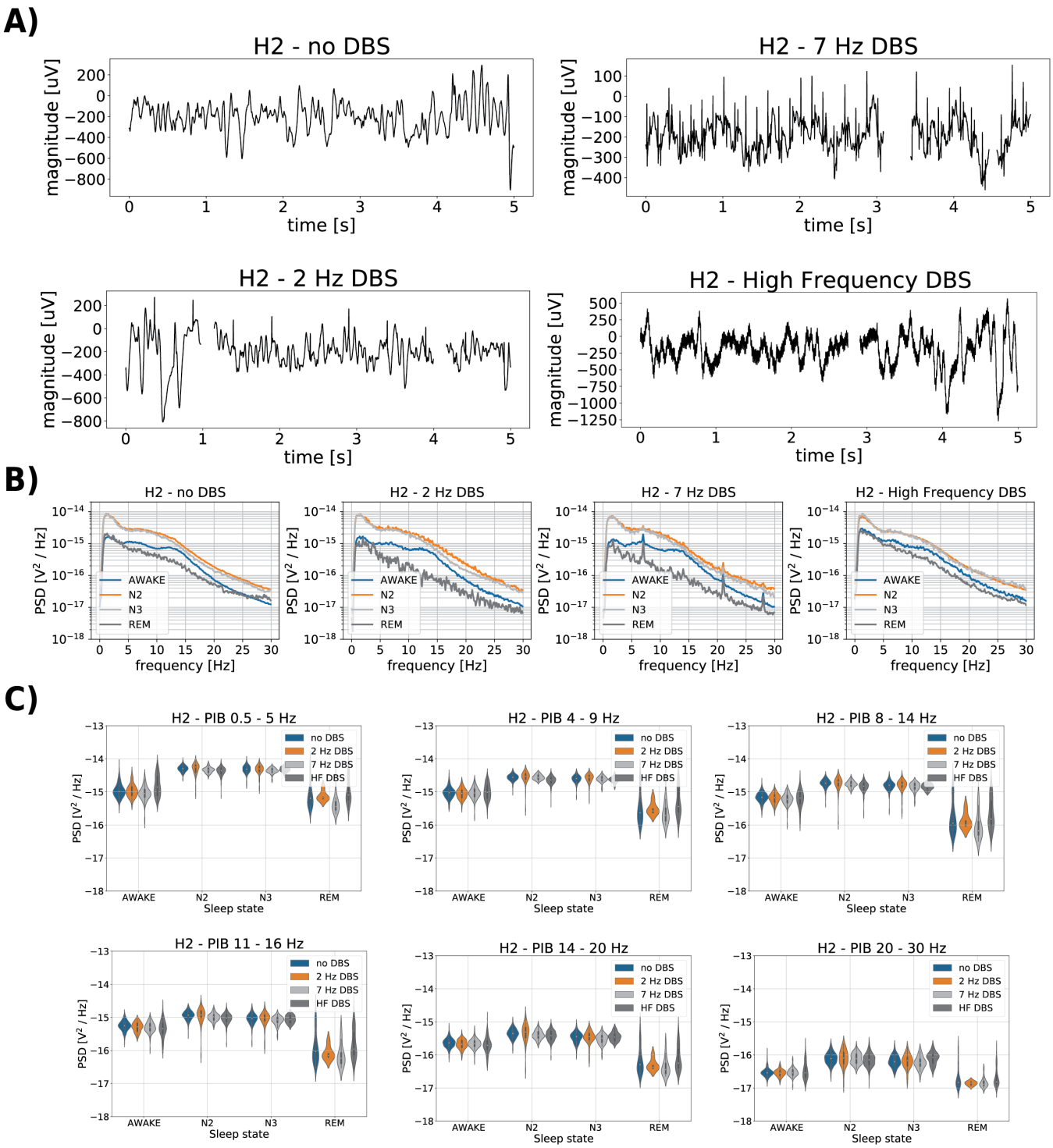


Supplementary Figure 3. Representative examples of intracranial EEG (iEEG) signal changes between different behavioral states (Awake, REM, N2 and N3) for patients H3 and H4. *Simultaneous scalp-EEG (Fz, Cz and Oz referenced to TP12) and iEEG (bipolar Left ANT, Right ANT, Left HPC, Right HPC) recordings for Awake, rapid eye-movement (REM), non-REM (N2 and N3) sleep.*

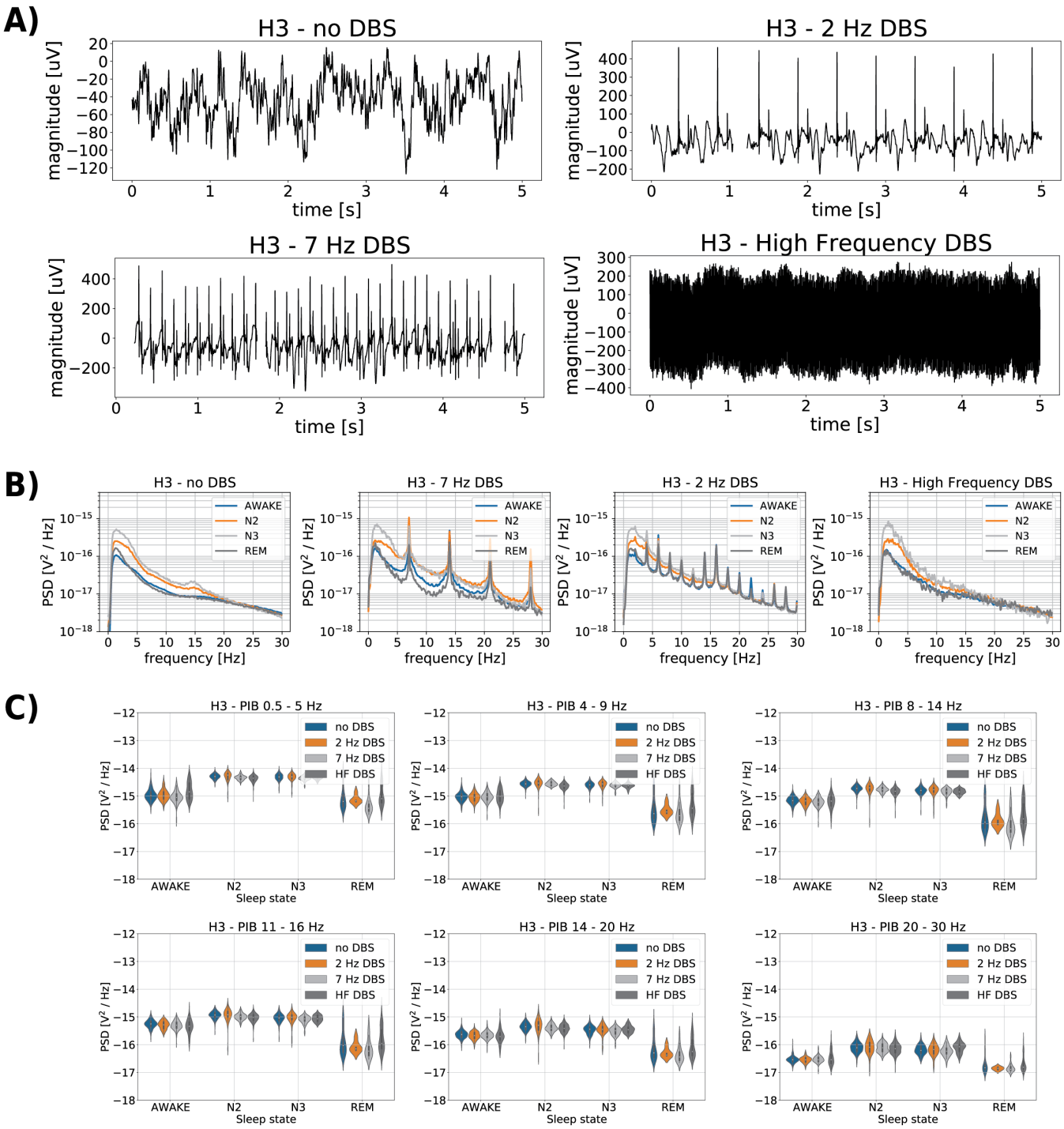


Supplementary Figure 4. **The effect of ANT DBS on iEEG signals. A)** The iEEG recorded from right hippocampus (HPC) (patient H1) for different ANT DBS frequencies (No DBS, 2, 7 Hz and HF DBS). **B)** Power spectral density (PSD) for different ANT DBS frequencies (No DBS, 2 Hz, 7 Hz and HF DBS): average of each sleep phase spectrum across three nights using 30-second window, estimated by Welch's method (Awake, N2, N3, REM); **C)** Power in band features (0.5 - 5 Hz; 4 – 9 Hz; 8 – 14 Hz; 11 – 16 Hz, 14 – 20 Hz, 20 – 30 Hz) extracted from raw HPC iEEG signals from each sleep states (Awake, N2, N3, REM), over three nights using 30-second window. These data from subject H3 are representative of all patients. High frequency (HF>100 Hz). Rapid eye-movement (REM) sleep, non-REM (N2, N3) sleep, Anterior nucleus of thalamus (ANT), intracranial EEG (iEEG), Hippocampus (HPC), Deep brain stimulation (DBS), Power spectral density (PSD)

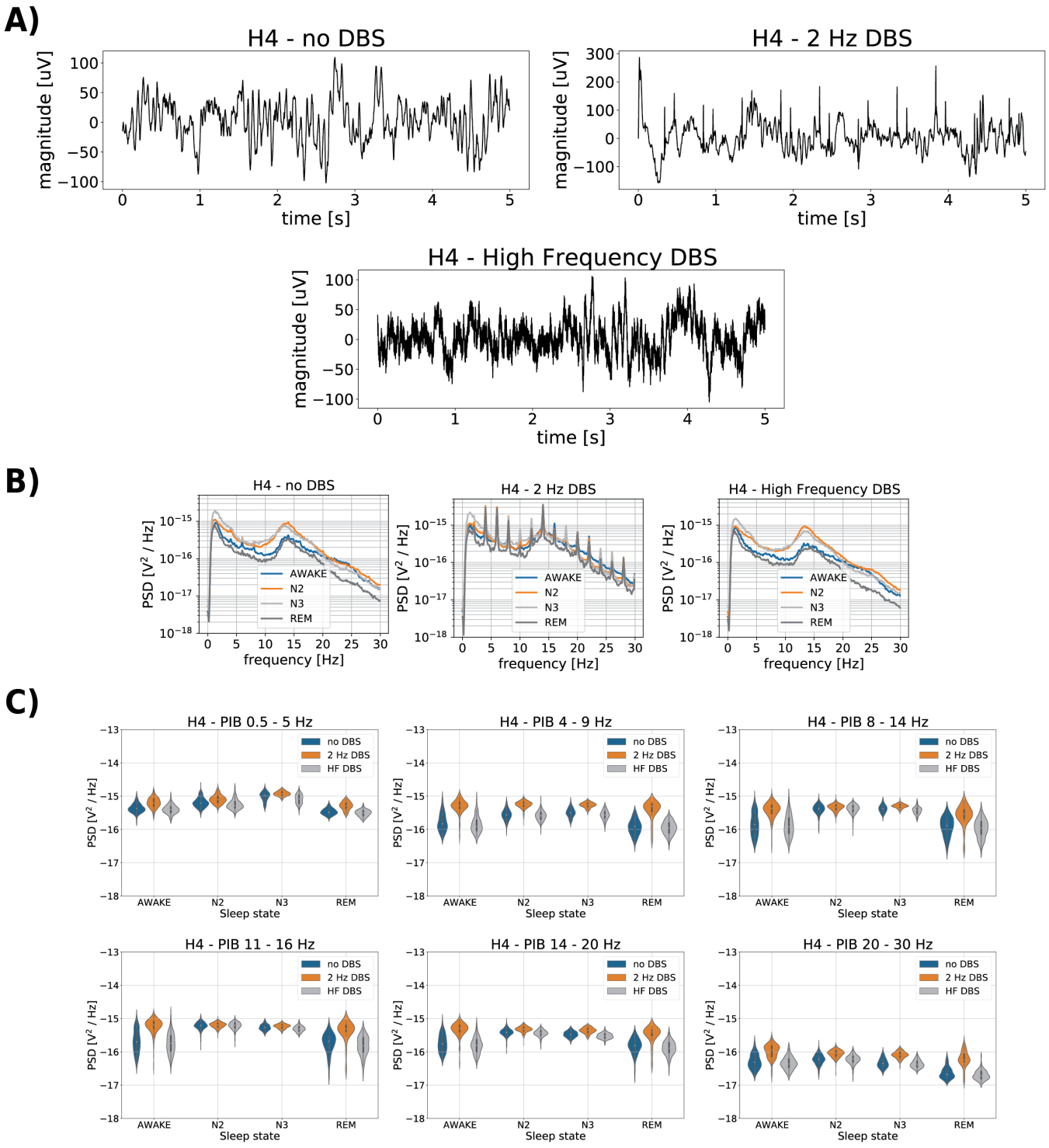
Supplementary Figure 1.



Supplementary Figure 5. **The effect of ANT DBS on iEEG signals. A)** The iEEG recorded from right hippocampus (HPC) (patient H2) for different ANT DBS frequencies (No DBS, 2, 7 Hz and HF DBS). **B)** Power spectral density (PSD) for different ANT DBS frequencies (No DBS, 2 Hz, 7 Hz and HF DBS): average of each sleep phase spectrum across three nights using 30-second window, estimated by Welch's method (Awake, N2, N3, REM); **C)** Power in band features (0.5 - 5 Hz; 4 – 9 Hz; 8 – 14 Hz; 11 – 16 Hz, 14 – 20 Hz, 20 – 30 Hz) extracted from raw HPC iEEG signals from each sleep states (Awake, N2, N3, REM), over three nights using 30-second window. These data from subject H3 are representative of all patients. High frequency (HF>100 Hz). Rapid eye-movement (REM) sleep, non-REM (N2, N3) sleep, Anterior nucleus of thalamus (ANT), intracranial EEG (iEEG), Hippocampus (HPC), Deep brain stimulation (DBS), Power spectral density (PSD)



Supplementary Figure 6. **The effect of ANT DBS on iEEG signals. A)** The iEEG recorded from right hippocampus (HPC) (patient H3) for different ANT DBS frequencies (No DBS, 2, 7 Hz and HF DBS). **B)** Power spectral density (PSD) for different ANT DBS frequencies (No DBS, 2 Hz, 7 Hz and HF DBS): average of each sleep phase spectrum across three nights using 30-second window, estimated by Welch's method (Awake, N2, N3, REM); **C)** Power in band features (0.5 - 5 Hz; 4 – 9 Hz; 8 – 14 Hz; 11 – 16 Hz, 14 – 20 Hz, 20 – 30 Hz) extracted from raw HPC iEEG signals from each sleep states (Awake, N2, N3, REM), over three nights using 30-second window. These data from subject H3 are representative of all patients. High frequency (HF>100 Hz). Rapid eye-movement (REM) sleep, non-REM (N2, N3) sleep, Anterior nucleus of thalamus (ANT), intracranial EEG (iEEG), Hippocampus (HPC), Deep brain stimulation (DBS), Power spectral density (PSD)



Supplementary Figure 7. **The effect of ANT DBS on iEEG signals. A)** The iEEG recorded from right hippocampus (HPC) (patient H4) for different ANT DBS frequencies (No DBS, 2 Hz and HF DBS). **B)** Power spectral density (PSD) for different ANT DBS frequencies (No DBS, 2 Hz and HF DBS): average of each sleep phase spectrum across three nights using 30-second window, estimated by Welch's method (Awake, N2, N3, REM); **C)** Power in band features (0.5 - 5 Hz; 4 – 9 Hz; 8 – 14 Hz; 11 – 16 Hz, 14 – 20 Hz, 20 – 30 Hz) extracted from raw HPC iEEG signals from each sleep states (Awake, N2, N3, REM), over three nights using 30-second window. These data from subject H3 are representative of all patients. High frequency (HF>100 Hz). Rapid eye-movement (REM) sleep, non-REM (N2, N3) sleep, Anterior nucleus of thalamus (ANT), intracranial EEG (iEEG), Hippocampus (HPC), Deep brain stimulation (DBS), Power spectral density (PSD)

*Supplementary Table S3. Results of automated behavioral sleep state classification (F1-score) into Awake, REM, N2, N3, sleep categories for all subjects under various settings of electrical deep brain stimulation (DBS) in anterior nucleus of thalamus (ANT). The classification score is reported for the general non-REM category comprising N2 & N3 as well. The feasibility of automated sleep classification using a single channel iEEG data recorded from HPC was performed using no DBS data. We used available iEEG data acquired without DBS during the first night to train the classifier and data acquired during the second and third night for pseudo-prospective (PP) testing. The nights without DBS, however, were not consistent across patients. If data without DBS were not available for the first night, the data without DBS acquired during the second night were used for training and the third night data were utilized for testing. For the 2, 7 Hz & HF DBS, we utilized classifiers trained using no DBS data and transferred the model to the stimulation (MT) data. The experiment was replicated twice, with and without band power cancelling, as introduced in "Cancelling of Band Bower at Stimulation Frequencies". Moreover, 20 % cross-validation testing (CV) proportionally sampled across all classification categories was performed for the high frequency DBS setups. Values marked by * were achieved using less than 10 samples and therefore are not considered valid.* High frequency (HF>100 Hz). Rapid eye-movement (REM) sleep, non-REM (N2, N3) sleep, Anterior nucleus of thalamus (ANT), intracranial EEG (iEEG), Hippocampus (HPC), Deep brain stimulation (DBS)

EBS Setup	Validation Method	Band Power Cancelling	Subject	Awake	REM	N2	N3	non-REM	All	All $_{non-REM}$
No DBS	PP	No	**H1**	.946	.703	.519	.723	.923	.800	.910
			H2	.848	.660	.740	.338	.944	.691	.893
			H3	.759	.497	.547	.563	.803	.669	.753
			H4	.798	.763	.621	.763	.924	.719	.890
			Average	**.838**	**.656**	**.607**	**.597**	**.899**	**.720**	**.862**
		Yes 2 Hz	**H1**	.941	.736	.415	.700	.923	.775	.910
			H2	.863	.712	.720	.196	.944	.691	.896
			H3	.677	.323	.074	.488	.748	.654	.736
			H4	.246	.000	.265	.204	.803	.576	.790
			Average	**.682**	**.443**	**.369**	**.397**	**.855**	**.674**	**.833**
		Yes 7 Hz	**H1**	.934	.613	.333	.709	.935	.779	.904
			H2	.844	.712	.774	.360	.952	.733	.909
			H3	.732	.503	.597	.613	.812	.666	.744
			H4	.829	.776	.533	.605	.899	.704	.879
			Average	**.835**	**.651**	**.484**	**.572**	**.900**	**.721**	**.859**
2 Hz	MT	No	**H1**	.991	.753	.455	.750	.897	.765	.892
			H2	.960	.714	.552	.440	.960	.755	.940
			H3	.383	.544	.804	.714	.920	.676	.763
			H4	.696	.491	.169	.522	.788	.480	.781
			Average	**.758**	**.626**	**.495**	**.607**	**.891**	**.669**	**.844**
		Yes 2 Hz	**H1**	.991	.848	.364	.721	.932	.789	.931
			H2	.955	.727	.437	.442	.932	.743	.936
			H3	.783	.426	.442	.712	.883	.683	.817
			H4	.286	.111	.127	.072	.763	.525	.768
			Average	**.754**	**.528**	**.343**	**.487**	**.878**	**.685**	**.863**
7 Hz	MT	No	**H1**	.977	.100*	.250	.635	.929	.756	.926
			H2	.964	.643	.446	.295	.973	.787	.957
			H3	.818	.700	.774	.750	.879	.807	.845
			H4	-	-	-	-	-	-	-
			Average	**.920**	**.672**	**.490**	**.560**	**.927**	**.783**	**.909**
		Yes 7 Hz	**H1**	.974	.353*	.444	.690	.949	.815	.941
			H2	.976	.914	.396	.491	.978	.829	.973
			H3	.870	.903	.886	.810	.935	.884	.918
			H4	-	-	-	-	-	-	-
			Average	**.940**	**.909**	**.575**	**.664**	**.954**	**.843**	**.944**

High Frequency > 100 Hz	MT	No	**H1**	.948	.767	.381	.689	.950	.768	.920
			H2	.506	.667	.522	.250	.896	.658	.814
			H3	.458	.353*	.478	.571*	.761	.574	.652
			H4	.774	.800	.841	.673	.971	.857	.939
			Average	**.672**	**.745**	**.556**	**.537**	**.895**	**.714**	**.831**
	CV	No	**H1**	.970	.894	.564	.771	.987	.850	.975
			H2	.703	.772	.613	.176	.944	.772	.902
			H3	.899	.716*	.693	.000*	.857	.826	.899
			H4	.767	.702	.926	.725	.975	.895	.926
			Average	**.835**	**.789**	**.699**	**.418**	**.941**	**.836**	**.926**