Propofol-induced Changes in α-β Sensorimotor Cortical Connectivity

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ABSTRACT

Background: Anesthetics are believed to alter functional connectivity across brain regions. However, network-level analyses of anesthesia, particularly in humans, are sparse. The authors hypothesized that propofol-induced loss of consciousness results in functional disconnection of human sensorimotor cortices underlying the loss of volitional motor responses.

Methods: The authors recorded local field potentials from sensorimotor cortices in patients with Parkinson disease (N = 12) and essential tremor (N = 7) undergoing deep brain stimulation surgery, before and after propofol-induced loss of consciousness. Local spectral power and interregional connectivity (coherence and imaginary coherence) were evaluated separately across conditions for the two populations.

Results: Propofol anesthesia caused power increases for frequencies between 2 and 100 Hz across the sensorimotor cortices and a shift of the dominant spectral peak in α and β frequencies toward lower frequencies (median ± SD peak frequency: 24.5 ± 2.6 Hz to 12.8 ± 2.3 Hz in Parkinson disease; 13.8 ± 2.1 Hz to 12.1 ± 1.0 Hz in essential tremor). Despite local increases in power, sensorimotor cortical coherence was suppressed with propofol in both cohorts, specifically in β frequencies (18 to 29 Hz) for Parkinson disease and α and β (10 to 48 Hz) in essential tremor.

Conclusions: The decrease in functional connectivity between sensory and motor cortices, despite an increase in local spectral power, suggests that propofol causes a functional disconnection of cortices with increases in autonomous activity within cortical regions. This pattern occurs across diseases evaluated, suggesting that these may be generalizable effects of propofol in patients with movement disorders and beyond. Sensorimotor network disruption may underlie anesthetic-induced loss of volitional control. **(Anesthesiology 2018; 128:305-16)**

PROPOFOL acts through γ-aminobutyric acid–mediated inhibition of neurons within the cortex, thalamus, brainstem, and spinal cord,[1,2] leading to unconsciousness by shifting cortical dynamics such that neuronal networks become functionally isolated in time and space.[3,4] Because neuronal networks are believed to communicate *via* synchronized oscillations, this functional isolation is most likely manifested as loss of connectivity across brain regions.[5,6]

Electroencephalography (EEG) studies indicate enhancement of α (8 to 12 Hz) and attenuation of β (13 to 30 Hz) oscillations as major features of propofol-induced unconsciousness.[3,7–10] Propofol also shifts the spatial distribution of α oscillations from an occipital focus in an awake state to a frontal focus in an unconscious state.[11] These frontal dominant α oscillations may emerge from the potentiation of γ-aminobutyric acid type A synaptic currents that alter thalamocortical connectivity,[12] including concurrent disruption of normal α rhythms in the posterior-projecting thalamic nuclei and the emergence of α activity in frontothalamic nuclei.[13] Dynamic causal modeling also suggests changes in cortical connectivity in propofol-induced unconsciousness, with a reduction in frontal-to-parietal connectivity, but preserved parietal-to-frontal connectivity.[14,15]

What We Already Know about This Topic

- Propofol-induced unconsciousness is accompanied by the loss of functional frontal-parietal cortical connectivity
- Such loss of connectivity occurs between sensory-motor cortices and it may underlie loss of volitional motor response

What This Article Tells Us That Is New

- Although propofol administration led to a local power increase in oscillations in both the sensory and motor cortices, the coupling between these two regions was significantly reduced
- The results support the premise that propofol induces a functional disconnection between cortical areas even though local activity in these areas may increase

The current study of propofol-induced changes in sensorimotor cortices was motivated by the propofol-related loss of motor responses.[16] General anesthetics such as propofol seem to disrupt cortical integration of incoming information.[17–19] While external sensory stimuli can activate the cortex in an anesthetized state, these stimuli fail to be experienced, suggesting a differential effect of anesthetics on functionally discrete cortices.[14,20,21] A nonhuman primate study of propofol revealed disruption of sensorimotor/premotor coherent β

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oscillations preceding loss of consciousness, suggesting that the transition to propofol-induced unconsciousness is associated with disruption of regional interactions between sensory and higher-order cortical networks.[17] This is consistent with the role of α and β oscillations in mediating intercortical connectivity,[22] and these oscillations, to some extent, impart an inhibitory control on brain circuits.[23] In the motor network, sensorimotor cortical synchrony has been reported in these frequencies, within and across cortices, and in relation to movement.[24,25] This synchrony is important for sensorimotor integration and formation of motor memories,[26] which are higher-level functions lost under anesthesia. Likewise, both α and β oscillations are associated with the "akinetic" state in motor networks,[27–29] inhibiting movement by modulating pyramidal tract neuronal firing rate.[24] It follows that propofol may result in modulation of these oscillatory signals both intra- and interregionally.

Although EEG studies have been critical in this field, electrocorticography (ECoG) provides increased spectral sensitivity and spatial resolution. Importantly, the spatial specificity of ECoG enables us to distinguish M1 from S1, which is not possible with EEG. Moreover, M1 and S1 are reciprocally connected and therefore make an interesting model to study corticocortical communication. We employed ECoG during deep brain stimulation (DBS) implantation surgery in subjects with either Parkinson disease or essential tremor to delineate common patterns of change associated with propofol administration despite disease-specific cortical pathophysiology. We hypothesized that similar to the findings of propofol-induced diminished connectivity between subcortical and cortical brain activity,[30] propofol administration decreases sensorimotor cortical α and β connectivity in cortices, signifying a functional disconnection of them.

Materials and Methods

Patients and Surgery

Twelve subjects with idiopathic Parkinson disease and seven subjects with essential tremor undergoing bilateral implantation of DBS leads between January 2014 and October 2016 were included in this study. No *a priori* power calculation was conducted to guide the sample size and recruitment was performed in accordance with our previous experience with intraoperative electrophysiologic studies from patients with movement disorders.[31,32] All subjects provided written informed consent approved by the institutional review board at the University of California, Los Angeles, California.

All long-acting and short-acting Parkinson disease–related medications were withdrawn at least 24 h and 12 h before the surgical procedure, respectively. In patients with Parkinson disease, the DBS leads were targeted to motor region of Globus Pallidus internus (2 to 4 mm anterior, 19 to 24 mm lateral, and 4 to 6 mm inferior to the mid-commissural point) with intraoperative microelectrode recording (MER) confirmation. In patients with essential tremor, the ventral intermediate nucleus of the thalamus was targeted for DBS electrode implantation (6 mm anterior to posterior commissure, 11 mm lateral to the third ventricular wall, and at the anterior commissure–posterior commissure line). All trajectories were confirmed with intraoperative awake macrostimulation testing.

Before right-sided DBS lead implantation, an eight-contact ECoG strip (platinum-iridium 4-mm contacts with 1-cm spacing; AdTech Medical, USA) was implanted subdurally *via* the right frontal burr hole placed for DBS implantation. The burr hole was always at, or up to, 1 cm in front of the coronal suture. Given central sulcus is located 3 to 5 cm behind the coronal suture, an eight-contact ECoG strip ensured coverage of the central sulcus through the burr hole. After implantation of the DBS electrode in each hemisphere, a single-view lateral fluoroscopy image was acquired to confirm DBS electrode placement. After ECoG recordings were acquired, the subdural strip was removed, the DBS electrode was locked into place, and the burr hole was sealed. After the procedure, a postoperative computerized tomography scan was obtained for confirmation of DBS electrode position. A detailed description of the ECoG strip localization and signals utilized in this study is provided as Supplemental Digital Content (http://links.lww.com/ALN/B552). We used three bipolar contact pairs for analyses: CS (spanning the central sulcus), post-CS (immediately posterior to CS), and pre-CS (immediately anterior to CS; fig. 1).

Data Recording and Preprocessing

ECoG recordings were obtained with a scalp ground and reference. Signal acquisition was performed using BCI2000 v2 connected to a g.USBamp 2.0 amplifier (Guger Technologies, Austria) at a sampling rate of 2,400 Hz. Before recordings, patients were off propofol and all other anesthetics for at least 1.5 h. In each subject, bilateral DBS local field potentials (Globus Pallidus internus for Parkinson disease and ventral intermediate nucleus for essential tremor) and simultaneous frontoparietal ECoG signals were initially recorded while subjects performed six blocks of alternating rest and finger tapping. We began recordings with patients resting awake with eyes open for 1 min, after which propofol was administered according to the attending anesthesiologist's clinical judgment. Recordings continued and patients were assessed verbally at least every 30 s after propofol administration to ensure and determine the timing of loss of responsiveness. We used the modified observer's assessment of alertness/sedation scale to evaluate the subject's level of alertness.[33] Each patient included in the study reached a score of 0/1, after which recordings continued for 1 min. Recordings continued for an average of 5 min after the start of propofol administration. Due to variations in propofol dosing, cardiac output, and blood volume across subjects, we expected substantial differences in circulation time and anesthetic induction across subjects. Therefore, we focused our analyses on prebolus and postinduction steady state signals, using the last minute of recording as the time period when subjects were completely anesthetized and no longer verbally responsive (hereafter referred to anesthesia period or Anes), and contrasted this with the preanesthesia (PreAnes) stage.

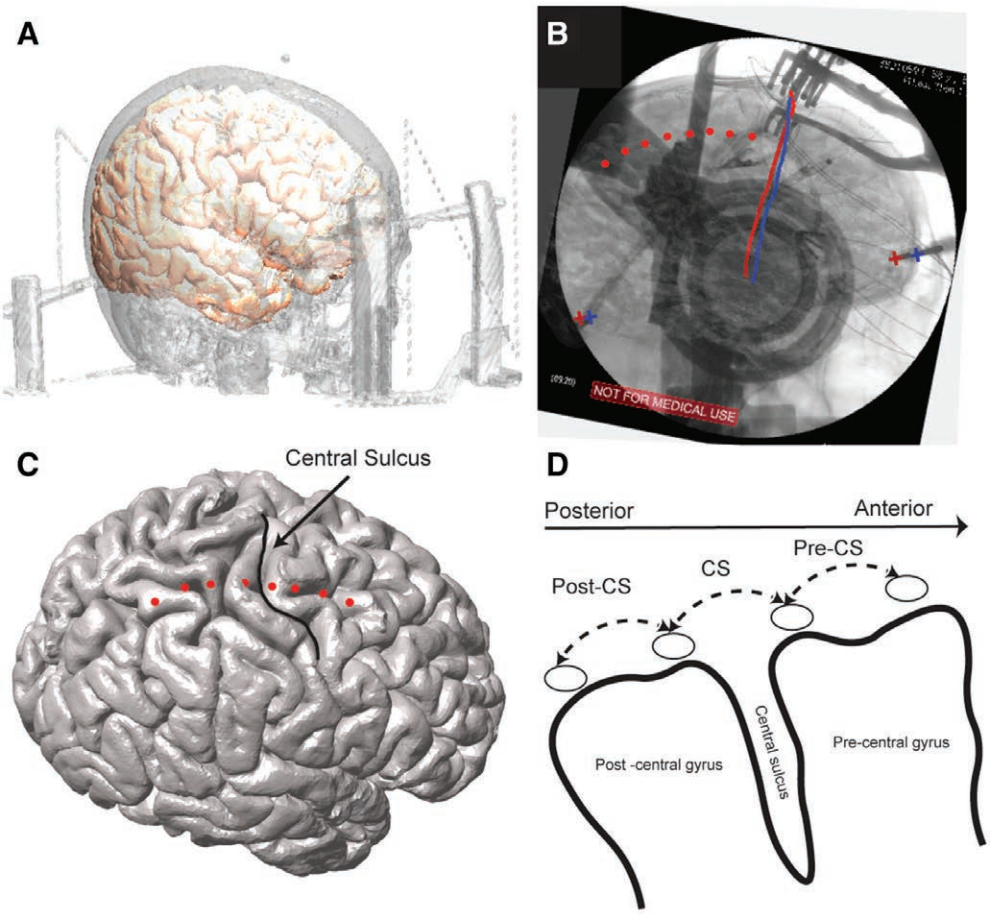

Fig. 1. Localization of cortical electrocorticography (ECoG) strip and cortical signals used for analysis. Registration of preoperative structural high resolution T1-weighted magnetic resonance imaging and computerized tomography to colocalize cortical brain surface and skull *(A)*. Tips of the stereotactic frame and deep brain stimulation leads (marked by + *signs* and *straight red and blue lines* on the image, respectively) are used as landmarks to complete two-dimenstional–three-dimensional fusion of fluoroscopic image and cortical surface *(B)*. Once the fusion is complete, cortical contacts (visible on the fluoroscopic image) are marked manually on the fused images. Marked ECoG contacts are shown on the cortical surface and identified relative to the central sulcus *(C)*. Three cortical bipolar signals spanning post- to precentral gyri/sensorimotor cortices (posterior to anterior: immediately posterior to the central sulcus [post-CS], spanning the central sulcus [CS], and immediately anterior to central sulcus [pre-CS]) are marked and used for all of the analyses *(D)*. For more detailed description of the registration method, please refer to the Supplemental Digital Content, http://links.lww.com/ALN/B552.

Signal analysis was performed in MATLAB (version 8.6, The Mathworks Inc., USA) using the Fieldtrip toolbox for EEG/magnetoencephalography-analysis[34] and the Chronux toolbox.[35] Bipolar re-referencing of adjacent contacts was used to emphasize local and minimize global signals. Raw ECoG data were first subjected to automatic artifact rejections and subsequently verified through visual inspection with an interactive waveform browser. Automatic artifact detection was accomplished by first performing a full-wave rectification, then taking the first derivative, and subsequently filtering with a five-point median filter to identify waveform segments that exceeded five standard deviations of the entire recorded session for each subject. Location windows of artifact segments were extended by 2 ms on each side. Artifact segments were then replaced using a piecewise cubic interpolation based on surrounding data. Preprocessed data were bandpass filtered for frequencies between 1 and 500 Hz using two-way least-squares finite impulse response filtering (eegfilt.m). Line noise and its harmonics (up to 500 Hz) were removed from the data using notch filter implemented in Fieldtrip toolbox. Of note, while deep brain local field potential was also recorded, the focus of the current study was on cortical dynamics. Therefore, analysis of these signals is deferred.

Power Spectral Density and Spectral Peak

Time frequency representation of power (TFR) for PreAnes and Anes conditions (1 min each) was calculated using the multitaper method[36] in 1-s consecutive time windows with no overlap for frequencies of 1 to 300 Hz with ±2 Hz frequency bandwidth (three tapers). Figure 2A shows TFR maps for an example subject from the Parkinson disease cohort. Average TFR maps for both conditions were then calculated

for each cohort at post-CS, CS and pre-CS. Tapered spectra were likewise derived using similar parameters to TFR maps. To account for intersubject variability in baseline power, each segmented spectra was normalized to the total power of the signal during PreAnes (excluding the line noise and its multiples). To evaluate changes in the dominant spectral peak frequencies with propofol, we averaged such dominant peaks for all three cortical signals to derive a single average peak frequency value per condition per subject. Average peak frequencies were then compared between the two groups.

While our primary focus was contrasting Anes and PreAnes conditions, we also preliminarily investigated relative temporal (as opposed to the absolute timing of) changes in spectral power across frequency bands. To do this, we analyzed TFR maps for the entire recording for each subject, defining average power over time for the frequency bands: δ (1 to 4 Hz), θ (4 to 8 Hz), α (8 to 12 Hz), β (13 to 30 HZ), γ (40 to 100 Hz). More controlled studies with weight- and cardiac output–adjusted dosing will be required in the future for more dynamic assessment of propofol effects.

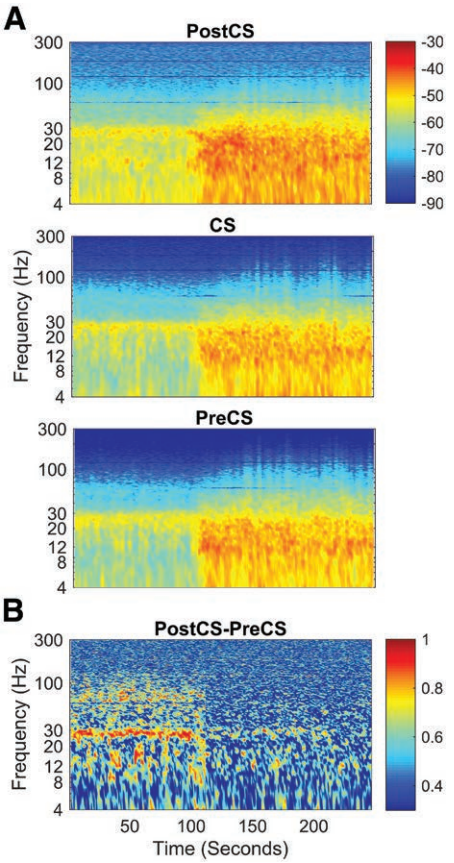

Fig. 2. Changes in sensorimotor power and coherence in an example subject. Time frequency representation of power for three cortical signals investigated (*top* to *bottom*), indicating local power increase for frequencies less than 100 Hz similarly at all sensorimotor cortices (immediately posterior to the central sulcus [post-CS], spanning the central sulcus [CS], and immediately anterior to central sulcus [pre-CS]; *A*). *Dashed vertical line* indicates timing of propofol injection (bolus). Time frequency representation of coherence (*i.e.*, coherogram) between signals recorded from pre- and postcentral gyri (preCS and postCS, respectively) (*B;* from the sample subject as in *A*), indicating de-coherence in β (13 to 30 Hz) between sensory and motor cortices.

Coherence and Imaginary Coherence

To describe the degree of covariability between the two signals, we estimated the magnitude squared coherence between pre-CS and post-CS (covering motor/premotor and sensory cortices, respectively, and not sharing a common contact) with 1-Hz frequency resolution. Magnitude squared coherence was calculated using a multitaper method with time window and frequency smoothing parameters identical to the analysis of power spectral density (frequencies of 1 to 300 Hz with ±2 Hz frequency bandwidth [3 tapers]). Figure 2B shows a sample coherogram (time frequency representation of coherence) for one subject (same as fig. 2A) for the entire period of recording.

We further explored effects of spurious volume conduction on coherence using imaginary coherence (iCoh).[37] Imaginary coherence is only sensitive to synchronization of two processes that are time-lagged to each other. iCoh is therefore insensitive to volume conduction of common signals and represents true coupling. Using similar parameters to those used for coherence analyses, we derived the imaginary part of coherency between the two signals for nonoverlapping time windows.

Statistical Analysis

Statistical significance of changes in spectral power between PreAnes and Anes conditions at each frequency (1 to 300 Hz) for each disease cohort was assessed using two group tests of the spectrum; the null hypothesis that Anes and PreAnes have equal spectra within disease groups was tested.[38] Since multitaper spectral analysis uses an orthogonal family of tapers (*i.e.*, Slepian sequences) and the analysis was done for nonoverlapping windows, obtained tapered spectra are assumed to be statistically independent. We calculated mean group spectra for two conditions (across each cohort), and corresponding Z statistics using asymptotic spectral probability distribution. The 95% CIs were then calculated based on Jackknife estimation of variance as previously described.[38] To address the issue of multiple comparisons, we note that differences in spectra due to chance are likely to be at isolated frequencies, while neurophysiologic differences are likely to occur across contiguous frequency ranges (*i.e.*, α, β). Since spectral estimates at frequencies separated by less than the bandwidth of the multitaper method (4 Hz) are inherently correlated, we rejected the null hypothesis for all candidate frequencies constituting bands with widths larger than 4 Hz.

Following an approach similar to spectral power comparison, average magnitude-squared coherence between two signals for two conditions were contrasted and statistically compared using two group test of the coherence.[38] Subsequent Z-statistics and CIs for a *P* value of 0.05 were calculated

to assess statistical significance. Correction for multiple comparisons was done in a similar fashion to the spectral analysis.

To assess the statistical significance of differences in group average iCoh between two conditions (PreAnes and Anes), we used permutation testing, pooling together values from all time segments for all subjects (considering that tapers are orthogonal and time windows are nonoverlapping, we could reasonably assume that tapered Fourier transforms are interchangeable). At each permutation (N = 10,000), a random subset of the cohort was selected for which the labels of the conditions were swapped, allowing for the creation of a null distribution of the group difference. Since the difference values at each frequency are bound between –1 and 1, the Fisher Z-transform of the condition difference could be assumed as approximately normally distributed under the null hypothesis. The significance of the condition difference was then assessed using $P = 0.05$ and corrected for multiple comparisons in a similar fashion to the spectral and coherence statistical analysis.

The Shapiro-Wilk test was used to explore normality of distributions when comparing peak spectral and coherence frequencies between the two disease groups and within each cohort to explore effects of propofol. Such analysis showed that distribution of the peak frequency values was significantly different from normal distribution ($P < 0.05$). Subsequently, we used a Mann-Whitney U test to compare frequency of dominant spectral peaks between Parkinson disease and essential tremor groups. We employed a Wilcoxon signed-rank test to assess changes in the peak frequencies between PreAnes and Anes states separately within each disease group.

Results

Patient Demographics and Anesthetic Induction and Maintenance

Nineteen patients were included in this study, including twelve patients with Parkinson disease (three female, nine male; average age, 65 ± 7 yr) and seven patients with essential tremor (four female, three male; average age, 69 ± 6 yr). Clinical evaluation of disease severity was done for both disease groups separately before the surgery while subjects were off medication. Unified Parkinson Disease Rating Scale (UPDRS) part 3 (motor examination) indicated mean ± SD of 41 ± 9, and a tremor rating scale for essential tremor indicated 53 ± 12 for severity of the symptoms in the two groups of patients. Average body weight across the cohort at the time of recording was 79.5 ± 19.2 kg. Propofol was administered intravenously with an initial bolus of 0.53 ± 0.31 mg/kg, followed by an average continuous infusion rate of $73 \pm 33\ \mu g \cdot kg^{-1} \cdot min^{-1}$.

Propofol-induced Changes in Cortical Spectral Power and Coherence

Propofol-induced loss of consciousness was associated with significant increases in cortical broadband power for frequencies between 2 and 100 Hz across all three sensorimotor cortical contacts. Such broadband power increase happened in both disease cohorts (fig. 3). These spectral changes were consistent across the duration of the entire examined segments, as illustrated in average TFR maps (fig. 3, A and C) including both PreAnes and Anes segments.

In addition to increases in spectral power between 2 and 100Hz, in both disease groups, the dominant spectral peak (8 to 35 Hz) in the anesthetized state was in the α band (fig. 3, B and D). In Parkinson disease, the median dominant spectral shifts from 24.5 ± 2.6 Hz (β range) to 12.8 ± 2.3 Hz ($P = 0.002$, paired sample Wilcoxon signed-rank test; fig. 3B, *inserts*). For essential tremor, the median spectral peak decreased, but not significantly, from 13.8 ± 2.1 Hz to 12.1 ± 1.0 Hz ($P = 0.23$, paired sample Wilcoxon signed-rank test; fig. 3D, *inserts*). While median spectral peaks for essential tremor and Parkinson disease were different PreAnes ($P = 0.0003$, Mann-Whitney ranked-sum test), an independent samples Mann-Whitney test showed no significant difference in median peak frequency between two groups in the Anes state ($P = 0.35$).

Analysis of propofol-induced cortical power changes also showed that in the Parkinson disease group, power at frequencies 150 to 300 Hz significantly decreased at pre-CS signal (fig. 3, A and B). Such 150- to 300-Hz power increase was not observed at post-CS and CS signals in Parkinson disease, nor any of the cortical signals in the essential tremor cohort.

Tracking band power changes over time showed a consistent pattern of relative timing between different frequency bands for 11 of 12 subjects in the Parkinson disease group, with the high β power (20 to 35 Hz) increase preceding changes in other frequency bands, especially the α/low β (13 to 20 Hz) band (fig. 4). This orderly pattern was observed irrespective of the dose or the timing of onset of therapeutic effect of propofol. In the essential tremor cohort, we observed no consistent pattern of timing in power change across different frequency bands.

Propofol Suppresses Sensorimotor Cortical Coherence

Despite broadband increases in spectral power at each cortical site, sensorimotor cortical coherence decreased with propofol anesthesia (fig. 5, A and B). Specifically, sensorimotor coherence significantly decreased in the Parkinson disease cohort in high β frequencies (18 to 29 Hz) and in the essential tremor cohort across frequencies between 10 and 48 Hz, including both α and β bands (two group coherence tests as described in the methods, $P < 0.05$). Median peak frequencies for coherence changed from 24.6 ± 3.1 Hz to 14.35 ± 3.7 Hz in the Parkinson disease group, and from 13.4 ± 2.0 Hz to 10.4 ± 2.8 Hz in the essential tremor group. A Wilcoxon signed-rank test revealed that across both cohorts, changes in dominant coherence peak frequency were statistically significant ($P = 0.002$ for Parkinson disease and $P = 0.028$ for essential tremor).

To confirm that coherence measures do not represent spurious volume conduction, we also evaluated iCoh between

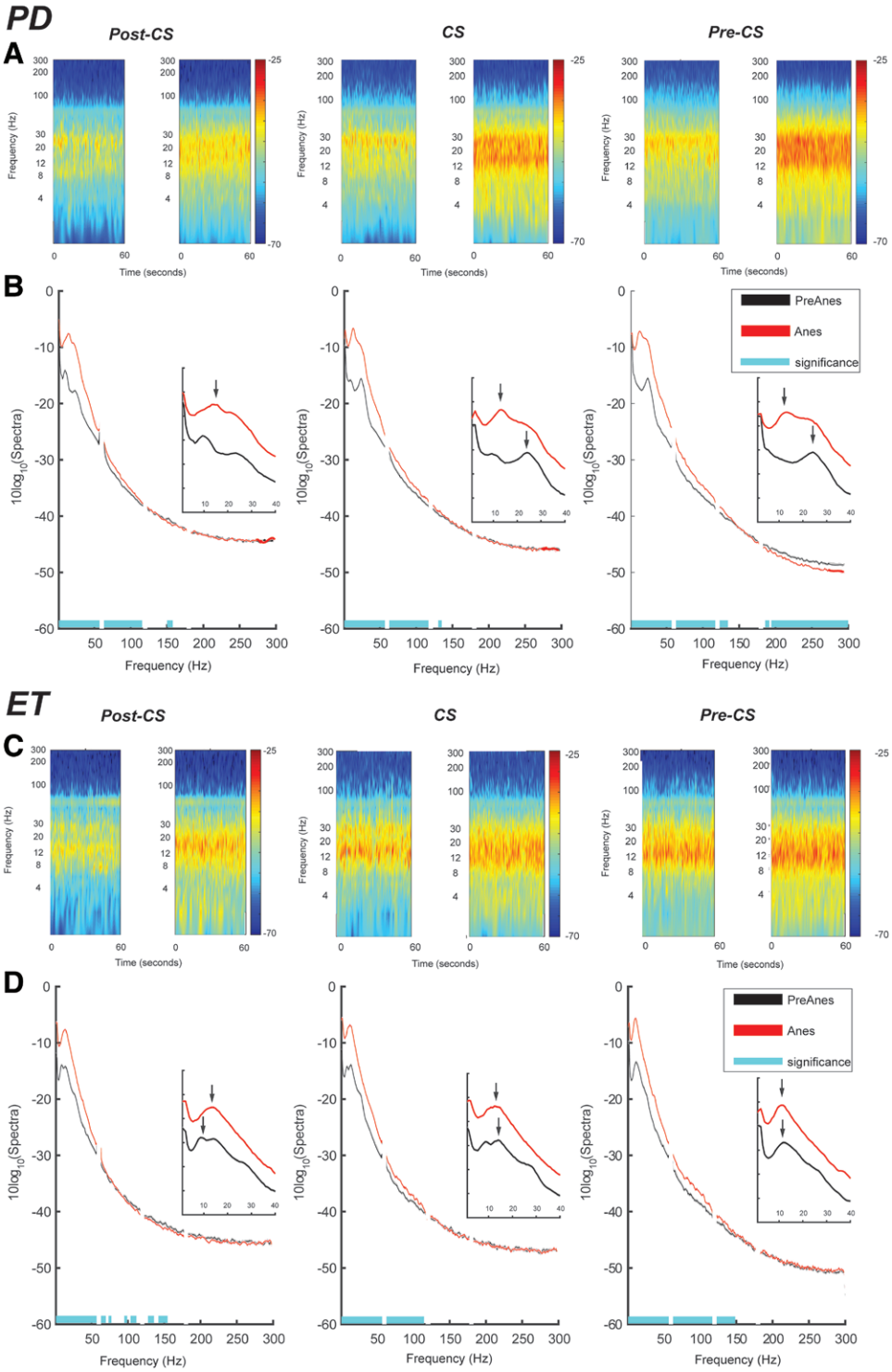

Fig. 3. Propofol-induced power spectral changes in sensorimotor cortical signals. Group average of time frequency representation of power comparing preanesthesia (PreAnes; *left*) and anesthesia (Anes; *right*) time segments across three bipolar channels (immediately posterior to the central sulcus [post-CS], spanning the central sulcus [CS], and immediately anterior to central sulcus [pre-CS]) investigated in Parkinson disease (PD; *A).* Group average of power spectral density comparing PreAnes (*black*) and Anes (*red*) across sensorimotor cortices in Parkinson disease. *Blue shade* shows significant difference of spectra between two conditions at $P = 0.05$ after correction for multiple comparisons. Inserts indicate shift of the dominant spectral peak from β frequencies to α with propofol anesthesia *(B)*. Similar to *(A)*, shows group average time frequency maps comparing PreAnes and Anes conditions for essential tremor (ET) group *(C)*. Similar to *(B)*, shows average power spectral densities in essential tremor cohort for two conditions across three cortical signals with significant difference at $P = 0.05$ (after correction for multiple comparisons), highlighted by *blue shades* (*D*). *Inserts* show that despite local power increase, dominant spectral peak remains in α frequencies in essential tremor group with propofol anesthesia.

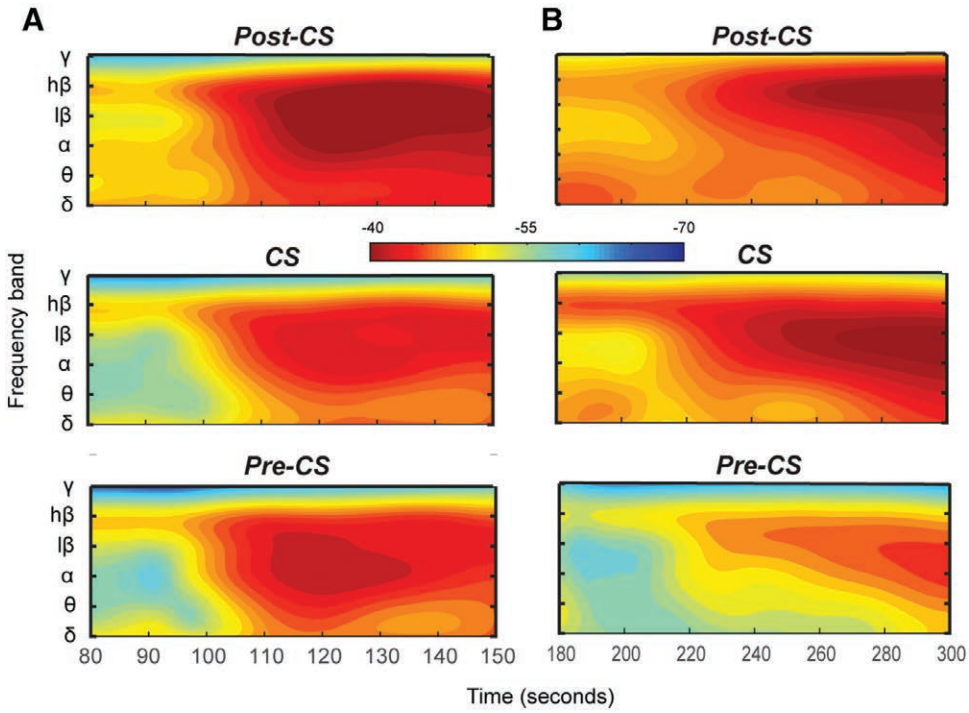

Fig. 4. High β-power changes precede changes in other bands in the Parkinson disease group with propofol anesthesia. Time frequency representation of relative timing between changes in band power changes for different frequency bands for two representative subjects, highlighting similarity in relative pattern despite the difference in timing of the changes. Time stamps are relative to the beginning of the recording (0 s) and propofol was injected at T = 60 s *(A* and *B)*. CS = bipolar contact pair spanning the central sulcus; Post-CS = bipolar contact pair immediately posterior to the central sulcus; Pre-CS = bipolar contact pair immediately anterior to the central sulcus.

cortical signals (fig. 5, C and D). In the Parkinson disease cohort, iCoh significantly decreased for frequencies in the high β range (18 to 29 Hz). In the essential tremor group, a significant decrease in iCoh was observed in frequency ranges of (12 to 20 and 27 to 44 Hz), including the α and β bands (permutation statistics, as described in the methods, $P < 0.05$). These results indicate that β coherence suppression with propofol was common across diseases while α coherence suppression with propofol was specific to the essential tremor cohort.

Discussion

Emerging evidence suggests that anesthetics exert influence by altering functional connectivity within brain networks, thereby disrupting cortical integration.[3,39–41] This study of propofol-induced changes in sensorimotor cortical activity in 19 patients with movement disorders demonstrates that propofol anesthesia is associated with local power increases in α and β oscillations along with concurrent reduction in intercortical sensorimotor coupling at these frequencies. Such a scenario emphasizes that functional disconnection is likely a product of altered phase-based connectivity, regardless of changes in the amplitudes of the signals. Therefore, it is likely that propofol induces a functional disconnection between cortical areas along with increases in autonomous activity within these regions. This pattern occurs similarly across diseases evaluated, suggesting these may be generalizable effects of propofol. Swann *et al.*,[30] who examined subcortical-motor cortex connectivity in a mixed group of patients with movement disorders, also observed propofol-induced reduction in subcortical-motor cortex coupling specific to β frequencies. Our current study further suggests that propofol administration results in the reduction of both intercortical and cortical-subcortical functional connectivity.

Identifying common signatures of anesthetic interaction with electrophysiologic activity is a fundamental step toward understanding anesthetic-induced unconsciousness.[42] A recent nonhuman primate study on the effects of ketamine in sensorimotor cortical activity similarly found functional disconnection between the sensory and motor cortices at β frequencies, with concurrent β power suppression isolated to the sensory cortex.[43] Despite some differences, which may at least be due to differences in anesthetic mechanisms of ketamine and propofol, a common theme emerges of sensorimotor disconnection in the anesthetized state.

Dissimilarities noted in the baseline sensorimotor α coherence observed between the two disease groups may be due to the difference in the disease-specific pathophysiologic mechanisms. Studies comparing cortical activity between Parkinson disease and essential tremors have shown that dominant spectral peaks for these disease states respectively reside within the β and α range.[44] The stronger α peak of essential tremors has been suggested as reflecting the

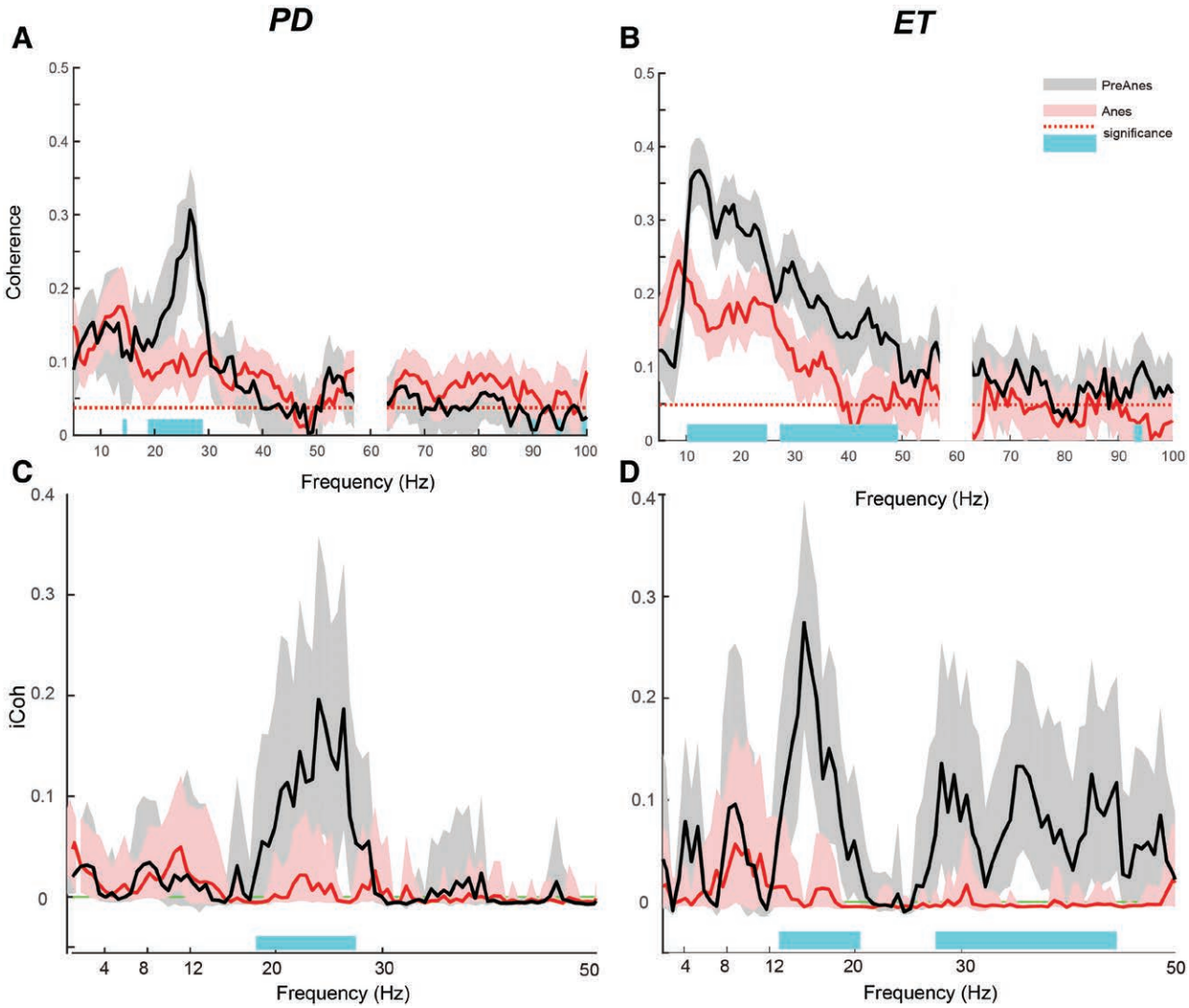

Fig. 5. Suppression of cortical sensorimotor α-β functional connectivity with propofol anesthesia. Contrasting sensorimotor coherence between preanesthesia (PreAnes; *black*) and anesthesia (Anes; *red*) conditions for the Parkinson disease (PD) and essential tremor (ET) groups, respectively (*A* and *B*). *Dashed lines* indicate 95% confidence level for coherence driven by Jackknife method, indicating that coherence values at PreAnes and Anes conditions are statistically significant. *Shades* around each average coherence curve show 95% CIs of the mean. Significant differences at $P = 0.05$ level highlighted in *blue* and corrected for multiple comparisons. Imaginary coherence (iCoh) between sensorimotor cortices for PreAnes (*black*) and Anes (*red*) for PD and ET groups, respectively (*C* and *D*). *Dashed lines* indicate 95% confidence level for coherence driven by Jackknife method, indicating that coherence values at PreAnes and Anes conditions are statistically significant. *Shades* around each average coherence curve show 95% CIs of the mean. Significant differences at $P = 0.05$ are highlighted with *blue* and corrected for multiple comparisons.

pathologic entrainment of basal ganglia-thalamo-cortical network at tremor and double tremor frequencies.[45,46]

Propofol-induced Loss of Consciousness Results in Dominance of Local α Activity in Sensorimotor Cortices

Propofol-induced enhancement of α oscillations are well described.[47,48] Our results also confirm that propofol amplifies α-band oscillations across sensorimotor cortices. Although baseline dominant spectral peaks differed across groups, propofol eliminated this difference, such that both disease groups had dominant α-band peaks after propofol administration. This propofol-induced α dominance is interesting in the context of movement suppression since α has been implicated to functionally inhibit unneeded neural networks within a hemisphere.[23,27] It has been suggested that these oscillations regulate the "akinetic" state of the basal ganglia-thalamo-cortical motor network,[27–29] possibly inhibiting movement through modulating pyramidal tract neuronal firing rate.[24]

Despite Reduced β Synchrony between Cortices, Local β Power Increases with Propofol

Discordances have been noted between simultaneously recorded ECoG and EEG signals in nonhuman primates in

which pharmacologic manipulation of brain activity has been shown to modulate EEG signals independent of changes observed *via* intracortical recordings.[49] This suggests that ECoG and EEGs can be decoupled due to a variety of electrophysiologic and anatomical variables.[17,49] Although we consistently observed increases in local cortical β power in all 19 subjects included in this study, this finding is at odds with most of the EEG literature, which suggests that cortical β power is suppressed with propofol, apart from transient "paradoxical" excitation in β power that has been associated with a hyperkinetic state.[8–10] Using intracranial EEG recordings, Verdonck *et al.*[50] found a similar 1- to 30-Hz power increase in the motor cortex with propofol. Moreover, a recent study of propofol-induced loss of consciousness in nonhuman primates showed that upon the onset of loss of consciousness, intercortical coherence β diminished while these oscillations remained locally coherent within sensorimotor cortices.[17] Interestingly, Swann *et al.*, using ECoG recordings during DBS surgery in similar groups of patients with movement disorders, did not report a β-power change across their cohort.[30] However, their subject-level analysis showed β-power increases in at least some subjects in their cohort, which is consistent with our current findings.

Our results are unlikely to be explained by paradoxical excitation, which is behaviorally manifested by disinhibition of movements, restlessness, agitation, talkativeness, small, spontaneous muscle movements, or dystonic or choreiform movements of the arms and legs during induction.[51,52] Paradoxical excitation is created by low doses of anesthetics and is marked by an increase in β-band activity and a decrease in activity of lower frequencies (α and θ) observed in the EEG signal.[53] A cortical model of this phenomenon attributes the generation of β-band activity at low doses of propofol to cortical dynamics involving the interaction of pyramidal neurons with inhibitory interneurons.[54] Since cortical pyramidal cells are thought to be a main source of the EEG signals, at the population level, this interaction manifests as an increase in the spiking frequency of pyramidal neurons in the β range.[9,54] ECoG does not face the low-pass filtering effects of skull and skin present in the EEG. Moreover, the uniformity of findings across subjects, across cortical contacts, and across doses of propofol with loss of verbal responsiveness and spontaneous movements in each patient suggests the current findings are not spurious, due to artifact, or due to the paradoxical excitation,[11] but rather true physiologic phenomenon.

Alternative Interpretation of Elevated Local β Activity

β oscillations play a key role in motor network physiology, controlling information coding capacity across the motor loops of the basal ganglia-thalamo-cortical circuit[24] and exhibiting strong movement-related modulation throughout the motor network.[25,55,56] Periods of elevated β power are associated with slowing of spontaneous movement and increased corrective responses to postural perturbation, suggesting that β actively stabilizes the current motor set.[57] This function becomes pathologically exaggerated in Parkinson disease, resulting in rigidity and bradykinesia.[58,59] However, even in Parkinson disease, the level of β activity is dynamic, likely fluctuating with moment-to-moment variations in dopaminergic activity in response to salient internal and external cues. In essential tremor, comparable levels of resting state β activity have been observed at sensorimotor cortices with no significant difference relative to Parkinson disease.[44,60] These findings suggest that aberrant β activity within the cortical sensorimotor region is likely a common manifestation between two different pathologies. Our variable result of propofol-induced β power increases in cortical activity may, therefore, be in part due to the underlying pathophysiology of Parkinson disease and essential tremors in the current patient population.

Potential Mechanisms for Propofol-induced Local α-β Power Increases and Interregional Disconnection

It remains unclear if propofol-induced increases in local cortical sensorimotor α-β power and suppression of interregional β synchrony are a consequence of alterations in corticocortical *versus* subcortical-cortical connectivity. Plausible explanations for these findings may include: 1) an elevation of the thalamocortical network activity that drives α oscillations, resulting in α-dominant spectral peaks across subjects, and 2) the reduction of sensorimotor cortical connectivity within the β band.

Network-level studies of anesthesia suggest a reduction in interareal connectivity from frontal to parietal cortices (feedback projections), but preserves parietal to frontal connectivity.[14,15,20,61] It has been suggested that feedforward projections represent incoming sensory data, whereas feedback projections play a modulating role in the information selection.[62] Therefore, selective inhibition of top-down feedback projection during loss of consciousness could be interpreted as decreased higher-order cognitive processing, while maintaining lower-order sensory processing.[20] Consistent with this theory, Schroeder *et al.*[43] provided evidence of disruption in top-down sensorimotor integration under ketamine anesthesia in a nonhuman primate model. Although we have not directly investigated the changes in effective connectivity or the encoding of sensory information from our recordings in the current study, our findings on functional disconnection of sensorimotor cortices by induction of anesthesia further support that disruption of frontoparietal information transfer is likely to be a common proxy of anesthetic-induced unconsciousness.

Limitations

The study of invasive electrophysiologic activity in the human brain is limited to neurosurgery patients. In some cases, recordings from patients with other non–movement-associated neurologic conditions (*e.g.*, epilepsy) are used for comparison instead of control groups.[46] The discrepancy of results between ECoG and EEG recordings are suggested to

be intensified during transitional states as also observed by Ishizawa *et al.*[17] Therefore, meticulous monitoring of subjects during induction of anesthesia is essential to understanding the microscale anesthetic-related changes in neuronal activity. Given the fact that patients included in this study are not intubated, and depth of anesthesia is being assessed only using standard anesthesia scales, the precision of timing with which loss of consciousness is assessed may not be optimal. Future studies would benefit from changing the induction protocol so that monitoring for induction of anesthesia could be preferably done using a target-controlled infusion to have an approximately stable serum concentration during the anesthetic phase. In particular, one must account for effects of variable dosing as well as variable cardiac output and blood volume that can lead to a substantial difference in circulation time and anesthetic induction across subjects. Finally, comparison of induction and emergence can provide greater insight into the causal relationships in these network signals.

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Competing Interests

The authors declare no competing interests.

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