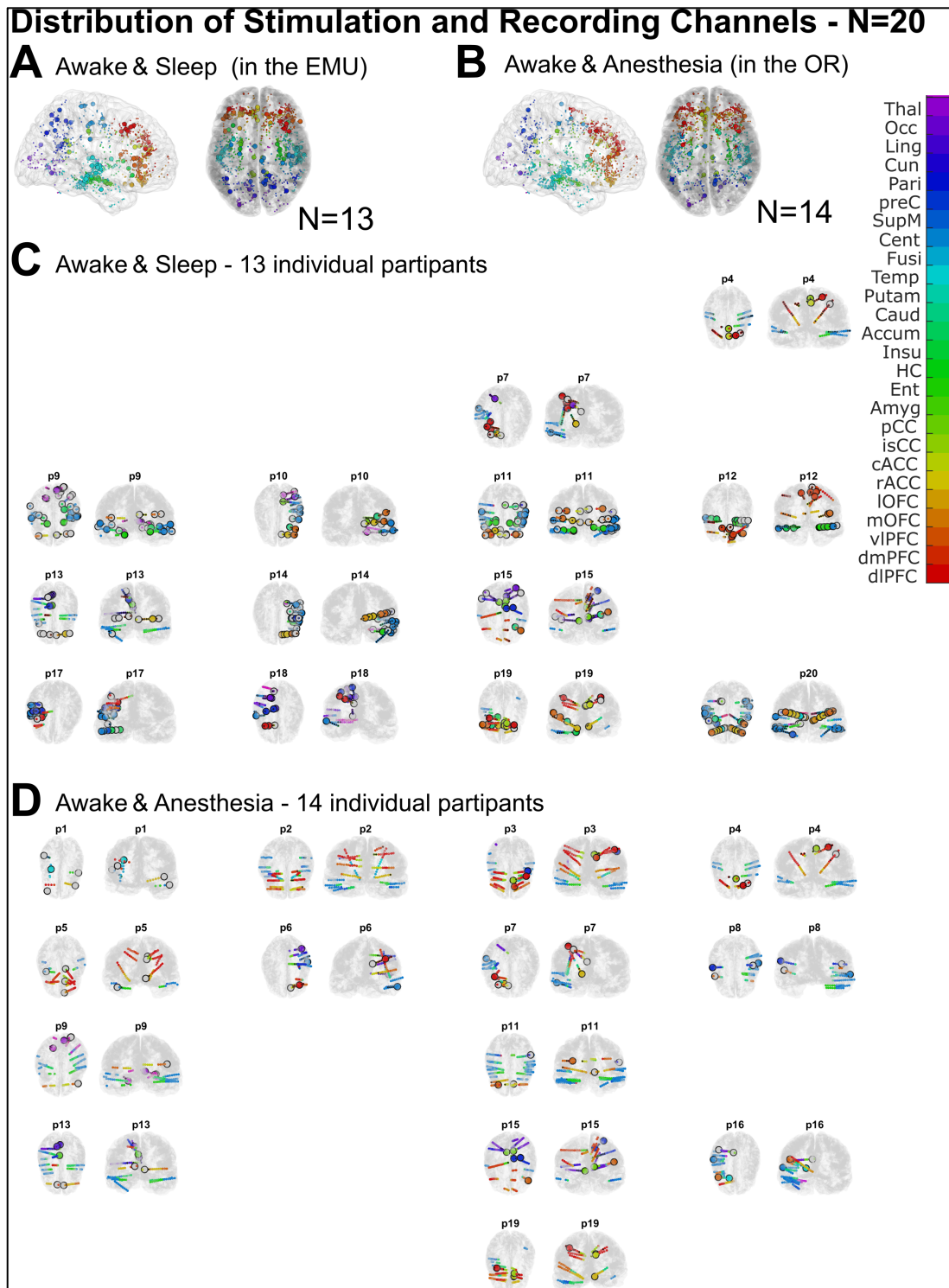


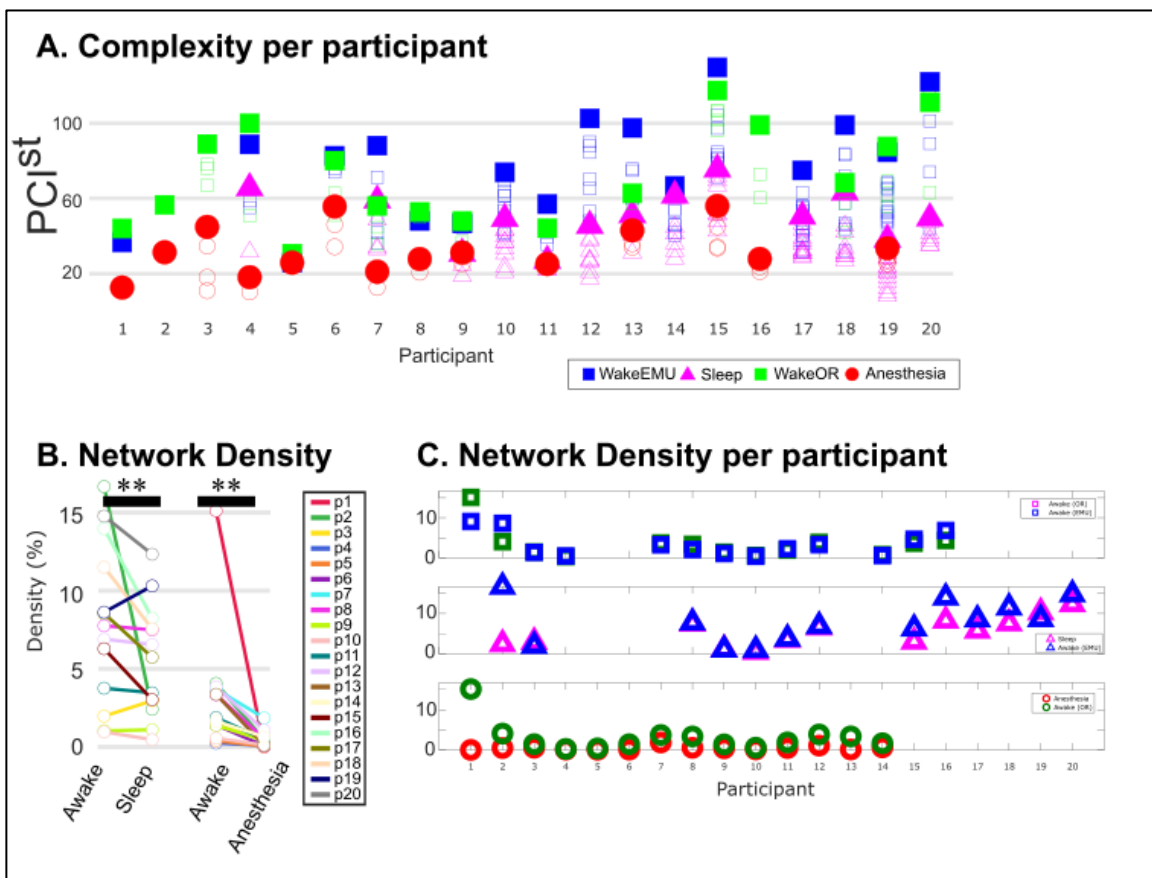
## Supplementary Figures

**Figure S1: Distribution of stimulation and recording across the N= 20 participants grouped by comparison of un/conscious states, related to Figure 1.**



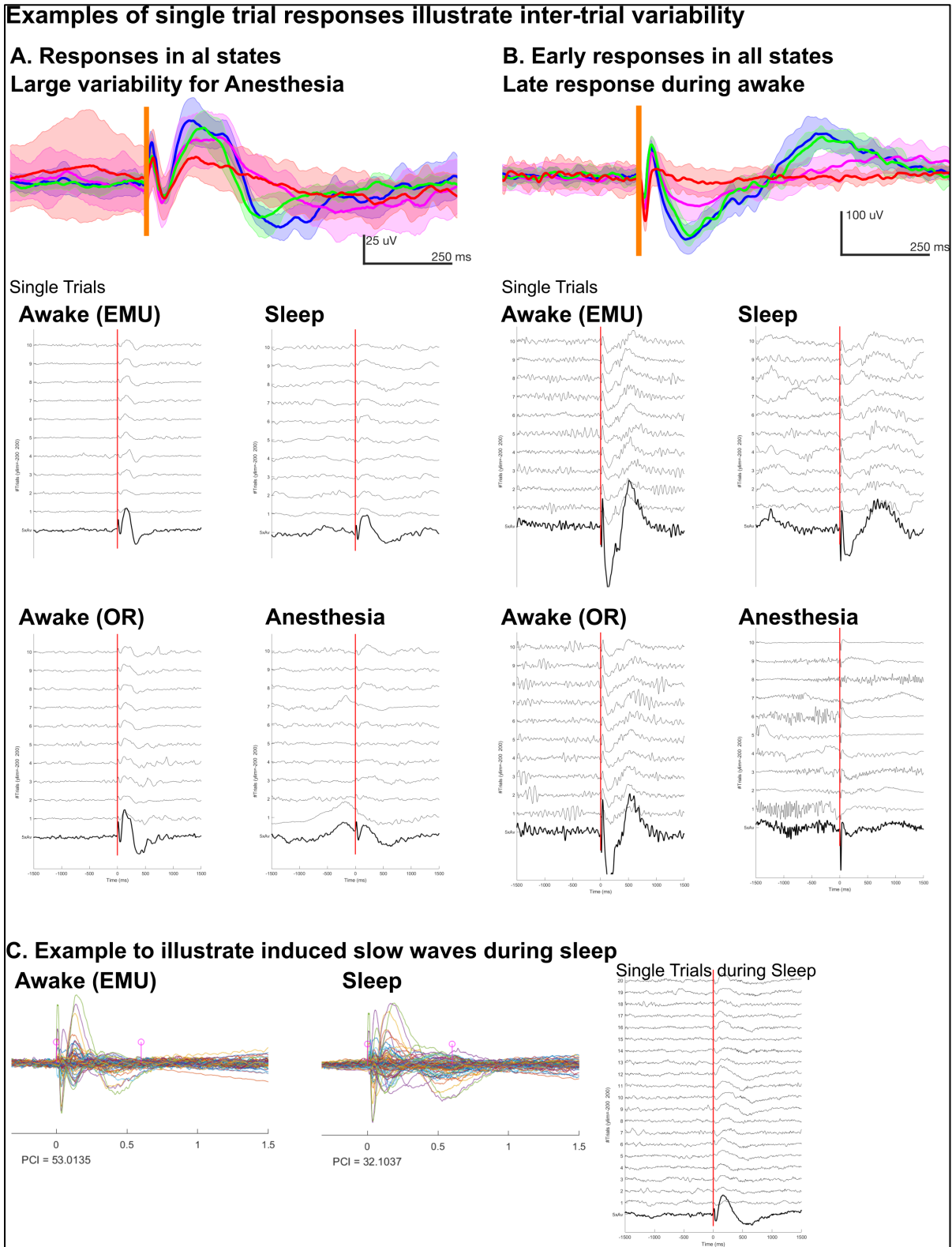
A) In 13 participants we compared awake and sleep in the epilepsy monitoring unit (EMU;  $s=99$  stimulation channels;  $r=1547$  recording channels). B) In 14 participants we compared awake and propofol-induced general anesthesia before electrode explantation in the operating room (OR;  $s=35$ ,  $r=1709$ ). Large circles: stimulation channels, small dots: recording channels. C) Distribution of recording and stimulating channels for individual participants that participated in awake and sleep in the EMU. D) Distribution of recording and stimulating channels for individual participants that participated in awake and anesthesia states in the OR. Colors represent brain regions. Gray circles: stimulation channels that were excluded since did not evoke responses (less than 5 recording channels with detected response in any state).

Figure S2: Perturbational complexity and density per participant, related to Figure 2.



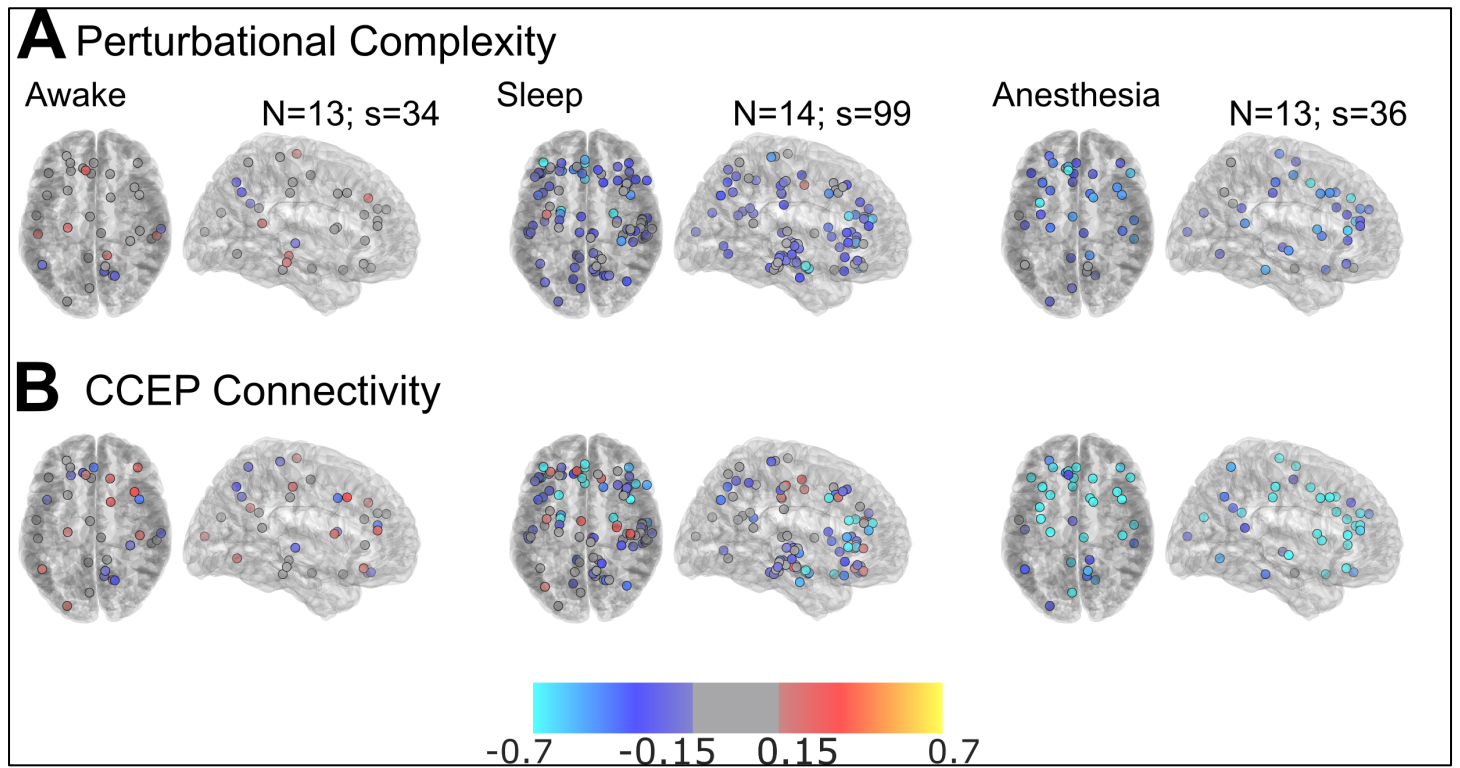
A) Perturbational complexity (measured with PCI<sup>st</sup>) for each stimulation channel, each participant, and during each state. The filled marker indicates the maximum PCI<sup>st</sup> for each state. Blue squares: awake (in the EMU); magenta triangles: sleep; green squares: awake (in the OR); red circles: anesthesia. The x-axis corresponds to individual participants (N=20). B) Comparison of density between conscious and unconscious states per participant. Density was reduced for each participant during anesthesia and for 10/13 participants during sleep. Colors represent participants C) Density per participant and per pair of states. Top: squares: awake; blue in the EMU, green in the OR. Middle: magenta triangles: sleep; blue triangles: awake in the EMU. Bottom: green circles: awake in the OR; red circles: anesthesia. \*\* indicates p<0.01 (U-Mann test).

**Figure S3: Examples of individual channels and individual trials, related to Figure 2 and Discussion.**



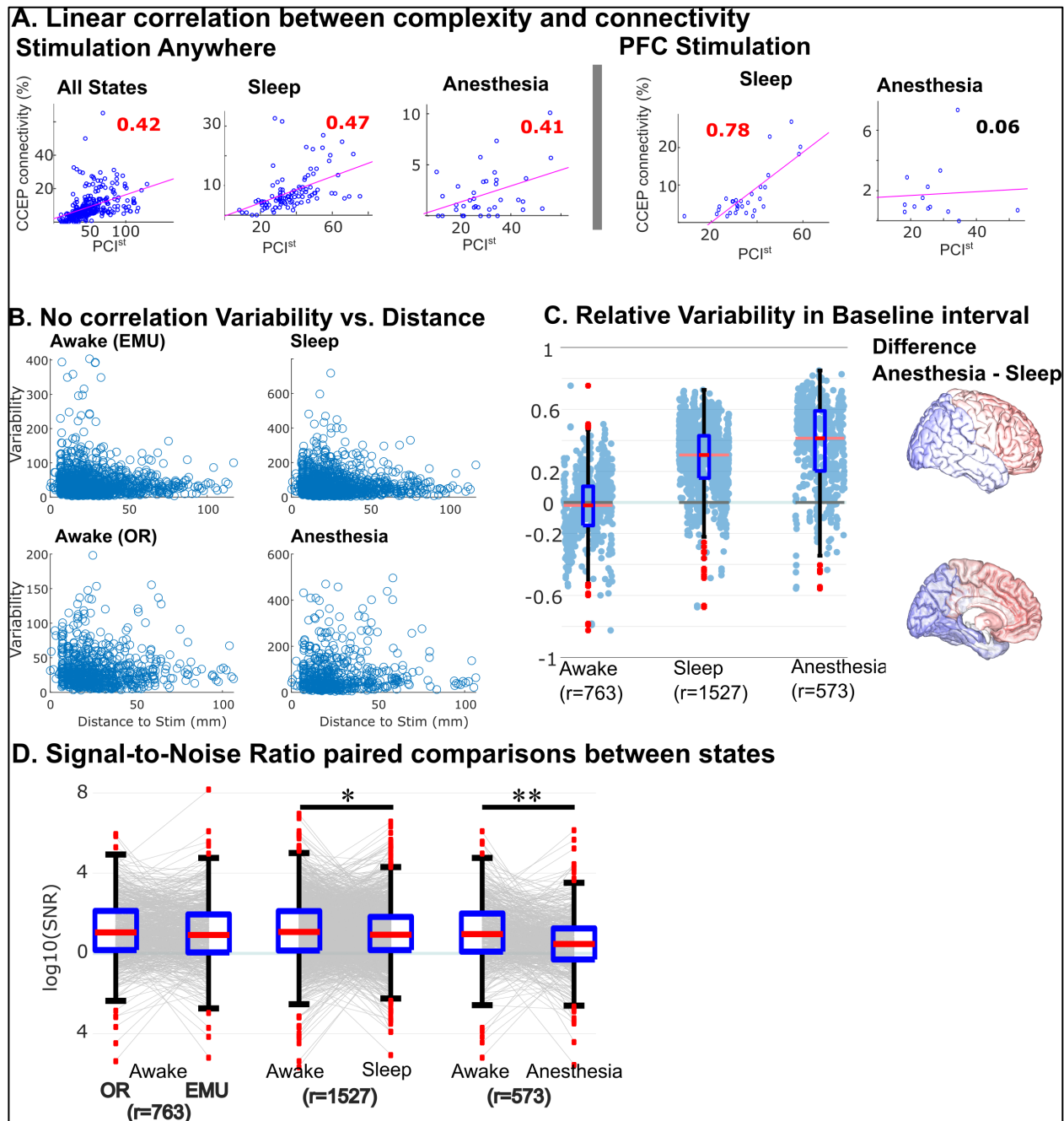
A & B) Mean and standard deviation (SD; shaded) in two representative channels. As in Fig. 2.B, variability (SD) was the largest for anesthesia. Below are 10 randomly selected individual trials for each state. C) Example of a stimulation channel that elicited slow oscillations during sleep. The butterfly plots of all the recorded channels following stimulation showed a larger amplitude and slower responses during sleep than during awake in several channels. On the right, single trials for one recording channel during sleep showed that slow oscillations were elicited in each individual trial in this case.

**Figure S4: Relative complexity and connectivity at individual stimulation channels, related to Figure 3.**



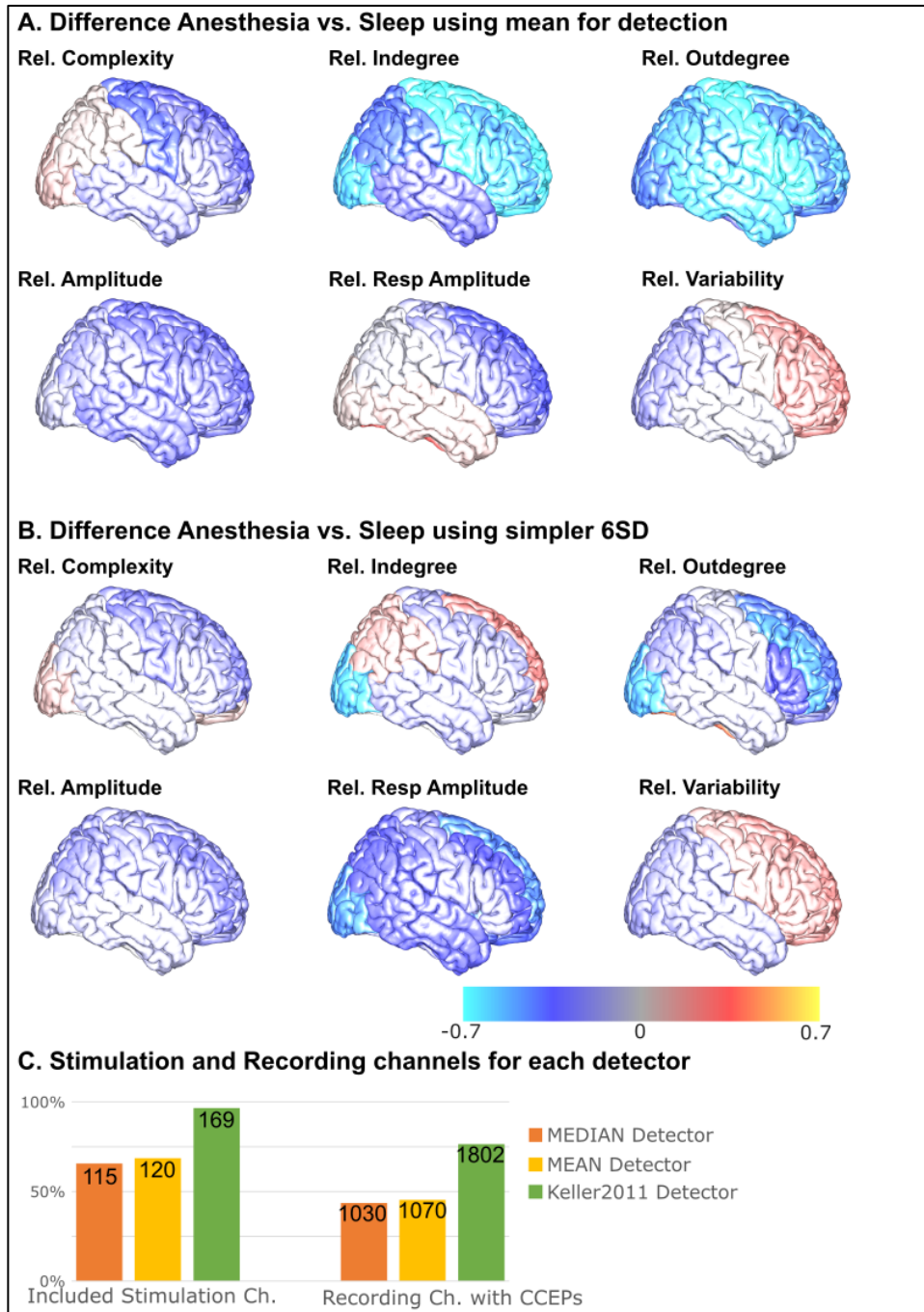
A) Relative perturbational complexity was similar for wake in different environments (left), decreased for most sites during sleep (middle), and decreased for all stimulation sites for anesthesia (right). For anesthesia, the most negative values were observed in anterior channels. B) Relative CCEP indegree connectivity fluctuated more for wake in different environments (left), and for sleep (middle). It was negative for all stimulation channels for anesthesia, with further decrease in most anterior channels. N: number of participants; s= number of stimulation channels.

**Figure S5: Additional measures and analyses: complexity vs. connectivity, variability vs. distance, variability in baseline interval, and signal-to-noise ratio, related to the STAR methods and the discussion.**



A) Correlation between complexity and connectivity with stimulation anywhere (right) and prefrontal stimulation (left). Relative Complexity ( $PCI^{st}$ ) and connectivity were linearly correlated with stimulation anywhere and with PFC stimulation during sleep. There was no correlation during anesthesia (Pearson correlation). In red correlation value when  $p < 0.01$ . B) Correlation between variability and distance to stimulation. There was no linear correlation between variability and distance between recording and stimulation sites. C) Comparison of variability in a baseline interval. As was the case for the response interval, relative variability was statistically larger during anesthesia than during sleep (permutation test). In addition, as was the case for the variability of the response, variability during baseline showed a regional dichotomy, with anterior regions larger and posterior regions smaller for anesthesia than sleep. D) The signal-to-noise ratio (SNR) was computed as the variance during the CCEP interval divided by the variance in the baseline. SNR was similar for awake in the EMU and OR. SNR was significantly smaller for sleep ( $p = 0.02$ ) and anesthesia than awake ( $p < < 0.001$ ; permutation test). *EMU*: epilepsy monitoring unit; *OR*: operating room; *r*: number of recording channels in the region (with stimulation anywhere and response detected in any state).

**Figure S6: Results are consistent if using other CCEP detection methods, related to the STAR methods and the discussion.**



A) Difference between anesthesia and sleep for all relative measures using the mean in the detection algorithm. Similar detections with similar findings were obtained when using the mean instead of the median for the detections. B) Difference between anesthesia and sleep for all relative measures using the Keller and colleagues' detector<sup>32</sup>. C. Percentage of stimulation channels included (with at least 5 channels with detected responses) and percentage of recording channels with detected CCEP for each detector. The *Median* Detector was the detector used in this study (115 of the 175 channels to which stimulation was delivered). The *Mean* detector was the same detector but with mean instead of median across trials (results in A). Indeed, CCEP responses were found in 45% of the recording channels from s=120 (s=104 for sleep vs. awake in the EMU, s=39 for anesthesia vs. awake in the OR). The *Keller* detector<sup>32</sup> tended to have more false positive detections with responses detected in 76% of channels, resulting in s=169 or 97% stimulation sites (s=136 for sleep vs. awake in the EMU, s=62 for anesthesia vs. awake in the OR). Because of this, CCEP indegree connectivity was similar during wake and sleep, which is consistent with previous studies<sup>45</sup>. Even with this less specific detection, for all other measures, findings were consistent with a reduction in complexity and amplitude and increased variability during unconscious states, which was more pronounced during anesthesia than sleep, particularly in the prefrontal regions.

## Supplementary Tables

**Table S1: Number of included and total stimulated channels, recording channels, and analyzed states per participant, related to Figure 1.**

Participant ID	Included stimulation channels	Stimulation channels	Channels with CCEPs	Recording channels	# States compared	WakeEMU (nTrials)	Sleep (nTrials)	WakeOR (nTrials)	Anesthesia (nTrials)
p1	1	5	15	29	3	1 (16)	0	1 (31)	1 (7)
p2	1	4	10	161	2	0	0	1 (14)	1 (25)
p3	4	4	29	169	2	0	0	1 (17)	1 (18)
p4	3	4	32	96	4	1 (20)	1 (14)	1 (20)	1 (17)
p5	1	5	5	110	3	1 (16)	0	1 (16)	1 (19)
p6	3	5	48	120	3	1 (19)	0	1 (15)	1 (13)
p7	6	9	72	107	4	1 (8)	1 (10)	1 (15)	1 (15)
p8	2	4	14	87	3	1 (18)	0	1 (14)	1 (10)
p9	3	9	19	121	4	1 (9)	1 (25)	1 (17)	1 (19)
p10	10	13	93	120	2	1 (14)	1 (9)	0	0
p11	3	9	33	177	4	1 (7)	1 (14)	1 (14)	1 (18)
p12	10	13	85	112	2	1 (15)	1 (12)	0	0
p13	6	13	45	131	4	1 (26)	1 (25)	1 (13)	1 (33)
p14	7	8	73	98	2	1 (16)	1 (20)	0	0
p15	9	12	85	144	4	1 (20)	1 (25)	1 (19)	1 (13)
p16	3	5	47	134	2	0	0	1 (17)	1 (22)
p17	14	18	45	84	2	1 (20)	1 (20)	0	0
p18	9	11	55	73	3	1 (19)	1 (20)	1 (12)	0
p19	13	16	110	123	4	1 (20)	1 (10)	1 (18)	1 (21)
p20	7	8	115	161	3	1 (18)	1 (20)	1 (12)	0
					<b>7</b>	<b>17</b>	<b>13</b>	<b>16</b>	<b>14</b>
<b>TOTAL</b>	<b>115</b>	<b>175</b>	<b>1030</b>	<b>2357</b>					
<b>min</b>	<b>1</b>	<b>4</b>	<b>5</b>	<b>29</b>					
<b>max</b>	<b>14</b>	<b>18</b>	<b>115</b>	<b>177</b>					
<b>median</b>	<b>5</b>	<b>8.5</b>	<b>46</b>	<b>120</b>					

Channels with CCEPs are channels with detected responses in any state, which are included for variability and amplitude calculation. *CCEP*: cortico-cortical evoked potentials; *WakeEMU*: awake state in the epilepsy monitoring unit; *WakeOR*: awake state in the operating room; *nTrials*: mean number of stimulation trials during that state.

**Table S2: Complexity and connectivity paired comparisons between conscious and unconscious states, related to Figure 2.**

		Complexity (PCIst)																																			
		Anesthesia vs. Awake (in the OR)												Sleep vs. Awake (in the OR)												Awake (in the OR) vs. Awake (in the EMU)											
		Anesthesia						Awake						Sleep						Awake						Awake (OR)						Awake (EMU)					
Region	pVal	median	(25 - 75)	median	(25 - 75)	s	N	pVal	median	(25 - 75)	median	(25 - 75)	s	N	pVal	median	(25 - 75)	median	(25 - 75)	s	N	pVal	median	(25 - 75)	median	(25 - 75)	s	N									
all	1.7E-07	28.5	21.2	34.5	60.9	48.9	83.7	36	14	1.1E-16	35.8	28.4	46.2	56.1	45.8	75.4	99	13	0.41	59.5	45.8	95.9	67.0	48.1	81.0	34	13										
prefrontal	0.0002	25.3	20.6	32.1	61.6	49.1	87.8	13	10	1.9E-06	33.2	29.2	41.5	55.3	46.0	71.1	30	12	0.58	61.6	45.8	101.9	57.0	51.8	83.0	11	8										
posterior	0.004	34.3	30.9	43.8	51.1	45.3	71.0	9	4	0.0001	42.9	30.9	49.9	60.8	46.1	77.2	20	6	0.56	49.5	43.7	62.7	71.5	46.7	75.6	10	5										
temporal	0.13	24.5	17.0	41.8	55.0	47.3	61.4	4	4	3.7E-06	32.6	28.2	43.3	54.6	43.6	72.9	31	9	0.81	62.7	54.3	75.0	73.8	43.4	76.1	5	4										
		CCEP Indegree Connectivity (% of channels with CCEPs)																																			
		Anesthesia vs. Awake (in the OR)												Sleep vs. Awake (in the OR)												Awake (in the OR) vs. Awake (in the EMU)											
		Anesthesia						Awake						Sleep						Awake						Awake (OR)						Awake (EMU)					
Region	pVal	median	(25 - 75)	median	(25 - 75)	s	N	pVal	median	(25 - 75)	median	(25 - 75)	s	N	pVal	median	(25 - 75)	median	(25 - 75)	s	N	pVal	median	(25 - 75)	median	(25 - 75)	s	N									
all	1.7E-07	1.5%	0.6%	3.4%	7.8%	5.9%	11.2%	36	14	2.1E-08	6.2%	4.3%	8.9%	9.2%	6.2%	13.7%	99	13	0.62	8.4%	6.4%	13.8%	9.7%	5.8%	19.0%	34	13										
prefrontal	0.0002	1.0%	0.7%	2.4%	7.8%	6.1%	20.5%	13	10	0.0005	5.0%	3.2%	7.6%	9.0%	5.7%	13.7%	30	12	0.81	10.2%	5.9%	18.6%	9.2%	5.8%	18.7%	11	8										
posterior	0.004	3.1%	1.6%	3.6%	7.0%	5.8%	9.1%	9	4	0.011	6.5%	5.1%	9.0%	7.8%	5.6%	15.3%	20	6	1	6.9%	5.9%	8.3%	7.4%	4.2%	10.9%	10	5										
temporal	0.13	3.8%	1.0%	7.9%	9.3%	6.4%	12.2%	4	4	0.000	7.4%	4.7%	11.7%	12.8%	8.7%	14.4%	31	9	0.31	11.4%	9.6%	15.5%	14.6%	10.4%	19.7%	5	4										
WM	0.0002	2%	1%	4%	8%	6%	23%	13	9	0.03	8%	5%	14%	11%	5%	19%	30	11	1	7%	6%	21%	11%	6%	20%	14	8										
GM	2.7E-05	1%	0%	3%	8%	6%	11%	23	13	3.4E-07	6%	4%	8%	9%	6%	13%	69	13	0.65	9%	7%	12%	8%	6%	18%	20	12										
		Outdegree																																			
		Anesthesia vs. Awake (in the OR)												Sleep vs. Awake (in the OR)												Awake (in the OR) vs. Awake (in the EMU)											
		Anesthesia						Awake						Sleep						Awake						Awake (OR)						Awake (EMU)					
Region	pVal	median	(25 - 75)	median	(25 - 75)	r	N	pVal	median	(25 - 75)	median	(25 - 75)	r	N	pVal	median	(25 - 75)	median	(25 - 75)	r	N	pVal	median	(25 - 75)	median	(25 - 75)	r	N									
all	2.6E-51	0%	0%	0%	25%	0%	33%	562	14	4.0E-23	11%	0%	20%	15%	10%	29%	860	13	0.23	25%	0%	33%	25%	0%	33%	644	13										
prefrontal	5.6E-25	0%	0%	0%	25%	0%	33%	250	12	8.2E-10	10%	0%	20%	15%	10%	30%	282	12	0.85	25%	0%	33%	25%	0%	33%	235	11										
posterior	3.9E-10	0%	0%	20%	20%	20%	33%	107	5	0.13	17%	10%	33%	17%	10%	33%	151	8	0.48	20%	0%	33%	20%	0%	33%	130	7										
temporal	1.6E-07	0%	0%	0%	29%	0%	33%	92	9	1.0E-08	14%	0%	14%	14%	11%	20%	292	11	0.04	25%	0%	25%	25%	0%	33%	160	10										

Paired comparison of anesthesia vs. awake in the OR, sleep vs. awake in the EMU, and awake in the EMU vs. in the OR (Wilcoxon tests). **Top:** Perturbational complexity was estimated with PCI<sup>st</sup>. **Middle:** The CCEP indegree connectivity, or casual indegree centrality, was estimated as the percentage of channels with responses per stimulation channel. **Bottom:** The casual outdegree centrality measure was estimated as the percentage of stimulations that produced responses per recording channel (only recording channels with CCEP responses during one of the compared states were included, to remove channels with no responses whatsoever). There were only four temporal stimulation channels during anesthesia. Green highlights p<0.01; yellow highlights 0.01<p<0.05. CCEP: cortico-cortical evoked potential; EMU: epilepsy monitoring unit; OR: operating room; r: number of recording channels (with stimulation anywhere). s: number of stimulation channels; N: number of participants.



**Table S3: Amplitude and variability comparisons between conscious and unconscious states, related to Figure 2.**

Fixed effects	Amplitude (LMM)						y (Amplitude) ~ Intercept + State+ nTrials + RecRegion + StimRegion + (Intercept   Participant) + (nTrials   Participant) + (RecRegion   Participant) + (StimRegion   Participant)
	Estimate	SE	tStat	DF	pValue	Lower Upper	
(Intercept)	2.02	0.28	7.14	4475	1.1E-12	1.46 2.57	
State	-0.34	0.01	-24.68	4475	3.6E-126	-0.37 -0.31	
nTrials	0.00	0.01	-0.11	4475	0.92	-0.03 0.03	
RecRegion	0.00	0.04	0.11	4475	0.91	-0.07 0.08	
StimRegion	-0.01	0.03	-0.24	4475	0.81	-0.07 0.06	

Amplitude (permutation tests)																								
Region	Anesthesia vs. Awake (in the OR)						Sleep vs. Awake (in the EMU)						Awake (in the OR) vs. Awake (in the EMU)											
	pVal	Anesthesia			Awake			r	pVal	Sleep			Awake			r	pVal	Awake (OR)			Awake (EMU)			r
		median	(25 -75)	median	(25 -75)	median	(25 -75)			median	(25 -75)	median	(25 -75)	median	(25 -75)			median	(25 -75)	median	(25 -75)	median	(25 -75)	
all	0.0001	1.7	1.2	3.0	5.5	3.6	8.9	573	0.0001	3.8	2.4	6.3	6.0	4.1	10.2	1527	0.0005	5.1	3.3	8.5	5.8	3.9	9.7	642
prefrontal	0.0001	1.6	1.3	2.5	5.4	3.5	8.4	253	0.0001	3.6	2.2	6.0	5.8	4.0	10.0	516	0.41	5.0	3.3	7.8	5.1	3.8	8.4	227
posterior	0.0001	2.7	1.5	4.4	6.5	4.0	9.8	123	0.0001	4.5	3.0	6.4	6.2	4.1	10.4	278	0.13	5.9	3.7	9.5	6.3	4.0	10.4	151
temporal	0.0001	1.2	0.8	3.4	5.1	3.2	8.8	69	0.0001	4.1	2.6	7.0	6.4	4.2	11.9	463	0.0006	5.1	3.3	9.3	7.2	4.3	13.6	128

Fixed effects	Variability (LMM)						y (Variability) ~ Intercept + State+ nTrials + RecRegion + StimRegion + (Intercept   Participant) + (nTrials   Participant) + (RecRegion   Participant) + (StimRegion   Participant)
	Estimate	SE	tStat	DF	pValue	Lower Upper	
(Intercept)	2.97	0.25	11.78	4475	1.5E-31	2.48 3.46	
State	0.18	0.02	11.70	4475	3.8E-31	0.15 0.21	
nTrials	0.01	0.01	0.93	4475	0.35	-0.01 0.04	
RecRegion	0.07	0.04	1.71	4475	0.09	-0.01 0.14	
StimRegion	0.01	0.04	0.30	4475	0.76	-0.06 0.09	

Variability (log(SD); permutation tests)																								
Region	Anesthesia vs. Awake (in the OR)						Sleep vs. Awake (in the EMU)						Awake (in the OR) vs. Awake (in the EMU)											
	pVal	Anesthesia			Awake			r	pVal	Sleep			Awake			r	pVal	Awake (OR)			Awake (EMU)			r
		median	(25 -75)	median	(25 -75)	median	(25 -75)			median	(25 -75)	median	(25 -75)	median	(25 -75)			median	(25 -75)	median	(25 -75)	median	(25 -75)	
all	0.0001	1.7	1.4	2.0	1.4	1.4	1.6	573	0.0001	1.7	1.5	1.9	1.4	1.5	1.7	1527	0.05	1.4	1.2	1.6	1.4	1.2	1.6	642
prefrontal	0.0001	1.8	1.6	2.1	1.4	1.6	1.7	253	0.0001	1.7	1.5	1.9	1.5	1.5	1.7	516	0.03	1.5	1.2	1.6	1.5	1.2	1.7	227
posterior	0.008	1.4	1.2	1.7	1.4	1.2	1.6	123	0.0001	1.6	1.4	1.8	1.4	1.4	1.6	278	0.60	1.4	1.2	1.6	1.4	1.2	1.6	151
temporal	0.003	1.7	1.4	1.8	1.5	1.4	1.7	69	0.0001	1.7	1.5	1.9	1.5	1.5	1.7	463	0.12	1.5	1.3	1.6	1.4	1.3	1.6	128

Linear mixed model (LMM) with Amplitude/Variability as the dependent variable followed by permutation test for comparisons between states. **Top:** Amplitude was computed as the maximum minus the minimum amplitude in the response period (600ms following stimulation). There are no units as it was z-scored normalized to baseline. **Bottom:** Inter-trial variability was estimated as the standard deviation (SD) across individual trials during the CCEP interval (5-600ms following stimulation). A logarithmic (base 10) was used for the statistical comparisons to produce a more normal distribution. Recording channels with detected CCEP response in any of the four states were included. For LMM, as indicated in equation: fixed effects were *State* (awake in the EMU, awake in the OR, asleep, under anesthesia); *nTrials*: average number of trials; *RecRegion*: region of the recording channel; *StimRegion*: region where stimulation was delivered. Random effect variable was *Participant*: participant's number. Possible regions for the LMM model were prefrontal, posterior, temporal, or other. *DF*: degrees of freedom; *Lower* and *Upper* corresponded to the 95% confidence interval. For permutation tests, because 10,000 combinations were used, the p-value is capped at 0.0001, but could correspond to a lower number. Green highlights p<0.01; yellow highlights 0.01<p<0.05. *EMU*: epilepsy monitoring unit; *OR*: operating room; *r*: number of recording channels in the region (with stimulation anywhere and response detected in any state). *s*: number of stimulation channels; *N*: number of participants.

**Table S4: Relative complexity and connectivity measures, comparison of Sleep vs. Anesthesia, related to Figures 3 and 5.**

		Relative Perturbational Complexity - Relative Sleep vs. Anesthesia - unpaired								
		Sleep / Awake in the EMU				Anesthesia/ Awake in theOR				
Region	pVal	median	(25	- 75)	s	median	(25	- 75)	s	Sleep > Anest?
all	0.001	-0.24	-0.32	-0.14	99	-0.37	-0.49	-0.26	36	TRUE
prefrontal	0.02	-0.25	-0.36	-0.13	30	-0.42	-0.50	-0.28	13	TRUE
posterior	0.52	-0.21	-0.29	-0.19	20	-0.19	-0.26	-0.14	9	
temporal	0.26	-0.25	-0.30	-0.12	31	-0.38	-0.52	-0.17	4	
		Relative CCEP connectivity - Relative Sleep vs. Anesthesia - unpaired								
		Sleep / Awake in the EMU				Anesthesia/ Awake in theOR				
Region	pVal	median	(25	- 75)	s	median	(25	- 75)	s	Sleep > Anest?
all	0.000	-0.18	-0.39	0.00	99	-0.74	-0.85	-0.45	36	TRUE
prefrontal	0.00	-0.22	-0.47	-0.07	30	-0.80	-0.84	-0.66	13	TRUE
posterior	0.00	-0.08	-0.25	-0.01	20	-0.56	-0.69	-0.37	9	TRUE
temporal	0.31	-0.20	-0.27	0.00	31	-0.30	-0.71	-0.16	4	
GM	4.3E-08	-0.20	-0.43	-0.03	69	-0.77	-0.96	-0.53	23	TRUE
WM	0.0001	-0.05	-0.25	0.09	30	-0.56	-0.81	-0.32	13	TRUE
		Relative Outdegree - Relative Sleep vs. Anesthesia - unpaired								
		Sleep / Awake in the EMU				Anesthesia/ Awake in theOR				
Region	pVal	median	(25	- 75)	r Sleep	median	(25	- 75)	r Anesthesia	Sleep > Anest?
all	2.8E-50	0	-1	0	860	-1	-1	-1	562	TRUE
prefrontal	5.4E-22	-0.33	-1	0	282	-1	-1	-1	250	TRUE
posterior	1.1E-10	0	-0.33	0	151	-1	-1	0	107	TRUE
temporal	6.7E-08	0	-1	0	292	-1	-1	0	92	TRUE
PFC subregions:										
dIPFC	2.2E-06	-0.33	-1	0	72	-1	-1	-1	93	TRUE
vlPFC	8.9E-05	-0.2	-1	0	69	-1	-1	-1	44	TRUE
dmPFC	7.0E-08	0	-0.53	0	64	-1	-1	-1	56	TRUE
OF	5.3E-07	-0.33	-1	0	77	-1	-1	-1	57	TRUE
ACC	0.005	-1	-1	0	39	-1	-1	-1	41	TRUE

Comparisons of relative complexity and connectivity for sleep vs. anesthesia, normalized to awake in that environment (unpaired U-Mann test). **Top:** Relative Perturbational Complexity. **Middle:** Relative CCEP indegree connectivity, including subdivision in WM and GM. **Bottom:** Relative outdegree connectivity, including PFC subregions and ACC. The last column indicates if the median of the relative measure is larger for sleep than for anesthesia in significantly different comparisons. *EMU:* epilepsy monitoring unit; *OR:* operating room; *s:* number of stimulation channels; *r:* number of recording channels; *PFC:* prefrontal cortex; *dIPFC:* dorsolateral PFC; *vlPFC:* ventrolateral PFC; *dmPFC:* dorsomedial PFC; *OF:* orbitofrontal; *ACC:* anterior cingulate; *WM:* white matter; *GM:* gray matter. Green highlights  $p < 0.01$ , yellow highlights  $0.01 < p < 0.05$ . Grey indicates only a few (<5) stimulated channels in that region.

**Table S5: Linear mixed model (LMM) with relative CCEP features and Variability as dependent variables followed by permutation test for Sleep vs. Anesthesia, related to Figures 3, 5, and 6.**

Relative Amplitude										
y (Relative Amplitude) ~ Intercept + State + nTrials + RecRegion + StimRegion + (Intercept   Participant) + (nTrials   Participant) + (RecRegion   Participant) + (StimRegion   Participant)					Sleep vs. Anesthesia - unpaired (permutation tests)					
					Sleep / Awake EMU			Anesthesia / Awake OR		
Region	pVal	median	(25 - 75)	r EMU	median	(25 - 75)	r OR	OR	Sleep > Anest?	
all	0.0001	-0.26	-0.43 -0.07	1527	-0.49	-0.63 -0.32	573		TRUE	
prefrontal	0.0001	-0.29	-0.45 -0.11	516	-0.51	-0.62 -0.36	253		TRUE	
posterior	0.0001	-0.22	-0.34 -0.06	278	-0.41	-0.57 -0.21	123		TRUE	
temporal	0.0001	-0.27	-0.44 -0.04	463	-0.51	-0.71 -0.32	69		TRUE	
<b>PFC sub-regions:</b>										
dIPFC	0.0001	-0.32	-0.50 -0.13	117	-0.55	-0.69 -0.34	100		TRUE	
vlPFC	0.0001	-0.30	-0.45 -0.10	119	-0.49	-0.54 -0.40	37		TRUE	
dmPFC	0.0001	-0.18	-0.37 -0.05	126	-0.52	-0.62 -0.37	59		TRUE	
OF	0.0001	-0.34	-0.46 -0.16	154	-0.46	-0.60 -0.35	57		TRUE	
ACC	0.0010	-0.37	-0.51 -0.13	82	-0.51	-0.67 -0.30	58		TRUE	
<b>Fixed effects</b>										
(Intercept)	Estimate	SE	tStat	DF	pValue	Lower	Upper			
(Intercept)	-0.17	0.04	-4.64	2095	3.6E-06	-0.24	-0.10			
State: Sleep vs. Anesthesia	-0.35	0.02	-14.04	2095	7.4E-43	-0.40	-0.30			
nTrials	0.00	0.01	-0.92	2095	0.36	-0.01	0.01			
Recording Region	0.01	0.01	0.88	2095	0.38	-0.01	0.03			
Stimulation Region	-0.01	0.02	-0.34	2095	0.73	-0.04	0.03			

Relative peak-to-peak amplitude of the detected CCEP										
y (Relative peak-to-peak CCEP) ~ Intercept + State + nTrials + RecRegion + StimRegion + (Intercept   Participant) + (nTrials   Participant) + (RecRegion   Participant) + (StimRegion   Participant)					Sleep vs. Anesthesia - unpaired (permutation tests)					
					Sleep / Awake EMU			Anesthesia / Awake OR		
Region	pVal	median	(25 - 75)	r EMU	median	(25 - 75)	r OR	OR	Sleep > Anest?	
all	0.0002	-0.21	-0.37 -0.04	732	-0.34	-0.50 -0.14	84		TRUE	
prefrontal	0.0001	-0.22	-0.37 -0.09	210	-0.48	-0.60 -0.36	27		TRUE	
posterior	0.3228	-0.21	-0.34 -0.10	165	-0.26	-0.41 -0.10	31			
temporal	0.3840	-0.22	-0.41 -0.01	254	-0.24	-0.33 0.04	16			
<b>PFC sub-regions:</b>										
dIPFC	0.0471	-0.26	-0.40 -0.05	41	-0.42	-0.59 -0.24	14		TRUE	
vlPFC	0.0183	-0.23	-0.41 -0.09	51	-0.60	-0.62 -0.49	3		TRUE	
dmPFC	0.0002	-0.16	-0.27 -0.03	64	-0.51	-0.70 -0.37	6		TRUE	
OF	0.0116	-0.24	-0.36 -0.14	54	-0.53	-0.68 -0.31	4		TRUE	
ACC	0.0308	-0.21	-0.38 -0.03	12	-0.51	-0.67 -0.34	4		TRUE	
<b>Fixed effects</b>										
(Intercept)	Estimate	SE	tStat	DF	pValue	Lower	Upper			
(Intercept)	-0.20	0.03	-6.41	811	2.5E-10	-0.26	-0.14			
State: Sleep vs. Anesthesia	-0.19	0.04	-5.24	811	2.0E-07	-0.26	-0.12			
nTrials	0.00	0.00	0.70	811	0.49	0.00	0.01			
Recording Region	-0.01	0.02	-0.31	811	0.76	-0.04	0.03			
Stimulation Region	0.01	0.01	0.83	811	0.41	-0.01	0.04			

Relative latency of the first peak of the detected CCEP									
y (Relative latency 1st peak) ~ Intercept + State + nTrials + RecRegion + StimRegion + (Intercept   Participant) + (nTrials   Participant) + (RecRegion   Participant) + (StimRegion   Participant)									
<b>Fixed effects</b>									
(Intercept)	Estimate	SE	tStat	DF	pValue	Lower	Upper		
(Intercept)	0.09	0.02	4.99	811	7.4E-07	0.05	0.12		
State: Sleep vs. Anesthesia	0.03	0.03	0.92	811	0.36	-0.03	0.08		
nTrials	0.00	0.00	0.82	811	0.41	0.00	0.01		
Recording Region	0.01	0.01	0.45	811	0.65	-0.02	0.03		
Stimulation Region	-0.03	0.01	-2.55	811	0.01	-0.06	-0.01		

Relative Variability										
y (Relative Variability) ~ Intercept + State + nTrials + RecRegion + StimRegion + (Intercept   Participant) + (nTrials   Participant) + (RecRegion   Participant) + (StimRegion   Participant)					Sleep vs. Anesthesia - unpaired (permutation tests)					
					Sleep / Awake EMU			Anesthesia / Awake OR		
Region	pVal	median	(25 - 75)	r EMU	median	(25 - 75)	r OR	OR	Sleep > Anest?	
all	0.0001	0.26	0.14 0.38	1527	0.38	0.14 0.53	573		FALSE	
prefrontal	0.0001	0.29	0.18 0.39	516	0.45	0.32 0.57	253		FALSE	
posterior	0.0003	0.21	0.10 0.33	278	0.11	-0.03 0.24	123		TRUE	
temporal	0.0234	0.24	0.08 0.37	463	0.15	0.02 0.31	69		TRUE	
<b>PFC sub-regions:</b>										
dIPFC	0.0001	0.29	0.20 0.40	117	0.45	0.31 0.54	100		FALSE	
vlPFC	0.0001	0.28	0.19 0.38	119	0.41	0.33 0.56	37		FALSE	
dmPFC	0.0001	0.25	0.15 0.35	126	0.43	0.24 0.58	59		FALSE	
OF	0.0001	0.32	0.19 0.40	154	0.47	0.58	57		FALSE	
ACC	0.0001	0.29	0.21 0.40	82	0.56	0.48 0.63	58		FALSE	
<b>Fixed effects</b>										
(Intercept)	Estimate	SE	tStat	DF	pValue	Lower	Upper			
(Intercept)	0.28	0.03	8.26	2095	2.6E-16	0.21	0.34			
State: Sleep vs. Anesthesia	0.14	0.02	7.67	2095	2.6E-14	0.10	0.17			
nTrials	0.00	0.01	-0.75	2095	0.45	-0.02	0.01			
Recording Region	-0.04	0.01	-4.33	2095	1.6E-05	-0.06	-0.02			
Stimulation Region	-0.01	0.01	-1.21	2095	0.23	-0.03	0.01			

Relative measures were calculated by normalizing by awake in that environment and are bounded between -1 and +1. From **Top to Bottom**: i) Relative **amplitude** was computed in each recording channel with response in any state as the maximum minus minimum amplitude following stimulation. ii) Relative **peak-to-peak amplitude** of the detected CCEP response to stimulation was computed from the peaks of detected CCEP responses. iii) Relative **latency** of the first peak of the detected CCEP response to stimulation was estimated from the peaks of detected CCEP responses. The LMM showed that the latency of the first peak of detected CCEPs did not depend on the state of unconsciousness, thus permutation tests were not performed. iv) **Relative Inter-trial Variability** was estimated in each recording channel with response in any state as the standard deviation during the CCEP interval. For LMM: fixed effects were *State*: sleep (normalized by awake in the EMU) vs. anesthesia (normalized by awake in the OR); *nTrials*: average number of trials; *RecRegion*: recording channel's region; *StimRegion*: region where stimulation was delivered; random effect variable was *Participant*; possible regions were prefrontal, posterior, temporal, or other; Lower/Upper: 95% confidence interval. Permutation tests for all channels and subregions of recorded channels, including PFC subregions and ACC. Last column indicates if median of the relative measure is larger for sleep than anesthesia in significantly different comparisons. Because 10,000 combinations were used, the p-value is capped at 0.0001, but could have corresponded to a lower number. *EMU*: epilepsy monitoring unit; *OR*: operating room; *DF*: degrees of freedom; *r*: recording channels in the region (with stimulation anywhere); PFC: prefrontal cortex; *dIPFC*: dorsolateral PFC; *vlPFC*: ventrolateral PFC; *dmPFC*: dorsomedial PFC; *OF*: orbitofrontal; *ACC* anterior cingulate. Green highlights p<0.01, yellow highlights 0.01<p<0.05.

**Table S6: Comparison of Relative measures for prefrontal vs. posterior vs. temporal regions, related to Figure 5.**

			Relative Perturbational Complexity					Relative CCEP indegree connectivity						
Relative States	Region1	Region2	pVal	median	median	s	s	Region1 < Region2?	pVal	median	median	s	s	Region1 < Region2?
				Region 1	Region 2	Region1	Region2		Region 1	Region 2	Region1	Region2		
<b>Anesthesia</b>	prefrontal	posterior	0.008	-0.42	-0.19	13	9	TRUE	0.025	-0.80	-0.56	13	9	TRUE
	prefrontal	temporal	0.78	-0.42	-0.38	13	4		0.14	-0.80	-0.30	13	4	
	posterior	temporal	0.26	-0.19	-0.38	9	4		0.39	-0.56	-0.30	9	4	
<b>Sleep</b>	prefrontal	posterior	0.40	-0.25	-0.21	30	20		0.07	-0.22	-0.08	30	20	
	prefrontal	temporal	0.52	-0.25	-0.25	30	31		0.43	-0.22	-0.20	30	31	
	posterior	temporal	0.75	-0.21	-0.25	20	31		0.29	-0.08	-0.20	20	31	
<b>Awake OR / EMU</b>	prefrontal	posterior	0.31	0.00	-0.01	11	10		0.67	0.00	0.06	11	10	
	prefrontal	temporal	0.91	0.00	0.03	11	5		0.53	0.00	-0.09	11	5	
	posterior	temporal	0.31	-0.01	0.03	10	5		0.22	0.06	-0.09	10	5	

			Relative Outdegree					Relative Amplitude						
Relative States	Region1	Region2	pVal	median	median	r	r	Region1 < Region2?	pVal	median	median	r	r	Region1 < Region2?
				Region 1	Region 2	Region1	Region2		Region 1	Region 2	Region1	Region2		
<b>Anesthesia</b>	prefrontal	posterior	0.0002	-1	-1	250	107	TRUE	0.0002	-0.51	-0.41	253	123	TRUE
	prefrontal	temporal	0.02	-1	-1	250	92	TRUE	0.59	-0.51	-0.51	253	69	
	posterior	temporal	0.50	-1	-1	107	92		0.04	-0.41	-0.51	123	69	FALSE
<b>Sleep</b>	prefrontal	posterior	0.0003	-0.33	0	282	151	TRUE	0.0003	-0.29	-0.22	516	278	TRUE
	prefrontal	temporal	0.020	-0.33	0	282	292	TRUE	0.034	-0.29	-0.27	516	463	TRUE
	posterior	temporal	0.05	0	0	151	292		0.16	-0.22	-0.27	278	463	
<b>Awake OR / EMU</b>	prefrontal	posterior	0.33	0	0	235	130		0.79	-0.03	-0.07	227	151	
	prefrontal	temporal	0.33	0	0	235	160		0.0001	-0.03	-0.18	227	128	FALSE
	posterior	temporal	0.04	0	0	130	160	FALSE	0.0002	-0.07	-0.18	151	128	FALSE

			Relative peak-to-peak Resp. Amplitude					Relative Variability						
Relative States	Region1	Region2	pVal	median	median	r	r	Region1 < Region2?	pVal	median	median	r	r	Region1 < Region2?
				Region 1	Region 2	Region1	Region2		Region 1	Region 2	Region1	Region2		
<b>Anesthesia</b>	prefrontal	posterior	0.0003	-0.48	-0.26	27	31	TRUE	0.0001	0.45	0.11	253	123	FALSE
	prefrontal	temporal	0.0002	-0.48	-0.24	27	16	TRUE	0.0001	0.45	0.15	253	69	FALSE
	posterior	temporal	0.15	-0.26	-0.24	31	16		0.17	0.11	0.15	123	69	
<b>Sleep</b>	prefrontal	posterior	0.59	-0.22	-0.21	210	165		0.0001	0.29	0.21	516	278	FALSE
	prefrontal	temporal	0.48	-0.22	-0.22	210	254		0.0001	0.29	0.24	516	463	FALSE
	posterior	temporal	0.84	-0.21	-0.22	165	254		0.21	0.21	0.24	278	463	
<b>Awake OR / EMU</b>	prefrontal	posterior	0.18	0.01	-0.07	110	93		0.006	-0.07	0.01	227	151	TRUE
	prefrontal	temporal	1.0E-04	0.01	-0.19	110	85	FALSE	0.0001	-0.07	0.04	227	128	TRUE
	posterior	temporal	1.0E-04	-0.07	-0.19	93	85	FALSE	0.0004	0.01	0.04	151	128	TRUE

**Top:** Relative Perturbational Complexity (left) and CCEP indegree connectivity (right). **Middle:** Relative outdegree connectivity (left) and Amplitude (right). **Bottom:** Relative peak-to-peak amplitude of the detected CCEPs (left) and inter-trial variability (right). Anesthesia / Awake: The relative measure during anesthesia was normalized by that measure during awake in the OR; Sleep / Awake: The relative measure during sleep was normalized by that measure during awake in the EMU; Awake OR / EMU: The relative measure during awake in the OR was normalized by that measure during awake in the EMU. For complexity, indegree, and outdegree unpaired U-Mann test was used. Relative measures are bounded between -1 and +1. For amplitude, peak-to-peak of CCEPs, and variability, a permutation test was used. Rightmost columns compared median values only for significantly different regions. The relative complexity, indegree connectivity, and peak-to-peak amplitude of the responses were significantly smaller (more negative) for the prefrontal than posterior regions during anesthesia; no significant differences between regions were found during sleep. The relative outdegree, amplitude in channels responsive in any state, and variability were significantly smaller (more negative) in the prefrontal than posterior regions during anesthesia and during sleep. Note, however, the smaller median values for anesthesia than for sleep. The relative variability was larger for the prefrontal than other regions for anesthesia and during sleep. Note, however, the larger median values for anesthesia than for sleep. For amplitude, peak-to-peak amplitude, and variability there was also a significant difference during sleep and awake, for temporal against the other regions. OR: operating room; EMU: epilepsy monitoring unit. Green highlights  $p < 0.01$ , yellow highlights  $0.01 < p < 0.05$ .