

## Cortical functional connectivity indexes arousal state during sleep and anesthesia

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1    **Abstract**

2    Disruption of cortical connectivity likely contributes to loss of consciousness (LOC) during both  
3    sleep and general anesthesia, but the degree of overlap in the underlying mechanisms is  
4    unclear. Both sleep and anesthesia comprise states of varying levels of arousal and  
5    consciousness, including states of largely maintained consciousness (sleep: N1, REM;  
6    anesthesia: sedated but responsive) as well as states of substantially reduced consciousness  
7    (sleep: N2/N3; anesthesia: unresponsive). Here, we tested the hypotheses that (1) cortical  
8    connectivity will reflect clear changes when transitioning into states of reduced consciousness,  
9    and (2) these changes are similar for arousal states of comparable levels of consciousness  
10   during sleep and anesthesia. Using intracranial recordings from five neurosurgical patients, we  
11   compared resting state cortical functional connectivity (as measured by weighted phase lag  
12   index) in the same subjects across arousal states during natural sleep [wake (WS), N1, N2, N3,  
13   REM] and propofol anesthesia [pre-drug wake (WA), sedated/responsive (S) and unresponsive  
14   (U)]. In wake states WS and WA, alpha-band connectivity within and between temporal,  
15   parietal and occipital regions was dominant. This pattern was largely unchanged in N1, REM  
16   and S. Transitions into states of reduced consciousness N2, N3 and U were characterized by  
17   dramatic and strikingly similar changes in connectivity, with dominant connections shifting to  
18   frontal cortex. We suggest that shifts from temporo-parieto-occipital to frontal cortical  
19   connectivity may reflect impaired sensory processing in states of reduced consciousness. The  
20   data indicate that functional connectivity can serve as a biomarker of arousal state and suggest  
21   common mechanisms of LOC in sleep and anesthesia.

22 **1. Introduction**

23 Elucidating the changes in the brain that occur upon loss and recovery of consciousness (LOC,  
24 ROC) is critical to our understanding of the neural basis of consciousness, and is a prerequisite  
25 for improving diagnosis and prognosis of disorders of consciousness and noninvasive  
26 monitoring of awareness in clinical settings (Bayne et al., 2017; Bernat, 2017; Stein and Glick,  
27 2016). A primary hurdle is identifying changes that are specific to LOC and ROC, as opposed to  
28 nonspecific changes in brain activity in response to endogenous or exogenous factors (e.g.  
29 neuromodulators during sleep or anesthetic agents). This can be clarified by investigating  
30 common features of LOC and ROC during sleep and anesthesia (Mashour, 2006; Shushruth,  
31 2013; Tung and Mendelson, 2004). A handful of studies have compared the changes in neural  
32 activity that occur during transitions between arousal states during sleep versus anesthesia in  
33 human subjects (Li et al., 2018; Murphy et al., 2011), but commonalities in neural mechanisms  
34 have been elusive, perhaps because sleep and anesthesia data in these studies were obtained  
35 in different subjects, or because of the metrics investigated, or both. Here, we compare  
36 changes in functional connectivity in the same subjects during sleep and propofol anesthesia.

37 Although endogenous sleep and arousal centers play a role in LOC/ROC under both  
38 sleep and anesthesia (Lydic and Baghdoyan, 2005), changes in the contents of consciousness  
39 are likely secondary to actions in neocortex (Voss et al., 2019), which is the focus of the current  
40 study. Common mechanisms for LOC/ROC under sleep and anesthesia are suggested by similar  
41 effects of LOC on sensory cortex observed under both conditions. For example, primary sensory  
42 cortex is still responsive to environmental stimuli, and basic organizational features such as  
43 frequency tuning in auditory cortex are preserved (Nir et al., 2015; Raz et al., 2014), while  
44 responses in higher order cortical sensory areas are largely suppressed (Liu et al., 2012; Wilf et  
45 al., 2016). In addition, cortical connectivity, which is central to leading theories of consciousness  
46 (Dehaene and Changeux, 2011; Friston, 2005; Tononi et al., 2016), is altered upon LOC during  
47 anesthesia (Boly et al., 2012a; Lee et al., 2017; Lee et al., 2013b; Murphy et al., 2011; Ranft et  
48 al., 2016; Sanders et al., 2018) and non-rapid eye movement (NREM) sleep (Boly et al., 2012b;  
49 Spoormaker et al., 2010).

50        These studies suggest that LOC under a variety of conditions converges on specific  
51    changes in cortical connectivity. However, a major impediment to identifying these changes is a  
52    lack of consensus on key details, for example whether overall or long-range connectivity  
53    decreases (Boly et al., 2012a; Lee et al., 2013b; Ranft et al., 2016; Spoormaker et al., 2010) or  
54    increases (Boly et al., 2012b; Lee et al., 2017; Monti et al., 2013; Murphy et al., 2011) upon LOC.  
55    Moreover, despite the evidence for common mechanisms of LOC under anesthesia and during  
56    NREM sleep, there are obvious differences between sleep and anesthesia as well (Akeju and  
57    Brown, 2017). Specifically, subjects are arousable from the latter but not from the former, and  
58    this maintained connectedness with the environment likely involves cortical activation. The  
59    structure of natural sleep, in its transitions between REM and multiple stages of NREM sleep, is  
60    not mimicked by steady-state anesthesia. A recent imaging study found substantial differences  
61    in the changes in functional magnetic resonance imaging (fMRI) functional connectivity that  
62    occur during sleep and propofol anesthesia (Li et al., 2018). Furthermore, delta-band activity  
63    during the deepest stages of NREM sleep (N3) most closely resembles brain activity under  
64    anesthesia (Murphy et al., 2011), but unresponsiveness (and presumably reduced level of  
65    consciousness) occurs as well in stage 2 NREM (N2) sleep (Strauss et al., 2015). Direct  
66    comparisons of changes in connectivity associated with LOC under natural sleep and anesthesia  
67    may help resolve these discrepancies.

68        Here, we investigated changes in cortical functional connectivity across arousal states  
69    under natural sleep and anesthesia. Intracranial recordings obtained from neurosurgical  
70    patients with pharmacologically resistant epilepsy allowed us to compare connectivity using  
71    data obtained from the same recording sites in the same subjects.

72 **2. Materials and Methods**

73 ***2.1. Subjects***

74 Experiments were carried out in five neurosurgical patients diagnosed with medically refractory  
75 epilepsy who were undergoing chronic invasive electrophysiological monitoring to identify  
76 seizure foci prior to resection surgery (Supplementary Table 1). Research protocols were  
77 approved by the University of Iowa Institutional Review Board and the National Institutes of  
78 Health, and written informed consent was obtained from all subjects. Research participation  
79 did not interfere with acquisition of clinically necessary data, and subjects could rescind  
80 consent for research without interrupting their clinical management. Subjects were right-  
81 handed, left language-dominant native English speakers. All subjects underwent standard  
82 neuropsychological assessment prior to electrode implantation, and none had cognitive deficits  
83 that would impact the results of this study. The subjects were tapered off their antiepileptic  
84 medication during chronic monitoring when overnight sleep data were collected (see below).  
85 All subjects had their medication regimens reinstated at the end of the monitoring period, prior  
86 to induction of general anesthesia for the resection surgery.

87

88 ***2.2. Experimental procedures***

89 Electrocorticographic (ECOG) recordings were made using subdural and depth electrodes (Ad-  
90 Tech Medical, Racine, WI). Subdural arrays consisted of platinum-iridium discs (2.3 mm  
91 diameter, 5-10 mm inter-electrode distance), embedded in a silicon membrane. Depth arrays  
92 (8-12 electrodes, 5 mm inter-electrode distance) were stereotactically implanted along the  
93 anterolateral-to-posteromedial axis of Heschl's gyrus (HG). Additional arrays targeted insular  
94 cortex and provided coverage of planum temporale and planum polare. This allowed for  
95 bracketing suspected epileptogenic zones from dorsal, ventral, medial and lateral aspects  
96 (Nagahama et al., 2018; Reddy et al., 2010; Supplementary Fig. 1). Depth electrodes also  
97 targeted amygdala and hippocampus, and provided additional coverage of the superior  
98 temporal sulcus. A subgaleal electrode was used as a reference. All electrodes were placed  
99 solely on the basis of clinical requirements, as determined by the team of epileptologists and  
100 neurosurgeons (Nourski and Howard, 2015).

101 Two sets of no-task, resting-state (RS) data were recorded: overnight sleep data and  
102 anesthesia data. RS ECoG, EEG and video data were collected from subjects during natural  
103 overnight sleep (Supplementary Fig. 2a). Sleep data were collected in the dedicated, electrically  
104 shielded suite in The University of Iowa Clinical Research Unit while the subjects lay in the  
105 hospital bed. Data were recorded using a Neuralynx Atlas System (Neuralynx Inc., Bozeman,  
106 MT), amplified, filtered (0.1–4000 Hz bandpass, 12 dB/octave rolloff), sampled at 16 kHz. Stages  
107 of sleep were defined manually using facial EMG and scalp EEG data based on standard clinical  
108 criteria (2017) by board-certified physicians who participate in the inter-scorer reliability  
109 program of the AASM. Scalp and facial electrodes were placed by an accredited technician, and  
110 data were recorded by a clinical acquisition system (Nihon Kohden EEG-2100) in parallel with  
111 research acquisition. Facial electrodes were placed following guidelines of the AASM<sup>90</sup> at the  
112 left and right mentalis for EMG and adjacent to left and right outer canthi for EOG. EEG was  
113 obtained from electrodes placed following the international 10-20 system at A1, A2, F3, F3, F4,  
114 O1 and O2 in all subjects, with the following additional electrodes: C3 and C4 in all subjects but  
115 R376; E1 and E2 in L372 and R376; CZ and FZ in L409 and L423; and F8 in L423. All subjects had  
116 periods of REM, N1 and N2 sleep identified; three out of five subjects had N3 sleep periods as  
117 well. One subject (L403) experienced multiple seizures in the second half of the night; those  
118 data were excluded from analysis.

119 Anesthesia RS data were collected in the operating room prior to electrode removal and  
120 seizure focus resection surgery. Data were recorded using a TDT RZ2 processor (Tucker-Davis  
121 Technologies, Alachua, FL), amplified, filtered (0.7–800 Hz bandpass, 12 dB/octave rolloff), and  
122 digitized at a sampling rate of 2034.5 Hz. We note that the highpass cutoff frequency on this  
123 hardware precluded analysis of frequencies below 1 Hz. Although no specific instructions were  
124 given about keeping eyes open or closed, subjects were observed to have eyes closed during  
125 nearly all resting state recordings. Data were recorded in 6-minute blocks, interleaved with an  
126 auditory stimulus paradigm as part of a separate study (Nourski et al., 2018a, b). Data were  
127 collected during an awake baseline period and during induction of general anesthesia with  
128 incrementally titrated propofol infusion (50 – 150 µg/kg/min; Supplementary Fig. 2b).

129 Awareness was assessed using the Observer's Assessment of Alertness/Sedation  
130 (OAA/S) scale (Chernik et al., 1990), and using the bispectral index [BIS (Gan et al., 1997)] (BIS  
131 Complete 4-Channel Monitor; Medtronic) recorded continuously throughout the experiment.  
132 OAA/S was assessed just before and just after collection of each RS data block. Two levels of  
133 anesthesia (arousal states) were targeted: sedated but responsive to command (S; OAA/S  $\geq 3$ )  
134 and unresponsive (U; OAA/S  $\leq 2$ ) (Nourski et al., 2018a). In four of five subjects, OAA/S values  
135 crossed the boundary between S and U over the course of the 6-minute RS block (e.g. RS block  
136 #1 in subject L372; see Supplementary Fig. 2b). In these cases, only the first and last 60-second  
137 segments of the block were analyzed; data from the first segment were assigned to the S state,  
138 and data from the second segment were assigned to the U state.

139

140 **2.3. Data analysis**

141 *2.3.1. Band power analysis*

142 Data were assigned to specific arousal states based on sleep scoring and OAA/S assessment. For  
143 each subject, sleep and anesthesia data were divided into segments of length 60 seconds for all  
144 analyses except the classification analysis (Fig. 5; see below), for which 10-second segments  
145 were used. Time-frequency analysis was performed using the demodulated band transform  
146 (DBT; Kovach and Gander, 2016), which optimizes frequency resolution for each frequency  
147 band specified, while minimizing spectral leakage across bands. PSDs were estimated for each  
148 data segment from the squared magnitude of the DBT. For each subject, PSDs were averaged  
149 across segments assigned to identical arousal states. ECoG band power was calculated as the  
150 average power across frequency in each band. Band power within ROI group was computed as  
151 the average across all recording sites in that ROI group, and arousal state-dependent changes in  
152 band power were evaluated using linear mixed effects models as follows. The data were  
153 normalized to total power and log transformed, then fit with a model incorporating fixed  
154 effects of state, ROI, and the interaction of state and ROI, and random effects for channels  
155 nested within subjects and with random slopes for brain state by subject, using the R package  
156 *lme4* (Bates et al., 2015). Estimated marginal means and 95% CIs for each ROI and state were  
157 calculated, as well as pairwise between-states contrasts within each ROI with *p*-values adjusted

158 by multivariate *t* for all comparisons within a band, using the R package emmeans (Lenth,  
159 2019).

160

161 *2.3.2. Connectivity analysis*

162 Connectivity was measured using the debiased weighted phase lag index (wPLI) (Vinck et al.,  
163 2011), a non-directed measure of phase synchronization that eschews synchronization near  
164 zero phase lag to avoid artifacts due to volume conduction. For each data segment, wPLI was  
165 estimated for every electrode pair from the sign of the imaginary part of the DBT-derived cross-  
166 spectrum at each frequency and averaged across frequencies within each band of interest  
167 (delta: 1-4 Hz, theta: 4-8 Hz, alpha: 8-13 Hz, beta: 13-30 Hz, gamma: 30-70 Hz; high gamma: 70-  
168 120 Hz). As the analysis results tended to be correlated in the frequency domain, we chose to  
169 present only the results for the delta, alpha and gamma band. Alpha-band wPLI in particular is a  
170 commonly used measure of functional connectivity (Blain-Moraes et al., 2014; Blain-Moraes et  
171 al., 2015; Lee et al., 2013a; Lee et al., 2017; van Dellen et al., 2014). In addition, we observed  
172 evidence for alpha-band oscillatory components in the resting state power spectra, further  
173 motivating focus on this band. Therefore, our primary measure of functional connectivity was  
174 alpha-band wPLI, but connectivity in delta and gamma bands is presented as well for  
175 comparison.

176

177 *2.3.3. Anatomical reconstruction and ROI parcellation*

178 Electrode localization relied on post-implantation T1-weighted structural MR images and post-  
179 implantation CT images. All images were initially aligned with pre-operative T1 images using  
180 linear coregistration implemented in FSL (FLIRT) (Jenkinson et al., 2002). Electrodes were  
181 identified in the post-implantation MRI as magnetic susceptibility artifacts and in the CT as  
182 metallic hyperdensities. Electrode locations were further refined within the space of the pre-  
183 operative MRI using three-dimensional non-linear thin-plate spline warping (Rohr et al., 2001),  
184 which corrected for post-operative brain shift and distortion. The warping was constrained with  
185 50-100 control points, manually selected throughout the brain, which aligned to visibly  
186 corresponding landmarks in the pre- and post-implantation MRIs.

187 To compare functional connectivity between arousal states, the dimensionality of the  
188 adjacency matrices (i.e. the wPLI connectivity matrices) was reduced by assigning electrodes to  
189 one of 37 specific ROIs organized into 7 ROI groups (Fig. 3; Table 1; Supplementary Table 2)  
190 based upon anatomical reconstructions of electrode locations in each subject. For subdural  
191 arrays, it was informed by automated parcellation of cortical gyri (Destrieux et al., 2010;  
192 Destrieux et al., 2017) as implemented in the FreeSurfer software package. For depth arrays,  
193 ROI assignment was informed by MRI sections along sagittal, coronal and axial planes. For  
194 recording sites in HG, delineation of core auditory cortex and adjacent non-core areas (HGPM  
195 and HGAL, respectively) was based on physiological criteria (Brugge et al., 2009; Nourski et al.,  
196 2016). Specifically, recording sites were assigned to the HGPM ROI if they exhibited phase-  
197 locked ECoG responses to 100 Hz click trains and if the averaged evoked potentials to these  
198 stimuli featured short-latency (<20 ms) components. Such response features are not present  
199 within HGAL. Additionally, correlation coefficients between average evoked potential  
200 waveforms recorded from adjacent sites were examined to identify discontinuities in response  
201 profiles along HG that could be interpreted as reflecting a transition from HGPM to HGAL.  
202 Recording sites identified as seizure foci or characterized by excessive noise, and depth  
203 electrode contacts localized to the white matter or outside brain, were excluded from analyses  
204 and are not listed in Supplementary Table 2.

205

#### 206 *2.3.4. ROI-based connectivity analysis*

207 Connectivity between ROIs was computed as the average wPLI value between all pairs of  
208 recording sites in the two ROIs. For analyses in which connectivity was summarized across  
209 subjects (see Fig. 4 and Supplementary Figs. 6 & 7), ROIs were only included if at least 3 out of 5  
210 subjects had electrode coverage in that ROI; 29 out of 37 ROIs met this criterion. For display  
211 purposes only, adjacency matrices for each subject were averaged across segments assigned to  
212 identical arousal states, and the matrices thresholded to retain only the 10% strongest  
213 connections. Quantitative analyses were based on unthresholded adjacency matrices.

214 Changes in connectivity with arousal state were evaluated by computing differences  
215 between adjacency matrices, and quantified by calculating the operator norm ( $d$ ) of the

216 difference matrix; smaller values of  $d$  indicate more similar matrices. This difference metric was  
217 chosen instead of either the Pearson correlation or the Frobenius norm because it retains  
218 information about the structure of the matrix. Specifically, for a matrix  $\mathbf{M}$ ,  $d_M$  is the maximum,  
219 over all vectors  $\mathbf{v}$  with  $||\mathbf{v}|| = 1$ , of  $||\mathbf{Mv}||$ , and indicates how much  $\mathbf{M}$  stretches these  
220 vectors; with  $\mathbf{M}$  representing the difference between adjacency matrices measured in two  
221 arousal states,  $\mathbf{v}$  could represent the inputs to or the activity of the nodes of the network at a  
222 particular time point, and  $\mathbf{Mv}$  would then be the effect on that activity of the difference in brain  
223 state. The operator norm [computed in Matlab as `norm(M)`] is related to the spectrum of  $\mathbf{M}^T\mathbf{M}$ :  
224  $d_M$  = the square root of the maximum eigenvalue of  $\mathbf{M}^T\mathbf{M}$ .  
225 To compare arousal state-dependent differences in  $d$  (for example, to see whether  $d_{WS,N1}$  is  
226 different than  $d_{N1,N2}$ ), effect sizes were calculated as Cliff's delta,  $\delta$ ; (Cliff, 1993). Cliff's delta  
227 ranges from -1 to 1 where 0 indicates completely overlapping distributions and -1 or 1 indicate  
228 distributions where all observed values of one group are less/greater than all observed values  
229 of the comparison group. Effect sizes were first calculated for each subject, and then reported  
230 as the mean effect size across subjects,  $\delta_{\square}$ . A permutation method was used to estimate  $p$ -  
231 values for these comparisons; within each subject and each experiment (sleep and anesthesia),  
232 restricted random permutations of state labels for the data segments, preserving the order of  
233 observations, produced an estimated distribution under the null hypothesis that the  
234 comparisons do not depend on arousal state (Besag and Clifford, 1989; Winkler et al., 2015).  
235 Independent  $p$ -values obtained within individual subjects for a given test were combined across  
236 subjects using Stouffer's Z-transform method (Heard and Rubin-Delanchy, 2018; Stouffer et al.,  
237 1949). Non-parametric approaches (Cliff's delta and permutation method) were preferable to  
238 parametric statistics for these data, as the distributions of operator norms and differences were  
239 skewed and the magnitude varied between subjects. Given the small number of subjects, these  
240 statistical methods treat each subject as a single-case and then combine results in a meta-  
241 analysis. Because  $p$ -values and effect sizes were first estimated in single subjects, this approach  
242 reduces the influence of possible outlier subjects and non-normally distributed measures.

243 *2.3.5. Classification analysis*

244 We used a classification analysis as an additional evaluation of changes in connectivity as a  
245 function of arousal state. Here, data from each subject was divided into 10-second segments,  
246 and adjacency matrices were computed for each segment. To ensure that the data from the  
247 two experiments (sleep and anesthesia) were on the same scale, adjacency matrices computed  
248 from the anesthesia data were scaled by the slope derived from a regression analysis that  
249 related wPLI values computed for sleep vs. anesthesia data for each subject. A linear classifier  
250 (implemented using SGDClassifier from Python's Scikit-Learn library) was trained on a subset  
251 (80%) of WS and N2 segments, and then applied to unseen data from all arousal states (WS, N1,  
252 N2, N3, REM, WA, S, U) in each subject. Data from the sleep experiment were chosen over  
253 those from the anesthesia experiment to train the classifier because the former yielded many  
254 more data segments (see Supplementary Fig. 2). Rather than using a binary classification, we  
255 applied a logistic weighting function that assigned each segment a weight from 0 (most 'N2-  
256 like') to 1 (most 'WS-like'). We report the median logistic prediction scores across all 25  
257 pairwise permutations of WS and N2 train/test splits (4/5 train, 1/5 test) in each subject. Given  
258 an unequal number of observations in WS and N2 datasets (see Supplementary Table 3),  
259 training sets were balanced in each permutation via random sampling. Hyperparameters  
260 corresponding to the strength of regularization (alpha parameter) and the tolerance threshold  
261 (i.e. when to stop training the model) were optimized for each training set permutation using  
262 three-fold cross-validation. Specifically, each training set was split into three folds, and one of  
263 those three folds was used as a test set to evaluate the performance of a given hyperparameter  
264 value when training a model on the remaining two folds. For each hyperparameter value  
265 evaluated, this process was repeated three times to average over all test sets. Hyperparameter  
266 values yielding the lowest average test set error were then used in the final model being  
267 applied to unseen data for each train/test permutation. Probability density functions for each  
268 arousal state and each subject were estimated from logistic prediction scores using kernel  
269 density estimation (ksdensity function in Matlab) and represented as violin plots (see Fig. 5 and  
270 Supplementary Fig. 8).

271 2.3.6. *Regional connectivity analysis*

272 State-dependent differences in regional connectivity were quantified by dividing ROIs into a  
273 posterior ('back') group (temporal, parietal and occipital ROIs), and an anterior ('front') group  
274 (frontal ROIs). Mean alpha-band wPLI across all pairs of recording sites within each group were  
275 used to calculate bias in connectivity, defined as the difference between within-posterior and  
276 within-anterior connectivity. State-dependence of long-range alpha-band connectivity was  
277 assayed by measuring wPLI across the top 25% most distant pairs of recording sites. Euclidean  
278 distances between sites were measured using standard 3D coordinates (Right-Anterior-  
279 Superior, RAS). Changes in within-posterior versus within-anterior connectivity and changes in  
280 long-range connectivity were assessed using permutation analysis as described above for state-  
281 dependent differences in  $d$ .

282 **3. Results**

283 ***3.1. Electrode coverage***

284 Data from a total of 864 recording sites from five subjects (Supplementary Table 1), spanning a  
285 total of 37 regions of interest (ROIs) were analyzed (Table 1). Each subject contributed between  
286 154 and 198 sites (median 172; Supplementary Table 2, Supplementary Fig. 1). The focus of this  
287 study was on changes in cortical connectivity across arousal states. As sensory awareness is a  
288 key element of consciousness (Boly et al., 2017), we centered our analysis around cortical  
289 hierarchical organization in the auditory modality, which is a convenient choice and a frequent  
290 focus of studies of both sleep and general anesthesia (e.g. Liu et al., 2012; Raz et al., 2014;  
291 Strauss et al., 2015). Clinical considerations dictated dense sampling of the temporal lobe,  
292 including auditory and auditory-related cortex, providing comprehensive electrode coverage  
293 across multiple levels of the auditory cortical hierarchy in all subjects.

294

295 ***3.2. Defining arousal states***

296 Polysomnography based on scalp electroencephalography (EEG), electrooculography,  
297 electromyography, and video was used to assign sleep stages. All five subjects exhibited  
298 overnight sleep patterns typical of healthy adult subjects (Supplementary Fig. 2a). There was a  
299 high correspondence between the ratio of delta to beta band power in frontal ECoG electrodes  
300 and the assigned sleep stage (cf. Kremen et al., 2019). Overnight recordings in all subjects  
301 featured wake (WS) state as well as N1, N2 and REM sleep stages; N3 was also observed in 3 of  
302 5 subjects (Supplementary Table 3). The total duration of scored recordings in each subject was  
303 between 306.8 and 649.6 minutes (median 534.4).

304 During the anesthesia experiment, all subjects transitioned from wake (WA) to sedated  
305 (S; OAA/S>2) and unresponsive (U; OAA/S ≤2) states as propofol infusion rate was increased  
306 (Supplementary Fig. 2b). OAA/S scores exhibited a good correspondence with bispectral index  
307 (BIS) values, as expected for sedation and anesthesia induced by propofol alone (Glass et al.,  
308 1997). WA, S and U states were characterized by median BIS values of 93 (range 80-98), 78  
309 (range 36-97) and 52 (range 33-74), respectively.

310 **3.3. Changes in spectral power under sleep and anesthesia**

311 Power spectral density (PSD) measurements made during WS and WA states exhibited shapes  
312 typical of resting state eyes-closed recordings, with power falling off approximately as  $1/f^2$  and  
313 broad peaks typically observed in the alpha and beta bands (Fig. 1; Supplementary Fig. 3). There  
314 were only small differences observed between WS and N1, and none between WA and S (Fig.  
315 2). By contrast, transitions into states N2 and U were characterized by large band- and region-  
316 specific changes in PSDs. As expected, N2 sleep was characterized by a widespread increase in  
317 delta power (see Fig. 2a). Of note, increases in alpha power in N2, as might be expected due to  
318 sleep spindles (Andrillon et al., 2011), were not consistent across subjects. Loss of  
319 responsiveness under anesthesia (U) was associated with large increases in delta power within  
320 PFC and sensorimotor areas, and a selective increase in alpha power in PFC (see Fig. 2b),  
321 consistent with previous observations (Purdon et al., 2013).

322

323 **3.4. Changes in functional connectivity under sleep and anesthesia**

324 Functional connectivity was assayed using the debiased weighted phase lag index (wPLI) (Vinck  
325 et al., 2011). As ECoG power spectra featured peaks in the alpha band, we focused on alpha-  
326 band wPLI, but presented analyses of functional connectivity in other canonical frequency  
327 bands as well. Like other phase-related measures, wPLI can be sensitive to uncorrelated noise  
328 (Vinck et al., 2011), leading to correlations with spectral power. However, in the dataset  
329 presented here power did not exhibit an appreciable correlation with wPLI residuals (mean  
330 across patients  $R^2 = 0.02$ , maximum  $R^2 = 0.04$ ) after accounting for state, indicating that spectral  
331 power changes did not contribute substantially to our measure of functional connectivity.

332 Adjacency matrices were computed first for each pair of recording sites (Fig. 3a), then  
333 transformed into ROI-based adjacency matrices (Fig. 3b), from which chord connectivity plots  
334 were created (Fig. 3c). Single-subject examples of chord connectivity plots for delta, alpha and  
335 gamma bands across arousal states during sleep and anesthesia are shown in Supplementary  
336 Figures 4 and 5. Qualitatively, in the wake states (WA, WS) alpha-band connectivity was  
337 dominated by connections within and between the temporal and parietal lobes in all five  
338 subjects (Fig. 4). This pattern was largely preserved in N1, REM and S states. By contrast, for N2

339 and U, alpha-band connectivity showed a shift to connectivity within prefrontal ROIs and  
340 between prefrontal cortex and select ROIs, including HGPM, insula, gyrus rectus and PMC (see  
341 Fig. 4, third column). More modest changes in connectivity were observed in other frequency  
342 bands (Supplementary Fig. 6). In the three subjects in whom N3 sleep was observed, the shift in  
343 alpha-band connectivity was even more pronounced in N3 compared to N2 (Supplementary Fig.  
344 7).

345

346 **3.5. Common neural signature of functional connectivity changes in sleep and anesthesia**  
347 A striking transition boundary in the alpha-band connectivity patterns between two sets of  
348 arousal states: [WS, N1, REM, WA, S] and [N2, N3, U] is apparent in the chord connectivity  
349 plots. Differences in the degree of conscious experience in these two sets suggest a functional  
350 boundary as well: the first set comprises states in which subjects are responsive (WS, WA, S), or  
351 have high incidence of reportable conscious experience within the context of dreaming (N1,  
352 REM), while the second set comprises states in which subjects are unresponsive and have low  
353 incidence of reportable conscious experience (Eer et al., 2009; Leslie et al., 2009; Siclari et al.,  
354 2013). To quantify these observations, changes in connectivity with arousal state were  
355 measured using the differences between un-thresholded ROI  $\times$  ROI adjacency matrices.  
356 Specifically, the magnitude of the difference in connectivity between states J and K was  
357 computed as  $d_{J,K} = ||\mathbf{A}_J - \mathbf{A}_K||$ , where  $\mathbf{A}$  is the adjacency matrix for that state and  $||\mathbf{M}||$  is the  
358 operator norm of the matrix  $\mathbf{M}$  (see Methods). Using this metric, functional connectivity was  
359 evaluated within each experiment (sleep, anesthesia) to test the hypothesis that differences  
360 across the transition boundary (sleep:  $d_{N1,N2}$  and  $d_{REM,N2}$ ; anesthesia:  $d_{S,U}$ ) were larger in  
361 magnitude than differences that do not cross that boundary (sleep:  $d_{WS,N1}$ ,  $d_{WS,REM}$ ; anesthesia:  
362  $d_{WA,S}$ ). Mean effect sizes across subjects (mean Cliff's delta,  $\delta$ , see methods) are reported and  
363 a permutation test was performed to estimate how chance arrangements of the data compare  
364 to the actual differences observed. We found that within the alpha-band,  $d_{WS,N1}$  was  
365 significantly smaller than  $d_{N1,N2}$  ( $\delta = 0.38$ ,  $p = 0.00013$ ), as was  $d_{WA,S}$  compared to  $d_{S,U}$  ( $\delta =$   
366  $0.70$ ,  $p = 0.046$ ). Additionally,  $d_{WS,REM}$  was significantly smaller than  $d_{REM,N2}$  ( $\delta = 0.25$ ,  $p =$

367 0.0025). Comparable results (i.e. both  $d_{WS,N1} < d_{N1,N2}$  and  $d_{WA,S} < d_{S,U}$  significant) were not found  
368 within delta and gamma bands (Supplementary Fig. 6; Supplementary Table 4).

369 Further support for a transition boundary distinguishing alpha-band connectivity profiles  
370 was provided by classification analysis (Fig. 5a). Rather than starting with the average  
371 connectivity profiles, as in the difference norms analysis above, the classification analysis was  
372 based directly on the minute-by-minute connectivity matrices measured during the overnight  
373 sleep experiment. The classifier was trained on data segments from two states appearing to fall  
374 on either side of the boundary, WS and N2, and then tested on data segments from all arousal  
375 states. We used a logistic weighting function to assign a value between 0 ('N2-like') and 1 ('WS-  
376 like') to each segment. For this analysis, adjacency matrices were calculated from shorter (10-  
377 second) segments of data to provide a larger dataset on which to train the classifier, and the  
378 analysis was performed on each subject separately. As expected, median prediction scores on  
379 N2 and WS were highly skewed toward 0 and 1, respectively (N2: 0.10; WS: 0.90). Separation in  
380 median prediction score for N2 and WS segments was greater for alpha (difference of medians  
381 = 0.80) compared to other frequency bands (delta, difference of medians = 0.54; gamma,  
382 difference of medians = 0.49). N3 data were classified as 'N2-like' (median logistic prediction  
383 score = 0.12). Importantly, both N1 and REM tended to be classified as 'WS-like' (median  
384 logistic prediction score = 0.68 and 0.56, respectively). These results were generally consistent  
385 across the five subjects (Supplementary Fig. 8).

386 The similarities between connectivity profiles measured during sleep and anesthesia  
387 (i.e. between WS and WA, between N1 and S, and between N2 and U; Fig. 4) suggest a  
388 commonality in the mechanisms governing transitions between arousal states in the two  
389 experiments. The hypothesis that certain pairs of states in sleep and anesthesia can be  
390 considered 'equivalent' (i.e. WS and WA, N1 and S, N2 and U) was tested by comparing the  
391 distances between alpha-band connectivity profiles measured in equivalent states with those  
392 measured in states hypothesized to be 'non-equivalent' (i.e. on opposite sides of the transition  
393 boundary in Figure 4). Thus,  $d_{Equiv}$  (i.e.  $d_{WS,WA}$ ,  $d_{N1,S}$  and  $d_{N2,U}$ ) were compared to  $d_{Non-equiv}$  [i.e.  
394 mean ( $d_{WS,U}, d_{WA,N2}$ ), mean ( $d_{N1,U}, d_{S,N2}$ ) and mean ( $d_{N1,U}, d_{S,N2}$ ), respectively]. We found that  
395  $d_{WS,WA}$  and  $d_{N1,S}$  were significantly smaller than their corresponding  $d_{Non-equiv}$  ( $\delta\Delta = 0.22$ ,  $p =$

396 0.0022 and  $\delta_{\square} = 0.23$ ,  $p = 0.00076$ , respectively) but  $d_{N2,U}$  was not ( $\delta_{\square} = 0.14$ ,  $p = 0.31$ ). These  
397 data indicate similarity in alpha-band connectivity profiles observed during N1 sleep and  
398 sedation. Comparable results (i.e. both  $d_{WS,WA}$  and  $d_{N1,S}$  significantly smaller than their  
399 corresponding  $d_{Non-equiv}$ ) were not found within delta and gamma bands (Supplementary Fig. 6;  
400 Supplementary Table 4).

401 Classification analysis also provided support for the idea that connectivity profiles under  
402 sleep and anesthesia overlap. Here, classifiers trained on WS and N2 data from the sleep  
403 experiment (see Fig. 5a) were applied to anesthesia data (Fig. 5b) in order to determine  
404 whether the transition boundary observed during sleep generalized to changes in arousal state  
405 under anesthesia. The classifiers tended to assign WA and S segments to the WS-like category  
406 (median logistic prediction score = 0.68 and 0.55, respectively) and assigned U segments with  
407 high probability to the N2-like category (median logistic prediction score = 0.11). Taken  
408 together, the results of these two analyses suggest substantial overlap in connectivity profiles  
409 between 'equivalent' sleep and anesthesia arousal states.

410

### 411 ***3.6. Regional distribution of functional connectivity strength across arousal states***

412 The changes in regional distribution of connectivity across the transition boundary, i.e. the shift  
413 from temporo-parietal to prefrontal connectivity, were strikingly similar in the sleep and  
414 anesthesia experiments (see Fig. 4). Boly and colleagues (Boly et al., 2017) presented evidence  
415 that the neural correlates of consciousness correspond primarily to activity in the 'back' of the  
416 brain, specifically involving broad regions in the temporal, parietal and occipital lobes, and  
417 excluding regions in the frontal lobe. Motivated by this perspective, we quantified the  
418 differences in regional connectivity observed across arousal states in the current study. We  
419 divided ROIs into two groups: a posterior group that included all temporal, parietal and occipital  
420 ROIs, and an anterior group that included all frontal ROIs. We then compared the mean alpha-  
421 band wPLI across all pairs of recording sites within each group, and calculated a regional bias in  
422 connectivity as the difference between within-anterior and within-posterior connectivity. Figure  
423 6a shows the bias in connectivity, with biases toward within-posterior connectivity indicated by  
424 negative values and within-anterior by positive values. There was a shift from posterior and

425 towards anterior connectivity with reduced arousal in both sleep [change in regional bias from  
426 N2-N1  $\delta$  = 0.69,  $p < 0.0001$ ; N2-WS  $\delta$  = 0.72,  $p < 0.0001$ ] and anesthesia (S-WA  $\delta$  = 0.98,  $p$   
427 = 0.0011; U-S  $\delta$  = 1.0,  $p = 0.00037$ ; U-WA  $\delta$  = 1.0,  $p < 0.0001$ ). The shift from WS to N1 was  
428 not significant (N1-WS  $\delta$  = 0.34,  $p = 0.093$ ). REM was different from N2 (N2-REM  $\delta$  = 0.81,  $p$   
429 < 0.0001) but not significantly different from wake (REM-WS  $\delta$  = 0.23,  $p = 0.30$ ). Thus, the  
430 data indicate that alpha-band connectivity in WS versus N2 and in WA versus U exhibits a  
431 similar shift from connectivity within posterior towards connectivity within anterior regions.

432 Finally, disruption in long-range cortico-cortical connectivity has been noted upon LOC  
433 during sleep and anesthesia in several studies (Boly et al., 2012a; Lee et al., 2013b; Ranft et al.,  
434 2016; Spoormaker et al., 2010), though these findings have been challenged by other studies  
435 (Boly et al., 2012b; Lee et al., 2017; Monti et al., 2013; Murphy et al., 2011). To investigate this  
436 issue in the dataset presented here, we assayed the state-dependence of long-range alpha-  
437 band connectivity by measuring wPLI across the most distant pairs of recording sites, defined as  
438 highest quartile of Euclidean distances in each subject (Fig. 6b). We found no evidence for a  
439 decrease in long-range functional connectivity, observing a rather modest increase in N2 and U  
440 relative to wake (N2-WS  $\delta$  = 0.56,  $p < 0.0001$ ; U-WA  $\delta$  = 0.74,  $p = 0.0061$ ) and N1/S (N2-N1  
441  $\delta$  = 0.63,  $p < 0.0001$ ; U-S  $\delta$  = 0.86,  $p = 0.0056$ ). We did not find significant changes in long-  
442 range connectivity between WS and N1 (N1-WS  $\delta$  = -0.19,  $p = 0.15$ ) or WA and S (S-WA  $\delta$  = -  
443 0.05,  $p = 0.68$ ), but long-range connectivity was reduced in REM (R-WS  $\delta$  = -0.69,  $p =$   
444 0.00041).

445 **4. Discussion**

446 The search for reliable biomarkers of LOC/ROC is of great scientific interest and clinical  
447 relevance for anesthesia (Drummond, 2000) as well as for diagnosis and prognosis of disorders  
448 of consciousness (Bayne et al., 2017; Bernat, 2017). Here, we leveraged a unique opportunity to  
449 obtain intracranial electrophysiological recordings from neurosurgery patients both during  
450 natural sleep and under propofol anesthesia. We found that different arousal states were  
451 associated with distinct patterns of functional connectivity. This association was similar for  
452 sleep and anesthesia, suggesting that cortical network configuration could index changes in  
453 consciousness.

454

455 ***4.1. ROI- and band-specific effects of sleep and anesthesia on power spectral density***

456 A practical biomarker of conscious vs unconscious state must generalize to multiple settings  
457 where LOC is encountered, including sleep and general anesthesia. Previous attempts to use  
458 band-specific power to distinguish arousal states under general anesthesia have been largely  
459 unsuccessful (Otto, 2008; Struys et al., 1998). This difficulty likely stems from agent-specific  
460 changes in power spectra, for example differing between propofol, ketamine and  
461 dexmedetomidine anesthesia (Mashour, 2020). The changes that we observed during natural  
462 sleep, specifically widespread increases in spectral power in the delta band (see Fig. 2a), are  
463 hallmarks of N2 and N3, but not N1, sleep (Prerau et al., 2017; Steriade et al., 1993). In contrast  
464 to observations during natural sleep, under propofol anesthesia we observed region-specific  
465 (not global) increases in delta power (see Fig. 2b), and increases in frontal alpha power (see Fig.  
466 2b). These observations under propofol are consistent with previous reports (Chennu et al.,  
467 2016; Feshchenko et al., 2004; Ni Mhuircheartaigh et al., 2013; Purdon et al., 2013; Supp et al.,  
468 2011; Tinker et al., 1977; Wang et al., 2014) and some have suggested that changes in frontal  
469 alpha and delta power are reliable indicators of loss of consciousness under propofol (Purdon  
470 et al., 2013). However, a recent study using the isolated forearm technique challenges the  
471 reliability of such an approach (Gaskell et al., 2017). Consistent with the latter findings, changes  
472 in power in the present study did not consistently distinguish N1 from N2 and S from U (see Fig.  
473 2). In addition, these changes across arousal states were not consistently paralleled by changes

474 in connectivity. For example, alpha power did not consistently increase in N2 compared to WS  
475 and N1 states, yet this band exhibited the most prominent connectivity changes observed  
476 during sleep (see Fig. 2, Fig. 4). Conversely, although the transition to N2 and N3 sleep was  
477 characterized by an increase in delta power in multiple ROIs, connectivity within and across  
478 these ROIs did not undergo a comparable degree of reorganization (see Fig. 2, Supplementary  
479 Fig. 6a). These results indicate that the observed changes in connectivity do not merely follow  
480 changes in power and instead reflect functional reorganization of cortical networks. The  
481 absence of meaningful correlations between connectivity and power (see Results) further  
482 support this idea.

483

#### 484 ***4.2. Changes in connectivity during sleep and anesthesia***

485 The sharing of information between cortical regions is a critical element in theories of  
486 consciousness and brain function (Dehaene and Changeux, 2011; Friston, 2005; Tononi et al.,  
487 2016). Altered cortical connectivity observed during sleep and anesthesia has been interpreted  
488 within this theoretical context to explain reduced awareness upon LOC (Alkire et al., 2008;  
489 Mashour and Hudetz, 2017). Although there have been studies that examined functional  
490 connectivity during sleep and anesthesia (Boly et al., 2012a; Boly et al., 2012b; Lee et al., 2017;  
491 Lee et al., 2013b; Murphy et al., 2011; Ranft et al., 2016; Spoormaker et al., 2010), no previous  
492 study has directly compared the two in the same subjects. Of particular relevance is the study  
493 by Murphy et al. (Murphy et al., 2011) that examined changes in neural activity during sleep  
494 and anesthesia. However, that study utilized data from two different sets of subjects and did  
495 not compare changes in functional connectivity between the two data sets. A recent study in  
496 human volunteers that did measure changes in functional connectivity patterns derived from  
497 fMRI during transitions in arousal state found substantial differences between sleep and  
498 propofol anesthesia (again, imaged in two different groups of subjects) (Li et al., 2018).  
499 Interestingly, the latter study found that cortical changes during NREM sleep were confined to  
500 frontal cortex, while changes under propofol anesthesia were widespread. Here, measuring  
501 ECoG-derived functional connectivity in the same subjects during sleep and anesthesia, we

502 found substantial overlap in the regional changes in functional connectivity during transitions in  
503 arousal state.

504 We observed consistent and pronounced changes in connectivity upon transitions into  
505 N2 and U, specifically increased connectivity within and between anterior (frontal) brain  
506 regions, as has been observed using electrophysiological measures previously under propofol  
507 anesthesia (Purdon et al., 2013; Supp et al., 2011), and reduced connectivity elsewhere. What is  
508 novel about the results presented here is the degree of overlap between changes in  
509 connectivity profiles across arousal states in sleep and anesthesia, including a pronounced  
510 transition boundary between N1 and N2 and between S and U (Fig. 4). On a superficial level,  
511 one might expect some overlap in arousal states, and thus in the changes upon transitions  
512 between arousal states, during sleep and anesthesia, yet differences are expected as well. For  
513 example, WS and WA are both wake states, but disparities in the time of day of the recordings  
514 (overnight versus morning), the behavioral state of the subject (e.g. WA was just prior to major  
515 surgery) and environment (monitoring suite versus operating room) could result in substantial  
516 differences in cortical network organization. Similarly, although both N2 and U are  
517 unresponsive states with low probability of reportable conscious experience, differences in  
518 brain state due to the presence of the anesthetic agent versus endogenous sleep factors might  
519 result in distinct brain connectivity patterns.

520 Previous studies of the incidence of dreaming and conscious experience under  
521 anesthesia suggest that the observed transition boundary may reflect entry into and out of  
522 conscious states. Specifically, on one side of the boundary are states in which subjects are likely  
523 having conscious experiences, i.e. responsive (WS, WA, S) or dreaming frequently and vividly  
524 with high incidence of reportable conscious experience (REM, N1). On the other side are  
525 arousal states in which subjects are unlikely to be having conscious experiences, i.e.  
526 unresponsive and with low incidence of reportable conscious experience (Leslie et al., 2009;  
527 Siclari et al., 2013). This boundary was observed both with difference norms and classification  
528 analyses applied to the ROI-by-ROI adjacency matrices (see Fig. 4, 5) and with the analysis of  
529 intra-regional and long-range connectivity (see Fig. 6). However, even though connectivity  
530 patterns during propofol sedation (S) generally aligned with other conscious states, both the

531 classification and intra-regional connectivity analyses were consistent with fluctuations in  
532 arousal level in this state (see Fig. 5b, 6a).

533 A recent essay on the neural correlates of consciousness (NCC) suggests an interesting  
534 interpretation of these changes in connectivity. Boly and colleagues (Boly et al., 2017)  
535 presented evidence from lesion studies and from experiments utilizing serial awakening during  
536 sleep to argue that the “full NCC”, that is the collection of all regions underlying specific  
537 contents of consciousness, comprises large portions of the parietal, occipital, and temporal  
538 lobes, whereas frontal lobe structures underlie functions associated with, but not necessary for,  
539 those conscious contents. The regions within the full NCC are most closely associated with  
540 sensory awareness, and thus would underlie the internal generative models central to theories  
541 of predictive processing and the mismatch detection and message passing functions critical to  
542 those schemes (Friston, 2005). Alpha-band power and phase synchronization in particular are  
543 associated with feedback connectivity in the visual cortical hierarchy (van Kerkoerle et al.,  
544 2014). Thus, it is possible that the shift in cortical connectivity from predominantly temporo-  
545 parieto-occipital (posterior) to frontal (anterior) upon LOC may reflect a reduction in predictive  
546 processing during states of reduced consciousness. This is consistent with the finding that  
547 anterior alpha synchronization of EEG in response to propofol correlates with disrupted sensory  
548 processing in human volunteers (Supp et al., 2011).

549 Although clinical considerations precluded electrode coverage of the thalamus, previous  
550 studies suggest that some of the changes in cortico-cortical connectivity observed in this study  
551 could be driven by altered thalamo-cortical synchronization (Saalmann et al., 2012). For  
552 example, the increased thalamo-cortical synchronization observed during sleep spindles  
553 (Andrillon et al., 2011) and during propofol anesthesia (Flores et al., 2017) may have a similar  
554 effect on functional connectivity within frontal cortex, as suggested by computational studies  
555 (Vijayan et al., 2013). However, the observations that the frontal shift in alpha-band  
556 connectivity was even more pronounced in N3 than it is in N2 (Supplementary Fig. 7), even  
557 though spindles are less common in N3 (Andrillon et al., 2011), and that significant changes in  
558 alpha power were not observed during sleep (see Fig. 2a), suggest that the changes in alpha-  
559 band connectivity were unlikely driven solely by sleep spindle activity.

560 The disintegration of cortical networks observed upon LOC during sleep, anesthesia and  
561 coma (Alkire et al., 2008) has been ascribed to disrupted long-range connectivity. For example,  
562 several reports suggest reduced resting-state cortico-cortical (fronto-parietal) feedback  
563 connectivity under a variety of anesthetic agents, including propofol (fMRI: Boly et al., 2012a;  
564 Ranft et al., 2016; EEG: Lee et al., 2013b), consistent with results using invasive  
565 electrophysiological recordings in rodent models (Imas et al., 2005; Raz et al., 2014). Disrupted  
566 long-range resting-state functional connectivity has also been reported in fMRI studies during  
567 NREM sleep (Spoormaker et al., 2010) and anesthesia (Ranft et al., 2016). However, other  
568 studies have shown no differences in changes in short- versus long-range connectivity (fMRI:  
569 Monti et al., 2013), or even increases in long-range connectivity during anesthesia (fMRI:  
570 Murphy et al., 2011; EEG: Lee et al., 2017) and sleep (fMRI: Boly et al., 2012b). Similarly, in the  
571 present study, we saw little evidence for decreases specifically in long-range connections (see  
572 Fig. 6b). The reasons for the diverse findings of the effects on connectivity are unclear. It is  
573 possible that the dynamics and heterogeneity of the resting state cortical network contribute to  
574 this diversity. For example, network configuration prior to LOC has been shown to influence  
575 observed changes in connectivity during sleep (Wilson et al., 2019). Application of methods to  
576 these data that can characterize connectivity at finer temporal resolution may address this  
577 issue.

578

#### 579 **4.3. Caveats and limitations**

580 The key limitations of this study are the small number of participants ( $n = 5$ ), and that the  
581 subjects had a neurologic disorder, and thus may not be entirely representative of a healthy  
582 population. These caveats are inherent to all human intracranial electrophysiology studies. Our  
583 statistical methods focused on within-subject comparisons between states and should be  
584 generalized with caution. However, results were consistent across subjects who all had  
585 different clinical histories of their seizure disorder, antiepileptic medication regimens, and  
586 seizure foci. Recordings from cortical sites confirmed to be seizure foci were excluded from  
587 analyses. Finally, all subjects participated in multiple additional research protocols over the  
588 course of their hospitalization, including a range of behavioral tasks. Behavioral and neural data

589 obtained in these other experiments were examined for consistency with a corpus of published  
590 human intracranial electrophysiology data (reviewed in Nourski, 2017). None of the subjects  
591 exhibited aberrant responses that could be interpreted as grounds for caution in inclusion in  
592 this study.

593 The motivation for exploring changes in connectivity across arousal states is to elucidate  
594 the neural underpinnings that define these states. We note, however, that the arousal states as  
595 defined in this study are likely non-uniform regarding consciousness. For example, healthy  
596 adults are able to report on conscious experience (i.e. dreaming) about 40% and 20% of the  
597 time in N2 and N3 sleep (Siclari et al., 2013). Dreaming also occurs under propofol anesthesia in  
598 about 20% of patients (Leslie et al., 2009). This suggests that differences in brain connectivity  
599 between the conscious and unconscious states may be even greater than those reported here,  
600 had it been possible to reliably distinguish dreaming vs. non-dreaming states in our data set.

601 We also note the challenges in assessing awareness under anesthesia, and specifically  
602 the delicate balance between interrogating a subject's awareness and changing the state of  
603 their arousal with that interrogation. The approach employed here, the OAA/S, is considered  
604 the gold standard for assessing awareness in the perioperative setting (Chernik et al., 1990),  
605 and it has been cross-validated using EEG-based measures such as BIS (Vanluchene et al., 2004).  
606 The BIS values recorded in the current study corresponded well to those associated with wake,  
607 sedated and unconscious states in previous reports (Vanluchene et al., 2004). Importantly, we  
608 did not observe consistent increases in BIS values post-OAA/S assessments compared to pre-  
609 OAA/S assessments (see Supplementary Fig. 2), indicating that our assessments likely did not  
610 alter the arousal state of the subjects.

611

#### 612 ***4.4. Functional significance and future directions***

613 The results presented here have broad implications for understanding the neural mechanisms  
614 associated with loss of consciousness and for better understanding and differential diagnosis of  
615 disorders of consciousness. We demonstrate a transition boundary in profiles of functional  
616 connectivity that separates states of different levels of consciousness. Phase synchronization is  
617 postulated to mediate rapid communication of conscious content over multiple spatial scales in

618 cortex, contributing importantly to the rich repertoire of human behavior that characterizes  
619 conscious states (Fries, 2015). The finding that changes in functional connectivity based on  
620 phase synchronization indexes arousal state similarly in both sleep and anesthesia motivates  
621 further exploration of the changes in brain activity and connectivity common to changes in  
622 consciousness. These findings have practical clinical ramifications as well. Connectivity can be  
623 measured non-invasively using EEG or fMRI in patients with disorders of consciousness.  
624 Algorithms that track region-specific functional connectivity may provide a basis for noninvasive  
625 monitoring of arousal state in patients otherwise inaccessible to standard assessments of  
626 arousal based on response to command. Future experiments aimed at exploring in more detail  
627 the differences between LOC in sleep and anesthesia, and generalizing to other anesthetic  
628 agents such as dexmedetomidine and volatile anesthetics, will elucidate further fundamental  
629 questions about the nature of consciousness and arousal that remain unresolved.

630

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637

### 638 **Author Contributions**

639 M.I.B and K.V.N. designed the experiments. M.I.B., C.K.K., H.K. and K.V.N. collected the data.  
640 M.I.B., B.M.K., C.M.E., D.I.C., C.K.K., M.E.D. and K.V.N. analyzed the data. M.I.B., B.M.K. and  
641 K.V.N. drafted and revised the manuscript.

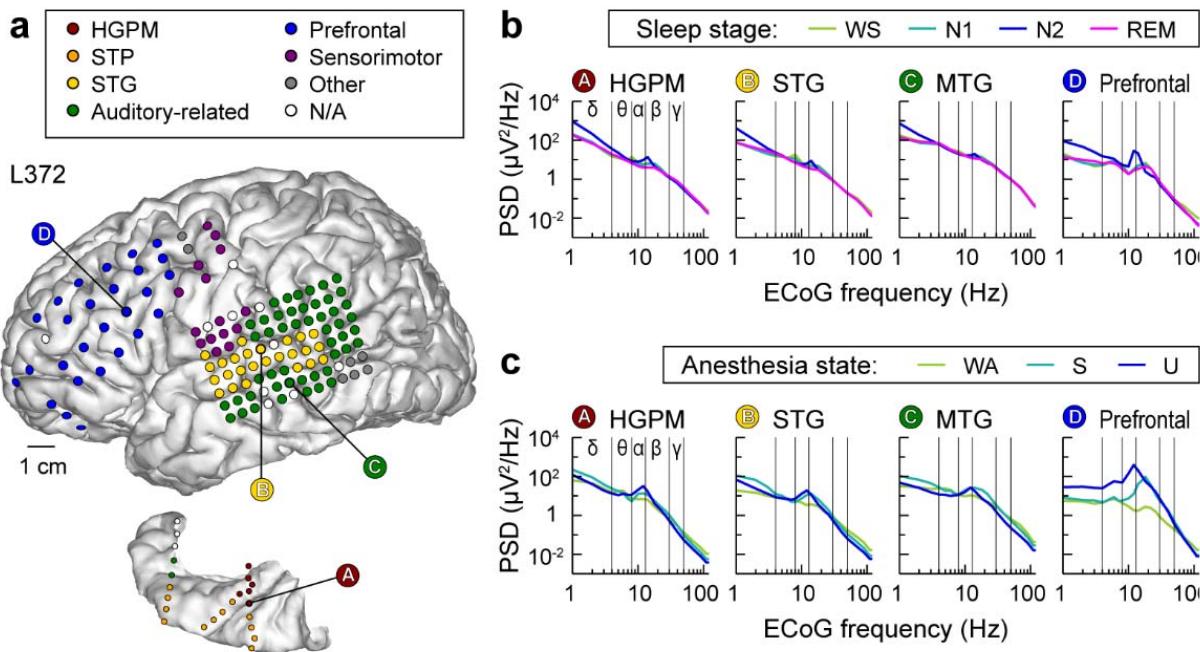
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### 643 **Competing Interests Statement**

644 The authors declare no competing financial interests.

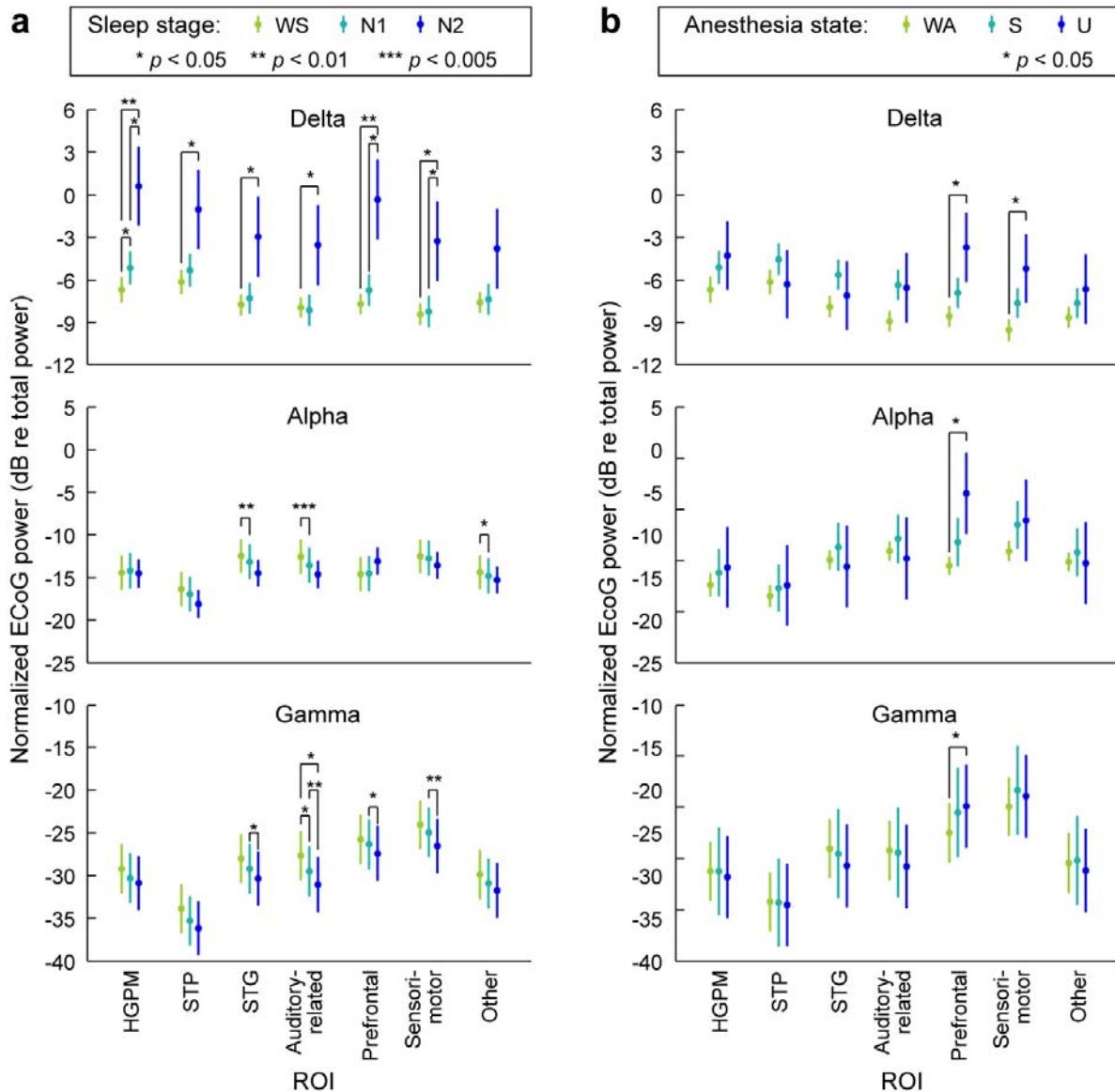
645 **Figures**

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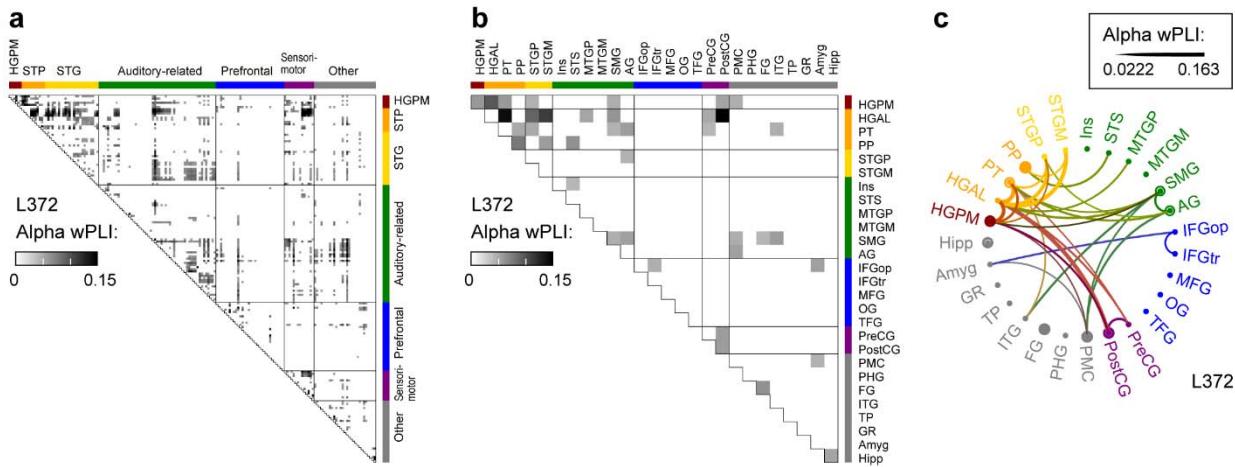
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648 **Fig. 1: Electrode coverage and electrocorticographic (ECoG) power spectra.** Exemplary data  
649 from subject L372. **a**, Electrode coverage of the lateral surface of the left cerebral hemisphere  
650 (top) and left superior temporal plane (bottom). Recording sites are color-coded according to  
651 the region of interest group (see Methods for details and Supplementary table 2 for  
652 abbreviation key). **b**, ECoG power spectra during sleep. Data from four representative sites  
653 (left-to-right). WS: wake (sleep experiment); PSD: power spectral density. **c**, ECoG power  
654 spectra during anesthesia. WA: wake (anesthesia experiment); S: sedated; U: unresponsive.



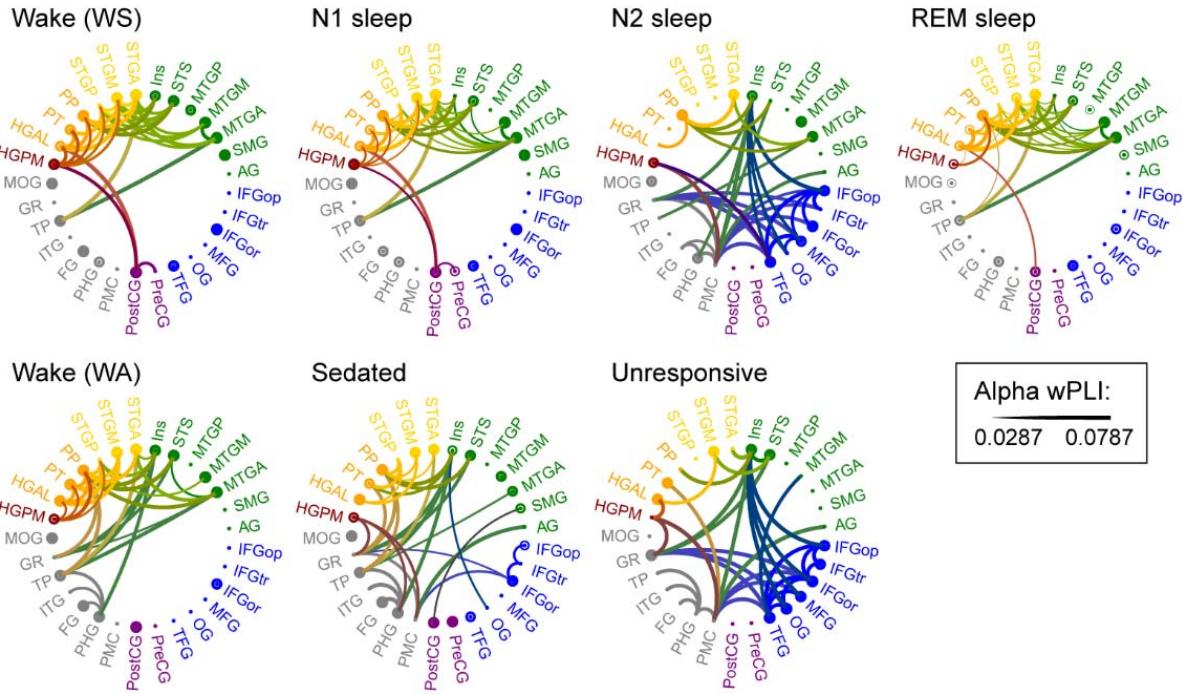
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656 **Fig. 2: Changes in ECoG band power across arousal states.** **a**, ECoG band power during sleep,  
657 plotted as marginal means and 95% confidence intervals. **b**, ECoG band power during  
658 anesthesia. Data from 5 subjects. Changes in delta, alpha and gamma power are shown in top,  
659 middle and bottom rows, respectively. WS: wake (sleep experiment), WA: wake (anesthesia  
660 experiment); S: sedated; U: unresponsive.



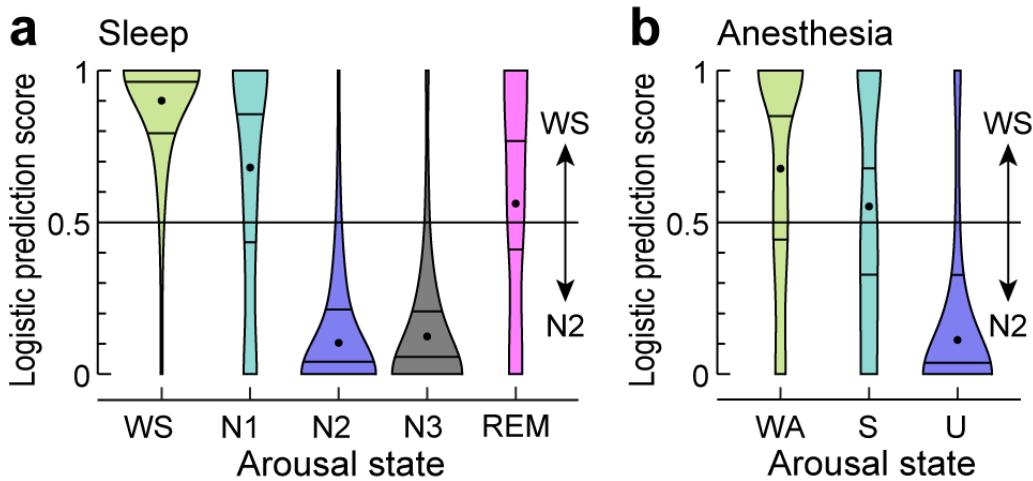
661

662 **Fig. 3: Analysis of alpha-band functional connectivity in wake state.** Example from subject  
663 L372. **a**, Adjacency matrix for all recording sites. **b**, Adjacency matrix, collapsed for all regions of  
664 interest (ROIs). **c**, Chord connectivity plot. Line thickness reflects mean wPLI values that  
665 characterize pairs of ROIs. For display purposes, the chord plot was thresholded to retain the  
666 10% strongest connections.



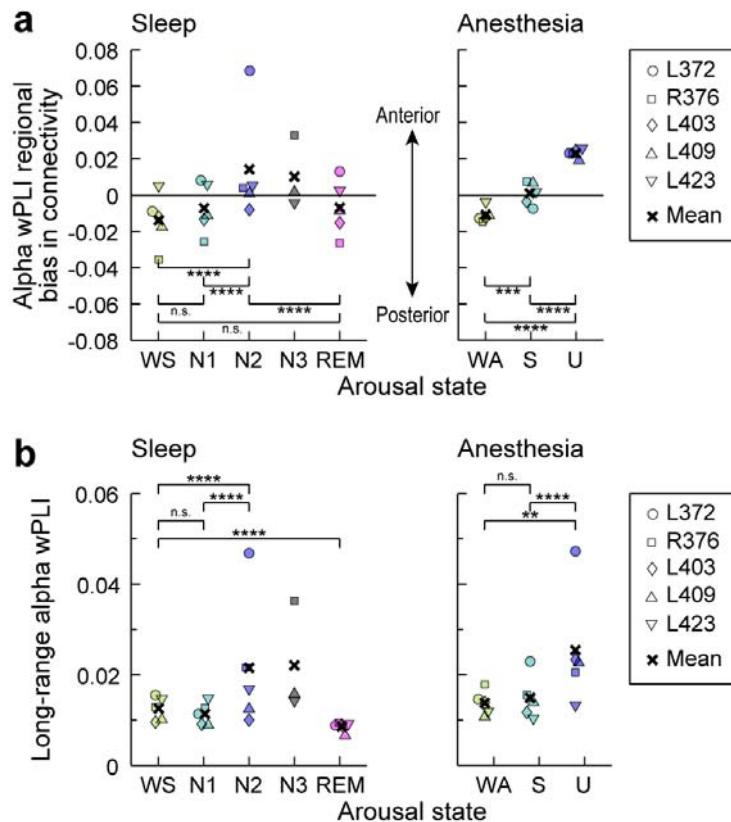
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668 **Fig. 4: ROI-based analysis of alpha-band functional connectivity across arousal states.** Data  
669 from five subjects. See caption of **Fig. 3c** for details.



670

671 **Fig. 5: Classification of data segments.** Logistic prediction distributions for adjacency matrices  
672 from sleep and anesthesia arousal states (panels a and b, respectively) analyzed by a linear  
673 classifier trained on a subset of WS and N2 data. Each violin plot shows the average distribution  
674 across five subjects (except for N3, which is for 3 subjects). Centered dot and surrounding  
675 horizontal lines represent each distribution's median and first and third quartiles, respectively.  
676 For distributions from individual subjects, see Supplementary Figure 8.



677

678 **Fig. 6: Intra-regional and long-range connectivity changes with arousal state. a:** Mean alpha  
679 wPLI averaged within posterior quadrants of the adjacency matrices minus the average within  
680 anterior quadrants. Values greater than zero indicate greater within-posterior connectivity  
681 compared to within-anterior connectivity. **b:** Mean alpha wPLI values for recording site pairs  
682 distanced greater than the 75th percentile. Significance: n.s.,  $p > 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p <$   
683 0.005; \*\*\*\*,  $p < 0.0001$  (permutation test). Although subject L372 exhibited larger effects than  
684 the others in N2 for both analyses, and in U for the long-range connectivity analysis, statistical  
685 significance and conclusions were robust to omitting that subject's (or any individual subject's)  
686 data from the analyses.

687 **Tables**

688 **Table 1.** Regions of interest.

ROI	ROI abbrev.
<i>Auditory core:</i>	
Heschl's gyrus, posterolateral	HGPM
<i>Superior temporal plane (STP):</i>	
Heschl's gyrus, anterolateral	HGAL
Planum temporale	PT
Planum polare	PP
<i>Superior temporal gyrus (STG):</i>	
Superior temporal gyrus, posterior	STGP
Superior temporal gyrus, mid	STGM
Superior temporal gyrus, anterior	STGA
<i>Auditory-related:</i>	
Insula	Ins
Superior temporal sulcus	STS
Middle temporal gyrus, posterior	MTGP
Middle temporal gyrus, mid	MTGM
Middle temporal gyrus, anterior	MTGA
Supramarginal gyrus	SMG
Angular gyrus	AG
<i>Prefrontal:</i>	
Inferior frontal gyrus, pars opercularis	IFGop
Inferior frontal gyrus, pars triangularis	IFGtr
Inferior frontal gyrus, pars orbitalis	IFGor
Middle frontal gyrus	MFG
Superior frontal gyrus*	SFG
Orbital gyrus	OG
Transverse frontopolar gyrus	TFG
Cingulate gyrus, anterior*	CGA
<i>Sensorimotor:</i>	
Precentral gyrus	PreCG
Postcentral gyrus	PostCG
<i>Other:</i>	
Premotor cortex	PMC
Parahippocampal gyrus	PHG
Fusiform gyrus	FG
Inferior temporal gyrus	ITG
Temporal pole	TP
Gyrus rectus	GR
Superior parietal lobule*	SPL
Middle occipital gyrus	MOG
Inferior occipital gyrus*	IOG
Lingual gyrus*	LG
Cingulate gyrus, mid*	CGM
Amygdala	Amyg
Hippocampus	Hipp

689 \*Limited coverage (present in 1 or 2 subjects out of 5)

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